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REVIEW

Inhibition of Th1 and Th17 Cells by Medicinal Plants and Their Derivatives: A Systematic Review

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Searching for new natural drugs that are capable of targeting Th1 and Th17 may lead to development of more effective treatments for inflammatory and autoimmune diseases. Most of the natural drugs can be derived from plants that are used in traditional medicine and folk medicine. The aim of this systematic review is to identify and introduce plants or plant derivatives that are effective on inflammatory diseases by inhibiting Th1 and Th17 responses. To achieve this purpose, the search terms herb, herbal medicine, herbal drug, medicinal plant, phytochemical, traditional Chinese medicine, Ayurvedic medicine, natural compound, inflammation, inflammatory diseases, Th1, Th17, T helper 1 or T helper 17 were used separately in Title/Keywords/Abstract in Web of Science and PubMed databases. In articles investigating the effect of the medicinal plants and their derivatives in inhibiting Th1 and Th17 cells, the effects of eight extracts of the medicinal plants, 21 plant-based compounds and some of their derivatives, and eight drugs derived from the medicinal plants' compounds in inhibiting Th1 and Th17 cells were reviewed. The results showed that medicinal plants and their derivates are able to suppress Th17 and Th1 T cell functions as well as cytokine secretion and differentiation. The results can be used to produce herbal drugs that suppress Th, especially Th17, responses. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: inflammation; medicinal plants; phytochemicals; immunoregulatory drugs; immunopharmacology.

Abbreviations: BALF, bronchoalveolar lavage fluid; EAE, experimental autoimmune encephalomyelitis; EAN, experimental allergic neuritis; EriB, Eriocalyxin B; FOXP3, forkhead box P3; JAK, Janus kinase; HBPDS, Hyungbangpaedok-san; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; LTB4, Leukotriene B4; MS, multiple sclerosis; NF-κB, nuclear factor-κB; PE, *Perilla frutescens* leaf extract; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E2; POLY, polydatin; RORγ, RAR-related orphan receptor gamma; SPE, *Salvia plebeia* extract; Skullcap, *Scutellaria baicalensis* extract; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor beta; UD, *Ulmus davidiana var. japonica* Nakai

INTRODUCTION

It has been established that Th1 and Th17 cells are proinflammatory subsets of T cells and are able to induce autoimmune and inflammatory processes (Zhang *et al.*, 2015a, b). Even, it has been suggested that Th17 cells are capable of inducing more severe pathologic effects (Qin *et al.*, 2010). Th1 cells release interferon (IFN)-γ and reduce the development of Th2, and therefore the imbalance of Th1/Th2 might contribute to severity of some autoimmune diseases. A wide variety of disorders including collagen-induced arthritis and experimental autoimmune encephalomyelitis (EAE) were previously considered to be Th1-mediated diseases and then reclassified as Th17-mediated inflammation (Komiyama *et al.*, 2006; Nakae *et al.*, 2003). In inflammation induced via activating various inflammatory mediators, in a wide variety of diseases such as rheumatoid arthritis, multiple sclerosis (MS), inflammatory bowel disease (IBD) (Debnath *et al.*, 2013; Ford *et al.*, 2011; Triantafyllidi *et al.*, 2015), systemic lupus erythematosus, psoriasis and Bechet's disease, the Th17 cells are considered potent inducers of tissues. Furthermore, the Th17 response is implicated in several models of infection (Netea and Marodi, 2010; Bagheri *et al.*, 2015a; Bagheri *et al.*, 2015b; Bagheri *et al.*, 2016; Shirzad *et al.*, 2011). Some other cells which promote response to pathogens, stress or injury produce IL-17 (Cua and Tato, 2010).

Specifically, many experiments have shown that the autoimmune responses of MS or EAE are predominantly induced by generation of a T helper cell and CD4+ T cells. It has been argued that auto reactive pathogenic Th cells are involved in the pathogenesis of MS and EAE (Zheng *et al.*, 2015; Qin et al., 2010; Komiyama *et al.*, 2006). Therefore, the pro-inflammatory cytokines attack the myelin and axon, resulting in demyelination and axonal injury in the onset of MS/EAE (Kroenke *et al.*, 2008). Th1 and Th17 cytokines may also play important roles in inducing of lupus nephritis. It has been stated that IL-17 is also

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implicated in patients with lupus nephritis (Tsai *et al.*, 2011). Type 1 diabetes mellitus is due to destruction of beta cells through T cells and severe islet inflammation (Cui *et al.*, 2009). The results of a study showed that the onset of type 1 diabetes in non-obese diabetic mice was associated with an imbalance between Treg cells and IL-17 producing Th17 cells (Shi *et al.*, 2009). The imbalance between Th1/Th2 and Treg/Th17 has also been reported in asthmatic patients (Ji *et al.*, 2014). Moreover, both Th1 and Th17 responses may also contribute to pathogenesis of human IBD and animal colitis (Li *et al.*, 2010; Iwasa *et al.*, 2012; Wangchuk *et al.*, 2015). Furthermore, blockade of IL-6 supresses the IL-17 inflammatory Th17 responses and reduces autoimmune arthritis (Fujimoto *et al.*, 2008). It has been reported that Th17 cells cause the chronic pathogenesis of rheumatoid arthritis (Gaffen, 2004; Fouser *et al.*, 2008). Indeed, at the early stages of arthritis, the Th17 cells stimulate generation of matrix metalloproteinase and proinflammtory cytokines (Nisar *et al.*, 2015). In addition, inhibiting the cytokines produced by Th17 especially IL-17A may contribute to reduction of HIV infection (Kapewangolo *et al.*, 2013). IL-17A has also been shown to modulate early neutrophilic lung inflammation in experimental silicosis (Chen *et al.*, 2015).

New drugs which are able to specifically target the pathogenic Th1 and Th17 cells and simultaneously spare other immune cells, including CD4+ CD25+ Foxp3+ regulatory T cells, can help greatly to develop more effective treatments for inflammatory diseases. In this regard, preparation of plant derived immunomodulatory and antiinflammatory drugs has attracted much attention (Bahmani *et al.*, 2014b; Sharafati-Chaleshtori *et al.*, 2011; Asgary *et al.*, 2014; Ghasemian *et al.*, 2016; Curro *et al.*, 2016; Pan *et al.*, 2017). These plants can exert many biological effects. In several studies, their effects on prevention and treatment of different diseases have been reported (Kafash-Farkhad *et al.*, 2013; Bahmani *et al.*, 2014g; Saki *et al.*, 2014a; Asadbeigi *et al.*, 2014; Asadi *et al.*, 2013; Shirzad *et al.*, 2009; Bahmani *et al.*, 2014a; Asadi-Samani *et al.*, 2014; Bahmani *et al.*, 2014c; Bahmani *et al.*, 2014e; Asadi-Samani *et al.*, 2016; Mahmoud *et al.*, 2016; Ki *et al.*, 2016; Talat *et al.*, 2015). They are a rich source of natural compounds for preparation of safe and effective medications which can be used to treat inflammatory diseases.

