REVIEW ARTICLE

Exploring the Potential of *Asl-us-Soos* (*Glycyrrhiza glabra L.*) in the Treatment of Respiratory Diseases—An Ethnomedicinal and Pharmacological Review

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ABSTRACT

Background • *Asl-us-Soos* (*Glycyrrhiza glabra* L.) has been used as a therapeutic agent in the treatment of respiratory, digestive, and neurological disorders since ancient times in Unani Medicine. Its therapeutic uses have been documented in Unani pharmacopeia, classical textbooks, and manuscripts based on experience in clinical practices. *Asl-us-Soos* (AS) and its compound preparations are recommended in the treatment of respiratory diseases such as Dhat al-Janb (pleurisy), Dhat al-Ri'a (pneumonia), Jamod us Sadr (pulmonary apoplexy), Diq al-Nafas (asthma), Sil (thiasis), and Diq (pulmonary tuberculosis).

Objectives • This review aimed to provide insight into ethno-medicinal uses, pharmacological activities, and phytochemical profile of AS. The review also highlights the prospects in the development of potential drug molecules for various respiratory ailments.

Methods • This review is based on a search of authentic Unani classical literature and major databases such as Science Direct, Medline (via PubMed), Google Scholar, Scopus, and Web of Science. The studies published between January 2001 and February 2022 were included in this study.

Results • This review found that AS had medicinal uses in various respiratory disorders. Its roots are used as single drug and compound formulations for the treatment of dry cough, bronchial asthma, bronchitis, and pneumonia. In addition, AS contains active phytoconstituents such as glycyrrhizin (glycyrrhizic acid), isoliquiritigenin, glabridin, and licochalcone A. They have been extensively studied using *in vitro* and *in vivo* models and were found to exhibit pharmacological effects in pulmonary tuberculosis, pulmonary carcinoma, emphysema, bronchial asthma, pneumonia, and upper respiratory tract infections. Moreover, glycyrrhizin has been found to possess therapeutic potential against COVID-19.

Conclusion • This review concludes that AS is a potent anti-tumor, anti-inflammatory, anti-microbial, anti-oxidant, expectorant, and antitussive drug. This plant could be an important source for the development of new drug compounds for various respiratory diseases. (*Altern Ther Health Med.* 2024;30(8):52-59).

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INTRODUCTION

Asl-us-Soos (*Glycyrrhiza glabra* L.) is one of the known oldest plant medicines used for the treatment of various respiratory, digestive, cardiovascular, dermatological, urinary, ophthalmic, and neurological disorders in traditional medicines.[1] Its earliest description could be traced to one of the oldest literature "The Code Humnubari" (2100 BC). In addition, Theophrastus (372-287 BC), the father of botany, described this plant in his book "Historia Plantarum" and mentioned its beneficial uses in upper respiratory disease 'cough' and lower respiratory disease 'asthma'.[2] Furthermore, Abu Ali Sina (980-1037 A.D.), the father of modern medicine, mentioned *Asl-us-Soos* (AS) as a remedy for respiratory and gastric diseases in his very famous medical treatise, The Canon of Medicine (medicine encyclopedia).[2] It has been used for medicinal benefits in Ayurveda, Siddha, Unani, and Chinese Medicines since time immemorial.[3]

AS is a very popular medicinal herb and is a member of the Fabaceae family.[4] Nowadays, it is cultivated for its roots and rhizome in some parts of Europe and Asia.[5] There are more than 30 species of the genus Glycyrrhiza.[6] Of them, *G. glabra*, *G. inflate*, and *G. uralensis* are used for nutritional and pharmacological benefits.[2] *Glycyrrhiza glabra* L., known as *Asl-us-Soos*, is mainly used as therapeutics in Unani Medicine (UM). It has different names in vernacular such as Liquorice or Licorice (English), Asl-us-Soos (Arabic), Bekh-i-Mehak (Persian), and Mulaithi (Urdu). It is also known as Yashtimadhu in Ayurveda.[7]

Figure 1. Pharmacological Actions of *Glycyrrhiza glabra* L. in Respiratory Disorders

AS has been used as a potent natural drug in the treatment of respiratory, gastric, and neurological disorders in UM.[7,8] The root of AS is used orally as a single drug. Therapeutically, it is used in the form of infusion and decoction prepared from natural raw roots and branches of AS plant. It is also used in combination with other plant medicines as compound preparations in the solid dosage form. The extract obtained by crushing the fresh raw root of AS is frequently used in the solid dosage form. The extract obtained by such a process is known as *Rub-us-Soos.* Galen was the great scholar of Unani Medicine who prepared *Rub-us-Soos* for the first time to use it as a better alternative to AS. The shelf life of *Rub-us-Soos* has been declared as 4 years. The temperament of *Rub-us-Soos* has been attributed as hot and dry 2°. It is used as a lozenge for cough in the dosage of 0.5 -1 gm.[9]

