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Ameliorative effects of *Glycyrrhiza glabra* L. (licorice) on animal and human pulmonary fibrosis: A review of current knowledge

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ABSTRACT

Air-borne inflammation plays an essential role in the pathogenesis of acute respiratory distress syndrome (ARDS), asthma, and chronic obstructive pulmonary disease (COPD). Anti-inflammatory therapy effectively improves the symptoms of these diseases. There are more than 30 species of the genus *Glycyrrhiza*, which are widely distributed worldwide. Licorice root extracts have beneficial effects on the treatment of throat infections, tuberculosis, respiratory and liver diseases, as well as antibacterial, anti-inflammatory, and immunodeficiency impacts. Therefore, the focus of this article is a review of the molecular mechanism of licorice extracts and its four flavonoids (isolycoirithigenin, licoirithigenin, lycalocone, and guanidine) and their therapeutic effects on respiratory distress syndrome and fibrosis caused by this disease. By its combination of flavonoid, triterpenoid, saponin, and isoflavones, licorice is essential in reducing inflammation, strengthening the immune system and antioxidant properties. Licorice can be a natural alternative to current treatment to eliminate new emerging pathogens, such as viral diseases with side effects. Based on this systematic review article, it is suggested that licorice effectively reduces lung inflammation caused by viral pathogens by inhibiting the infiltration of inflammatory cells and the release of inflammatory mediators, which subsequently results in neutrophil recruitment in the lung and neutrophil-mediated oxidative damage, edema and reducing congestion. Therefore, products that target transforming growth factor (TGF)-β1 signaling proteins, Smads, and phosphorylated Smads (p-Smads), with the ability of epithelial cells to adopt mesenchymal phenotypes, may be helpful in the development of therapies. New pulmonary fibrosis should be followed by respiratory distress syndrome.

Keywords: Licorice, Acute respiratory distress syndrome, Animal, Pulmonary fibrosis, Pathogen.
Article type: Review Article.

INTRODUCTION

Pulmonary fibrosis (PF) is a severe lung disorder characterized by excessive extracellular matrix (ECM) accumulation. In the early stages of pulmonary fibrosis, the affected lungs mainly have inflammatory cell infiltration, edema, and congestion. In the later stages, damage to alveolar epithelial cells (AEC), abnormal proliferation of ECM-producing cells and mesenchymal cells including fibroblasts (FB) and myofibroblasts (MFb), excessive production of ECM such as collagens, laminin, tenascin-C, etc. occur, which ultimately lead to progressive scarring and loss of lung function (Crouch 1990; Koli *et al.* 2006; Chanda *et al.* 2019). So far, many studies have shown that the molecular mechanisms of PF in severe inflammation, such as activation and release of inflammatory cytokines, activation of macrophages, epithelial-mesenchymal transition, conversion of epithelial phenotype to fibroblastic phenotype, disruption of matrix metalloproteinase (MMP)/ balance, oxidative stress and

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several pathways signalling are activated. It has been confirmed that one of the main pathological mechanisms of PF is an imbalance between ECM synthesis and degradation. While ECM degradation is mainly regulated by MMP and inhibitor of metallopeptidase 1 or TIMP, most ECM components are degraded by MMP (Matute-Bello *et al.* 2007; Bormann *et al*. 2022). TIMP is a primary MMP inhibitor, while overproduction of TIMP exacerbates fibrosis. During the epithelial-mesenchymal transition, levels of epithelial markers such as E-cadherin and levels of mesenchymal cell markers such as α-smooth muscle actin (α- SMA), vimentin, N-cadherin, fibronectin (FN) changes. Also, transforming growth factor (TGF)-β1 signalling proteins, Smads, and phosphorylated Smads (p-Smads) are associated with the ability of epithelial cells to adopt mesenchymal phenotypes. Therefore, agents targeting these events may aid in developing novel PF therapies (Selman *et al.* 2000; Manoury *et al.* 2007). It is well known that the treatment options for pulmonary fibrosis include antioxidants, cytokine inhibitors, anti-fibrotic agents, and lung transplantation. However, these are mainly limited to focusing on one or two aspects of the process of lung injury and repair. Due to various complications, the extensive treatment plan of corticosteroids, immunosuppressive drugs, and antioxidants (N-acetylcysteine) may no longer be suitable. Although pirfenidone has been shown to be the preferred drug for the treatment of PF in clinical practice, it is only a conditional drug, and its efficacy and safety for long-term use are still unknown (Glasser *et al.* 2016; Glass *et al.* 2022). Therefore, more efforts are still necessary to develop new strategies to prevent this treatment-resistant respiratory disease. Traditional medicine, one of the main parts of medical practice, is precisely a natural chemical library that creates synergistic effects through the synergistic mechanism, enhanced functions, and less toxicity of the original main ingredients. It often applies a broader spectrum of action in managing medical disorders, such as monotherapy or in combination with standard medical treatments. Nature has always been a great source of medicinal products and provides us with various medicinal plants that produce plant-based chemicals. Licorice is known by the scientific name *Glycyrrhiza glabra* L., which belongs to the Leguminosae family. *G. glabra* is a commonly used medicinal plant which is found throughout Asia and in parts of Europe (Farhadi *et al.* 2014; Peirzadeh *et al.* 2014). Licorice is believed to have originated in Iraq. *G. glabra* is the most widespread species in Italy, Spain, Türkiye, Caucasus, Western China, and Central Asia. In contrast, *G. uralensis* is found in Central Asia as far as China and Mongolia. This plant is grown commercially in Italy, Spain, Greece, France, Iran, Iraq, Türkiye, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, India, China, USA and England. Licorice is one of the most commercially valuable plants in the world, with broad applications in tobacco, cosmetics, food, and pharmaceutical industries. Phytochemical and pharmacological analyses of licorice have been widely investigated. In traditional Chinese medicine, *G. glabra* L. is considered an "important herbal medicine". According to a traditional Chinese medicine belief, "nine out of ten formulas contain licorice" and it is one of the most effective herbal medicines to reduce toxicity and increase the effectiveness of other herbal medicines when used together. It may also be a healthy food product and natural sweetener (Dastagir & Rizvi 2016; Dang *et al.* 2024). Iranian medicine is rich in content and theoretically complete, and its achievements in physiology, pathology, treatment, and pharmacology have not only greatly contributed to Chinese medicine but have also attracted the attention of the world of medicine for a long time. On the other hand, today, many treatments for lung diseases have limited efficacy or are associated with side effects. As a result, this review can be a reference for the development of new drugs without complications and significant therapeutic effects for the treatment of pulmonary fibrosis following viral pneumonia, thus improving the quality of life of patients and prolonging their survival time.

MATERIALS AND METHODS

Literature materials were obtained from scientific databases, including PubMed and Web of Science databases and Google Scholar search engine, and to identify studies on the anti-fibrotic role of licorice as well as possible mechanisms, search keywords for these works included "Lung fibrosis" or "Pulmonary fibrosis" and "Traditional medicine", "Sherin Bayan", "Licorice", "Glycyrrhiza glabra L.", "Respiratory viruses", "Respiratory distress syndrome" and "Extract" or "Plant" were in all fields. Names of chemical constituents listed in the present review are based on the journal's plant list.

