

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Complementary Therapy with Traditional Chinese Medicine for Childhood Asthma

Bei-Yu Wu, Chun-Ting Liu, Yu-Chiang Hung and Wen-Long Hu

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/62333>

Abstract

Asthma is a heterogeneous disease that is typically characterized by chronic airway inflammation and obstruction of airflow; it frequently presents in early childhood and is the leading chronic disease in children in the western world. This review presents a brief description of the pathophysiology of asthma and summarizes recent research results on the mechanisms of action of anti-asthma Chinese herbal medicine commonly used in clinical practice. Other interventions of traditional Chinese medicine (TCM), such as acupuncture, tai chi, and meditation are also briefly discussed. We believe that this contribution is theoretically and practically relevant because the prevalence of asthma is increasing and, in addition to standard treatment, the use of complementary therapy is increasing and there is increasing scientific evidence demonstrating that TCM has potential for the treatment of childhood asthma.

Keywords: Childhood asthma, traditional Chinese medicine, Acupuncture, complementary and alternative medicine

1. Introduction

Asthma is a heterogeneous disease that is typically characterized by chronic airway inflammation and obstruction of airflow. Asthma is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough [1]. Both these symptoms and airflow limitation characteristically vary over time as well as in intensity. These variations are often triggered by external factors, such as exercise, allergen or irritant exposure, change in the weather, or viral respiratory infections [2]. Symptoms and airway limitation may resolve with or without medication and may sometimes be absent for weeks or months at a time.

Asthma, a life-long condition, frequently presents in early childhood and is the leading chronic disease in children in the Western world. Although the prevalence of childhood varies widely across the world as described in the Phase III ISAAC study [3], most studies have reported that this prevalence has increased in recent decades [4–6]. This increase has been associated with a rise in atopic sensitization and other allergic disorders, such as eczema and rhinitis [6]. Approximately 25.9 million Americans (including 7.1 million children) had asthma in 2011, which equates to a rate of 84.8 per 1,000 in the population. The highest prevalence rate was seen in those in the 5–17 years of age bracket (105.5 per 1,000). Overall, the rate in those under the age of 18 years (94.9 per 1,000) was significantly greater than that in those over 18 years (81.6 per 1,000). The current asthma prevalence rate for boys under 18 years (101.7 per 1,000) was 16% higher than the rate among similarly aged girls (87.8 per 1,000) [7]. In 2008, the condition accounted for an estimated 14.4 million lost school days in children and 14.2 million lost work days in adults. Asthma is thus a leading cause of activity limitation and amounts to \$56.0 billion in health care costs annually in the United States [7].

Approximately 80 percent of children with asthma develop symptoms before 5 years of age, but the disease is frequently misdiagnosed or not suspected, particularly in infants [8]. Coughing and wheezing are the most common symptoms of childhood asthma. Breathlessness, chest tightness or pressure, and chest pain have also been reported [1, 2]. Descriptors may vary between cultures and by age; for example, children may be described as having heavy breathing [2]. Confirmation of the diagnosis of asthma in children requires a careful review of a child's current and past medical history, family history, as well as a physical examination.

Asthma is characterized by variable expiratory airflow limitation. Pulmonary function tests are sometimes needed to diagnose asthma and to rule out other possible causes of the symptoms. Spirometry is the most common pulmonary function test; it measures the flow and volume of air blown out after a child takes a very deep breath and then forcefully exhales. The important parameters derived from spirometry include forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), flow between 25% and 75% of the vital capacity (FEF 25–75%), and peak expiratory flow rate (PEFR) [9]. The greater the variation in lung function, or the more times excess variation is seen in a patient with respiratory symptoms, the more likely the diagnosis is to be one of asthma. The FEV_1/FVC ratio is normally >0.75 – 0.80 and usually exceeds 0.90 in children [10]. In asthma, at least once during diagnostic process, the FEV_1 is low, confirming that the FEV_1/FVC ratio is reduced. Generally, an increase in FEV_1 of $>12\%$ of that predicted after inhalation of a rapid-acting bronchodilator and/or average daily diurnal peak expiratory flow (PEF) variability exceeding 13% indicates that a child has asthma [2]. In young children, in whom lung function testing is not feasible, including most preschool children, asthma is defined by the presence of variable respiratory symptoms.

Traditional Chinese medicine (TCM), particularly herbal medicine, has been used for the treatment of asthma for hundreds of years, as documented in the *Yellow Emperor's Inner Canon (Huangdi Neijing)* and the *Essential Prescriptions from the Golden Cabinet (Jin Gui Yao Lue)*. In Taiwan, Chinese herbal medicine is commonly used as complementary and alternative therapy for the treatment of atopic diseases such as asthma, allergic rhinitis, and atopic

dermatitis. The medicines used for the prevention and treatment of asthma have received much attention in recent years. The cellular and molecular details of the underlying mechanisms of action of Chinese herbal medicine efficacious for treating asthma are just beginning to be understood.

This chapter presents a brief description of the pathophysiology of asthma and summarizes recent research results on the mechanisms of action of anti-asthma Chinese herbal medicine commonly used in clinical practice. Other interventions of TCM, such as acupuncture, *tai chi*, and meditation, are also briefly discussed.

2. Pathophysiology and pathogenesis of asthma

Asthma can be classified as atopic/allergic (extrinsic), which is the most common form, or nonatopic/nonallergic (intrinsic) asthma, which is more rare, has a later onset, and tends to be more severe than atopic asthma [11]. Atopic asthma involves inflammation mediated by specific IgE antibodies directed against common environmental allergens, whereas nonatopic asthma involves inflammation and airway constriction mediated by local production of IgE antibodies that are possibly directed at bacterial or viral antigens. The pathophysiology of nonatopic asthma is very similar to that of atopic asthma, but it is not caused by exposure to an allergen [2, 11].

The gross pathology of asthma reveals significant overinflation of the lungs [12]. Microscopically, this overinflation of lungs is manifest as marked distension of the alveoli. Notable airway smooth muscle (ASM) hyperplasia, basement membrane thickening, mucous gland hyperplasia, mucosal epithelium sloughing, and tissue edema are also seen [12]. This increase in muscle mass, mucous gland tissues, and tissue edema leads to a thickened airway wall, with a resultant decrease in airway caliber [12, 13]. These structural changes have been described as remodeling, a term used to define complex morphological changes that involve all of the structures of the bronchial wall [12, 13].

The initiation of bronchial epithelial damage by environmental agents (allergens, viruses, irritants, etc.) or their inflammatory products activates a sequence of events that amplify the inflammation and induce airway remodeling [13, 14]. Bousquet et al. suggested that asthma pathophysiology involved overlapping interactions of smooth muscle dysfunction, airway inflammation, and airway remodeling [13]. The inflammatory, physiological, and structural factors that contribute to the pathogenesis of asthma will be described below.

2.1. Airway inflammation

Inflammation plays a central role in the pathophysiology of asthma [15]. Airway inflammation remains a consistent pattern throughout the distinct phenotypes of asthma (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma) [16]. Airway inflammation involves an interaction of many cell types and multiple mediators with the airway, which eventually results in the characteristic pathophysiological features of asthma. The principal

cells involved in airway inflammation are mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes [12, 13].

T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Airway inflammation in asthma may indeed represent a loss of the normal balance between Th1 and Th2 lymphocytes [12, 16]. Th1 cells produce interleukin (IL)-2 and interferon gamma (IFN- γ), which are critical in the defense mechanisms of cells in response to infection. Th2 cells, in contrast, generate a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can stimulate the growth, differentiation, and recruitment of mast cells, basophils, eosinophils, and B-cells, all of which are involved in humoral immunity and in the allergic response [13, 14, 16].

IgE plays an essential role in type I hypersensitivity, which results in various allergic diseases, such as allergic asthma, most types of sinusitis, allergic rhinitis, food allergies, and specific types of chronic urticaria and atopic dermatitis [17]. Antigen-specific IgE is partly responsible for the initiation of an allergic response in asthma. IgE primes the IgE-mediated allergic response by binding to Fc receptors expressed on the surface of mast cells, basophils, eosinophils, monocytes, macrophages, or platelets in humans [18]. Antigens cross-link to the IgE on mast cells, which then release bronchoconstricting mediators (histamine, cysteinyl-leukotrienes, prostaglandin D₂) and further amplify the inflammatory response by damaging local tissue and attracting other lymphocytes [17]. IL-4 produced by Th2 cells stimulates IgE production in B-lymphocytes and expression of vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells, whereas IL-5 stimulates eosinophil differentiation and mobilization to inflammatory sites [13, 16]. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhere to the endothelium by means of binding between integrins and members of the immunoglobulin superfamily of adhesion proteins, namely VCAM-1 and intercellular adhesion molecule 1 (ICAM-1) [13, 16]. As the eosinophils enter the matrix of the airway through the influence of various chemokines, such as monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP-1 α), eotaxin or RANTES, and cytokines, their survival is prolonged by IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [13, 16]. Upon activation, the eosinophils release inflammatory mediators, such as leukotrienes and granule proteins, which injure airway tissues [19]. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and thereby contribute to persistent airway inflammation [16]. Eosinophils are the most characteristic cells accumulated in asthma and allergic inflammation; their presence is often related to disease severity. Eosinophils are recruited or activated by IL-5, the eotaxin family of chemokines, via the eosinophil-selective chemokine receptor CCR3, and by Toll-like receptors (TLRs). Activated eosinophils produce lipid mediators, such as leukotrienes and platelet-activating factor, which mediate smooth muscle contraction; toxic granule products (e.g., major basic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, or eosinophil cationic protein) that can damage airway epithelium and nerves; and cytokines, such as GM-CSF, transforming growth factors (TGF)- α and β , and interleukins, which may be involved in airway remodeling and fibrosis [13]. Recently, Th regulatory cells that exclusively produce IL-17 cytokines (TH17 cells) have been

identified in patients with severe asthma [19]. The involvement of TH17 responses in the pathogenesis of asthma has been shown by the overexpression of IL-17 mRNA in the airways of asthma model mice [19]. It is now suggested that TH17-related cytokines play a critical role in airway remodeling and may be involved in interactions with structural cells [13, 19].

