BJNS
Brazilian Journal of Natural Sciences

TRADITIONAL CHINESE HERBAL MEDICINE AND CORTICOSTEROIDS IN ASTHMA: A SHORT REVIEW.

Gustavo Carrião dos Santos[1]; Eduardo Schmidt Eler[1]; Maria Eduarda Honorato de Oliveira[1]; Nathalia Rocha[1]; Paula Lobo Guimarães[1]; Rafaela Santana Curiele[1]; Carlos Rocha Oliveira[1],[2].[A]

[1]Anhembi Morumbi University, School of Medicine, Avenida Deputado Benedito Matarazzo 6070, São José dos Campos/SP, Brazil, 12230-002.
[2]Federal University of São Paulo (UNIFESP), Post-graduation Program in Biomedical Engineering, Rua Talim 330, São José dos Campos/SP, Brazil, 12231-280.

ABSTRACT

Asthma is a prevalent chronic inflammatory disease that has gold standard treatment with corticosteroids, but these are associated with important long-term side effects. On this basis, Traditional Chinese Medicine contributes with therapeutic techniques such as the herbal Anti-Asthma Herbal Medicine Intervention (ASHMI). In this context, this study aims to evaluate the effectiveness of treatment with ASHMI compared to conventional therapy, considering the need for new therapeutic approaches. An integrative review was performed, according to the PRISMA methodology. Articles published between 2011 and 2021 that related Herbal Medicines of Traditional Chinese Medicine, asthma and corticosteroids were examined. The searches took place in October and November 2021 in the Scopus, PubMed, Web of Science, Google Scholar, and Scielo databases. The selection comprised steps such as: search, pre-selection and inclusion of articles. The results of the herbal medicine and its isolated components were demonstrated, with three studies being clinical trials with humans and four pre-clinical studies. From the results, the efficacy of the herbal medicine and its components compared to corticosteroids were evaluated. It was reported that ASHMI, unlike corticosteroids, does not suppress the hypothalamic-pituitary-adrenal axis and the immune system, having mild adverse effects and significant inflammatory response, albeit late. The components showed positive responses in inhibiting asthma inflammation, which improved symptoms and quality of life. In conclusion, ASHMI, in addition to being effective for asthma, also showed safety and tolerability when compared to corticosteroids with long-term effects.

Keywords: asthma; ASHMI; phytotherapy.

INTRODUCTION

Asthma is a chronic inflammatory condition of the airways that affects children and adults, affecting approximately 262 million people in 2019 and causing 461,000 deaths[1]. Corticosteroids are considered gold standard in the treatment of asthma, however, they are associated with many long-term side effects[2]. Regarding the damage caused by steroids, the suppression of the hypothalamic-pituitary-adrenal axis, reduction in growth rate, diabetes and suppression of cellular immunity are important, as they impact on the quality of life of patients, and from that onwards, investigation is necessary regarding new therapeutic approaches[2,3]. Traditional Chinese Medicine (TCM) is an ancient science that uses a series of techniques, such as Chinese herbal medicine, to treat various pathologies. This technique aims to study medicinal plants and their properties, as well as their benefits, toxicity and mechanism of action[4].

ASHMI, anti-asthmatic herbal medicine developed by the Chinese Prof. Dr. Xiu-Min Li is a drug approved by the Food and Drug Administration for the treatment of asthma[5]. This

[A]Corresponding author: Carlos Rocha Oliveira - E-mail: pharmacologia@hotmail.com - ORCID: https://orcid.org/0000-0001-8634-2850.

DOI: https://doi.org/10.31415/bjns.v4i1.152 - Article received on: January 29, 2022; accepted on February 3, 2022; published on February 11, 2022 in the Brazilian Journal of Natural Sciences, ISSN: 2595-0584 - Vol. 4 - N.2. Online at www.bjns.com.br. All authors contributed equally to the article. The authors declare no conflict of interest.

compound contains the roots of *Sophora flavescens* (Ku-Shen) and *Glycyrrhiza uralensis* (Gan-Cao), and the fruiting bodies of the fungus *Ganoderma lucidum* (Ling-Zhi)[6]. Studies report that ASHMI seems to be a safe and effective alternative drug for the treatment of this chronic disease[7].

