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A comprehensive review on an important Unani drug mulethi (Root of *Glycyrrhiza glabra* Linn)

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Abstract

The roots of a plant *Glycyrrhiza glabra* Linn constitute an important drug in the ancient Unani literature, commonly known as Mulethi or Aslus Soos or liquorice. It is one of the most widely used plants from the ancient medical history, both as a medicine and as a flavouring herb. Historically, liquorice has been used from more than 4000 years. The drug was also mentioned by Theophrastus and Dioscorides. It is interesting to find that it maintains even today its role in medicine and pharmacy. The plant is well suited to warm climatic conditions with long growing session. It grows best on sandy loam soils. The light soils promote better root development. *Glycyrrhiza glabra* Linn is a hardy herb or undershrub and a tall perennial plant attaining a height of 1.8 mt. The roots are sweet in taste, thick, having many branches with red or lemon color outside or yellowish or pale yellow inside. The underground part in some varieties consists of a rootstock with a number of long, branched stem, in others, the rootstock which is stout, throws off a large number of perennial roots. It is used for allaying coughs and catarrhal affections. It is also useful in irritable conditions of the mucous membranes of urinary organs. Its extract is a constituent of cough syrups, throat lozenges and pastilles and it is employed in the form of aromatic syrups and elixirs for masking the taste of nauseous medicines. The extract is reported to exert a healing effect on gastric ulcers, is also reported to be useful in treatment of Addison's disease. Externally liquorice is applied with ghee and honey for cuts and wounds. Keeping in view the high medicinal importance of the drug in Unani Medicine, the present review provides available information on traditional uses, phytochemistry and pharmacological properties of the Unani drug Mulethi.

Keywords: *Glycyrrhiza glabra*, mulethi, aslus-soos

Introduction

The root of *Glycyrrhiza glabra* Linn commonly known as Mulethi/Aslus Soos/liquorice sweet wood is one of the most widely used herb from the ancient medical history, both as a medicine and as a flavouring herb ^[1].

It is native to Mediterranean and certain areas of Asia ^[2]. The liquorice is to genus *Glycyrrhiza* which contains about 14 species ^[3]. The word *Glycyrrhiza* is derived from Greek term glykos (meaning sweet) and rrhiza (meaning root). *Glycyrrhiza glabra* belongs to leguminous family ^[1].

Historically liquorice has been used from more than 4000 years. The earliest record of its use in medicine is found in code Humnubari (2100 BC). It was also one of the important plants mentioned in Assyrian herbal (400 BC) mentioned its use as a remedy of ulcers and quenching of thirst. The drug was also mentioned by Theophrastus and Dioscorides ^[3].



Fig 1: *Glycyrrhiza glabra*

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It is interesting to find that even to this day liquorice maintains its role in medicine and pharmacy [4].

It is a tall perennial shrub, leaves compound, imparipinnate, alternate in 4-7 pairs of oblong, elliptical or lanceolate leaflet. Flowers are in axillary spikes, lavender to violet in colour. Pods up to 1.5 cm long, erect, glabrous and 3-5 brown, reniform seeds [3].

Cultivation

Attempts have been made to cultivate *G. glabra* in several places of India, notably Baramulla, Srinagar and Jammu in Kashmir, Dehradun and Delhi. Its cultivation is likely to be successful in the temperate Himalaya's and in the hilly districts of south India [5]. The crop can be successfully cultivated in Haryana [6].

Climate and soil

The crop is well suited to warm climatic conditions with long growing session. It grows best on sandy loam soils. The light soils promote better root development [6].

Root yielding and storage

Roots are ready for harvest after 2.5-3 years of planting. Digging should be done preferably in February so that the root cutting can be used for further planting. Normally the root contains 50-60% moisture and should be dried in sunlight for 2-3 days and then in shade for 4-5 days. The roots are cut into pieces of 15-20 cm. and are stored after complete drying. Preferably the roots should be classified in various categories according to thickness [6].

