



Traditional Chinese Medicine (TCM) and Allergic Diseases

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Abstract

Purpose of Review This paper purports to review recent relevant publications on the efficacy of traditional Chinese medicine in treating allergic diseases, to illustrate the pertinent mechanisms of action of TCM, and to explore the possible role of TCM in the management of allergic diseases in the foreseeable future. As TCM embodies multiple treatment modalities, only the most popular two, namely CHM (Chinese herbal medicine) and acupuncture, were discussed. Publications, especially reviews involving randomized controlled trials (RCTs) on the use of TCM on allergic diseases, published up to June 2019 were reviewed and analyzed. Papers reporting the mechanisms of action of TCM in allergic diseases were also included. Other publications in Chinese were also discussed.

Recent Findings A startling escalation in the incidence of allergic diseases in the last several decades has posed tremendous social and financial burdens on the community. Failing to locate a cure for these chronic diseases, patients have resorted to using alternative medications of which traditional Chinese medicine (TCM) is a popular one. Thus CHM has been extensively employed for treating allergic diseases. Some investigations have been conducted to ascertain the therapeutic efficacy of CHM for allergic diseases.

Summary Although CHM has been widely deployed for treating allergic diseases, it appears from the published data that there is a dearth of conclusive evidence to establish the effectiveness of CHM for allergic diseases. It is recommended that more large-scale RCTs with prolonged durations be carried out to corroborate the efficacy of CHM for allergic diseases. On the other hand, there is ample evidence indicating that acupuncture is useful when administered alone in allergic rhinitis and asthma or when applied as an adjunct to conventional western therapy. Evidence of its utility in atopic eczema and urticaria is not definitive. It is recommended that acupuncture be integrated into the therapy of allergic rhinitis and asthma, and that CHM be used as an adjunct in the treatment of allergic diseases on an individual basis.

Keywords Acupuncture · Allergic rhinitis · Asthma · Chinese herbal medicine · Eczema · Food allergy · Traditional Chinese medicine · Urticaria

Introduction

There is an alarming surge in the prevalence of allergic diseases over the past few decades due to hygiene hypothesis [1], environmental changes, and epigenetic modifications [2]. Allergic diseases constitute a group of chronic heterogeneous diseases, some of which, such as asthma, allergic rhinitis, atopic eczema, and anaphylaxis, ensue in mortality or debilitating morbidity. Treatments for these patients are

symptomatic, and control of symptoms has become the main goal of the treatments. So far, there is no cure available for these patients. Indeed, over the past few decades, advances have been made in the understanding of immunological responses of patients to allergens and thereafter, many exquisite but costly drugs that target specific immunoglobulins and cytokines which elicit these cascades of allergic reactions and symptoms have been developed. Yet, disease-modifying agents that can cure allergic diseases have not emerged. Consequently, many patients remain disconcerted with the side effects of conventional western treatment and seek alternative and affordable treatments [3, 4]. The survey conducted by the American Academy of Allergy, Asthma and Immunology on its members in 2016 revealed that as many as 67.6% of the patients had used herbal medicines, and TCM was one of them [3, 4].

In China, Taiwan, Hong Kong, Korea, and Japan, TCM forms part of the mainstream healthcare. A recent study

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performed in Taiwan showed that up to 30–50% of allergic patients had been prescribed TCM for their diseases and that their hospitalization rate was lower than their counterparts treated with western conventional medicine alone [5].

This review aims to examine recent publications reviewing the efficacy of traditional Chinese medicine (TCM) on allergic diseases and the associated mechanisms, and also to explore the possible role of TCM in the management of allergic diseases in the near future.

Introduction to TCM

Traditional Chinese medicine is an effective medical therapy system with a long history of a few thousand years [6]. It is one of the earliest models of medical treatment in the world history (others include Egyptian and Babylonian) that is still being practiced extensively today. In China, Korea, Japan, Taiwan, and Hong Kong, TCM is part of the prevailing medical system used daily to treat and prevent diseases [7].

Unlike modern evidence-based western medicine, TCM is an experience-based medicine with its own distinctive theory in defining the etiology of diseases, diagnosis of disease syndromes, prevention, and treatments.

According to TCM, every human represents a small universe that lives and interacts with the vast external universe. Nonetheless, men and nature are one and not separate. Humans living in dissimilar environments and social systems are considered to be affected by the disparate climates, foods, geography, and social relations and thus must be treated differently. Disease syndromes occur when the balanced state of the human body is perturbed, either due to endogenous factors (Fig. 1) or external evils (Fig. 2). Treatment is aimed at restoring homeostatic balance to the human body [6].

A human body is considered to consist of different parts. There are altogether five organs, six hollow organs, five senses, nine external openings, five body parts, four limbs, and a meridian system that links all of them together. Chi, blood, and essence are the elements that enable the human body to function as a unique entity.

The organ systems are governed by the rule of the five paths (Fig. 3) and by yin yang. Deficiency or excess in any of the organs will not only exert an impact on other organs but will also affect other body parts giving rise to various symptoms and problems [6, 8, 9, 10, 11].

TCM is a type of personalized medicine. Each patient is evaluated on the basis of family history as well as personal history, physical signs such as facial complexion, odor, morphological conditions of the tongue, and characteristics of the pulse, and is then assigned a disease syndrome. Once his syndrome is diagnosed, he will be prescribed appropriate treatments which may encompass herbal therapy, topical treatment, bone setting, acupuncture/acupressure, moxibustion, physical exercises, chi gong, diet management, or a combination of them. Treatment will be modified daily or weekly until homeostatic balance is reinstituted and the patient is considered to have resumed a normal balanced state [6].

Herbal Therapy: Chinese Herbal Medicine

Herbal therapy is the mainstay treatment modality in TCM. Most herbal concoctions are combinations of a few herbs for rectifying the different imbalances in the patient's internal milieu. It is formulated with the underlying principle of emperor, minister, assistant, and messenger herbs. The main imbalance is normalized by the emperor herb with the remainder of the herbs in the herbal formula bolstering the main herb to

Fig. 1 Seven emotions



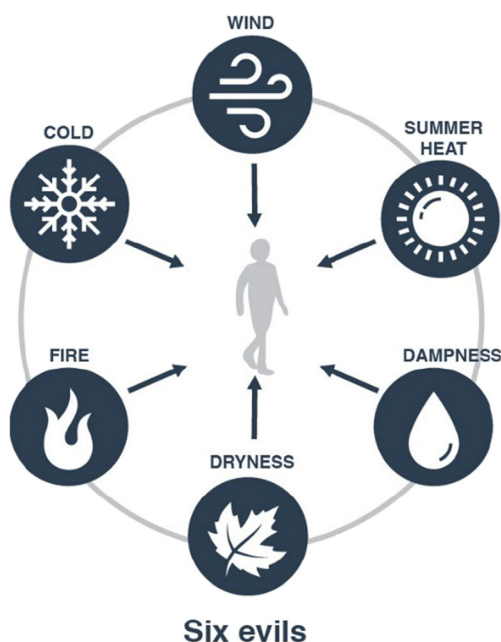


Fig. 2 Six evils

fulfill the main therapeutic purpose. Most concoctions are often comprised of four or more herbs but the total number could vary enormously, from merely one to approximately a hundred [6].

