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The Immunoregulatory Effects of Traditional Chinese Medicine on Treatment of Asthma or Asthmatic Inflammation

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Abstract: Asthma is a chronic respiratory symptoms with variable airflow limitation and airway hyperresponsiveness (AHR), and causes high economic burden. Traditional Chinese medicine (TCM) has a long-lasting history of using herbal medicine in the treatment of various respiratory diseases including asthma. In the last several decades, an increasing number of herbs have been shown to be effective in the treatment of asthma in clinical trials or asthmatic inflammation in animal models. Literature about the effects of TCM on the immune system were searched in electronic databases such as PubMed, Google Scholar and Scopus from 2000 to 2014. ‘TCM’ and ‘asthma’ were used as keywords for the searches. Over 400 literatures were searched and the literatures about the immune system were selected and reviewed. We only reviewed literatures published in English. Accumulating evidence suggests that TCM can directly inhibit the activation and migration of inflammatory cells, regulate the balance of Th1/Th2 responses, and suppress allergic hyperreactivity through inducing regulatory T cells or attenuating the function of dendritic cells (DCs). These studies provided useful information to facilitate the use of TCM to treat asthma. This review was conducted to classify the findings based on their possible mechanisms of action reported.

Keywords: Traditional Chinese Medicine; Asthma; Th1; Th2; Regulatory T Cells; Dendritic Cells; Review.

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Introduction

Asthma is a chronic inflammatory disease with high incidence, which affects about 300 million people worldwide (Masoli *et al.*, 2004). Annual worldwide deaths from asthma have been estimated at 250,000 (Bateman *et al.*, 2008). The prevalence has increased, especially in children, in the past few decades (Akinbami *et al.*, 2009). The chronic inflammation of asthma is associated with airway hyperresponsiveness (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning (Bateman *et al.*, 2008). Many categories of drugs were developed to treat asthma, such as Bronchodilators (β-adrenergic agonists, anticholinergics and methylxanthines) and anti-inflammatory agents (corticosteroids, antileukotrienes and mast cell stabilizers) (reviewed in Mali and Dhake (2011)). Conventional treatment for asthma works quickly and directly relaxing constricted muscles around the airways for easy breathing and can stop an asthma attack from occurring. Although the drugs are generally effective, current synthetic drugs used in the pharmacotherapy of asthma are unable to act at all the stages and targets of asthma. Relapse after therapy withdrawal is common (Sevinc *et al.*, 2003). There are also concerns regarding both the systemic and local side effects from chronic use of current drugs including osteoporosis, hypothalamic–pituitary–adrenal axis suppression, immune suppression resulting in increased susceptibility to infections, development of cataracts in elderly patients, mood changes and pharyngitis (Li, 2011).

Although corticosteroids, as the most effective anti-inflammatory medication, improve the clinical symptoms of asthma (Busse and Lemanske, 2001; Barnes, 2008), many patients with asthma remain poorly controlled (Cazzoletti *et al.*, 2007; Bergqvist *et al.*, 2015). It has been reported that the poor clinical control is associated with alveolar T helper type 2 (Th2) immunity in atopic asthma (Bergqvist *et al.*, 2015). Due to the lack of preventive and curative therapy for asthma management, new therapeutic strategies are needed, such as complementary and alternative medicine (CAM) treatment (Jin *et al.*, 2014; Liang *et al.*, 2014). In the United States, approximately 26% of children are currently using CAM to treat asthma, especially children with poorly controlled asthma and cost barriers to conventional healthcare (Shen and Oraka, 2012), up to 80% of adolescents (Cotton *et al.*, 2011) and around 40% of adults (Knoeller *et al.*, 2012) with current asthma have used CAM for symptom management. In the United Kingdom, 60% of moderate asthma and 70% of severe asthma sufferers use CAM (Singh *et al.*, 2007). Herbal remedies are the most popular modalities among CAM (Arguder *et al.*, 2009; Sibbritt *et al.*, 2013). The use of herbal medicine has increased dramatically in the last several decades in all over the world (Shergis *et al.*, 2013; Li *et al.*, 2014a; Yang *et al.*, 2014). More than 400 medicinal plant species have been used ethanopharmacologically and traditionally to treat the symptoms of asthmatic and allergic disorders worldwide (Mali and Dhake, 2011). Some herbal alternatives are proven to provide symptomatic relief and assist in the inhibition of disease progression for asthma.