Licorice plant

Nature has always been a great source of medicinal substances and provides various medicinal plants that produce valuable phytochemicals. Licorice is known by its scientific name *Glycyrrhiza glabra* L. and belongs to the Leguminosae family (Fig. 1; Dastagir & Rizvi 2016). Isoliquiritigenin extracted from licorice root has a chalcone

structure that exhibits a strong anticancer effect. Glycyrrhizin, glycyrrhizinic acid, isolicyritin and glycyrrhizic acid are other main chemicals of this plant with anti-atherogenic, anti-cancer, anti-diabetic, antimicrobial, anti-spasm, anti-inflammatory and anti-asthma properties (Dang *et al.* 2024). Licorice has also been proven to help relief fatigue and weakness. In addition, it acts as an anti-inflammatory, reduces allergic responses and prevents liver damage. According to the World Health Organization (WHO), licorice is used as a soothing agent for sore throats and an expectorant for bronchial disorders and coughs (Peng *et al.* 2015). There have been no reports of potentially toxic compounds from the species studied so far. However, some adverse consequences, such as the use of high doses over a long period, which lead to serious diseases, are known. However, this plant may be used for medicinal purposes in small amounts for serious ailments and there are no known side effects (Dastagir & Rizvi 2016; Dang *et al.* 2024).

Fig. 1. Licorice plant with scientific name *Glycyrrhiza glabra* L.
https://www.bio-botanica.com/product/licorice-root-glycyrrhiza-glabra-licorice-root-extract/.

Many chemical compounds of licorice have been studied for their remarkable pharmacological properties, such as anticancer, antibacterial, anti-inflammatory, cardioprotective, hepatoprotective, against respiratory infection, and many others. According to the available literature, licorice has attracted the attention of many researchers in recent years, and they are discovering its active compounds and their mechanism of action. Licorice flavonoids are one of the most important extracts of its stem and root and have shown promising biological activities. Licorice extract and its four flavonoids (isolycoirithigenin, licoirithigenin, lycalocone and glabidine) have medicinal activities. Licorice can be a natural alternative to current treatment to eliminate new emerging disorders with mild side effects (Kaur & Dhindsa 2013).

Secondary metabolites of *Glycyrrhiza glabra* L.

Plant secondary metabolites are divided into several groups based on their chemical structure. Therefore, it is vital to investigate the main pharmacological activities of various secondary metabolites of licorice, such as flavanones, coumarins, chalcones, isoflavones, and many others that are present in triterpenoid saponins and phenolic compounds of licorice (Kovalenko *et al.* 2004; Dastagir & Rizvi 2016). About 400 compounds have been isolated from licorice, including approximately 300 flavonoid compounds. Biologically active compounds are mainly secondary metabolites and their derivatives, such as alkaloids, glycosides, flavonoids, phenols, saponins, tannins, terpenes, and steroids. Licorice extract contains sugars, starch, bitter, resin, essential oil, tannin, mineral salts, and low levels of nitrogen compounds such as proteins, individual amino acids, and nucleic acids. The main active ingredients are glycyrrhizin, glycyrrhetinic acid, and triterpenoid derivatives. Glycyrrhizin can be converted to glycyrrhetinic acid in humans through a metabolic mechanism. Hence, the pharmacological results of glycyrrhetinic acid are similar to glycyrrhizin. Glabridin is the root's most abundant isoflavone (Kovalenko *et al.* 2004; Pastorino *et al.* 2018). The different primary and secondary metabolites and components are mentioned in Figs. 2-3.

Flavonoids

It has been reported that more than 300 flavonoids have been found in different species of licorice. Among the commonly used types of flavonoids are flavonones, chalcones, isoflavones, and flavones. A number of licorice flavonoids were identified: licooritin, licooritigin, liciviritine opiozide, grabranine, gulathawrol, licoflavonon, isiulicooritigin, nevizolicooritin, leicurakia, lycocalicone, licoritin, liocoflavanol, glyzaglabrin, lycoisoflavanone, glabro isoflavanone, glabron, licorice and gancaonin. Licorice extract has a yellow color due to the presence of flavonoids, e.g., licoricetin and isolichyretin (Hayashi *et al.* 1996; Hayashi *et al.* 1996; Li *et al.* 2000). Baicalein

(BAI) is a natural plant flavonoid that exhibits various biological activities. Baicalein (0.1-100 μM) can inhibit the oxidative and arachidonate metabolism of alveolar macrophages (AMs) from alveolar bronchoalveolar lavage of patients with PF. In a mouse model, daily administration of BAI (50 and 100 mg kg^{-1}) from day 1 to 28 after exposure to bleomycin reduced the degree of pulmonary fibrosis and significantly reduced a-SMA levels as it reduced the main ingredient of collagen. Further evidence showed that BAI treatment fully restored the normal liver lipid profile and greatly improved lipid abundance and composition in the bleomycin-induced animal model. These protective effects may be achieved by suppressing inflammation, improving antioxidant activity, improving miR-21 function and the TGF-β/Smad signalling pathway, as well as less adverse effects on fatty liver disease (Yang *et al.* 2013; Eghlima *et al.* 2020; Kim *et al.* 2020).

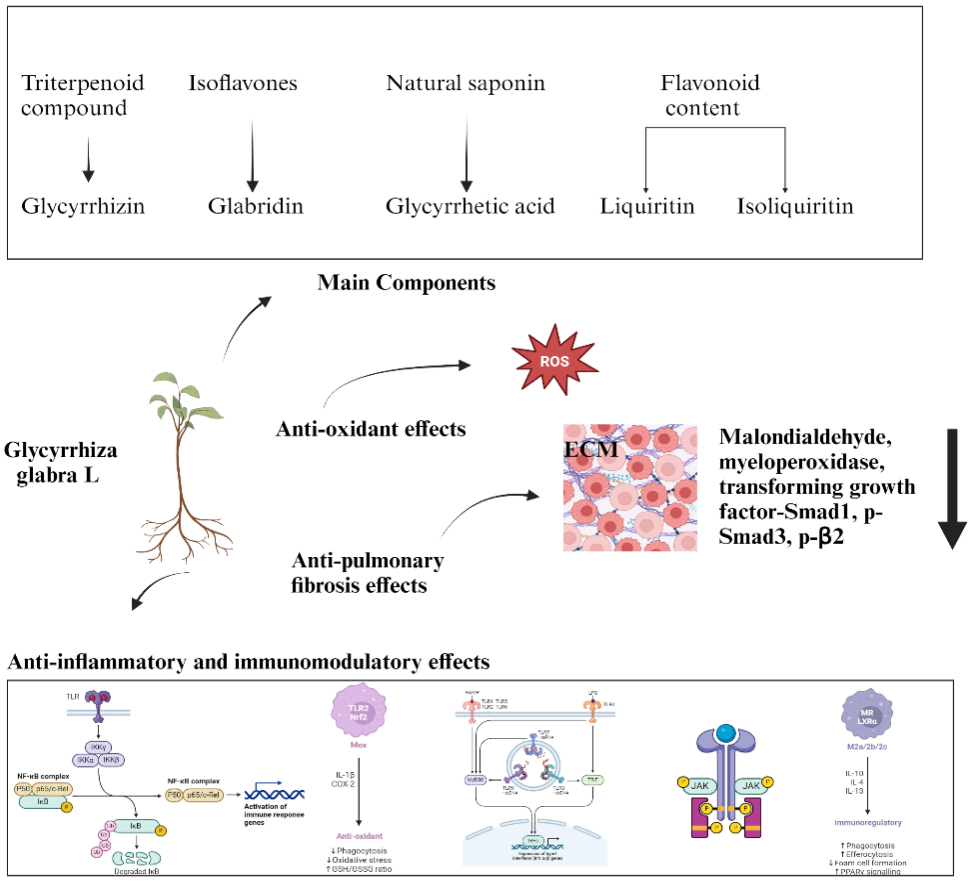

Fig. 2. The main constituents and performance of *Glycyrrhiza glabra* L.

