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A systematic review of antioxidant and antimicrobial activities in the different extracts of licorice as a valuable plant for ameliorating respiratory infectious disorders

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ABSTRACT

Licorice, known scientifically as *Glycyrrhiza glabra*, has garnered significant attention in traditional and modern medicine due to its extensive therapeutic properties. This systematic review explores various licorice extracts' antioxidant and antimicrobial activities, particularly in respiratory infectious disorders. The review highlights the efficacy of licorice as a sedative agent for sore throats and an expectorant for bronchial conditions, as recognized by the World Health Organization. Despite the potential for adverse effects with prolonged high doses, licorice is generally safe when used in moderation, exhibiting a range of pharmacological effects, including antiviral, anti-inflammatory, and antioxidant activities. The review provides literature from scientific databases, focusing on the anti-fibrotic role of licorice and its mechanisms against respiratory pathogens. It underscores the need for innovative therapeutic strategies to combat treatment-resistant respiratory ailments, particularly pneumonia, which poses a significant health risk globally. The findings suggest that licorice extracts could serve as effective complementary therapies, enhancing the efficacy of conventional treatments while minimizing side effects. This review provides a foundational reference for future research aimed at developing new therapeutic agents derived from licorice, ultimately improving patient quality of life and survival rates in respiratory infections.

Keywords: Licorice, Respiratory infections, Pathogen, Antioxidant, Anti-Inflammatory.
Article type: Review Article.

INTRODUCTION

Pneumonia can be characterized as a pulmonary infection that predominantly affects the alveolar region. Without a corresponding inflammatory response, detecting microorganisms within the alveolar space signifies colonization and does not equate to pneumonia. Numerous other infection types may also impact the lung and can be

categorized based on their primary site of infection. Pneumonia is categorized in multiple distinct ways (Nelson *et al.* 1995). These classifications predominantly pertain to clinical criteria that generally delineate variations in the possible spectrum of involved pathogens. The most prevalent categorization is based on the patient's environment at infection acquisition. Another widely recognized classification is determined by the causative pathogen(s). In the past, confirming a microbiological diagnosis often took several days. However, with the development of rapid, point-of-care diagnostic technologies, it is now possible to obtain microbiological confirmation within minutes or hours of a patient's clinical presentation. As a result, this classification is expected to become more pertinent in informing patient management strategies at the time of presentation (Meyer Sauteur 2020; Miyashita 2022). Assessing the severity of illness is critical in managing individuals suffering from pneumonia. This evaluation directs key decisions concerning the appropriate treatment environment, whether it be in the community, a hospital, or an intensive care unit, the level of diagnostic scrutiny required, the urgency of initiating treatment, and the specifics of the treatment plan, which includes the choice of antimicrobial agents and the route through which they are administered (Nelson *et al.* 1995; Meyer Sauteur 2020). Consequently, there remains a pressing need for enhanced efforts to devise innovative strategies aimed at preventing this treatment-resistant respiratory ailment. Traditional medicine, a cornerstone of medical practice, serves as a natural repository of chemical compounds that can produce synergistic effects through their combined mechanisms, thereby enhancing efficacy and reducing the toxicity of primary ingredients. This approach often encompasses a broader range of therapeutic actions, whether utilized as a standalone treatment or in conjunction with conventional medical therapies (Hosseini *et al.* 2021; Razmjoue *et al.* 2023). Nature has consistently been a rich source of medicinal resources, offering a variety of plants that yield bioactive compounds. One such plant is licorice, scientifically known as *Glycyrrhiza glabra*, which is classified within the Leguminosae family. This widely utilized medicinal plant is prevalent across Asia and certain regions of Europe. It is believed that licorice originated in Iraq, with *G. glabra* being the most commonly found species in Italy, Spain, Turkey, the Caucasus, Western China, and Central Asia. In contrast, *G. uralensis* is distributed in Central Asia, extending to China and Mongolia. Commercial cultivation of this plant occurs in various countries, including Italy, Spain, Greece, France, Iran, Iraq, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, India, China, the USA, and England (Abu-Odeh & Talib 2021; Colak *et al.* 2021; Kukkar & Patel 2021). Licorice is recognized as one of the most economically significant plants globally, with extensive applications across the tobacco, cosmetics, food, and pharmaceutical sectors. The phytochemical and pharmacological properties of licorice have been the subject of considerable research. In traditional Chinese medicine, *G. glabra* is regarded as a fundamental herbal remedy. It is commonly believed that "nine out of ten formulas contain licorice," highlighting its role as a potent herbal agent that mitigates toxicity and enhances the efficacy of other herbal treatments when combined. Additionally, it may serve as a nutritious food product and a natural sweetener (Kukkar & Patel 2021). The field of Iranian medicine is characterized by its extensive content and theoretical completeness, with notable achievements in physiology, pathology, treatment, and pharmacology. These contributions have significantly influenced Chinese medicine and attracted sustained global medical attention (Bahmani *et al.* 2014; Mohammadi *et al.* 2024). In contrast, many current therapies for lung diseases demonstrate restricted efficacy or present undesirable side effects. Consequently, this review aims to provide a foundational reference for the innovation of new therapeutic agents that are effective and free from complications, specifically targeting pulmonary fibrosis following viral pneumonia, thereby improving patient quality of life and increasing survival rates.