2.2. Airway remodeling and ASM dysfunction

The histopathologic changes of airway remodeling include damage or loss of the normal pseudostratified structure of airway epithelium, an increase in the proportion of mucous-producing goblet cells, fibrotic thickening of the subepithelial reticular basement membrane or "lamina reticularis," increased numbers of myofibroblasts, increased vascularity, increased ASM mass, and increased extracellular matrix [20]. These structural changes contribute to bronchial wall thickening, alterations in the physiological consequences of smooth muscle contraction, or loss of airway-parenchymal interdependence [13, 20].

Epithelial alterations in asthma include epithelial shedding, destruction of ciliated cells, goblet cell hyperplasia, upregulation of growth factor release, and overexpression of receptors, such as the epidermal growth factor receptors [21]. Loss of epithelial surface and the resultant denudation of the basement membrane may decrease this protective effect, thereby increasing the propensity for allergic insult to the airway [21]. A second important feature of airway remodeling is subepithelial fibrosis, which has been consistently reported in asthma of all levels of severity, in patients with atopic rhinitis, and even in children with treatment-resistant asthma [21]. Subepithelial fibrosis occurs in the lamina reticularis, immediately below the basement membrane, resulting in thickening of the basement membrane just below the epithelium [22]. In the asthmatic airway, fibroblasts are activated and differentiate into myofibroblasts, which secrete proinflammatory mediators and extracellular matrix proteins, including collagens I, III, and V; fibronectin; tenascin; lumican; and biglycan [21, 22]. Asthmatic airway fibroblasts promote fibrosis through expression of a higher ratio of tissue inhibitor of metalloproteinase (TIMP)-2 to matrix metalloproteinase (MMP)-2, resulting in increased matrix deposition [21]. MMPs are a family of proteases implicated in collagen degradation. MMP-2, MMP-3, MMP-8, and MMP-9 have been associated with asthma [20]. Among these, MMP-9 levels have been reported to be significantly higher in the sputum of patients with asthma than in that of control subjects [20–23].

Respiratory ASM cells are the critical effector cells that modulate airway tone [22]. In asthmatic airways, smooth muscle mass is increased due to a coordinated increase in the size (hypertrophy) and number (hyperplasia) of ASM cells [21, 22]. ASM remodeling is considered to be the primary cause of airway obstruction [21]. ASM cells participate in the inflammatory and remodeling process through the expression of cellular adhesion molecules, receptors for cytokines (e.g., TNF- α), chemokines (RANTES, eotaxin, MIP-1 α , and IL-8), and TLRs [21]. Additionally, the migration of ASM cells toward the epithelium contributes to remodeling. A wide range of inflammatory mediators, such as TNF- α , IL-1b, and IFN- γ , have been shown to induce the expression of ICAM-1 and VCAM-1 on cultured ASM cells [21]. The surface expression of cellular adhesion molecules by ASM cells might be pivotal in regulating interactions with a variety of inflammatory cells, including eosinophils and T cells [21].

Additionally, accumulating evidence has indicated an abnormal increase in the number and size of microvessels within bronchial tissue in remodeled airways [21]. This occurs mainly below the basal lamina, in the space between the muscle layer and the surrounding parenchyma [21]. An imbalance between vascular endothelial growth factor (VEGF) and angiopoietin-1 has been shown to be involved in these abnormalities [21]. In fact, VEGF acts by increasing the permeability of these abnormal blood vessels, resulting in vessel dilation and edema, which contribute to airway narrowing [21, 22]. In addition to providing nutrition to the airways, these vessels are the source of inflammatory cells and plasma-derived mediators and cytokines [21].

3. Conventional treatment of childhood asthma

The optimal treatment of childhood asthma depends upon a number of factors, including the child's age, the severity and frequency of asthma attacks, and the ability to properly use the prescribed medications [2]. For the vast majority of children, asthma treatment can control symptoms, allowing the child to participate fully in all activities, including sports. Identifying and avoiding asthma triggers, the factors that set off or worsen asthma symptoms, are essential for preventing asthma flare-ups [2]. Common asthma triggers generally include allergens (such as dust, pollen, and furred animals), respiratory infections, irritants (such as tobacco smoke, chemicals, and strong odors or fumes), physical activity, certain medicines (such as beta blockers, aspirin, or other nonsteroidal anti-inflammatory medications), and emotional stress [2]. After identifying potential triggers of asthma, the parent and health care provider should develop a plan to deal with the triggers. If possible, the child should completely avoid or limit exposure to the trigger [2].

The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbation, fixed airflow limitation, and side effects of treatment [2]. In control-based asthma management, pharmacological and nonpharmacological treatment is adjusted continuously in a cycle that involves assessment, treatment, and review of the response [2]. Asthma severity is determined by considering the following factors: the symptoms reported over the previous 2 to 4 weeks, the current level of lung function (FEV_1 and FEV_1/FVC values), and the number of instances of exacerbation requiring oral glucocorticoids per year [2]. The classification of severity in children aged 5–11 years or in adolescents over the age of 12 years is similar to that in adults [2]. The severity in children under the age of 4 years, however, is classified somewhat differently and includes intermittent, mild persistent, moderate persistent, and severe persistent asthma [2].

3.1. Categories of asthma medications

Medication for asthma is mainly divided into two categories: controller medications and reliever (rescue) medications [2]. Controller medications, such as inhaled corticosteroids (ICS) and long-acting beta-adrenoceptor agonists (LABA), are used for regular maintenance treatment [24–26]. These medications reduce airway inflammation, control symptoms, and reduce future risks, such as exacerbations and decreased lung function. Reliever medications,

such as short-acting beta-2-adrenoceptor agonists (SABA), are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening of asthma or exacerbations [24–26]. They are also recommended for short-term prevention of exercise-induced bronchoconstriction [2]. Reducing and, ideally, eliminating the need for reliever treatment are both an important goal in asthma management and a measure of the success of asthma treatment. Add-on therapies for patients with severe asthma may be considered when patients have persistent symptoms and/or exacerbations, despite optimized treatment with high-dose controller medications (usually a high-dose ICS and a LABA) and treatment of modifiable risk factors [2].

The initiation of asthma therapy in a stable patient who is not already receiving medications is based upon the severity of asthma in the individual. Patients with mild intermittent asthma are best treated with an inhaled SABA, which should be taken as needed for the relief of symptoms [2]. Patients in whom triggering of asthmatic symptoms can be predicted (e.g., exercise-induced bronchoconstriction) are encouraged to use their inhaled beta agonist approximately 10 min prior to exposure, to prevent the onset of symptoms [2]. For mild persistent asthma, the preferred long-term controller is a low-dose ICS [2]. Regular use of ICS reduces the frequency of symptoms (and the need for SABAs for symptom relief), improves the overall quality of life, and decreases the risk of serious exacerbations [2]. Alternative strategies for treatment of mild persistent asthma include leukotriene receptor antagonists, theophylline, and cromoglycate [2, 26].

For moderate persistent asthma, the preferred therapy is low doses of ICS plus an inhaled LABA, or medium doses of ICS [2]. Alternative strategies include adding a leukotriene modifier (leukotriene receptor antagonist or lipoxygenase inhibitor) or theophylline to low-dose ICS [2]. For severe persistent asthma, the preferred treatments are medium (Step 4) or high (Step 5) doses of ICS, in combination with an inhaled LABA [2]. In addition, for patients who are inadequately controlled on high-dose ICS and LABAs, the anti-IgE therapy omalizumab may be considered, if there is objective evidence of sensitivity to a perennial allergen (by allergy skin tests or in vitro measurements of allergen-specific IgE) and if the serum IgE level is within the established target range [2].