The medicinal benefits of the AS plant in respiratory disorders have been documented in the authentic textbooks and pharmacopeia of UM. AS root has been indicated in respiratory diseases such as Dhat al-Janb (pleurisy), Dhat al-Ri'a (pneumonia), Jamood-us-Sadr (pulmonary apoplexy), Diq al-Nafas (asthma), Sil (thiasis), and Diq (pulmonary tuberculosis).[10–12] The medicinal properties attributed to AS root are munzij-i-balgham (concoctive of phlegm), mulaṭṭif (demulcent), jāli (detergent), muqawwi-i-ā'sāb (nervine tonic), mugharri (mucilaginous), muḥallil-i-warm (antiinflamatory), munaffith-i-balgham (expectorant), kāsir-ireyāḥ (carminative), daf-i-humuḍat-i-mi'da (antacid), mudirr-i-bawl (diuretic), muddirr-i-ḥayḍ (emmenogogue), muqawwi-i-dimāgh (brain tonic), muqawi-i-bāh (aphrodisiac), mulayyen (laxative), musakkin (sedative), musakkin ʿutāsh (sedative of thirst), daf-i-ḥummā (antipyretic), and daf-i-tawaḥḥush (antianxiety).[9,13] Figure 1 displays the pharmacological actions of AS for therapeutic applications in respiratory diseases.

Natural medicines have always been an important source of cures for ailments. The immense health benefits of AS have attracted researchers, physicians, and academicians to exploit its application as a first-line therapy in clinical practice. Recent research has identified the phytochemicals present in the root part of AS plant and has shown that AS roots possess antiviral,[14] antiallergic,[15,16] antioxidative, and anticancer activities.[17]

The phytochemistry of AS roots has demonstrated that there are several chemical compounds in them. Of them, glycyrrhizin is a major active constituent which is a triterpene glycoside consisting of one molecule of 18-β-glycyrrhetinic acid and two molecules of glucuronic acid having structure, 18-beta-glycyrrhetinic acid-3-O-beta-d-glucuronopyranosyl-(1 → 2)-beta-d-glucuronide.[16] Pharmacological effects like anti-inflammatory, anti-viral, anti-tumor, and hepatoprotective properties of AS have been associated with this compound.[16]

Literature reports that AS has been used as a mainstay in the treatment of respiratory diseases. In India, Unani Medicine has been recognized by the Government of India and plays a crucial role in the primary healthcare delivery system. The National List of Essential AYUSH Medicines (NLEAM) published in 2022 by the Ministry of AYUSH, Government of India included AS with its therapeutic indications in Sual (cough), Khushunat-e-Halaq (throat irritation), Bohat-us-Saut Haad (hoarseness of voice), Zeequn Nafas (bronchial asthma), and Hirqatul-Baul (burning micturition).[18]

This review aims to explore the current knowledge about ethnomedicinal uses of AS in the treatment of respiratory diseases and to find out the scientific rationale for the therapeutic applications of AS in the management of respiratory diseases. We also included the pharmacology, mechanism of action, and drug targets of AS and the pharmacological activities of its secondary metabolites. The information presented in this review may be used to develop treatment strategies for respiratory disease. The anti-inflammatory, bronchodilator, antibiotic, antiallergic, mucolytic, and anti-tumor properties of AS and its compounds may be further exploited for the better treatment of respiratory ailments. Physicians, researchers, and academicians may benefit from this comprehensive review.

METHODS

In this study, we manually searched Unani classical literature and Unani pharmacopeia recognized by the Government of India such as *Al-Qanoon fil Tib* (The Law in Medicine), *Kitab al-Hawi* (The Comprehensive Book of Medicine), *Kitab al-Mansoori* (Book dedicated to Caliph Mansoor), *Kitab al-Mukhtarat fil-Tib* (The Book on Choice of Medicine), Unani Pharmacopoeia of India, and Alqarabadeen for ethnomedicinal usage of AS. We also searched major online databases such as Science Direct, PubMed Central, Medline, Google Scholar, Scopus, and Web of Science for preclinical and clinical evidence for the safety and efficacy of AS and its metabolites in the treatment of respiratory diseases.

We used the terms "asl-us-soos" OR "glycyrrhiza" OR "liquorice" OR "glabra" OR "glycyrrhizin" OR "glycyrrhizic" OR "glycyrrhizinic" AND "asthma" OR "pulmonary" OR/ AND tuberculosis" OR "bronchitis" OR "pneumonia" OR "carcinoma" OR "infections" to retrieve published research articles. The articles published between January 2001 and February 2022 were included in this review.