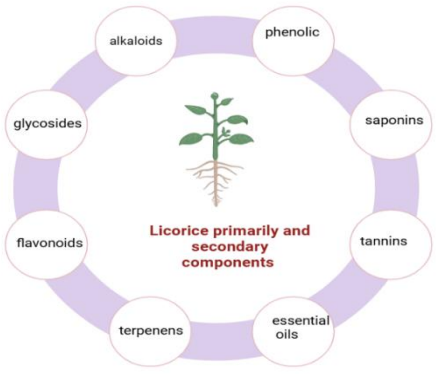

Fig. 3. The main primary and secondary metabolites and components of *Glycyrrhiza glabra* L.

Licorice contains glycyrrhizin, oleanane triterpenoids, glucose, and flavonoids. Its flavonoids are known for various biological activities, including enzyme inhibition, antioxidants, and anti-inflammatory properties. Glabrin/Glabridin is an isoflavone compound that is one of the most essential licorice flavonoids, which shows inhibitory effects on the expression of inducible nitric oxide synthesis and improves the survival of mice in an experimental model of septic shock (Kang *et al.* 2005; Yu *et al.* 2008). Recently, it has been reported that glabridin exerts a neuroprotective effect on brain damage caused by middle cerebral artery occlusion in rats and staurosporine-induced damage in cultured rat cortical neurons by modulating multiple apoptosis-related pathways. However, whether licorice flavonoids exert an anti-inflammatory effect on pulmonary inflammation and the possible molecular mechanisms that explain how flavonoids suppress the inflammatory response are unknown. Published data show that the anti-inflammatory compounds of flavonoid extracts reduce lung fibrosis induced by pulmonary inflammation following LPS exposure by inhibiting the infiltration of inflammatory cells, reducing oxidative stress, and reducing the release of pro-inflammatory mediators in the lung (Kang *et al.* 2005; Yu *et al.* 2008). Tectorigenin is a methylated isoflavone that significantly inhibited the proliferation of lung fibroblasts in bleomycin-treated mice. In addition, tectorigenin significantly increases the expression of lung miR-338 and decrease the levels of fibroblastic matrix proteins procollagen type 1, fibronectin, and lysophosphatidic acid receptor 1 (LPA1), which are involved in many biological responses such as cell differentiation and apoptosis. This suggests a potential inhibitory role of tectorigenin in the pathogenesis of PF; however, there is little information regarding its role in pulmonary patients (Niu *et al.* 2020; Wang *et al.* 2020). Also, quercetin is a flavonoid that is found in a wide variety of plants and offers a wide range of biological activities. It has been clinically observed that frequent consumption of quercetin-rich foods is inversely related to the risk of lung cancer (Tahoori *et al.* 2019). To evaluate the preventive effects of quercetin on lung fibrosis in an animal model, liposomal quercetin was injected intravenously 1 day before the administration of bleomycin (BLM) and continued until the end of the study (for 4 weeks). As a result, the increase in the number of macrophages and the number of neutrophils and lymphocytes in the bronchoalveolar lavage fluid (BALF) on both days 7 and 14 were reduced in the liposomal quercetin-treated group compared to the BLM-induced group (Wang *et al.* 2020; Gad El-Hak *et al.* 2022). Meanwhile, the levels of tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 in BALF were significantly decreased on day 7 after liposomal quercetin treatment. Furthermore, treatment with liposomal quercetin reduced PF areas and collagen deposition by decreasing TGF-β1 expression as assessed by histopathology. However, histopathological evaluation and cell counts in BALF showed that there was no significant difference between the groups treated with liposomal quercetin and the BLM model when applying late treatment strategies with liposomal quercetin administered after intratracheal injection of BLM for 7 days. This indicated that the main role of liposomal quercetin was in reducing the initial injury responses induced by BLM, but not the level of fibrosis after the onset and development of pro-inflammatory responses (Li & Kan 2017; Hosseini *et al.* 2021). In another study on human embryonic lung fibroblasts (HELFs) incubated with cultured supernatant collected from BALF of PF patients, quercetin-1 (20 and 40 μmol L^{-1}) was able to significantly reverse the decrease in MMP-1 expression and increase TIMP production induced by SiO_2. These data suggest that quercetin may provide a strategy to protect PF patients, but further clinical studies are still needed (Li & Kan 2017; Hosseini *et al.* 2021). Bioactive flavonoid compounds such as liquiritigenin and isoliquiritigenin have been isolated and identified from the crude extract of *G. uralensis*. In 2011, Francelli *et al.* identified licochalcone C, the structural isomer of licochalcone A. Other flavonoids such as lycoagrodin, lycoagrochalcones, glyinflanin B and glycirdione A have also been reported by several studies (Franceschelli *et al.* 2011). Manfredi *et al.* (2001) isolated and identified the bioactive compounds golpidotin B and golpidotin A from *G. lepidota* extract (Manfredi *et al.* 2001). Williamson (2003) isolated and identified isoflavonoid derivatives, i.e., glabrine, galberine, glabrone, synpterocarpine, lycoisoflavones A and B, formonontin, glycerin and comatacinin. In other studies, hispaglabrin A, hispaglabrin B, methylglabridine were identified from *Glycyrrhiza* species (Williamson 2003). Kinoshita *et al.* (2005) identified several compounds from the root of *G. glabra*, including: glabrin, glabrocoumarone, glabrone, synpterocarpine, licoisoflavones A and B, formonontin, glycerin, comatacin, hispaglabrin A, hispaglabrin B, glabroisoflavone, and glabroisoflavone (Kinoshita *et al.* 2005).

Saponins

Licorice root contains triterpenoid saponins (glycyrrhizin, and glycyrrhizic acid), which are the main constituents of licorice and are responsible for the sweet taste. Glycyrrhizic acid is the main triterpenoid saponin in licorice root and the plant's main sweetener, 50 times sweeter than sugar. Licorice and licorice aglycone are believed to

accelerate the healing of gastric ulcers (Nagao *et al.* 1996). Glycyrrhizic acid has shown anti-inflammatory and anti-arthritic activities in animal studies, and other triterpenes, i.e., licorice acid, glycyrrhizin, glabrolide, isoglyburlide, and licorice acid, have been described. Vashist & Sharma (2013) reported the presence of ammonium glycyrrhizinate (3.4%) and calcium glycyrrhizinate (4%) in the ethanolic extract of *G. glabra* (Vashist & Sharma 2013). Zhang & Ye (2009) identified several saponins derived from the species, including 22β-octylglycerisin, apioglycerisin, araboglycerisin, and plant saponin E2. Evaluation of saponin in pneumococcal pneumonia showed anti-inflammatory effects in infected mice (Zhang & Ye 2009).

Phenolic compounds

There are many reports on the phenolic compounds of licorice species. The main phenols include licoricetin, isoleiciretin, licoricetin apiozide, and isoprenoid-substituted flavonoids, chromenes, coumarins, and dihydrostilbenes. Nomura *et al.* (2002) studied phenolic compounds from different licorice species and isoprenoid-substituted flavonoids including pyranoisoflavan and glabrin in *G. glabra*, isoflavan in *G. uralensis*, licochalcone A in *G. inflate*, licorice in G. eurycarpa, licorrhizoflavan A in G. aspera, isobavachine in G. pallidiflora, sigmoidin B in G. uralensis, and liquiritigenin were observed in different licorice species (Nomura *et al.* 2002). Zhang & Ye described several phenolic compounds derived from licorice species, including glycicoumarin, glabrocoumarin, glycerin, inflacoumarin A, lycopyranocoumarin, isoglycerol, neoglycerol, lycobenzofuran, lycocoumarone, glabrocoumarone, glabrocoumarone, glabrocoumarone, glabrocoumarone, glabrocoumarone, and and glabrocoumarone (Zhang & Ye 2009). In another study, Ammar *et al.* (2012) isolated phenolic compounds, i.e., licoricetin, licoricetin apioside, neoliciritin apioside, isoliquiritin, isoliquiritin apioside, licorice, and isoliquiritin from the total extract of licorice.