Occurrence and distribution

It is native to the Mediterranean countries and China. The drug is imported into India from Asia Minor, Iraq, Persia and other central Asian countries [7]. It is cultivated in Jammu and Kashmir, Punjab and sub Himalayan tracts [8], Arabia, Persian, Gulf, Afghanistan, Asia Minor, Siberia etc. [9]. Root is also cultivated in the Punjab, sub Himalayan tracts from the Chenab eastwards, Sind and Peshawar valley, Burma and Andaman Islands [10]. It is also distributed in the sub-tropical and warm temperate regions of the world, none of the liquorice yielding species occurs in India, but cultivation of *Glycyrrhiza glabra* on an experimental scale has been undertaken in several places [5] like Delhi, Indore and Anand. A Russian accession was found suitable in terms of growth, yield and glycyrrhizin content at Indore and Anand. The crop can be successfully cultivated in Haryana [6]. The Egyptian variety is considered superior to Arabic and Turkish varieties [7].

Ethnobotanical description

It is a tall perennial plant about a meter high [9, 11], a hardy herb or undershrub attaining a height of 1.8 m [8].

Flower: These are in axillary racemes or heads, 1 cm long [9], are small, light violet in colour [11] or lavender to violet in color and papilionaceous [8].

Seed: Seeds are 2-5, reniform, flat and deep grey [8].

Root: They are sweet in taste [9], thick, having many branches with red or lemon color outside or yellowish or pale yellow inside [8]. The underground part in some varieties consists of a rootstock with a number of long, branched stem, in others, the

rootstock which is stout, throws off a large number of perennial roots [5].

Leaf: These are odd pinnate in 4-7 pairs [9] and are imparipinnate, ovate-lanceolate, smooth [8], and are multi foliate [5].

Pods: Oblong to linear 1-3 cm long, flattened, straight in more or less densely echinate, glandular [9].

Fruits: Fruits are 1-3 cm long, flat, covered all over the small spinous outgrowths [11], fruits in August [8].

Vernaculars

The plant is known by different vernacular names in different language, areas and traditions: *Aslussies* (Arab); *Makk*, *Sus* (Afghanistan); *Muraithi* (Behar); *Jashtimadhu*, *Jaishbomadhu* (Bengali); *Jashtimadhu* (Bombay); *Noekhiyu*, *Noekhiyuanu* (Burma); *Kan Ts'ao* (Chinese); *Lakris* (Danish); *Meethi lakdi* (Deccan); *Zoethout* (Dutch); *Liquorice/Licorice* (English); *Boisdoux* (France); *Liccarissa*, *Recanicu*, *Rigolicia* (Genoa); *Lackrizen*, *Suessholz* (German); *Jethi Madha* (Gujrati); *Mulhatti*, *Jethimadhu* (Hindi); *Malkhuzi*, *Malkhuzzi* (Hindubagh); *Cam thao* (Indo-China); *Liquirizia*, *Legorizia*, *Regolizia* (Italian); *Yashtimadhuka*, *Atimadhura* (Kannad); *Kam chow* (Malaya); *Iratimadthuram* (Malyalam); *Jeshtamadhu* (Marathi); *Liquirizia* (Naples); *Muleti* (North western provinces); *Lakris* (Norwegian); *Jatimadhu* (Oriya); *Bikhe-Mahak* (Persian); *Lakrycia* (Polish); *Alacuz*, *Regoliz* (Portuguese); *Alasus*, *Jetimadh*, *Muleti* (Punjab); *Khwazha*, *Malkhuzi* (Quetta); *Dubez solotkoi* (Russian); *Madhuka*, *Yashtimadhu* (Sanskrit); *Aregolizia* (Sardinia); *Gurigulizia*, *Legmo dolce* (Sicily); *Athimadthuram* (Siddha); *Orozuz*, *Palo dulce*, *Regaliza* (Spanish); *Lakritz* (Swedish); *Atimadthuram* (Tamil); *Ashtimadhukam*, *Atimadthuramu* (Telgu); *Meyan* (Turkish) and *Asl-us-Soos* (Unani) [5, 7, 12-13].