This study aims to evaluate the effectiveness of treatment with ASHMI compared to conventional corticosteroid therapy, considering the need for new therapeutic approaches for asthma since conventional treatment can cause a number of long-term complications.

METHODS

This study consists of an integrative literature review that aims to gather similar ones and analyze them about the benefits of the usage of ASHMI herbal in the treatment of asthma. The review of process was based on the recommendations from the Preferred Reporting checklist Items for Systematic Reviews and Meta-Analyses (PRISMA). Databases, Scopus, Web of Science PubMed, Google Scholar, and Scielo were searched for eligible articles, consulting the following keywords and their combinations in Portuguese and English: asthma and ASHMI; asthma and herbal medicine and corticosteroids; asthma and *Ganoderma lucidum*; *Glycyrrhiza uralensis*; *Sophora flavescens* and asthma; corticosteroids and asthma; corticosteroids and adverse effect. Two reviewers independently performed the literature search and study selection. The inclusion criteria for the selection of relevant studies included those that addressed use of ASHMI herbal, use of corticosteroids to treat asthma, use of herbal to treat asthma, and composition of ASHMI herbal. Exclusion criteria were as follows: letters, conference abstracts, case reports or series, and comments. Furthermore, publications in English and Portuguese were included and those indexed and published in the databases in the last ten years. The pre-selection of articles was made by preliminary reading of titles and abstracts. The pre-selected studies were read in full for the final selection of articles for analysis. Two reviewers independently performed the literature search and study selection.

RESULTS

Were identified 112 articles in the databases according to the search strategies. Then, after careful analysis, 85 studies were excluded. Finally, 10 studies met the inclusion criteria as well as the quality assessment. **Figure 1** shows the search flow diagram.

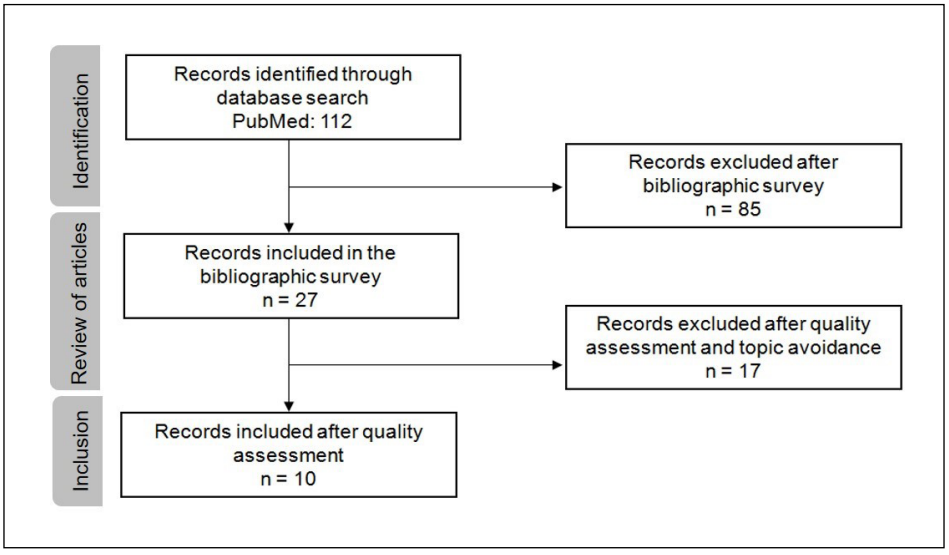

Figure 1: Flowchart for the selection of articles.

Regarding the ASHMI herbal medicine, JAYAPRAKASAM, et al. (2013) demonstraded that in murine Th2 cells, the herbal ASHMI produced a concentration-dependent inhibition of the production of IL-4, which is a cytokine released by Th2 cells and involved in allergic airway inflammation in asthma. The constituents in synergy contributed to the suppression of the production of IL-5, a cytokine involved in eosinophil activation. Eotaxin-1 was inhibited by a high concentration of ASHMI (500 µg/mL) and isolated Ling-Zhi[8].