4. Status and purpose

Currently, according to the guidelines published by the Global Initiative for Asthma (GINA), conventional medicines are the mainstay for managing asthma; these include steroids, beta-2 adrenergic agonists, leukotriene modifiers, theophylline, and anti-IgE therapies [2]. However, current conventional medications for childhood asthma are not yet satisfactory. The side effects of long-term use of steroids and beta-2 adrenergic agonists are major concerns for parents, in that growth, bone turnover, and adrenal gland function may be suppressed under, particularly higher doses of steroids [24, 25]. Due to the chronic and potentially life-threatening nature of asthma, and the lack of definitive preventive and curative therapies, many families look to complementary and alternative medicine (CAM) for treatment. CAM is popular in the

treatment of asthma and encompasses many therapies, including mind–body techniques, nutritional manipulation, dietary and herbal supplements, TCM (including acupuncture), exercise, manual therapies, and homeopathy [26]. Reportedly, CAM is commonly used in children who have mild or moderate persistent asthma, those receiving high-dose ICS, and patients who experience poor symptom control or require frequent physician visits, including emergency room visits [26]. One retrospective longitudinal cohort study showed that initiation of CAM treatment does not decrease future adherence to conventional asthma medications, suggesting that alternative or integrative medicine use does not necessarily compete with conventional asthma therapies [27]. As CAM use becomes more prevalent, it will become increasingly important for physicians attending to asthmatic children to be aware of CAM use. TCM is the major component of CAM therapies used in the United States and Taiwan. TCM is one of the oldest medical practices in the world and has played an important role in preventing and treating diseases in China for centuries, where it is still used as a monotherapy or as part of an integrated medicine approach. Evidence has increased showing the efficacy of TCM for the treatment of childhood asthma. Below, we explore complementary therapy, involving TCM therapy for childhood asthma.

5. Chinese herbal formulas use in children with asthma

TCM formulas have been used to treat asthma for centuries. A number of well-controlled clinical studies of several TCM formulas, including modified Mai-Men-Dong-Tang (mMMDT, five herbs), Ding-Chuan-Tang (DCT, nine herbs), and STA-1 (the combination of Mai-Men-Dong-Tang and Liu-Wei-Di-Huang-Wan, 10 herbs), and anti-asthma herbal medicine intervention (ASHMI, three herbs) provided evidence of clinical efficacy, safety, and immunomodulatory effects [24]. Typically, the traditional TCM formulas that are prescribed combine several single herbs to treat a specific disease. Recent research [25] from the National Health Insurance Research Database (NHIRD) in Taiwan has revealed the core herbal treatments for children with asthma. The most commonly used herbal formulas for the treatment of childhood asthma are Ma-Xing-Gan-Shi-Tang and Xiao-Qing-Long-Tang; the former is used for excess heat congested in the lung, whereas the latter is used for the exterior wind-cold with internal accumulation of retained fluid in the lung. These herbal formulas (shown in Table 1) and several single herbs commonly used for the treatment of childhood asthma are described below. The immunomodulatory effects of suppressing Th2 cells and decreasing subsequent cytokine secretion of these herbal remedies will also be investigated. Other commonly prescribed formulas that are used mainly to relieve asthma-related symptoms, such as productive cough (Xing-Su-San, Zhi-Sou-San), coughing with a sore throat (Yin-Qiao-San), and nasal congestion (Xin-Yi-Qing-Fei-Tang, Cang-Er-Zi-San, Shin-Yi-San), do not fall within the scope of this review.

5.1. ASHMI

ASHMI is the first herbal medicine to receive approval for phase I and II clinical trials as a US Food and Drug Administration investigational new drug (IND No. 71526) for treating asthma.

Formula	Composition	Possible mechanisms
ASHMI	Ling Zhi (<i>Ganoderma Lucidum</i>), Ku Shen (<i>Radix Sophorae Flavescentsis</i>), and Gan Cao (<i>Radix Glycyrrhizae</i>)	Decreases Th2 response; increases IFN- γ levels; decreases IL-4, IL-5, IL-13, eotaxin, TNF- α , total and specific IgE levels; reduces AHR, mucous production, neutrophilic and eosinophilic inflammation; improves FEV ₁ and PEF [24, 28–30]
Modified Mai-Men-Dong-Tang (mMMDT)	Mai Men Dong (<i>Radix Ophiopogonis</i>), Ban Xia (<i>Rhizoma Pinelliae</i>), American Ren Shen (<i>Radix Panacis Quinquefolii</i>), Gan Cao (<i>Radix Glycyrrhizae</i>), and Lantern Tridax (<i>Herba Tridacis procumbentis</i>)	Antitussive effect, bronchial dilation via beta-2 adrenergic effect; decreases IL-4, total IgE, and specific IgE; reduces AHR; improves FEV ₁ [24, 31–33]
STA-1	Mai Men Dong (<i>Radix Ophiopogonis</i>), Ban Xia (<i>Tuber Pinellia</i>), American Ren Shen (<i>Radix Panacis Quinquefolii</i>), Gan Cao (<i>Radix Glycyrrhizae</i>), Shu Di Huang (<i>Radix Rehmanniae Preparata</i>), Mu Dan Pi (<i>Cortex Moutan Radicis</i>), Shan Zhu Yu (<i>Fructus Corni</i>), Fu Ling (<i>Poria</i>), Ze Xie (<i>Rhizoma Alismatis</i>), and Shan Yao (<i>Radix Dioscoreae</i>)	Reduces symptom scores, systemic steroid dose, airway inflammation, AHR, total IgE, and specific IgE; improves FEV ₁ [34, 35]
Ma-Xing-Gan-Shi-Tang	Ma Huang (<i>Herba Ephedrae</i>), Xing Ren (<i>Semen Armeniacae Amarum</i>), Shi Gao (<i>Gypsum Fibrosum</i>), and Gan Cao (<i>Radix Glycyrrhizae</i>)	Antitussive effect, beta-2 adrenergic effect; reduces neutrophilic inflammation [36, 37]
Xiao-Qing-Long-Tang	Ma Huang (<i>Herba Ephedrae</i>), Gui Zhi (<i>Ramulus Cinnamomi</i>), Ban Xia (<i>Rhizoma Pinelliae</i>), Gan Jiang (<i>Rhizoma Zingiberis</i>), Xi Xin (<i>Herba Asari</i>), Wu Wei Zi (<i>Fructus Schisandrae</i>), Bai Shao Yao (<i>Radix Paeoniae</i>), and Gan Cao (<i>Radix Glycyrrhizae</i>)	Decreases Th2 response; increases IFN- γ ; decreases IL-4, IL-5, IL-10, IL-13, IgE, RANTES, eotaxin, and MCP-1 levels; suppresses histamine release, reduces airway inflammation, remodeling, and immunomodulation; bronchial dilation, partial beta-2 adrenergic effect [38–40]
Ding-Chuan-Tang	Ma Huang (<i>Herba Ephedrae</i>), Gan Cao (<i>Radix Glycyrrhizae</i>), Ban Xia (<i>Rhizoma Pinelliae</i>), Bai Guo (<i>Semen Ginkgo</i>), Kuan Dong Hua (<i>Flos Farfarae</i>), Sang Bai Pi (<i>Cortex Moris</i>), Su Zi (<i>Fructus Perillae</i>), Xing Ren (<i>Semen Armeniacae Amarum</i>), and Huang Qin (<i>Radix Scutellariae</i>)	Improves AHR, symptoms, and medication; reduces eosinophilic inflammation; beta-2 adrenergic effect [41, 42]

Table 1. Herbal formulas frequently used for asthmatic children

ASHMI is composed of the aqueous extracts of Ling Zhi (*Ganoderma lucidum*), Ku Shen (*Sophora flavescens*), and Gan Cao (*Glycyrrhiza uralensis*) [24]. ASHMI improved lung function (FEV₁), reduced symptom scores, and decreased beta-2-adrenoceptor agonist use, to a degree similar as that achieved by prednisone in adults with moderate to severe asthma, but without the adverse effect of prednisone on adrenal function and with no overall immune suppression. Individually, Ling Zhi, Ku Shen, and Gan Cao extracts and ASHMI (the combination of individual extracts) inhibited production of IL-4 and IL-5 by murine memory Th2 cells and that of eotaxin-1 by human lung fibroblast cells [28]. ASHMI synergistically inhibited eotaxin-1 production as well as Th2 cytokine production. In another mouse model of asthma, ASHMI also reduced the levels of ovalbumin (OVA)-specific IgE and Th2 cytokines, including IL-4, IL-5, and IL-13 in the lung, and increased IFN- γ secretion [29]. Moreover, ASHMI markedly reduced airway hyperresponsiveness (AHR), mucous production, neutrophilic inflammation, and TNF- α , IL-8, and IL-17 levels and also decreased eosinophilic inflammation and Th2 responses in vivo [30].

