***Review Article***

**Ethnopharmacological Insights on *Rubb-us-Soos* (*Glycyrrhiza glabra*)**

.

ABSTRACT

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| In Unani system of medicine, the roots and rhizomes of *Glycyrrhiza glabra* (GG) or Licorice have been used clinically for centuries for their anti-inflammatory, antiulcer, expectorant, antimicrobial, antipyretic, analgesic, and anxiolytic activities. The roots are highly valued for their nutritional and medicinal properties and have been employed by the Greeks, Arabs, and Indians since ancient times in the treatment of cough and asthma. A decoction of roots, when further heated and converted into a jellified form known as *Rubb-us-soos* (extract of GG), has been used by Unani Physicians for ages for gastrointestinal ailments. Avicenna also recommended the use of licorice roots for treating cutaneous ulcers, kidney and urinary bladder diseases, gastritis, fever, lung disorders like bronchial asthma and chronic bronchitis, as well as heart diseases.  It is commonly added to bitter laxative formulations such as those containing Senna, Aloe vera, and Cascara, to improve flavor due to the sweet taste of glycyrrhizin. It is also used to enhance flavor in toothpaste, mouthwash, and breath purifiers. Besides, it is also employed in chewing gum, confectionery, soft drinks, liqueurs, ice creams, puddings, bakery products, soy sauce and soybean-protein meat substitutes.  In the last couple of decades, a strong awareness of the safety, efficacy, easy availability and cost-effectiveness of GG has been developed among the general public, thus increasing its importance and popularity. The current paper aims to highlight and appraise the botanical background, phytochemical composition, and ethnopharmacological properties of *Rubb-us-soos*. |

*Keywords: Rubb-us-soos, Aslus soos, Licorice, Glycyrrhiza glabra, Mulethi, Unani medicine*

1. INTRODUCTION

The Unani drug, *Asl us Soos,* consists of dried, roots and stolon of the plant, botanically named as *Glycyrrhiza glabra* Linn. (GG) of Leguminosae family (Anonymous, 1997, Aly, et al., 2005; Kaur, et al., 2013; Anonymous, 2006a). The word Glycyrrhiza is derived from two Greek words ‘glykos’ meaning ‘sweet’ and ‘rhiza’ meaning ‘root.’ It was later Latinized to ‘liquiritia’ and then finally to licorice in English (Isbrucker, 2006). In the Arabic lexicon, ‘*Asl’* means roots, ‘*Soos’* means GG plant, and the most beneficial content of *Soos* is its *Usara* (decoction) which is 60-70 times sweeter than cane sugar (Aly, et al., 200; Isbrucker, et al., 2006; Anonymous, 2005]. Its Unani name is ‘*Aluqarya*’ meaning sweet, therefore can be used as a sweetening agent or flavoring agent in pharmaceutical preparations (Aly et al., 2005; Kaur, et al., 2013; Baytar, 1999; Murray, 2020).

The medicinal use of licorice is about 4000 years old (Fukai, et al., 2002). The earliest documented record of the medicinal use of GG is found on the ‘Code of Hammurabi (1755-1750 BCE)’ of Babylonian period. It is also mentioned in the Assyrian Herbal (2000 BCE). Buqrat recommended the use of *Asl-us-Soos* for the treatment of ulcers (Kaur, et al., 2013). Since ancient times, *Asl-us-Soos* was considered an important drug in Egyptian, Chinese, Greek, Indian, and Roman civilizations for its therapeutic actions in various respiratory and gastrointestinal ailments (Kaur, et al., 2013; Kirtikar & Basu 2005; Zadeh et al., 2013). It was the most commonly prescribed herb in Ancient Egyptian, Roman, Greek, East China, and the West from the Former Han era (Wahab, et al., 2021). Licorice is the most commonly used crude drug in Kampo medicines (traditional Chinese medicines modified in Japan).

Carbenoxolone, a succinate derivative of glycerrhetinic acid, was created in London in the early 1960s and has since become the most popular form of licorice used for ulcer healing (Aly, et al., 2005). Licorice acts as synergist in many Chinese and Ayurvedic preparations (Evans, 2009). More than 30 species of the genus *Glycyrrhiza* are present over the globe.

It is known by different vernaculars, for instance, Asl-us-**soos,** Oodusoos (Arabic); Licorice root, Liquorice root, Sweetwood, Glycyrrhiza radix (English); **Mulethi, Mulathi, Mulhatti, Jethi-madh, Jethimadhu, Meethilakdi (Hindi);** Beekhe muhik (Persian); Jalayashti, Madhuka, Yashti-madhu (Sanskrit); Mulatthi (Urdu) and Aluqarya (Unani) (Anonymous, 1997; Baytar, 1999; Kirtikar & Basu 2005; Anonymous, 1992; Khare, 2007). Plant Root (*Aslus soos*) and its extract (*Usara*) or concentrated extract (*Rubb-us-soos*) are medicinally used (Anonymous, 1997; Baytar, 1999; Murray, 2020; Dymock, et al., 2005; Baghdadi, 2006).

1. **BOTANICAL BACKGROUND**
   1. **Taxonomy**

It belongs to Kingdom- Plantae; Division- Tracheophyta; Class- Magnoliopsida; Order- Fabales; Family- Fabaceae; Genus: *Glycyrrhiza* and Species- *glabra*

* 1. **Botanical Description**

The perennial GG plant is 3-7 ft. in height (Murray, 2020). The leaves are compound, imparipinnate, alternate, having 4-7 pairs of oblong, elliptical or lanceolate leaflets. Violet flowers are narrow and borne in axillary spikes. The calyx is short and campanulate, with lanceolate tips and glandular hairs. The fruit is a compressed legume or pod, up to 1.5 cm long, erect, glabrous, somewhat reticulately pitted, and usually contains 3-5 brown, reniform seeds. The straight, thick, cylindrical main taproot subdivides into subsidiary roots, from which the horizontal woody stolon arises. The stolons when dried and cut, together with the main root, constitute commercial licorice. The pieces of root break with a fibrous fracture (Kaur, et al., 2013; Zadeh et al., 2013). The 20-50 cm long and 2 cm broad roots are sweet in taste with a characteristic odor. The unpeeled root is wrinkled, yellowish brown externally, and yellow internally while the peeled root is fibrous without wrinkles and pale yellow in color (Aly, 2005; Anonymous, 2005; Kokate, 2017; Al-Snafi, 2018).