Coumarin

Several coumarins were identified from *G. glabra*, including lycomarin, glabrocoumarone A and B, hernirin, amblyferon, and glycerin (Wahab *et al.* 2022). Kinoshita *et al.* (2005) studied plant coumarins and identified lycomarin, glabrocoumarin A and B, phetacarin, umbelliferone, glycocoumarin, lycofuranocoumarin, lycopyranocoumarin and glabrocoumarin (Kinoshita *et al.* 2005). Recent studies by Qiao *et al.* (2014) identified glycerol, glycocoumarin, and dehydroglyaspirin from *G. uralensis* root extract.

Essential oils and other compounds

Other secondary metabolites such as fatty acids, phenol, guaiacol, asparagines, glucose, sucrose, starch, polysaccharides, and sterols such as beta-sitosterol, dihydrostigmesterol have also been reported. Ali (2013) studied the composition of essential oil of *G. glabra* and found compounds such as α-pinene, β-pinene, octanol, γ-terpinene, estragole, isofenone, beta-caryophyllene, citronyl acetate, caryophyllene oxide and geranyl hexanolate. Among these compounds, geranyl hexanolate represented the highest percentage (34%), while β-pinene was the lowest (1.7%).. Khalaf *et al.* (2010) studied the phytoestrogens of *G. glabra* roots from Syria and identified daidzein, daidzein, genistein, ononein, glycinin, genistein, and coumestrol.

Anti-inflammatory activity

The utilization of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of various diseases and inflammatory conditions is on the rise; however, these medications are associated with numerous side effects. Concurrently, there is a growing interest in herbal remedies for inflammation, as they tend to have fewer adverse effects. Licorice has shown anti-inflammatory activities due to the reduction of PGE2, MMPs, TNF, and free radicals, which is confirmed by its traditional uses, such as relieving cough, clearing phlegm, stimulating digestive functions, reducing pain, and many others. In rats, processed licorice products significantly reduced the symptoms of rheumatoid arthritis. Licorice-processed products in blood and cell supernatants upregulated matrix metalloproteinases, inflammatory cytokines, and vascular endothelial growth factors. This study concluded that licorice-processed products exhibited anti-inflammatory effects through the TLR4/NF-kβ/NLRP3 signalling pathway on CIA rats and LPS-induced RAW264.7 cells, and metabolic profiling in the management of rheumatoid arthritis (Loni *et al.* 2017; Jiang *et al.* 2020). *In vivo*, anti-inflammatory activities have been shown by total flavonoids isolated from licorice, and licorice extract through suppression of COX-2 gene, iNOS, and mitogen-activated protein kinases (MAPKs) signals. Flavonoids maintain an integrated mechanism of action of multiple

pathways, thus exhibiting anti-inflammatory properties. Consequently, licorice flavonoids are a potential drug for inflammation with few side effects (Mishra *et al.* 2011). Examining the effects of licorice extract containing saponin showed anti-inflammatory effects in the pulmonary pneumonia model in mice and reduced pulmonary fibrosis (Safdarpour *et al.* 2022). Secondary metabolites and licorice extract have shown anti-inflammatory activities for the treatment of various diseases besides acute kidney disease. Isoliquiritigenin attenuates LPS-stimulated acute kidney injury by suppressing TNF-α-stimulated NF-kβ and HMGB. it reduces inflammation and fibrosis in the kidneys caused by unilateral ureteral obstruction (Nassan *et al.* 2021). It also inhibits inflammatory cytokines, pro-inflammatory cytokines, and the NF-kβ and Nrf2 pathways, all involved in Ang II-stimulated hypertensive renal injury. Neutrophils produce ROS at the site of inflammation, which reduces tissue damage by licorice and glycyrrhizin extract (Tang *et al.* 2018; Nassan *et al.* 2021; Sun *et al*. 2021). H_5N_1 virus induces ROS and inhibits H_5N_1 proliferation in lung cells by suppressing JNK, NF-kβ, p38 with glycyrrhizin. Ovalbumin-stimulated bronchial asthma models were used to investigate the effect of three different doses of licorice extract on bronchoalveolar lavage oxidative stress indices. It decreased interleukin IL-13, (IL)-5 and IgE. Study results have shown that licorice (10 mg kg^{-1}) inhibits mucus and protects against OVA-induced lung inflammation. This study concluded that the lowest dose of licorice is more effective against anti-inflammatory and antioxidant effects. Licochalcone-A showed anti-inflammatory effects by inhibiting the production of MMP-1, MMP-3, and MMP-13 in IL-1β-stimulated chondrocytes. The anti-inflammatory effect of licochalcone-C is carried out by reducing NF-kβ and other downstream molecules, such as inducible iNOS, ICAM-1, and VCAM-1(Traboulsi *et al.* 2015).

Licorice in the treatment of respiratory tract infections

Asthma, COPD, and acute respiratory distress syndrome (ARDS) are caused by inflammation of the airways. Anti-inflammatory treatments have been proven effective in respiratory tract infections by various studies. However, the leading cause of death worldwide is COPD, and one of the most essential factors is cigarette smoke. Chronic inflammation and oxidative stress are the causes of COPD, which is due to pulmonary disorders. For hundreds of years, herbal medicines have been used to treat many ailments. They show promising results and increase physical performance (Najafipour *et al.* 2022). Isoliquiritigenin is a natural flavonoid obtained from licorice root. It has shown anti-inflammatory and antioxidant properties. Researchers tested its effect on cigarette smoke-induced COPD in a mouse study. The results of this study have shown that isoliquiritigenin has reduced the penetration of inflammatory cells and inflammatory cytokines. Furthermore, it regulated NF-kβ and Nrf_2 signalling pathways and protected against cigarette smoke-induced COPD. In another study, a mouse model was used to know the effectiveness of the herbal medicinal combination of *Agastache rugosa* and *G. glabra* L. containing glycyrrhizic acid, active compounds for the treatment of COPD. It has been shown that this compound is effective as an anti-COPD agent and reduces the histopathological damage of the lung. In addition, glycyrrhizic acid and flavonoids, essential components of licorice, have shown anti-asthmatic effects (Gao *et al.* 2020; Yu *et al.* 2018). A clinical trial was conducted to conclude on *Boswellia carterii* (Olibanum) and *G. glabra* L. as bronchodilators. It affected 54 patients participating in this trial. Clinical examinations such as serum electrolytes: calcium, selenium, calcium and potassium have been performed with pulmonary function tests. *G. glabra* L. has shown superiority over *B. carterii* for managing chronic bronchial asthma. Glycyrrhizin helps inhibit fibrosarcoma and lung cancer. Glycyrrhetinic acid has shown inhibition of bile acid-induced necrosis and apoptosis (Ali 2013; Kim *et al.* 2020; Wahab *et al.* 2022). An inflammatory mouse model was used to investigate the effect of sweet expression on the ovalbumin model of airway hyperstimulation. It was found that licorice glabridin may have the potential to treat asthma. The anti-inflammatory effect of licorice is done by reducing serum IgE level, total protein, WBC count, and improving respiratory function (Sun & Pan 2006; Dogan *et al.* 2020). The findings of the preclinical model show that quercetin has anti-inflammatory and antioxidant properties, reducing inflammation and oxidative stress by neutralizing free radical species and increasing the expression of antioxidant enzymes. In addition, quercetin competes for adenosine triphosphate (ATP) binding sites to inhibit various proteins and lipid kinases to reduce inflammatory pathways. In addition, there are saponins in licorice root that help loosen accumulated mucus so it can be more easily expelled from the lungs. Unfortunately, respiratory tract infections cause mortality and morbidity, and current standard treatments are insufficient (Chen *et al.* 2019; Almatroodi *et al.* 2021). Several review articles concluded that the antiviral activity of licorice extract has been reported against various viruses, including SARS-CoV and influenza. Licorice extract has been shown to inhibit the growth of viruses and show strong inhibitory activity against virus entry (Cinatl *et al.* 2003; Sinha *et al.* 2021).