Traditional Chinese medicine (TCM) has a long history of human use (Li *et al.*, 2014b; Shan *et al.*, 2014; Wang *et al.*, 2014). Anti-asthma simplified herbal medicine intervention (ASHMI) is the first herbal medicine to receive US Food and Drug Administration (FDA) investigational new drug approval for clinical trials for treating asthma (Zhang *et al.*, 2010) and a phase I study confirmed that ASHMI is safe and well-tolerated clinically (Kelly-Pieper *et al.*, 2009). Recently, several clinical studies showed that TCM is safe and effective for the treatment of asthma (Li and Brown, 2009; Li, 2011). TCM could ameliorate asthma directly through spasmolytic effects to inhibit the AHR and block acetylcholine-induced tracheal ring constriction (Chan *et al.*, 2006; Shi *et al.*, 2009; Huang *et al.*, 2013; Srivastava *et al.*, 2013), or inhibition of the inflammatory cell infiltration (eosinophils, neutrophils, lymphocytes, and macrophages) into lung tissue or in bronchoalveolar lavage fluids (BALF) (Kao *et al.*, 2004; Chang *et al.*, 2006b, 2011; Fu *et al.*, 2012). Moreover, TCM inhibited the production of IgE and the expression of inflammatory cytokines including TNF-α, IL-1β, IL-6, and macrophage-inflammatory peptide (MIP)-2 by attenuating the activation of nuclear factor-κB (NF-κB) (Li *et al.*, 2009; Wei *et al.*, 2012, 2013; Zhong

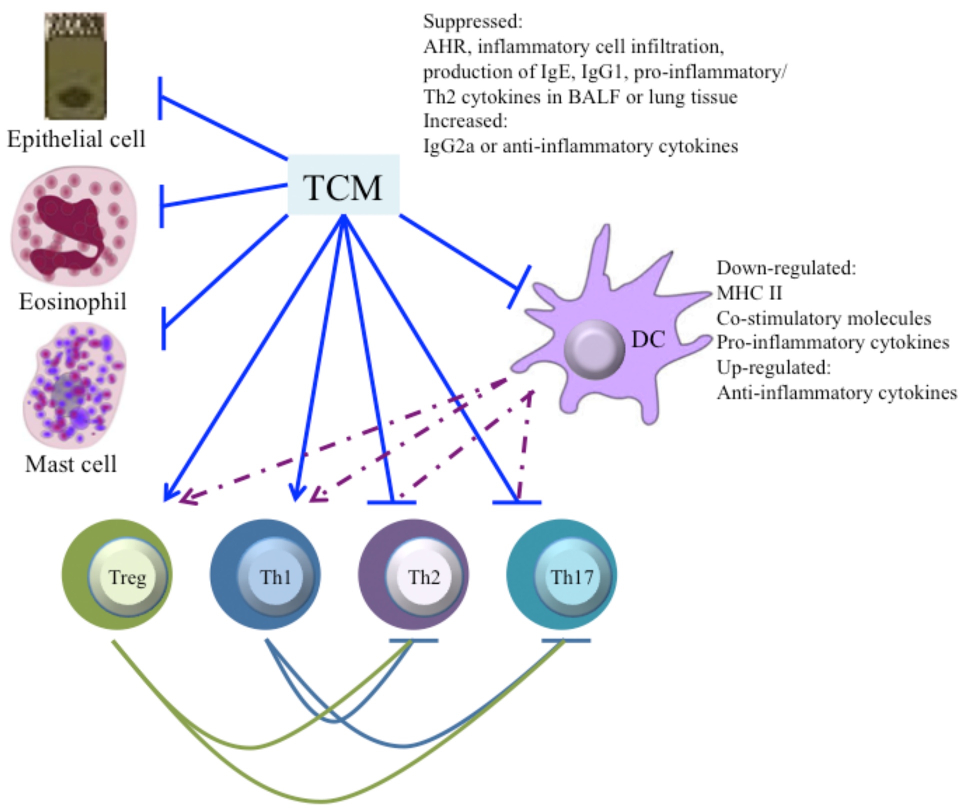

Figure 1. TCM treatments of asthma through the regulation of immune system. TCM suppresses AHR, inflammatory cell infiltration, producion of IgE, IgG1, pro-inflammatory/Th2 cytokines (IL-4, IL-6, IL-13, IL-1β, TNF-α and so on) in BALF and lung tissues. But TCM increases the production of IgG2a, IFN-γ, and IL-10. TCM suppresses Th2 and Th17 responses and increases Th1 responses that also suppresses Th2 and Th17 responses. Tregs induced by TCM may also suppress Th2 or Th17 responses. TCM suppresses the maturation and pro-inflammatory cytokine production of DCs, which may decrease Th2 and Th17 responses. The attenuated DC producing IL-10 may also induce Tregs. All these factors contribute TCM on the treatment of asthma.

et al., 2013; Shi *et al.*, 2014). Accumulating evidence has shown that TCM exerts the effect on the treatment of asthma by regulating the immune system (Fig. 1). This review is focused on the role of TCM in the regulation of the immune system for the treatment of asthma or asthmatic inflammation. Because herbal medicines used in Japan (Kampo) and Korea were developed based on TCM, these medicines also included in this review.

