A narrative review of clinical studies of herbal treatment of difficult to manage Asthma

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BGO conceptualized the review. HL searched for the Chinese database. HC searched for the English database. HL and HC drafted the manuscript. LM and BGO wrote the practice, perspective, and the potential use of TCM in western medical practice. All authors read and approved the final manuscript.

Abstract

Asthma can be complex and difficult to manage. Patients often seek alternative treatment options, including Traditional Chinese Medicine (TCM). The paradigms that inform TCM treatments include a philosophy focusing on modifying the whole body status ('bian zheng') to treat the lungs. TCM practitioners use personalized treatment plans based on clusters of clinical patterns (eg. cold-related wheezing, kidney insufficiency/energy-deficiency-related wheezing). TCM includes herbal remedies and non-oral therapies such as cupping, acupuncture, and massage. The efficacy of TCM treatments of asthma is not well described as the majority of studies are published only in Chinese literature. We reviewed all available clinical trials in CNKI, Chaoxin, Wanfang, CQVIP, Springer-link, Science Direct, and Pubmed. Papers in Chinese were translated by dual lingual TCM and Western medicine doctors. Based on the identified studies, TCM is a safe additive treatment to Western medicine that can improve both symptoms and quality of life for patients with asthma.

Keywords: Asthma, clinical trials, respiratory function tests.

1. Introduction

Asthma is characterized by episodic airway inflammation and chronic airway remodeling, which contribute to airflow obstruction giving rise to the symptoms of cough and wheeze. Corticosteroids, the most potent nonspecific anti-inflammatory agents, are the cornerstone of asthma treatment (Leonard and Sur, 2002). However, in patients with severe asthma, corticosteroids are often ineffective at controlling airway inflammation, symptoms, and exacerbations (Barnes, 2010). In patients with severe asthma, corticosteroids are used at the high doses required to partially control symptoms, at high doses they are commonly associated with significant side effects including mood instability, weight gain, impaired glycaemic control (glucose intolerance, type 2 diabetes), adrenal suppression and growth retardation in children (Eid et al., 2002; Visser et al., 2004; Wen et al., 2005). Additional treatment regimens in Western medicine now include biological therapies (Global Initiative for Asthma, 2019). Throughout the world, patients seek to supplement and sometimes replace Western asthma treatments with alternative treatment options, such as Traditional Chinese Medicine (TCM).

The latest guidelines from the Global Initiative for Asthma (GINA) 2019 stage asthma treatment based upon symptom control, starting with as-needed low dose inhaled corticosteroid (ICS)-formoterol (Global Initiative for Asthma, 2019). If symptoms are not controlled there is a step-wise increase in ICS dose +/- leukotriene receptor antagonists/antimuscarinics and at the most severe treatment step the addition of biological therapies (Global Initiative for Asthma, 2019). In patients with corticosteroids resistant asthma, there is now good evidence for the efficacy of anti-IgE therapy for the subgroup of patients with severe allergic asthma and for anti-IL5 therapy for the subgroup with eosinophilic asthma (Global Initiative for Asthma, 2019).

Asthma severity is assessed when the patients have been on a regular controller treatment for several months. If a patient requires Step 4 or 5 treatment, eg. a high dose of ICS-LABA to prevent it from being ‘uncontrolled’, or asthma that remains ‘uncontrolled’ despite this treatment, a diagnosis of severe asthma is made (Global Initiative for Asthma, 2019). Many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with

adherence or comorbidities, such as obesity.

Severe is often also used to describe the severity of asthma symptoms, airway obstruction, and exacerbation frequency by both patients and clinicians. In the TCM literature, 'severe asthma' may refer to this definition, instead of the GINA definition. In this review, we are unable to determine which definition was used in studies which we have identified due to the lack of information in the original papers. Therefore, we took the conservative approach and refer to asthma as uncontrolled rather than severe.

TCM has been practised in China, Japan, Korea, and Thailand for over two thousand years, although the name in each country can be different and is increasingly recognized and practiced in other parts of the world. One of the main reasons for TCM's popularity is the belief that most herbal medicines being of 'natural' origin are harmless and pose no side effects (Chan et al., 1993). This, of course, is an oversimplification, as many plants, such as poison ivy, are in fact quite toxic. In the latest version of the International Statistical Classification of Diseases (ICD-11), the WHO has also included the diagnostic basis of TCM based on symptom patterns. However, evidence from randomized clinical trials (RCTs) is still required to demonstrate the efficacy of TCM.

2. Asthma diagnosis and treatment methods in TCM

TCM theory divides asthma symptoms into two types, 1) wheezing in the throat (phlegm sound), and; 2) wheezing in the chest and difficulty in breathing. In TCM, asthma is a paroxysmal disease of phlegm, with wheezing detected in the throat/chest, difficulty in breathing and exhalation, and in severe cases difficulties lying down. In terms of treatment, TCM strategies normally address both coughing and wheezing. The etiology, pathogenesis, and symptoms of asthma were described in the first TCM medical text, Huangdi Neijing (also called Inner Canon of the Yellow Emperor or Esoteric Scripture of the Yellow Emperor), which is more than two thousand years old. In Jingui Yaolue, one of the four classical Masterpiece medical texts of TCM，Zhang Zhongjing first described the characteristics of asthma exacerbations and the treatment of using Sheganmahuang decoction, which is still widely used by TCM clinicians.

The diagnosis of asthma (asthmatic pattern) in TCM has now been standardized. The diagnosis requires three key features; 1) recurrent wheezing; 2) wheezing onset during the rest period, with fatigue or poor appetite; 3) familial history. There are 3 types, cold-related (cold-flu related), heat-related (inflammation), and wind phlegm (allergy related). The diagnostic criteria using TCM diagnostic methods have been summarised in Table 1.

Based on the 3 types of asthma according to TCM theory, 3 major treatment theories have been developed. The most common type is the 'cold' asthma, and two decoctions have been commonly prescribed including Sheganmahuang decoction, and Xiaoqinglong decoction (Committee of Pharmacopoeia of the PRC, 2015). The former is used for patients with wheezing and coughing symptoms; while the latter is predominately used for those with cold symptoms. In addition, Dingchuan decoction is commonly used for the 'heat' type of asthma, while Sanziyangqin decoction is commonly used for 'wind phlegm' type of asthma (Committee of Pharmacopoeia of the PRC, 2015). In a Western medicine context, there are internationally recognized stepwise guidelines for the introduction of pharmacotherapy for asthma that is based on lung function abnormalities, persisting symptoms despite current therapy, and frequency of exacerbations (GINA Guidelines 2019)(Global Initiative for Asthma, 2019). In contrast, the TCM clinician will choose different herbal combinations or acupuncture points, based on the symptom type and the TCM clinicians' clinical experience. Surprisingly, although it is hard to draw similarities among the choices from one trial to another, most trials demonstrated some level of efficacy in managing the symptoms of uncontrolled asthma as an addition to Western medication alone. These trials will be introduced in Section 4.

3. Search methods

Database searches were performed using the keywords 'severe asthma', 'Traditional Chinese Medicine', 'herbal medicine', and 'randomized clinical trial' in databases which contain Chinese literature (CNKI, Chaoxin, Wanfang, CQVIP) and the English language databases (Springer-link, Science Direct, and Pubmed). All publications in Chinese were reviewed and translated by a TCM medical doctor, and a Western medical doctor to ensure consistency and correct interpretation of TCM and Western diagnoses of asthma. The TCM treatment strategies were into three categories; herbal

decoction, herbal extracts, and non-oral treatments, such as acupuncture, massage, and cupping.

4. Results

We found this research topic is a niche area in both English and Chinese literature. In total, we found 40 papers published in the Chinese literature and one research thesis, among which 19 were RCTs on patients with severe asthma. There were 9 papers in the English literature and of these 3 were RCTs including patients with severe asthma. The studies that used herbal medicine have been listed in Table 2. Although TCM has been used to manage mild-moderate asthma patients, the practice of admission of patients with severe or difficult to manage asthma occurs mainly in Western medical hospitals, where standard Western medicines are used (even when TCM is used as an adjunct therapy). We think that this might be part of the reason why there are so few RCTs as clinically the use of TCM may be under recognized.