Based on this, another study evaluated the response in relation to the decrease of eosinophils, neutrophils and airway hyperresponsiveness (AHR) in the use of dexamethasone and ASHMIII was compared and the herbal medicine showed a decrease in the AHR and in the percentage of neutrophils mainly. Furthermore, the treatment resulted in remarkable reductions in the levels of chemokines and cytokines involved in the recruitment of neutrophils and eosinophils. In vitro models suggest that C1 ganoderic acid (GAC1) performs an inhibition of tumor necrosis factor alpha (TNF-α) through the suppression of nuclear factor kappa B (NF-kB) [9].

WEN MC, et al. (2005) performed a double-blind, placebo-controlled, randomized clinical trial, where 45 subjects received 4 ASHMI capsules three times daily and prednisone-like placebo

 DOI: https://doi.org/10.31415/bjns.v4i1.152

tablets and another 46 subjects received oral prednisone tablets and placebo capsules. ASHMI for 4 weeks. The treatment effect on lung function was significantly greater in the prednisone group than in the ASHMI group, as the number of peripheral eosinophils was reduced in both groups. All pre-treatment subjects had serum cortisol slightly below normal, and after treatment, the prednisone group showed a significant reduction in serum cortisol levels, unlike the ASHMI group, which had increased levels. Regarding the reduction of inflammatory cytokines (IL-5 and IL-13), the prednisone group obtained a higher result than the ASHMI group. The group treated with ASHMI had high levels of interferon-gamma (IFN-γ) compared to the prednisone group, which had reduced levels after treatment. Finally, the study also showed that in both treated groups there was a decrease in the use of inhaled beta 2-agonists, and that ASHMI completely blocked airway hyperreactivity, significantly reducing eosinophilic inflammation in the lung[7].

PIEPER K, et al (2009) performed a double-blind, placebo-controlled, randomized clinical trial to assess the safety and tolerability of the herbal medicine ASHMI. At the end of the selection process, there were a total of 20 individuals, where 12 received ASHMI and another 8 received placebo. The majority of adverse events were mild to moderate grade II gastrointestinal complaints that did not require treatment. Synthesis of inflammatory markers remained normal during 1 week of ASHMI treatment, suggesting that there was no detrimental impact on the short-term immune response. The study highlighted that there were no acute asthma exacerbations during the study period[6].

Studies involving the isolated components of the ASHMI formulation were listed in this review in order to help understand the immunomodulatory and anti-inflammatory effect of the herbal compound. Thus, regarding *Sophora flavescens*, HOANG BX, et al. (2007) carried out a study with 14 individuals with moderate to severe asthma, aged between 22 and 70 years. These patients had been on asthma medication for 3-6 years, but still reported episodes of disease exacerbation. In the study, the extract was given in capsules at a dose of 4g of dried root, three times a day for 3 months, twice a day for 6 months and once a day for the next 27 months. After 3 years of follow-up, it was observed that daytime asthma symptoms were reduced by 97% and nighttime symptoms by 98%, the dose of beta 2-agonist was reduced by 97%, and no patient used inhaled corticosteroids. In addition to the peak expiratory flow rate (PEFR) which increased by 21%, all patients reported an improvement in general health, quality of life and sleep pattern during the trial[10].

Another study performed with *Sophora flavescens* demonstrated the allergic inflammatory reaction using human mast cells-1 (HMC-1). It was observed that *Sophora flavescens* inhibits the histamine release induced by the synthetic compound 48/80 at concentrations of 0.2mg/mL in a murine model; furthermore, it significantly suppressed the mast cell-dependent passive cutaneous anaphylaxis reaction at the concentration of 200mg/kg in murine model. *Sophora flavescens*-pretreated mast cells showed reduced expression of IL-8 and IL-6 after application of the stressors phorbol 12-myristate 13 acetate (PMA) and calcium ionophore (A23187). Finally, the molecular investigation showed that HMC-1 cells treated with *Sophora flavescens* and then induced with PMA and A23187 had a decrease in p38 Mitogen Activated Protein Kinases (MAPK) and (c-Jun N-terminal cinase) JNK, in addition to blocking the nuclear translocation of NF-kB and this inhibited the production of pro-inflammatory cytokines (TNF-α, IL-6 and IL-8)[11].