5.2. Modified Mai-Men-Dong-Tang

Mai-Men-Dong-Tang is a herbal TCM that has been used for the treatment of bronchitis, bronchial asthma, and cough. The compositions of Mai-Men-Dong-Tang are Mai Men Dong (*Ophiopogon japonicus*), Ban Xia (*Pinellia ternata*), Ren Shen (*Panax ginseng*), Gan Cao (*Glycyrrhiza uralensis*), Da Zao (*Ziziphus jujuba*), and Geng Mi (*Oryza sativa*). Mai-Men-Dong-Tang was shown to have an antitussive effect, based on improved airway clearance. The pharmacological effect of this antitussive effect is suggested to involve the inhibition of C-fibers, bronchodilation, anti-inflammatory effects, suppression of mucosal excretion, and augmentation of surfactant secretion [31]. Mai-Men-Dong-Tang was shown to potentiate beta-adrenergic function in ASM, which may reflect the efficacy on AHR and asthma [32]. mMMDT contains five herbs, including Mai Men Dong (*Radix Ophiopogonis*), Ban Xia (*Rhizoma Pinelliae*), American Ren Shen (*Radix Panacis Quinquefolii*), Gan Cao (*Radix Glycyrrhizae*), and Lantern Tridax (*Herba Tridacis procumbentis*) [33]. mMMDT was shown to decrease serum total IgE and house dust mite-specific IgE significantly and downregulate the expression of IL-4 in allergen-sensitized mice. The effect of mMMDT on changes in FEV₁ was studied as the first efficacy end point, given its validity for monitoring airway obstruction, which showed significant improvement in FEV₁ in patients treated with mMMDT [33]. Moreover, mMMDT also relieved asthma symptoms, including coughing, wheezing, and breathlessness [33].

5.3. STA-1

STA-1 is a combination of mMMDT (four herbs) and Lui-Wei-Di-Huang-Wan (six herbs) [34]. The four herbs of mMMDT comprise Mai Men Dong (*Radix Ophiopogonis*), Ban Xia (*Tuber Pinellia*), American Ren Shen (*Radix Panacis Quinquefolii*), and Gan Cao (*Radix Glycyrrhizae*) without Lantern Tridax (*Herba Tridacis procumbentis*). The six herbs of Lui-Wei-Di-Huang-Wan are Shu Di Huang (*Radix Rehmanniae Preparata*), Mu Dan Pi (*Cortex Moutan Radicis*), Shan Zhu Yu (*Fructus Corni*), Fu Ling (*Poria*), Ze Xie (*Rhizoma Alismatis*), and Shan Yao (*Radix Dioscoreae*). STA-1 was able to inhibit mite-induced IgE synthesis, reduce inflammation-associated

accumulation of eosinophils and neutrophils in the airway, and relieve AHR in a murine model [35]. Clinical evaluation of STA-1 in the treatment of mild-to-moderate chronic asthma revealed a significant reduction of symptom scores, systemic steroid dose, total IgE, and specific IgE in patients treated with STA-1 [34]. Furthermore, STA-1 also improved lung function (FEV₁) as compared with placebo after 6 months' treatment and with only minimal side effects [34].

5.4. Ma-Xing-Gan-Shi-Tang

Ma-Xing-Gan-Shi-Tang, a TCM, has been used in the treatment of bronchial asthma for several centuries. Ma-Xing-Gan-Shi-Tang consists of Ma Huang (*Herba Ephedrae*), Xing Ren (*Semen Armeniacae Amarum*), Shi Gao (*Gypsum Fibrosum*), and Gan Cao (*Radix Glycyrrhizae*). A murine cough model, induced by sulfur dioxide gas, was used to investigate the antitussive effect of Ma-Xing-Gan-Shi-Tang [36]. Both Ma Huang and Xing Ren inhibited cough induction in a dose-dependent manner. However, Ma-Xing-Gan-Shi-Tang, which contains Ma Huang and Xing Ren, showed stronger antitussive effects than the individual crude drugs [36]. In a guinea pig model of allergic asthma, Ma-Xing-Gan-Shi-Tang was efficacious in stimulation of beta-2-adrenoceptors on bronchial smooth muscle and had an anti-inflammatory effect, involving inhibition of neutrophil infiltration into the airway [37]. Ma-Xing-Gan-Shi-Tang is typically indicated in syndromes involving wind-heat on the lung or stagnated wind-cold that has turned into heat and that stayed in the lung. In Taiwan, asthma triggered by respiratory tract infection among asthmatic children is much more common than that triggered by cold exposure and weather change. Asthma triggered by respiratory tract infection is the most important indication for Ma-Xing-Gan-Shi-Tang [25].

5.5. Xiao-Qing-Long-Tang

Xiao-Qing-Long-Tang (XQLT) has been widely used clinically for the treatment of allergic diseases, including bronchial asthma and allergic rhinitis. XQLT consists of Ma Huang (*Herba Ephedrae*), Gui Zhi (*Ramulus Cinnamomi*), Ban Xia (*Rhizoma Pinelliae*), Gan Jiang (*Rhizoma Zingiberis*), Xi Xin (*Herba Asari*), Wu Wei Zi (*Fructus Schisandrae*), Bai Shao Yao (*Radix Paeoniae*), and Gan Cao (*Radix Glycyrrhizae*).

XQLT was shown to reduce bronchial inflammatory cell infiltration and airway remodeling in repetitive *Dermatogoides pteronyssinus*-challenged mouse model of chronic asthma [38]. XQLT inhibited *D. pteronyssinus*-induced total IgE and *D. pteronyssinus*-specific IgG1 in serum and changed the Th2-bios in bronchoalveolar lavage fluid (BALF) by inhibiting the activation of nuclear factor-Kappa B (NF- κ B). The same study also showed that XQLT treatment increased the protein levels of IL-12, but decreased that of TNF- α , TGF- β 1, IL-5, IL-6, and IL-13 by inhibiting expression of the genes including IL-10, IL-13, eotaxin, RANTES, and MCP-1 in the lung. Moreover, collagen assays and histopathology indicated that XQLT reduces airway remodeling in the lung [38]. XQLT treatment could inhibit the secretion of IL-5 in the serum and downregulate mRNA expression of genes encoding eotaxin, RANTES, and MCP-1 in lung tissues, which may contribute to a reduction in eosinophils and monocytes recruited to the airway.

Studies on the OVA-sensitized allergic airway inflammation model in mice revealed that XQLT significantly inhibited the antigen-induced immediate asthmatic response and late asthmatic response in actively sensitized mice. XQLT was shown to reduce the production of Th2-associated cytokines, IL-4 and IL-5, and to restore the production of the Th1 cell-associated cytokine, IFN- γ [39]. Anti-OVA IgE antibody levels were reduced in the BALF of sensitized mice after oral administration of XQLT [39]. Furthermore, XQLT was shown to have an anti-asthmatic effect, which is partly mediated by stimulation of beta-2-adrenoceptors, leading to bronchorelaxation; furthermore, XQLT inhibits the infiltration of eosinophils into the airway [40].

5.6. Ding-Chuan-Tang

Ding-Chuan-Tang (DCT), another TCM, has been used in the treatment of bronchial asthma for several centuries. DCT is composed of nine herbs, including Ma Huang (*Herba Ephedrae*), Gan Cao (*Radix Glycyrrhizae*), Ban Xia (*Rhizoma Pinelliae*), Bai Guo (*Semen Ginkgo*), Kuan Dong Hua (*Flos Farfarae*), Sang Bai Pi (*Cortex Mori*), Su Zi (*Fructus Perillae*), Xing Ren (*Semen Armeniacae Amarum*), and Huang Qin (*Radix Scutellariae*). According to TCM principles, this decoction is frequently prescribed for children with coughing, wheezing, and chest tightness.

One study of a murine OVA-sensitized allergic airway inflammation model revealed that DCT significantly inhibited the increase of eosinophils in the airway and caused concentration-dependent bronchorelaxation via a beta-2 adrenergic effect [41]. A randomized, double-blind clinical trial [42] conducted to assess the add-on effect of DCT showed that AHR significantly improved after weeks of DCT treatment compared with that after placebo use. In addition, patients in the DCT group also showed superior clinical improvement and used less medication than in the placebo group. This study suggested that addition of DCT to conventional treatment could further improve AHR, even in patients with well-controlled asthma. However, this study did not find a significant reduction in IgE levels and FEV₁ with DCT treatment, as compared to placebo [42].

6. Chinese single herbs use in children with asthma

We described several single herbs frequently used for asthmatic children in Taiwan (shown in Table 2), including Zhe Bei Mu (*Fritillaria thunbergii*), Xing Ren (*Semen Armeniacae Amarum*), Huang Qi (*Astragalus membranaceus*), Qian Hu (*Peucedanum praeruptorum* Dunn), Gan Cao (*Glycyrrhiza uralensis*), Sang Bai Pi (*Cortex mori radiceis*), Ban Xia (*Pinellia ternate*), Bo He (*Mentha haplocalyx*), Da Huang (*Rheum palmatum*), Jie Geng (*Platycodon grandiflorum*), Huang Qin (*Scutellaria baicalensis*), and Yu Xing Cao (*Houttuynia cordata* Thunb.).

6.1. Zhe Bei Mu

Zhe Bei Mu is used as an antitussive therapy and expectorant in TCM. Its extract inhibited histamine release from rat peritoneal mast cells in a concentration-dependent manner. Moreover, it also inhibits the production of inflammatory cytokines (IL-6, IL-8, and TNF- α) in

human mast cell line-1 (HMC-1) cells and components of the mitogen-activated protein kinase (MAPK) pathway in mast cells [43].

6.2. Xing Ren

Xing Ren has long been used in TCM to control acute lower respiratory tract infection and asthma as a result of its expectorant and anti-asthmatic activities. Xing Ren was shown to have anti-asthmatic activity and selectively inhibit the Th2 response in a mouse model by decreasing eosinophils and IL-4 in the airway [44].