4.1 Herbal decoction

4.1.1 Oral treatment of herbal decoction

Herbal decoctions are the most common form of TCM treatment strategy. They are rapidly absorbed, have a rapid onset of effect and flexible dosing. In the literature, the most commonly used decoctions in RCTs for uncontrolled asthma are Xiaoqinglong decoction (Cheng, 2014; Deng, 2013; Liu, 2015), Shegan Mahuang decoction, and Sanzi Yangqin decoction (Committee of Pharmacopoeia of the PRC, 2015). Mahuang (*Herba ephedrae*) is the most frequently used herb in most decoctions (Table 2), which can relieve cold symptoms through promoting sweating, as well as reducing cough and wheeze. However, it needs to be noted that Mahuang contains ephedrine, an adrenergic receptor agonist. The raw herb form of Mahuang is not available as an over the counter medication in several countries, including the US and Australia. In some countries, the extracts can be used for limited applications, such as treating nasal congestion in Canada.

Although TCM is the mainstream medicine in some Asian countries, especially China, it is still considered complementary medicine in the majority of the world. Even in China, TCM approaches

are commonly used in conjunction with conventional Western medicine in patients with asthma. As a result, in the RCTs, the control group was given conventional Western medicine, whereas in the treatment group, it was combined with a TCM decoction. The outcome measures included either change in symptoms which we considered to be soft outcomes or changes in lung physiology which we considered to be more robust or hard outcomes.

4.1.1.1 Studies that have reported changes in symptoms as the primary outcome.

4.1.1.1.1 Personalised approach

TCM treatment is well known for its personalized approach by modifying the same decoction based on the variation of TCM patterns in different patients. In general, patients with asthma are further divided into three TCM patterns; cold-related (cold-flu related), heat-related (inflamed), and wind phlegm (allergy related). Therefore, targeting the individual's TCM pattern via personalized decoctions has also been adopted in several RCTs. This has some similarities to identifying phenotypic subgroups in Western medicine (e.g. frequent exacerbators or severe eosinophilic asthma) but with whole body symptom clusters rather than biomarkers. In addition, in some RCTs, the patterns related to asthma can be further accompanied by complications in other organs, which further complicated the combination of herbs used in the decoction. Here, we don't attempt to make a judgment on the decoctions themselves, but report their effectiveness of managing uncontrolled asthma.

In a study by Chen et al. (Chen and Ding, 2018) on 60 patients (n=30 in each group), the control group was treated with routine Western medicine (Aminophylline and Ipratropium Bromide, followed by inhalation of Salmeterol and Fluticasone propionate twice daily). No objective asthma severity measurements were reported in this study. Nevertheless, in the treatment group, in addition to the same medication as the control group, a base decoction modified from the Sanzi Yangqin decoction was used. Additional herbs were added to the base decoction according to the TCM patterns (cold, heat, or phlegm) of the patients (details in Table 2). At the start of the study, participants were not divided into sub-groups based on the TCM patterns, maybe due to the small sample size. The outcomes included improvement in chest congestion, reduction in wheezing sound, coughing and

short of breath, and the treatment duration for symptom relief. The effective rate of symptom relief in the control group was 80% (24 patients), and the treatment group was 100% (30 patients). It seems that all formulas for different patterns were effective when they were used in combination with western treatments although the success rate for the western treatment alone was also quite high. Symptom relief occurred quicker in the treatment group, ranging from 2.13 to 4.47 days for different symptoms to be relieved while it took 3.19 - 6.29 days for the control group. However, in this study, no statistical analysis was reported for any of the measurements, resulting in low-quality evidence of the efficacy of the treatment. It needs to be noted that the efficacy was still based on the patient-reported improvements in symptoms and not objective lung function measurements, serum biomarkers, or exacerbation frequency which are currently standard outcome measures in western asthma therapy trials.

A similar design was used in the study by Zhou et al. (Zhou, 2005) where 60 patients were randomly divided into two groups (n=30) with mixed sexes. The control group was given standard asthma treatments for 2 sessions (7 days/session). Different from the above study by Chen et al. (Chen and Ding, 2018), 3 different decoctions (including one invented by the authors) were given to the treatment group based on the TCM patterns for the same period. The outcome measures included symptom relief and reduction/disappearance of the wheezing sound. After the first session and second session, the symptom improvement in the control group was 23.3% (7 patients) and 86.7% (26 patients) respectively, while the treatment group was 63.3% (19 patients) and 93.3% (28 patients) respectively. These were statistically significant differences (chi-squared test) for both time points. The study reported that the additional decoctions used in this trial yielded fast and effective improvement after one week of the treatment, where most patients in the control group only responded well after the second week of western medicine treatment alone.

In Wang's study (Wang, 2017), the control group used "Western treatments" (oxygen, oral aminophylline tablets, magnesium sulfate, dopamine i.v., again with no ICS nor oral steroids, n=43) and the intervention group was additionally given extracted powder of Yupingfeng decoction (oral, n=43). However, a minor modification (adding 1 herb) was made based on two TCM patterns, qi deficient (a state of reduced energy) and spleen deficiency (poor with digestion and absorption). The

absence of clinical symptoms after the treatment was considered an effective endpoint measurement. Adverse reactions were also evaluated. The symptom remission rate in the control group was 88.37%, while that in the treatment group was 100%, suggesting all modified formulas were effective to facilitate western medicine in completely diminishing the symptoms. These differences were reported to be statistically significant (chi-squared tests).

Some studies only enrolled patients with one TCM pattern to simplify the study design. For example, Tang et al. (Tang et al., 2013) only recruited patients with asthma who had kidney-deficiency patterns (low energy, considered as a common complication of severe asthma) according to TCM diagnosis. Both genders were included in this study. After the randomization (control n=69, treatment n=74), both groups were given Western medicine according to GINA guidelines at that time (budesonide [AstraZeneca AB, London, UK] 100-300 mg, twice daily, or beclomethasone [GlaxoSmithKline Plc, UK] 200-400 mg, twice daily) and β2 agonists (such as salbutamol [Glaxo-SmithKline Plc] 100-200 mg, as needed). The treatment group was additionally treated with an oral herbal paste consisting of 18 herbs (composition see Table 2) in the winter solstice (starting on 21st - 23rd December). The dose was 25g twice a day for 60 days along with standard western medicine treatment. At the end of the trial, patients in both groups were followed up once a month for one year. Compared with the control group, the frequencies of catching a cold (3.1±1.6 time/year in the treatment versus 4.3±2.2 times/year in the control, $P<0.05$), asthma exacerbation (3.1±1.7/year in the treatment versus 6.2±3.1/year in the control, $P<0.05$), cold-flu related asthma exacerbation (0.8±0.6 in the treatment versus 2.8±1.7 in the control, $P<0.05$). There was no significant difference in the Asthma Control Test (ACT) scores between the two groups before or after treatment. This study suggests that adjunct TCM treatment can reduce the chance of catching a cold, thereafter reducing cold-related asthma onset and exacerbations, especially during the high-risk winter season for cold and flu.

4.1.1.1.2 Studies with the same decoction for all patients

Some studies also tried to use one decoction to address all patients with uncontrolled asthma regardless of the TCM pattern. Such decoctions are normally invented and prepared by the practitioners, however, often they still include the common herbs for treating cough, breathing difficulties, sputum production, and strengthening immune function. If this approach was efficacious,

it would make it easier to be used by the herbal practitioners in other complementary medical systems.