The aim of this systematic review is to identify and introduce plants or plant derivatives that are effective on inflammatory diseases by inhibiting Th1 and Th17 responses.

Methods

To conduct this systematic review, the databases such as Web of Science and PubMed were searched for the articles about the role of Th1 and Th17 in inflammatory diseases published between 2000 and 2016. The search terms medicinal plant or herb or herbal medicine or traditional Chinese medicine or Ayurvedic medicine or natural compound or phytochemical or herbal drugs and inflammation, inflammatory diseases, Th1 or Th 1 or Th17 or Th 17 or T helper 1 or T helper 17 or TH-1 or TH-1 were used and separately searched in Title/Keywords/Abstract. The articles retrieved from both databases were analyzed once.

The abstracts were reviewed based on predefined inclusion and exclusion criteria. The full texts were retrieved to assess study eligibility if necessary. The articles without English abstracts and available English full texts were excluded. Only the articles that directly investigated the effect of the medicinal plants and their derivatives in inhibiting Th1 and/or Th17 cells or their responses were included in the analysis (Fig. 1).

Results

In articles investigating the effect of the medicinal plants and their derivatives in inhibiting Th1 and Th17 cells, the effects of eight extracts of the medicinal plants, 21 plant-based compounds and some of their derivatives and eight drugs derived from the medicinal plants' compounds in inhibiting Th1 and Th17 cells were reviewed. The results below are presented separately on the medicinal plants, the medicinal plants-derived compounds and herbal drugs. Besides that, Table 1 shows the effect of these agents in inhibiting inflammatory diseases.

Phytotherapy for the Prevention and Treatment of Inflammatory Diseases

Medicinal plants. Hyungbangpaedok-san (HBPDS) which is a traditional herbal medicine is used to treat MS. Hyungbangpaedok-san could diminish the development/progression of EAE through activation of microglia, macrophages, Th1, Th17 and Treg cells as well as regulating the recruitment/infiltration in the spinal cord. The methanol extract of HBPDS reduced mRNA expression of pro-inflammatory cytokines (TNF-α, IL-6 and IL-1 β), iNOS and chemokines (MCP-1, MIP-1 α and RANTES) in the spinal cord. The onset treatment with HBPDS decreases the elevated population of CD4+/IL-17+ T cells, and CD4+, CD4+/IFN-γ+ in the spinal cord and increases the enhanced population of CD4+/CD25+/Foxp3+ and CD4+/Foxp3+/Helios+ T cells of mice with EAE (Choi *et al.*, 2015a).

Salvia plebeia extract (SPE) is used as an antioxidant in many countries including Korea and China. It suppresses atopic dermatitis-like skin lesions. *Salvia plebeia* extract (2, 10, 50 mg/kg) decreased Th1, Th2 and Th17 expansion in the lymph node and the expression of Th1, Th2 and Th17 cytokines through the down-regulation of mitogen-activated protein kinase, nuclear factor-kappaB and STAT1 in HaCaT cells in the ear tissue (Choi *et al.*, 2014). In addition, SPE blocked the inflammatory response ina murine model of arthritis as well as in human rheumatoid synovial fibroblasts.It also decreased Th1, Th2 and Th17 expansion in inguinal lymph nodes and expression of inflammatory mediators including cytokines, MMP-1 and MMP-3 by down-regulating NF-kappaB, Akt and mitogen-activated protein kinases (Choi *et al.*, 2015b).

Specific extract of *Wedelia chinensis*, a medicinal herb commonly used in Asia, has nutritional potential for development and treatment of IBD. Administration with *W. chinensis* extract at 50 mg/kg body weight for

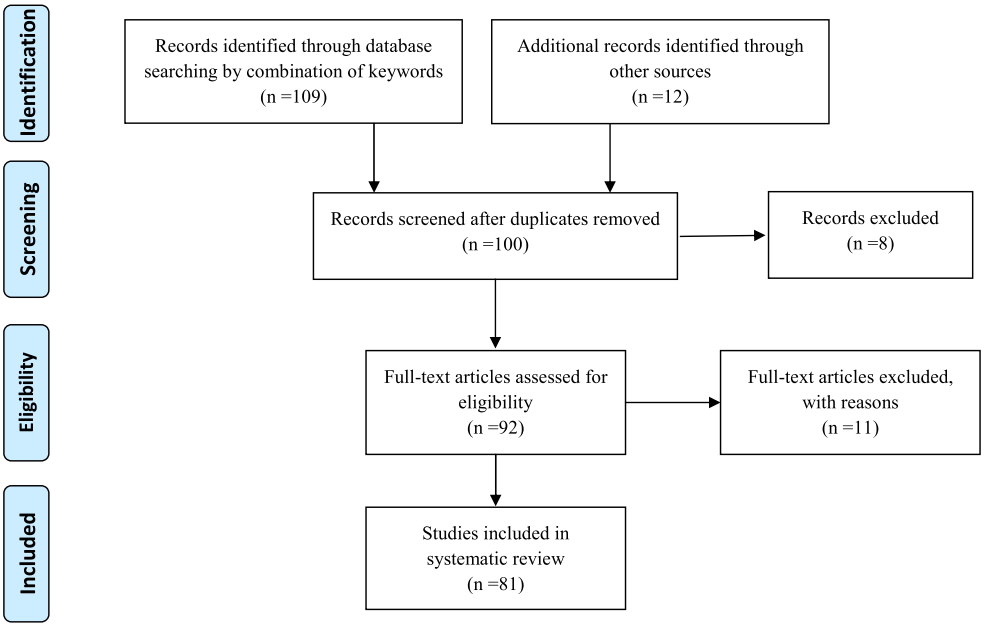

Figure 1. Flow diagram of study. [Colour figure can be viewed at wileyonlinelibrary.com]

one week attenuated dextran sulfate sodium-induced colitis in mice. *W. chinensis* treatment was able to suppress the Th1 and Th17 response in dendritic cells of DSS-induced colitis mice (Huang *et al.*, 2013).

Antiinflammatory properties of the ethanolic extract of *Plectranthus barbatus* (50 and 25 g/mL) were investigated using a Th1, Th2 and Th17 cytometric bead array technique. The results showed a decrease in cytokine production of pro-inflammatory cytokines IL-2, IL-6, IL-10, TNF and IL-17A (Kapewangolo *et al.*, 2013).