In this review, we documented information regarding ethnomedicinal use, pharmacological properties, and therapeutic applications of AS in clinical practice. We collected review articles, original articles based on preclinical and clinical studies, Unani pharmacopeia, classical textbooks, and manuscripts. We extracted information about respiratory diseases in the literature on Unani medicine and the therapeutic uses of AS in the treatment of respiratory ailments. We also included the pharmacological activities of the chemical compounds isolated from the AS roots, their mechanism of action, and their potential to be developed as a promising drug candidate for the treatment of respiratory disorders.

RESULTS

Ethno-medicinal Uses

We found the description of respiratory diseases and their symptoms along with remedies in the classical textbooks of UM. The treatise *Al-Asbab wa-Alamat* (the book of causes and symptoms) authored by the Persian scholar Najeebuddin Samarqandi (d. 1222 CE) contains the treatment of respiratory diseases including upper respiratory infections.[19] The diseases like bronchial asthma, pleurisy, and pneumonia may worsen the prognosis of the diseases.[19] We went through the legendary books *Al-Qanoon fil Tib* (The Law in Medicine)[20], *Kitab al-Hawi* (The Comprehensive Book of Medicine), *Kitab al-Mansoori* (Book dedicated to Caliph Mansoor), and *Kitab al-Mukhtarat fil-Tib* (The Book on Choice of Medicine) and noted that respiratory ailments have been mentioned and several prescriptions have been described effective and safe for their treatment. These formulations have been documented after a long time of exposure and experience in clinical practice. So, their recommendation has been used since then for the successful treatment of upper respiratory diseases like Sual (Cough), Khushunat-e-Halaq (throat irritation), Bohat-us-Saut (hoarseness of voice)[21] and lower respiratory diseases like Dhat al-Janb (pleurisy), Dhat al-Ri'a (pneumonia), Jamood-us-Sadr (pulmonary apoplexy), Diq al-Nafas (asthma), Sil (thiasis), Diq (pulmonary tuberculosis).[10,12] The Unani pharmacopoeial formulations and their indications have been displayed in Table 1.

We focused on extracting information on the ethno-medicinal usage of AS for respiratory diseases in traditional medicine. It is a recommended drug for respiratory disorders, especially bronchial asthma. The dried root powder of AS is recommended three times a day in the dosage of 1.0 to 5.0 g for asthma. However, its extract is used in a dosage of 0.25 to 0.3 g three times a day for asthma.[3]

In addition, the plant AS has been elaborately described in terms of pharmacological actions, therapeutic uses, dosage, dosage forms, and toxic effects in authentic and recognized books based on the subject Advia Mufrada. These books are referred to for medical indications in clinical practice, and we found that AS has been recommended for the treatment of upper and lower respiratory tract diseases including infectious diseases.[19]

Table 1. Pharmacopoeial Compound Preparations Recommended for Respiratory Diseases[9-11]

