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The Review of in Vitro and in Vivo Studies over the Glycyrrhizic Acid as Natural Remedy Option for Treatment of Allergic Asthma

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ABSTRACT

Allergic asthma is the most common type of allergy which have become increasingly prevalent in all around the world. Airway eosinophilic inflammation is a major feature of allergic asthma. Glycyrrhiza uralensis (licorice) is one of the regular herbs in traditional Chinese medicine (TCM) as it has many effects on the immune system such as anti-inflammatory and immune regulatory activity; antiviral and antitumor effects.

This review focuses on the "licorice" components, mainly glycyrrhizic acid (GA) and derivatives structure that evaluate its effects on the allergic asthma. We performed searching articles in Pubmed, Web of Science, and Scopus data bank from 1990 to 2017. The search syntax were: "glycyrrhizin" OR " glycyrrhizic acid" OR " glycyrrhizinic acid" OR" glycyrrhiza glabra" OR " liquorice root" OR "G. glabra" OR "glycyrrhizic Acid" AND "allergic asthma" OR "bronchial asthma" OR "asthma, bronchial" OR "airway hyper-responsiveness" OR "airway inflammation".

Several molecular mechanisms and inflammatory mediators may possibly be responsible for efficacy of glycyrrhizin. Some in vitro studies indicated to the fact that possible mechanisms of anti-inflammatory effects could be through reduction of pro-inflammatory mediator's synthesis that motivates eosinophil, basophils and mast cells to release cytokines for the differentiation of T helper cells into Th2 cells to secrete interleukins.

Furthermore, some transcription factors such as NF-ϰB, STAT6 and HDAC2 go between modulations of anti-asthmatic effects. The last but not the least it can be said that glycyrrhizin is potentially a good herbal drug with the lower most adverse effects for asthma treatment.

Keywords: Allergic asthma; Glycyrrhizic acid; Herbal medicine; Inflammation

INTRODUCTION

Asthma is a common inflammatory disease of the lungs' airways that is considered by variable and recurring symptoms. Its symptoms and indicators are consisting of coughing, shortness of breath, wheezingand chest tightness.[1] The incidence rates of asthma have increased notably since the 1960s.[2] A dramatic increase has been seen in the prevalence of allergic asthma, in the United States around fifteen million people are suffer ring from allergic asthma.[3]

In 2015,359 million people globally had asthma

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which is more than 183 million in 1990.[4]

The common type of asthma is associated with allergy which involves an extensive range of aeroallergens.[5] Allergic asthma is characterized by Airway Hyper Responsiveness (AHR) to a different range of specific and nonspecific allergens, extreme airway mucus production, chronic pulmonary eosinophilia, elevated serum immunoglobulin E (IgE).[6] It is a consequence of polarization of the mucosal T cell response to a T helper 2 (Th2) phenotype that leads to the selective enrollment of mast cells, basophils, eosinophils and B cells switching to produce allergen-specific IgE and finally leads the inflammatory response.[7]

The pathophysiology of allergic asthma is mainly connected to the aberrant expansion of CD4+ T cells producing the type 2 cytokines interleukin-4 (IL-4), IL-5 and IL-13.[8] However, discovering more subtypes of helper T cells and their cytokines such as Th17, Th9, Th22 and Th25 led to re-consider the immunopathology of asthma.[9]

CD4+CD25+Foxp3+regulatory T cells (Treg cells) are distinct subsets fromTh1 and Th2 cells that expressing the fork head/winged helix transcription factor (Foxp3) and have some anti-inflammatory role through straight contact with cells or anti-inflammatory cytokines like IL-10 and transforming growth factor-β1 (TGF- β1) release and then Treg cells suppress the allergic airway disease.[10]

Although progress in our understanding of the pathogenesis of asthma increased significantly in the past two decades, it is still very difficult to control asthma. Generally, treatment strategy is lessening symptoms by avoiding triggers, such as allergens and irritants, and by using of inhaled corticosteroids, long-acting beta agonists (LABA) or anti-leukotriene agents.[11,12]