In the RCT study by Zhang et al. (Zhang, 2016), the patients in the control group were given routine Western medicine (doxophylline i.v, methylprednisolone i.v., ipratropium bromide inhalation); while the treatment group was given a homemade decoction named 'Asthma No.1' (herbal combination in Table 2) in addition to the treatment in the control group for 3 months (n=27 in each group). Improvement in chest congestion and a reduction in wheezing sound was used as the outcome measurements. Three months later, 70.4% of the patients in the control group were improved, whereas 88.9% in the treatment group were improved. No statistical analysis was carried out in this study, which was reported to be due to the simplicity of the outcome measurement and a single centre. Therefore, the quality of the evidence in this study is low.

4.1.1.2 Outcomes based on changes in lung physiology

For Western medical doctors, lung function is one of the most reliable criteria for judging the efficacy of any given treatment of asthma. A few TCM RCTs reported lung function changes.

Cheng et al. (Cheng, 2014) and Liu et al. (Liu, 2015) used the same classical decoctions recorded in ancient herbal literature (Xiaoqinglong decoction, Sanziyangqin decoction, and modified Yupingfeng decoction powder) in the treatment group. In Cheng's study, 68 patients with uncontrolled asthma were recruited (n=34)(Cheng, 2014), while in Liu's study, 80 patients were recruited (n=40)(Liu, 2015). Both studies used a treatment period of 3 weeks. Both studies used similar TCM patterns and herbs to modify the existing decoctions. The changes in Forced Expiratory Volume in the first second (FEV1) were used to evaluate the efficacy in both studies. In Liu's study (Liu, 2015), clinical symptoms and improvement in FEV1 were evaluated. It was found that the effective rate was 90.0% in the treatment group (20 patients FEV1 improved by > 35% with variation < 20%, 10 patients FEV1 improved between 25-35% with variation < 20%, 6 patients FEV1 improved between 15-24%, and 4 patients showed no effect) and 70.0% in the control group (7 patients FEV1 improved by > 35% with variation < 20%, 13 patients FEV1 improved between 25-35% with variation < 20%,8 patients FEV1 improved between 15-24%, and 12 patients showed no effect)($P<0.05$ by chi-square test). Cheng et al. (Cheng, 2014) found that 88.2% of the patients in the treatment group were improved (15 patients

FEV1 improved by > 35% with variation < 20%, 10 patients FEV1 improved between 25-35% with variation < 20, 5 patients FEV1 improved between 15-24%, 4 patients showed no effect), while 70.5% of the patients in the control group were improved (6 patients FEV1 improved by > 35% with variation < 20%, 10 patients FEV1 improved between 25-35% with variation < 20, 8 patients FEV1 improved between 15-24%, 10 patients showed no effect)($P<0.05$ by t test and chi-square test). Both studies had a small sample size and performed, however, the efficacy of the standard decoction for asthma (Xiaoqinglong decoction) and another two not traditionally used in asthma (Sanziyangqin decoction, reducing sputum and improving digestion; and Yupingfeng decoction, improving immune function) were reported to increase the success rate (by ~30%) of managing patients with uncontrolled asthma compared with standard Western medicines alone, suggesting the feasibility of using it to improve the symptom control in patients with uncontrolled asthma. However, it needs to be noted that even with the additional herbal treatment, there were still patients who failed to respond to the combined treatment, only less than half of those failing to respond with western medicine treatment only.

In the study by Deng et al. (Deng, 2013), Xiaoqinglong decoction was used in conjunction with routine Western treatments (oral montelukast sodium tablets before bedtime and budesonide aerosol inhaled morning and night) in the treatment group, while the control group used routine Western treatments only (n=48 in each group). Symptoms (coughing, wheezing, shortness of breath), the frequency of salbutamol use, improvements in peak expiratory flow (PEF), FEV1, FEV1/forced vital capacity ratio (FEV1/FVC%), and adverse reactions were evaluated. After the first course (4 weeks), the effective rate in the control group was 93.8%, while the treatment group was 97.9%. Although the effective rate seems similar, with only 1 patient in the treatment group and 3 patients in the control group failing to respond to any treatment, the average FEV, FEV1, and FEV1/FEV ratio were all higher in the treatment group, suggesting an additive role of Xiaoqinglong decoction to Western medication to manage the patients with uncontrolled asthma. However, we can't comment on the quality of the evidence in this study as the statistical methods were not reported in the paper.

He et al. (He et al., 1997) chose a different formula, Tinglipingchuan decoction (meaning 'reducing wheezing') as an additive to the standard Western treatments (antibiotics, oxygen inhalation, oral β2-

receptor agonist, i.v aminophylline, and dexamethasone) in the treatment group (n=52). The control group had standard Western treatments only (n=46). Symptoms and hemorheology (whole blood specific viscosity，plasma specific viscosity, hematocrit) were assessed on the 3rd and 10th day of the treatment. If the patient's wheezing sounds disappeared without the use of steroids and aminophylline, it was considered as 'cured'. If the patient's wheezing sounds were reduced without the use of steroids but still requiring aminophylline, it was considered as 'improved'. The improvement rate and the cure rate in the treatment group reported in the original paper were significantly higher than those in the control group (improvement rate: 3rd day, 48% in the treatment versus 19.6% in the Control groups; 10th day, 78.8% in the treatment versus 39.1% in the Control groups; cure rate: 3rd day, 40.4% in the treatment versus 52.2% in the control; 10th day, 17.3% in the treatment versus 43.5% in the control). The treatment group also had lower values in their blood viscosity parameters (whole blood specific viscosity, plasma specific viscosity, hematocrit), although the statistical analysis was only performed to compare before and after treatment within the same group. This still suggests adjunct Tinglipingchuan decoction further improved blood stasis.

In the study by Wang (Wang, 2014), inhaled budesonide-formoterol, steroids, and β2 agonists were used in the control group. In the treatment group, a decoction invented by the authors (named Xuanfeiyiqi decoction) was used in addition to the treatments in the control group (n=45). Assessments included serum inflammatory markers (IL-4, IL-5) and respiratory function (PEF and FEV1/FVC%). After 4 weeks of treatment, PEF and FEV1/FVC% values were described as improved after treatment in both groups (treatment group: PEF 64.2±8.4 mL/s and FEV1/FVC (57.2±7.8%) and the control group: PEF 74.2±9.6 mL/s, FEV1/FVC 65.8±8.5%, $P<0.05$ between groups). Serum IL-4 was not changed (1.3±0.2 ng/ml in the treatment versus 2.4±0.4 ng/ml in the control group, $P < 0.05$). IL-5 was lower in the treatment group (105.8±16.2 ng/ml treatment versus 172.5±25.2 ng/ml Control groups, $P < 0.05$). In this study, the treatment duration is longer than most TCM RCTs (10-14 days). Although the authors did not report the number of patients in each group who failed to respond to the treatments, the studies findings based on simple statistics (unpaired t-tests) suggests that overall, an additional herbal decoction can improve lung function and reduce systemic inflammation in patients with uncontrolled asthma.

In another larger size long-term study (Ma, 2014), 3 decoctions were used to treat 3 TCM patterns (cold, hot, phlegm mentioned in session 1.1.1) in the treatment group (n=84), in addition to Western medicine (salmeterol, ipratropium bromide, aminophylline, expectorant, and oxygen inhalation) used in the control group (n=66). FEV1, change in PEF rate (calculated using ((highest PEF-lowest PEF of the same day) x 2 / (highest PEF+lowest PEF of the same day)) x 100%), and symptom remission rates were measured after 4 weeks of treatment. In both groups, FEV1 and change in PEF rate were improved by the respective treatments. FEV1 in the treatment group was also higher than that in the control group (2.38±0.07L in the treatment versus in 2.15±0.14L in the control groups), while the change in PEF rate was lower than that in the control group (16.99±1.92% in the treatment versus 22.01±1.83% in the control groups). In this study, the statistical methodology is not described, meaning that the study efficacy data is low. However, given the large sample size and the fact that data were presented as mean ± standard error, the omission of the statistical methodology might be an oversight of the authors.