MATERIAL 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 "Pneumonia" or "Pulmonary infection" and "Traditional medicine", "Licorice", "Respiratory pathogens", "*Glycyrrhiza glabra* ", " Anti-inflammatory" and " Antioxidant" were in all fields. Names of chemical constituents in the present review follow the journal plant list.

Infectious pulmonary disease

Pneumonia is characterized as an infection of the lower respiratory tract that arises from the failure to eliminate pathogens from the lower airways and alveoli effectively. The release of cytokines and local inflammatory mediators results in additional lung damage, primarily through the accumulation of white blood cells and fluid,

which can lead to the formation of pus within the lung parenchyma (Nelson *et al.* 1995). The category of pleuropulmonary infections comprises various disorders, such as bronchitis and bronchiolitis, pneumonia marked by inflammation of the lung parenchyma, the development of lung abscesses, cavity formation, allergic bronchopulmonary responses, as well as pleural effusion and empyema, which is the accumulation of pus in the pleural space. According to the Infectious Diseases Society of America, pneumonia is identified by the presence of new lung infiltrates alongside clinical indicators of infection, such as the onset of fever, purulent sputum, leukocytosis, and a decrease in oxygen saturation. Notably, lower respiratory infections are recognized as the leading cause of mortality among communicable diseases (Organization 2014; Lim 2021). Pneumonia can be classified into three distinct types: (i) community-acquired, (ii) hospital-acquired, and (iii) ventilator-associated. A diverse array of microorganisms can invade the pulmonary system, encompassing viruses, bacteria, fungi, and parasites (Quinton *et al.* 2018; Lim 2021). The specific pathogen involved is often contingent upon the clinical context. For instance, common agents of community-acquired pneumonia include *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. Atypical forms of community-acquired pneumonia are attributed to *Mycoplasma pneumoniae, Chlamydia* species, and various viruses such as respiratory syncytial virus (RSV) and parainfluenza virus in pediatric populations, as well as influenza A and B in adults. In contrast, nosocomial infections may arise from pathogens like *Klebsiella* species, *Escherichia coli, Pseudomonas* species, and penicillin-resistant *S. aureus* (Biscevic-Tokic *et al.* 2013; Lim 2021).

Licorice plant

Throughout history, nature has proven to be an essential source of medicinal agents, supplying numerous plants that generate valuable phytochemicals. Licorice, identified scientifically as *G. glabra*, is categorized within the Leguminosae family (Fig. 1; Dastagir & Rizvi 2016). The World Health Organization recognizes licorice's efficacy as a sedative agent for sore throats and an expectorant in treating bronchial disorders and coughs. To date, there have been no documented instances of toxic compounds associated with the species examined. Nonetheless, it is acknowledged that prolonged use of high doses can result in severe health issues. Conversely, licorice may serve medicinal purposes for severe conditions when utilized in small quantities, with no known adverse effects (El-Saber Batiha *et al.* 2020). It has been documented to exhibit a wide array of pharmacological effects, including antiviral, anticancer, anti-ulcer, anti-diabetic, antioxidant, anti-thrombotic, antimalarial, antifungal, antibacterial, immunostimulant, anticonvulsant, antiallergenic, and expectorant activities (Damle 2014). Studies have also indicated that the roots possess antidepressant, hypotensive, hepatoprotective, and spasmolytic and are capable of enhancing memory. The demulcent property of licorice roots is particularly noteworthy. In addition, this plant is recognized for its therapeutic applications in conditions such as gout, asthma, sore throat, tonsillitis, flatulence, sexual debility, epilepsy, hyperdipsia, fever, coughs, skin ailments, swellings, acidity, leucorrhea, bleeding, jaundice, hiccups, hoarseness, and disturbances in vata dosha, along with gastralgia, cephalalgia, ophthalmopathy, and pharyngodynia (Vashist & Sharma 2013; Zadeh *et al.* 2013).