Phosphodiesterase inhibitor regulate the generation of IL-4 and IL-13 from human basophils. It has important role in regulating mast cell b2-adrenoceptors.[13,14] The cyclic adenosine mono phosphate /protein kinase A (cAMP/PKA) pathway may be inhibitory to the IgE and non-IgE-dependent release of mediators from basophils.[15]

Additionally, Treg cells also modulate immune responses via establishment of a balance between Th1/Th2 cell-related responses. Thus, immunotherapeutic agents which lead to increase the number and/or functions of Th1/Treg cells may be considered as a suitable candidate for the treatment of asthma. Presently, several adjuvants [especially toll like receptors (TLR_s) agonists] are introduced as main inducers of Th1 and/or Treg cells.[16,17]

Current conventional medications for this chronic disorder are not fully satisfactory and prolonged usage often causes serious side effects. Thus effective and safe alternative medicines are needed to improve the asthma treatment. All the way over the history of medicine, medications have been resulting from the traditional medicine and some of these herbal interventions work in the desire way much better than chemical ones because of their satisfactory efficacy in clinic and low toxicity.[18] Pharmacological activities of several medical plant derived compounds have been demonstrated over the last three decades and there has been increasing interest in Complementary and Alternative Medicine (CAM).[19,20]

Licorice (*Glycyrrhiza glabra* L. or *G.uralenesis* Fisch, Leguminosae) is one of the most commonly used traditional medicines in different countries.[21] Glycyrrhizin and flavonoids such as liquiritigenin ,are as the major components of the licorice.[22,23] In fact, licorice extracts and its principle component, glycyrrhizin, have extensive use as complementary or alternative medicines in asthma.[24-26] In written document form starting with the ancient Greeks it is shown that licorice root has even been utilized in Europe since prehistoric times.[27] During the last two decades several controlled clinical studies of "anti-asthma" herbal remedies have been published.[28] Several studies have reported using of glycyrrhizin as an anti-inflammation factor in order to appease the asthma symptoms or even asthma remedies.[29] Licorice and its components have several pharmacological effects including estrogen like,[30] anti-carcinogenic,[31,32] antiasthmatic, antiallergic,[33] antimicrobial[34] and antiviral activities.[35] This review will be useful for researching GA to consider it characteristics and derivatives impacts on allergic asthma as a novel herbal drug.

Glycyrrhizin Characteristics and Components

Glycyrrhiza is a genus plant, consists of around eighteen prominent species in the legume family (Fabaceae) that spreading in Asia, Australia, Europe and the Americas. These 18 species include: *Glycyrrhiza acanthocarpa* (native liquorice), *Glycyrrhiza aspera*, *Glycyrrhiza astragalina*,

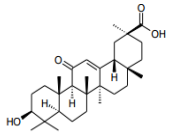
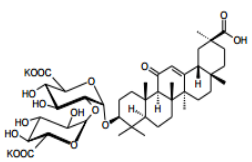
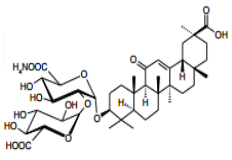
Glycyrrhiza bucharica , *Glycyrrhizaechinata*, *Glycyrrhiza eglandulosa*, *Glycyrrhiza foetida*, *Glycyrrhiza foetidissima*,*Glycyrrhiza glabra* (liquorice, licorice), *Glycyrrhiza gontscharovii*, *Glycyrrhiza iconica*, *Glycyrrhiza inflata*, *Glycyrrhiza korshinskyi*, *Glycyrrhiza lepidota*, *Glycyrrhiza pallidiflora* , *Glycyrrhiza squamulosa*, *Glycyrrhiza triphylla* ,*Glycyrrhiza uralensis*, *Glycyrrhiza yunnanensis*. The class is best known for liquorice (British English; licorice in the American English), *G. glabra*, a species native to the Mediterranean region, from which the confectionery liquorice is produced. Very little *G. glabra* is grown in the North America, but American licorice *G. lepidota* is a common native species there. Russian liquorice (*G.echinata*) and Chinese Liquorice (*G. uralensis*).[36,37]