A single study in the literature envolving moleculrs aspects of *Ganoderma Lucidum* and inflammation showed that GAC1 extracted from *Ganoderma lucidum* was effective in inhibiting TNF-α synthesis by murine macrophages stimulated by lipopolysaccharides (LPS) and peripheral blood mononuclear cells (PBMCs) from patients with asthma, due to suppression of the signaling pathway NF-kB by suppressing the activator protein 1 (AP1) and MAPK pathways[12].

DISCUSSION

Asthma is an inflammatory airway disease with exacerbation of eosinophils (allergic asthma) and neutrophils (neutrophilic asthma). The first, allergic asthma, is usually treated with corticosteroids, while the second, neutrophilic asthma, which is associated with more severe and refractory asthma, and is therefore resistant to corticosteroids. Studies indicate that the synergy of the phytochemical constituents present in the ASHMI formulation **(Table 1**), contributes to suppress the production of cytokines, such as IL-5, IL-13, involved in the recruitment of neutrophils and eosinophils[8,9]. Eotaxin-1 was almost completely inhibited at high concentrations of the herbal medicine[8].

Table 1. Bioactive components of ASHMI herbal medicine.

	Herb	Bioactive components	References
ASHMI	*Sophora flavescens* (Ku-Shen)	Alkaloids: matrin and oxithrin	[11]
	Ganoderma lucidum (Ling-Zhi)	Triterpenoids: C1 ganoderic acid	[13]
	Glycyrrhiza uralensis (Gan-Cao)	Flavonoids and triterpene pentacyclic saponins	[14]

Moreover, the neutrophilic inflammation mediated by citokynes as TNF-α, IL-8 and IL-17, was the subject of investigation by Srivastava, wich observed that after the administration of the herbal medicine ASHMI and ASHMIII there was a significant reduction in the aforementioned cytokines. It is known that TNF-**α** is an important contributor to the pathophysiology of asthma, acting on airway hyperreactivity, mucus hyperproduction and smooth muscle cell proliferation. With the inhibition of this substance, these

 DOI: https://doi.org/10.31415/bjns.v4i1.152

processes become milder[9].

Corticosteroids are currently the mainstay treatment for asthma due to their anti-inflammatory action. Despite its effective action, the prolonged use of this drug can cause important adverse effects. One of these effects is the suppression of the hypothalamic–pituitary–adrenal (HPA) axis, which results in a decrease in serum cortisol levels, on the other hand, it was observed that after treatment with ASHMI, the levels that were previously reduced were normalized. Furthrmore, the treatment with ASHMI increased the serum levels of IFN-γ, suggesting an important immunomodulatory effect, in opposition, therefore, to the classic suppression of cellular immunity observed in the use of corticosteroids. Adverse effects with the use of ASHMI were mild gastrointestinal symptoms that did not require treatment, demonstrating safety and tolerability. Comparing corticosteroids and the ASHMI formulation, the herbal complex appears to have a late onset in symptom resolution, but it has been suggested that this long-term therapy may be more effective.[6,7].

Understanding the mechanism of action of a phytocomplex requires a view of the isolated functioning of each compound in the formulation. **Table 2** summarize the main bioactive components involved in the mechanism of action of ASHMI and herbs that are part of the formulation.

Table 2. ASHMI and its components: interventions and mechanism of action.

	Mechanism of Action	Intervention	References
ASHMI	- Inhibition of IL-4 and IL-5 production;	Clinical trial with 91 humans, within a period of 4 weeks	[7]
	- Inhibition of IL-4 production;	Murine Th2 cells	
	- Inhibition of eotaxin-1 production;	Human lung fibroblast in vitro	[8]
	- Blockade of airway hyper-reactivity, significantly reducing eosinophilic inflammation in the lung;		
	- TNF-α inhibition;		[9]
	- Inhibition of IL-4 and IL-5 production;	Murine macrophages	
Sophora flavescens	- Inhibition of the expression of pro-inflammatory cytokines (TNF-α, IL-6 and IL-8), by regulating the activation of MAPKs and NFkB;	Clinical trial with 14 humans over a 3-year period.	[10]
	- Suppresses the mast cell-dependent PCA reaction;		
	- Inhibits histamine release induced by the synthetic compound 48/80.	Human HMC-1 cells in culture.	[11]
Ganoderma lucidum	- Inhibition of TNF-α synthesis from macrophages when induced by LPS and PBMCs;	Human macrophages and PBMCs from asthma patients	[12]
	- Inhibition of eotaxin-1.	Human lung fibroblasts in vitro.	[8]
Glycyrrhiza uralensis	- Inhibition of inflammatory cell infiltration; - Decrease in oxidative stress; - Reduction in the production of pro-inflammatory mediators (TNF-α, IL-1β).	Animals and models of angiotensin-II induced abdominal arctic aneurysm.	[14]