Fig. 1. Licorice plant with scientific name *Glycyrrhiza glabra; https://murmureskin.com/pages/licorice-glycyrrhiza-glabra*

Numerous chemical constituents of licorice have been investigated for their significant pharmacological effects, including anticancer, antibacterial, anti-inflammatory, cardioprotective, and hepatoprotective properties, as well as efficacy against respiratory infections. Recent literature indicates a growing interest among researchers in licorice, focusing on its active compounds and their mechanisms of action. Among these, licorice flavonoids, derived from the stem and root, have demonstrated considerable biological activity. The extract of licorice, along with its four key flavonoids (isolycoirithigenin, licoirithigenin, lycalocone, and glabidine), exhibits notable medicinal properties, positioning licorice as a potential natural alternative for addressing emerging health issues with minimal side effects (Hayashi *et al.* 1996; Zadeh *et al.* 2013; Hamad *et al.* 2020). Secondary metabolites in plants are categorized into various groups according to their chemical structures. Consequently, it is essential to explore the primary pharmacological properties of different secondary metabolites found in licorice, including flavanones, coumarins, chalcones, isoflavones, and others, alongside triterpenoid saponins and phenolic compounds. Approximately 400 distinct compounds have been extracted from licorice, with around 300 of these being flavonoids. The biologically active constituents primarily consist of secondary metabolites and their derivatives, which include alkaloids, glycosides, flavonoids, phenols, saponins, tannins, terpenes, and steroids (Zadeh *et al.* 2013; El-Saber Batiha *et al.* 2020). Licorice extract comprises sugars, starch, bitter compounds, resin, essential oils, tannins, mineral salts, and trace amounts of nitrogenous substances such as proteins, individual amino acids, and nucleic acids. The principal active components are glycyrrhizin, glycyrrhetinic acid, and triterpenoid derivatives. In humans, glycyrrhizin can be metabolized into glycyrrhetinic acid, resulting in pharmacological effects comparable to glycyrrhizin. Among the isoflavones present, glabridin is the most prevalent in the roots (Zadeh *et al.* 2013; Fig. 2). The *G. glabra* Linn. roots are characterized by glycyrrhizin, a notably 60 times sweeter saponin than cane sugar. The flavonoid-rich extracts from these roots include liquiritin, isoliquertin, liquiritigenin, and rhamnoliquirilin, as well as five newly discovered flavonoids: glucoliquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin, and 1-methoxyphaseolin. These compounds have been successfully isolated from the dried roots. Additionally, researchers have isolated and determined the structures of licopyranocoumarin, licoarylcoumarin, glisoflavone, and a new coumarin known as GU-12. Moreover, four novel isoprenoid-substituted phenolic constituents—semilicoisoflavone B, 1-methoxyficifolinol, isoangustone A, and licoriphenone—have been identified from the roots (Vashist & Sharma 2013; Nassan *et al.* 2021;).

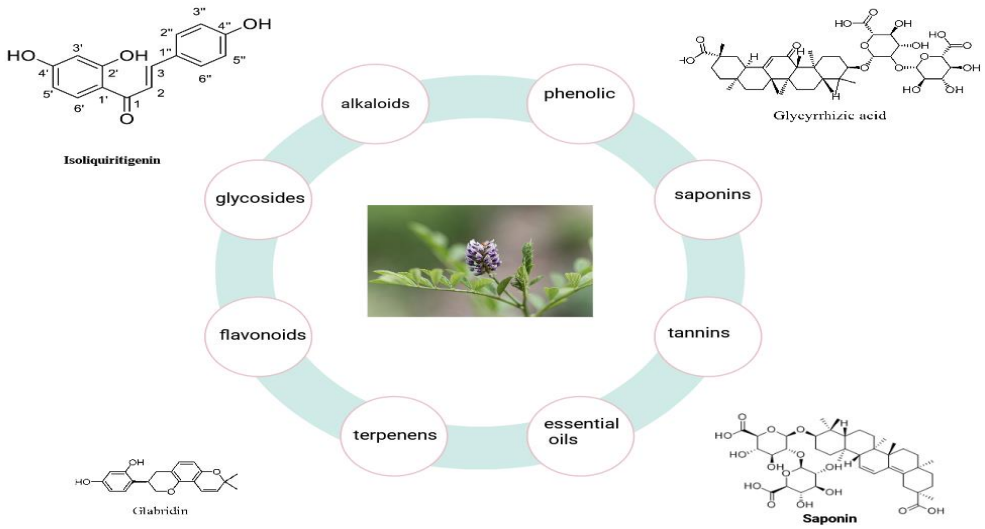

Fig. 2. The componenet of Licorice plant and chemical structure of saponin, glaridin, glycyrrhizic acid and isoliquiritigenin.

The botanical origins reveal the presence of various 2-methylisoflavones, alongside a distinctive coumarin known as C liquocoumarin, specifically 6-acetyl-5-hydroxy-4-methyl coumarin. Additionally, asparagine is identified within this context. Glycyrrhizin, also referred to as glycyrrhizic acid or glycyrrhizinate, constitutes approximately 10–25% of the extract derived from licorice root and is recognized as the principal active component. This saponin compound consists of a triterpenoid aglycone, glycyrrhetic acid (alternatively known as glycyrrhetinic acid or enoxolone), which is linked to a disaccharide of glucuronic acid (Colak *et al.* 2021).