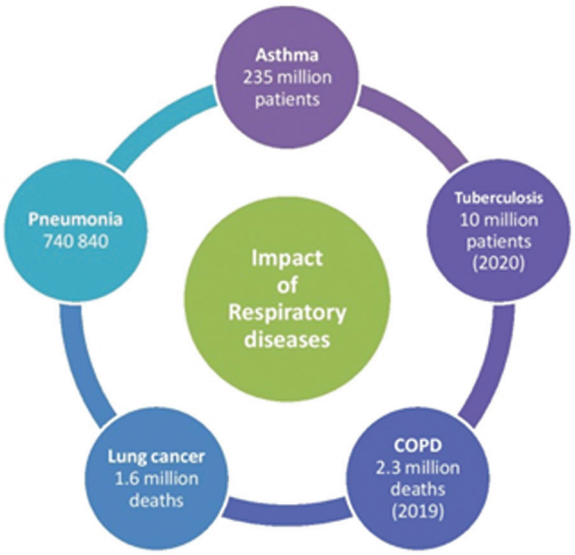
S. No.	Name of formulations	Therapeutic uses	Dosage	Dosage forms
1	Qairooti aarad karsana	Dhat al-Janb (Pleurisy), Dhat al-Ri'a (pneumonia), pulmonary apoplexy, muscular pain, Diq al-Nafas (asthma),	Topical application	Ointment
2	Lauq-i-badam	Sil (thiasis), sual –i-yabis (dry cough)	5-10 gm	Semisolid
3	Lauq sapistan	Nazla (common cold), Sual (cough), Munaffis-i-balgham (expectorant)	5-10 gm	Semisolid
4	Lauq motadil	Sual (dry cough), nazla haar (catarrh), zukam (common cold)	10 gm	Semisolid
5	Lauq-i-nazli	Nazla (catarrh) and sual (cough)	5-10 gm	Semisolid
6	Asanasiya-i-sagheer	Ribu (bronchial asthma), sual-i-muzmin (chronic cough), qai-ud-dam (haematemesis)	2-3 gm	Semisolid
7	Aseer-i-sagheer	Uvula paralysis	5 gm local	Semisolid
8	Tiryaq-i-nazla	Sual (cough) and iltehab-i-tajaweef anf (chronic rhinosinusitis)	5-10 gm	Semisolid
9	Habb-i- kakra senghi	Sual (cough) and Diq al-Nafas (asthma),	One pill twice daily	Solid
10	dayaqooza	Sual (dry cough)	5-10 gm	Semisolid
11	Sharbat aizaj	Sil wa diq (thiasis and pulmonary tuberculosis), sual (dry cough)	25-50 ml	Liquid
12	Habb-i-surfa	Sual (dry cough), Buhuha al-Sawt (hoarseness of voice)	Two pills twice or thrice daily	Solid
13	Sharbat Ustukhuddus	iltehab-i-tajaweef anf (chronic rhinosinusitis)	25-50 ml	Liquid
14	Qur-i-sartan kafoori	Sil wa diq (thiasis and pulmonary tuberculosis), sual (dry cough)	Two pills twice daily	Solid
15	Qurs-i-tabasheer lolwi	Sil wa diq (thiasis and pulmonary tuberculosis), sual (dry cough)	Two pills twice daily	Solid
16	Qurs-i-Kafoor	Sil wa diq (thiasis and pulmonary tuberculosis)	Two pills twice daily	Solid
17	Sharbat Zufa murakkab	Sual (cough) and Diq al-Nafas (asthma)	25-50 ml	Liquid

In an online search of the databases, we found several articles such as reviews, systematic reviews, studies on animal models, and clinical studies based on the efficacy of AS and its metabolites on various respiratory diseases. We focused on the articles based on the outcomes of preclinical and clinical trials. This review shows that research has been conducted to evaluate the efficacy of the root of AS in raw and natural form or its extract. At the same time, the efficacy of the metabolite glycyrrhizin has been studied to explore its therapeutic potential in COVID-19, bronchial asthma, pulmonary tuberculosis, pulmonary carcinoma, and chronic obstructive pulmonary disease (COPD).

Phytochemistry

The roots and stems of AS plant are rich in secondary metabolites. Studies conducted so far have found approximately 400 compounds which include 300 flavonoid compounds,[3] 49 phenolic, and 15 different saponins compounds.[22] It has been found that the phytochemicals of AS belong to a diverse range of compounds such as sugars, proteins, amino acids, vitamins (B1, B2, B3, B5, E, and C), bitters, resins, alkaloids, glycosides, flavonoids, phenolics, saponins, tannins, terpenes, essential oils, steroids, gums, and mineral salts.[1,2] Glycyrrhizin (glycyrrhizinic acid), glabridin, glabrene, glabrol, licoflavonol, glycyrol, licoricone, formononetin, phaseollinisoflavan, hispaglabridin A and B, 3-hydroxy glabrol, 3-methoxy glabridin, glabranin isomer, narigenin, and lupiwightenone have been isolated from roots of AS as metabolites.[17,23]

Figure 2. Impact of Respiratory Diseases on the Human Population



Burden of respiratory diseases

The respiratory system comprises structures like the nasal cavity, pharynx, trachea, bronchi, bronchioles, and lungs. The etiopathology involved in the disease causation of the respiratory system may be inflammatory, allergic, infectious, neoplastic, or traumatic. Respiratory diseases impact the quality of life of the patients and require hospital admissions or hospital visits worldwide. Bronchial asthma, COPD, pulmonary tuberculosis, pneumonia, cystic fibrosis, and lung cancer are the frequently reported respiratory disease conditions in clinical practice.

In the present health scenario around the world, respiratory diseases have become a major cause of morbidity and mortality. In 2017, 544.9 million patients were affected by chronic respiratory diseases, making it the third leading cause of mortality worldwide.[24] An increase in the number of deaths by 18% due to chronic respiratory diseases has been observed between 1990 and 2017.[25] In addition, during the previous 2 years, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has further worsened the respiratory health of the people. Novel COVID-19 infections often cause pneumonia and respiratory failure leading to the death of patients. In addition, persistent exposure to risk factors such as tobacco smoke, occupational clouds of dust and chemicals, air pollution, and frequent episodes of lower respiratory infections during childhood have increased the risk of respiratory disease by many folds. World Health Organization (WHO) has initiated a chronic respiratory diseases program to reduce the toll of morbidity, disability, and premature mortality related to chronic respiratory diseases, specifically asthma and COPD. Causing 3.23 million deaths in 2019, COPD is the third leading cause of death worldwide. According to WHO, COPD causes more than 3 million deaths each year, an estimated 6% of all deaths worldwide.[26] In 2019, there were approximately 262 million patients with asthma around the globe.[26] In 2019, an estimated 10 million people suffered from tuberculosis (TB) worldwide including 5.6 million men, 3.3 million women, and 1.1 million children.[27] In addition, the emergence of multidrug-resistant tuberculosis has become a global public health concern. WHO estimated that there are 484 000 new cases of multi-drug resistant tuberculosis every year.[28] The impact of respiratory diseases on human health worldwide has been shown in Figure 2.