Treatments containing elements of the bark of *Ulmus davidiana var. japonica* Nakai (UD) (5 g/kg) upregulated eosinophils and suppressed Th1 and Th17 cells in the small intestine. The numbers and frequencies of Th1 and Th17 cells significantly decreased in the UD-treated mice in comparison to PBS controls by down-regulating the Th1 and Th17 responses via IL-4 secretion and contributing to intestinal homeostasis (Lee *et al.*, 2013).

Anti-arthritic activity of ethanolic extract of *Atropa accuminata* was revealed in polyarthiritis test in both phases of the disease in rats. Treatment with ethanolic extract of *A. accuminata* (62.5 to 500 mg/kg b.w.) significantly decreased the levels of Th1 cytokines in serum and paw. Maximal decrease was seen at the highest dose (500 mg/kg b.w). This extract results in up-regulation of Th2 cytokines (IL-4 and IL-10), and the suppression of Th1–Th17 cytokines (IL-2, TNF-α, IFN-γ, IL-12, IL-17, IL-6) and pro-inflammatory mediators (PGE2, NO, IL-1 β and LTB4) is dose dependent (Nisar *et al.*, 2015).

Scutellaria baicalensis extract (Skullcap) decreased food allergy. A dose of 25 mg/kg of skullcap was orally administered every day from day 17 to 34 in a mouse model of food allergy. Th17 cytokine (IL-17) and Th2-related cytokines (IL-4, IL-5, IL-10 and IL-13), which were enhanced with food allergy, were significantly decreased by skullcap treatment (Shin *et al.*, 2014).

Perilla frutescens (PE) leaf extract (0.54% PE solution given for 10 days) ameliorated DSS-induced colitis by inhibiting proinflammatory cytokines and enhancing antiinflammatory cytokines. An experiment was performed on luteolin, apigenin and rosmarinic acid, prepared from PE leaf extract. Luteolin (10 and 25 μM for 48 h) decreased generation of proinflammatory cytokines, including IL-1β, IL-6, IL-17A and TNF-α. Apigenin (5 and 50 μM for 48 h) reduced the secretion of IL-17A and enhanced the antiinflammatory cytokine IL-10. Also, rosmarinic acid (5 and 25 μM for 48 h) enhanced the regulatory T cell population (Urushima *et al.*, 2015).

Natural compounds (Fig. 2). Celastrol, a bioactive compound from the traditional Chinese medicine Celastrus, controlled autoimmune inflammation through alteration of Th17/Treg balance in the joints of rats with adjuvant arthritis. Celastrol treatment (1 mg/kg/d) decreased Th17 cells but enhanced Treg in the joints, and reduced Th17 differentiation; however, it promoted Treg differentiation through blocking the activation of pSTAT3. Also, Celastrol blocked the generation of Th17-differentiating cytokines and chemokines (CCL3, CCL5) (Astry *et al.*, 2015).

Proanthocyanidin fraction (627.5 mgPE/g) from the bark of *Metasequoia glyptostroboides* was able to ameliorate the allergic contact dermatitis in mice through blockage of T cell activation and Th1 and Th17 responses. Proanthocyanidin fraction significantly down-regulated the mRNA expression levels in activated T-cells and reduced the generation of Th1/Th17 specific cytokines (IL-2, IFN-γ and IL-17) (Chen *et al.*, 2015).

Berberine (Sigma, 200 mg/kg body weight), an alkaloid derivative from *Berberis vulgaris* L., in type 1 diabetic mice differentially modulated the activities of ERK, p38 MAPK and JNK to suppress Th17 and Th1 T cell differentiation. Furthermore, daily gavage of berberine for 2 weeks decreased Th17 and Th1 cytokine secretion and progression of type 1 diabetes in half of the NOD mice. Berberine also reduced the Th1 and Th17 differentiation by decreasing the expression of lineage markers. It also down-regulated the activity of STAT1 and STAT4 by reduction of p38 MAPK and

Table 1. Medicinal plants and their derivatives that affect Th1 and Th17 mediated diseases with inflammatory origin

Diseases	Medicinal plants or their derivate	Type	Ref.
Multiple sclerosis	Hyungbangpaedok-san	An extract of medicinal plant	(Choi *et al.*, 2015a)
	Oleanolic acid	A natural compound	(Martin *et al.*, 2012)
	Erythrodiol	A natural compound	(Martin *et al.*, 2012)
	Berberine	A natural compound	(Qin *et al.*, 2010)
	Curcumin	A natural compound	(Xie *et al.*, 2009)
	Baicalin	A natural compound	(Zhang *et al.*, 2015b)
	Salvianolic acid B	A natural compound	(Dong *et al.*, 2016)
	Triptolide	A natural compound	(Wang *et al.*, 2008)
	Astragaloside IV	A natural compound	(He *et al.*, 2013)
	Matrine	A natural compound	(Kan *et al.*, 2013)
	Eriocalyxin B	A natural compound	(Lu *et al.*, 2013)
	Plumbagin	A natural compound	(Jia *et al.*, 2011)
	Arctigenin	A natural compound	(Li *et al.*, 2013)
	1032	A new derivative of sinomenine	(Yan *et al.*, 2010)
	Bu Shen Yi Sui	A plant formula	(Zheng *et al.*, 2015)
Asthma	Ligustrazine	A natural compound	(Ji *et al.*, 2014)
	Ma Huang Tang (Ephedra decoction, MHT)	A plant formula	(Ma *et al.*, 2014)
	BuShenYiQi	A plant formula	(Wang *et al.*, 2014)
Atopic dermatitis-like skin lesions	*Salvia plebeia*	A extract of medicinal plant	(Choi *et al.*, 2014)
Dermatitis	Proanthocyanidin	A natural compound	(Chen *et al.*, 2015)
Type 1 diabetes	Berberine	A natural compound	(Cui *et al.*, 2009)
Arthritis	*Atropa accuminata*	An extract of medicinal plant	(Nisar *et al.*, 2015)
	Salvia plebeia	An extract of medicinal plant	(Choi *et al.*, 2015b)
	Celastrol	A natural compound	(Astry *et al.*, 2015)
	Baicalin	A natural compound	(Yang *et al.*, 2013)
	Daphnetin	A natural compound	(Tu *et al.*, 2012)
Airway inflammation	Baicalin	A natural compound	(Liu *et al.*, 2015)
	Puerarin	A natural compound	(Zhang *et al.*, 2015b)
	BSYQF	A natural compound	(Wei *et al.*, 2015)
Alergy	*Scutellaria baicalensis*	An extract of medicinal plant	(Shin *et al.*, 2014)
Renal inflammation	DCB-SLE1	A plant formula	(Tsai *et al.*, 2011)
Experimental autoimmune uveitis	Qingkailing	A plant formula	(Tian *et al.*, 2012)
Inflammatory responses in septic condition	Huang-Lian-Jie-Du-Tang	A plant formula	(Wei *et al.*, 2013)
Inflammatory bowel disease	*Wedelia chinensis*	An extract of medicinal plant	(Huang *et al.*, 2013)
	Perilla frutescens	An extract of medicinal plant	(Urushima *et al.*, 2015)
	Triptolide	A natural compound	(Li *et al.*, 2010)
	Icariin	A natural compound	(Tao *et al.*, 2013)
	Artesunate	A natural compound	(Yang *et al.*, 2012)
	Daikenchuto	A plant formula	(Iwasa *et al.*, 2012)
Psoriasis	Paeoniflorin	A natural compound	(Zhao *et al.*, 2015)
Experimental autoimmune neuritis	Curcumin	A natural compound	(Han *et al.*, 2014)
Inflammatory diseases	polydatin	One of derivatives of resveratrol	(Lanzilli *et al.*, 2012)
Intestinal disorders	*Ulmus davidiana var. japonica* Nakai	An extract of medicinal plant	(Lee *et al.*, 2013)