G. glabra L. root extract components have been reported to inhibit many RNA viruses' growth and cellular diseases. Aqueous extract of licorice shows antiviral activity against several viruses such as human respiratory syncytial virus (HRSV) and Enterovirus 71 in human skin fibroblast cell line (Wahab *et al.* 2022). This extract greatly reduced HRSV infection by inhibiting viral adhesion, uptake, and stimulation of IFN secretion. However, the methanol extract of licorice root showed higher anti-HIV activity than the aqueous extract. It was also found that it has more anti-hepatitis C virus activity than glycyrrhizin. The ethanolic extract of licorice has shown a vital property in inhibiting the secretion of RANTES by bronchial epithelial A549 infected with H_1N_1 cells (Wahab *et al*. 2022). In addition, randomized controlled trials confirmed that licorice extract reduces liver cell damage in chronic hepatitis B and C. Recently, it has been found that this extract can be a potent inhibitor of the main protease of SARS-CoV2, but glycyrrhizin has higher affinity and better ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties than other licorice constituents (Cinatl *et al.* 2003; Sinha *et al.* 2021). In another study, Cinati *et al.* (2003) observed *in vitro* antiviral effects for viruses that cause respiratory tract infections, such as influenza and acute respiratory syndrome coronavirus (SARS) and human immunodeficiency virus (HIV). The active substances of licorice extract that have antiviral activity are triterpenoids, flavonoids, and triterpene saponins of the oleanane type. Glycyrrhizin, glycyrrhetinic acid, and its derivatives are licorice extract's main triterpenoid active components. These compounds have broad-spectrum antiviral activity against many RNA and DNA viruses such as SARS coronavirus, herpes virus, HIV, hepatitis virus, influenza virus, cytomegaloviruses, and respiratory syncytial virus. In the case of respiratory syncytial virus and influenza, it was observed that glycyrrhizin induces antioxidant activity in influenza H_5N_1 virus-infected cells and thus inhibits virus replication. Other researchers confirmed that glycyrrhizin inhibited influenza A/H_1N_1 by preventing the uptake of the virus into cells. Antiviral activities of glycyrrhizin against coronavirus and SARS-related influenza virus have also been demonstrated. Antiviral mechanisms of glycyrrhizin are through inhibition of viral uptake and penetration in the early stages of the life cycle. Glycyrrhizin was most effective when administered during and after viral uptake period.

Immunomodulatory effects

The immune status of the human body is closely related to the incidence, development, and prognosis of the COVID-19 infection. Clinical studies have shown that SARS-COV2 causes overactivation of immune cells in the lungs, produces a series of inflammatory factors to form a cytokine storm, and accumulates many immune cells and tissue fluid. Accumulated in the lungs, it affects the gas exchange between the alveoli and capillaries, leading to hypoxemia, acute respiratory distress, and even respiratory failure. Effective physical immune responses have been shown to play an essential role in virus clearance and disease prevention. Licorice has recently been reported to improve immunity against viruses, indirectly reduce the degree of inflammatory response, and protect organ function (Shehu & Datta 2022). Licorice has the advantages of fewer side effects, multi-target, multi-level, etc., regulation mechanism of cytokine release, immune cell activity, and pulmonary vascular permeability and impact on cytokine storm process and aspects. Licorice is an effective immunomodulator that regulates the immune system by acting on the mitogen-activated protein kinase (MAPK) signalling pathway, the Toll-like receptor signalling pathway, and the activity of immune cells to play an immunomodulatory role. It stimulates macrophages, and NK cells. For example, licorice combined with fucose-mannose ligand can inhibit the production of IL-10 in activated macrophages, enhance IL-12, and increase the immunomodulatory effect of glycoprotein on macrophages. These results show that licorice can stimulate immune cells through multiple targets and pathways to regulate immune function. Studies have shown that it can enhance the immune status by regulating the proliferation of Treg cells. Among them, Treg cells inhibit T cells and antigen-presenting cells and reduce the production of pro-inflammatory cytokines and antibody secretion, increasing the immune system's performance. Therefore, Treg cells must prevent autoimmunity and control the immune response. Consequently, the selective increase of Treg cells *in vivo* has a broad therapeutic significance for autoimmune and inflammatory diseases. Other studies have shown that isoliquiritigenin and naringenin are also effective components that regulate the immune response induced and suppressed by Treg cells and can significantly increase the proliferation of Treg cells in mice. These two flavonoids can induce more Treg cells in doses lower than licorice. These results suggest that glycyrrhizin can enhance the function of the immune system by regulating immune cells. The above results show the immunomodulatory effects of licorice, which suggests that it can be used as a candidate for developing new immunomodulatory medicine. However, studies on the immunomodulatory effects of licorice are

limited. Therefore, more reliable data are needed to confirm the immunomodulatory effects of licorice (Bisht *et al.* 2022; Shehu & Datta 2022; Robin *et al.* 2023).

Table 1. Studies conducted on respiratory infectious diseases with licorice therapeutic approach.

Study	Disease	Results	Ref
Buder *et al.* 2022	SARS-CoV-2	Licorice consumption significantly decreased both cell membrane ACE2 expression and plasma HMGB1 levels in healthy subjects after 7 days. Half of the subjects had at least a 30% reduction in ACE2 levels. HMGB1 levels were significantly higher in patients with covid-19 and mild ARDS patients with and without covid-19 compared to healthy subjects, but did not differ between covid-19 and non-covid respiratory distress syndrome.	(Buder *et al.* 2022)
James *et al.* 2022	Fibrosis	Collagen accumulation in the in vitro model decreased with increasing licorice extract concentration, and the maximum decrease was observed at a concentration of 200 μg mL^{-1}. Kruskal-Wallis test was performed to analyze the difference in collagen accumulation. The present study shows the anti-fibrotic effect of licorice in cell lines and hence, this agent can be used for the therapeutic management of fibrosis.	(James *et al.* 2022)
Ding *et al.* 2020	SARS-CoV-2	Here we report a case of non-hospital covid-19 that showed a significant positive response to licorice treatment. Although the exact action of licorice against SARS-CoV-2 infection and associated immunopathology awaits further investigation, it is possible that the therapeutic effects of licorice observed in this severe COVID-19 patient are the result of the combined antiviral and anti-inflammatory effects of licorice. be an expression in the respiratory and nervous systems. Given these encouraging pharmacological effects, demonstrated safety, and the low cost and wide availability of licorice, we suggest that a combination of these may be a good candidate for alternative medicine against COVID-19. Implementation of this treatment regimen may be worth further attention, and further research in clinical trials could be considered to confirm its effects in relieving severe symptoms and reducing mortality from COVID-19 in a larger cohort. For suspected COVID-19 patients who cannot be hospitalized and have no place for specific COVID-19 prescriptions, the combination of licorice and vitamin C may be a promising candidate as an alternative medication to help relieve severe symptoms of COVID-19. 19 during personal quarantine. .	(Ding *et al.* 2020)
Safdarpour *et al.* 2022	*Streptococcus pneumonia*	COX-2 protein expression, Tnf-α gene expression and IL-4 serum level were decreased compared to the pneumonia group. The histopathology results showed that the amount of inflammation, mucus secretion, pulmonary bleeding, thickening of the alveolar wall, and the secretion of inflammatory cells were lower in the nano saponin group than in other groups. This study shows that *Glycyrrhiza glabra* L. saponin and saponin encapsulated by oral administration of ferritin nanoparticles with anti-Tnf-α effect in addition to reducing the expression of COX-2 protein allows recovery in mice with pneumonia.	(Safdarpour *et al.* 2022)
Li *et al.* 2021	SARS-CoV-2	Experimental and computational simulation data showed that licorice potentially targets S protein-mediated cell binding for its antiviral activity. Licorice interacted with protein S with high affinity and blocked binding of recombinant protein S to host cells.	(Yi *et al.* 2022)
Moisy *et al.* 2012	Wild-type A/WSN/33 influenza virus	Glycyrrhizin, which reduces HMGB1 binding to DNA, inhibits influenza virus polymerase activity. Our data suggest that HMGB1 protein can play an important role in the intranuclear replication of influenza viruses.	(Hoever *et al.* 2005)
Hoever *et al.* 2005	Corona virus	Glycyrrhizin (GL) was shown to inhibit SARS-coronavirus replication in vitro. The anti-SARS-CoV activity of licorice derivatives was tested. Introduction of 2-acetamido-β-d-glucopyranosylamine to the GL glycosidic chain resulted in a 10-fold increase in anti-SARS-CoV activity compared to licorice. GL amides and GL conjugates with two amino acid residues and a free 30-COOH function showed up to 70-fold increased activity against SARS-CoV but also increased cytotoxicity, leading to a decrease in selectivity.	(Hoever et al. 2005)