Bronchial asthma

Asthma is a chronic inflammatory respiratory disorder. The existing therapy in conventional medicine is not adequate and several adverse effects are associated with it. In such circumstances, the potential therapeutic molecule preferably of natural origin should be developed.[16] In the quest for drug molecules of natural origin, species of Glycyrrhiza have been extensively studied. It has been observed that several flavonoids isolated from *Glycyrrhiza uralensis* such as Isoliquiritigenin, 7, 4'-dihydroxyflavone (7, 4'-DHF), and liquiritigenin can significantly suppress IL-4 and IL-5 production in a dose-dependent manner in allergic asthma.[30] Among them, 7, 4'-DHF is considered the most potent. It suppresses the effects on D10 cell proliferation, GATA-3 expression, and IL-4 mRNA expression resulting in no loss of cell viability. In addition, the long-term treatment with 7, 4'-DHF is reported to significantly reduce eosinophilic pulmonary inflammation, serum IgE levels, IL-4, and IL-13 levels in a murine model of allergic asthma. It was also observed that 7, 4'-DHF increases IFN-γ production in lung cell cultures in response to antigen stimulation.[29] In an animal model, Glycyrrhiza extract has been observed to exhibit an anti-asthmatic effect, attenuate IL-5 levels, and reduce eosinophilic inflammation with a decrease in IL-13 levels, resulting in the reduction of mucus secretion.[30]

In another study, the anti-allergic effects of glycyrrhizin, 18β-glycyrrhetinic acid, isoliquiritin, and liquiritigenin such as anti-scratching behavior and inhibition of IgE production were assessed.[31] These molecules were found to inhibit the production of IgE in ovalbumin-induced asthma mice. However, liquiritigenin had little effect. This study demonstrated the antiallergic effects of AS roots which may be attributed to glycyrrhizin and 18β-glycyrrhetinic acid, , in relieving IgE-induced allergic asthma. Moreover, glycyrrhizin, 18β-glycyrrhetinic acid, isoliquiritin, and liquiritigenin have exhibited anti-inflammatory and immunomodulatory effects which could potentially ameliorate bronchial asthma.[15]

In another *in vivo* study glycyrrhizin exhibited its efficacy on asthmatic features in a mouse model of asthma. This study demonstrated that glycyrrhizin alleviated asthmatic features in mice. This property of glycyrrhizin could be useful for developing an effective therapeutic molecule in the future. In another study, licochalcone A had shown an anti-asthmatic effect. Licochalcone A suppressed polyinosinic-polycytidylic acid (poly-IC)-induced thymic stromal lymphopoietin (TSLP) expression in a dose- and time-dependent manner. Thus, this compound could be therapeutically beneficial in treating virus-induced asthma.[32]

In another study based on an asthmatic animal model, licochalcone A was found to alleviate oxidative stress, inflammation, and pathological changes by inhibiting Th2-associated cytokines. Thus, licochalcone A demonstrated therapeutic potential for improving asthma.[33]

A preclinical study demonstrated that glycyrrhizin ameliorated the established histopathological changes in the mouse model of asthma.[34] While another study showed that glycyrrhizin could alleviate experimental allergic asthma in mice.[16] In addition, AS has also been found effective in chronic bronchial asthma in human participants.[35]

The powder of AS and its extract are beneficial for the treatment of sore throat, cough, and bronchial asthma. Liquiritin apioside has been isolated from the methanolic extract of liquorice. This compound has been found to actively inhibit capsaicin-induced cough in an animal model. In a clinical study, the herbal mixture containing AS roots was tested for a short duration and it significantly ameliorated the severity of coughs and nighttime awakenings in comparison to the placebo. However, the changes in peak expiratory flow rate (PEFR) and forced expiratory volume over 1 second (FEV_1) were insignificant.[36]

Chronic obstructive pulmonary disease (COPD)

The incidence of COPD (chronic bronchitis, chronic bronchiolitis, and emphysema) is on the rise due to air pollution. The pathogenesis of these respiratory problems could be explored. Long-term exposure to toxins and irritants causes inflammation of the airways and mucus production.[26] The persistent injury due to these agents causes damage to the alveolar structures of the lungs. In COPD, the progression of the disease is associated with the recruitment of T lymphocytes, especially in the small airways. Smokers who suffer from COPD have an increased number of neutrophils, lymphocytes, and macrophages.[26]

Pulmonary emphysema is also an inflammatory disease. It is usually associated with oxidative stress.[3] So, plants containing antioxidant effects can reduce inflammation in pulmonary emphysema patients and can reduce apoptosis of lung cells. These types of plants can be used as an adjunct treatment for pulmonary emphysema.