Inhibition of Th2 Responses

In the past several decades, the Th1–Th2 paradigm has dominated the field of asthma research. The Th1–Th2 balance is necessary to maintain healthy immune homeostasis (Feng *et al.*, 2014; Nisar *et al.*, 2014). Under allergic asthma, Th1–Th2 balance was lost and immune responses were shifted toward a Th2 profile, which decreased the production of Th1-type cytokines (interferon (IFN)-γ and interleukin (IL)-12) and increased the production of Th2-type cytokines (IL-4, IL-5, and IL-13). The Th2-type cytokines promote IgE production, eosinophil activation and recruitment, and airway remodeling (Busse and Rosenwasser, 2003; Bochner and Busse, 2004; Lambrecht and Hammad, 2013). In contrast, Th1-type cytokines inhibit IgE secretion and eosinophil infiltration (Iwamoto *et al.*, 1993, 1996). It has been reported that patients with severe asthma had significantly reduced IFN-γ production in response to house dust mite allergen compared to control subjects and subjects with resolved asthma (Busse and Rosenwasser, 2003). Therapies targeted at IgE, IL-4, IL-4 receptor, IL-5, and IL-13 have been enrolled into the clinical trials, but the outcomes of many trials are disappointing (reviewed in Bice *et al.* (2014)).

Accumulating evidence has shown that TCM ameliorates asthma through the inhibition of Th2 responses (Table 1). The water or ethanol extracts from one medicinal herb or formula reduced the levels of IL-4, IL-5, IL-13, TNF-α, and IgE, as well as AHR in an asthma animal model (Li *et al.*, 2000; Do *et al.*, 2006; Lee *et al.*, 2008c; Hsieh *et al.*, 2010; Kim *et al.*, 2011; Lee *et al.*, 2011; Chu *et al.*, 2012; Lee *et al.*, 2012; Shin *et al.*, 2012; Jayaprakasam *et al.*, 2013; Lee *et al.*, 2013). Several studies have shown that the extracts inhibit the activity of NF-κB, which might mediate the decrease of Th2 cytokines (Chu *et al.*, 2012; Lee *et al.*, 2012, 2013). Interestingly, Jayaprakasam *et al.* (2013) compared the effects of the individual Lingzhi (*Ganoderma Lucidum*), Kushen (*Sophora flavescens*), and Gancao (*Glycyrrhiza uralensis*) extracts and ASHMI (the combination of individual extracts) on the inhibition of Th2 cytokine production by murine Th2 memory cells and eotaxin secretion by human lung fibroblasts. They found that constituents in ASHMI synergistically inhibited eotaxin-1 production as well as Th2 cytokine production (IL-4 and IL-5). However, these studies did not detect or mention the Th1 responses. The inhibition of Th2 responses may be achieved differently, including the direct effect of TCM on the inhibition of Th2 responses, or through the enhancement of Th1 responses to inhibit Th2 responses, or both.

Enhancement of Th1 Responses

It has been shown that the enhancement of Th1 responses and suppression of Th2 responses are beneficial for asthma management, suggesting that the best way to treat

Table 1. Inhibition of Th2 Responses

Name of Plant or Formula	Extract/Component	Doses	Type of Model	Results	References
Artemisia iwayomogi	Water extract	0.5, 5, and 50 mg/kg body weight	OVA-induced murine asthma model	Reduce IL-4, IL-5, and TNF-α levels in the lung and IgE in serum	Lee *et al.* (2008c)
Anoectochilus formosanus	Water extract	0.5 and 1.0 g/kg body weight	OVA-inhaled airway allergic murine model	Reduce IL-4, TNF-α, and IgE levels in BALF, and AHR	Hsieh *et al.* (2010)
Samchulkunbi-tang (shen-zhu-jian-pi-tang in Chinese)	Water extract	200 mg/kg or 400 mg/kg body weight	OVA-induced murine asthma model	Reduce the number of inflammatory cells, IL-4, IL-13, IL-33, TNF-α, and eotaxin levels in BALF	Lee *et al.* (2012)
Crataegus pinnatifida	Ethanol extract	100 mg/kg or 200 mg/kg body weight	OVA-induced murine asthma model	Reduce the number of inflammatory cells, IL-4, IL-5, IL-13, eotaxin and IgE levels in BALF, and AHR	Shin *et al.* (2012)
Semen armeniacae amarum	Water extract	0.1 mL of 10 or 100 mg/ml	OVA-induced murine asthma model	Reduce the number of inflammatory cells, IL-4 level in BALF, and AHR	Do *et al.* (2006)
MSSM-002	Water extract	1 ml/mouse	Conalbumin-induced murine asthma model	Reduce the number of inflammatory cells in BALF, IgE in blood, IL-4, IL-5, IL-13 levels in splenocytes, and AHR	Li *et al.* (2000)
Ganoderma Lucidum, Sophora flavescens, Glycyrrhiza uralensis	Water extract	4, 20, 100, and 500 μg/ml	D10.G4.1 and HLF-1 cells *in vitro*	Inhibit production of IL-4 and IL-5 by murine memory Th2 cells, and eotaxin-1 production by HLF-1 cells	Jayaprakasam *et al.* (2013)

Table 1. (*Continued*)