Classification

Kingdom: Plantae
Division: Angiospermae
Class: Dicotyledoneae
Order: Rosales
Family: Leguminosae
Genus: *Glycyrrhiza*
Species: *Glabra* Linn

Part used

The dried, peeled or unpeeled underground stems and roots constitute the drug, known in the trade as liquorice [5].

Mizaj (Temperament)

Unani physicians described the *Mizaj* of *Aslus Soos* as Hot and Dry in second degree [11], according to Avicenna it is neutral in all four temperament and according to Karmani it is *Murakkabul-Quwa* (having compound action) [14], while some others categorized in Hot in 2nd degree and Dry in 1st degree [15, 16].

Dose

3-5 gm [7]

Afaal (Actions)

In classical Unani literature, various actions of the drug *Aslus Soos* (*Glycyrrhiza glabra*) have been described such as *Munzij-e-akhlata-e-ghaliza* (concoctus of viscous humour) [15].

^{17-19]}, *musakkin*, *gasil azae batni* (abluent of internal organs), *muqawwi* (tonic), *kasir-e-riyah* (carminative) ^[18], *mundamil-e-qarookh* (wound healer), *mulattif*, *munzij-e-balgham* (cooctive of phlegm) ^[17], *muhallil-e-riyah* (flatulence dissolvent) ^[14, 15, 19], *jali* (detergent) and *mulayyin* (laxative) ^[14, 18], *maullid mani* (semen productive) and *mushtahi* (appetizer) ^[14] *munaqqi-e-sadr wa reya*, *musaffi aawaz* (voice purifier) ^[19], *mudir bol wa haiz* (diuretic & emmenogouge) ^[14, 15, 18], *musakkin atash* (thirst allaying) ^[14, 15, 18-19], *muqawwi aasab* (nervine tonic) ^[15, 18-19], *munaffis-e-balgham* (expectorant) ^[17, 18], *dafe tap-e-muzmena* (antipyretic for chronic fever) ^[15, 18].

Istemat (Uses)

It gives strength to nerves. It is helpful in flatulence, asthma, lung diseases, piles, chronic fever, thirst ^[14, 15], reduces cough. It is beneficial in diseases of brain and nerves and useful in palpitation. It is used in nausea, vomiting, and *fasaad-e-safra*. Its decoction is used to improve vision power ^[14].

It is beneficial in sore throat, hoarseness of voice. It is useful in burning micturition, gonorrhoea, *qurooh-e-masaana wa gurda*. It is also used in liver and spleen diseases. It relieves nervine pain ^[19].

Muzir (Adverse effect)

It has adverse effect on kidney and spleen ^[15]. It also leads to fluid retention ^[6].

Musleh (Corrective)

Katira (gum of *Cochlospermum religiosum*), Gule Surkh (*Rosa damascena* Mill) ^[19], Unnab (*Ziziphus jujuba*) ^[16] are used as corrective for kidney, while Gule Surkh (*Rosa dascemena*) for spleen ^[15].

Badal (Substitute)

Katira is used as substitute ^[19].

Pharmacological action

(As described in ethnobotanical and traditional literature)

The drug *Glycyrrhiza glabra* is described in detail in ethnobotanical and scientific literature and various actions have been reported to possess by it. Some pharmacological actions and therapeutic uses are as follows:

Laxative, demulcent ^[5, 10], cooling effect, diuretic ^[10], tonic, expectorant ^[5, 9-10], sedative, deobstruent ^[9], anti-inflammatory, anti-ulcerous, anti-viral ^[20] and emmenogouge ^[6].