AS root has the potential to modulate the immune system, possess anti-inflammatory properties, inhibit virus growth, and inactivate viruses. Therefore, it could be used in the treatment of respiratory infections caused by viruses and bacteria. In an animal model, a formulation containing AS root extract showed a good anti-inflammatory response.[37] AS is a potent mucolytic drug. The mucolytics have antioxidant and anti-inflammatory properties. In COPD, mucolytics are commonly used to aid clearance.[38]

In a clinical study, the Unani formulation containing AS showed improvement in FEV_1 % predicted > 75 after 45 days of treatment in chronic bronchitis participants.[39] In another clinical study, it was reported that Qurs-i-sartan kafoori and Sharbat Zufa Murakkab, which contained AS, ameliorated symptoms of chronic bronchitis along with a significant change in $FEV_{1.}$[40]

Pulmonary tuberculosis

It has been reported that *Mycobacterium tuberculosis* is becoming resistant to conventional anti-tubercular drugs resulting in the emergence of multidrug-resistant tuberculosis.[41] The spread of pulmonary tuberculosis is unabated and uncontrolled. So, tuberculosis is one of the ten leading causes of death worldwide.[42] In such a scenario, the development of novel anti-tubercular drugs has become the focus area of research for biomedical scientists.

AS has been identified as one of the plants for potential anti-tubercular drugs in the plant kingdom. The AS roots contain bioactive compounds such as glabridin, Isoliquiritigenin, and liquiritigenin which have shown antimicrobial activity against *M. tuberculosis*.[23] The antimicrobial activity of AS roots against viruses, bacteria, and fungi has been studied.[7] Glabridin, one of the phytoconstituents of AS roots, was found to possess antitubercular activity with 20 times higher potency than the crude extract.[23]

In addition, using molecular docking, the natural compounds of AS roots such as Glycyrrhizin, Swertiamarin, and Laccaic acid showed significant binding affinities with their corresponding *Mycobacterium tuberculosis* target proteins. Among these compounds, Glycyrrhizin displayed a considerably high binding affinity with the C-terminal extracellular domain of EmbC (Arabinosyltransferase), 20-O-methyltransferase TlyA (5KYG), and oxidoreductase InhA (5VRL).[41] Moreover, 18β-glycyrrhetinic acid was characterized as a major anti-tubercular agent using bioactivity-guided isolation of compounds from the AS roots. Moreover, Isoliquiritigenin and liquiritigenin, the bioactive compounds isolated from the rhizomes of AS plant have shown an inhibitory effect against *Mycobacterium tuberculosis*[43] In an *in vitro* study, the antimycobacterial activity of acetone extract of AS has also been demonstrated.[44]

Pulmonary carcinoma

The compounds isolated from AS roots and stolon have been studied as cancer chemopreventive agents in the recent past. These are phenolic compounds such as formononetin, glabridin, hemileiocarpin, hispaglabridin B, isoliquiritigenin, 4'-O-methylglabridin, and paratocarpin B.[3] These compounds were tested using an authentic peroxynitrite anti-oxidant assay. The most potent anti-oxidant property was shown by hispaglabridin B, isoliquiritigenin, and paratocarpin B phenolic compounds. In an animal model, isoliquiritigenin was demonstrated to prevent the incidence of 1, 2-dimethylhydrazine-induced colon and lung tumors at a dose of 300 mg/kg.[45]

Licochalcone A, a flavonoid isolated from AS roots, was found capable of regulating rat vascular smooth muscle cell (rVSMC) proliferation, suggesting that licochalcone A inhibits the proliferation of rVSMCs by suppressing the platelet-derived growth factor (PDGF)-induced activation of the ERK1/2 pathway and retinoblastoma (Rb) protein phosphorylation, resulting in the cell cycle arrest.[3]