Name of Plant or Formula	Extract/Component	Doses	Type of Model	Results	References
Morus alba L.	Water extract	50 mg/kg or 200 mg/kg body weight	OVA-induced murine asthma model	Reduce the number of eosinophil in BALF, IgE in serum, IL-4, IL-5, IL-13 production in mediastinal lymph node cells, and AHR	Kim *et al.* (2011)
Rheum palmatum L.	Emodin	0.1% (v/v)	OVA-induced murine asthma model	Reduce the number of eosinophil, IL-4, IL-5, IL-13 levels in BALF, and IgE in serum	Chu *et al.* (2012)
Pinellia ternate	Water extract	23.3 mg/kg or 46.6 mg/kg body weight	OVA-induced murine asthma model	Reduce the number of inflammatory cells, and IL-4, IL-13, and TNF-α levels in BALF	Lee *et al.* (2013)
Mentha haplocalyx	Ethanol extract	100 mg/kg body weight	OVA-induced murine asthma model	Reduce the number of inflammatory cells, and IL-4, IL-5, and IgE levels in BALF	Lee *et al.* (2011)

asthma is not only through the suppression of Th2 responses but also through the enhancement of Th1 responses (Kline *et al.*, 1999). A large body of evidence has shown that TCM for asthma treatment enhanced Th1 responses and/or inhibited Th2 responses (Table 2).

Dr. Xiu-Min Li's group showed that ASHMI and the Chinese herbal formula MSSM-002 containing 13 herbs, the precursor of ASHMI, enhanced Th1 responses including the increase of IFN-γ, IL-12, and IgG2a, but suppressed Th2 responses including the decrease of IL-4, IL-5, and IL-13 (Li *et al.*, 2000; Srivastava *et al.*, 2004, 2014). ASHMI and MSSM-002 also showed reduced AHR, mucous production, neutrophilic and eosinophilic inflammation, eotaxin, IgE, and TNF-α levels (Li *et al.*, 2000; Srivastava *et al.*, 2004, 2014). Interestingly, ASHMI induced long-lasting post-therapy (8 weeks) tolerance to OVA-induced inflammation and AHR. Decreased allergen-specific IgE and Th2 cytokine levels (IL-4, IL-5, and IL-13), and increased IFN-γ levels also persisted at least 8 weeks post-therapy. ASHMI effects were eliminated by the neutralization of IFN-γ during therapy (Srivastava *et al.*, 2010). They further showed that the similar effects were observed in OVA-induced aged mice (Busse *et al.*, 2010). The critical studies suggested that the antigen-specific memory responses might be induced by TCM treatment, which might play an important role in a long lasting regulation of Th1/Th2 responses against asthma.

SST (Sho-seiryu-to, Xiao-Qing-Long-Tang in Chinese) decreased IL-4, IL-5, IL-13, IgG1, and IgE levels but increased IFN-γ, IL-2, and IL-12 levels (Ko *et al.*, 2004b; Nagai *et al.*, 2004; Wang *et al.*, 2012). Another study further showed that the anti-allergic effects of SST were enhanced by the co-administration of lysed *Enterococcus faecalis* FK-23 (Shimada *et al.*, 2010). *Astragalus membranaceus* water extract decreased AHR, inflammatory infiltration, and mucus secretion in the lung tissues, reduced IL-4, IL-5, and IL-13 levels and increased IFN-γ levels in OVA-induced animal models (Shen *et al.*, 2008; Jin *et al.*, 2013). Astragaloside IV treatment, the active constituent of *A. membranaceus*, relieved AHR, decreased the inflammatory cells but increased the IFN-γ level in BALF (Yuan *et al.*, 2011). Coumarins from *Peucedanum praeruptorum* Dunn reduced AHR, airway eosinophilic inflammation, levels of IL-4, IL-5, and IL-13 in BALF and OVA-specific IgE in serum, and up-regulated the level of IFN-γ in BALF (Xiong *et al.*, 2012c). They further found that praeruptorin A, one kind of coumarin, had similar effect on the treatment of asthma, inhibited the IκBα degradation, NF-κB nuclear translocation, and the expression of TGF-β1 and pSmad2/3, up-regulated the expression of Smad7 in lung tissue (Xiong *et al.*, 2012a,b). Glycyrrhizic acid, the main bioactive ingredient of *Glycyrrhiza glabra*, reduced eosinophilia in lung tissue and airway tissue, decreased the levels of IL-4, IL-5, and IL-13 in the BALF but increased IFN-γ levels in OVA-induced mouse model (Ma *et al.*, 2013b). These studies suggest that one main bioactive ingredient may achieve the similar effect on the treatment of asthma compared with the total extract of medical herb. TCM may have the synergistic effect with other factors (e.g., FK-23). Therefore, it is helpful to identify the main bioactive ingredient of TCM and search for the synergistic factor, which may vary among different herbs or formulas.