JNK activation. It could also control the stability of STAT4 through the ubiquitin–proteasome pathway (Cui *et al.*, 2009). Berberine (administered intragastrically at 200 mg/kg daily) was also effective in ameliorating the EAE. It decreased differentiation of Th1 and Th17 cells directly through JAK/STAT pathway. However, it had no effect on the relative number of Tregs. Berberine, however, indirectly influenced Th1 and Th17 cell functions by production of IL-6 and expression of costimulatory molecules (Qin *et al.*, 2010).

Salvianolic acid B (Sal B) is a major water-soluble bioactive component of the famous traditional Chinese medicine Salvia miltiorrhiza. Daily administration (30 mg/kg) of mice with Sal B for 14 days, after the onset of MOG-induced EAE, ameliorated CNS autoimmunity by suppressing Th1 responses. Sal B downgraded the infiltration of inflammatory cells, reduced Th1 responses and astrogliosis rather than that of Th17 (Dong *et al.*, 2016).

Curcumin (100 mg/kg/day), isolated from the rhizome of *Curcuma longa*, ameliorated rat experimental autoimmune neuritis. It altered T cell helper differentiation through blocking IFN-γ (+) CD4(+) Th1 cells in experimental allergic neuritis (EAN) lymph node and spleen. Oral administration of curcumin to the Lewis rats at 100 or 200 mg/kg daily for 14 days ameliorated EAE which was probably due to inhibition of differentiation and development of Th17 cell dependence on down-regulating expression of IL-6, IL-21, RORγT signaling and inhibition of STAT3-phosphorylation (Xie *et al.*, 2009). Curcumin also

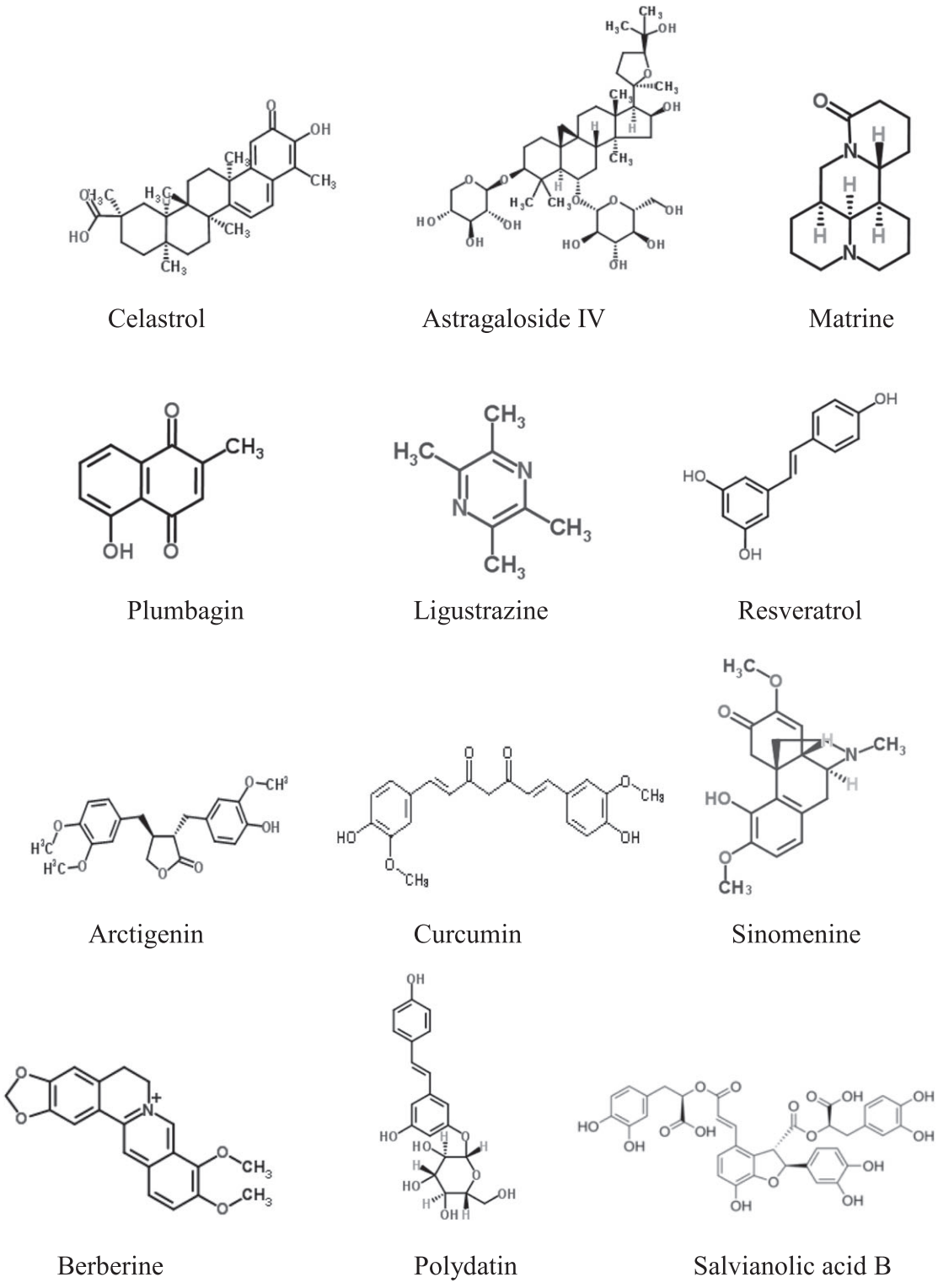

Figure 2. The effective phytochemical compounds on suppression of Th1, Th17 or both.

blocked the TNF-α, interleukin (IL)-1β, inflammatory cell accumulation and the expression of IFN-γ and IL-17 (Han *et al.*, 2014).