* 1. **Variations**

There are three varieties of *G. glabra*. The Spanish licorice or *G. glabra var. typica* has blue-colored papilionaceous flowers. It gives out a large number of stolons. The second is Russian licorice or *G. glabra var. glandulifera*, it has a large rootstock along with a number of elongated roots but does not bear stolons. The third, Persian licorice, or *G. glabra var. violacea* has violet flowers (Kokate, et al., 2017).

* 1. **Distribution**

GG is native to Mediterranean regions and some regions of Asia (Kaur, et al., 2013; Zadeh et al., 2013). In India, it is found in sub-Himalayan tracts, South India, Andaman Islands and is mainly cultivated in Punjab and Jammu and Kashmir (Anonymous, 1992). It is also found in Armenia, Azerbaijan, Iran, Iraq, Afghanistan, Uzbekistan, Turkmenistan, Georgia, Russian Federation, China, Italy, Spain, England, Turkey, and France (Anonymous, 1997; Kokate, et al., 2017; Al-Snafi, 2018).

The propagation of plant is done with young pieces of stolon which are planted in March. The plant requires fertile, deep sandy soil preferably near a river stream for enough irrigation (Kaur, et al., 2013). The roots are harvested 3-4 years after planting when they show sufficient growth. Rhizomes and roots are dug up in October after the withering of leaves, preferably from plants that have not borne the fruits (Anonymous, 1997; Kokate, et al., 2017). After washing the drug, it is dried first under the sun and then in shades, during which it loses about 50 percent of its weight (Kokate, et al., 2017).

* 1. **Ethnobotanical Description as per Unani Literature**

It is also called as ‘*Oodus Soos*’ by Baytar. It is long, round, wrinkled and straight root inside the soil. It has an inside yellow and an outside yellowish-brown color with a strange nauseatic smell and a peculiar sweet taste with a bitter tinge. The peeled root used medicinally is yellow and devoid of wrinkles. Its strength can last up to 10 years. The *Asl-us-Soos* which is sweet and less fibrous is considered better. The unpeeled root is wrinkled and darker in color (Ghani, 2011).

* + 1. **Mizaj (Temperament)**

|  |  |
| --- | --- |
| *Asl* (Root) | *Har* (Hot) *Ratab* (Moist) (Baghdadi, 2006)  *Har* (Hot) *Yabis* (Dry) (Nabi, 2007)  *Moatadil* (According to Buqrat) (Ghani, 2011) |
| *Usara* (Extract) | *Moatadil* (in *hararat* and *buroodat*) and Ratab (Baytar, 1999) |
| *Rubb* (Concentrated extract) | *Har* (Hot)2° *Yabis* (Dry)2° (Anonymous, 1997; Multani, ynm] |

* + 1. **Miqdare Khurak (Dose)**

|  |  |
| --- | --- |
| Root | 6g-9g (Multani, ynm) |
| *Rubb* | 500 mg-1g (Anonymous, 1997) |

* + 1. **Muzir (Adverse Effect)**

For kidney and spleen (Anonymous, 1997)

* + 1. **Musleh (Corrective)**

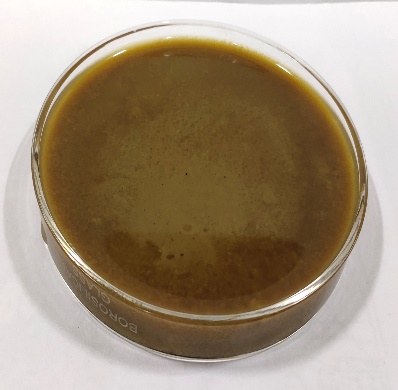
*Gule surkh* (*Rosa damascena*), *Kateera* (*Astragalus gummifer*) (Anonymous, 1997; Multani, ynm), *Unnab* (*Zizyphus jujuba)* (Multani, ynm).

* + 1. **Badal (Substitute)**

Substitute of *Rubb us soos* is *Aslus Soos* in double dose (Anonymous, 1997)

**2.5.6 Method of Preparation of *Rubb-us-soos***

The roots are crushed and boiled with water (1:4 ratio) and then pressed. The decoction thus obtained is allowed to clear by standing and is then run off which is further dried and given shape of small sticks or balls. Then these sticks are further dried, wrapped in polythene and kept in air tight containers (Anonymous, 1997).



**PREPARATION**

**OF**

***RUBB-US-SOOS***



**Fig. 1. Preparation of *Rubb-us-Soos***

1. **Phytochemistry**

The main constituent of roots is glycyrrhizin (about 2-9%), a triterpene saponin, also known as glycyrrhizic acid or glycyrrhizinic acid, that is almost 50 times sweeter than sucrose. Glycyrrhizin is hydrolyzed by intestinal flora into glycyrrhetinic acid (0.5-0.9%) and a sugar moiety, resulting in their absorption (Khare, 2007). The concentration of glycyrrhizin is influenced by the method of extraction and root source which can go up to 15% (Kokate, et al., 2017; Fugh-Berman & Ernst 2001). Glycyrrhizin represents about 10% of liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrrhizic acid that varies between 2% and 25% (Anonymous, 1997; Pastorino, et al., 2018).