In another animal model with Lewis lung carcinoma and Ehrlich tumor, AS extract and glyciram prepared from this plant enhanced the antitumor effect of cyclophosphamide. Glyciram also decreased the toxic effect of the cytostatic on peripheral blood leukocytes. Additionally, the AS extract inhibited the growth of the Ehrlich tumor and prevented the development of metastases. Glyciram was also found to exhibit an anti-metastatic effect and prevented relapses of carcinoma.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) has been recognized as a chronic lung disease characterized by dyspnea and progressive loss of lung function. It is considered an aging disorder and impacts the quality of life of the patient with an average life expectancy of 3–5 years after diagnosis if left untreated.[24] In an *in vivo* study, AS was reported to prevent and treat pulmonary fibrosis and inflammation in rats.[46]

Chronic Cough

The AS powder and its extract are extremely useful in treating sore throat, cough, and bronchial catarrh.[13] It contains an active compound glycyrrhizin, a potent antitussive, demulcent, and expectorant that helps to reduce congestion in the upper respiratory tract and increases tracheal mucus secretion.[3] Another active compound, known as Liquiritinapioside, found in its methanolic extract can inhibit capsaicin, which induces cough.[1]

Upper respiratory tract infections

In clinical practice, upper respiratory tract infections (URTI) such as allergic rhinitis, rhinosinusitis, pharyngitis, and tonsillitis are common presentations. Allergic rhinitis affects 28.7% population in India.[47] Chronic URTI patients frequently visit clinics and dispensaries to consult Unani/Ayurvedic physicians for their treatment in India. Nowadays real-time data of the patients consulted at government health facilities can be viewed at the NAMASTE portal.

AS-containing herbal preparations are widely used for the treatment of URTI.[3,9] The patients familiar with Unani herbal preparations have been using them as over-the-counter medicine for self-treatment. Along with a long history of the use of the Unani pharmacopoeial preparations in the treatment of URTI, clinical studies have been conducted to validate the efficacy and safety of Unani formulations in human participants. A clinical study on Tajaweef-e-Anaf (Sinusitis) using an oral herbal preparation containing AS showed that it was effective and safe in sinusitis participants.[48] Several clinical studies conducted for evaluation of the safety and efficacy of Unani formulations containing AS as one of the constituents in sinusitis/rhinosinusitis reported a good response to nasal congestion, tenderness, and nasal discharge.[49–51]

In another clinical trial, the combo Unani compound preparations containing *Rub-us-Soos* ameliorated the symptoms of URTI such as dry cough, stuffy nose, sore throat, and hoarseness of voice.[52] In a clinical study, licorice nasal irrigation prepared from aqueous licorice extracts effectively treated allergic rhinitis patients.[47]

Safety and toxicity

In classical literature, AS is reported to have harmful effects on the kidneys and spleen.[13] The side effects of AS root and glycyrrhizin have also been reported in clinical studies. The commonest side effect of AS reported in the literature is elevated blood pressure.[2,5] Hypertension, after the use of AS may be due to the phenomenon of pseudo-aldosteronism. The saponins present in the AS bind to mineral-corticoid receptors in the kidneys and as such potentiate the action of aldosterone. This effect of AS on the rennin-angiotensin-aldosterone system may be responsible for hypertension. It has also been reported that the onset and severity of the side effects of AS are dose and duration-dependent. The amount of AS taken by the patients in the dosages of 1.5 g and 250 g per day may cause side effects. In addition, another side effect reported in the literature is hypokalemic-induced secondary disorders.[5] The patients may present edema due to hypokalemia and sodium retention. It is observed that these side effects may disappear after discontinuation of the use of AS. These side effects are increased by hypokalemia, prolonged gastrointestinal transient time, decreased type 2 11-beta-hydroxysteroid dehydrogenase activities, hypertension, anorexia nervosa, old age, and female sex.[2] However, the safety of AS has not been established during pregnancy and lactation.[5,17]

DISCUSSION

In our comprehensive review, we have explored the remarkable ethnopharmacological and pharmacological potentials of AS roots and stolons. We found that AS roots have been used for ages in the treatment of upper and lower respiratory ailments in Unani medicine. It has been recommended for upper respiratory diseases like rhinitis, rhinosinusitis, pharyngitis, tonsillitis, and chronic cough. It has been indicated in lower respiratory diseases such as pulmonary tuberculosis, pneumonia, bronchial asthma, pleurisy, chronic bronchitis, and emphysema. It is used for children as well as adults in clinical practice.