Anti-inflammatory activity

The increasing use of non-steroidal anti-inflammatory drugs (NSAIDs) for treating a range of diseases and inflammatory disorders is noteworthy; however, these drugs are linked to a variety of side effects. In parallel, there is an escalating interest in herbal treatments for inflammation, which are often associated with fewer adverse effects. Many medicinal plants and their bioactive compounds have played a crucial role in formulating therapies for diverse health issues (Račková *et al.* 2007; Bisht *et al.* 2022). Licorice, a medicinal herb with a rich historical background, has been used to combat inflammatory ailments since ancient times. This article offers an extensive examination of licorice, its isolated constituents, and their mechanisms of action and establishes a foundation for future investigations focused on treating inflammatory conditions. Licorice has demonstrated anti-inflammatory properties by decreasing levels of PGE2, MMPs, TNF, and free radicals, corroborated by its traditional applications such as alleviating cough, clearing mucus, enhancing digestive processes, mitigating pain, and also in experimental studies involving rats, processed licorice products significantly alleviated symptoms of rheumatoid arthritis (Račková *et al.* 2007). The upregulation of matrix metalloproteinases, inflammatory cytokines, and vascular endothelial growth factors was observed in blood and cell supernatants following treatment with licorice-processed products. The findings of this study indicated that licorice-processed products exerted anti-inflammatory effects via the TLR4/NF-kβ/NLRP3 signaling pathway in collagen-induced arthritis (CIA) in rats and lipopolysaccharide (LPS)-induced RAW264.7 cells, alongside metabolic profiling in the context of rheumatoid arthritis management (Meng *et al.* 2022; Amin *et al.* 2024). The flavonoids derived from licorice and its extracts have demonstrated significant *in vivo* anti-inflammatory effects by inhibiting the expression of the COX-2 gene, iNOS, and the signaling pathways associated with mitogen-activated protein kinases (MAPKs). These flavonoids operate through a coordinated mechanism that engages multiple biological pathways, exhibiting their anti-inflammatory capabilities. As a result, flavonoids from licorice present a promising therapeutic option for managing inflammation with minimal adverse effects. Furthermore, research on licorice extract containing saponins has revealed its anti-inflammatory properties in a mouse model of pulmonary pneumonia and its ability to mitigate pulmonary fibrosis. Additionally, secondary metabolites and licorice extracts have anti-inflammatory effects in treating conditions beyond acute kidney disease (Jiang *et al.* 2018; Frattaruolo *et al.* 2019). Isoliquiritigenin has been shown to alleviate LPS-induced acute kidney injury by inhibiting TNF-α-mediated NF-kβ and HMGB pathways. It also reduces inflammation and kidney fibrosis resulting from unilateral ureteral obstruction. Moreover, isoliquiritigenin suppresses inflammatory cytokines and modulates the NF-kβ and Nrf2 pathways, which are implicated in Ang II-induced hypertensive renal damage. Neutrophils generate reactive oxygen species (ROS) at inflammation sites, and the licorice and glycyrrhizin extracts contribute to minimizing tissue damage (Shirazi *et al.* 2012; Gao *et al.* 2020). The experimental *in vitro* study indicated that treatment with licoflavanone significantly reduced the phosphorylation and activation of p38, JNK, and ERK1/2 in LPS-stimulated RAW 264.7 cells (Kim *et al.* 2008). Additionally, licoflavanone's interference with the NF-kB/MAPKs signaling pathway led to a notable decrease in the mRNA expression of various pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNFα), Interleukin-1 beta (IL 1β), and Interleukin-6 (IL 6; Chu *et al.* 2012; Wu *et al.* 2022). The pharmacological profile of licoflavanone aligns with other flavanones derived from plants, suggesting that the capacity to modulate the MAPK/NF-kB pathway is a characteristic shared among various flavonoid classes. Comparable effects have been documented in different experimental contexts for several flavones, flavonols, and flavanones, such as pinocembrin, naringenin, quercetin, and luteolin, all of which have demonstrated the ability to inhibit MAPK activation, prevent NF-kB translocation to the nucleus, and reduce the synthesis of pro-inflammatory cytokines (Frattaruolo *et al.* 2019). Eltahir *et al.* (2024), manifested *G. glabra*'s phenolic compounds exhibit anti-inflammatory activity by inhibiting inflammatory markers in RAW 264.7 macrophage cells. Specifically, isolates like liquiritin, neoisoliquiritin, and glabridin demonstrated effectiveness, while isoliquiritin and isoliquiritin apioside did not inhibit inflammation. In the other study, licorice root extract (*G. glabra*) exhibits significant anti-inflammatory activity through the inhibition of the cyclooxygenase-2 (COX-2) enzyme, primarily due to glycyrrhizin, with 18β-glycyrrhetic acid showing the best anti-inflammatory potential among its compounds (Eltahir *et al.* 2024). NO is an inflammatory mediator produced through the enzymatic activity of iNOS, which is upregulated by inflammatory triggers such as bacterial lipopolysaccharides (LPS) via toll-like receptor 4 (TLR4). The expression of iNOS is primarily regulated by the transcription factor NF-kB, a key player in the inflammatory response. In light of the observed effects of licoflavanone on NO production in LPS-activated RAW 264.7 cells in previous experimental studies, alongside the known capacity of other