In summary, although most of these trials were small and endpoint measurements were limited, the addition of TCM to Western asthma treatments was reported to be associated with reduced symptoms, reduce serum inflammatory cytokine levels, and improved lung function (PEF、FEV1、FEV1 /FVC%) compared to Western medicine alone. Although using symptom relief can be subjective, in some studies, the recovery of lung function was also better than western medicine alone. However, the choice of decoctions was not consistent from one RTC to another. Even using the same classical base formula, different research groups would add additional herbs depending on the additional pattern in the other organ system, aiming for personalized treatment. However, such studies still found efficacy and support the use of some classical base formula for uncontrolled asthma, e.g. Xiaoqinglong decoction for cold-type asthma.

4.1.1.3 Potential mechanisms of how herbal preparations have efficacy in controlling asthma symptoms.

Due to the nature of herbal medicine practice in TCM, different TCM clinicians have different choices of herbs based on their education and experience. Most of the herbal decoctions such as the abovementioned ones were tested in patients for efficacy, and rarely is mechanistic research (pharmacology) undertaken. It is most likely that from a TCM perspective, such mechanisms are not

critical to guide their use compared to their clinical efficacy. On the other hand, understanding the potential mechanisms is important from a Western medical perspective, and perhaps critical for Western medical doctors who have patients taking a mixture of TCM and Western medicines.

Xiaoqinglong decoction is one of the most commonly prescribed base decoctions for cold type asthma and other cold flu induced conditions and has been well studied (Chen and Chen, 2013; Eng et al., 2019; Fan et al., 2019; Li et al., 2016). Some of the key active chemical compositions, such as quercetin, kaempferol, schisandrin A, schisandrin B, and α-cubebenoate, are all reported to have anti-inflammatory effects (Chen and Chen, 2013; Eng et al., 2019; Fan et al., 2019; Li et al., 2016). Glycyrrhizic acid in the herb liquorice (one ingredient of the Xiaoqinglong decoction) activates the glucocorticoid receptor and inhibits inflammation via PI3K/Akt/GSK3β signalling pathways (Kao et al., 2010). Paeoniflorin from peony, another herb in the decoction, is anti-inflammatory, modulating Th1/Th2 balance and inhibiting platelet-derived growth factor (PDGF)-BB induced airway smooth muscle hypotrophy *in vitro* (Zhang et al., 2015; Zhou et al., 2018). In animal models, Xiaoqinglong decoction can decrease eosinophils count, IgE levels, and histamine release, as well as inhibiting IL-4 and inducting IFN-γ levels (Eng et al., 2019). It can also inhibit other airway inflammatory markers, including IL-13, TGF-β1, and NF-κB and TNF signalling pathways (Eng et al., 2019; Fan et al., 2019; Lu et al., 2015; Qi et al., 2017; Xie et al., 2016). In addition, Vascular Endothelial Growth Factor A, Catalase, and cGMP-dependent protein kinase (PKG) signalling are also proposed key targets, which may promote airway smooth muscle relaxation in asthma (Fan et al., 2019; Myoishi et al., 2009).

Bronchodilatation may occur due to the inclusion of one key herb in the Xiaoqinglong decoction, Ma Huang, which contains ephedrine hydrochloride (David Van and Brian, 2015). The Xiaoqinglong decoction has been shown to improve ciliation and mucus clearance (Qi et al., 2017; Wang, N. et al., 2016). Whilst there are many different TCM decoctions, it is likely that in each decoction there may be other active chemicals which act on inflammatory and bronchodilator pathways. This requires further investigations to confirm.

4.1.2 Atomization

Atomization of TCM decoctions is also widely used in the clinic and therefore has been studied in clinical trials. In two studies (Chinese), the researchers have adopted laboratory examinations as

outcome measures.

In the study reported in Hao's thesis (Hao, 2012), the control group (n=30) was given routine Western medicine (β2 agonists, aminophylline, corticosteroids, anticholinergic drugs, and steam inhalation) while the treatment group (n=30) was given Tanqingning decoction (meaning 'to reduce sputum') inhalation in addition to the Western medication in the control group. Water extraction (200ml) was prepared using a commercialized decoction preparation device. After sterilization, the decoction aerosol was delivered to the patients using a CSW-1 type ultrasonic atomizer (3 ml/min for 20 min, 50ml/6 hours, 36°C) with a mask or a nozzle. The control group received the inhalation of distilled water with the same frequency. Seven days later, the patients were assessed for symptom relief, blood $PaCO_2$, PaO_2, SaO_2, and any side effects. More patients (22/30) in the treatment group had symptom relief than those in the control group (14/30) ($P < 0.05$ by chi-square test). $PaCO_2$, PaO_2, SaO_2 levels were improved by respective treatments in both groups ($P < 0.05$, t test), and the treatment group was improved more than the control group ($P < 0.05$, by t test which is perhaps the incorrect statistical approach). Inhalation of Tanqingning decoction seems to be effective to improve symptoms and gas exchange in the lung. This may be due to the advantage of local administration and the frequency of administration (4 times/day) even with the treatment for 7 days only.

In the study by Lu et al. (Lu et al., 2015), 60 asthmatic patients with severe exacerbations in the previous 2-24 hours were randomly assigned into treatment and control groups (n=30 in each). The control group received routine Western medicine treatments including low flow oxygen (20-40%), Aminophylline (nebulization or iv), Methylprednisolone (80mg, twice daily), and correction for blood pH and electrolytes for 2 weeks. Within the treatment group, 3 different decoctions based on the three standard TCM patterns (cold, heat, and phlegm, n=10) were used for inhalation (20 min each time, every 6 hours) in addition to the Western medicine treatments in the control group. All patients in the treatment group were grouped together for analysis. Arterial O_2, CO_2, and SaO_2 were measured at 72 hours after the initiation of the treatment. Average PaO_2 was 13% higher while $PaCO_2$ was 14% lower in the treatment group than that in the control group. Oxygen satiation SaO_2 was 93.5% in the treatment group compared with 89.5% in the control group. At the end of 2 weeks, 6 in the control group patients did not respond to the treatments, compared with only 1 patient in the treatment group. More patients returned to their asymptomatic status (16/30) with additional TCM treatment

than Western treatment alone (10/30). During the following up period (2 months after the discharge), 15 patients in the control group had exacerbations again, while only 2 in the treatment group had an exacerbation. The authors did not perform statistical analysis between the treatment and control groups meaning the quality of evidence from this study is low.

4.2 Extracts of a decoction or single herb

Traditionally, TCM clinicians prescribe the herbs and the patients prepare the decoction at home. Even with clear instructions, the quality of the final product can vary, depending on who was preparing, often by cooking, and how strictly the instructions were followed. Manufactured extraction of the herbal decoction and concentrating into capsules or re-formulating into pills or reconstitutable powder make the preparation process more standardized. It also makes it easier for the patients to take orally compared with the self-made decoction from raw herbs. Intravenous infusion formulas can also be made possible with such preparations when strict good manufacture practice guidelines are followed.

Such extracts normally arise from a much smaller number of herbs (in general 1-3 herbs) than those used in a decoction (in general >10 herbs) as shown in Table 2. The number was mostly decided by narrowing down from a decoction by keeping the must-have herbs. However, there has been a limited number of clinical trials to examine whether such manufactured herbal preparations are as effective as the decoction (Li, 2018; Wang, N. et al., 2016; Wang, Z.H. et al., 2016; Wen et al., 2005), although most TCM clinicians believe that decoctions works better. Nevertheless, clinical trials can still provide information on whether extracted formulations are effective in managing patients with uncontrolled asthma, giving evidence-based recommendations not just to the practitioners, but also to manufactures (Wang, Z.H. et al., 2016).