CONCLUSION

Licorice is one of the most effective herbal medicines for reducing toxicity and increasing the effectiveness of other medicines when taken simultaneously. However, the biochemical research of licorice and its natural composition has been widely studied, and it still needs to be focused on to confirm its efficacy in improving various diseases. Various licorice compounds and their biological targets need to be studied to understand their mechanism of action. Further studies are needed to establish a synergy between the efficacy and toxicity of other

compounds in the combination preparation. The use of licorice in the pharmaceutical industry may increase and should be controlled properly. This review gave results on the effects of licorice and its biological role in combating respiratory diseases associated with respiratory distress syndrome and pulmonary fibrosis and developing promising pharmaceutical preparations. In summary, licorice consumption reduces ACE2 expression. It modulates inflammatory cytokines, and the efficacy of licorice in several respiratory viral diseases identifies it as a potential drug in respiratory infections that is widely available, inexpensive, and safe. Prophylactic use and combination with existing therapeutic drugs could be promising for controlling respiratory diseases of fibrosis but should be further investigated in clinical trials.

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REFERENCES

Ali, EM 2013, 'Phytochemical composition, antifungal, antiaflatoxigenic, antioxidant, and anticancer activities of *Glycyrrhiza glabra* L. and *Matricaria chamomilla* L. essential oils. *Journal of Medicinal Plants Research*, 7: 2197–2207.

Almatroodi, SA, Alsahli, MA, Almatroudi, A, Verma, AK, Aloliqi, A, Allemailem, KS, Khan, AA & Rahmani, AH 2021, Potential therapeutic targets of quercetin, a plant flavonol, and its role in the therapy of various types of cancer through the modulation of various cell signaling pathways. *Molecules* (*Basel, Switzerland*), 26 (5).

Ammar, NM, El-Hawary, SSE-D, El-Anssary, AA, Othman, N, Galal, M & El-Desoky, AH 2012, Phytochemical and clinical studies of the bioactive extract of *Glycyrrhiza glabra* L. Family Leguminosae. *International Journal of Phytomedicine*, 4: 429.

Bisht, D, Rashid, M, Arya, RKK, Kumar, D, Chaudhary, SK, Rana, VS & Sethiya, NK 2022, Revisiting liquorice (*Glycyrrhiza glabra* L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight. *Phytomedicine Plus*, 2: 100206.

Bormann, T, Maus, R, Stolper, J, Tort Tarrés, M, Brandenberger, C, Wedekind, D, Jonigk, D, Welte, T, Gauldie, J & Kolb, M 2022, 'Role of matrix metalloprotease-2 and MMP-9 in experimental lung fibrosis in mice. *Respiratory Research*, 23: 180.

Buder, F, Selejan, S-R, Hohl, M, Kindermann, M, Herr, C, Lepper, PM, Bals, R, Salzberger, B, Mahfoud, F & Böhm, M 2022, 'Glycyrrhizin through liquorice intake modulates ACE2 and HMGB1 levels-A pilot study in healthy individuals with implications for COVID-19 and ARDS. *PloS One*, 17(10): e0275181.

Chanda, D, Otoupalova, E, Smith, SR, Volckaert, T, De Langhe, SP & Thannickal, VJ 2019, Developmental pathways in the pathogenesis of lung fibrosis. *Molecular Aspects of Medicine*, 65: 56–69.

Chen, H, Muhammad, I, Zhang, Y, Ren, Y, Zhang, R, Huang, X, Diao, L, Liu, H, Li, X, Sun, X, Abbas, G & Li, G 2019, 'Antiviral activity against infectious bronchitis virus and bioactive components of *Hypericum perforatum* L. *Frontiers in Pharmacology*, 10: 1272.

Cinatl, J, Morgenstern, B, Bauer, G, Chandra, P, Rabenau, H & Doerr, H 2003, 'Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *The Lancet*, 361: 2045–2046.

Crouch, E 1990, 'Pathobiology of pulmonary fibrosis. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 259:159–184.

Dang, L, Jin, Y, Yuan, Y, Shao, R & Wang, Y 2024, The King of Chinese Medicine- *Glycyrrhiza glabra* L. (Licorice): All-round Inquiry in its chemical composition, pharmacodynamics, traditional and medicinal value. *Acupuncture and Herbal Medicine*, LWW, pp. 1097.

Dastagir, G & Rizvi, MA 2016, '*Glycyrrhiza glabra* L. (Liquorice). *Pakistan Journal of Pharmaceutical Sciences*, vol. 29, no. 5.

Ding, H, Deng, W, Ding, L, Ye, X, Yin, S & Huang, W 2020, Glycyrrhetinic acid and its derivatives as potential alternative medicine to relieve symptoms in nonhospitalized COVID-19 patients. *Journal of Medical Virology*, 92: 2200–2204.

Dogan, MF, Parlar, A, Cam, SA, Tosun, EM, Uysal, F & Arslan, SO 2020, 'Glabridin attenuates airway inflammation and hyperresponsiveness in a mice model of ovalbumin-induced asthma. *Pulmonary Pharmacology & Therapeutics*, 63: 101936.

Eghlima, G, Kheiry, A, Sanikhani, M, Hadian, J, Aelaei, M & Ebrahimi, SN 2020, *Glycyrrhiza glabra* L., *International Journal of Horticultural Science and Technology*, 7(4).

Farhadi, L, Mohammadi-Motlagh, H-R, Seyfi, P & Mostafaie, A 2014, 'Low concentrations of flavonoid - rich fraction of shallot extract induce delayed - type hypersensitivity and TH_1 cytokine IFN-gamma expression in Balb/C mice. *International Journal of Molecular and Cellular Medicine*, vol. 3, no. 1, viewed <http://ijmcmed.org/ article-1-127-en.html>.

Franceschelli, S, Pesce, M, Vinciguerra, I, Ferrone, A, Riccioni, G, Patruno, A, Grilli, A, Felaco, M & Speranza, L 2011, 'Licocalchone-C extracted from *Glycyrrhiza glabra* L. inhibits lipopolysaccharide-interferon-γ inflammation by improving antioxidant conditions and regulating inducible nitric oxide synthase expression. *Molecules* (*Basel, Switzerland*), 16: 5720–5734.