The yellow color of liquorice is due to the flavonoid content. The flavonoids identified belong to different classes, including flavanones, flavones, flavanonols, chalcones, isoflavans, isoflavenes, isoflavones, and isoflavanones. The major flavonoids are glycosides of liquiritigenin and isoliquiritigenin, such as liquiritin, isoliquiritin, liquiritin apioside, and licuraside. Five new flavonoids have been isolated from dried roots: glucoliquiritin apioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1‐methoxyphaseolin. Pinocembrin and licoflavanone were also isolated from the leaves. Glabridin is the principal isoflavone identified, ranging between 0.08% and 0.35% of roots' dry weight. Furthermore, many volatile components are present in roots, such as geraniol, pentanol, hexanol, terpinen‐4‐ol, and α‐terpineol, conferring the characteristic odour. The essential oil obtained from *G. glabra* is also rich in propionic acid, benzoic acid, furfuraldehyde, 2,3‐butanediol, furfurylformate, maltol, 1‐methyl‐2‐formylpyrrole, and trimethylpyrazine (Fukai, et al., 2002; Zadeh, et al., 2013; Khare, 2007; Kokate, et al., 2017; Pastorino, et al., 2018).

Carnbenoxolone is an oleandane derivative prepared from glycyrrhiza and possesses significant mineralocorticoid activity. It is used as an antiulcer drug. It changes the composition of the mucus and increases the mucosal barrier for acid diffusion. It is postulated that carbenoxolone inhibits enzymes that inactivate prostaglandins and suppress the activation of pepsinogen (Al-Snafi, 2018).

1. **Ethnopharmacology**

The ethnopharmacological details of *Aslus soos* are given in Table 1.

**Table 1. The ethnopharmacological details of *Aslus soos***

|  |  |  |
| --- | --- | --- |
| Ethnomedicinal action | Ethnomedicinal indication | References |
| *Munaffise wa mukhrije balgham* (Mucolytic & Expectorant) | * *Iltehabe Shuab* (Bronchitis) * *Su’al yabis* (Dry cough) * *Behtussout* (Hoarseness of voice) * *Ribu* (Asthma) * *Warm-e-halaq* (Pharyngitis) | Kaur, et al., 2013; Baytar, 1999; Murray, 2020; Kirtikar & Basu, 2005; Khare, 2007; Baghdadi, 2006; Nabi, 2007; Schulz, et al., 2001 |
| *Muqawwie meda* (stomachic/gastro-tonic) | * *Mundamile qurooh* (Wound healing) * *Amraze meda* (Gastric disorders) * *Sozishe meda* (Retrosternal burning) * *Fasade hazm* (Dyspepsia) * Abdominal pain | Kaur, et al., 2013; Baytar, 1999; Baghdadi, 2006; Nabi, 2007; Schulz, et al., 2001 |
| *Muhallile awram* (anti-inflammatory) | * *Khushunat Qasbaturiya*   (Irritation of trachea)   * *Sozishe masana*   (Burning micturition) | Baytar, 1999; Khare, 2007; Baghdadi, 2006 |

1. **Important Formulations**

The important formulations of *Aslus soos* are given in Table 2.

**Table 2. Important formulations of *Aslus soos***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| S. No. | Part(s) used | Dosage form | Name of Compound Formulation | References |
|  | Root (A*sl us soos*) | *Arq* (distillate), *Dayaqooza* (a type of syrup), *Gharghara* (gargles), *Habb* (tablet), *Laooq* (a semi-solid dosage form especially for throat and respiratory disorders), *Itrifal* (a semi-solid dosage form) | *Arq hara bhara, Arq maul laham mako kasni vala, Dayaqooza, Gharghara munaqi dimagh, Habbe ghariqoon, Habbe nazla, Habbe zeequn nafas, Itrifal fauladi, Laooq khashkhash, Laooq khyarshambar, Habbe habbul qutn, Habbe sual musakkin, Itrifal mundi, Itrifal muqawwi dimagh, Laooq pambadana, Laooq sapistan, Laooq surfa, Majoon jadwar, Majoon mundi, Majoon sana, Marham jadwar, Namak Sulemani, Qabzeen, Qairooti arad karasna, Qurs mullayyan, Qurs sartan, Qurs zarishk, Roghan sanan, Roghan mukhtara, Roghan nafe warme niqras, Safoof sat gilo salajeet, Safoof qalai kushta, Sharbat zoofa murakkab, Surfeen, Wajur* | Baghdadi, 2006; Anonymous, 2006b; Anonymous, 2007; Anonymous, 2001; Anonymous, 2006c; Anonymous, 2011 |
|  | Distillate (*Arq mulethi*) | *Jawarish* (semi solid dosage form) | *Jawarish falafili* | Baghdadi, 2006 |
|  | Peeled root (*Asl us soos muqashar*) | *Joshanda* (decoction),  *Laooq* (a semi-solid dosage form especially for throat and respiratory disorders) | *Joshanda zoofa, Laooq hulba, Habbe baqla, Safoof asl us soos, Sharbat aejaz, Sharbat faryadras, Sharbat sadar, Sharbat ustukhuddus* | Baghdadi, 2006; Kabiruddin, 2012; Anonymous, 2006b; Anonymous, 2008 |
|  | Dried extract (*Rubb-us-soos*) | *Akseer,* *Banadiq* (a type of larger pill resembling the size of soap nut), *Dawa*, *Habb* (Pill), *Qurs* (Tablet), *Laooq* (a semi-solid dosage form especially for throat and respiratory disorders) | *Akseer surfa, Banadiqul buzoor, Dawa kurkum kabeer, Dawa luk kabeer, Habbe afyun, Habbe banafsha, Habbe bars, Habbe behtassout, Habbe filfil, Habbe Jawahar kafoori, Habbe Jawahar muallif, Habbe loban, Habbe maghze badam, Habbe maghziyat, Habbe nafasuddam silli, Habbe sadr, Habbe shaheeqa, Habbe sil, Habbe suaal, Habbe surfa, Habbe taiyabul nikhat, Habbe yaqut, Habbe zafran, Habbe salarus, Laooq badam, Laooq behidana, Majoon Kindi, Qurs anjabar, Qurs bard, Qurs gul, Qurs kafoor, Qurs khashkhash, Qurs tabasheer qabiz, Qurs ward, Qurs zatul janab, Safoof ziabetus qawi, Tiryaq nazla, Tiryaq suaal* | Baghdadi, 2006; Kabiruddin, 2012; Anonymous, 2006b; Anonymous, 2007; Anonymous, 2001; Anonymous, 2006c; Anonymous, 2011 |
|  | Root (*Asl us soos*) and dried extract (*rubb-us-soos*) both | *Laooq* (a semi-solid dosage form especially for throat and respiratory disorders), *Habb* (pill), *Qurs* (Tablet) | *Laooq motadil, Laooq nazli, Habbe baqla, Qurs sailan kafoori, Qurs sartan kafoori* | Kabiruddin, 2012; Anonymous, 2006b; Anonymous, 2007; Anonymous, 2001; Anonymous, 2006c; Anonymous, 2008 |