flavanones, such as pinocembrin, to inhibit inflammatory signaling through the NF-kB pathway. The findings from this investigation demonstrated that licoflavanone effectively reduced NF-kB translocation into the nucleus and significantly inhibited the transcription of its target genes, thereby suggesting that the observed effects on NO production were not attributable to a direct inhibitory effect on iNOS. These results underscore the important role of licoflavanone in modulating the NF-kB signaling pathway, a phenomenon also noted with the leaf extract of *G. glabra* L., from which this valuable natural compound was derived (Frattaruolo *et al.* 2019). Glycyrrhizin, constituting 2-25% of licorice's dry weight, is crucial in its anti-inflammatory properties. Flavonoid compounds such as glabridin and isoliquiritigenin have shown the potential to inhibit inflammatory pathways by targeting key receptors like COX-2 and IL-1R. Licorice root extract has demonstrated superior inhibition of COX-2 compared to conventional NSAIDs, suggesting its potential as a safer alternative for treating inflammatory conditions. The phenolic compounds from licorice can inhibit the production of pro-inflammatory cytokines in macrophage cell lines, reducing inflammation effectively (Sharma *et al.* 2017; Yang *et al.* 2017; Quinton *et al.* 2018; Frattaruolo *et al.* 2019).

Antioxidative effects of licorice

Reactive oxygen species (ROS) are generated continuously as a byproduct of the body's metabolic processes, particularly during respiration and certain immune responses. This category of molecules encompasses free radicals, including superoxide anion ($O_2^{\cdot -}$) and hydroxyl radicals ($OH^{\cdot}$), as well as non-radical species such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$; Bahmani, Rafieian-Kopaei *et al.* 2014; Mohammadi *et al.* 2024). These reactive species possess the potential to inflict damage on essential biomolecules, including nucleic acids, lipids, proteins, polyunsaturated fatty acids, and carbohydrates, which may result in DNA damage and subsequent mutations. Without effective scavenging mechanisms by cellular components, ROS can initiate free radical chain reactions, leading to further damage to proteins, lipids, and nucleic acids, ultimately contributing to various disease states. The involvement of ROS has been associated with over 100 different diseases (Visavadiya *et al.* 2009; Sultana *et al.* 2010; Esmaeili *et al.* 2019). Antioxidant compounds are vital as they can effectively scavenge free radicals and prolong the shelf life of food and pharmaceutical products by decelerating lipid peroxidation, which is a primary cause of product deterioration during processing and storage. Furthermore, antioxidants protect the human body from the harmful impacts of free radicals and reactive oxygen species (ROS). They are instrumental in slowing the progression of numerous chronic diseases alongside lipid peroxidation. This has prompted a growing interest in discovering alternative, natural, and safe sources of food antioxidants, particularly those of plant origin, which has significantly intensified in recent years. Antioxidants are commonly added to food items to neutralize the radical chain reactions that lead to oxidation, inhibiting both the initiation and propagation stages, thereby facilitating the termination of the reaction and postponing the oxidation process (Tohma & Gulçin 2010). The antiradical properties, protective effects against lipid peroxidation in liposomal membranes, and the inhibitory effects on the release of reactive oxygen species (ROS) from whole blood were evaluated for the crude extract of *G. glabra* and its primary component, glycyrrhizin by Račková *et al.* (2007) . The licorice extract demonstrated significant activity across all three assay systems in a dose-dependent manner. It exhibited notable reactivity with the stable free radical DPPH, showed inhibitory effects on peroxidatively damaged unilamellar dioleoyl phosphatidylcholine (DOPC) liposomes, and inhibited ROS chemiluminescence generated by whole blood in response to both receptor-bypassing stimuli (PMA) and receptor-mediated stimuli (Opz). These observed activities are likely due to the presence of phenolic antioxidants, including isoflavan derivatives, coumarins, and chalcones. In contrast, the triterpene saponin glycyrrhizin did not demonstrate efficacy in the DPPH reaction or the peroxidation of liposomal membranes, and it exhibited minimal inhibition of chemiluminescence produced by inflammatory cells. So, these findings suggested that the anti-inflammatory mechanism of glycyrrhizin likely does not involve ROS, indicating that this principal component is not responsible for the inhibitory effects of licorice extract on neutrophil functions (Račková *et al.* 2007; Sharad & Kapur 2021). To assess and compare the antioxidant capabilities of *G. glabra* L. leaf extracts, DPPH and ABTS assays were conducted by Frattaruolo *et al.* (2019). The results revealed a consistent antioxidant profile across the various extracts, with IC_{50} values ranging from 13.49 to 18.05 µg mL^{-1} for the DPPH assay and 5.88 to 6.76 µg mL^{-1} for the ABTS assay. This finding correlates with the similar total phenolic content observed in each extract. Additionally, similar evaluations were carried out on three isolated compounds to determine their roles in the notable antioxidant properties of the extracts. The findings indicated that a prenyl group enhances the antioxidant profile of flavanones, corroborating previous research. Specifically, the prenyl group at position 8 in glabranin