Modern CHM in China is regulated. The Chinese Pharmacopoeia 2015 [12] lists more than six hundred types of herbs, defining their taxonomy, functions, recommended dosages, and standards. GMP factories that vend raw materials

in their entirety or in slices are obligated to use herbs that meet with these standards. Pharmaceutical factories that manufacture CHM drugs have to employ standardized raw materials. The State Food and Drug Administration (SFDA) registers almost one thousand five hundred herbal drugs, each with its own specific indications, standards, and registered manufacturing process. Hospitals that rely on herbal concoctions must utilize either standardized herbs or registered drugs that meet with government regulations as stipulated in the Pharmacopoeia.

Despite relentless efforts from the authority and the industry, standardization of herbs and herbal formulas is less than desirable and major work remains to be accomplished in the road ahead.

Acupuncture

Acupuncture is another popular means of TCM treatment modality. It has been broadly practiced in Asia and in the west and has proven to be safe and devoid of overt untoward effects [13]. According to the TCM theory [6], the human body comprises twelve main or primary meridians which are bilateral (lung, heart, large intestine, small intestine, liver, spleen, bladder, gall bladder, triple energizer, kidney, stomach, and pericardium) and eight special or extraordinary meridians (governing, conception, belt, thrusting, yin link, yang link, yin heel, and yang heel). Although meridians have never been physically identified in live or deceased human bodies, their functional presence can hardly be disputed. All meridians have not only been mapped very precisely according to different anatomical landmarks, but also by palpation and based on patients' feedback. The meridians interconnect internal organ systems, blood, chi, and essence and facilitate their interactions with the external universe.

In the human body, there are totally over four hundred acupoints, each with its own specific qualities and functions. Often, stimulating different acupoints based on the diagnosed syndrome is conducive to the patient's regain of the balanced state. Acupuncture is often performed with needles manually or via a small electric current. Contemporarily, needles are sterilized disposable steel needles made in China or in Germany. Practitioners can opt to use thumbs and fingers instead of needles to carry out acupressure, or deploy warm sticks to administer moxibustion, or vacuum cups to conduct cupping, for similar effects. Laser acupuncture guns, extensively studied in Russia and China, are becoming popular as they are less intrusive than steel needles. Standardization of wavelength, depth, and energy is necessary for further refinement of laser acupuncture [14]. Acupoints in the ears and in the feet which correspond to counterparts in the main meridians are often utilized, albeit more for health than for treatment.



Fig. 3 The rule of 5 paths

Other Treatment Modalities

Many other treatment modalities of TCM like bone setting are very efficacious but are, however, seldom used in the treatment of allergic diseases.

TCM and Allergic Diseases

In the viewpoint of the TCM theory, most allergic diseases are manifestations of deficiency syndromes. Most patients are deficient in spleen qi, lung qi, or kidney qi [15] while others, especially those suffering from asthma, may have excessive wind in the liver with obstruction of qi as well [16]. Treatment consists of replenishing deficiencies, removing excesses, and unblocking Qi. This may be achieved with either one of the aforementioned modalities or a combination of different treatment modalities.

Mechanisms of CHM (Herbal Concoctions)

The results of various studies revealed that some herbs and herbal concoctions were able to downregulate many allergic reactions [17]. In a review on the mechanisms of CHM for treatment of asthma, it was uncovered that CHM exerts multifarious actions (Fig. 4). It can directly thwart the activation and migration of inflammatory cells and eosinophils, hamper the release of different cytokines from epithelial cells, regulate

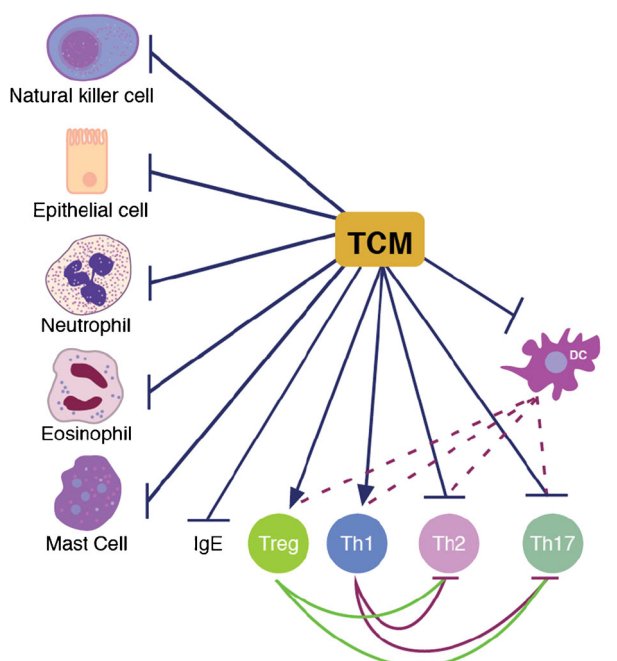
the balance of Th1/Th2 responses, downregulate degranulation of mast cells [18•], retard NK cell infiltration into the nasal epithelium [19], accelerate apoptosis of eosinophils [20], and suppress allergic hyper-reactivity through inducing regulatory T cells or attenuating the function of dendritic cells (DCs) [21, 22].

Evidence has emerged to substantiate the action of CHM in regulating the balance of Th1/Th2 by enhancement of Th1 responses and inhibition of Th2 responses in an asthmatic environment [23, 24, 25, 26, 27•]. Several Chinese herbal formulas, including ASHMI, Bu-Shen-Yi-Qi-Tang, and Sheng-Fei-Yu-Chuan-Tang, not only attenuated Th2 responses but also mitigated the expression of IL-17 [27•, 28, 29•]. Others, like SST (Sho-seiryu-to), a common concoction that dispels wind and cold in asthma and allergic rhinitis, curtailed IL-4, IL-5, IL-13, IgG1, and IgE levels but augmented IFN-gamma, IL-2, and IL-12 levels [30•]; Bu-zhong-yi-qi-tang, which was used to treat yang-deficient asthma as well as allergic rhinitis, alleviated eosinophilia, IL-4, and IL-5 production in the airway, while elevating IFN-gamma, suppressing IgE and IgG1, and augmenting IgG2 in the serum [31]. Liu-Wei-Di-Huang Wan, a traditional Chinese herbal formula for the treatment of yin-deficient 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-gamma) in peripheral blood [32]. ASHMI, a formula which had been tested in a phase I clinical trial in the USA, enhanced Th1 responses as indicated by the increase of IFN-gamma, IL-12, and IgG2a levels, but suppressed Th2 responses as seen in the decline of IL-4, IL-5, and IL-13 concentrations. It also blocked the early IgE airway response, reduced histamine and leukotriene release, modulated airway smooth muscle contraction, and probably arrested airway remodeling [29•, 33, 34].