1. **Adverse Effects and Toxicity**

One of the most commonly reported side effects of licorice supplementation is elevated blood pressure (Zadeh, et al., 2013). Licorice, containing the active component glycyrrhizic acid, has a mineralocorticoid-like action and its long-term use (>3g/day of GG root for more than 6 weeks or glycyrrhizin >100 mg/day) leads to “pseudo aldosteronism” syndrome resulting in hypertension, hypokalemia, sodium and water retention, low plasma renin activity, and suppressed urine and serum aldosterone levels. Symptoms disappear after discontinuation of the drug (Murray, 2020).

An acute toxicity study of hydroalcoholic extract of GG was conducted at different doses viz. 10, 100, 1000, 1600, 2900 and 5000 mg/kg, per orally on Swiss mice. The results showed that mice treated with dose <1600 mg/kg produced no signs of acute toxicity or death during the 14 days of observation. The animals showed signs of hypoactivity, mild depression and ataxia during the first 30 min and for a period of up to 6 h after administration at doses between 2900-5000 mg/kg, P.O. The LD50 was estimated at about 2950 mg/kg when administered orally in mice (Jalilzadeh-Amin, et al., 2015).

According to a case report, a 30-year-old patient who drank 1 litre of licorice syrup as a regional beverage for four days and 2.5 litres on the fifth day, started to experience weakness and swelling in both legs and had laboratory findings of hypokalemia, mild metabolic alkalosis, and thrombocytopenia (Wahab, et al., 2021).

1. **Pharmacological Studies**

**7.1 Mucolytic and Anti-tussive activity** (Anonymous, 1997; Murray, 2020; Kirtikar & Basu, 2005; Anonymous, 1992; Schulz, et al., 2001)

1. Kuang, Y. used the classical ammonia-induced cough model and phenol red secretion model in mice to evaluate expectorant and antitussive activities, respectively. The chemical components, liquiritinapioside, liquiritin, and liquiritigenin, demonstrated a significant 30-78% reduction in cough frequency at 50 mg/kg (p <0.01) and by 25-59% (*p* <0.05) at 200 mg/kg after 3 days of treatment and could be effectively used (Kuang, et al., 2018).
2. The antitussive effect of the GG granule formulation on SO2 gas-induced cough in experimental animals, compared to standard codeine sulfate, was tested. Codeine sulfate, as a potent antitussive agent, inhibited cough by 25.29 %, 33.33 %, and 47.13% at doses of 10, 15, and 20 mg/kg, respectively, after 60 minutes of the experiment. The test group of mice showed 41.17% inhibition of cough upon treatment with GG granules at 200 mg/kg body weight after 60 min of the experiment (Shitole, et al., 2019).
3. The antibacterial effect of Licorice on *Streptococcus pyogenes* isolated from tonsillitis patients in the age group of 4 months to 64 years was studied. The aqueous and ethanol extracts of GG showed statistically significant antibacterial activities against *S. pyogenes* isolates, where ethanol extracts were two-fold more effective than aqueous extracts (p< 0.05). These results indicate that GG has more active compounds against *S.* *pyogenes* soluble in ethanol than in water, which could be used for remedial purposes (Kazia, et al., 2014).
4. The effect of a modified traditional Persian medicine preparation, licorice pastille, was evaluated in healing chronic cough. A randomized, double-blind, placebo-controlled clinical trial was performed on 70 patients. The outcome was measured as the daily cough score and quality of life according to the Leicester Cough Questionnaire. At baseline, there were no significant differences, but at the end of the trial (week 2) and follow-up (week 4), the efficacy of the licorice pastille in terms of the cough severity score against the placebo group showed a significant decrease in the intervention group (1.2 ± 0.93) compared to the placebo one (1.8 ± 1.03) at follow-up (Ghaemi, et al., 2020).
5. The water-extracted arabinogalactan protein-enriched fraction of GG administered orally at a dose of 50 mg/kg body weight decreased the number of citric acid-induced cough efforts in guinea pigs more effectively than codeine. It did not induce a significant change in the values of specific airway resistance or provoke any observable adverse effects (Saha, et al., 2011).
6. When the glycyrrhizin and dexamethasone groups were compared, there was no statistically significant difference between the two groups in the histopathologic parameters, including thickness of the basement membrane, sub-epithelial smooth muscle, epithelium and number of mast and goblet cells. Oral administration of glycyrrhizic acid (50 and 100 mg/kg body weight) significantly protected against benzopyrene-induced debilities in the lungs of Wistar rats (Qamar, et al., 2012).
7. The effectiveness of treatment in chronic bronchitis patients has increased in the cases of intrabronchial administration of 3.0–5.0 mL of licorice thick extract water solution. The root decoction extract in combination with other medicinal herbs is used in the traditional monotherapy treatment of patients with pneumonia (Pleskanovskaya, et al., 2019).
8. Dai et al., found that liquiritigenin protected human lung cells (A549) from Staphylococcus aureus α-hemolysin-mediated injury. Low concentrations of liquiritigenin remarkably decreased Staphylococcus aureus α-hemolysin production in a dose-dependent manner (Dai, et al., 2013).