6.3. Huang Qi

Huang Qi has a long history of medicinal use for asthma treatment in China. It increases metabolism and stimulates tissue regeneration, and it is used to treat colds, allergies, digestive problems, and fatigue in TCM. Huang Qi was shown to inhibit the Th2 response. It significantly reduced AHR, eosinophil counts, and IL-4, IL-5, and IL-13 levels and increased INF- γ levels in BALF. Histological studies showed that Huang Qi markedly decreased inflammatory infiltration, mucus secretion, and collagen deposition in lung tissues. CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Tregs) play a significant role in the regulation of asthma, and the induction of allergen-specific Tregs has become one appealing strategy for asthma therapy [45–47]. Huang Qi was shown to increase the population of CD4⁺CD25⁺Foxp3⁺ Tregs and promote *Foxp3* mRNA expression in a rat model of asthma [47]. This suggests that the anti-asthmatic effects of Huang Qi are at least partially associated with CD4⁺CD25⁺Foxp3⁺ Tregs.

6.4. Qian Hu

Qian Hu is a TCM commonly used for the treatment of asthma. Its major constituents, coumarins, were presumed to be responsible for its efficacy. Qian Hu was shown to reduce AHR and airway eosinophilic inflammation significantly, improve pathologic lesions of the lungs, reduce levels of IL-4, IL-5, and IL-13 in BALF and OVA-specific IgE in serum, inhibit the expression of TGF- β 1 in lungs, and upregulate levels of IL-10 and IFN- γ in BALF, as well as the percentage of CD4⁺CD25⁺Foxp3⁺ regulatory T cells in the spleen [48, 49]. This suggests that Qian Hu has great therapeutic potential for the treatment of allergic asthma.

6.5. Gan Cao

Gan Cao, commonly called “licorice,” is one of the most commonly used herbs in TCM. Airway eosinophilic inflammation is a major feature of allergic asthma. Eotaxin-1 is involved in the recruitment of eosinophils to sites of antigen-induced inflammation in asthmatic airways. Licorice flavonoids can inhibit eotaxin-1 secretion by human fetal lung fibroblasts in vitro [50]. Licorice flavonoids also significantly reduced eosinophilic pulmonary inflammation, serum IgE, IL-4, and IL-13 levels but also increased IFN- γ production in lung cell cultures in response to antigen stimulation [51]. Glycyrrhizic acid is the main bioactive ingredient of licorice and has been shown to exert anti-asthmatic effects by modulating Th1/Th2 cytokines (IL-4, IL-5, IL-13 inhibition, IFN- γ increase in BALF) and enhancing CD4⁺CD25⁺Foxp3⁺ Tregs in OVA-

sensitized mice [52]. Histological studies demonstrated that glycyrrhizic acid substantially inhibited OVA-induced eosinophilia in lung and airway tissues [52].

6.6. Sang Bai Pi

Sang Bai Pi (*Cortex mori radices*), the root epidermis of *Morus alba* L., has been traditionally used for cough treatment in TCM. In OVA-induced asthma model mice [53], Sang Bai Pi significantly reduced AHR, inhibited the production of histamine and IgE in serum, and decreased airway eosinophil infiltration in BALF and lung tissue. Sang Bai Pi significantly attenuated the secretion and mRNA levels of Th2 cytokines, such as IL-4, IL-5, and IL-13. In addition, Sang Bai Pi significantly increased mRNA expression of IFN- γ , a Th1 cytokine. Furthermore, Sang Bai Pi can exert anti-asthmatic effects by enhancing CD4⁺CD25⁺Foxp3⁺ Tregs.

6.7. Ban Xia

Ban Xia is a commonly used Chinese herb, with high bioactivity against cough and vomiting, and eliminating the stagnation of phlegm. Ban Xia significantly attenuated OVA-induced influx of the total number of leukocytes, eosinophils, neutrophils, macrophages, and lymphocytes into the lungs, decreased airway mucus production, and attenuated levels of IL-4, IL-5, IL-13, and TNF- α , in a dose-dependent manner. Ban Xia also significantly reduced the plasma levels of histamine, total IgE and OVA-specific IgE [54, 55].

6.8. Bo He

Bo He has been reported to have pharmacological effects, including the lowering of body temperature and relaxation of the muscles of the digestive tract. The herb is traditionally used for the treatment of high fever, mild chills, cough, thirst, and sore throat and to combat nausea, vomiting, and flatulence. Bo He significantly inhibited eosinophils, neutrophils, lymphocytes, macrophages, and total cells in BALF of OVA-challenged mice. Bo He also decreased specific IgE and Th2 cytokines, such as IL-4 and IL-5, in BALF and lung tissue. Airway inflammation and hyperreactivity in asthma are likely to involve oxidative stress to the lung, and excess production of reactive oxygen species (ROS) by immune cells may play an important role in airway injury. An increase in the generation of ROS in the airway and BALF has been noted in OVA-induced asthma models. Bo He has been shown to reduce the ROS in the BALF of asthmatic model mice, as did montelukast, which has been used widely as an anti-asthmatic drug [56].

6.9. Da Huang

Da Huang is used to cure stomach illness and as a “cathartic” to relieve severe constipation as well as a poultice for fevers and edema caused by inflammation. Emodin, one of the major compounds of Da Huang, displays a number of biological activities, such as anti-microbial, immunosuppressive, anti-inflammatory, anti-tumor, and anti-atherosclerotic activities. Moreover, emodin attenuates mast cell-dependent passive anaphylactic reactions in IgE-sensitized mice. Emodin has also been shown to reduce IgE and Th2 cytokine levels in OVA-

induced asthma mice. The inhibition of AHR by emodin may be associated with the reduction of IL-4, IL-5, and IL-13 production and eosinophilia aggregation into the lungs [57].

6.10. Jie Geng

Jie Geng is commonly used as a cough suppressant and expectorant for treatment of common colds, cough, sore throat, tonsillitis, and chest congestion. An aqueous extract of Jie Geng inhibited OVA-specific IgE levels in BALF. Inflammatory cell infiltration and mucus hypersecretion were also inhibited by Jie Geng extracts. Furthermore, Jie Geng extracts decreased the generation of ROS in BALF, as well as NF- κ B nuclear translocation in OVA-induced asthma mouse model [58]. Jie Geng is abundant in saponins, which inhibit IgE antibody-induced increases in IL-4 and TNF- α expression in RBL-2H3 cells. Saponins suppressed dinitrophenyl (DNP)-IgE antibody-induced phosphorylation of Syk, and further downstream, Changkil saponins (CKS) also inhibited the phosphorylation of Akt and MAPKs [59].




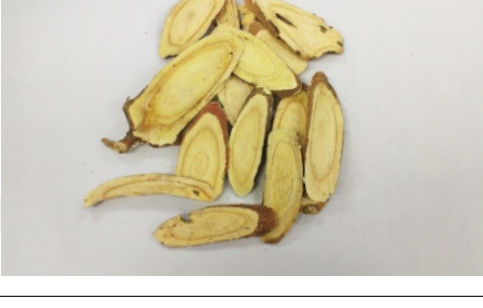

6.11. Huang Qin






Huang Qin is one of the most widely used medicinal herbs for the treatment of inflammation. Ethanol extracts of Huang Qin may effectively suppress inflammation by downregulating the expression of various inflammatory mediators (such as histamine) and reducing the production of inflammatory cytokines (such as IL-8 and TNF- α) as well as MAPK activation [60]. Skullcapflavone II is a flavonoid derived from Huang Qin (*Scutellaria baicalensis*). Skullcapflavone II significantly reduced AHR, airway eosinophilia, Th2 cytokine production, and TGF- β 1 levels in BALF and lungs in an OVA-induced asthma mouse model [61].

6.12. Yu Xing Cao

Yu Xing Cao is also used in folk medicine for diuresis and detoxification and for its anti-viral, anti-bacterial, and anti-leukemic activities. It has been used for the treatment of cough, pneumonia, bronchitis, uteritis, eczema, herpes simplex, acne, and chronic sinusitis. Ethanol extracts of Yu Xing Cao downregulate the expression of IL-4, IL-5, thymus and activation-regulated chemokine (TARC), and CCR4 receptor but do not have the same effect on IFN- γ [62].