Table 2. Enhancement of Th1 Responses

Name of Plant or Formula	Extract/ Component	Doses	Type of Model	Results	References
ASHMI	Water extract	4.5 mg twice daily or 10 mg/d per mouse	Ragweed- or OVA-induced murine asthma model	Increase IgG2a and IFN-γ levels; decrease IL-4, IL-5, IL-13 and IgE levels, eosinophilic inflammation, and AHR	Srivastava *et al.* (2014); Busse *et al.* (2010)
MSSM-002	Water extract	1, 5, 50 or 500 μg/ml *in vitro*; 1 ml/d per mouse	D10.G4.1 cells *in vitro*; Conalbumin-induced murine asthma model	Increase IFN-γ level; decrease IL-4, IL-5, and IgE levels, eosinophilic inflammation, and AHR	Srivastava *et al.* (2004); Li *et al.* (2000)
Xiao-Qing-Long-Tang (Sho-seiryu-to in Korean)	Water/ ethanol extract	10, 20, 40, 80, 100 μg/ml; 0.5 g/kg; 1 g/kg body weight	CD4 T cells *in vitro*; OVA-induced murine asthma model; *Dermatogoides pteronyssinus*-challenged chronic asthmatic mice model	Increase IFN-γ, IL-2 and IL-12 levels; decrease IL-4, IL-5, IL-13, TNF-α, IgE, and IgG1 levels	Ko *et al.* (2004); Nagai *et al.* (2004); Wang *et al.* (2012)
Astragalus membranaceus	Water extract/ Astragaloside IV	2.5, 5 or 10 g/kg; 50 or 150 mg/kg body weight	OVA-induced murine asthma model	Increase IFN-γ level; decrease IL-4, IL-5, IL-13 levels, inflammatory infiltration, and AHR	Shen *et al.* (2008); Jin *et al.* (2013); Yuan *et al.* (2011)
Peucedanum praeruptorum Dunn	Light petroleum extract/d praeruptorin A	50, 100 and 200 mg/kg body weight	OVA-induced murine asthma model	Increase IFN-γ level; decrease IL-4, IL-5, IL-13, and IgE levels, eosinophilic inflammation, and AHR	Xiong *et al.* (2012c)
Glycyrrhiza glabra	Glycyrrhizic acid	10, 20, and 40 mg/kg body weight	OVA-induced murine asthma model	Increase IFN-γ level; decrease IL-4, IL-5, IL-13 levels, and eosinophil inflammation	Ma *et al.* (2013a)

Table 2. (*Continued*)

Name of Plant or Formula	Extract/ Component	Doses	Type of Model	Results	References
Chung-Yeul-Gue-Soup-Sa-Gan-Tang	Ethanol extract	0, 1, 2, 5, and 20 μl/ml	CD4 T cells *in vitro*	Increase IFN-γ level; decrease IL-4 level	Ko *et al.* (2004)
Danggui Buxue Tang	Water extract	0.3, 1, and 3 g/kg body weight	OVA-induced murine asthma model	Increase IgG2a and IFN-γ levels; decrease IL-4, IL-5, IL-13, IgG1 and IgE levels, eosinophil inflammation, and AHR	Lin *et al.* (2011)
Yu-Ping-Feng-San (*Gyokuheifusan* in Japanese)	Water extract	25 ml/kg body weight	OVA-induced murine asthma model	Increase IFN-γ level; decrease IL-4 level	Fang *et al.* (2005)
Bu-Shen-Yi-Qi-Tang	Water extract	12 g/kg body weight	OVA-induced murine asthma model	Increase IFN-γ level; decrease IL-4, IL-5, IL-1β and TNF-α levels	Luo *et al.* (2014)
Sceptridium ternatum Lyon	Ethanol extract	1.935, 9.675 and 19.35 g/kg body weight	OVA-induced murine asthma model	Elevate the ratio of Th1/Th2	Yuan *et al.* (2013)
Sheng-Fei-Yu-Chuan-Tang	Water extract	1 g/kg body weight	*Dermatogoides pteronyssinus*-challenged chronic asthmatic mice model	Increase IFN-γ and IL-12 levels; decrease IL-4, IL-5, IL-13, IgG1 and IgE levels, inflammatory infiltration, and AHR	Lin *et al.* (2013a)
Bu-zhong-yi-qi-tang (*Hochu-ekki-to* in Japanese)	Water extract	1 g/kg body weight	OVA-induced murine asthma model	Increase IgG2a and IFN-γ levels; decrease IL-4, IL-5, IgG1 and IgE levels, and eosinophilia infiltration	Ishimitsu *et al.* (2001)

More evidences are coming to show that TCM regulates the balance of Th1/Th2 by the enhancement of Th1 responses and the inhibition of Th2 responses in asthma environment (Ko *et al.*, 2004a; Fang *et al.*, 2005; Lin *et al.*, 2011, 2013a; Yuan *et al.*, 2013; Luo *et al.*, 2014). The oral administration of Bu-zhong-yi-qi-tang (*Hochu-ekki-to* in Japanese) reduced eosinophilia, IL-4, and IL-5 production in the airway, whereas it increased IFN-γ. The levels of OVA-specific IgE and IgG1 were significantly decreased in serum, whereas the level of OVA-specific IgG2a was increased. IL-4 production by spleen T cells in response to OVA was significantly suppressed, while IFN-γ production was increased (Ishimitsu *et al.*, 2001). Another study showed that Liu-Wei-Di-Huang Wan, a traditional Chinese herbal formula for the treatment of asthma, inhibited the expression of all cytokines (Th2-type: IL-4, IL-5, IL-10 or IL-13 and Th1-type: IL-2 and IFN-γ) in Peripheral blood mononuclear cells (PBMC) stimulated with phorbol 12-myristate 13-acetate (PMA) and ionomycin (Shen *et al.*, 2003). It is critical to comprehensively and carefully evaluate the role of TCM in the regulation of immune responses to help understand the mechanism of TCM.