The major chemical constituents in *Glycyrrhiza* are triterpenoids and flavonoids with anti-inflammatory effects.[38] Triterpenoid saponins are triterpenes which contains 30 carbon atoms. Flavonoids usually have the unique structure of a 15-carbon skeleton and are made of two phenyl rings and heterocyclic ring.[39]

Chemically, glycyrrhizin is a sulphated polysaccharide named (3-beta,20-beta)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-O-beta-D-glucopyranuronosyl-alpha-D-glucopyranosiduronic acid. The active component of the drug and the standardization of licorice is based on glycyrrhizin content. The standardized extracts of licorice sold in the market contain 20% of glychrrhizin. Glycyrrhizin is converted into glychyrrhetic acid by an enzyme, glycaronidase.[40]

In fact, *Glycyrrhiza glabra*, has been famous for its long use as a sweeter, because it contains glycyrrhizin which is a potent sweetener and is also known as glycyrrhizic acid. As it is shown in Table1 when it is hydrolized, its triterpenic derivative glycyrrhizic acid may be used for its soothing characteristics as a lenitive compound in skin care applications, whereas the form of salted ammonium or potassium of glycyrrhizic acid are strong sweeteners. Glycyrrhizic acid possess a great variety of pharmacological and biological properties such as anti-inflammatory, anti-ulcerogenic, anti-allergic, anti-oxidant, anti-hepatotoxic, anti-tumor and antiviral activities.[41-43]

Table 1. Some characteristics of glycyrrhetinic acid derivatives

Name	18beta-GLYCYRRHETINIC ACID	18beta-GLYCYRRHETINIC ACID PHYTOSOME ®	DIPOTASSIUM GLYCYRRHIZINATE	GLYCAMIL® (MONO AMMONIUM GLYCYRRHIZINATE)
Assay	≥98.0 ≤102.0% of 18beta-glycyrrhetinic acid by HPLC referred to the anhydrous substance	≥27.0≤31.0% of 18beta-glycyrrhetinic acid by HPLC	≥96.0≤102.0% of dipotassiumglycyrrhyzinate by spectrophotometry	≥98.0≤102.0% of monoammoniumglycyrrhizinate by potentiometry
Form	white / off white crystalline powder	White / off white powder	White / yellowish-white powder	White / yellowish-white powder
Dosage	0.5-3%	0.5-3%	up to 1%	0.01–0.05%
Solubility	Soluble in 96% ethanol, propylene glycol, ethoxydiglyco	Soluble in ethoxydiglycol, Isopropyl myristate, C10-18 triglycerides, C12-15 alkyl benzoate, triticumvulgare (wheat germ oil), Triclocarban	freely soluble in water	Slightly soluble in water, soluble in acidic or basic diluted solutions
Molecular structure				

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Methodology

In order to retrieve the related research for running this review article. We performed searching articles in Pubmed, Web of Science, and Scopus data bank from 1990 to 2017. The search syntax were: "Glycyrrhizin" OR " glycyrrhizic acid" OR " glycyrrhizinic acid" OR" Glycyrrhiza glabra" OR "liquorice root" OR "G. glabra" OR "Glycyrrhizic Acid" AND "Allergic Asthma" OR "Bronchial Asthma" OR "Asthma, Bronchial" OR "airway hyper-responsiveness" OR "airway Inflammation". Both in vitro and in vivo studies had taken into the considerations in order to evaluate anti asthmatic effect of Glycyrrhizic acid. Unpublished thesis works and congresses communications were excluded. All final selected articles should be written in English.