Herbal name (Latin name)	Pictures	Possible mechanisms
Zhe Bei Mu (<i>Fritillaria thunbergii</i>)		Inhibits mast cell recruitment; decreases serum IL-6, IL-8, and TNF- α ; and inhibits MAPK pathway [43]

Herbal name (Latin name)	Pictures	Possible mechanisms
Xing Ren (<i>Semen Armeniacae Amarum</i>)		Decreases Th2 response; reduces IL-4 levels, eosinophilic inflammation, and AHR [44]
Huang Qi (<i>Astragalus membranaceus</i>)		Decreases Th2 response; increases IFN- γ level; decreases IL-4, IL-5, IL-13, and TGF- β 1 levels; reduces eosinophilic and neutrophilic inflammation; reduces AHR, collagen deposition, and mucus secretion; increases CD4 ⁺ CD25 ⁺ FoxP3 ⁺ regulatory T cells [45–47]
Qian Hu (<i>Peucedanum praeruptorum</i> Dunn)		Decreases Th2 response; increases IFN- γ and IL-10 levels; decreases IL-4, IL-5, IL-13, specific IgE, and TGF- β 1 levels; reduces AHR, eosinophilic inflammation; increases CD4 ⁺ CD25 ⁺ FoxP3 ⁺ regulatory T cells [48, 49]
Gan Cao (<i>Glycyrrhiza uralensis</i>)		Decreases Th2 response; increases IFN- γ ; decreases IL-4, IL-5, IL-13, specific IgE, and eotaxin-1 levels; reduces eosinophilic inflammation; increases CD4 ⁺ CD25 ⁺ FoxP3 ⁺ regulatory T cells [50–52]
Sang Bai Pi (<i>Cortex mori radidis</i>)		Decreases Th2 response; decreases IL-4, IL-5, IL-13, and specific IgE levels; reduces AHR, eosinophilic inflammation, and histamine release; increases CD4 ⁺ CD25 ⁺ FoxP3 ⁺ regulatory T cells [53]

Herbal name (Latin name)	Pictures	Possible mechanisms
Ban Xia (<i>Pinellia ternate</i>)		<p>Reduces IL-4, IL-5, IL-13, specific IgE, and TNF-α levels; reduces eosinophilic inflammation and mucus production [54, 55]</p>
Bo He (<i>Mentha haplocalyx</i>)		<p>Decreases Th2 responses; decreases IL-4, IL-5, and specific IgE levels; reduces eosinophilic inflammation and mucus production [56]</p>
Da Huang (<i>Rheum palmatum</i>)		<p>Decreases IL-4, IL-5, IL-13, and specific IgE levels; reduces eosinophilic inflammation [57]</p>
Jie Geng (<i>Platycodon grandiflorum</i>)		<p>Decreases serum IgE, ROS scavenger; decreases IL-4 and TNF-α; decreases Syk-dependent cascades; inhibits MAPK and Akt pathways [58, 59]</p>
Huang Qin (<i>Scutellaria baicalensis</i>)		<p>Restores serum IL-8 and TNF-α; inhibits MAPK pathways; decreases Th2 response; decreases IL-4, IL-5, IL-13, specific IgE, and TGF-β1 levels; reduces AHR and eosinophilic inflammation [60, 61]</p>

Herbal name (Latin name)	Pictures	Possible mechanisms
Yu Xing Cao (<i>Houttuynia cordata</i> Thunb.)		Decreases Th2 response; decreases IL-4, IL-5, and TARC levels [62]

Table 2. Single herbs frequently used for asthmatic children

7. Acupuncture use in children with asthma

Acupuncture is a TCM therapeutic approach involving the stimulation of points on the body by using needles. For thousands of years, acupuncture has been used to treat several conditions, including asthma. Other methods of stimulation are traditionally used, such as electroacupuncture, laser acupuncture, and transcutaneous electrical nerve stimulation. There is evidence that acupuncture can reduce eosinophils in peripheral blood and decrease secretory IgA (sIgA) and total IgA levels in the saliva and nasal secretions of patients with allergic asthma [63]. The role of eosinophil activation in asthma has been well documented. sIgA is a potent stimulus for eosinophils and represents the main trigger for eosinophil degranulation. After acupuncture treatment, the reduction of sIgA levels and the decrease in the numbers of eosinophils may be associated with the amelioration of eosinophilic inflammation in patients with allergic asthma [63]. The numbers of CD3⁺, CD4⁺, and CD8⁺ T lymphocytes in the peripheral blood were significantly increased, without significant cortisol changes, in patients with allergic asthma treated by acupuncture [63]. It has been shown that electroacupuncture is prominent in promotion of CD4⁺CD25⁺FoxP3⁺ Tregs in an OVA-induced experimental model [64]. Furthermore, acupuncture has also been shown to inhibit AHR, eosinophils, neutrophils, specific IgE, Th1 cytokines, and the NF-κB pathway in OVA-induced experimental asthma [65].

8. Acupuncture point application

Acupuncture point application therapies, combining Chinese herbal medicine and acupuncture points, have been extensively applied for the treatment of allergic rhinitis (AR) and asthma [66]. Summer acupuncture point application treatment, also known as San-Fu-Tie or San-Fu-Jiu, is one type of direct moxibustion administered in the summer through the direct application of an irritating herbal paste to acupuncture points. The basic herbal prescription of San-Fu-Tie is usually composed of Bai Jie Zi (*Semen Sinapis Albae*), Xi Xin (*Herba Asari*), Gan Sui

(*Radix Kansui*), and Yan Hu Suo (*Rhizoma Corydalis*) [66, 67]. These herbs are ground into a powder, mixed, and made into paste using stale ginger juice. The standard acupoints include Fei-shu (BL-13) and Feng-men (BL-12), the meridians named Taiyang Bladder Meridian of Foot [67]. Numerous studies have shown significant efficacy through acupoint stimulation in treatment of asthma, such as improvement of lung function, a decrease in cytokines (IL-4, IL-6, IL-8, and IL-10), and restoring the Th1/Th2 balance toward Th1 [66, 67]. Few adverse effects have been reported, except for mild skin allergy, or local swelling and blisters.

9. Mind–body exercise

Mind–body exercise, such as *tai chi*, yoga, and meditation, may benefit people with chronic diseases. *Tai Chi Chuan* (*tai chi*), a Chinese traditional mind–body exercise with low-to-moderate exercise intensity, is thought to improve cardiopulmonary function in patients with chronic disease. *Tai Chi Chuan* has been shown to improve pulmonary function of asthmatic children [68]. Yoga training was reported to improve pulmonary function tests (FEV₁ and PEF_R), quality of life, and decrease in the weekly number of asthma attacks, scores for drug treatment, and peak flow rate [69–71]. Meditation has also been shown to be a useful adjunct for treating asthma [72].

10. Further research

There is increasing evidence for the efficacy of TCM or other complementary therapies in the treatment of children with asthma, but this is still insufficient evidence for making recommendations about the value of TCM as an asthma treatment, as well-designed double-blind, randomized clinical trials are lacking.

11. Conclusion

Asthma is the leading cause of chronic illness and missed school days among childhood. In addition to standard treatment, the use of complementary therapy is increasing. TCM is a popular CAM in East Asia and throughout the world. There is increasing scientific evidence demonstrating that TCM has potential for the treatment of childhood asthma.

12. Abbreviations

AHR: airway hyperresponsiveness

ASM: airway smooth muscle

BALF: bronchoalveolar lavage fluid(s)

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GM-CSF: granulocyte-macrophage colony-stimulating factor

ICAM-1: intercellular adhesion molecule 1

ICS: inhaled corticosteroids

IFN- γ : interferon gamma

IL: interleukin

LABA: long-acting beta-adrenoceptor agonists

MAPK: mitogen-activated protein kinases

MCP: monocyte chemotactic protein

MIP: macrophage inflammatory protein

MMP: matrix metalloproteinase

NF- κ B: nuclear factor-Kappa B

OVA: ovalbumin

PEFR: peak expiratory flow rate

RANTES: regulated on activation, normal T cell expressed and secreted

SABA: short-acting beta-2-adrenoceptor agonists

TARC: thymus and activation-regulated chemokine

TCM: Traditional Chinese medicine

TGF: transforming growth factors

TLRs: Toll-like receptors

TNF: tumor necrosis factor

VCAM-1: vascular cell adhesion molecule 1

VEGF: vascular endothelial growth factor

Author details

Bei-Yu Wu¹, Chun-Ting Liu¹, Yu-Chiang Hung^{1,2} and Wen-Long Hu^{1,3,4*}

*Address all correspondence to: oolonghu@gmail.com

1 Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan

3 Kaohsiung Medical University College of Medicine, Kaohsiung, Taiwan

4 Fooyin University College of Nursing, Kaohsiung, Taiwan

References

- [1] P.L. Brand, M.J. Makela, S.J. Szeffler, T. Frischer, and D. Price. Monitoring asthma in childhood: symptoms, exacerbations and quality of life, *Eur Respir Rev*, vol. 24, no. 136, pp. 187–193, 2015.
- [2] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2015. Available from: www.ginasthma.org, accessed November 17, 2015.
- [3] C.K. Lai, R. Beasley, J. Crane, S. Foliaki, J. Shah, and S. Weiland. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC), *Thorax*, vol. 64, no. 6, pp. 476–483, 2009.
- [4] N. Pearce and J. Douwes. The global epidemiology of asthma in children, *Int J Tuberc Lung Dis*, vol. 10, no. 2, pp. 125–132, 2006.
- [5] C. Anandan, U. Nurmatov, O.C. van Schayck, and A. Sheikh. Is the prevalence of asthma declining? Systematic review of epidemiological studies, *Allergy*, vol. 65, no. 2, pp. 152–167, 2010.
- [6] M. Masoli, D. Fabian, S. Holt, and R. Beasley. The global burden of asthma: executive summary of the GINA Dissemination Committee report, *Allergy*, vol. 59, no. 5, pp. 469–478, 2004.
- [7] American Lung Association. Trends in Asthma Morbidity and Mortality, 2012. www.lung.org/assets/documents/research/asthma-trend-report.pdf, accessed November 1, 2015.
- [8] A.N. Speight, D.A. Lee, and E.N. Hey. Underdiagnosis and undertreatment of asthma in childhood, *Br Med J (Clin Res Ed)*, vol. 286, no. 6373, pp. 1253–1256, 1983.
- [9] M.L. Levy, P.H. Quanjer, R. Booker, B.G. Cooper, S. Holmes, and I. Small. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG)1 document, in association with the Association for Respiratory Technology & Physiology (ARTP)2 and Education for Health3 1