The quest to ascertain the active herb and the active ingredient of each concoction has been launched. For instance, several ingredients from different herbs, including coumarins [35], glycyrrhizic acid [36], and curcumin, upregulated the expression of Foxp3 and the percentage of CD4tCD25t Foxp3t Tregs in asthma animal models [37]. *Cordeceps*, a CHM herb commonly prescribed for asthma, when administered in an investigation to a group of asthmatic patients, significantly depressed serum titers of IgE, SICAMI, MMP-9, and IL-4, to a greater extent than those observed in the control group, with a potential in arresting airway remodeling [33]. Water extracts of *Astragalus membranaceus* and *Morus alba* were noted in two studies to increase CD4tCD25t, Foxp3t Tregs population, and enhance Foxp3t mRNA expression in asthmatic animal models [38, 39].

From the formula ASHMI, which is used to treat asthma, the ingredients of two herbs were identified. Glycyrrhizic acid [36], the main bioactive ingredient of *Glycyrrhiza glabra* which is one of the herbs in the formula, reduced eosinophilia in lung and airway tissues, suppressed the levels of IL-4, IL-5,

Mechanisms of TCM on the Allergic Cascade



Balance Th1/Th2 responses, downregulate Th17 related cytokines, downregulate degranulation of mast cells, downregulate IgE production, block antigen binding, inhibit the release of biologically active substance, retard NK cells migration, accelerate eosinophils apoptosis, reduce neutrophil count, antagonize the role of allergic media.

Fig. 4 Mechanism of TCM on allergic cascade [17]

and IL-13 in the BALF, and heightened IFN-gamma levels in an ovalbumin-induced mouse model [36]. *Ganoderma*, especially ganoderic acid, one of its notable active ingredients, has been shown to upregulate production of IL-10, IL-12, and IFN-gamma and downregulate production of TNF-alpha and IL-6 [17]. Nonetheless, exactly how CHM works on the immune system has not been fully elucidated.

Mechanisms of Acupuncture

Stimulation of acupoints located at lines of meridians that correspond to the flow of energy through the body presumably elicits anti-inflammatory effects via reflexive central inhibition of the innate immune system.

In the treatment of allergic diseases, downregulation of basophil counts was detected in patients suffering from atopic eczema [40]. A pronounced reduction in the neutrophil count was achieved after manual acupuncture at BL13+ST36 ($P = 0.005$) while the eosinophil count was lowered after manual acupuncture, both at BL13 ($P = 0.007$) and BL13+ST36 ($P = 0.006$). Reduction in the bronchiolar epithelial and smooth muscle thickness and the number of goblet cells was accomplished following manual acupuncture at BL13 ($P = 0.001$, $P = 0.001$, and $P = 0.002$, respectively) and BL13+ST36 ($P = 0.001$, $P = 0.002$, and $P = 0.001$, respectively) [41].

Stimulating Feishu acupoint undermined acetylcholine synthesis and release and downregulated inflammatory infiltration of lung tissue [42]. After stimulating acupoints including GV14, BL12, and BL13, on alternate days for 5 weeks, the concentrations of sIgA and total IgA in the saliva ($P < 0.01$, $P < 0.02$) and nasal secretions ($P < 0.02$, $P < 0.02$) plummeted in patients with allergic asthma. The levels of total IgE in sera ($P < 0.001$), the counts of IL-2R + T lymphocytes ($P < 0.001$), and the absolute and differential numbers of eosinophils ($P < 0.01$, $P < 0.01$) in the peripheral blood of these patients also dropped appreciably [43•].

Acupuncture has been shown to balance the immune response in allergic diseases [44] but its total effects have not yet been fully decoded.

Review of CHM and Allergic Diseases

CHM and Allergic Rhinitis

A recent meta-analysis on the use of CHM for treatment of allergic rhinitis involving eleven RCT studies and more than 300 patients arrived at the conclusion that CHM may significantly improve the quality of life of patients. Significant improvement in sneezing symptom and total nasal symptoms scores were not observed following CHM treatment. Nevertheless, the improvement in symptom of itchy nose just missed statistically significant difference, probably due to a small sample size [45].

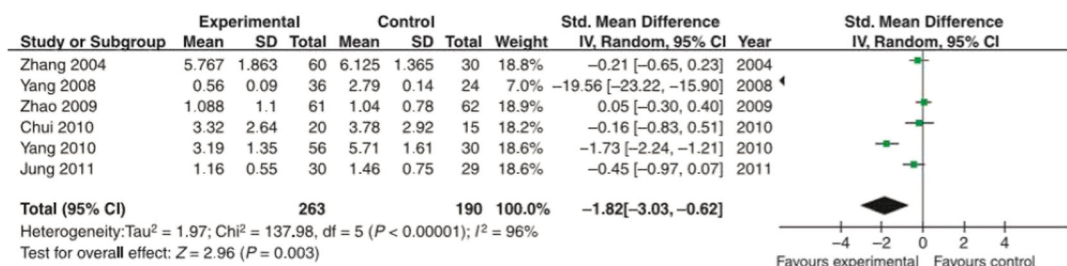
Another meta-analysis of papers published in the Cochrane Library, China National Knowledge Infrastructure, EMBASE, MEDLINE, and Wanfang database from 1999 to 2011, involving 533 patients with persistent allergic rhinitis in seven RCTs, also led to the conclusion that CHM reduced total nasal symptom scores. However, the decline in reducing the total serum IgE level was not statistically significant (Table 1) [46].

A different review of 19 studies evaluating the efficacy of CHM in treatment of children with allergic rhinitis disclosed that CHM was effective in reducing symptoms score, recurrence rates, and was superior to controls in efficacy rate [47].

Some traditional herbal concoctions for treatment of allergic rhinitis have been extensively evaluated. One such concoction was Yu Ping Fung San, a traditional formula consisting of Huang Qi, Fang Feng, and Bai Shu, which was originally used to stave off pathogens by strengthening wei qi. In one review, out of 22 RCTs, YPFs was found to be comparable with histamine receptor blockers in efficacy and to potentiate their effects if administered for a duration exceeding 3 weeks [48].

Xin Yi San was another formula found to be potent in reducing nasal congestion, sneezing, and rhinorrhea, decreasing nasal airway resistance, and increasing the nostril area compared with the placebo in a randomized double-blind placebo control trial. It has also suppressed serum titers of IgE and house dust mite-specific IgE [49, 50]. A TCM nasal drop

Table 1 Forest plot showing SMD (with 95% CI) for total nasal symptom scores of eligible studies comparing CHM with control in a random effect model [46]



preparation ARND improved nasal symptoms and heightened the quality of life of allergic rhinitis patients compared with controls [51].

CHM and Asthma

CHM brought about lowering of IgE, IL-6 levels in subjects afflicted with allergic rhinitis, and decrement of levels of IgE, IL-6, IL-10, and Th17 (IL-17a, IL-17b, and IL-22) related cytokines in asthmatic patients [44].

A meta-analysis of 20 RCTs evaluating the safety and efficacy of addition of CHM for treating CVA (cough variant asthma) in children reported a higher total effective rate, with improvements in cough, and asthma, and a lower recurrence rate among the study group. Lung function and cough sensitivity LgC5 improved, while total immunoglobulin E and the eosinophil count fell. There were no major untoward reactions to the treatment [52].