4.2.1 oral treatment of herbal extracts

In a study by Wen et al. (Wen et al., 2005) the participants in the treatment group received oral anti-asthma Herbal Medicine Intervention (ASHMI, n=45) capsules (an extract of 3 herbs, Table 1, Weifang Pharmaceutical affiliated with Weifang Asthma Hospital) and prednisone placebo tablets (Shandong Luoxin Ltd, Weifang.) The control group received prednisone (20 mg once daily in the morning) tablets and ASHMI placebo capsules (prednisone group, n=46) for 4 weeks. There were three categories of outcomes. 1) The use of salbutamol (puffs/d), lung function (FEV1 and PEF),

serum total IgE, IL-5, IL-13, IFN-γ, and cortisol levels, venous blood eosinophil counts, and symptom scores (based on the Guidelines for Clinical Research into New Chinese Medicines issued by the Ministry of Public Health of the People's Republic of China). The symptom scores were evaluated daily over a 1-week period before the treatments to establish a baseline and weekly during the treatment. Three aspects were scored from 0 (absence of) to 3 (severe) by a physician with a maximum score of 9: day-time symptoms, nocturnal symptoms, and allergic nasal occlusive symptoms. Grading of adverse events were done following the World Health Organization recommendations for grading of acute and subacute toxicity. Haematology and serum peripheral eosinophil count and electrocardiograms were carried out pre/post-treatment. The authors found the TCM treatment was found to be a safe and effective alternative medicine for treating patients with uncontrolled asthma. After 4 weeks of treatment, the symptom scores were reduced in patients treated with ASHMI (5.0 [4-8] to 2.0 [0-4], P<0.001) and those treated with prednisone (5.0 [4-7] to 2.0 [0-4], P<0.001); however, the improvement in symptom scores was similar in both groups. Lung function markers were improved by both treatments, reflected by the changes in FEV1 (ASHMI, 64.9±3.6 to 84.2±5.0; P<0.001; prednisone, 65.2±3.7 to88.4±8.0; P<0.001) and PEF (ASHMI, 64.6±3.5 to 84.8±5.4, P<0.001; prednisone, 65.0±3.5 to 88.1±7.0, P<0.001), however, the increase in the prednisone group was significantly greater than that in the ASHMI group (P =0.02 and 0.04, respectively). β2-agonist use in both treatment groups was reduced to a similar level (ASHMI, 4.7 [3.5-5.7] to 0.9 [0.14-2.3], P<0.001; prednisone, 4.7 [3.5-5.6] to 0.6 [0.3-1.0], P <0.001). Blood eosinophils counts in both groups were also significantly reduced (ASHMI, 0.52±0.24 to 0.27±0.14×10^9/L, P<0.001; prednisone, 0.53±0.21 to 0.19±0.1×10^9/L, P< 0.001). The reduction in serum IgE, IL-5, and IL-13 levels were also similar between the 2 treatment groups. Interestingly, serum cortisol level was reduced in the prednisone group (5.1±3.0 to 3.7±2.3 mg/dL, P<0.001), whereas it was increased in the ASHMI group (5.4±2.8 to 7.7±2.3 mg/dL, P<0.001). ASHMI had no adverse effect on adrenal function and had a beneficial effect on TH1 (IFN-γ and IgG2a production) and TH2 (IL-4, IL-5, and IgE production) balance. This study aimed to use to replace prednisone to minimize the side effects, and provides good quality evidence of the efficacy of this particular herbal medicine to manage uncontrolled asthma.

Wang et al. (Wang, N. et al., 2016) studied a single herb *Cordyceps Sinensis* in patients with moderate-to-severe asthma in conjunction with standard Western medicine in the treatment group. In the control

group, inhaled corticosteroids and long-acting β2-adrenergic agonists (n=60) were given, and additional Cordyceps Sinensis (1.2g, 3 times per day) was given in the treatment group (n=60) for three months. Juniper's Asthma Quality of Life Questionnaire (AQLQ), spirometry measurements for lung function (FVC, PEF, and FEV1), asthma control, and serum IgG, IgE, MMP9, IFN-γ, IL-4, and ICAM-1 levels were evaluated before and after the treatment. The results showed that the treatment group had a significant increase in AQLQ scores, and lung function compared with the control group. The levels of the inflammatory markers, IgE, ICAM-1, IL-4, and MMP-9 in the serum were decreased and IgG was increased in the treatment group compared with the control group ($P<0.05$). We consider the statistical methods in this paper sufficient. Therefore, it seems that Cordyceps Sinensis extract is effective in improving health related quality of life, asthmatic symptoms, lung function, and serum inflammatory profile in patients with moderate-to-severe asthma.

Cordyceps Sinensis has been shown to improve immune function, along which other broad effects to improve kidney and liver function (Zhang et al., 2011). It is widely used by TCM clinicians to treat respiratory conditions. However, when *Cordyceps Sinensis* was used with other herbs in a decoction, the decoction failed to show any improvement in lung function in children with asthma (Wong et al., 2009). This can be a dose difference when used in a decoction and used alone. In an in vitro model, *Cordyceps Sinensis* has shown to suppress the activation of lung cells (Kuo et al., 2001). In a mouse model of asthma induced by ovalbumin, *Cordyceps Sinensis* suppressed airway inflammation and improve airway hyperresponsiveness, but to a less extent than prednisolone and montelukast (Hsu et al., 2008). Therefore, we suggest that *Cordyceps Sinensis* is only suitable as an addition to the standard Asthma treatment using Western medicine.

4.2.2 Intravenous Transfusion formulation

Ginaton (Yuekang Pharmaceutical Group Co., Ltd.) is the extract from *Ginkgo Biloba*, containing 17.5mg *Ginkgo Biloba* extract, 4.2mg ginkgo flavones glycosides (Wang, Z.H. et al., 2016). It has a strong anti-coagulant and often used for ischemic brain injury or myocardial infarction. It was used in a study in 31 patients for one week (dissolved in 500 mL saline, i.v., once a day), in adjunction with Western treatments (corticosteroids, and if necessary noninvasive bi-level positive airway pressure) (Wang, Z.H. et al., 2016). Pulmonary function (FVC, FEV1, PEF), airway function (PFV, 25/PF, VT, ME/MI), and serum inflammatory cytokine levels (IL-6, IL-13, TNF-α) were evaluated.

Post-treatment, all pulmonary function markers and airway function markers were improved in both groups, however, the improvement of pulmonary function was greater in the treatment group than that of the control group ($P < 0.05$). TNF-α and IL-6 levels were decreased and IL-10 was increased in the treatment group compared with the control group, suggesting that the level of airway inflammation factors in the treatment group was better than in the control group. Such an administrative method is difficult for non-hospital setting, and restricted by whether such preparation is approved by local drug authorities, e.g. Food and Drug Administration in the US and Therapeutic Goods Administration in Australia.

4.2.3 Atomization

There is one study using aerosol generated from the extract of *Astragalus Mongholicus*, which is generally used to treat fatigue, allergy, and general cold (Li et al., 2017). In a mouse model of asthma induced by ovalbumin, *Astragalus Mongholicus* was shown to reduce eosinophils count, lung infiltration of immune cells, collagen deposition, and Th2 cytokine expression (Chen et al., 2014). In children with allergic asthma (Wang et al., 2018), oral *Astragalus Mongholicus* solution alone for 6 months significantly improved FEV1, and Pediatric Asthma Quality of Life Questionnaire compared with the placebo control group ($P<0.05$). *Astragalus Mongholicus* modulated the immune function. Serum Th2 cytokines were reduced whilst the anti-inflammatory cytokine IL-10 was increased with an increased percentage of $CD4^+$ T cells, $CD4^+CD25^+$ T cells, $CD4^+CD25^{high}$ Treg cells, $CD4^+CD25^+FoxP3^+$ Treg cells, and $CD4^+CD25^{high}CD127^{low}$ Treg cells in the peripheral blood (Wang et al., 2018).