Gad El-Hak, HN, Mohamed, OE & Nabil, ZI 2022, Evaluating the protective role of deglycyrrhizinated licorice root supplement on bleomycin induced pulmonary oxidative damage. *Toxicology Mechanisms and Methods*, 32: 180–193.

Gao, Y, Lv, X, Yang, H, Peng, L & Ci, X 2020, Isoliquiritigenin exerts antioxidative and anti-inflammatory effects via activating the KEAP-1/Nrf2 pathway and inhibiting the NF-κB and NLRP3 pathways in carrageenan-induced pleurisy. *Food & Function*, 11: 2522–2534.

Glass, DS, Grossfeld, D, Renna, HA, Agarwala, P, Spiegler, P, DeLeon, J & Reiss, AB 2022, Idiopathic pulmonary fibrosis: Current and future treatment. *The Clinical Respiratory Journal*, 16: 84–96.

Glasser, SW, Hagood, JS, Wong, S, Taype, CA, Madala, SK & Hardie, WD 2016, Mechanisms of lung fibrosis resolution. *The American Journal of Pathology*, 186: 1066–1077.

Hayashi, H, Hiraoka, N, Ikeshiro, Y & Yamamoto, H 1996, Organ specific localization of flavonoids in *Glycyrrhiza glabra* L., *Plant Science*, 116: 233–238.

Hayashi, H, Yasuma, M, Hiraoka, N, Ikeshiro, Y, Yamamoto, H, Yeşilada, E, Sezik, E, Honda, G & Tabata, M 1996, Flavonoid variation in the leaves of *Glycyrrhiza glabra*. *Phytochemistry*, *Elsevier*, 42: 701–704.

Hoever, G, Baltina, Lidia, Michaelis, M, Kondratenko, R, Baltina, Lia, Tolstikov, GA, Doerr, HW & Cinatl, J 2005, Antiviral activity of glycyrrhizic acid derivatives against SARS−coronavirus. *Journal of Medicinal Chemistry*, vol. 48, no. 4, ACS Publications, pp. 1256–1259.

Hosseini, SA, Zahedipour, F, Sathyapalan, T, Jamialahmadi, T & Sahebkar, A 2021, Pulmonary fibrosis: Therapeutic and mechanistic insights into the role of phytochemicals. *BioFactors*, 47: 250–269.

James, A, Gunasekaran, N, Krishnan, R, Arunachalam, P & Mahalingam, R 2022, 'Anti-fibrotic activity of licorice extract in comparison with colchicine on areca nut-induced fibroblasts: An *in vitro* study. *Journal of Oral and Maxillofacial Pathology: JOMFP*, 26: 173–178.

Jiang, R-H, Xu, J-J, Zhu, D-C, Li, J-F, Zhang, C-X, Lin, N & Gao, W-Y 2020, Glycyrrhizin inhibits osteoarthritis development through suppressing the PI3K/AKT/NF-κB signaling pathway *in vivo* and *in vitro*. *Food & Function*, vol. 11, no. 3, Royal Society of Chemistry, pp. 2126–2136.

Kang, JS, Yoon, YD, Cho, IJ, Han, MH, Lee, CW, Park, S-K & Kim, HM 2005, Glabridin, an isoflavan from licorice root, inhibits inducible nitric-oxide synthase expression and improves survival of mice in experimental model of septic shock. *Journal of Pharmacology and Experimental Therapeutics*, 312: 1187–1194.

Kaur, R, Kaur, H & Dhindsa, AS 2013, *Glycyrrhiza glabra*: A phytopharmacological review. *International Journal of Pharmaceutical Sciences and Research*, 4: 2470.

Khalaf, I, Vlase, L, Lazăr, D, Corciovă, A, Ivanescu, B & Lazăr, MI 2010, HPLC-MS study of phytoestrogens from *Glycyrrhiza glabra*', *Farmacia*, 58: 89–94.

Kim, S-H, Hong, J-H, Yang, W-K, Geum, J-H, Kim, H-R, Choi, S-Y, Kang, Y-M, An, H-J & Lee, Y-C 2020, Herbal combinational medication of *Glycyrrhiza glabra*, *Agastache rugosa* containing glycyrrhizic acid, tilianin inhibits neutrophilic lung inflammation by affecting CXCL2, interleukin-17/STAT3 signal pathways in a murine model of COPD. *Nutrients*, 12: 926.

Kinoshita, T, Tamura, Y & Mizutani, K 2005, The isolation and structure elucidation of minor isoflavonoids from licorice of *Glycyrrhiza glabra* L. origin, *Chemical and Pharmaceutical Bulletin*, 53: 847–849.

Koli, K, Myllärniemi, M, Vuorinen, K, Salmenkivi, K, Ryynänen, MJ, Kinnula, VL & Keski-Oja, J 2006, Bone morphogenetic protein-4 inhibitor gremlin is overexpressed in idiopathic pulmonary fibrosis. *The American Journal of Pathology*, 169: 61–71.

Kovalenko, PG, Antonjuk, VP & Maliuta, SS 2004, Secondary metabolites synthesis in transformed cells of *Glycyrrhiza glabra* L. and *Potentilla alba* L. as producents of radioprotective compounds', *Ukrainica Bioorganica Acta*, 1: 13–22.

Li, L-C & Kan, L-D 2017, 'Traditional Chinese medicine for pulmonary fibrosis therapy: Progress and future prospects', *Journal of Ethnopharmacology*, 198: 45–63.

Li, W, Asada, Y & Yoshikawa, T 2000, Flavonoid constituents from *Glycyrrhiza glabra* L. hairy root cultures. *Phytochemistry*, 55: 447–456.

Loni, F, Maghsodi, H & Shiri, S 2017, The effect of *Glycirrhiza glabra* on osteoarthritis: Suppression of TNF-a, IL-1b, Cox-2, iNOS gene expression and prostaglandin E2 and nitric oxide production in chondrocytes and monocyte/macrophages. *Health Biotechnology and Biopharma*, 1: 70–82.

Manfredi, KP, Vallurupalli, V, Demidova, M, Kindscher, K & Pannell, LK 2001, 'Isolation of an anti-HIV diprenylated bibenzyl from *Glycyrrhiza lepidota*. *Phytochemistry*, 58: 153–157.

Manoury, B, Nénan, S, Guénon, I, Lagente, V & Boichot, E 2007, Influence of early neutrophil depletion on MMPs/TIMP-1 balance in bleomycin-induced lung fibrosis. *International Immunopharmacology*, 7: 900–911.

Matute-Bello, G, Wurfel, MM, Lee, JS, Park, DR, Frevert, CW, Madtes, DK, Shapiro, SD & Martin, TR 2007, Essential role of MMP-12 in Fas-induced lung fibrosis', *American Journal of Respiratory Cell and Molecular Biology*, 37: 210–221.

Mishra, NK, Bstia, S, Mishra, G, Chowdary, KA & Patra, S 2011, Anti-arthritic activity of G*lycyrrhiza glabra, Boswellia serrata* and their synergistic activity in combined formulation studied in freund's adjuvant induced arthritic rats. *Journal of Pharmaceutical Education and Research*, 2: 92.

Nagao, Y, Sata, M, Suzuki, H, Tanikawa, K, Itoh, K & Kameyama, T 1996, Effectiveness of glycyrrhizin for oral lichen planus in patients with chronic HCV infection', *Journal of Gastroenterology*, 31: 691–695.

Najafipour, R, Mohammadi, D, Momeni, M & Moghbelinejad, S 2022, 'ACE-2 Expression and Methylation Pattern in Bronchoalveolar Lavage Fluid and Bloods of Iranian ARDS Covid-19 Patients', *International Journal of Molecular and Cellular Medicine*, 11 (1), viewed <http://ijmcmed.org/article-1-1867-en.html>.