Few Cochrane reviews on TCM treatment of asthma were available and only isolated studies were reported [21,53,54]. The most extensively studied formula was Ashmi [55], which has been approved by the FDA for clinical trial and was shown to produce effects comparable to steroids in improving forced expiratory volume in 1 s (FEV1) and peak expiratory flow values, as well as reducing symptoms and use of inhaled beta 2-agonists in patients with moderate-to-severe asthma in two randomized controlled clinical trials. It was shown that the mechanism of ASHMI involved blocking the IgE-mediated early phase airway response, airway hyper-reactivity, pulmonary inflammation, and airway remodeling [56, 57•, 58].

Patients treated with the formula STA-1 demonstrated better symptom scores, augmented lung function (FEV1), reduced need for systemic glucocorticoid treatment, and diminished total and dust mite-specific IgE levels compared with the baseline [59].

A review of 9 studies involving 2453 patients treated with Mai Men Dong Tang, a common concoction used in the treatment of asthma, failed to provide conclusive evidence that it improved cough [60]. On the other hand, atopic children treated in a RCT for over 4 months with a Mai Men Dong Tang exhibited amelioration in FEV1, clinical symptoms, and downregulation of serum IgE and serum specific IgE for house dust mites [61].

In a review examining the efficacy of CHM in conjunction with conventional western medicine in treating asthmatic patients with GERD [61], it was shown in six RCTs which met the inclusion criteria, additional CHM significantly lowered the GER score and improved asthmatic symptoms [62].

In another meta-analysis comprising 360 patients on the action of CHM in combination with western medicine, it was reported that integrating both types of therapy

significantly improved symptoms, lung function tests, and curtailed the need for conventional western medication [21].

Formulas such as Ding Chuan Tang [63], Liu-Wei-Di-Huang-Wan [32], Shen-Ling-Bia-Shu-San, and Jai-Wei-Si-Jun-Zi-Tang have all been investigated and positive results were reported. However, as the trials were not well blinded, further well-designed studies are necessitated to verify their efficacy [53].

Observational studies done in China on more than 360 patients revealed that adding CHM to conventional therapy improved symptoms and minimized drug use [64].

CHM and Eczema

“Si Wan Feng” is the comparable term used in Chinese medicine for atopic eczema [65•]. It made its first appearance in classical Chinese medicine literature in A.D. 1665 and was synonymous with any pruritic skin condition characterized by the involvement of fossae of the legs and ankles which relapsed regularly.

According to traditional Chinese medicine theory, atopic eczema is often caused by hereditary predisposition, spleen, stomach and/or lung deficiency, excessive heat of the heart, blood deficiency with wind-dryness, and an imbalance among these organ systems [66], some of which may be comparable with etiological factors in the viewpoint of western medicine.

In a Cochrane review of 28 RCT studies involving over 2000 patients which examined the efficacy of CHM on atopic eczema, it was found that total effective rate, itch, quality of life, and overall severity score were improved in the study groups. The authors could not reach the conclusion that CHM was effective for atopic eczema due to the poor quality of the evidence [65•].

Another review conducted by the same group, which was completed in 2016 and published in 2017, reviewed evidence of TCM for the treatment of atopic eczema based on three systematic reviews and two RCTs from 2013 to June 2016 [67]. It shared the same view that although CHM may improve the quality of life of patients with moderate atopic eczema, evidence that TCM reduced the severity of atopic eczema was inconclusive.

One different review covering ten studies of topical TCM on atopic eczema involving over 1000 patients [68] also fell short of presenting conclusive proof that topical TCM was superior to corticosteroids owing to heterogeneity in the designs of the studies, inclusion and exclusion criteria, outcomes, and blinding. The commonest herbs used were those with anti-inflammatory effects, encompassing Huangbai (*Cortex phellodendri*), Huanglian (*Rhizoma coptidis*), Shechuangzi (*Fructus cnidii*), Zicao (*Radix arnebiae*), and Bingpian (*Borneolum syntheticum*). Nevertheless, improvements in the clinical symptoms and quality of life were discerned in some patients compared with controls.

Other authors looked at combination therapy [69•]. Reviewing seven studies revealed that TCM acting in concert with conventional western medical therapy, compared with western medicine alone, produced a significant attenuation in the disease severity score ($P < 0.00001$). In comparison with placebo, CHM revealed significant improvement in erythema ($P < 0.00001$), surface damage ($P < 0.0001$), pruritus ($P < 0.0001$), sleep scores ($P < 0.00001$), and quality of life ($P < 0.05$). CHM also significantly reduced the need for concurrent pharmacotherapy ($P < 0.00001$). However, the quality of these studies leaves much to be desired and the results have to be viewed with some caution.

A few other formulas studied included Xiao Feng San, one of the most commonly prescribed concoctions [70], and Pei Tu Qing Xin Tang, both of which improved clinical symptoms and quality of life compared with controls, and also Pentaherbs which improved quality of life and was cortisone saving [71, 72].

No severe adverse side effects were encountered in all these reviews.

CHM Formula for Food Allergy

There are few equivalent Chinese syndromes with food allergy and thus few historic CHM for such disease [106].

Only a few reviews on clinical RCT involving TCM for food allergy were found in the literature [7, 73, 74, 75, 76]. However, in the past decade, FDA approved a TCM formula, designated as Food Allergy Herbal Formula-2 (FAHF-2), for clinical studies on food allergy [7, 73, 74, 75, 76, 77].

A multicenter, randomized, double-blind, placebo-controlled phase II clinical trial indicated that FAHF-2 is a safe herbal medication for subjects with food allergy. Nonetheless, the efficacy for improving tolerance to food allergens was not demonstrated at the dose and duration used. This study was probably limited by poor drug adherence [74, 75, 76]. The mechanism of action of FAHF-2 involves an immunomodulatory effect on T cells, and suppression of basophil activation. Its refined forms, B-FAHF-2 and E-B-FAHF-2, are now being tested as adjuncts to oral immunotherapy of three food allergies [78]. Researchers engaged in this trial are striving to identify compounds from the herbs that could inhibit food allergies in a much smaller dose.

The traditional Japanese herbal medicine kakkonto, which consists of five herbs, suppressed allergic diarrhea and decreased the number of mast cells in murine intestinal mucosa [79, 80]. This formula is also being tested as an adjunct to oral immunotherapy in a mouse model [81].

CHM and Urticaria

In Taiwan, the commonest herbal concoction used is Xia Feng powder (XFP) which was prescribed in 38,000 among 98,000

prescriptions. The anti-allergy effect of XFP [82] is displayed via inhibiting globulin E (IgE) release from mast cells derived from mouse bone marrow cells. A RCT study conducted in Taiwan [83] using a combination of XFP and Qing-Shang-Fang-Feng-Tang (QSFFT) successfully treated 56 patients for 6 months with symptoms improved and no recurrence.

In Korea, an investigation on the efficacy of Gwakhyangjeonggisang (GJS) [84] in chronic urticaria manifested a significant diminution in urticaria activity scores (UAS) after 6 months of treatment compared with controls. Nearly half of the patients reported that their symptoms were completely eliminated. In Japan, administration of Yokukansan (YKS, Yi-Gan San in Chinese) [85] was found to be a suitable complementary therapy for intractable chronic urticaria.