**7.2 Anti -inflammatory Activity** (Murray, 2020; Evans, 1992; Khare, 2009; Kokate, 2017; Akbar, 2020)

1. Liquiritigenin and 18β-glycyrrhetinic acid potently inhibited passive cutaneous anaphylactic reaction and scratching behaviour in mice induced by compound 48/80. These components inhibited the production of IgE in ovalbumin-induced asthma mice but liquiritigenin had little effect. The results suggested that the anti-allergic effects of licorice were mainly due to glycyrrhizin, 18β-glycyrrhetinic acid, and liquiritigenin, which could relieve IgE-induced allergic diseases, such as dermatitis and asthma. At a non-toxic concentration of 10 μM, isoliquiritigenin blocked the induction of vascular cell adhesion molecule-1 and E-selectin in activated human umbilical vein endothelial cells and markedly interfered with THP-1 monocyte adhesion to TNF-α-activated endothelial cells (Kwon, et al., 2007).  In a study, anti-inflammatory effect of hydroalcoholic extract of GG root was studied against carrageenan-induced rat paw oedema at dose levels of 100, 200, and 300 mg/kg orally. At 200 mg/kg, the hydro-alcoholic extract showed maximum inhibitory activity of 46.86% and prevented leukocyte migration which was comparable to standard drug indomethacin (10 mg/kg) producing 63.34% of leukocyte inhibition (Nirmala & Selvaraj, 2011).
2. Anti-inflammatory activity of GG aqueous extract and glycerrhitinic acid in comparison to diclofenac sodium was evaluated in 36 male albino rats through carrageenan-induced paw oedema model. The results showed the reduction of oedema by GG aqueous extract (66.8%), glycerrhitinic acid (58.6%), diclofenac sodium (73.9%), combination of GG aqueous extract and diclofenac sodium (76.1%), combination of glycerrhitinic acid and diclofenac sodium (78.3%) (Aly, et al., 2005).
3. A study was conducted to review the therapeutic effect of topical licorice on Recurrent aphthous stomatitis (RAS). Six studies with 314 subjects were included after screening. The result showed licorice has significant effects on RAS pain reduction, ulcer size, and healing time. Its effectiveness is related to its dose-dependent anti-inflammatory and antioxidant effects through several mechanisms. It also has antibacterial effects against *Streptococci mutans* and *Porphyromonas gingivalis.* Licorice and can elevate the epidermal growth factor level compared to the control group. Licorice extract was used in different dosage forms, including paste, patch, and mouthwash with concentrations of 1% or 5%. Licorice did not show any adverse effect in the intervention groups, indicating its effectiveness and safety (Dorsareh, et al., 2023).
4. Oral administration of GG root extract to rats caused a significant reduction in pedal inflammation and swelling induced by formalin compared to the control group (Shalaby, et al., 2004).
5. A double-blind clinical trial was conducted in 30 patients with atopic dermatitis. Treatment with licorice extract prepared as a 2 % licorice topical gel was more effective than 1 % in reducing the scores for erythema, oedema, and itching over 2 weeks. The quantity of glycyrrhizinic acid was determined 20.3 % in the extract and 19.6 % in the topical preparation (Saeedi, et al., 2003).
6. Licorice root extract lipids produced statistically significant suppression of inflammatory oedema growth induced by 1 % carrageenan and 3 % formalin solutions in mice compared to that in the untreated control and their anti-inflammatory effect was comparable with that of the reference drug ortophen (Denisova, et al., 2007).
7. In animal studies, glyderinine, a derivative of glycyrrhizic acid isolated from GG was found to exert a pronounced anti-inflammatory effect exceeding that of hydrocortisone and amidopyrine (Azimov, et al., 1988).
8. Ma et al., 2013 demonstrated that glycyrrhizic acid exerted anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4 + CD25 + Foxp3+ regulatory T cells in ovalbumin (OVA)-sensitized mice. Glycyrrhizic acid inhibited OVA-induced increases in Raw and eosinophil count; interleukin (IL)-4, IL-5, IL-13 levels were recovered in bronchoalveolar lavage fluid, and increased IFN-γ levels in bronchoalveolar lavage fluid. Separate studies demonstrated that liquiritigenin exerted anti-inflammatory effects, through inhibition of NF-kappa B activation in Raw 264.7 macrophages, thereby decreasing production of iNOS and pro-inflammatory cytokines (Ma, et al., 2013).
9. A prospective randomized vehicle-controlled clinical trial was carried out to assess the anti-irritative efficacy of cosmetic formulations containing licochalcone in a post-shaving skin irritation model and on UV-induced erythema formation. Topical licochalcone A caused a highly significant reduction in erythema relative to the vehicle control in both the shave- and UV-induced erythema tests, demonstrating its anti-irritative properties (Kolbe, et al., 2006)
10. Injection of carrageenan into the pleural cavity of mice elicited an acute inflammatory response and carrageenan-induced pleurisy which were attenuated by glycyrrhizin. It was found that prevention of the activation of NF-κB and STAT-3 by glycyrrhizin reduced the development of acute inflammation. 18β-Glycyrrhetinic acid ameliorated acute Propionibacterium acnes -induced liver injury in C57BL/6 mice through reduced macrophage inflammatory protein (MIP)-1α expression in Kupffer cells by down-regulating MyD88 expression and inhibiting NF-κB activation (Xiao, et al., 2010).