- www.gpiag.org 2 www.artp.org 3 www.educationforhealth.org.uk, *Prim Care Respir J*, vol. 18, no. 3, pp. 130–147, 2009.
- [10] P.H. Quanjer, S. Stanojevic, T.J. Cole, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, *Eur Respir J*, vol. 40, no. 6, pp. 1324–1343, 2012.
- [11] E.H. Bel. Clinical phenotypes of asthma, *Curr Opin Pulm Med*, vol. 10, no. 1, pp. 44–50, 2004.
- [12] P. Fireman. Understanding asthma pathophysiology, *Allergy Asthma Proc*, vol. 24, no. 2, pp. 79–83, 2003.
- [13] M. Frieri. Asthma concepts in the new millennium: update in asthma pathophysiology, *Allergy Asthma Proc*, vol. 26, no. 2, pp. 83–88, 2005.
- [14] L. Maddox and D.A. Schwartz. The pathophysiology of asthma, *Annu Rev Med*, vol. 53, pp. 477–498, 2002.
- [15] R. Djukanovic. Airway inflammation in asthma and its consequences: implications for treatment in children and adults, *J Allergy Clin Immunol*, vol. 109, no. 6 Suppl, pp. S539–548, 2002.
- [16] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Section 2, Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma. Available from: www.ncbi.nlm.nih.gov/books/NBK7223/.
- [17] S. Hall and D.K. Agrawal. Key mediators in the immunopathogenesis of allergic asthma, *Int Immunopharmacol*, vol. 23, no. 1, pp. 316–329, 2014.
- [18] K.D. Stone, C. Prussin, and D.D. Metcalfe. IgE, mast cells, basophils, and eosinophils, *J Allergy Clin Immunol*, vol. 125, no. 2 Suppl 2, pp. S73–80, 2010.
- [19] K. Nakagome and M. Nagata. Pathogenesis of airway inflammation in bronchial asthma, *Auris Nasus Larynx*, vol. 38, no. 5, pp. 555–563, 2011.
- [20] C. Bergeron, M.K. Tulic, and Q. Hamid. Airway remodelling in asthma: from benchside to clinical practice, *Can Respir J*, vol. 17, no. 4, pp. e85–93, 2010.
- [21] S. Al-Muhsen, J.R. Johnson, and Q. Hamid. Remodeling in asthma, *J Allergy Clin Immunol*, vol. 128, no. 3, pp. 451–462; quiz 463–454, 2011.
- [22] A. Shifren, C. Witt, C. Christie, and M. Castro. Mechanisms of remodeling in asthmatic airways, *J Allergy (Cairo)*, vol. 2012, Article ID 316049, 2012.
- [23] S. Saglani and C.M. Lloyd. Novel concepts in airway inflammation and remodelling in asthma, *Eur Respir J*, vol. 46, no. 6, pp. 1796–1804, 2015.

- [24] X.M. Li. Complementary and alternative medicine in pediatric allergic disorders, *Curr Opin Allergy Clin Immunol*, vol. 9, no. 2, pp. 161–167, 2009.
- [25] H.Y. Chen, Y.H. Lin, P.F. Thien, et al. Identifying core herbal treatments for children with asthma: implication from a chinese herbal medicine database in Taiwan, *Evid Based Complement Alternat Med*, vol. 2013, Article ID 125943, 2013.
- [26] J.D. Mark. Pediatric asthma: an integrative approach to care, *Nutr Clin Pract*, vol. 24, no. 5, pp. 578–588, 2009.
- [27] J.C. Philp, J. Maselli, L.M. Pachter, and M.D. Cabana. Complementary and alternative medicine use and adherence with pediatric asthma treatment, *Pediatrics*, vol. 129, no. 5, pp. e1148–1154, 2012.
- [28] B. Jayaprakasam, N. Yang, M.C. Wen, et al. Constituents of the anti-asthma herbal formula ASHMI(TM) synergistically inhibit IL-4 and IL-5 secretion by murine Th2 memory cells, and eotaxin by human lung fibroblasts in vitro, *J Integr Med*, vol. 11, no. 3, pp. 195–205, 2013.
- [29] P.J. Busse, B. Schofield, N. Birmingham, et al. The traditional Chinese herbal formula ASHMI inhibits allergic lung inflammation in antigen-sensitized and antigen-challenged aged mice, *Ann Allergy Asthma Immunol*, vol. 104, no. 3, pp. 236–246, 2010.
- [30] K.D. Srivastava, D. Dunkin, C. Liu, et al. Effect of Antiasthma Simplified Herbal Medicine Intervention on neutrophil predominant airway inflammation in a ragweed sensitized murine asthma model, *Ann Allergy Asthma Immunol*, vol. 112, no. 4, pp. 339–347, 2014.
- [31] K. Irifune, H. Hamada, R. Ito, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients, *Phytomedicine*, vol. 18, no. 8–9, pp. 630–633, 2011.
- [32] J. Tamaoki, A. Chiyotani, K. Takeyama, T. Kanemura, N. Sakai, and K. Konno. Potentiation of beta-adrenergic function by saiboku-to and bakumondo-to in canine bronchial smooth muscle, *Jpn J Pharmacol*, vol. 62, no. 2, pp. 155–159, 1993.
- [33] C.H. Hsu, C.M. Lu, and T.T. Chang. Efficacy and safety of modified Mai-Men-Dong-Tang for treatment of allergic asthma, *Pediatr Allergy Immunol*, vol. 16, no. 1, pp. 76–81, 2005.
- [34] T.T. Chang, C.C. Huang, and C.H. Hsu. Clinical evaluation of the Chinese herbal medicine formula STA-1 in the treatment of allergic asthma, *Phytother Res*, vol. 20, no. 5, pp. 342–347, 2006.
- [35] T.T. Chang, C.C. Huang, and C.H. Hsu. Inhibition of mite-induced immunoglobulin E synthesis, airway inflammation, and hyperreactivity by herbal medicine STA-1, *Immunopharmacol Immunotoxicol*, vol. 28, no. 4, pp. 683–695, 2006.

- [36] M. Miyagoshi, S. Amagaya, and Y. Ogihara. Antitussive effects of L-ephedrine, amygdalin, and makyokansekito (Chinese traditional medicine) using a cough model induced by sulfur dioxide gas in mice, *Planta Med*, no. 4, pp. 275–278, 1986.
- [37] S.T. Kao, T.J. Yeh, C.C. Hsieh, H.B. Shiau, F.T. Yeh, and J.G. Lin. The effects of Ma-Xing-Gan-Shi-Tang on respiratory resistance and airway leukocyte infiltration in asthmatic guinea pigs, *Immunopharmacol Immunotoxicol*, vol. 23, no. 3, pp. 445–458, 2001.
- [38] S.D. Wang, L.J. Lin, C.L. Chen, et al. Xiao-Qing-Long-Tang attenuates allergic airway inflammation and remodeling in repetitive *Dermatogoides pteronyssinus* challenged chronic asthmatic mice model, *J Ethnopharmacol*, vol. 142, no. 2, pp. 531–538, 2012.
- [39] T. Nagai, Y. Arai, M. Emori, et al. Anti-allergic activity of a Kampo (Japanese herbal) medicine “Sho-seiryu-to (Xiao-Qing-Long-Tang)” on airway inflammation in a mouse model, *Int Immunopharmacol*, vol. 4, no. 10–11, pp. 1353–1365, 2004.
- [40] S.T. Kao, C.S. Lin, C.C. Hsieh, W.T. Hsieh, and J.G. Lin. Effects of xiao-qing-long-tang (XQLT) on bronchoconstriction and airway eosinophil infiltration in ovalbumin-sensitized guinea pigs: in vivo and in vitro studies, *Allergy*, vol. 56, no. 12, pp. 1164–1171, 2001.
- [41] S.T. Kao, C.H. Chang, Y.S. Chen, S.Y. Chiang, and J.G. Lin. Effects of Ding-Chuan-Tang on bronchoconstriction and airway leucocyte infiltration in sensitized guinea pigs, *Immunopharmacol Immunotoxicol*, vol. 26, no. 1, pp. 113–124, 2004.
- [42] C.K. Chan, M.L. Kuo, J.J. Shen, L.C. See, H.H. Chang, and J.L. Huang. Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial, *Pediatr Allergy Immunol*, vol. 17, no. 5, pp. 316–322, 2006.
- [43] I.H. Cho, M.J. Lee, J.H. Kim, et al. *Fritillaria ussuriensis* extract inhibits the production of inflammatory cytokine and MAPKs in mast cells, *Biosci Biotechnol Biochem*, vol. 75, no. 8, pp. 1440–1445, 2011.
- [44] J.S. Do, J.K. Hwang, H.J. Seo, W.H. Woo, and S.Y. Nam. Antiasthmatic activity and selective inhibition of type 2 helper T cell response by aqueous extract of semen *armeniacae amarum*, *Immunopharmacol Immunotoxicol*, vol. 28, no. 2, pp. 213–225, 2006.
- [45] X. Yuan, S. Sun, S. Wang, and Y. Sun. Effects of astragaloside IV on IFN-gamma level and prolonged airway dysfunction in a murine model of chronic asthma, *Planta Med*, vol. 77, no. 4, pp. 328–333, 2011.
- [46] H.H. Shen, K. Wang, W. Li, et al. *Astragalus Membranaceus* prevents airway hyper-reactivity in mice related to Th2 response inhibition, *J Ethnopharmacol*, vol. 116, no. 2, pp. 363–369, 2008.