Therapeutic uses

It is used for allaying coughs and catarrhal affections. It is also useful in irritable conditions of the mucous membranes of urinary organs. Extract is a constituent of cough syrups, throat lozenges and pastilles and it is employed in the form of aromatic syrups and elixirs for masking the taste of nauseous medicines. The extract is reported to exert a healing effect on gastric ulcers, is also reported to be useful in treatment of Addison, S disease. Externally liquorice is applied with ghee and honey for cuts and wounds ^[5].

Root is used in scorpion sting. Root in infusion, decoction, extracts or lozenge is useful in inflammatory affection or irritable conditions of bronchial tubes, bowels and catarrh of the genito-urinary passages as cough, hoarseness, sore throat, asthma, dysuria etc. it is also used as a slight laxative. Inspissated juice is an ingredient of various laxative powders, cough syrups, confections, lozenges, pastilles etc. Root mixed with lime juice and linseed makes a homely valuable remedy

for coughs and cold, feverishness, pain, distress of breathing and to ally thirst ^[10]. It is used in cough, fever, and paralysis ^[9]. Oral doses of liquorice can be used for gastric, duodenal and esophageal ulceration or inflammation, heartburn and mouth ulcers. It is used for the treatment of asthma, acute and chronic bronchitis and chronic cough. Liquorice is a mild anti-inflammatory drug for arthritis and rheumatism ^[6]. Oral liquorice preparations are used in the treatment of viral infections (common cold, viral hepatitis, HIV, AIDS), premenstrual syndrome, inflammations, and as a sweetening agent. DGL is used in ulcerative conditions of gastro-intestinal tracts. Topical preparations are used in eczema, herpes and psoriasis ^[7]. Powder of root is prescribed in coughs, hoarseness and in respiratory troubles. Infusions, decoctions, or extract is laxative and a useful medicine in urinary diseases, bronchial and gastric troubles ^[8].

Phyto-chemistry

It contains many organic as well as inorganic constituent that are as follows:

Organic: Steroid, Terpenoids, Resins, Flavonoids, Carbohydrate, Starch, Proteins, Saponin ^[9].

Inorganic: Iron, atrontium, calcium, magnesium, potassium and sodium ^[9].

The major constituents are triterpine saponins. Glycyrrhizin (glycyrrhizic acid/glycyrrhizinic acid) is the major component (2-9%). Other constituents are flavonoids (isoflavones: liquiritin, isoliquiritin, formononetin), polysaccharides, sterols, coumarins, asparagine ^[7]. The principle constituent of liquorice to which it owes its characteristic sweet taste is glycyrrhizin which is present in different varieties in a concentration of 2-14%. Other constituent present in liquorice are glucose (up to 3.8%), sucrose (2.4-6.5%), mannite starch (c.30%), asparagine, bitter principles, resins (2-4%), a volatile oil (0.03-0.035%) and coloring matter. The yellow color is due to the anthoxanthin glycoside, isoliquiritin which undergoes partial conversion to liquiritin. Both isoliquiritin and liquiritin are bitter with a sweet after taste. A steroid estrogen (possibly sterol) is also reported to be present in liquorice. Glycyrrhizin occurs in liquorice as the calcium or potassium salt of the trihydroxy acid, glycyrrhizic acid ^[5]. Roots contain a flavonoside, liquiritoside of low toxicity which depresses smooth muscle action. Liquiritigenine chalcone of spasmolytic properties is found in the plant ^[21]. The root also contains glycyrrhizin, saponin, flavon, isoflavones, coumarins, glabridin, glabrene, glabrol, glycyrrhizic acid ^[20].