In Vitro Studies of Glycyrrhizin Impact on Asthma

Several studies provide the scientific basis for the anti-inflammatory effects of glycyrrhizin extract to develop and evaluate herbal preparations.[44-48] For example, the licorice extract and its three bioactive components, glycyrrhizic acid (GA), liquiritin (LQ) and liquiritigenin (LG),inhibited LPS-stimulated elevation of pro-inflammatory mediators like inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF)-alpha, IL-1beta and IL-6 in BV2 (mouse brain microglia) cells,[49] IL-4 and IL-5 secretion.[50] According to the research findings, both glycyrrhizin and dexamethasone inhibited transactivation of nuclear factor (NF)-kappaB, without inhibiting translocation of the NF-kappaB p65 subunit to the nucleus. NF-κB (nuclear factor kappa-light-chain-enhancer of the activated B cells) is a protein complex that controls transcription of DNA, cytokine**.** Only glycyrrhizin inhibited DNA binding of p65 to the IL-8 promoter region. Thus, it might be possible that glycyrrhizin inhibitory effect on IL-8 production via a mechanism that differs from that of glucocorticoids.[51] Because glycyrrhizin had a glucocorticoid-like, thus it could be an encouraging treatment for asthma. In another study, glycyrrhizic acid inhibits inflammation via PI3K/Akt/GSK3β pathway to reduce cytokine production, while 18β-glycyrrhetinic acid leads to the dissociation of a glucocorticoid receptor (GR)-HSP90 complex to block inflammation. Therefore, they display anti-inflammatory activities but inhibit inflammation through different mechanisms.[52] Glycyrrhizin component extends the dormancy time of histamine–acetylcholine aerosol-induced collapse. It relaxes guinea-pig trachea through a multiple of intracellular actions, including soluble guanylate cyclases GC activation, inhibition of cGMP-specific phosphodiesterase (PDEs) and associated activation of the cyclic Guanosine Mono Phosphate-dependent Protein Kinase G (cGMP/PKG) signaling cascade, leading to the opening of calcium activated Big Potassium Channels (BKCa channels) and calcium [Ca2+] decrease through Protein Kinase G (PKG) dependent mechanism and thus to tracheal relaxation.[53]

Glycyrrhizin attenuated significantly the MUC5AC protein and mRNA expression by tumor growth factor (TGF)-α in cultured NCI-H292 cells, Therefore, glycyrrhizin has an inhibitory effect on mucus hyper production through the inhibition of MUC5AC gene transcription.[54] Glycyrrhetinic acid also increases circulating and salivary levels of unconjugated deoxycorticosterone and dehydroepiandrosterone by inhibiting their conjugation at source within the adrenal cortex through changing the expression of SULT 2A1 Mrna.[55]

The results of another study showed that significantly decreased phorbol 12-myristate 13-acetate (PMA) stimulated NCI-H292 human airway epithelial cell MUC5AC gene expression and mucus production inhibition was associated with the suppression of NF-κB, STAT6 activation and enhanced HDAC2 expression.[56]

In the same way, in vitro studies on human fetal lung fibroblasts (HFL-1) has been established that constituents in anti-asthma herbal medicine intervention (ASHMI) synergistically inhibited eotaxin-1 production as well as Th2 cytokine production.[50,57] In the allergic asthma, the eosinophilic inflammation is a major feature. Eotaxin-1 (eotaxin) is responsible to take on eosinophils to the exact site of antigen-induced inflammation which its major source is the human lung fibroblasts. There is a more possibility that *Glycyrrhiza* flavonoids has capacity of eotaxin-1 secretion inhibition through the human fetal lung fibroblasts.[57] GA could increase the permeability (about 60%) and to decreased elasticity modulus of cell membranes even in micro-molar concentrations.[58]

Table 2 summarizes some of anti-asthmatic and anti-inflammatory effects of licorice and its bioactive components in vitro.