In mainland China, a study comparing the clinical efficacy of a 8-week therapy using western medicine (cetirizine 10 mg/day) on chronic urticaria with treatment employing a herbal decoction, consisting of Radix Astragali Mongolici, Fructus Jujubae, Rhizoma Dioscoreae Oppositae, Poria, Radix Angelicae Sinensis, and prepared Radix Polygoli Multiflori, disclosed that cetirizine performed better in the early stage whereas this herbal decoction yielded better results at a later stage and the efficacy of the herbal concoction seemed to improve as time went on [86].

Review of Acupuncture and Allergic Diseases

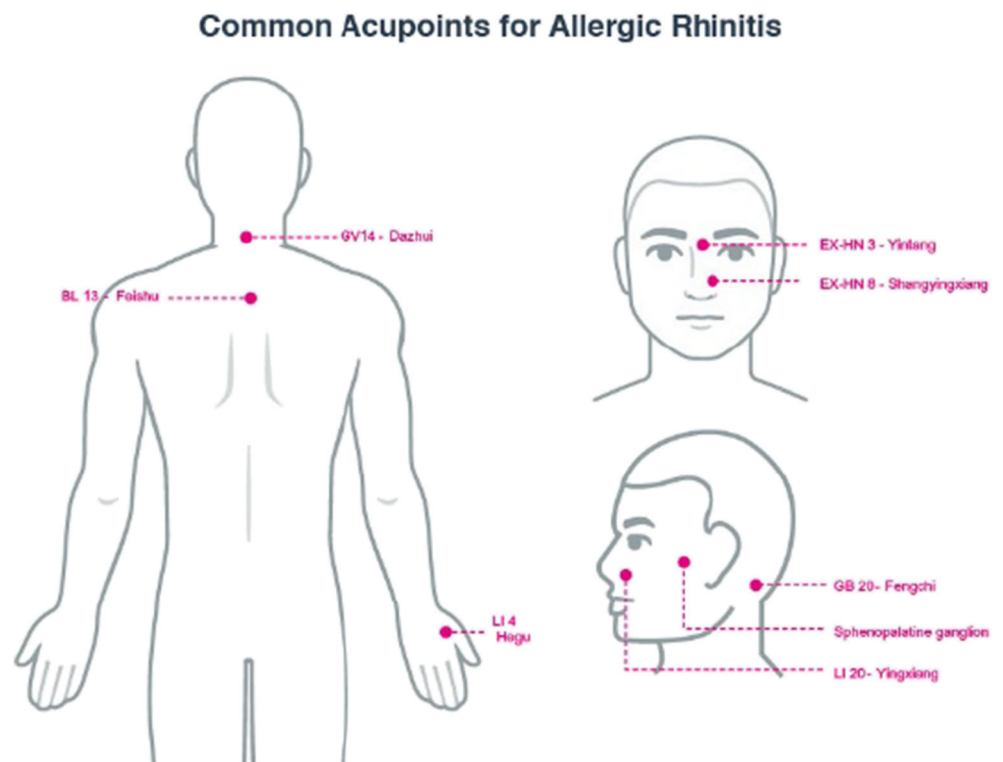
Acupuncture and Allergic Rhinitis

The common acupoints for allergic rhinitis are shown in Fig. 5. Mounting evidence has emerged to show that acupuncture is effective in the treatment of allergic rhinitis [87, 88, 89, 90, 91]. A meta-analysis of over 2000 patients in thirteen trials demonstrated that acupuncture, compared with controls, was potent in reducing symptom scores, medication scores, and serum IgE level as well as elevating the quality of life assessed using the SF-36 form [91–92].

In a study using acupuncture for seasonal rhinitis or hay fever, it was found that in the patients involved, the number of days requiring the use of histamine was significantly reduced, while the quality of life and SAR symptoms were improved [87].

In one of the reviews written in 2015 involving more than 1200 patients regarding the effect of acupuncture on allergic rhinitis, the authors remarked in the conclusion that there was high-quality evidence on the efficacy of acupuncture in treating symptoms of both seasonal and perennial allergic rhinitis as well as improving the quality of life in the patients but also noted the cost-effectiveness of acupuncture over other forms of treatment [88].

Fig. 5 Common acupoints for allergic rhinitis



The same acupoints, named Dazhui (GV 14), Dingchuan (EX-B1), Feishu (BL 13), Pishu (BL 20), Mingmen (GV 4),

Gaohuang (BL 43), Shenshu (BL 23), and Qihai (CV 6), were used in the four groups (Fig. 6).