**7.3 Anti-ulcer activity beneficial in *Quroohe meda wa am’a* (Gastric and duodenal ulcers)** **and *Warme meda* (Gastritis)** (Aly, et al., 2005; Baytar, 1999; Fukai, et al., 2002; Kokate, et al., 2017; Schulz, et al., 2001)

1. A special liquorice extract known as deglycyrrhizinated liquorice made up by removing the glycyrrhizin molecule and containing flavonoids is used in the treatment of peptic ulcer. Active components present in it are flavonoids (Khare, 2007).
2. A study was carried out to assess the wound-healing property of GG plant extracts by using an *in vitro* scratch assay test to evaluate their cellular toxicity. *In vitro* scratch assay showed that the healing process of the cell line was increased by 23.33% when compared with the controlled cell lines and GG plant extracts had no cytotoxic effects on the cells. Therefore, it can be concluded that GG has *in vitro* wound healing capabilities and can be suggested as a possible source of compounds that treat wounds (Roy, et al., 2023).
3. A study was conducted to evaluate the anti-inflammatory and healing effects of licorice extract in acetic acid-induced ulcerative colitis in rats as an animal model. Administration of oral 100 and 150 mg/kg and intracolonic 150 mg/kg of licorice extract significantly reduced the colonic inflammatory response and oedema. Intracolonic administration of licorice extract showed more anti-inflammatory and healing effects in comparison to other groups (Takshid, et al., 2012).
4. A study was conducted to demonstrate that GutGards, a flavonoid-rich extract of GG, exhibits anti-Helicobacter pylori activity, effective in dyspepsia through the inhibition of protein synthesis, DNA gyrase, and dihydrofolate reductase. GutGards exhibited anti-Helicobacter pylori activity in both agar dilution and microbroth dilution methods. Glabridin, the major flavonoid present in GutGards exhibited superior activity against Helicobacter pylori. Additionally, GutGards showed a potent inhibitory effect on DNA gyrase and dihydrofolate reductase with IC50 value of 4.40 mg/ml and 3.33 mg/ml respectively (Asha, et al., 2013).
5. Anti-ulcer activity of hydro-alcoholic extract of GG was observed on HCl/ethanol-induced, ethanolic-induced, indomethacin-induced and hypothermic restrained stress-induced ulcers in Swiss mice. The results revealed that ulcer index of 15.33 ± 0.19 control was significantly inhibited by higher dose (200mg/kg) of GG extract (10.33 ± 0.28) which was comparable to standard drug omeprazole (10.23 ± 0.78) in HCl/ethanol-induced ulcer model. In indomethacin-induced ulcers, the control drug cimetidine showed maximum reduction in ulcer index (8.35 ± 0.63) when compared with control (18.54 ± 0.14) (Jalilzadeh-Amin, et al., 2015).
6. The present study investigated the effect of GG extract on full-thickness wound healing in Guinea pig model. GG creams (5% and 10% w/w) significantly increased epidermal formation, collagen deposition and neovascularization, and decreased acute inflammation in comparison to the control group. Wound healing rates were increased in GG10%cream than 5% w/w (Hanafi, et al., 2018).
7. An in-vivo experiment on Sprague Dawley male rats was carried out to investigate the wound healing potential of GG aqueous extract ointment. During histopathological and biochemical analysis, GG aqueous extract ointment significantly (p ≤ 0.05) decreased the level of the wound area, total cell, macrophage, lymphocyte, and neutrophil, and enhance the level of wound contracture, fibrocyte, hexuronic acid, and hydroxyproline as compared with the basal ointment and control groups (Zangeneh, et al., 2019).
8. The healing effect of licorice extract was investigated on open-skin wounds in rabbits. Hairs of lower back and left flank of animal were shaved. Full-thickness wound (15x15 mm) was made on the shaved area. Hydroalcoholic extract of licorice was prepared by maceration method. Creams of 5%, 10% and 15% (w/w) extract in eucerin base were prepared and applied 2 times daily. Dexpanthenol ointment was used as standard control. Healing was determined by reduction in wound area. The results of this study proved that licorice cream of 10% was a potent healing agent even better than dexpanthenol cream (Zaki, et al., 2005).
9. The wound healing potential and the mechanism by which liquorice alcoholic extracts modulate cutaneous wound healing was studied. Licorice extract administration significantly increased total and differential leucocyte counts, phagocytic activity of neutrophils, and antioxidant biomarkers and histopathological findings detected complete re-epithelialization with increasing collagen synthesis (Assar, et al., 2021).
10. A study was conducted to evaluate the preventive effects of GG in ibuprofen-induced gastroduodenal ulcers in rats. All doses of GG could significantly (p ≤ 0.05) reduce the raised levels of ALP, AST, ALT, GGT, cholesterol, LDL, triglyceride, total and conjugated bilirubin, urea, creatinine, IL-1, IL-6, IL-12, IL-18, IFN-γ, and TNF-α and increase HDL, total protein, albumin, WBC, platelet, RBC, IL-4, IL-5, IL-10, IL-13, and IFN-α as compared to the untreated group. The results obtained clearly indicated the hepatoprotective, nephroprotective, haematoprotective, immunoprotective, and gastroduodenal protective properties of GG aqueous extract (Goorani, et al., 2021).
11. Glycyrrhiza glabra extract is used as a treatment in gastric and duodenal ulcers at a dose of 100 mg three times a day. Licorice enhances prostaglandins' concentration in the digestive system and promotes mucus secretion from the stomach, prolonging the life span of surface cells in the stomach. As a result, an anti-pepsin effect is observed too. Fraction FM-100 isolated from licorice roots inhibits gastrin secretion, thus, licorice acts as an antiulcerogenic agent (Hasan, et al., 2021).