Nassan, MA, Soliman, MM, Aldhahrani, A, Althobaiti, F & Alkhedaide, AQ 2021, Ameliorative impacts of *Glycyrrhiza glabra* L. root extract against nephrotoxicity induced by gentamicin in mice. *Food Science & Nutrition*, 9: 3405–3413.

Niu, W, Wu, F, Cui, H, Cao, W, Chao, Y, Wu, Z, Fan, M & Liang, C 2020, Network pharmacology analysis to identify phytochemicals in traditional Chinese medicines that may regulate ACE2 for the treatment of COVID-19. *Evidence-Based Complementary and Alternative Medicine*, 1: 7493281.

Nomura, T, Fukai, T & Akiyama, T 2002, Chemistry of phenolic compounds of licorice (*Glycyrrhiza* species) and their estrogenic and cytotoxic activities', *Pure and Applied Chemistry*, 74: 1199–1206.

Pastorino, G, Cornara, L, Soares, S, Rodrigues, F & Oliveira, MBPP 2018, Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. *Phytotherapy Research*, 32: 2323–2339.

Peirzadeh, S, Fakhari, S, Jalili, A, Mirzai, S, Ghaderi, B & Haghshenas, V 2014, Glycyrrhetinic acid induces apoptosis in leukemic HL60 Cells through upregulating of CD95/ CD178. *International Journal of Molecular and Cellular Medicine*, 3 (4), viewed <http://ijmcmed.org/article-1-172-en.html>.

Peng, F, Du, Q, Peng, C, Wang, N, Tang, H, Xie, X, Shen, J & Chen, J 2015, A review: The pharmacology of isoliquiritigenin. *Phytotherapy Research*, 29: 969–977.

Qiao, X, Liu, C-F, Ji, S, Lin, X-H, Guo, D-A & Ye, M 2014, Simultaneous determination of five minor coumarins and flavonoids in Glycyrrhiza uralensis by solid-phase extraction and high-performance liquid chromatography/ electrospray ionization tandem mass spectrometry. *Planta Medica*, 80: 237–242.

Robin, Kaur, P, Kaur, J, Kaur, K & Miglani, S 2023, Plant-derived immunomodulators targeting COVID-19 (SARS-CoV-2): Preclinical evaluation and clinical trials. *Bioprospecting of Tropical Medicinal Plants*, Springer, pp. 1515–1531.

Safdarpour, S, Eftekhari, Z, Eidi, A & Doroud, D 2022, Encapsulated saponin by ferritin nanoparticles attenuates the murine pneumococcal pneumonia. *Microbial Pathogenesis*, 172: 105731.

Selman, M, Ruiz, V, Cabrera, S, Segura, L, Ramírez, R, Barrios, R & Pardo, A 2000, TIMP-1,-2,-3, and-4 in idiopathic pulmonary fibrosis. A prevailing nondegradative lung microenvironment? *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 279: 562–574.

Shehu, IA & Datta, A 2022, Therapeutic profile of *Glycyrrhiza glabra*: A ray of hope in treating COVID-19', *Malaysian Journal of Pharmaceutical Sciences*, 20: 147–167.

Sinha, SK, Prasad, SK, Islam, MA, Gurav, SS, Patil, RB, AlFaris, NA, Aldayel, TS, AlKehayez, NM, Wabaidur, SM & Shakya, A 2021, Identification of bioactive compounds from *Glycyrrhiza glabra* L. as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: A pharmacoinformatics study. *Journal of Biomolecular Structure and Dynamics*, 39: 4686–4700.

Sun, H-X & Pan, H-J 2006, 'Immunological adjuvant effect of *Glycyrrhiza uralensis* saponins on the immune responses to ovalbumin in mice', *Vaccine*, 24: 1914–1920.

Sun, L, Yang, Z, Zhang, J & Wang, J 2021, Isoliquiritigenin attenuates acute renal injury through suppressing oxidative stress, fibrosis and JAK2/STAT3 pathway in streptozotocin-induced diabetic rats', *Bioengineered*, 12: 11188–11200.

Tahoori, F, Ahmad, M, Nejadsattari, T, Ofoghi, H & Iranbakhsh, A 2019, Qualitative and quantitative study of quercetin and glycyrrhizin in in vitro culture of Liquorice (*Glycyrrhiza glabra* L.) and elicitation with $AgNO_3$. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, 47: 143–151.

Tang, Y, Wang, C, Wang, Y, Zhang, J, Wang, F, Li, L, Meng, X, Li, G, Li, Y & Wang, L 2018, Isoliquiritigenin attenuates LPS-induced AKI by suppression of inflammation involving NF-κB pathway', *American Journal of Translational Research*, 10: 4141.

Traboulsi, H, Cloutier, A, Boyapelly, K, Bonin, M-A, Marsault, É, Cantin, AM & Richter, M V 2015, The flavonoid isoliquiritigenin reduces lung inflammation and mouse morbidity during influenza virus infection. *Antimicrobial Agents and Chemotherapy*, 59: 6317–6327.

Vashist, H & Sharma, D 2013, Pharmacognostical aspects of *Glycyrrhiza glabra*. *Asian Journal of Pharmaceutical and Clinical Research*, 6: 55–59.

Visavadiya, NP, Soni, B & Dalwadi, N 2009, 'Evaluation of antioxidant and anti-atherogenic properties of *Glycyrrhiza glabra* L. root using *in vitro* models. *International journal of food sciences and nutrition*, 60: 135–149.

Wahab, S, Ahmad, I, Irfan, S, Siddiqua, A, Usmani, S & Ahmad, MP 2022, 'Pharmacological efficacy and safety of *Glycyrrhiza glabra* L. in the treatment of respiratory tract infections. *Mini Reviews in Medicinal Chemistry*, 22: 1476–1494.

Wang, J-F, Liu, S-S, Song, Z-Q, Xu, T-C, Liu, C-S, Hou, Y-G, Huang, R & Wu, S-H 2020, 'Naturally occurring flavonoids and isoflavonoids and their microbial transformation: A review. *Molecules*, 25: 5112.

Williamson, EM 2003, Potter's cyclopedia of herbal medicine. CW Daniel, Saffron Walden, pp. 269–271.

Yang, N, Patil, S, Zhuge, J, Wen, M, Bolleddula, J, Doddaga, S, Goldfarb, J, Sampson, HA & Li, X 2013, *Glycyrrhiza uralensis* flavonoids present in anti-asthma formula, ASHMITM, inhibit memory Th2 responses in vitro and in vivo', *Phytotherapy Research*, 27: 1381–1391.

Yi, Y, Li, J, Lai, X, Zhang, M, Kuang, Y, Bao, Y-O, Yu, R, Hong, W, Muturi, E & Xue, H 2022, 'Natural triterpenoids from licorice potently inhibit SARS-CoV-2 infection', *Journal of Advanced Research*, 36: 201–210.

Yu, D, Liu, X, Zhang, G, Ming, Z & Wang, T 2018, Isoliquiritigenin inhibits cigarette smoke-induced COPD by attenuating inflammation and oxidative stress via the regulation of the Nrf2 and NF-κB signaling pathways. *Frontiers in Pharmacology*, 9: 1001.

Yu, X-Q, Xue, CC, Zhou, Z-W, Li, C-G, Du, Y-M, Liang, J & Zhou, S-F 2008, *In vitro* and *in vivo* neuroprotective effect and mechanisms of glabridin, a major active isoflavan from *Glycyrrhiza glabra* L. (licorice). *Life Sciences*, 82: 68–78.

Zhang, Q & Ye, M 2009, 'Chemical analysis of the Chinese herbal medicine Gan-Cao (licorice)', *Journal of Chromatography A*, 1216:1954–1969.

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