- [47] H. Jin, Q. Luo, Y. Zheng, et al. CD4+CD25+Foxp3+ T cells contribute to the antiasthmatic effects of *Astragalus membranaceus* extract in a rat model of asthma, *Int Immunopharmacol*, vol. 15, no. 1, pp. 42–49, 2013.
- [48] Y.Y. Xiong, J.S. Wang, F.H. Wu, J. Li, and L.Y. Kong. The effects of (±)-Praeruptorin A on airway inflammation, remodeling and transforming growth factor-beta1/Smad signaling pathway in a murine model of allergic asthma, *Int Immunopharmacol*, vol. 14, no. 4, pp. 392–400, 2012.
- [49] Y.Y. Xiong, F.H. Wu, J.S. Wang, J. Li, and L.Y. Kong. Attenuation of airway hyper-reactivity and T helper cell type 2 responses by coumarins from *Peucedanum praeruptorum* Dunn in a murine model of allergic airway inflammation, *J Ethnopharmacol*, vol. 141, no. 1, pp. 314–321, 2012.
- [50] B. Jayaprakasam, S. Doddaga, R. Wang, D. Holmes, J. Goldfarb, and X.M. Li. Licorice flavonoids inhibit eotaxin-1 secretion by human fetal lung fibroblasts in vitro, *J Agric Food Chem*, vol. 57, no. 3, pp. 820–825, 2009.
- [51] N. Yang, S. Patil, J. Zhuge, et al. Glycyrrhiza uralensis flavonoids present in anti-asthma formula, ASHMI, inhibit memory Th2 responses in vitro and in vivo, *Phytother Res*, vol. 27, no. 9, pp. 1381–1391, 2013.
- [52] C. Ma, Z. Ma, X.L. Liao, J. Liu, Q. Fu, and S. Ma. Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4(+)/CD25(+)/Foxp3+ regulatory T cells in ovalbumin-sensitized mice, *J Ethnopharmacol*, vol. 148, no. 3, pp. 755–762, 2013.
- [53] H.J. Kim, H.J. Lee, S.J. Jeong, H.J. Lee, S.H. Kim, and E.J. Park. Cortex Mori Radicis extract exerts antiasthmatic effects via enhancement of CD4(+)/CD25(+)/Foxp3(+) regulatory T cells and inhibition of Th2 cytokines in a mouse asthma model, *J Ethnopharmacol*, vol. 138, no. 1, pp. 40–46, 2011.
- [54] M.Y. Lee, I.S. Shin, W.Y. Jeon, H.S. Lim, J.H. Kim, and H. Ha. *Pinellia ternata* Breitenbach attenuates ovalbumin-induced allergic airway inflammation and mucus secretion in a murine model of asthma, *Immunopharmacol Immunotoxicol*, vol. 35, no. 3, pp. 410–418, 2013.
- [55] I.S. Ok, S.H. Kim, B.K. Kim, J.C. Lee, and Y.C. Lee. *Pinellia ternata*, *Citrus reticulata*, and their combinational prescription inhibit eosinophil infiltration and airway hyper-responsiveness by suppressing CCR3+ and Th2 cytokines production in the ovalbumin-induced asthma model, *Mediators Inflamm*, vol. 2009, Article ID 413270, 2009.
- [56] M.Y. Lee, J.A. Lee, C.S. Seo, H. Ha, N.H. Lee, and H.K. Shin. Protective effects of *Mentha haplocalyx* ethanol extract (MH) in a mouse model of allergic asthma, *Phytother Res*, vol. 25, no. 6, pp. 863–869, 2011.

- [57] X. Chu, M. Wei, X. Yang, et al. Effects of an anthraquinone derivative from *Rheum officinale* Baill, emodin, on airway responses in a murine model of asthma, *Food Chem Toxicol*, vol. 50, no. 7, pp. 2368–2375, 2012.
- [58] J.H. Choi, Y.P. Hwang, H.S. Lee, and H.G. Jeong. Inhibitory effect of *Platycodi Radix* on ovalbumin-induced airway inflammation in a murine model of asthma, *Food Chem Toxicol*, vol. 47, no. 6, pp. 1272–1279, 2009.
- [59] E.H. Han, J.H. Park, J.Y. Kim, Y.C. Chung, and H.G. Jeong. Inhibitory mechanism of saponins derived from roots of *Platycodon grandiflorum* on anaphylactic reaction and IgE-mediated allergic response in mast cells, *Food Chem Toxicol*, vol. 47, no. 6, pp. 1069–1075, 2009.
- [60] H.S. Jung, M.H. Kim, N.G. Gwak, et al. Antiallergic effects of *Scutellaria baicalensis* on inflammation in vivo and in vitro, *J Ethnopharmacol*, vol. 141, no. 1, pp. 345–349, 2012.
- [61] H.Y. Jang, K.S. Ahn, M.J. Park, O.K. Kwon, H.K. Lee, and S.R. Oh. Skullcapflavone II inhibits ovalbumin-induced airway inflammation in a mouse model of asthma, *Int Immunopharmacol*, vol. 12, no. 4, pp. 666–674, 2012.
- [62] J.S. Lee, I.S. Kim, J.H. Kim, J.S. Kim, D.H. Kim, and C.Y. Yun. Suppressive effects of *Houttuynia cordata* Thunb (Saururaceae) extract on Th2 immune response, *J Ethnopharmacol*, vol. 117, no. 1, pp. 34–40, 2008.
- [63] Y.Q. Yang, H.P. Chen, Y. Wang, L.M. Yin, Y.D. Xu, and J. Ran. Considerations for use of acupuncture as supplemental therapy for patients with allergic asthma, *Clin Rev Allergy Immunol*, vol. 44, no. 3, pp. 254–261, 2013.
- [64] Y. Kwon, S.H. Sohn, G. Lee, et al. Electroacupuncture attenuates ovalbumin-induced allergic asthma via modulating CD4(+)CD25(+) regulatory T cells, *Evid Based Complement Alternat Med*, vol. 2012, Article ID 647308, 2012.
- [65] Y. Wei, M. Dong, H. Zhang, et al. Acupuncture Attenuated Inflammation and Inhibited TH17 and Treg Activity in Experimental Asthma, *Evid Based Complement Alternat Med*, vol. 2015, Article ID 340126, 2015.
- [66] C.Y. Wen, Y.F. Liu, L. Zhou, H.X. Zhang, and S.H. Tu. A systematic and narrative review of acupuncture point application therapies in the treatment of allergic rhinitis and asthma during Dog Days, *Evid Based Complement Alternat Med*, vol. 2015, Article ID 846851, 2015.
- [67] X. Wu, J. Peng, G. Li, W. Zhang, G. Liu, and B. Liu. Efficacy evaluation of summer acupoint application treatment on asthma patients: a two-year follow-up clinical study, *J Tradit Chin Med*, vol. 35, no. 1, pp. 21–27, 2015.
- [68] Y.F. Chang, Y.H. Yang, C.C. Chen, and B.L. Chiang. Tai Chi Chuan training improves the pulmonary function of asthmatic children, *J Microbiol Immunol Infect*, vol. 41, no. 1, pp. 88–95, 2008.

- [69] A.J. Bidwell, B. Yazel, D. Davin, T.J. Fairchild, and J.A. Kanaley. Yoga training improves quality of life in women with asthma, *J Altern Complement Med*, vol. 18, no. 8, pp. 749–755, 2012.
- [70] R. Nagarathna and H.R. Nagendra. Yoga for bronchial asthma: a controlled study, *Br Med J (Clin Res Ed)*, vol. 291, no. 6502, pp. 1077–1079, 1985.
- [71] T. Saxena and M. Saxena. The effect of various breathing exercises (pranayama) in patients with bronchial asthma of mild to moderate severity, *Int J Yoga*, vol. 2, no. 1, pp. 22–25, 2009.
- [72] A.F. Wilson, R. Honsberger, J.T. Chiu, and H.S. Novey. Transcendental meditation and asthma, *Respiration*, vol. 32, no. 1, pp. 74–80, 1975.