Table 2. Some of anti-asthmatic and anti -inflammatory effects of licorice and its bioactive components in vitro

Component	Method	Mechanism	References
Glycyrrhizic acid, liquiritin and liquiritigenin	BV2 Cells	Inhibition of LPS-stimulated elevation of pro-inflammatory mediators like iNOS, COX-2, TNF-α,Il-1β, Il-4, IL-5 and Il-6	49, 50
Glycyrrhizin	Lung epithelial cells	Inhibition of DNA binding of NF-kappaB p65 subunit to the IL-8 promoter region.	50
Glycyrrhizin **18β-Glycyrrhetinic acid**	BALB/c macrophage cell line (RAW264.7)	Inhibition of inflammation via PI3K/Akt/GSK3β pathway to dissociation of a glucocorticoid receptor (GR)-HSP90 complex	52
Glycyrrhizin	Guinea-pig trachea	Tracheal relaxation through Protein Kinase G (PKG)dependent mechanism	53
Glycyrrhizin	NCI-H292 cells	Inhibition of MUC5AC gene transcription	54
Glycyrrhetinic acid	Adrenocortical H295 cells	Changing the expression of SULT 2A1 mRNA	55
G. *uralensis* flavonoid 7,*4*'-dihydroxyflavone (7,*4*'-DHF)	Human pulmonary epithelial cell line NCI-H292	Decrease of MUC5AC gene expression associated with the suppression of NF-κB, STAT6 activation and enhanced HDAC2 expression	56
Constituents in ASHMI	Human fetal lung fibroblasts	Inhibition of eotaxin-1 and Th2 cytokine production	50, 57
Glycyrrhizin	Human erythrocytes	Increase the permeability and decrease the elasticity modulus of cell membranes	58

LPS: Lipopolysaccharide, iNOS: Inducible nitric oxide synthase, COX-2: Cyclooxygenase-2, TNF-α: Tumor necrosis factor-α, IL-4: Interleukin 4, HSP90: Heat shock protein 90, MUC5AC: Mucin 5AC, SULT 2A1: Sulfotransferase family 2A member 1, STAT6: Signal transducer and activator of transcription 6 , HDAC2 : Histone deacetylase 2, ASHMI: Antiasthma simplified herbal medicine intervention.

In Vivo Studies of Glycyrrhizin Impacts on Asthma

Immunomodulatory effects of different components and adjuvants for asthma treatment has been checked several times in different animal models.[16,17,59,60] Due to the beneficial properties of the bioactive components within licorice root and plant, it has been adopted by traditional herbal medicine in many cultures. For example, licorice appears in approximately 60% of the traditional Chinese medicine prescriptions as an effective agent in the treatment of allergic asthma, fatigue, dry cough, bronchitis, excessive phlegm and for relieving drug toxicity.[61,62] Additionally, the expression levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in the livers of a tert-butylhydroperoxide t-BHP-treated mice models has been repressed as well.[49] Some beneficial effects in long-term histo-pathologic changes of the lung in the asthmatic mouse model

have been shown, including considerably higher numbers of goblet and mast cells more than increased thickness of epithelium, basement membrane, and sub-epithelial smooth muscle layers.[63] Rat lung beta2-adrenergic receptor (β2-AR) mRNA level measurement after using glycyrrhizin in combination with salbutamol by real-time RT- PCR shown an intracellular accumulation of cyclic adenosine monophosphate. Consequently, the synergistic anti-asthmatic effects of glycyrrhizin and salbutamol offer the possibility of a therapeutic application of glycyrrhizin in combination with β2-AR agonists in the treatment of asthma.[64,65] As GA regulated the Th1/Th2 balance through suppression of OX40-OX40L signaling and p38 MAPK activity. Thus, it has a therapeutic effect on the ovalbumin (OVA)-induced allergic asthma.[66] Glycyrrhizin has a preventive influence on mucus hyper production both in vivo and in vitro through the inhibition of MUC5AC gene transcription.[54] *G.uralensis* flavonoid 7, 4'-dihydroxyflavone (7, 4'-DHF) treated mice compared with the control mice shown a noticeable decrease in the MUC5AC secretion in the Broncho Alveolar Lavage (BAL) fluid. 7,4'-DHF also as a newly identified component of G. *uralensis* regulates the MUC5AC expression and secretion via the regulation of NF-κB, STAT6 and HDAC2.[56] According to the findings of another study, GA effectively ameliorates the airway inflammation of asthma via inhibiting the Th2 responses though modulating the expressions of CD86, MHC-II, CD40 and OX40L on CD11c(+) DCs.[67]