Astragaloside IV, a saponin small molecule found in *Astragalus membranaceus* (Fisch.) Bge., attenuates EAE of mice through antioxidant activity and challenging oxidative stress at multiple levels. Following the administration of Astragaloside IV (50 mM), the enhanced expressions of IL6, IFNgama and TNF-α were significantly down-regulated. Astragaloside IV did not suppress proliferation but attenuated IL17, IFN gamma and TNFa secretion (He *et al.*, 2013).

Ligustrazine (80 mg/kg/day in 200 μL of ligustrazine each day from days 18 to 20 consecutively) corrected the Treg/Th17 and Th1/Th2 imbalance in a mouse asthma model. Ligustrazine was able to modulate the expression of transcription factors for Th1 and Th2 in asthma via the re-balance of cytokine profiles and

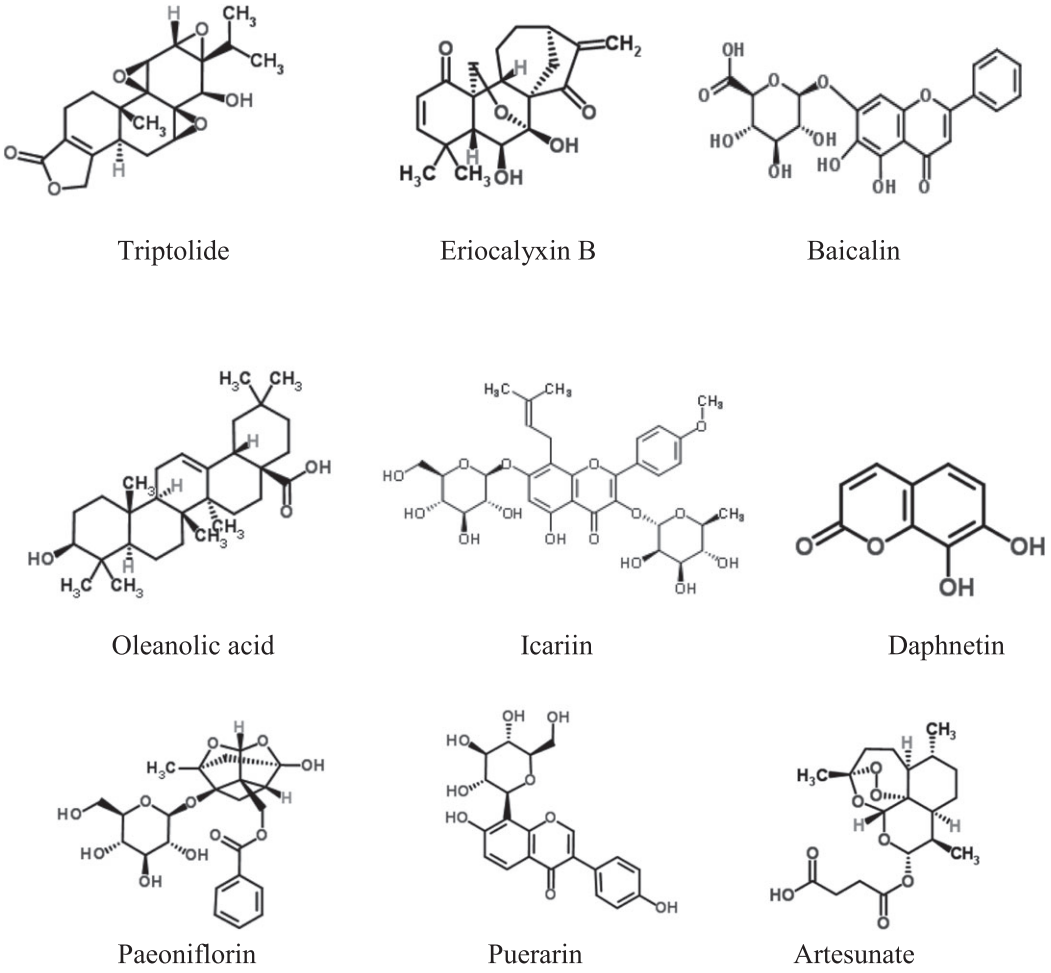

Figure 2. (continued)

of ratios of transcription factors, Th1/Th2 and Foxp3/RORγT (Ji *et al.*, 2014).

Plumbagin (PL) is a natural bicyclic naphthoquinone found in the plants from Droseraceae, Plumbaginaceae, Ancistrocladaceae and Dioncophyllaceae families. A 100 mM solution of PL, derived from roots of *Plumbago zeylanica*, ameliorates the EAE through down-regulation of JAK–STAT and NF-kappaB signaling pathways. Plumbagin attenuated some pro-inflammatory molecules including IL-6, IFN-γ and iNOS, accompanied by suppression of IkappaB degradation and NF-kappaB phosphorylation (Jia *et al.*, 2011).

Matrine, a quinolizidine alkaloid prepared from medicinal plant Radix sophorae Flave, was able to decrease clinical EAE. Matrine (150, 200 and 250 mg/kg) attenuated the expression and production of key chemokines (CCL3 and CCL5), which attract inflammatory cells into the CNS and significantly inhibit the TLR4/MD2 pathway, which plays an important role in the induction of Th1 and Th17 cells in EAE (Kan *et al.*, 2013).

It confirmed the antiinflammatory activity of resveratrol and its derivatives and suggests a potential clinical relevance in the treatment of inflammatory diseases. In this regard, the effects of polydatin (POLY), one of derivatives of resveratrol, were investigated on the *in vitro* production of IL-17 in a model of inflammation. The results showed that POLY treatment (at 0.01, 0.1, 1, 2.5, 5, 10 and 20 μg/mL) of activated peripheral blood mononuclear cells (PBMC) induced a marked inhibition of IL17 statistically stronger than the inhibition obtained with RES at the same concentration. Particularly, POLY treatment at 20 μg/mL induces an almost complete inhibition (98%) whereas RES treatment at 20 μg/mL shows no more than a 50% of inhibition (Lanzilli *et al.*, 2012).