Common Acupoints for Asthma

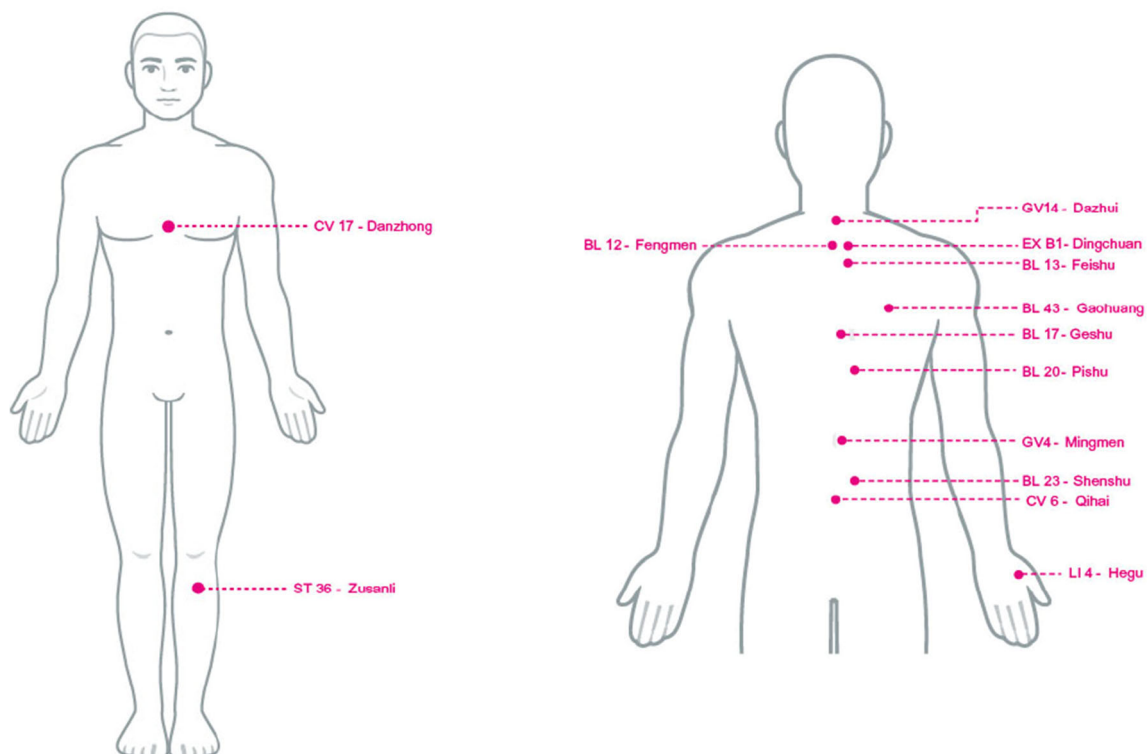


Fig. 6 Common acupoints for asthma

Taw et al. [93] summarized six randomized controlled trials on acupuncture for allergic rhinitis [93]. There were three trials on patients with perennial allergic rhinitis involving 24, 81, and 238 patients respectively; two trials on patients with seasonal allergic rhinitis involving 384 and 422 patients respectively; and one trial on 66 patients with allergic rhinitis. True acupuncture according to traditional Chinese medicine theory (12 treatments over 4, 6, 8, and 12 weeks/20 days depending on the study) was administered and the efficacy was compared with waitlist, sham acupuncture, rescue medication (cetirizine/loratadine/desloratadine), or sham acupuncture plus rescue medication. The primary (secondary) outcomes examined were changes in subjective symptoms from baseline at 2, 3, 4, 6, and 16 weeks (posttreatment) which, depending on the study, included some of the following: Total Nasal Symptom Score, Total Nonnasal Symptom Score, Rhinitis Quality of Life Questionnaire, Visual Analog Scale, Short Form 36, quality-adjusted life years, incremental cost-effectiveness ratio, total and specific immunoglobulin E levels, interleukin-10, interleukin-4, and interferon- γ levels. The results disclosed an improvement of 0.5 to 2.49 points and 18% to 80% over sham acupuncture or rescue medication achieved by true acupuncture.

In another systematic review involving meta-analysis of 11 studies and over one thousand patients, the effect of acupuncture through stimulating sphenopalatine ganglion acupoint alone was compared with controls that received treatments other than acupuncture. The results showed that there were significant improvements in symptoms and quality of life in the acupunctured group [94].

A review on using catgut implantation at acupoints involving 285 patients could not conclusively demonstrate the positive effect of this form of acupuncture [95].

A retrospective study comparing patients undergoing immunotherapy as well as add-on acupuncture with a control group without add-on therapy disclosed that the group with add-on acupuncture had significant improvements in nasal symptoms and quality of life [96].

Evidence suggests that acupuncture may be cost-effective in terms of money spent in return for an improved quality of life [97]. A review covering 981 patients in Europe for the cost-effectiveness of acupuncture demonstrated that acupuncture was beneficial at a relatively low cost and could play an increasingly important role as an evidence-based therapy in the form of an adjunct for relief of allergic rhinitis.

Acupuncture and Asthma

Reviews of the consequence of acupuncture treatment in asthmatic patients indicated abated airway resistance and symptomatic relief in some studies.

In a review [98] of the action of acupuncture on asthma including eight studies involving 1083 patients, the

aggregated results acquired indicated that acupoint application improved forced expiratory volume in 1 s (FEV1) (SMD, 0.32; 95% CI 0.04–0.60; $P=0.03$), FEV1/forced vital capacity (SMD, 0.89; 95% CI 0.70–1.09; $P<0.00001$), interleukin (SMD, -0.26 ; 95% CI -0.50 to -0.01 ; $P=0.04$), and immunoglobulin E (SMD, -0.49 ; 95% CI -0.83 to -0.16 ; $P=0.004$) in patients with asthma, but not eosinophilic cation protein levels (SMD, -0.58 ; 95% CI -1.42 to 0.26 ; $P=0.18$). The authors concluded that acupoint application may be a valid complementary and alternative therapy for asthma in adults. It contributes especially to improving pulmonary function and diminishing the levels of interleukin and immunoglobulin E.

A different review [99] of 32 articles on seven studies covering 410 pediatric patients was unable to furnish conclusive evidence regarding the effectiveness of acupuncture for treating childhood asthma. However, there was suggestive evidence that peak expiratory flow (PEF) and FEV1 and FVC were significantly improved in some studies (Table 2). Furthermore, there have been reports on the successful use of low-dose laser acupuncture on ameliorating symptoms in asthmatic children [14].

Another review of nine studies which examined the effect of acupuncture on complementing conventional western therapy reported that the two types of therapy acting in concert elevated the symptom response rate (OR = 7.87, 95% CI = [4.13, 14.99], $P<0.00001$) and significantly undermined interleukin-6 (IL-6) levels (MD = -11.42 ; 95% CI = [-15.28 , -7.56], $P<0.00001$) without affecting results of lung function tests (Table 3) [100].

Acupoint Herbal Patching

Six studies entailing 657 patients were identified. Tian jiu therapy was more effective than control intervention (odds ratio [OR], 3.51; 95% confidence interval [CI], 2.05–6.00; $P<0.00001$; $I(2)=18\%$). The treatment group exhibited a more conspicuous decline in IgE level (standard mean difference [SMD], -1.40 ; 95% CI, -2.18 to -0.63 ; $P=0.0004$; $I(2)=85\%$) and eosinophil (Eos) count (SMD, -4.26 ; 95% CI, -6.28 to -2.23 ; $P<0.00001$; $I(2)=91\%$) compared with the control group [101, 102].

Twenty studies embracing over 2438 patients have been reviewed to assess its effect on allergic rhinitis. It was noted that adding acute herbal patching to conventional therapy significantly lowered the recurrence rate compared with western medicine alone and ameliorated the quality of life in the subsequent 3 months [102]. Another review on San Fu Tie and San Fu Jiu also reported advantages in limiting the recurrence of asthmatic attacks [103].

Table 2 Outcomes for medication use, symptoms, and quality of life (data reported for three of seven studies). For the references cited in this table, readers are referred to the reference list found in the original paper containing this table [99]