Dendritic Cells (DCs)

DCs play a crucial role in controlling the various aspects of the adaptive immune responses in the lung to protect the lung from overt damage or generate allergic airway inflammation (Lambrecht and Hammad, 2012). It has been shown that mainly CD11b$^+$ conventional DCs (cDCs) but not CD103$^+$ cDCs induced Th2 cell immunity in house dust mite-specific T cells *in vitro* and asthma *in vivo* (Plantinga *et al.*, 2013). FcεRI$^+$ DCs (CD11c$^+$MHC II$^+$) were necessary and sufficient for the induction of Th2 immunity and features of asthma (Hammad *et al.*, 2010). However, plasmacytoid DCs induced anti-inflammatory effects and prevented asthma development (de Heer *et al.*, 2004; Kool *et al.*, 2009). Our studies showed that the transfer of regulatory DCs (CD11c$^+$MHC II$^+$CD40^{low}IL-10$^+$) could ameliorate inflammatory bronchitis in OVA-induced mouse model through inducing antigen-specific regulatory T cells (Tregs) (Li *et al.*, 2012, 2013a). Our preliminary data showed that *Glycyrrhiza uralensis* ethanol extract (GUEE) did not change the expression of co-stimulatory molecules and MHC II on bone marrow (BM) derived-DCs but decreased the production of pro-inflammatory cytokines (IL-12, IL-6, and TNF-α), suggesting that GUEE has an anti-inflammatory effect (not published). Shikonin, the major components of root extracts of *Lithospermum erythrorhizon*, inhibited the expression of MHC II, CD80, CD86, CCR7, and OX40L on BM-DCs induced by OVA (Lee *et al.*, 2010). AIP1, carbohydrate fraction 1 from the water extracts of *Artemisia iwayomogi*, either decreased the surface levels of CD11c and MHC II in lung DCs or reduced the percentage of CD11c$^+$MHC II$^+$ DCs and the allogeneic T cell stimulating ability of the cells (Lee *et al.*, 2008b,c). Expressions of several proteins including TNF receptor-associated factor (TRAF) 5-like protein, pyruvate kinase M2 (PKM2), and coactosin-like protein 1 (CLP1) were down-regulated upon AIP1 treatment in BM-DCs (Lee *et al.*, 2008a). Due to the important role of DCs in the immune system, the effect of TCM on DCs in the asthmatic environment should be extensively explored.

Tregs

Tregs play a central role in the maintenance of immunological self-tolerance and immune homeostasis (Sakaguchi, 2004; Sakaguchi *et al.*, 2006). The numbers of pulmonary $Foxp3^+$ Tregs were reduced in asthmatic children and the transfer of Tregs suppressed asthma in animal models (Hartl *et al.*, 2007; Kearley *et al.*, 2008). The aqueous extract of *Anoectochilus formosanus* increased the population of $CD4^+CD25^+$ Tregs (Hsieh *et al.*, 2010). Recently, two studies reported that water extracts of *Astragalus membranaceus* and *Morus alba* increased $CD4^+CD25^+Foxp3^+$ Tregs population and enhanced $Foxp3^+$ mRNA expression in asthma animal models (Kim *et al.*, 2011; Jin *et al.*, 2013). Further, several ingredients from different herbs, including coumarins, glycyrrhizic acid and curcumin, increased the expression of Foxp3 and the percentage of $CD4^+CD25^+Foxp3^+$ Tregs in asthma animal models (Xiong *et al.*, 2012c; Ma *et al.*, 2013a,b). These studies suggest that Tregs may play a role in the immuno-suppression of allergic hyperreactivity treated by TCM, at least a part of TCM. However, the function of Tregs needs to be deeply investigated.

Th17 Cells

With the progress of asthma and immunology, the view that asthma is an exclusively Th2-dominated disease has been challenged by the discovery that other cytokines, such as IL-9, IL-17, and IL-22, are frequently found co-expressed with Th2 cytokines in the airways of mouse models of asthma or in humans with asthma (Lambrecht and Hammad, 2013; Choi *et al.*, 2014). It has been suggested that asthma could be divided into at least two distinct molecular phenotypes defined by the degree of Th2 inflammation (Th2- and non-Th2-driven asthma) (Woodruff *et al.*, 2009). Therefore, inhibitors of Th2 cytokines are likely to be beneficial in only a subset of patients with asthma. The evidence showed that the cotransfer of Th17 cells with Th2 cells enhanced eosinophilic airway inflammation in mice (Wakashin *et al.*, 2008). Further study showed that IL-17-producing Th2 cells markedly enhanced recruitments of eosinophils, neutrophils, macrophage, and lymphocytes into the airway (Wang *et al.*, 2010). It has been shown that several Chinese herbal formulas, including ASHMI, Bu-Shen-Yi-Qi-Tang and Sheng-Fei-Yu-Chuan-Tang, not only decreased Th2 responses but also reduced the expression of IL-17 (Lin *et al.*, 2013a; Luo *et al.*, 2014; Srivastava *et al.*, 2014). In an OVA-induced mouse model, curcumin decreased IL-17 level in BALF and frequency of Th17 cells in spleen (Ma *et al.*, 2013a). Future studies should explore the role of TCM in the inhibition of Th17 responses and the effect of the inhibition of Th17 responses on the treatment of asthma.