Arctigenin, as an herb compound extract from *Arctium lappa*, inhibits Th17 cells, ameliorating EAE through AMPK and PPAR-γ/RORγ signaling. Arctigenin (5, 10 μM = 5, 10 mg/kg) significantly restrains the differentiation of Th17 cells in mice. Following *in vitro* and *in vivo* arctigenin treatment, the transcription factor T-bet, the Th1 cytokine IFN-γ and the Th17 cytokines IL-17A, IL-17F as well as the transcription factor RORγ were significantly attenuated (Li *et al.*, 2015).

Eriocalyxin B (EriB), a diterpenoid isolated from *Isodon eriocalyx*, ameliorated EAE by suppressing Th1 and Th17 cells. The mechanism of EriB-induced effects has been suggested to increase in reactive oxygen species, and blockage of Th1 and Th17 cell differentiation through Janus Kinase/Signal transducer and activator of transcription and nuclear factor-kappaB signaling pathways (Lu *et al.*, 2013).

Baicalin, a flavonoid compound derived from the root of the Chinese herb Huangqin (*S. baicalensis* Georgi), blocked the IL-17-mediated joint inflammation in arthritis. One hundred microliter Baicalin solution injected intraperitoneally to mice attenuated vascular

cell adhesion molecule 1, IL-6, TNF-α mRNA expression, IL17-mediated lymphocyte adhesion and IL-17-induced intercellular adhesion molecule 1 in cultured synoviocytes (Yang *et al.*, 2013). In addition, it had therapeutic effect (100 mg/kg/d) on EAE which was mediated by SOCS3 regulatory pathway. Baicalin attenuated the Th1 and Th17 cell differentiation through STAT/NFkappaB signaling pathways, and reduced expression of proinflammatory molecules and chemokines and infiltration of immune cells into the CNS. Baicalin increased Treg cell differentiation and regulatory activity, attenuated the T-cell proliferation and IFN-gamma and enhanced IL-4 production (Zhang *et al.*, 2015a). Furthermore, baicalin (2 mg in 100 μL of 5% $NaHCO_3$ aqueous solution) alleviated the silica-induced lung inflammation and fibrosis by inhibition of Th17 response in mice. Baicalin also decreased Th17 cells through stimulation of Treg cells and IL-6 and IL-23 (Liu *et al.*, 2015).

Oleanolic acid and erythrodiol (50 mg/kg/day, i.p. each), as natural triterpenes, modulated immune-inflammatory markers of EAE. The EAE-mice pretreated with triterpene exhibited higher expression of Th2 cytokines in both serum and spinal cord, lower levels of Th1 and Th17 cytokines and less leptin secretion. It also switched cytokine production toward a Th2/regulatory profile (Martin *et al.*, 2012).

Icariin, a natural flavonoid glucoside, reduced the disease progression and alleviated the pathological changes of colitis in a female C57BL/6 mice model. Icariin treatment (oral administration with 3, 10 mg/kg) inhibited the production of Th1 and Th17 through inhibition of phosphorylations of STAT1 and STAT3 in CD4(+) T cells (Tao *et al.*, 2013).

The beneficial effects of daphnetin, a monomeric compound derived from *Daphne odora* var. marginata (*D. marginata*), have been shown on collagen-induced arthritis. Daphnetin treatment (with purity over 99.4%) attenuated the levels of Th1, Th2 and Th17 type cytokines in spleen lymphocytes in collagen-induced arthritis rats. It also increased the expression of Foxp3, which can down-regulate the activity of Th17 cells (Tu *et al.*, 2012).

Paeoniflorin, the predominent component of *Radix paeoniae* rubra and *Radix paeoniae* alba, inhibited imiquimod (IMQ)-induced psoriasis in a mouse model. Paeoniflorin (2 and 20mug/mL) attenuated the mRNA expression of Th17 cytokines and phosphorylation of Stat3 in spleen cells under Th17 polarizing conditions. The finding may suggest that paeoniflorin probably reduces the IMQ-induced psoriasis by regulating Th17 cell response and cytokine secretion through phosphorylation of Stat3 (Zhao *et al.*, 2015).

Triptolide, a diterpenoid triepoxide, the major component isolated from the Chinese herb *Tripterygium wilfordii* Hook. f. modulates T-cell inflammatory response and EAE in mice. Triptolide (100 and 200 mg/kg) is able to significantly attenuate the mRNA expression of both Th1/Th (IL-17) as well as Th2 cytokines in spleen mononuclear cells and spinal cord tissues. Furthermore, the expression of Foxp3 was up-regulated in spleen mononuclear cells following triptolide treatment. Blockage of NF-kappaB-DNA binding activity also enhanced the expression of inhibitor of IkappaB-α and reduced the expression of pIkappaB-α in spleen mononuclear cells in 19-triptolide-treated EAE mice (Wang *et al.*, 2008). It also ameliorated IL-10-deficient mice colitis through down-regulation of IL-17 and attenuation of IL-6/STAT3 signaling pathway (Li *et al.*, 2010).

A new derivative of sinomenine, named 1032 which is an alkaloid isolated from the Sinomenium acutum, improved immune suppression in EAE. 1032 (15 mg/kg) decreased encephalitogenic T cell responses and ameliorated EAE. The results were attributed to selective inhibitory effect of 1032 on the production of IL-17. It also suppressed Th17, but not Treg and cell differentiation. These results were attributed to its inhibitory effect on IkappaB-α degradation as well as on TNF-α and IL-6 secretion in BMDCs. It was speculated that 1032 probably targets DC to block IL-6 production, terminating Th17 cell development (Yan *et al.*, 2010).

Puerarin, found in a number of plants and herbs including the root of Pueraria (*Radix puerariae*), was able to suppress the inflammatory responses in gunpowder smog-induced acute lung injury in rats. Hence, it might be a potential therapeutic agent for smoke inhalation injury. This compound (100 mg/kg) also enhanced Th1 immunity and decreased Th2 and Th17 responses and thereby ameliorated the smoke inhalation-induced Th1, Th2 and Th17 imbalance (Zhang *et al.*, 2015b).

Artesunate, one of the derivatives of artemisinin from *Artemisia annua* L., ameliorated DSS colitis and TNBS colitis in mice with no positive effect on oxazolone colitis. Artesunate (150 mg/kg/day) attenuated TNF-α expression and Th1/Th17 response in TNBS colitis model. Artesunate reduced the levels of IFN-γ, IL-17, and TNF-α in TNBS colitis or DSS colitis. In addition, the expression of NF-kappaBp65 and p-IkappaB-α decreased in artesunate-treated TNBS colitis compared with untreated TNBS colitis (Yang *et al.*, 2012).