Author (year)	Intervention	Medication use		Symptoms				Quality of life (mean $\pm$ SD)				Scale used
		Before	After	Follow-up	Before	After	Follow-up	Before	After	Follow-up	Scale used	
Karlson and Bennicke (2013) [15]	Acupuncture	β -Mimetics (puffs/24 h) 2.2 $\pm$ 2.1	β -mimetics (puffs/24 h) 0.7 $\pm$ 1.1	β -mimetics (puffs/24 h) 0.4 $\pm$ 1.0	*Significant reduction in symptoms between groups at 3 months; however, no significant difference at 12 months			-	-	-	-	-
		IHS (μ g/day) 537 $\pm$ 260	IHS (μ g/day) 126 $\pm$ 209*									-
	No acupuncture	β -Mimetics (puffs/24 h) 2.8 $\pm$ 4.2	β -Mimetics (puffs/24 h) 0.9 $\pm$ 1.3	β -Mimetics (puffs/24 h) 0.5 $\pm$ 1.0				-	-	-	-	-
		IHS (μ g/day) 477 $\pm$ 271	IHS (μ g/day) 342 $\pm$ 287									-
Scheewe et al. (2011) [16]	Acupuncture	Controller (frequency/day) 1 use: 23	Controller (frequency/day) 1 use: 9	Controller (frequency/day) 1 use: 4	(Per day) Morning: 18 Day: 19	(Per day) Morning: 13 Day: 13	(Per day) Morning: 18 Day: 18	Overall: 3.8 $\pm$ 0.7	Overall: 4.3 $\pm$ 0.5	Overall: 4.2 $\pm$ 0.6	PAOLO	
								Activity: 3.2 $\pm$ 0.9	Activity: 4.0 $\pm$ 0.8	Activity: 3.9 $\pm$ 1.0		
	No acupuncture							Symptom: 3.5 $\pm$ 0.9	Symptom: 4.2 $\pm$ 0.7	Symptom: 3.9 $\pm$ 0.0-9		
								Emotion: 3.8 $\pm$ 1.0	Emotion: 4.5 $\pm$ 0.6	Emotion: 4.3 $\pm$ 0.9		
		≥ 2 uses: 18	≥ 2 uses: 25	≥ 2 uses: 36	Night: 10	Night: 7	Night: 9	Trait: 32.4 $\pm$ 5-.8	Trait: 32.5 $\pm$ 8-.2	Trait: 29.1 $\pm$ 7.3		
								State: 41.5 $\pm$ 8-.1	State: 38.4 $\pm$ 8-.7*	State: 37.6 $\pm$ 8.2		
	No acupuncture	Controller (frequency/day) 1 use: 30	Controller (frequency/day) 1 use: 9	Controller (frequency/day) 1 use: 6	(Per day) Morning: 13 Day: 11	(Per day) Morning: 11 Day: 14	(Per day) Morning: 18 Day: 15	Overall: 3.4 $\pm$ 0.8	Overall: 4.1 $\pm$ 0.6	Overall: 3.9 $\pm$ 0.9	PAOLO	
								Activity: 3.2 $\pm$ 0.8	Activity: 4.2 $\pm$ 0.7	Activity: 4.0 $\pm$ 0.7		
		≥ 2 uses: 13	≥ 2 uses: 26	≥ 2 uses: 34	Night: 4	Night: 4	Night: 9	Symptom: 3.7 $\pm$ 0.8	Symptom: 4.2 $\pm$ 0.6	Symptom: 4.1 $\pm$ 0.8		
								Emotion: 4.0 $\pm$ 0.9	Emotion: 4.5 $\pm$ 0.6	Emotion: 4.3 $\pm$ 0.7		
								Trait: 30.4 $\pm$ 9.5	Trait: 30.4 $\pm$ 9.5	Trait: 30.4 $\pm$ 9.5	STAIC	

Table 2 (continued)

Author (year)	Intervention	Medication use		Symptoms			Quality of life (mean $\pm$ SD)			Scale used
		Before	After	Follow-up	Before	After	Follow-up	Before	After	Follow-up
Stockert et al (2007) [18••]	Laser acupuncture	β -Mimetics (puffs/week) 8.7 ± 15.4	β -Mimetics (puffs/week) 9.1 ± 15.4	-	-	-	-	Trait: 36.4 ± 8.9	Trait: $33.6 \pm 1-0.0$	-
								State: 45.2 ± 8.8	State: 44.4 ± 9.2	
	Placebo acupuncture	β -Mimetics (puffs/week) 3.1 ± 6.2	β -Mimetics (puffs/week) 3.7 ± 6.7	-	-	-	-	State: 42.5 ± 10.3	State: 49.3 ± 23.8	ACQ
								62.1 ± 20	54.9 ± 25.4	
								47.8 ± 9.5	34.6 ± 16.6	38.7 ± 17.1

*Significant difference between groups

-Not reported

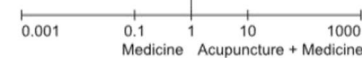
IHS, inhaled steroids; PAOLO, Paediatric Asthma Quality of Life Questionnaire; STAIC, State Trait Anxiety Inventory for Children; ACQ, Asthma Control Questionnaire

Table 3 Efficacy of conventional treatments plus acupuncture on the response rate [100]

	Acupuncture + Medicine		Medicine			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 chronic phase							
Lv Guifen 2012	30	30	27	30	5.8%	7.76 [0.38, 157.14]	
Zhang Wenpeng 2006	39	53	8	39	31.7%	10.79 [4.02, 29.01]	
Subtotal (95% CI)		83	69	37.4%		10.33 [3.99, 26.73]	
Total events	69		35				
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%							
Test for overall effect: Z = 4.81 (P < 0.00001)							
1.1.2 acute phase							
Zhang Zhilong 2005	57	60	27	30	23.4%	2.11 [0.40, 11.15]	
Wang Wenyan 2010	34	35	28	35	10.4%	8.50 [0.99, 73.28]	
Jiang Suqun 2012	77	80	59	80	28.8%	9.14 [2.60, 32.09]	
Subtotal (95% CI)		175	145	62.6%		6.40 [2.68, 15.31]	
Total events	168		114				
Heterogeneity: Chi² = 2.08, df = 2 (P = 0.35); I² = 4%							
Test for overall effect: Z = 4.17 (P < 0.0001)							
Total (95% CI)		258	214	100.0%		7.87 [4.13, 14.99]	
Total events	237		149				
Heterogeneity: Chi² = 2.85, df = 4 (P = 0.58); I² = 0%							
Test for overall effect: Z = 6.28 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%							

0.001 0.1 1 10 1000

Medicine Acupuncture + Medicine



Acupuncture and Atopic Eczema

In reviews deciphering the effect of acupuncture on atopic eczema, it was discovered that although itch was relieved [104], SCORAD scores were not conclusively improved in any of the studies. However, some small-scale studies on the treatment of atopic eczema with acupuncture [40, 105, 106] yielded favorable results including relief of itch and insomnia on a VAS scale as well as significant reduction of SCORAD scores, although positive results from large-scale studies are nonexistent.

Acupuncture and Food Allergy

Detailed studies or reviews on the use of acupuncture for food allergy are unavailable. There are only isolated reports describing comparability of its effects on food allergy to that of antihistamines.

Acupuncture for Urticaria

In one review conducted in 2016 in which 6 RCTs encompassing 406 patients were analyzed, acupuncture was found to significantly allay global symptoms, either singularly or as an adjunct to histamine blockers. Acupoints used comprised SP10, Xuehai, LI 11, and ST 36 Zusanli in most of the trials while Sanyinjiao, Pishu, Ganshu, Shendao, and Hegu were included in only some of the trials (Fig. 7). The authors deduced that there was only meager evidence that acupuncture was useful for treating chronic urticaria [107].

Discussion

In reviewing the effect of TCM on allergic diseases, a variety of problems were encountered. Despite availability of

substantial information on the use of TCM for the treatment of allergic diseases in the Chinese medical journals, most of the investigations were merely studies of a small scale and a single formula was seldom used. This, of course, is easily comprehensible, as it is often difficult to deploy one CHM in the form of a single herb, or a single formula to treat one allergic disease as allergic diseases in TCM are considered different syndromes, each requiring unique treatments. Further, TCM is a personalized form of medicine, thus tailored medicine for individual patients is allowed; yet, this heterogeneity engenders difficulty in evaluating the efficacy of TCM, and the quality of the studies was consequently downgraded. Studies reviewed were carefully selected but their qualities were often compromised by a number of factors and hence the results, albeit positive, cannot be regarded as conclusive [108]. This is an intrinsic quality of TCM: it works well for individual patients, but large-scale, westernized RCTs are difficult to conduct. In the future, researches on CHM should be conducted in such a way that some minor individual modifications are permissible, but the basic CHM formula or herb should be the “Emperor” and must be adhered to.