Sophora flavescens (Ku-Shen) an oriental herb that presents as bioactive components the alkaloids matrin and oxithrin, was evaluated in study carried out for 3 years, there was a significant decrease in daytime and nighttime asthma symptoms in patients who received the extract at a dose of 4g per capsule, in addition to a 21% increase in PEFR. Patients showed a progressive improvement in symptoms from the second week of treatment onwards, and a consequent improvement in quality of life. In addition, a safety profile of the herb was reported, with very low toxicity, with only five episodes of mild diarrhea being observed in the first week of therapy[11]. This component was also responsible for inhibiting airway smooth muscle contraction, an effect that is independent of the use of corticosteroids[12].

Allergic asthma is mediated by eosinophils and mast cells, and with activation of the latter, TNF-a, and interleukins are released, playing an important role in allergic inflammation. The

 DOI: https://doi.org/10.31415/bjns.v4i1.152

effects of the species *Sophora flavescens* were demonstrated in a study based on the induction of stressors such as the synthetic compound 48/80, in which the inhibition of histamine release and PCA suppression by the use of *Sophora flavescens* was observed. Furthermore, other stressors such as PMA and A23187 tested using *Sophora flavescens* resulted in blocking the expression of TNF-α, IL-6 and IL-8 cytokines[11].

Another component of ASHMI is the fungus *Ganoderma lucidum* (Ling-Zhi) which was tested in isolation due to its better efficacy in inhibiting the synthesis of TNF-α compared to other components of ASHMI. Among the 15 compounds isolated, GAC1 was the highlight in the suppression of TNF-α[13]. Eotaxin-1 is a chemokine produced in pulmonary fibroblasts, responsible for inducing the migration of eosinophils from the bloodstream to the lung, being an important factor in inflammatory mediation[8]. In this sense, it was seen that the ASHMI compound inhibited the production of this chemokine almost completely at high concentrations, as did Ling-Zhi alone[8].

The component of ASHMI is the root of *Glycyrrhiza uralensis* (Gan-Cao), also known as licorice[15], is traditionally used for asthma due to its anti-inflammatory action, related to the inhibition of inflammatory cell infiltration, decrease in oxidative stress and reduction in the synthesis of inflammatory mediators (TNF-α and IL-1β)[16].

Therefore, based on cellular and molecular findings that try to explain, even partially, the isolated action of medicinal plants from ASHMI formulation, we suggest that the TCM formulation has beneficial effects in patients with asthma.

CONCLUSION

This review indicates that the TCM formulation known as ASHMI can be useful in relieving asthma symptoms, also indicating positive aspects related to safety and tolerability, when compared to corticosteroids.

However, the reduced number of publications on the subject, such as clinical trials, are importants limitations of this review, especially in relation to the evaluation of the effectiveness of corticosteroids when compared to the ASHMI formulation.

FUNDING INFORMATION

This study had no financial support and is not associated with funding agencies, so this work has not been modified according to the requirements of these agencies and grant-making bodies.

REFERENCES

1- World Health Organization. **Asma.** Acess in 29 oct 2021. Available in https://www.who.int/news-room/fact-sheets/detail/asthma.

2- Leonard P, Sur S. **Asthma: future directions**. Med Clin North Am. 2002 Sep;86(5):1131-56. Acess in 29 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/12428548/.

3- Heffler E, Madeira LNG, Ferrando M, Puggioni F, Racca F, Malvezzi L, Passalacqua G, Canonica GW. Inhaled **Corticosteroids Safety and Adverse Effects in Patients with Asthma**. J Allergy Clin Immunol Pract. 2018 May-Jun;6(3):776-781. Acess in 29 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/29408385/.

4- Meneses AS. **Chinese Herbal Medicine**. [Dissertation]. Porto: UFP; 2016.