Mast Cells

Allergen-binding to the mast cell- and basophil cell-bound IgE leads to release of vasoactive amines (such as histamine), lipid mediators (such as prostaglandin D, platelet-activating factor, leukotriene C4 (LTC4), LTD4, and LTE4), chemokines (CXC-chemokine ligand 8 (CXCL8), CXCL10, CC-chemokine ligand 2 (CCL2), CCL4 and CCL5) and other cytokines (such as IL-4, IL-5, and IL-13), causing the immediate symptoms of allergic responses (Larche *et al.*, 2006; Stone *et al.*, 2010; Jutel and Akdis, 2011; Moon *et al.*, 2013). TCM could directly exert effects on the mast cells to attenuate the allergic responses (Kim *et al.*, 2012; Park *et al.*, 2014). Wu-Hu-Tang, a Chinese herbal formulation for the treatment of asthma, could inhibit the immediate hypersensitivity by decreasing the degranulation of mast cells and the release of anaphylactic mediators from sensitized lung tissues of guinea pigs (Dai *et al.*, 1997). Guo Min Kang, a TCM formula, abrogated the levels of conalbumin-induced histamine release and significantly reduced the number of degranulated mast cells (Li *et al.*, 2009). Water extracts from *Anemarrhena asphodeloides* Bunge, *Houttuynia cordata*, *Isodon japonicus* Hara, *Lycopus lucidus* Turcz and *Rhus javanica* reduced degranulation, histamine release and calcium uptake of rat peritoneal mast cells induced by compound 48/80 or IgE (Shin *et al.*, 2004; Kim *et al.*, 2005; Li *et al.*, 2005; Shin *et al.*, 2005; Chai *et al.*, 2013), and inhibited the secretion of TNF-α, IL-1β, and IL-6 in PMA-stimulated rat peritoneal mast cells (Shin *et al.*, 2004; Kim *et al.*, 2005; Shin *et al.*, 2005; Chai *et al.*, 2013). The inhibition of inflammatory cytokine production is mediated by attenuating the activation of p38 mitogen activated protein kinase (MAPK) and the nuclear translocation of NF-κB (Shin *et al.*, 2005). Polydatin, a component of *Polygonum cuspidatum* Sieb. et Zucc, administration suppressed mast cell degranulation by inhibiting FcεRI-mediated Ca^{2+} increase (Yuan *et al.*, 2012). Baicalein, a major bioactive flavonoid component of *Scutellaria baicalensis* Georgi (Huang qin) (Chang *et al.*, 2013; Chen *et al.*, 2014; Huang *et al.*, 2014), inhibited the production of IL-6, IL-8, and MCP-1 in IL-1β- and TNF-α-activated HMC-1 mast cells by inhibiting NF-κB activation (Hsieh *et al.*, 2007).

Eosinophils

Several studies showed that TCM directly regulated the activation and migration of eosinophils (Lee *et al.*, 2006; Gu *et al.*, 2012). Astragaloside IV modulates eosinophil activation and trafficking in response to Der p 1 (the house dust mite allergen *Dermatophagoides pteronyssinus* 1) through inhibition of the expression of CCR3 and ICAM-1, secretion of IL-1β, IL-5, TNF-α, and GM-CSF (Gu *et al.*, 2012). The wheeze-relief formula dose-dependently suppressed eosinophil cationic protein release from eosinophils activated with GM-CSF and platelet activating factor (PAF) and inhibited the expression of CCR3 and CD49d on PAF-activated eosinophils (Lee *et al.*, 2006).

Epithelial Cells

Allergen could trigger epithelial cell pattern recognition receptors (PRRs) by pathogen-associated molecular patterns (PAMPs) to promote NF-κB activation and the release of pro-Th2 cytokines to induce Th2 immunity and allergy (Lambrecht and Hammad, 2013). San-ao Decoction and osthol, the major component of *Cnidii monnieri fructus* extract, decreased the expression of eotaxin of IL-4-stimulated human bronchial epithelial cell (Chiu *et al.*, 2008; Li *et al.*, 2000). Water extract of *Schisandra chinensis* Baillon