significantly improved the antioxidant capacity compared to its non-prenylated counterpart, pinocembrin. Furthermore, licoflavanone exhibited the most favorable antioxidant profile, suggesting that either the position of the prenyl group or the presence of an additional hydroxyl group on the C ring of the flavanone structure can substantially influence the antioxidant efficacy of these natural compounds (Frattaruolo *et al.* 2019). The dose-dependent aqueous and ethanolic extracts in an *in vitro* model study exhibited significant scavenging activity against various radicals, including nitric oxide, superoxide, hydroxyl, DPPH, and ABTS•+. Additionally, both extracts demonstrated robust reducing power and iron-chelating abilities. In the Fe^{2+}/ascorbate system, they effectively inhibited lipid peroxidation in mitochondrial fractions. In models of copper-catalyzed oxidation involving human serum and low-density lipoprotein, both extracts significantly extended the lag phase while reducing the oxidation rate, as well as the formation of conjugated dienes, lipid hydroperoxides, and thiobarbituric acid reactive substances (Fuhrman *et al.* 1997; Tohma & Gulçin 2010). The antioxidant capacity of *G. glabra* L. (licorice) rhizomes and roots was evaluated. The antioxidant potential of the methanol/water extract is likely linked to the flavones (mainly derivatives of apigenin), flavanones (primarily derivatives of liquiritin), a methylated isoflavone, and a chalcone that were identified in the extract. The most notable antioxidant effect was the inhibition of lipid peroxidation. This was succeeded by free radical scavenging activity and reducing power (Cruz-Martins *et al.* 2015; Chagas *et al.* 2022). Many studies have established a link between phenolic compounds and their bioactive properties. In the case of *G. glabra*, various classes of compounds, including flavonoids, saponins, coumarins, and stilbenoids, have been associated with these bioactive effects. To date, several compounds such as licochalcone A, B, C, D, and echinatin, along with certain isoflavones and their derivatives—specifically glabridin, an isoflavan, as well as hispaglabridin A, hispaglabridin B, and 4′-O-methylglabridin—have been identified as exhibiting significant antioxidant properties. These compounds inhibit lipid peroxidation, function as radical scavengers, and prevent oxidative processes (Kim *et al.* 2008; Tohma & Gulçin 2010; Esmaeili *et al.* 2019). *G. glabra* extracts demonstrated significant antioxidative activity, reducing oxidative stress signals by 31-83% in cell-based assays by Teichmann *et al.* (2022). The active compound glabridin correlated with this bioactivity, highlighting the importance of flavonoids in the antioxidative effects of liquorice samples (Teichmann *et al.* 2022). In conclusion, the plant *G. glabra* L. is abundant in antioxidant substances, particularly flavonoids, and triterpenoids. These bioactive compounds are instrumental in reducing lipid buildup in non-alcoholic fatty liver disease through activating Nrf2 and promoting autophagy, which collectively enhances its antioxidant potential (Gao *et al.* 2020).