In patients with uncontrolled asthma (Li, 2018), aerosol *Astragalus Mongholicus* extract was used along with routine treatment (doxophylline i.v., methylprednisolone i.v, inhalation of ipratropium bromide aerosol, and noninvasive positive pressure ventilation therapy), while the control group was only given the routine treatment (n=40 in each group). The endpoint measurement includes 8-iso-PG、IL-25、ET-1; and lung function measurements. After 7 days of treatment, in both groups, plasma levels of 8-iso-PG, IL-25, ET-1 were significantly decreased ($P < 0.05$), and lung function (PFV, VT, 25/PF, ME/MI, FVC, FEV1, PEF, FEV1/FVC) were significantly increased ($P < 0.05$). The effects on the above parameters in the intervention group were significantly better than those in the control

group ($P < 0.05$). The incidence of complications, tracheal intubation rate and the total cost of hospitalization in the intervention group were significantly lower than those in the control group ($P < 0.05$), and the length of hospitalization was significantly shorter than that in the control group ($P < 0.05$). Taking into consideration another trial (Hao, 2012) described earlier using a decoction, local administration by atomization using herbs seems to be an effective method to apply additional TCM treatments.

4.3 Other strategies

Acupuncture, acupoint injection, and cupping have also been used by TCM practitioners. Acupuncture is often used as an adjunct treatment to either control asthma symptoms or to prevent exacerbations. However, there is no evidence to show that it can improve lung function nor reduce asthma symptoms (Linde et al., 2003; Martin et al., 2002). The use of acupuncture in managing severe asthma symptoms is not common, perhaps due to concerns around the risk of pneumothorax. Although there were some studies using acupuncture in patients with uncontrolled asthma, this method was always used in combination with herbal decoction or other methods (Lu, 2004; Wang, 2003). Therefore, this treatment is not included in this review.

Acupoint injection was invented in the 1950s, which injects TCM or Western medicines (such as vitamin B12, Vitamin D2 calcium fructose, *Salvia Miltiorrhiza* extract, *Angelica Sinensis* extract, *Astragalus Membranaceus* extract) into a relevant acupoint to treat diseases (Wang et al., 2010). It can relieve pain, and improve immune function (Li-hua, 2005; Xie et al., 2020). In the clinic, it is mostly used for the treatment of controlled asthma. The common acupoint used in asthma includes Zusanli (ST36), Feishu (BL13), Quchi (LI11) (Li-hua, 2005). However, it is not a mainstream treatment choice for uncontrolled asthma. There are only 2 small published clinical trials of acupoint injection.

In the study by Lei et al. (Lei, 2005), 32 patients who failed to respond to routine Western treatment for one month were recruited. Additional acupoint injection with extracted Chuanshanlong decoction (2ml/day) was given to those patients at FeiShu (BL13) point. FVC, FEV1, PEF, and symptom scores were measured 2 weeks later. Among them, 78% (25/32 non-responding patients) responded to the

routine treatment with acupoint injection, and their lung function was also improved ($P<0.05$ by t test).

In 2001, a study of acupoint injection versus standard Western treatment protocols for patients with severe exacerbations of asthma in the ICU was reported in a Chinese medical journal (Lin, 2001). FeiShu (BL13) and DingChuan (EX-B1) points were chosen for acupoint injection. This study used acupoint injection as a method for subcutaneous delivery of Western medicine rather than TCM medicines. Aminophylline 50mg, desemisone 5mg, anisodamine 5mg, and lidocaine 40mg mixture were combined in the subcutaneous injections for the treatment group twice daily for 3 days (n=58). The patients in the control group were treated with standard western medicine approaches (n=54), including antibiotics, hydrocortisone, aminophylline, supplementary oxygen, airway clearance advice, and fluid resuscitation. There were no significant differences in lung function between the 2 groups before and after the trial, although more patients 'felt better' in the treatment group (93.1%) than the control group (73.6%). Four patients died in the Control group during the trial. No additional benefits were reported for lung function as there was no difference in the PEF and FEV1 after the treatments between 2 groups. The trial was too short to report any change in other outcomes. It also needs to be noted that the selection criteria only included patients having no treatments with steroids, β-agonist, and aminophylline in the past 3 months, which may cause such severe acute exacerbations requiring ICU level of care and a high death rate. The high death rates in this trial raise major questions about the study design and the type of care prior to the admission, the efficacy, and safety of the routine care to manage asthma exacerbations, and in our opinion should not be attempted again.

5. Discussion and Conclusions

In the RCTs available for review, Western medicine treatments (not standardized and not guideline-based, not all steroid containing) were effective in reducing asthma symptoms in patients over a two-week period in at least 70% of participants; while the addition of TCM increased this to 89-100%. (Chen and Ding, 2018; Cheng, 2014; Deng, 2013; He et al., 1997; Lin, 2001; Liu, 2015; Wang, 2017; Zhang, 2016; Zhou, 2005). The addition of TCM reported in these studies was not associated with significant adverse events, or side effects and was well tolerated. The exception is the trial in patients with severe exacerbations in the ICU, where patients in the control group died, but no deaths occurred in the trial group (Lin, 2001). However, we need to acknowledge that not every RCTs reviewed in

this paper included side effects as an endpoint measurement, therefore the conclusion was only based on those that reported such assessment.

There were several challenges faced by the authors of this review. The first is the issue of definitions and translation into English. This was seen in patient-reported outcomes, and the use of the term severe asthma. Many of the studies quoted refer to severe asthma, but because it is difficult to ascertain if a failure stepwise approach to asthma management occurred or patients were not controlled with Western medicines, it was impossible to ascertain if asthma was truly severe in these patients. The details of the trial suggested the word "severe' was used to imply troublesome or burdensome symptoms. Only one trial of TCM took this into account and recruited patients who failed to respond to Western routine treatment for one month (Lei, 2005). Most of the published trials in TCM are in fact addressing the treatment of acute exacerbation of symptoms that are described by patients as severe with short time frames and patient-reported symptom improvements. Western medicine recognizes that ongoing airway inflammation (even in the absence of symptoms) is a strong predictor of future exacerbations and correlates with hospital admissions and deaths (Holgate et al., 2015). None of the trials included in this review included airway inflammation as a measurement. The second challenge is the difference in the construct of pathophysiology between Western medicine and TCM. In TCM, the diagnosis is of asthma is based on different body energies that can cause symptoms. In Western medicine, asthma is defined as an inflammatory airway disease with multiple triggers and a complex (if incompletely understood) cascade of cellular pathways that each have the potential for targeted therapy (Holgate et al., 2015). None of these studies allow us to speculate on the effect of any one or combination of chemicals present in these herbs that might be targeting these pathways.

Unfortunately, there are no head to head, or large multicentre RCTs in the use of TCM treatments for asthma. Several problems would exist around the feasibility of doing such trials based upon the personalized treatment approach in TCM and the difference in diagnostic criteria, and the funding needed to carry out such large trials (there is no big pharmaceutical company equivalent in TCM). However, it would be possible to phenotype patients according to both TCM and Western medicine criteria and carry out such trials, and provide the evidence base to allow Western doctors to understand the utility of TCM treatments.

6. The take-home message for Western medical practitioners

Based on our review of the data, there appear to be some therapeutic properties in certain TCM treatments. Furthermore, there are known pharmacological effects of compounds found within various TCM treatments. However, the efficacy of such preparations is highly likely to vary depending upon where the herbs are sourced from, how they are prepared (raw, boiled, etc.), and if the herbs have been extracted and transformed into a more regulated tablet-like formulation. There are situations when the TCM treatment needs to be investigated further. The first is when patients with both western and TCM treatments are experiencing unusual side effects. The second situation is when the patients have intermittent loss of control of their asthma symptoms which is not due to known precipitant. It is worth remembering that TCM treatments are often short term, and the herbal combination can regularly change.