Identity, purity, strength and assay

Ash values (%)

Total ash: 0.82

Water soluble ash: 0.26

Acid insoluble ash: 0.32

Loss on drying at 105 °C: 7.47%

Solid contents: 50.12%

Successive extractive value %

Pet ether (60-800): 0.12

Chloroform: 0.33

Acetone: 0.43

Ethanol: 13.15

Distilled water: 47.17

Pharmacological studies

A number of studies have been carried out on *Glycyrrhiza glabra* in recent decades revealing that it possesses a lot of

different pharmacological actions. Some of the important pharmacological effects are as follows:

Antibacterial

In a study Anti-bacterial activity of *Glycyrrhiza glabra* was determined by using disc diffusion methods. Because of the presence of secondary metabolites such as; saponins, alkaloids, flavonoids in hydro-methanolic root extract of *Glycyrrhiza glabra*, the extract exhibits potent antibacterial activity against both gram positive and gram negative bacteria [22].

Anticancer

G. glabra extract has been used in herbal formulations for combating cancers like PC-SPEs, a polyherbal composition used for prostate cancer. The licorice extract induced the Bcl2 phosphorylation and G2/M cycle arrest in tumour cell lines as done by clinically used antimicrotubule agent Paclitaxel. 1-(2, 4- dihydroxyphenyl) -3-hydroxy- 3-(4'-hydroxyphenyl)1-propanone (β -hydroxy-DHP) was identified in the licorice extract, which induced Bcl2 phosphorylation in breast and prostate tumour cells, G2/M cell cycle arrest, apoptosis demonstrated by Annexin V and TUNEL assay, decreased cell viability demonstrated by tetrazolium (MTT) assay, and altered microtubule structure 44. 70% Methanol soluble fraction of licorice acetone extract was found to induce apoptosis in human monoblastic leukaemia U937 cells [23].

Anticoagulant

In a study Glycyrrhizin isolated from *Glycyrrhiza glabra* was identified as inhibitor of thrombin. It is found to prolong the thrombin and fibrinogen clotting time. It also increases plasma recalcification duration. Glycyrrhizin causes inhibition in thrombin induced platelet aggregation. But there was no effect of glycyrrhizin on Platelet Aggregating Factor (PAF) and Collagen induced agglutination [24].

Antifungal

Methanolic extract of liquorice was reported to have fungicidal activity against *Arthrinium sacchari* M001 and *Chaetomium funicola* M002. Glabridin was found to be the active compound giving anti-fungal activity [25].

Antihyperglycemic

A study was carried out to evaluate the anti-hyperglycemic effects of 18 β - glycyrrhetic acid, aglycone of glycyrrhizin, on streptozotocin-diabetic rats. Diabetes was induced in adult male albino rats of the Wistar strain, weighing 180-200 g, by administration of streptozotocin (40 mg/kg of body weight) intraperitoneally. Diabetic rats showed increase of plasma glucose and glycosylated haemoglobin (HbA1c) and a decrease of plasma insulin and haemoglobin (Hb). Activities of gluconeogenic enzymes such as glucose 6- phosphatase, fructose 1, 6-biphosphatase increased and glucokinase, glucose 6-phosphate dehydrogenase decreased in the liver along with glycogen. Oral administration of 18 β -glycyrrhetic acid (50, 100, or 200 mg/kg of body weight) or glibenclamide (600 μ g/kg of body weight) in 5% dimethyl sulfoxide, for 45 days, prevented the above changes and improved towards normalcy [26].

Anti-inflammatory

It is reported that glycyrrhetic acid in liquorice extract gives anti-inflammatory effect similar to glucocorticoids and mineralocorticoids. Carbenoxolone (Biogastron), a

glycyrrhetic acid analog, is reported to inhibit two enzymes that are important in metabolism of prostaglandin, 15-hydroxyprostaglandin dehydrogenase and Δ 13 prostaglandin thereby raising prostaglandin levels. Prostaglandins stimulate mucous secretion and cell proliferation. Thus, ulcer healing is promoted [27].

Antimalarial

Licochalcone A (a chalcone) present in liquorice has reported to possess very good antimalarial activity. All *Glycyrrhiza* species have this compound in different amounts and it can be isolated from them. *In vivo* studies against *P. yoelii* in mice with oral doses of 1000 mg kg⁻¹ have shown to eradicate malarial parasite completely. Also no toxicity was observed [28].