Table 3. Clinical Trials

Name of Formula	Doses	Subjects	Outcome Measures	References
ASHMI	600, 1200, and 1800 mg twice daily	18–55 years old subjects with physician-diagnosed asthma and positive skin tests or serum specific IgE	Safe and well tolerated	Kelly-Pieper *et al.* (2009)
Ding Chuan Tang	6 g/d	8–15 years old children with mild-to-moderate asthma	Improve AHR, symptom and medication scores without adverse effects	Chan *et al.* (2006)
ASHMI	3.6 g/d	18–65 years old subjects with moderate-severe, persistent asthma	Improve lung function, reduce clinical symptom scores, use of b2-bronchodilators, and serum IgE, IL-5, and IL-13 levels, but increase IFN-γ level	Wen *et al.* (2005)
STA-1	80 mg/kg/d	5–20 years old subjects with episodes of dyspnea, cough and wheezing requiring intermittent or frequent bronchodilator treatment	Reduce the symptom scores, systemic steroid dose, total IgE and specific IgE with minimal side effects	Chan *et al.* (2006)
Mai-Men-Dong-Tang	40 and 80 mg/kg/d	8–15 years old children with episodes of dyspnea, coughing, and wheezing, requiring intermittent or frequent bronchodilator treatment	Improve lung function, reduce total IgE and relieve asthma symptoms without adverse effects	Hsu *et al.* (2005)
Lung Support formula	1000 mg twice daily	Over 50 years old subjects either with symptoms like chronic cough, expectoration, dyspnea for more than 1 month or chronic pharyngitis, laryngitis, tracheitis, bronchitis or COPD	Decrease the percentage of patients reported to have chronic cough, chronic expectoration and chronic bronchitis, and the respiratory symptoms scores without adverse effects	Cai *et al.* (2013)
The established Chinese herbal formulas	10 ml of this mixture 3 times a day	3–12 years old children with pattern of phlegm-heat obstruction and cold fluid-retention in lungs at the acute stage, or with pattern of lung–spleen deficiency and kidney *Qi* deficiency at the remission stage of asthma based on TCM syndrome differentiation diagnosis	Decrease the expression of IL-4 and cysteinyl leukotriene receptor 1, and increase the expression of IFN-γ	Li *et al.* (2013b)

dose-dependently inhibited NO production and reduced IL-8 and MCP-1 secretions in human lung alveolar epithelial-derived A549 cells induced by IL-1β, TNF-α, and IFN-γ (Bae *et al.*, 2012). Water extract of *Eriobotrya japonica* leaves (Pi-Pa-Ye) suppressed LPS-induced cytokine productions (TNF-α, IL-1β, and IL-8) and the expression of iNOS and COX-2 through the inhibition of IκB-α phosphorylation and NF-κB activation in A549 cells (Lee *et al.*, 2008a). Xia-Bai-San, a TCM, suppressed the expression of IL-8 and ICAM-1, and the activation of NF-κB in A549 cells stimulated by LPS (Lee *et al.*, 2009). TCM formula Sheng-Fei-Yu-Chuan-Tang decreased TNF-α and MCP-1 mRNA expression in LPS-stimulated lung epithelial cell (Lin *et al.*, 2013b). The *Vitex rotundifolia* treatment suppressed eotaxin secretion and down-regulated the expression of inflammation-related genes and cell adhesion-related genes in A549 cells (Sohn *et al.*, 2009).

Clinical Trials

Many clinical trials have been done to evaluate the safety and efficacy of TCM for the treatment of asthma. The double-blind, randomized, placebo-controlled clinical trials are summarized in Table 3. Generally, TCM is safe, relieves asthma symptoms, and/or decreases IgE and Th2 type cytokine levels, and increases Th1 type cytokine level (Hsu *et al.*, 2005; Wen *et al.*, 2005; Chan *et al.*, 2006; Chang *et al.*, 2006a; Kelly-Pieper *et al.*, 2009; Cai *et al.*, 2013; Li *et al.*, 2013b). However, it is very hard to compare the efficacy of TCM in these clinical trials, due to the differences in standards used to enroll subjects in all these clinical trials. Due to the complexity of TCM components and the different doses of TCM used in clinical trials, more well-designed clinical trials need to be done to evaluate the efficacy of TCM and explore the mechanism (Gao *et al.*, 2013; Ma *et al.*, 2013c; Tong *et al.*, 2013). The formulas of TCM are quite complex and almost formulas are used for a long time, which need to be optimized according to the recently found effects and mechanism of TCM.

Conclusion

Findings in animal models suggest that TCM can ameliorate asthma or asthmatic inflammation through different ways. TCM directly inhibits the activity and migration of inflammatory cells including mast cell and eosinophil, and Th2 and Th17 responses. TCM can modulate the balance of Th1/Th2 through increasing Th1 responses and/or decreasing Th2 responses. TCM suppresses allergic hyperreactivity by attenuating the maturation and activation of DCs. TCM also decreases allergic hyperresponsiveness through the induction of Tregs. The clinical trials showed that TCM is relatively safe and well tolerated without serious side effects. Some clinical trials show TCM regulates the balance of Th1/Th2. TCM may effectively improve symptoms of asthma and enhance patients' quality of life. Since various limitations still existed in these clinical trials, well-designed, larger-scale, multicenter, placebo-controlled studies for diverse populations are definitely needed. But current evidence is promising for clinical investigators to do further in-depth researches. The formulas of TCM need to be optimized according to the effects of TCM and its components to improve the clinical efficacy of TCM. The active components of TCM need to be identified and its immunoregulatory effects on asthma or asthmatic inflammation need also to be investigated. The action mechanism of TCM treatment of asthma needs to be researched in a more convincing and comprehensive manner, which is helpful for improving the clinical efficacy of TCM.

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