Glossaries: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; FEV1, Forced Expiratory Volume in the first second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; PEF, peak expiratory flow; RCTs, randomized clinical trials; TCM, Traditional Chinese Medicine.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1: Asthma types in TCM

TCM Type	Sputum	Cold/hot sensation	Complexion	Tongue	Pulse	Other symptoms
Cold-related (cold-flu related)	small amount of white sputum, difficult to cough out	cold intolerance	green barley complexion	white and slippery tongue coating	string tight or shallow tight	induced by cold weather or flu-like illness
Heat-related (inflamed)	white or yellow thick sputum, difficult to cough all out	sweating and thirsty with/without fever	red complexion	red tongue with yellow coating	slippery or string slippery	symptoms onset frequently in the summer
Wind phlegm (allergy related)	white sputum which is difficult to cough out	no cold/heat intolerance	green barley complexion	thick turbid tongue coating	smooth slippery pulse	rapid onset of asthmatic symptoms induced by allergy-like responses (itching nose, throat, eyes and ears, and frequent sneezing with congested running nose); difficulties to lie down due to a large amount of secretion in the lung

Table 2 Summary of the herbal preparations used in the clinical trails

Reference	Decoction	Base formula composition (g as in raw herb)	Modified version based on TCM patterns (g as in raw herb)
(Wen et al., 2005)	ASHMI capsules	Ling-Zhi (Ganoderma lucidum), Ku-Shen (Radix Sophora flavescentis), Gan-Cao (Radix Glycyrrhiza uralensis) (dose not provided)	
(Chen and Ding, 2018)	Authors' invention	Suzi (Perillaseed) 10g, Xingren (Almo-nd) 10g, Laifuzi (Semenraphani) 10g, Baiqian (Cynanchum glaucescens) 10g, Zhimahuang (Honey-fried herba ephedrae) 5g, Chenpi (Pericarpium citri Reticulatae) 5g, Baijiezi (Semen brassicae)5g, Zhibanxia (Pinellia ternata) 2g.	Cold type, additional Guizhi (Cassia twig) 6g, Ganjiang (Dried ginger) 3g, Baishao (Radices paeoniae alba) 9g, Gancao (liquorice) 1g, Zhimahuang (Honey-fried herba ephedrae) 5g, Zhibanxia (Pinellia ternata) 7g, Xixin (Asarum) 3g, Wuweizi (Schisandra chinensis) 6g. Heat type, additional Baiguo (Ginkgo) 15g, Suzi (Perillaseed) 5g, Zhibanx-ia (Pinellia ternata) 8g, Dilong (Lumbricus) 20g, Huangqin (Radix scutellariae) 15g, Yuxingcao (Herba houttuyniae) 30g, Zhitiannan-xin (System of rhizoma arisasmatis) 10g, Chantui (Periostracum cicagae) 15g, Zhisangbaipi (System of Cortex mori) 15g, Fangfeng (Saposhnicovia divaricata) 6g, Kuandong hua (Tussilago farfara) 9g, Baiguo (Ginkgo) 15g, Suzi(perillaseed) 5g, Zhibanxia (Pinellia ternata) 8g, Dilong (Lumbricus) 20g, Huangqni (Radix scutellariae) 15g, Yuxingcao (Herba houttuyniae) 30g, Tiannanxin (Rhizoma arisasmatis) 10g, Chaitui (Periostracum cicagae) 15g, Zhisangbaipi

			(System of Cortex mori) 15g, Fangfeng (Saposhnicovia divaricata) 6g, Kuandonghua (Tussilago farfara) 9g; Wind phlegm, additional Suzi (Erillaseed) 10g, Laifuzi (Semenraphani) 10g, Baijiezi (Semen brassicae) 15g, Tinglizi (Semen lepidii) 20g, Zhimahuang (Honey-fried herba ephed -rae) 5g, Shegan (Rhizoma belamcandae) 12g, Chaitui (Periostracum cicagae) 15g, Jiangchan (Bombyx batryticatus) 15g, Fangfeng (Saposhnicovia divaricata) 10g.
(Zhou, 2005)	Asthma of cold type, modified Xiaoqinglong decoction; Asthma of heat type, modified Dingchuan decoction. Asthma of wind phlegm type, authors' own decoction (aiming to remove wind-phlegm, reduce blood stasis, and relieving asthmatic symptoms).	Asthma of cold type: Muhuang (Herba ephedrae)10g, Guizhi (Cassia twig) 6g, Baishao (radices paeoniae alba) 9g, Ganjiang (dried giger) 3g, Banxia (Pinellia ternata) 9g, Xixin (Asarum) 3g, Wuwei-zi (Schisandra chinensis) 6g, Gancao (Liquorice) 6g, Shegan (Rhizoma belamcandae) 15g, Jiaomu (Papper orders) 10g, Asthma of heat type: Baiguo (Ginkgo) 12 pieces，Zisuzi (Perillaseed) 15g, Zhibanxia (Pinellia ternata) 9g, Zhitiannanxing (System of rhizoma arisasmatis) 9g, Dilong (Lumbricus) 15g, Huangqin (Radix scutellariae) 15g, Yuxingcao (Herba houttuyniae) 30g, Xingren (Almond) 9g, Zhisangbaipi (Honey-fried Cortex mori) 15g, Zhikuandonghua (System of tussilago farfara) 9g, Zhimahuang (Honey-fried herba ephedrae) 9g, Fangfeng (Saposhnicovia divaricata) 6g, Chantui (Periostracum cicagae) 15g.	Cold type with; Yang-deficiency (reduced heat production), adding Shufuzi (Practice of latera) l6g; Oliguria and water retention in lower limbs, adding Fuling (Paria cocos) 30g, Baizhu (atractylodes) 9g. Heat type with; Toxin syndrome (eg. haemorrhoids, erysipelas, furuncle): adding Shengdahuang (raw rhubarb) 9g; The need to nourish Qi and Yin: adding Shengmai decoction (dose not provided)

		Asthma of wind phlegm type: Zhimahuang (Honey-fried herba ephedrae) 9g, Shegan (Rhizoma belamcandae) 15g, Chantui (Periostracum cicagae) 15g, Jiangchan (Bombyx batryticatus) 15g, Lufengfang (Nidus vespae) 10g, Fangfeng (Saposhnicovia divaricata) 10g, Tinglizi (Semen lepidii) 15g, Zisuzi (Perillaseed) 15g, Laifuzi (Semenraphani) 15g, Eguanshi (Balanophyllia sp) 30g, Haigeqiao (Concha meretricis seu cyclinae) 30g, Taoren (Semen persicae) 9g.	
(Wang, 2017)	Modified Yupingfeng decoction (extracted powder)	Banxia (Pinellia ternata) 15g, Baishao (Adices paeoniae alba) 10g, Guizhi (Cassia twig) 12g, Huangqi (Astragalus) 9g, Baizhu (Atractylodes) 14g, Wuweizi (Schisandra chinensis) 7g, Zhigancao (Honey-fried liquorice) 5g.	Qi deficiency (a general short of energy), added Duzhong (Eucommia ulmoides) 10g; Spleen deficiency (poor with digestive and absorption functions), additional Yiyiren (Coix seed) 12g.
(Tang et al., 2013)	Herbal paste	Yinyanghuo (Herba Epimedii Brevicornus), Bajitian (Radix Morindae Officinalis), Huangqi (Radix Astragali Mongolici), Dangshen (Radix Codonopsis), Heshouwu (Radix Polygoni Multiflori), Huangjing (Rhizoma Polygonati Sibirici), Shudihuang (Radix Rehmanniae Preparata), Shanzhuyu (Fructus Corni), Maidong (Radix Ophiopogonis Japonici), Yeqiaomaigen (Fagopyrum Dibotrys Hara), Hutuiye (Lithocarpus Elaeagnifolia), Huangjingzi (Fructus Viticis Negundo), Fabanxia (prepared Pinellia Tuber) , Pugongying (Herba Taraxaci Mongolici), Ejiao (Colla Corii Asini), Guijiao (Colla Carapacis Et Plastri Testudinis), Gejie (Gecko), Ziheche	