Antioxidant

In a study antioxidant activity of liquorice flavonoids was found to be over 100 times stronger than that of antioxidant activity of vitamin E. A dose of 2.58 mg/ml liquorice flavonoids can scavenge more free radicals (20.6% scavenging) than 258 mg/ml of vitamin E (11.2% scavenging). It has been reported that flavonoids from liquorice are currently the strongest natural antioxidants known [29].

Antitussive and expectorant

Glycyrrhizin is responsible for demulcent action of liquorice. Liquiritin apioside, is an active compound present in the methanolic extract of liquorice which inhibits capsaicin induced cough [30]. Ethanol extract of *G. glabra* was found to be responsible for inhibition of 35.62% SO₂ gas induced cough in experimental animals (mice) [31].

Antiulcer

Liquorice can raise the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach; it was also reported that liquorice prolongs the life span of surface cells in the stomach and has an anti-pepsin effect [32].

Antiviral

The outbreak of SARS warrants the search for antiviral compounds to treat the disease. At present, no specific treatment has been identified for SARS-associated coronavirus infection. We assessed the antiviral potential of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients with SARS. Of all the compounds, glycyrrhizin was the most active in inhibiting replication of the SARS-associated virus. The findings suggested that glycyrrhizin should be assessed for treatment of SARS [33].

Hepatoprotective

Glycyrrhizin induced a significant reduction in serum aminotransferases and improved the liver histology when compared with the placebo. It has also been implicated that long-term usage of glycyrrhizin prevents development of hepatocellular carcinoma in chronic hepatitis C. *In vitro* studies have indicated that glycyrrhizin modifies the intracellular transport and up presses hepatitis B virus (HBV) surface antigen (HbsAg) [34, 35].

It has been found that 18 β -glycyrrhetic acid (GA), an aglycone of glycyrrhizin decreases the expression of P450 E1 thereby protecting the liver [36].

Immunomodulator

Polysaccharide fractions obtained from *Glycyrrhiza glabra* stimulate macrophages and hence elevate and assist immune stimulation [37]. Also animal studies have revealed its efficacy against the influenza A virus that is mediated by stopping the virus replication. Glycyrrhizic acid present in the plant inhibits virus growth and inactivates virus particles is a potential source of immunomodulator [38].

Memory enhancing

The effects of *Glycyrrhiza glabra* on learning and memory was investigated in mice. Elevated plus-maze and passive avoidance paradigm were used to test learning and memory. Three doses of aqueous extract of liquorice were administered (75, 150 and 300 mg/kg p.o.). The study was conducted for 7 successive days in separate groups of animals. Significant improvement in learning and memory of mice was reported at the dose of 150 mg/kg. But, the exact mechanism of action is unknown and needs further investigation [39].

Skin lightening

In vitro tyrosinase enzyme inhibition studies has showed that 21.2 μ g/ml of methanolic extract of liquorice caused 50% tyrosinase enzyme inhibition. The inhibition of tyrosinase enzyme and reduction in enzyme activity is caused due to modification of action site of the enzyme. Due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity [40].

Conclusion

Glycyrrhiza glabra Linn (Mulethi) is a common ingredient in many Unani compound formulations and has been in use since times immemorial to treat wide range of indications. It has been subjected to quite extensive phytochemical, experimental and clinical investigations. Experimental studies have demonstrated its antibacterial, anticancer, anticoagulant, antifungal, anti-hyperglycemic, anti-inflammatory, antimalarial, antioxidant, antitussive and expectorant, antiulcer, antiviral, hepatoprotective, immunomodulator, memory enhancing and skin lightening effects. The scientific studies have proved most of the claims of traditional medicines. These results are very encouraging and indicate this drug should be studied more extensively to confirm other potential therapeutic effects. Clinical trials using *Mulethi* for a variety of conditions should also be conducted to use it judiciously and cautiously in Unani as well as other systems of medicine.

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