Further immune regulatory and anti-asthmatic effects of glycyrrhizic acid via modulation of Th1/Th2 cytokines and enhancement of CD4 Treg cells in the ovalbumin-sensitized mice have been shown.[68] later study show that GA inhibit OVA-induced increases in airway resistance and eosinophil count; IL-4, IL-5, IL-13levels were recovered in bronchoalveolar lavage fluid (BALF), increased IFN-γ level in BALF; histological studies demonstrated that GA substantially inhibited OVA-induced eosinophilia in lung tissue and airway tissue compared with model group.[68]The study comprised of 63 patients with bronchial asthma showing that a compound made of *Boswellia serrata*, *Curcuma longa* and glycyrrhizin has a pronounced effect in the management of bronchial asthma due to changing the level of plasma leukotriene C4 (LTC4), nitric oxide (NO) and malondialdehyde (MDA).[46]

Licorice has been repeatedly used in the traditional medicine to treat inflammatory and allergic diseases because the main isolated components (glycyrrhizin, 18β-glycyrrhetinic acid, isoliquiritin and liquiritigenin) from licorice have some anti-allergic effects, such as anti-scratching behavior and IgE production-inhibitory activity. Actually these three components inhibited IgE production in ovalbumin-induced asthma mice but liquiritigenin had slighter effect. Thus, antiallergic properties of licorice are mostly related to glycyrrhizin, 18β-glycyrrhetinic acid, and liquiritigenin.[69]

More than a few flavonoids were isolated from the *Glycyrrhiza uralensis* as an anti-asthmatic herbal medicine intervention. One of the valuable components is called (ASHMI) which is the only anti-asthma herbal product that has the Food and Drug Administration (FDA or USFDA) approved and appeared in some clinical trials.[70] Subsequently, many different explorations about ASHMI's special effects and mechanisms of actions in animal models and cultured cells were being followed.[71]

The *Glycyrrhiza uralensis* flavonoids present in the ASHMI inhibited memory Th2 cells in vitro and suppressed powerfully GATA-3 (key Th2 cell transcription factor) production as well. The persistence of the ASHMI effects following therapy in a murine model (BALB/c) mice have been shown by decreasing the allergen-specific IgE and Th2 cytokine levels and increasing IFN-gamma levels.[70,72]

ASHMI eliminated early phase airway responses (EAR), which was associated with considerably reduced histamine, leukotriene C4 and ovalbumin-specific IgE levels. In addition, it is associated with the BALF eosinophils reduction, and lesser Th2 cytokine levels in the BALF and cultures of splenocyte.[70] It has also been shown that Complex Traditional Chinese Medicine (CTCM) eliminate the increased lung resistance induced by challenge with ovalbumin in the early asthmatic response (EAR). In addition, higher serum levels of IgE were seen in the serum of sensitized guinea pigs than in the unsensitized controls.[73] ASHMI induced long-lasting post-therapy tolerance to antigen-induced inflammation through IFN-γ as a critical mediator.[72,74] We must stress that antiasthma herbal medicine intervention is a safe and effective alternative medicine for treating asthma for the reason that in contrast with prednisone, ASHMI had no adverse effect on adrenal function and had a

beneficial effect on Th1and Th2 balance.[75] In the course of a randomized, double-blinded phase I study safety and tolerability of ASHMI in the adult subjects with asthma has shown that the vital signs, electrocardiogram findings, and laboratory results obtained at pre- and post-treatment visits remained within normal range. No abnormal immunologic alterations were detected. Thus, ASHMI (Gan Cao from *Glycyrhhiza uralensis* is one component of ASHMI) can be considered a possible alternative therapy for patients suffering from asthma.[76]

Table 3 summarizes some of anti-asthmatic and anti-inflammatory effects of licorice and its bioactive components in vivo.