Licorice in the treatment of respiratory tract infections

The primary viral agents responsible for respiratory infections include influenza, respiratory syncytial virus, rhinoviruses, and human coronaviruses. Antibiotics are primarily effective against bacterial infections and do not relieve viral conditions such as sinusitis, sore throats, bronchitis, influenza, and other common respiratory ailments (Organization 2014; Yönden *et al.* 2022). Currently, no specific antiviral medications are available, leaving only symptomatic treatments as viable options. Nevertheless, extensive research is underway globally to develop vaccines and drug-based strategies targeting respiratory viruses. Additionally, traditional medicine is gaining attention for its potential in treating various diseases. Evaluating medicinal plants to identify new compounds exhibiting antiviral and antimicrobial properties is essential. *G. glabra* L. (Licorice) has demonstrated pharmacological effects that can modulate the immune response, inhibit viral proliferation, exert anti-inflammatory effects, and inactivate viruses (Fiore *et al.* 2008). Licorice, particularly *G. uralensis* and *G. glabra*, has been recognized for its therapeutic potential in treating respiratory tract infections. Its bioactive compounds, such as liquiritin and glycyrrhizin, exhibit significant anti-inflammatory and antimicrobial properties, making them valuable in managing respiratory ailments. Liquiritin has demonstrated the ability to suppress the JNK/Nur77/c-Jun signaling pathway, reducing inflammation in models of acute lung injury. Glycyrrhizin, a key component of licorice, has shown promise in modulating immune responses and reducing inflammation associated with respiratory infections. Licorice root is included in herbal formulations that improve symptoms of bacterial respiratory infections, enhancing recovery when combined with antibiotics. The active compounds in licorice have been linked to antimicrobial activities, potentially aiding in the treatment of respiratory tract infections (Sharad & Kapur 2021; Eltahir *et al.* 2024). Recent research has indicated that glycyrrhizin and licorice extract may offer significant advantages in combating the novel coronavirus by interacting with ACE2, inhibiting the virus's entry and subsequent penetration into host cells (Buder *et al.* 2022). Glycyrrhizin has emerged as a potential