5- Hong ML, Song Y, Li XM. **Effects and mechanisms of actions of Chinese herbal medicines for asthma**. Chin J Integr Med. 2011 Jul;17(7):483-91. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/21725872/.

6- Kelly-Pieper K, Patil SP, Busse P, Yang N, Sampson H, Li XM, Wisnivesky JP, Kattan M. **Safety and tolerability of an antiasthma herbal Formula (ASHMI) in adult subjects with asthma: a randomized, double-blinded, placebo-controlled, dose-escalation phase I study**. J Altern Complement Med. 2009 Jul;15(7):735-43. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/19586409/.

7- Wen MC, Wei CH, Hu ZQ, Srivastava K, Ko J, Xi ST, Mu DZ, Du JB, Li GH, Wallenstein S, Sampson H, Kattan M, Li XM. **Efficacy and tolerability of anti-asthma herbal medicine intervention in adult patients with moderate-severe allergic asthma**. J Allergy Clin Immunol. 2005 Sep;116(3):517-24. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/16159618/.

8-Jayaprakasam B, Yang N, Wen MC, Wang R, Goldfarb J, Sampson H, Li XM. **Constituents of the anti-asthma herbal formula ASHMI(TM) synergistically inhibit IL-4 and IL-5 secretion by murine Th2 memory cells, and eotaxin by human lung fibroblasts in vitro**. J Integr Med. 2013 May;11(3):195-205. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/23743163/.

9- Srivastava KD, Dunkin D, Liu C, Yang N, Miller RL, Sampson HA, Li XM. **Effect of Antiasthma Simplified Herbal Medicine Intervention on neutrophil predominant airway inflammation in a ragweed sensitized murine asthma model**. Ann Allergy Asthma Immunol. 2014 Apr;112(4):339-47.e1-2. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/24679734/.

10- Hoang BX, Shaw DG, Levine S, Hoang C, Pham P. **New approach in asthma treatment using excitatory modulator**. Phytother Res. 2007 Jun;21(6):554-7. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/17295384/.

11- Hong MH, Lee JY, Jung H, Jin DH, Go HY, Kim JH, Jang BH, Shin YC, Ko SG. **Sophora flavescens Aiton inhibits the production of pro-inflammatory cytokines through inhibition of the NF kappaB/Ikappa B signal pathway in human mast cell line (HMC-1).** Toxicol In Vitro. 2009 Mar;23(2):251-8. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/19118619/.

12- Liu F, Xuan NX, Ying SM, Li W, Chen ZH, Shen HH. **Herbal Medicines for Asthmatic Inflammation: From Basic Researches to Clinical Applications.** Mediators Inflamm. 2016; 2016:6943135. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/27478309/.

13- Liu C, Yang N, Song Y, Wang L, Zi J, Zhang S, Dunkin D, Busse P, Weir D, Tversky J, Miller RL, Goldfarb J, Zhan J,

Li XM. **Ganoderic acid C1 isolated from the anti-asthma formula, ASHMI™ suppresses TNF-α production by mouse macrophages and peripheral blood mononuclear cells from asthma patients. Int Immunopharmacol**. 2015 Aug;27(2):224-31. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/26004313/.

14- Zhang Y, Wang X, Zhang H, Tang H, Hu H, Wang S, Wong VKW, Li Y, Deng J. **Autophagy Modulators From Chinese Herbal Medicines: Mechanisms and Therapeutic Potentials for Asthma**. Front Pharmacol. 2021 Jul 23; 12:710679. Acess in 15 oct 2021. Available in https://pubmed.ncbi.nlm.nih.gov/34366865/.

15. Maria Pia GD, Sara F, Mario F, Lorenza S. **Biological Effects of Licochalcones**. Mini Rev Med Chem. 2019;19(8):647-656. doi: 10.2174/1389557518666180601095420. PMID: 30049263.

16. Yang R, Yuan BC, Ma YS, Zhou S, Liu Y. **The anti-inflammatory activity of licorice, a widely used Chinese herb**. Pharm Biol. 2017 Dec;55(1):5-18. doi: 10.1080/13880209.2016.1225775. Epub 2016 Sep 21. PMID: 27650551; PMCID: PMC7012004.