**7.4 Hepato-protective Activity** (Murray, 2020; Wahab, et al., 2021; Evans, 2009; Khare, 2007; Gupta, et al., 2008; Schulz, et al., 2001)

1. A study was carried out to investigate the protective effects of GG, *Curcuma longa*, and *Moringa oleifera* against DIC-induced hepatic toxicity in male rats. Pre-treatment with any of the three herbs attenuated the DIC-induced elevation of serum ALT activity. In comparison to DIC group, a significant decrease in ALT level (P<0.001 with *Curcuma longa*, P<0.01 with GG, P<0.001 with *Moringa oleifera*) was observed in rats pre-treated with herbal extracts. The increase in ALT level was reduced by about 47%, 43%, and 27% after pre-treatment with *Moringa oleifera*, *Curcuma longa*, or GG respectively (Hamza, et al., 2007).
2. The hepato-protective effect of aqueous extract of GG roots (2 gm/kg/day orally for 7 days) in rabbit models with acute liver injury induced by Carbon tetrachloride at a dose of 1.25 ml/kg as a mixture with olive oil was evaluated. Significant reduction in the hepatic enzyme levels, serum bilirubin and improvement of serum protein was found in animals treated with the extract. Results demonstrated that the aqueous extract of GG had a significant effect in ameliorating liver functions as well as restoring hepatic tissue in acute liver diseases (Al-Razzuqi, et al., 2012).
3. The present study was aimed at evaluating the hepato-protective and antioxidant effects of GG extract (2.5, 5 and 10 µg/ml) on the carbon tetrachloride-induced carp hepatocyte damage in vitro. Pre-treatment (5 µg/ml) and pre- and post-treatment (5 and 10 µg/ml) of the hepatocytes with GG extract significantly reduced the elevated levels of lactate dehydrogenase, glutamate oxalate transaminase, glutamate pyruvate transaminase and malondialdehyde and increased the reduced levels of superoxide dismutase and glutathione peroxidase by carbon tetrachloride; post-treatment of the hepatocytes with GG extract at 5 µg/ml reduced the glutamate pyruvate transaminase and glutamate oxalate transaminase levels and increased the glutathione peroxidase level (Yin, et al., 2011).
4. Oral administration of GG extract (200 mg/kg, body weight) protected against paracetamol-induced liver damage in rats. All altered levels of biochemical markers were restored to near-normal levels in a dose-dependent manner. Histological examination of the liver tissues confirmed the hepato-protective effect of GG (Tajua, et al., 2011).
5. In-vivo studies demonstrated that liquiritigenin, an aglycone of liquiritin in licorice root, efficaciously protected the liver from acute injuries induced by acetaminophen-induced or from acetaminophen plus buthionine sulfoximine-induced severe injuries in rats. Liquiritigenin pretreatments significantly reduced the potentiated liver necrosis, decreasing mortality (Kim, et al., 2006).
6. An interesting study showed that the protective effects of 18β-glycyrrhetinic acid against carbon tetrachloride-induced hepatotoxicity in mice may be due to its ability to block the bio-activation of carbon tetrachloride, primarily by inhibiting the expression and activity of P450 2E1, and its free radical scavenging effects (Jeong, et al., 2002).
7. El-Tahawy et al., found that pretreatment with glycyrrhizin protected against lipopolysaccharide/ D-galactosamine-induced acute hepatitis in albino rats by its anti-inflammatory and anti-apoptotic effects (El-Tahawy, et al., 2011).
8. A study was carried out on 1249 patients with chronic hepatitis with or without cirrhosis and it was found that long-term glycyrrhizin injection therapy significantly decreased the incidence of hepatocellular carcinoma in patients with interferon-resistant active chronic hepatitis C, whose average aminotransferase value was twice or more of the upper limit of normal after interferon (Ikeda, 2007).
9. In a study of 38 patients with non-severe aplastic anaemia, the combination therapy of glycyrrhizin and cyclosporine was found to be an effective treatment for non-severe aplastic anaemia in terms of improvement of response rate, reduction in cyclosporine-related liver injury, and attenuation of severity of nausea and other adverse events (Ren, et al., 2013).

**7.5 Stomachic or Gastro-tonic Activity** (Kaur, et al., 2013; Fukai, et al., 2002)

1. A study was carried out to investigate the gastro-protective effect of aqueous extracts of Licorice, Pulasari stem bark (*Alyxia reinwardtii*) and Sembung leaf (*Blumea balsamifera*) against aspirin-induced gastric ulcer model in rats. The extracts combination markedly exhibited protective effects indicated by less number and smaller area of gastric ulcers in comparison to those of aspirin group. The score of mucosal damage was also decreased in plants extracts combination groups. The number of eosinophils and mast cells in herbal combination groups was observed to be smaller than that of aspirin group (Nugroho, et al., 2016).

2. To evaluate the effect of licorice in *H. pylori* eradication, a randomized controlled trial was conducted on 120 positive rapid urease test patients suffering from dyspepsia either with PUD or non-ulcer dyspepsia against the standard triple regimen treatment based on clarithromycin. Peptic ulcers were present in 30% of both groups. Six weeks after therapy, the response to the treatment was 83.3% and 62.5% in the study group receiving licorice in addition to standard treatment and the control group receiving only standard treatment, respectively (Haji Agha Mohammadi, et al., 2016).