therapeutic agent for COVID-19 in China. Given the structural similarities between SARS-CoV and SARS-CoV-2, along with the established efficacy of glycyrrhizin against SARS-CoV, numerous researchers have posited that glycyrrhizin could serve as a viable treatment for COVID-19 by binding to ACE2 and obstructing the entry of the novel coronavirus. Furthermore, studies proposed that glycyrrhizin and its metabolites may exert their effects through two distinct mechanisms: directly inhibiting the expression of transmembrane serine protease type 2 (TMPRSS2), which is essential for viral entry and modulating mineralocorticoid receptor (MR) activation. This downregulation of ACE2 expression may confer protective effects against COVID-19. Notably, glycyrrhizic acid has been reported to exhibit the highest efficacy in disrupting the interaction between the receptor binding domain (RBD) of SARS-CoV-2 and ACE2, suggesting a broad-spectrum anti-coronavirus activit (Sinha *et al.* 2021; Wahab *et al.* 2022; Cinatl *et al.* 2003). Research has indicated that certain derivatives of glycyrrhizic acid, commonly known as glycyrrhizin, exhibit a tenfold enhancement in antiviral efficacy. Specifically, the anti-SARS-CoV properties of glycyrrhizic acid can be significantly amplified up to 70 times when combined with either one amide or two amino acid residues. However, this increase in antiviral activity is accompanied by a rise in cytotoxicity, reducing the selectivity index. Furthermore, recent investigations have demonstrated that the glycyrrhizic acid derivatives can effectively inhibit the dengue virus. Notably, Dong *et al.* (2020) reported that glycyrrhizic acid-based carbon dots (Gly-CDs), which are semi-synthetic derivatives of glycyrrhizic acid, exhibit multi-target antiviral inhibition and possess unique antiviral properties, positioning them as promising candidates for the treatment of viral infections, including respiratory syndromes. Additional studies have suggested that glycyrrhizin may serve as a foundational compound for the development of novel antiviral agents against influenza (Dang *et al.* 2024). *Radix glycyrrhizae* and *R. glycyrrhizae preparata* demonstrated a dose-dependent inhibition of HRSV-induced plaque formation in HEp-2 and A549 cell lines. Notably, *R. glycyrrhizae* exhibited superior efficacy compared to *R. glycyrrhizae preparata* in HEp-2 cells, while no significant differences were observed in their anti-HRSV effects on A549 cells. Glycyrrhizin, in contrast, showed no effectiveness. However, 18β-GA was identified as having strong anti-HRSV properties. The efficacy of *R. glycyrrhizae* was enhanced when administered before viral inoculation, likely due to its ability to inhibit both viral attachment and penetration into host cells. This anti-HRSV activity was corroborated through RT-PCR and qRT-PCR analyses, with 300 μg mL^{-1} of *R. glycyrrhizae* significantly reducing viral loads in both cellular and suspension environments. Additionally, *R. glycyrrhizae* may promote the secretion of IFN-β from mucosal cells, thereby aiding in the defense against viral infections (Feng Yeh *et al.* 2013). A notable clinical case study highlighted a patient's recovery with severe COVID-19 following treatment with diammonium glycyrrhizinate (DG), a compound derived from glycyrrhetinic acid. The authors proposed that the combination of DG with vitamin C could serve as a promising alternative therapeutic approach for alleviating severe COVID-19 symptoms during quarantine (Visavadiya *et al.* 2009). In a separate investigation focused on pneumonia, the administration of saponin extracted from licorice reduced COX-2 protein expression, TNF-α gene expression, and IL-4 serum levels compared to the pneumonia control group. Histopathological analyses indicated that the nano saponin group exhibited significantly lower levels of inflammation, mucus production, pulmonary hemorrhage, alveolar wall thickening, and inflammatory cell infiltration than the other groups. This research suggests that *G. glabra* saponin, mainly when delivered via ferritin nanoparticles with anti-TNF-α properties, may facilitate recovery in pneumonia-affected mice (Safdarpour *et al.* 2022). Previous findings suggest that GL effectively reduces *S. aureus*-induced acute lung injury by lowering the expression of key cytokines such as IL-6, TNF-α, IL-8, IL-1β, and HMGB1. Furthermore, GL inhibits critical signaling pathways, including NF-kB, p38, and ERK1/2, while preventing inflammasome activation and pyroptosis. In the context of *S. aureus*-infected A549 cells, the anti-inflammatory properties of GL are primarily attributed to its action on the p38 signaling pathway. Consequently, GL may represent a promising therapeutic option for treating *S. aureus*-induced ALI (Yao & Sun 2019). The clinical trial study evaluated the efficacy of licorice root extract incorporated into the D-reglis® tablet as an adjunctive treatment for critically ill patients suffering from COVID-19. The primary finding indicated a notable reduction in the duration of ICU hospitalization. Nevertheless, the extract did not demonstrate a statistically significant impact on mortality rates, the sequential organ failure assessment (SOFA) score, the incidence of mechanical ventilation, or oxygen saturation levels (Alikiaie *et al.* 2023). 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 and 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). A clinical trial was conducted to conclude *Boswellia carterii* (Olibanum) and *G. glabra* 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* 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). 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* root extract has been shown to contain elements that inhibit the growth and associated cellular diseases of various RNA viruses. The aqueous extract of licorice has been found to possess antiviral activity against several pathogens, including human respiratory syncytial virus (HRSV) and Enterovirus 71 when tested in human skin fibroblast cell lines (Wahab *et al.* 2022). This extract effectively reduced HRSV infection by hindering viral adhesion, uptake, and the stimulation of IFN secretion. Interestingly, the methanol extract of licorice root was found to have a higher anti-HIV activity than the aqueous extract. Additionally, research indicated that the methanol extract of licorice root exhibits more potent anti-hepatitis C virus activity than glycyrrhizin. The ethanolic extract of licorice has also been shown to play a crucial role in inhibiting RANTES secretion from bronchial epithelial A549 cells infected with H_1N_1 (Wahab et al. 2022). Cinati *et al.* (2003) identified *in vitro* antiviral properties against viruses responsible for respiratory tract infections, including influenza, severe acute respiratory syndrome coronavirus (SARS), and human immunodeficiency virus (HIV). The active components of licorice extract exhibiting antiviral effects comprise triterpenoids, flavonoids, and oleanane-type triterpene saponins. Notably, glycyrrhizin, glycyrrhetinic acid, and their derivatives represent the primary triterpenoid constituents of licorice extract. These compounds demonstrate broad-spectrum antiviral efficacy against various RNA and DNA viruses, including SARS coronavirus, herpes virus, HIV, hepatitis virus, influenza virus, cytomegaloviruses, and respiratory syncytial virus. Specifically, in the context of respiratory syncytial virus and influenza, glycyrrhizin has been shown to enhance antioxidant activity in cells infected with the influenza H_5N_1 virus, thereby inhibiting viral replication (Cinatl *et al.* 2005). Additional studies have corroborated that glycyrrhizin obstructs the entry of influenza A/H_1N_1 into host cells. Furthermore, glycyrrhizin's antiviral effects against coronaviruses and SARS-related influenza viruses have been substantiated. The mechanisms underlying glycyrrhizin's antiviral action involve the inhibition of viral uptake and penetration during the initial phases of the viral life cycle, with optimal efficacy observed when administered during and after the viral entry period. Additionally, glycyrrhizin has been found to promote the production of Beclin 1, enhancing its antiviral effects against resistant viral strains, suggesting that the prophylactic potential of glycyrrhizin and licorice extract against significant human pathogens warrants further exploration (Wahab *et al.* 2022).

CONCLUSION

Licorice, scientifically known as *G. glabra*, has demonstrated various pharmacological effects, including antioxidant and antimicrobial activities, making it a valuable plant for treating respiratory infectious disorders. Licorice extracts demonstrate notable antioxidant and antimicrobial activities, making them valuable in treating respiratory infections, including pneumonia and bronchial disorders. The review highlights the diverse pharmacological effects of licorice, including anti-inflammatory, antiviral, and expectorant properties, which contribute to its effectiveness in managing respiratory ailments. While prolonged high doses of licorice can lead to adverse effects, its use in moderate amounts is generally safe and beneficial for various health conditions. The findings underscore the urgent need for new therapeutic strategies to address treatment-resistant respiratory infections, suggesting that licorice could serve as a complementary treatment alongside conventional therapies. These conclusions provide a comprehensive understanding of licorice's role in respiratory health and its potential for future therapeutic applications.

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