Herbal drugs (herbal drug formula). Ma Huang Tang (Ephedra decoction, MHT) is a famous classical formula from Shang Han Lun by Zhang Zhongjing in the Han Dynasty and may effectively ameliorate the progression of asthma. It (5, 10 and 20 mg/kg) ameliorates asthma though modulation of Th1 and Th2 cytokines and inhibition of Th17 cells in ovalbumin-sensitized mice (Ma *et al.*, 2014).

Oral administration with Daikenchuto, a traditional Japanese herbal medicine (extract of the following three crude drugs: processed ginger (*Zingiber officinale* ROSCOE, rhizome), ginseng (*Panax ginseng* C.A. MEYER, radix) and zanthoxylum fruit (Zanthoxylum piperitum DE CADOLLE) in the ratio of 5:3:2) suppresses colitis induced by naive CD4+ T cell transfer into SCID mice. Indeed, analyses of cytokine mRNA revealed that Th17 cytokines were significantly decreased in colons of mice that received Daikenchuto (Iwasa *et al.*, 2012).

Bu Shen Yi Sui Capsule (BSYSC) is composed of ten plants including: *Rehmanniae radix praeparata*, *Radix Rehmanniae*, *Radix Polygoni Multiflori, Radix et Rhizoma Rhei*, *Leonurus japonicas Houtt.*, *Bulbus Fritillariae Thunbergii*, *Hirudo*, *Scorpio*, *Rhiazoma Gastrodiae* and *Fructus Forsythiae*. The proportions of these herbs were 10:10:10:2:10:6:3:2:3:6 and had a strong neuroprotective effect on EAE mice. BSYSC (3.02 g/kg) decreased the cytokines of IL-17A, IL-6, IL-23 and

TGF-β 1 in the brain and dropped the ratio of IL-17A and FoxP3 mRNA and protein in the brain or spinal cord at different stages. The protective mechanisms of BSYSC may be associated with mediating the regulation of Th17 and Treg cells (Zheng *et al.*, 2015).

BuShenYiQi formula, composed of *A. membranaceus* (Fisch.) Bunge., Epimedium brevicornu Maxim. and Rehmannia glutinosa Libosch. with a ratio of 6:4:3 (w:w:w), strengthens Th1 response and suppresses Th2–Th17 responses in mice with RSV-induced asthma exacerbation. BSYQF (2.5, 5 and 10 g/kg/day) could down-regulate Th2–Th17 cell proportions with lower expressions of GATA3, STAT6 and RORγT, and up-regulate Th1 cell proportion with higher expression of T-bet (Wang *et al.*, 2014). A study indicated that Bu-Shen-Yi-Qi formulae suppressed chronic airway inflammation and regulated Th17/Treg imbalance in the murine ovalbumin asthma model. BSYQF treatment (oral administration of 5, 10 and 20 g raw herbs/kg body weight) caused a distinct reduction in IL-6, IL-10 and IL-17A levels in serum, and induced a significant improvement of IL-6 and IL-10 as well as a marked decrease in TGF-β 1 and IL-17A levels in bronchoalveolar lavage fluid (BALF) of OVA-induced asthmatic mice. Actually, BSYQF decreased RORγ and increased Foxp3 expression in the lung tissue (Wei *et al.*, 2015).

Huang-Lian-Jie-Du-Tang (HLJDT) is a traditional formula (Rhizoma Coptidis, Radix Scutellariae, Cortex Phellodendri and Fructus Gardeniae were mixed in a ratio of 3:2:2:3) could limit excessive inflammatory responses in septic condition. HLJDT treatment (oral administration with 120 or 270 mg/kg) suppressed the production of proinflammatory cytokines, including TNF-α, IL-1, IL-6 and IL-17A. HLJDT could reverse the shift from Th1 to Th2 response and promote Th1/Th2 balance toward Th1 predominance in septic rats (Wei *et al.*, 2013).

Qingkailing, is a well-known composite formula of traditional Chinese medicine, mainly comprising of eight medicinal materials or extracts composed of adenosine, geniposide, chlorogenic acid, baicalin, ursodeoxycholic acid, cholic acid and hyodeoxycholic acid, alleviates experimental autoimmune uveitis in rats via inhibiting Th1 and Th17 effector cells. It (at a dose of 40 mg/kg) inhibits the differentiation toward Th1 and Th17 effector cells and the secretion of relevant cytokines. The therapeutic effect of Qingkailing injection may also be regulated through increased secretion of IL-10 (Tian *et al.*, 2012).

DCB-SLE1, an extract of a mixture of four traditional Chinese medicinal herbs (*Atractylodis macrocephalae* Rhizoma, *Eucommiae cortex*, *Lonicerae caulis* and *Hedyotidis diffusae* Herba) with equal amounts can inhibit renal inflammation in animal model. DCB-SLE1 (12.5 g/kg body weight) significantly ameliorated the hematuria, proteinuria, renal dysfunction and severe renal lesions by (i) suppression of B cell activation and decreased autoantibody production; (ii) negative regulation of T cell activation/proliferation and natural killer cell activity; (iii) suppression of IL-18, IL-6 and IL-17 production and blocking of NF-kappaB activation in the kidney; and (iv) prevention of lymphoid and renal apoptosis. Actually, DCB-SLE1 inhibited renal inflammation by suppression of Th1 and Th17 cytokine production and NF-kB activation (Tsai *et al.*, 2011).

Shenghua decoction (SHD) is a mixture of Chinese herbs (600-g *Leonurus japonicus* Houtt., 600-g *Codonopsis pilosula* (Franch.) Nannf., 600-g Astragalusmembranaceus (Fisch.) Bge., 240-g *Prunus persica* (L.) Batsch, 240-g Angelica sinensis, 180-g Ligusticum chuanxiong Hort. and 120-g Glycyrrhiza uralensis Fisch.) prescription reduces uterine bleeding and regulates T-cell paradigm in human deciduas of RU486 medical abortion. The ratios of Th1 to Th2 and Th17 toTreg cells elevated markedly after SHD treatment. The mRNA expression of Th1- and Th17-type cytokines (IFNγ and IL-17A) was up-regulated, while that of Th2-type and Treg-produced cytokines (IL-4 and TGF-β) was down-regulated significantly after SHD administration with 2.58 g/mL of this decoction (Li *et al.*, 2013).

Possible Mechanisms. Th1 and Th17 cells are pro-inflammatory subsets which are responsible for inducing inflammatory processes. Therefore, inhibition of Th1 and Th17 cells can be a choice to prevent and treat these diseases. Evidence from human diseases suggests that differentiation factors responsible for the generation and functions of Th1 and Th17 cells have revealed an interesting reciprocal relationship with regulatory T cells which prevent tissue inflammation and mediate self-tolerance. Generation and function of Th1 and Th17 cells are regulated via a complex network of cytokines and transcription factors (Fig. 3).