3. Aqueous extracts from the roots of GG are widely used for treatment of stomach ulcer. The clinically proven effects are related to the presence of anti-inflammatory 12-keto-triterpensaponinsin the extracts. A study was aimed to investigate the influence of GG secondary compounds on the bacterial adhesion of *Porphyromonas gingivalis.* Apart from that, the influence of GG extract on the bacterial adhesion of Helicobacter pylori to stomach tissue was to be investigated. *In vitro* cytotoxicity against *Helicobacter pylori* was investigated by agar diffusion assay. Aqueous extract of GG significantly inhibited the adhesion of *Helicobacter pylori* to human stomach tissue. This effect was related to the polysaccharides isolated from the extract, as the main active polymer. Aqueous extracts and polysaccharides from the roots of GG are strong antiadhesive systems, which may be used as potent tools for further development of cytoprotective preparations with anti-infectious potential (Wittschier, et al., 2009).

4. The protective effects of GG extract on indomethacin-induced gastritis and other gastrointestinal toxicities in Wistar rats were evaluated. Study shows that GG extract significantly protects the stomach mucosa against indomethacin-induced gastritis in rats, where the inflammation grade caused by a combination of extract of GG and indomethacin in the intervention group was less than that of the test group with indomethacin alone. Furthermore, GG extract significantly increases gastric pH, decreases the stomach’s secretion volume and total acidity, and enhances serum iron, hemoglobulin, and vitamin B12 levels (Shoaib, et al., 2023).

5. GG and *Lactobacillus paracasei* have been reported as having beneficial effects on Helicobacter pylori infection. A study was aimed to assess the efficacy and safety of fermented milk containing *L. parac*asei HP7 and GG in patients with H pylori infection. This randomized, double-blind, placebo-controlled clinical trial on 142 patients was conducted in 2 hospitals for 8 weeks. Compared to baseline data, the quantitative value of 13C-UBT at 8 weeks was significantly reduced in the treatment group (from 20.8±13.2% to 16.9± 10.8%), but not in the placebo group. Chronic inflammation improved significantly only in the treatment group, whereas neutrophil activity deteriorated significantly only in the placebo group. Moreover, the treatment group had significant improvement in gastrointestinal symptoms and quality of life (Yoon, et al., 2019).

6. In a randomized, double-blind clinical trial, the use of an over-the-counter licorice-medicated intraoral adhesive patch for the treatment of recurrent aphthous ulcers significantly reduced ulcer size and pre-stimulus pain in treated subjects compared with placebo (Martin, et al., 2008).

7. Experimental studies have shown that dry extract of GG dissolves in water, stimulates the production of mucus, and increases the cell mitotic activity as well as the number of cells in the main gland and in the pit of the white rat stomach. The functional activity of the specialized cells of the stomach increases and due to this regenerative process is activated in the mucus of stomach. These GG extract tablets are effective in the stomach due to their hyperfunction in the glandular system diseases (Pleskanovskaya, et al., 2019).

8. Oral administration of GG root extract caused a significant reduction in the length of gastric ulcer induced by ethanol in rats. The curative ratios from gastric ulceration were 40.0, 65.9 and 67.3 % in groups of rats given the extract at 200, 400 and 800 mg/kg, respectively (Shalaby, eta l., 2004).

9. Aqueous extract (1 mg/mL) of GG significantly inhibited the adhesion of Helicobacter pylori to human stomach tissue (Wittschier, et al., 2009).

10. In a double-blind clinical trial study of 60 patients with peptic ulcer disease, 4 weeks of treatment with licorice was found to be as effective as bismuth in Helicobacter pylori eradication. (Momeni et al., 2014) They suggested that in patients whom bismuth was contraindicated, licorice could be used safely instead (Momeni, et al., 2014).

1. Conclusion

*Rubb-us-Soos* (Glycyrrhiza glabra), widely recognized for its medicinal properties across various traditional healing systems, holds a rich and significant ethnobotanical and ethnopharmacological importance. Its use in Unani, Ayurveda, Traditional Chinese Medicine, and other folk medicine traditions spans centuries, with documented applications of particularly its root and rhizome parts in treating respiratory disorders, gastrointestinal ailments, liver diseases, inflammatory conditions and a variety of other human ailments. The plant's rich phytochemical profile, primarily comprising glycyrrhizin, flavonoids, saponins, and coumarins, underlies its diverse pharmacological activities, including antitussive, anti-inflammatory, antimicrobial, antioxidant, antiulcer, anticancer, hepatoprotective, neuroprotective, and immunomodulatory effects.

These diverse pharmacological actions of GG and its derived compounds were mentioned in the classical Unani literature years before, which are now being validated and proved with the help of various research models. GG is one of those ancient plants, which have been used in traditional pharmacopeias for its multifaceted activities against a variety of systematic and nonsystematic ailments. The chemical foundations of GG have been discovered in the last era and hold a strong promise for providing new molecules that could play a significant role in the drug discovery and the development of new medications in present era.

Future research should focus on bridging the gap between traditional knowledge and modern pharmacological validation. Rigorous clinical trials are essential to confirm therapeutic claims, establish precise dosage guidelines, and explore potential drug interactions. Additionally, advancements in extraction techniques and formulation development may enhance the bioavailability and therapeutic efficacy of GG-derived compounds while minimizing adverse effects.

Furthermore, sustainable cultivation and conservation strategies should be emphasized to ensure the continued availability of GG, given its increasing demand in the pharmaceutical, cosmetic, and food industries. The integration of ethnopharmacological wisdom with cutting-edge scientific methodologies holds immense potential for the development of novel GG-based therapeutics, reinforcing its role in contemporary medicine while ensuring safety and efficacy for diverse patient populations.

Consent

It is not applicable.

Ethical approval

It is not applicable.

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