Another factor is that Chinese herbal medicine aims at restoring homeostatic balance and holistic well-being rather than curing specific symptoms. It often takes much longer for CHM to manifest its efficacy, yet most studies were short-term, and thus the equivocal results procured could be attributed to an insufficiently long duration and not ineffectiveness of the treatment. It is, therefore, not surprising to discover that, according to most reviewers, the efficacy of CHM on treating allergic diseases was not conclusive. Therefore, it is suggested that, in order to demonstrate efficacy, studies on CHM should be performed over months and years, as in immunotherapy, instead of briefly in a matter of only weeks. Large-scale well-planned blinded placebo trials of proper duration on a “single” intervention will be

Common Acupoints for Urticaria

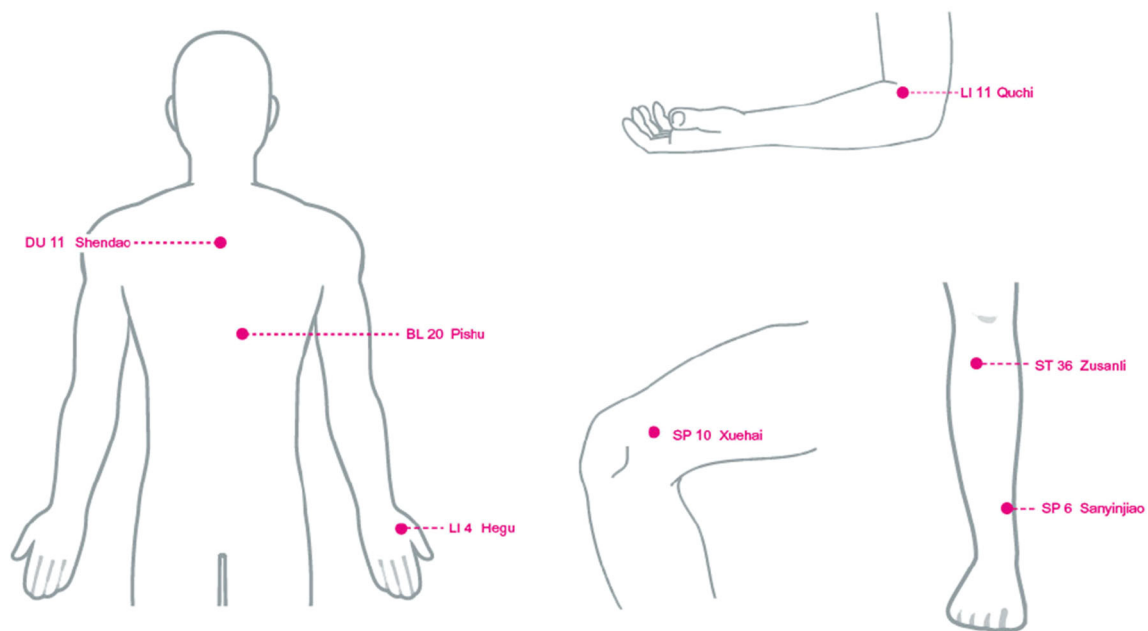


Fig. 7 Common acupoints for urticaria

able to yield conclusive evidence of CHM on allergic diseases.

Attempts to produce botanical drugs as novel therapy for food allergy (E-B-FAH-2) and asthma (ASHMI) have been undergoing in the past decade in the USA with some success. Scientists have also identified compounds in the CHM concoctions that exert specific anti-allergic effects like anti TNF-alpha [109] and these efforts may eventually culminate in popularization of new botanically derived drugs.

Although TCM has been used for thousands of years in Asia and is considered part of the mainstream medicine in some Asian countries, in the USA, CHM is considered a dietary supplement [110]. On the contrary, in other countries, CHM may be reckoned as a drug. However, as control measures on the manufacturing, quality, chemical, standardization, batch-to-batch consistency, and safety of CHM drugs may vary from jurisdiction to jurisdiction; rendering comparisons technically difficult and eroding confidence, it is no wonder that CHM has not gained popularity in the west. Recently, the FDA published guidelines for botanical drugs with stipulated requirements on chemical, manufacturing, control, and quality and safety data for raw herbs, extracts, and finished drugs. This has led to the prospects of investigating CHM as botanical drugs in the USA [110].

Reviews on acupuncture, on the other hand, turned out to be more positive and favorable. Apparently, acupuncture could be effectual in a shorter duration. It effectively relieves symptoms and downregulates immune reactions in allergic

rhinitis and chronic urticaria, improves asthmatic symptoms but is relatively less potent on atopic eczema and food allergy.

Encouragingly, in reviewing thousands of papers, no reports of significant adverse reactions to TCM treatments were spotted. In view of these gratifying findings, and the fact that many patients prefer natural and complementary treatment, it is recommended that acupuncture be integrated into the treatment of allergic rhinitis and perhaps asthma to complement western medical treatment. Acupuncture and CHM may serve as an adjunct to conventional western treatment and immunotherapy of other allergic diseases on an individual basis to upgrade the quality of life of patients and to minimize the use of western therapy with untoward side effects.

It is opportune time to ascertain a cure for allergic diseases. As judged from the available preliminary data, and based on the principles of the TCM theory, it is possible to identify a disease-modifying treatment for allergic diseases in TCM that can arrest further progression of allergic diseases with minimal side effects and is procurable at an affordable price.

Unfortunately, it is often not an easy task to patent CHM traditional formulas. Research is expensive and time consuming. Without a patentable herbal formula or a patentable ingredient, and devoid of adequate financial support rendered to commercial pharmaceutical companies, scientists are destitute of the requisite funding for them to engage in large-scale TCM RCT studies.

Fortunately, in treating allergic diseases, TCM is relatively cost-effective compared with conventional western

medicine and thus could save the government billions of dollars. Governments should promptly take the initiative to foster and promulgate these most worthwhile investigations in order to reap from the cost-effectiveness of TCM. These researches may help to ultimately uncover or generate a cure for allergic diseases which works by restoring homeostatic balance to patients and curbing the progression of allergic diseases.

Conclusion

Notwithstanding the fact that CHM is extensively utilized to treat allergic diseases, to date, according to published studies, there is a lack of convincingly conclusive evidence to certify that CHM can lessen the severity of allergic diseases clinically. Although there were studies that advocate integrated western and TCM therapy over conventional western treatment [18•], more high-quality RCT studies should be conducted over an extended duration to corroborate the beneficial effects CHM on allergic diseases.

Further work must be done on the control of the manufacture of CHM drugs, global standardization of formulas and herbs, identification of active ingredients, study of genetics, elucidation of molecular structures, and further pharmacological and pharmacokinetics investigations. All these may lead to the invention and popularization of novel anti-allergic CHM botanical drugs in the west.

As there is compelling evidence that acupuncture could significantly palliate clinical symptoms of allergic rhinitis, chronic urticaria, and asthma, integrating acupuncture into the conventional treatment may constitute an affordable option for many patients. CHM may be applied as an adjunct to conventional western therapy, including immunotherapy, for allergic diseases.

In conclusion, relentless well devised clinical researches should be undertaken to investigate the feasibility of using TCM as an affordable disease-modifying agent for allergic diseases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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