In the field of Unani medicine, the onset of diseases is mainly based on the theory of four humors. A humoral disproportion in the body manifests as a disease. Respiratory diseases may develop due to the domination of phlegmatic humor in the body. The principle of treatment for phlegmatic disorders is, therefore, excretion of excess phlegm from the body. AS has mucolytic and other properties. It is therefore recommended in the treatment of respiratory diseases.[3,13]

The biological effects of the AS roots have been mainly assessed through *in vivo* and *in vitro* experiments. Glycyrrhiza plant extracts have been majorly assessed for their antioxidant, antimicrobial, anti-inflammatory, antiproliferative, and cytotoxic activities.[22] Generally, the assessment of the pharmacological effects of *Glycyrrhiza glabra* is mostly related to its principal components, glycyrrhizin and glycyrrhetinic acid.[22]

The rationale for the usage of AS in the therapy of respiratory diseases has been explored. The complex and

variable combinations of compounds in the roots of AS have been identified such as glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid), isoliquiritigenin, hydrophobic flavonoids, formononetin, glabridin, hemileiocarpin, hispaglabridin B, 4'-Omethylglabridin, paratocarpin B. Licochalcone A., 18 β-glycyrrhetinic acid, isoliquiritin, liquiritigenin, and glyciram.[3,6] These compounds have shown therapeutic potential in pulmonary tuberculosis, pulmonary carcinoma, bronchial asthma, and COPD.[3] The mechanistic approach to search the drug targets has been studied especially in pulmonary carcinoma, bronchial asthma, and COPD.[3] So far, we have come to know that glycyrrhizin and glabrin may be developed as novel drug molecules in the future.

Although AS has been used for the treatment of digestive, neurological, dermatological, urinary, and joint diseases[4], it has shown great potential in the treatment of respiratory diseases. Unani physicians use compound formulations containing AS roots in place of AS roots alone based on the severity of the diseases. So, it is recommended to exploit the synergistic actions of the chemical compounds for better efficacy and treatment outcomes. The chemical compounds isolated from AS roots are the emerging drugs for the chemoprevention of lung carcinoma. Glycyrrhizin and glycyrrhetinic acid are potent inhibitors of cortisol metabolism due to their steroid-like structures. Recent research has shown that glycyrrhizin may be an efficacious therapeutic agent against COVID-19 infections.[53] Preclinical and clinical studies have demonstrated that glycyrrhizin may be effective in the prevention and treatment of COVID-19.[4,54] It may be further considered for the evaluation of its efficacy in the treatment of patients with COVID-19.[55]

Glycyrrhizin has been found safe clinically.[56] However, its side effects have been reported in clinical practices like hypertension.[2,5] Clinical trials may be conducted to further establish the safety and efficacy of glycyrrhizin and other phytoconstituents of AS. Furthermore, the indications of AS mentioned in the Unani pharmacopoeia, particularly in respiratory disorders, are required to be validated for clinical practice.[57]

Future perspective

In the present scenario, we have observed that research approaches to exploit the beneficial effect of AS, its metabolites, and its compound preparations in respiratory disorders may be divided into two groups. One group comprises researchers, Unani scholars, traditional Unani physicians, and academicians who believe that AS as a single drug may be used in natural and raw forms or its formulations may be recommended for the treatment of respiratory diseases. So, they give priority to the research for validation of their therapy or intervention to generate evidence. The outcomes of these types of research may strengthen traditional Unani medicine practice.

The other group comprising pharmacologists, phytochemists, pharmacologists, and biologists who have a reductionist approach to drug development recommends extensive research at the molecular level. Nowadays the reductionist approach is accepted worldwide in search of drug candidates. The division of approaches has led to the deviation from the direction of research and development of the drug. So, it is important to mention here that these two approaches of research for drug development should be taken into consideration.

So far, we have come to know that the pharmacological actions of AS plants and glycyrrhizin like anti-inflammatory, anti-allergic, anti-oxidant, and anti-viral have immense importance in the development of a new drug. It may be possible that the side effects of glycyrrhizin may be reduced by modifying its structure. The potential of glycyrrhizin, glycyrrhetinic acid, glabridin, and isoliquiritigenin have been exploited in several studies to gain an understanding of their mechanism of action and drug targets of these compounds. Further studies may be conducted for the development of new drugs for lung carcinoma, pneumonia, and pulmonary tuberculosis.

CONCLUSION

Glycyrrhiza glabra L (AS) has a long history of ethno-medicinal uses in treating respiratory disorders. Nowadays, Unani physicians use it in clinical practice to treat cough, bronchial asthma, chronic bronchitis, acute tonsillitis, pneumonia, and emphysema. It is used as a single drug and a constituent of compound preparations for various therapeutic purposes. In the recent past, several *in vivo* and clinical studies have been conducted to generate evidence for its efficacy and safety in the treatment of respiratory ailments. Glycyrrhizin has been identified as an active metabolite and has shown its therapeutic effects in bronchial asthma, emphysema, pulmonary tuberculosis, and pneumonia. At the same time, studies have to be conducted to establish the safety and toxicity of AS and glycyrrhizin in humans.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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