		(Placenta Hominis), Baishen (White Ginseng), crystal sugar, and maltose.	
(Zhang, 2016)	Authors' invention Asthma No. 1	Shegan (Rhizoma belamcandae) 12g, Zhimahuang (Honey-fried herba ephedra) 6g, Xingren (Almonds) 10g, Ziwan (Radix asteris) 10g, Kuandonghua (Tussilago farfara) 10g, Xixin (Asarum) 3g, Qingbanxia (Alum processed pinellia) 9g, Wuweizi (Schisandra Chinensis) 10g, Chaihu (Bupleurum) 15g, Fangfeng (Saposhnicovia divaricata) 10g, Wumei (Dack plum) 12g, Changpu (Calamus) 10g, Yujin (Curcuma) 10g.	
(Cheng, 2014)	The combination of Xiaoqinglong decoction (raw herb), Sanziiyangqin decoction (raw herb), and Yupingfeng decoction (extracted powder)	Baijiezi (Semen brassicae) 6g, Ganjiang (Dried ginger) 9g, Zhigancao (Honey-fried liquorice) 9g, Wuweizi (Schisandra chinensis) 9g, Zisuzi (Perillaseed) 9g, Laifuzi (Semenraphani) 9g, Mahuang (Herba ephedrae) 9g, Baishao (Radices paeoniaealba) 9g, Guizhi (Cassia twig) 9g, Banxia (Pinellia ternata) 9g, Huangqi (Astragalus) 10g, Baizhu (Atractylodes) 10g, Fangfeng (Saposhnicovia divaricata) 5g.	Deficiency in spleen qi, additional, Yiyiren (Coix seed) 15g; Deficiency in Lung qi, increas the dosage of Wuweizi (Schisandra chinensis) and Huangqi (Astragalus); Deficiency in Kidney qi, additional Duzhong (Eucommia ulmoides) 12g.
(Liu, 2015)	Xiaoqinglong decoction, Sanziiyangqin decoction and Yupingfeng powder modified, added herbs who have the effect off promoting blood	Fangfeng (Saposhnicovia divaricata)15g, Huangqi (Astragalus) 15g, Baizhu (Atractylodes)15g, Banxia (Pinellia ternata)15g, Guizhi (Cassia twig) 10g, Zisuzi (Perillaseed)15g, Laifuzi (Semenraphani)15g, Wuweizi (Schisandra chinensis)10g, Zhigancao (Honey-fried liquorice) 10g, Baijiezi (Semen brassicae) 10g, Dilong	Deficiency in spleen qi, additional Yiyiren (Coix seed) 15g; Deficiency in Kidney qi, additional Duzhong (Eucommia ulmoides) 12g.

	circulation to remove obstruction.	(Lumbricus) 10g, Huangqin (Radix scutellariae) 10g, Danshen (Salviae miltiorrhizae) 20g.	
(Deng, 2013)	Xiaoqinglong decoction	Mahuang (Herba ephedrae) 15g, Ganjiang (Dried ginger) 15g, Zhigancao (honey-fried liquorice) 15g, Guizhi (Cassia twig) remove the peel 15g, Baishao (radices paeoniae alba) 15g, Xixin (Asarum) 6g, Wuweizi (Schisandra chinensis) 6g, Zhibanxia (Pinellia ternata) 10g.	modified according to the pattern of the patient.
(He et al., 1997)	Tingli relieving asthma decoction.	Tinglizi (Semen lepidii) 20g, Xingren (Almond) 10g, Sangbaipi (Cortex mori) 10g, Suzi(Perillaseed) 10g, Baijiezi (Semen brassicae) 10g, Laifuzi (Semenraphani) 10g, Chenpi (Pericarpium citri reticulatae) 10g, Banxia (Pinellia ternata) 10g, Yunfuling (Poria cocos) 10g, Danshen (Salviae miltiorrhizae) 10g, Taoren (Semen persicae)10g, Gancao (liquorice) 10g.	
(Wang, 2014)	The author's own invention - Xuanfeiyiqi decoction.	Huangqi (Astragalus) 25g, Baizhu (At-ractylodes) 12g, Chaobaizhu (Fried atractylodes) 8g, Fangfeng (Saposhnicovia divaricata) 10g, Xinyi (Flos magnoliae) 6g, Baizhi (Radix angelicae dahuricae) 9g, Wuweizi (Schisandra chinensis) 10g, Guizhi (cassia twig) 15g, Cangerzi (Fructus xanthii) 6g, Gancao (Glycyrrhiza) 3g, Jingjie (Herba schizonepetae) 10g, Jinyinhua (Honeysuckle) 15g.	
(Ma, 2014)	Asthma of cold type, Xiaoqinglong decoction modified; Asthma of heat type,	Asthma of cold type: Mahuang (Honey-fried herba ephedrae) 10g, Guizhi (Cassia twig) 6g, Baishao (Radices paeoniae alba) 9g, Ganjiang (Dried ginger) 3g, Banxia (Pinellia ternata) 9g, Xixin (Asarum) 3g,	

	Dingchuan decoction modified; Asthma of wind phlegm type, Sanziyangqin decoction modified.	Wuweizi (Schisandra chinensis) 6g, Gancao (Liquorice) 6g; Asthma of heat type: Baiguo (Ginkgo)15g, Zisuzi (perillaseed) 15g, Zhibanxia (Pinellia ternata) 10g, Zhitiannanxing (System of rhizoma arisasmatis) 10g, Dilong (Lumbricus) 20g, Huangqin (Radix scutellariae) 15g, Yuxingcao (Herba houttuyniae) 30g, Xingren (Almond) 9g, Chantui (Periostracum cicagae) 15g, Fangfeng (Saposhnicovia divaricata) 6g, Zhisangbaipi (System of cortex mori) 15g, Zhikuandonghua (System of tussilago farfara) 9g, Zhimahuang (honey-fried herba ephedrae) 10g. Asthma of wind phlegm type: Zisuzi (perillaseed) 20g, Laifuzi (seme-nraphani) 20g, Baijiezi (semen brassicae) 2g, Tinglizi (Semen lepidii) 20g, Zhimahuang (Honey-fried herba ephedrae) 10g, Shegan (Rhizoma belamcandae) 12g, Chantui (Periostrac-um cicagae) 5g, Jiangcan (Bombyx batryticatus) 15g, Fangfeng (Saposhnicovia divaricata) 10g .	
(Hao, 2012)	Tanqingning decoction inhalation	Chuanbei (Tendrilleaved fritillarybul) 15g, Banxia (Pinellia ternata) 15g, Jiegen (Platycodon grandiflorum) 15g, Jinyinhua (Honeysuckle) 15g, Sangbaipi (Cortex mori) 15g, Gancao (Glycyrrhiza) 10g.	
(Lu et al., 2015)	Asthma of cold type, modified Xiaoqinglong decoction; Asthma of heat type, modified Tanningqing; Asthma of wind phlegm	Asthma of cold type: Mahuang (Honey-fried herba ephedrae) 10g, Guizhi (Cassia twig) 6g, Baishao (Radices paeoniae alba) 9g, Ganjiang (Dried ginger) 3g, Banxia (Pinellia ternata) 15g, Xixin (Asarum) 3g, Wuweizi (Schisandra chinensis) 6g, Gancao (Liquorice) 6g, Shegan (Rhizoma belamcandae) 15g, Jiaomu	

	type, Authors' invention	(Bunge pricklyash seed) 10g; Asthma of heat type: Chuanbeimu (Fritillaria cirrhosa) 20g, Jiaomu (papar orders) 10g, Jiegeng (Radix platycodis) 15g, Jinyinhua (Honeysuckle) 15g, Zhisangbaipi (System of cortex mori) 20g, Gancao (Liquorice) 10g; Asthma of wind phlegm type: Zhimahuang (Honey-fried herba ephedrae) 15g, Shegan (Rhizoma belamcandae) 12g, Laifuzi (seme-nraphani) 15g, Haigeqiao (Concha meretricis seu cyclinae) 25g, Eguanshi (Balanophyllia sp) 25g, Jiangcan (Bombyx batryticatus) 12g, Fangfeng (Saposhnicovia divaricata) 9g, Chantui (Periostrac-um cicagae) 15g.	