The JAK/STAT pathway is one of the main signaling pathways which are responsible for regulation of Th1 and Th17 cell differentiation and their functions (Rafieian-Kopaei *et al.*, 2013). In this regard, STAT1 and STAT4 are specifically important members of the JAK/STAT family involved in Th1 differentiation. They are activated through JAK2 and Tyk2 following IL-12 stimulation (Rafieian-Kopaei *et al.*, 2012). However, STAT3, a key signaling molecule which is essential for Th17 lineage commitment, is activated by IL-6 and IL-23 (Shirzad *et al.*, 2015; Amirmohammadi *et al.*, 2014). STAT3 is needed for IL-6 induction and IL-21 mediated Th17 differentiation. These STAT-signaling molecules are mediated through T-bet for STAT1 and STAT4 and RORγT for STAT3 (Bahmani *et al.*, 2014d; Karamati *et al.*, 2014). Overexpression of RORα can cause Th17 differentiation as well as IL-17 expression up-regulation. RORα deficiency has been shown to result in reduction of IL-17 expression. Moreover, RORα and RORγT co-expression synergistically cause further Th17 differentiation, particularly under non-favorable conditions (Amini *et al.*, 2012). The interaction between Th17 and Treg cells is also regulated through the secretion of a group of cytokines including IL-17 and TGF-β1, and specific transcription factors, such as RORγT and FoxP3 (Bahmani *et al.*, 2014d; Zheng *et al.*, 2015; Bahmani *et al.*, 2014f). IFN-γ and IL-17 reduction is suppressed through STAT1/STAT4/T-bet pathway which is critical for Th1 differentiation, or through STAT3/RORγ pathway which is essential for Th17 differentiation (Jia *et al.*, 2011). Furthermore, it is well known that APCs are essential for full activation of T cells by Ag presentation through the tricomplex of MHC, Ag and TCR. They are also critical for expression and function

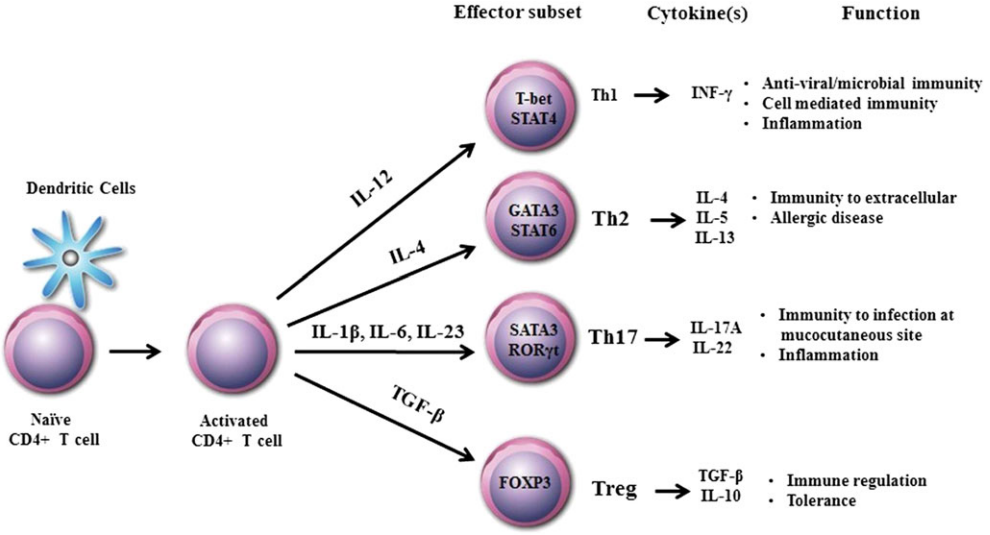

Figure 3. Complex network of cytokines and transcription factors for generation and function of Th1 and Th17 cells. [Colour figure can be viewed at wileyonlinelibrary.com]

of costimulatory molecules, such as CD80, CD86 and PD-L1 (Saki *et al.*, 2014b). It should be noted that Mnk1/2 has not an essential role in T cell development and activation; however, it may regulate non-T cell lineages to control Th1 and Th17 differentiation (Gorentla *et al.*, 2013).

The medicinal plants and their derivatives are able to inhibit the production of inflammatory cytokines through affecting some of the receptors on cell surface such as TLR4/MD2, the involved proteins in MAPK and NF-kB pathways (Calixto *et al.*, 2003) and the transcription factors including STAT3, STAT1, STAT4, T-bet and RORγT. They are able to become involved through inhibition of the TLR4/MD2 receptors; reduction in the expression of inflammatory mediators such as pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β, IL-2, IL-6, IL-12, IL-17, IL-17A, IL-17F, IL-21, IL22, IL23) (Wangchuk *et al.*, 2015; Wangchuk *et al.*, 2013; Wu *et al.*, 2011), lipid mediators (such as LTB4), macrophage products (such as NO) and PGE2 by down-regulation of MAPK and NF-kB pathways; up-regulation of Th2-related cytokines (IL-4, IL-5, IL-10, IL-13); secretion of IL-4; suppression of transcription factors such as STAT1, STAT3, STAT4, T-bet, RORγT; reduction in the of MMP-1 and MMP-3; reduction in the expression of chemokines (MCP-1, MIP-1α, RANTES, CCL3, CCL5); increase in the antiinflammatory cytokine IL-10 (Wu *et al.*, 2011); promoting Treg cell differentiation and regulatory activity; increase in Treg cell population by blocking the activation of pSTAT3; increase in the expression of Foxp3; correction of Th1/Th2 and Treg/Th17 imbalance; reversing the shift from Th1 to Th2 response and promotion of Th1/Th2 balance, and blockage of Th1/17 responses and therefore helping to inhibit of inflammatory diseases.

CONCLUSION

Increased secretion of pro-inflammatory cytokines induced by Th1 and Th17 responses and the imbalance of Th1/Th2 and Treg/Th17 responses can influence the onset and severity of inflammatory and autoimmune diseases. Resetting of these responses offers an attractive approach to control autoimmunity. Medicinal plants and their derivatives suppress Th17 and Th1 T cell differentiation as well as their cytokine secretion and functions. Meanwhile, Th1 blocks responses more frequently than Th17. Taken together, in addition to reduction in inflammation severity, inflammation and subsequent autoimmune diseases can be prevented by herbal drugs that block T helper cell responses, especially those of Th17 cells.

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Conflict of Interests

We wish to confirm that there are no known conflicts of interest associated with this publication.

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