Table 3. Some of anti-asthmatic and anti -inflammatory effects of licorice and its bioactive components in vivo

Component	Method	Mechanism	References
Glycyrrhizic acid, Liquiritin and Liquiritigenin	Butyl hydroperoxide t-BHP-treated mice models	Inhibition of the expression levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in the livers of t-BHP-treated mice models.	49
Glycyrrhizin	OVA-induced mice	Higher numbers of goblet and mast cells more than increased thickness of epithelium, basement membrane, and sub-epithelial smooth muscle layers	63
Glycyrrhizin	Rat lung Guinea pig asthma model	Inhibition of NF-κB activation, degradation of I-κB and production of interleukin-8	64, 65
Glycyrrhizin	OVA-induced mice	Regulation of Th1/Th2 balance through suppression of OX40-OX40L signaling and p38 MAPK activity	66
Glycyrrhizin	Airway mucus hyper-producing mouse models	Inhibition of MUC5AC gene transcription	54
G. *uralensis* flavonoid 7,4'-dihydroxyflavone (7,4'-DHF)	OVA-induced mice	Inhibition of MUC5AC gene transcription	56
Glycyrrhizin	OVA-induced mice	Inhibiting the Th2 responses though modulating the expressions of CD86, MHC- class II, CD40, OX40L on CD11c(+) DCs.	67
Glycyrrhizic acid	OVA-induced mice	Modulation of Th1/Th2 cytokines and enhancement of CD4 Treg cells	68
Glycyrrhizin, 18β-glycyrrhetinic acid, Isoliquiritin and Liquiritigenin	OVA-induced mice	Inhibition of IgE production	69
Glycyrrhizin	Patients with bronchial asthma	Changing the level of plasma leukotriene C4, nitric oxide and malondialdehyde	46
ASHMI	OVA-induced mice	Decreased allergen-specific IgE and Th2 cytokine levels, and increased IFN-γ levels	72
CTCM	Sensitized guinea -pigs	Elimination of the increased lung resistance	73
ASHMI	OVA-induced mice	Reduction of eosinophilic pulmonary inflammation, serum IgE levels, IL-4 and IL-13 levels, increase of IFN-γ production in lung cell cultures in response to antigen stimulation.	72,74
ASHMI	Patients with moderate-severe, persistent asthma with prednisone therapy.	Beneficial effect on Th1and Th2 balance	75

ASHMI: Antiasthma simplified herbal medicine intervention, CTCM: Complex traditional Chinese medicine, OVA: ovalbumin

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CONCLUSION

In this review, we report that the results of the in vitro and in vivo studies supports the beneficial effects of glycyrrhizin as a potential herbal therapy on the allergic asthma with the minimum adverse effects. Studies listed in this document indicate that glycyrrhizin could modulate various molecular pathways in the allergic asthma through different transcription factors.

Several molecular mechanisms, anti-inflammatory and immunomodulatory molecules may possibly be responsible for the efficacy of these agents. The relevant feature that can also contribute to the development of this plant is its use in clinical practice; to date, there are some studies showed that ASHMI (Gan Cao from Glycyrhhiza uralensis is one component of ASHMI) was safe and well tolerated in human trials and showed beneficial clinical and immunological effects. However, it should be noted that identification of active compounds in ASHMI will enhance our understanding of the pharmacological mechanisms of ASHMI and accelerate the process for its developing as botanical drug. Thus, it is expected that future studies with licorice compounds especially GA will help to define various molecular mechanisms and targets for asthma.

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