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REVIEW ARTICLE

PHARMACOGNOSY

GLYCYRRHIZA GLABRA Linn. - "KLITAKA": A REVIEW

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ABSTRACT

Herbal medicines are the synthesis of therapeutic experiences of generations of practising physicians of indigenous systems of medicine for over hundreds of years. Herbs have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. *Glycyrrhiza glabra* commonly known as Yashtimadhu, is a popular herb, which has since long been used in traditional Ayurvedic and Chinese medicine for its magical effects to cure various diseases. This plant is also pharmacologically studied for its antiulcerogenic, antioxidant, antimicrobial, and anti-inflammatory properties. This review attempts to highlight the available literature on *Glycyrrhiza glabra* with respect to its ethnobotany, pharmacognostic characteristics, traditional uses, chemical constituents and summary of its various pharmacologic activities and clinical effects. Other aspects, such as toxicology and precautions are also discussed. This will be helpful to create interest towards licorice and may be useful in developing new formulations with more therapeutic and economical value.

KEYWORDS

Glycyrrhiza glabra, glycyrrhizin, peptic ulcer and Yashtimadhu.

INTRODUCTION

Glycyrrhiza glabra has been known in pharmacy for thousands of years. In old Chinese pharmacy, it was considered to belong to drugs of the first class and to it was ascribed the rejuvenating property when consumed for long periods. It plays an important part in Ayurveda and is one of the principal drugs in Sushruta Samhita. In ancient Egypt, Greece and Rome licorice was frequently used. It was referred to by Theophrastus. The Roman writers referred to it as Radix dulcis. Also it was much used in Europe in the middle ages. Even today licorice is maintaining its place in medicine and pharmacy. Its use from then, till today, proves its efficacy. [1]

CLASSIFICATION

The plant classification details are [2, 13]
Kingdom: Plantae – Plants
Subkingdom: Tracheobionta – Vascular plants
Super division: Spermatophyta – Seed plants
Division: Magnoliophyta – Flowering plants
Class: Magnoliopsida – Dicotyledons
Subclass: Rosidae
Order: Fabales
Family: Fabaceae – Pea family
Genus: Glycyrrhiza L. – licorice
Species: *Glycyrrhiza glabra* L. – cultivated licorice

REGIONAL NAMES: [3-7]

Regional names of plants are based on:
Arab: Aslussiera, Asla-soos (root)
Beng & Bomb: Jashtimadhu, Yashto-madho
Can: Jestamaddu
Eng: Sweetwood, Liquorice, Licorice
Hindi: Mulhatti, Jethimadh, Mithilakdi
Fr: Bois Doux
Guj: Jethimadha
Ger: Sussholz
Kannad: Jeshthamadhu
Malayalam: Itarttimadhuram, Erattimadhuram
Mar: Jeshtamadhu
Ori: Jatimadhu
Punj: Muleti
Pers: Ausareha mahaka, Bikhe mahaka
Sans: Yashtimadhu, Madhuka, Klitaka
Tamil: Atimadhuram
Telugu: Atimadhuramu
Latin name: *Glycyrrhiza glabra* Linn.

DISTRIBUTION/ HABITAT: [8, 14]

It is distributed in Southern Europe, Syria, Iran, Afghanistan, Russia, China, Pakistan and Northern India. This plant is cultivated in Russia, UK, USA, Italy, France, Germany, Spain, China and Northern India (Punjab and Sub-Himalayan tracts). Large scale commercial cultivation is seen in Spain, Sicily and England.

PROPAGATION

The propagation of the plant is done with young pieces of stolons and each piece should exhibit 2-3 buds of aerial shoot. The plant requires a soil 3 to 4 feet deep or more, having a light, loamy and stone-free texture. It is usually grown continuously on the same land. The pieces of stolons are planted in March at 2' by 3' distance. The fertilizers are to be supplied when the green parts are developing. The crop is kept free of weeds. The roots are harvested 3-4 years after planting when they show sufficient growth. The plants are also produced from runners or underground stems which are cut into pieces 4 inches long, each having at least 2 buds. [9] Dry conditions at planting time and for the next two months give best chance

for a good crop. If cold weather prevails in May or June, some percentage of the crop fails to grow. This forms one of the chief hazards of liquorice cultivation and in conjugation with high costs of lifting, must weigh heavily in favour of low priced liquorice collected wild. Liquorice occupies the land for a period of five, or sometimes four years. A yield of two tons of roots per acre for bailing, plus 3-4 cwt of trimmings or offal is considered satisfactory. [1]

CULTIVATION

Rhizomes and roots are dug up in October, preferably from the plants which have not borne the fruits. Buds and rootlets are removed, and the drug is washed. Some pieces are peeled and divided into small pieces. The drug is dried first under sun and then in shades, during which it loses about 50 per cent of its weight. [1, 9]

DESCRIPTION OF THE PLANT:

1) Macroscopic

It is a perrineal herb/subshrub for subtropical and temperate zone. The plant attains a maximum height up to 2m. The underground stem grow horizontally up to 2m length, highly branched consisting of short taproot with large number of rhizomes. [10] The diameter of the root varies from 0.75 to 2.5 cm, grey- brown exterior and yellow interior. Externally, it is longitudinally wrinkled with patches of cork. [15] It has a characteristic pleasant sweet taste. Leaves alternate, pinnate, yellow green leaflets 4-7 pairs are covered with soft hairs on underside. Flowers appear in axil of terminal and axillary leaves in raceme, pea-like, lavender to purple in color. Seed pod is 2-2.5cm long containing 2-5 seeds. [8] Flowering-fruiting is from August to February. [7]

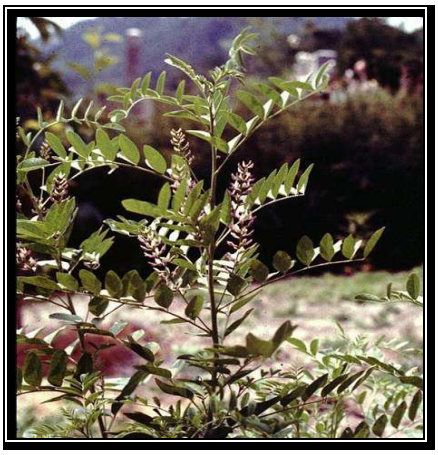

Figure 1
***Glycyrrhiza glabra* plant**

Figure 2
***Glycyrrhiza glabra* root**

2) Microscopic

Stolon- Transverse section of stolon shows cork of 10-20 or more layers of tabular cells, outer layer with reddish-brown amorphous contents, inner 3 or 4 rows having thicker, colourless walls; secondary cortex usually of 1-3 layers of radially arranged parenchymatous cells containing isolated prisms of calcium oxalate; secondary phloem a broad band, cells of inner part cellulosic and outer lignified, radially arranged groups of about 10- 50 fibres, surrounded by a sheath of parenchyma cells, each usually containing a prism of calcium oxalate about 10- 35 µ long; cambium form tissue of 3 or more layers of cells; secondary xylem distinctly radiate with medullary rays, 3-5 cells wide, vessels about 80-200 µ in diameter with thick, yellow, those of phloem; xylem parenchyma of two kinds, those between the vessels having thick pitted walls without inter-cellular spaces, the remaining with thin walls; pith of parenchymatous cells in longitudinal rows, with inter- cellular spaces. [12]

Root- Transverse section of root shows structure of closely resembling that of stolon except that no medulla is present; xylem tetrarch; usually four principal medullary rays at right angles to each other; in peeled drug cork shows phelloderm and sometimes without secondary phloem; all parenchymatous tissues containing abundant, simple, oval or rounded starch grains, 2-20 µ in length. [11, 12]

DIFFERENT VARIETIES OF G. glabra: [9]

1. *G. glabra* var. *typica*: (Spanish liquorice): This plant has purplish blue coloured papilionaceous flowers. It gives out large number of stolons.
2. *G. glabra* var. *glandulifera* (Russian liquorice): It has a big root stock along with a number of elongated roots, but does not bear stolons.
3. *G. glabra* var. *violacea* (Persian liquorice): This plant shows violet flowers.

PARTS USED

Roots [16]

PROPERTIES: [17]

The Ayurvedic properties of plants based on following parameters:

Rasa: Madhur
Veerya: Sheeta
Vipaka: Madhur
Guna: Guru, Snigdha
Doshaghnata: Vatapittashamaka
Karma: Yashtimadhu alleviates vata and pitta dosha. It is daahshamaka, Keshya, Vedanasthapana, Shothahar, Naadibalyakar, Medhya, Chhardinigrahana, Trishnanigrahana, Vatanulomana, Mrudurechana, Shonitasthapana, Kaphanissarak, Kanthya, Mutrala, Mutravirajneeya, Shukravardhak, Kandughna, Jwarashamak, Jeevaneeya, Sandhaneeya, Rasayana, Balya, and Chakshushya.
Rogaghnata: Vranashotha, Khalitya, Nadidaurbalya, Aamvata, Shiroroga, Vamana, Trishna, Udarashoola, Amlapitta, Raktalpata, Kasa, Shwasa, Swarabheda, Yakshma, Urogata vrana-kshata, Parshwashool, Mutrakruchha, Puyameha, Paittik prameha, Shukrameha, Kandu, Jeernajwara, Netraroga.

PHYTOCHEMISTRY

The chief constituent of liquorice is glycyrrhizin, which is present in the drug in the form of the potassium and calcium salts of glycyrrhizic acid. [9] Glycyrrhizin is 50 times sweeter than sucrose. [19-21] Glycyrrhizic acid is not a glycoside since it yields on hydrolysis one molecule of glycyrrhetic acid and two molecules of glycuronic acid but no sugar. Glycuronic acid is, however, very closely related to the hexose sugars, and glycyrrhetic acid has a haemolytic action like that of the saponins. Liqourice also contains glucose (up to 3.8 per cent.), sucrose (2.4 to 6.5 per cent.), bitter principles, resins, mannite, asparagines (2 to 4 per cent.) and fat (0.8 per cent). [1]

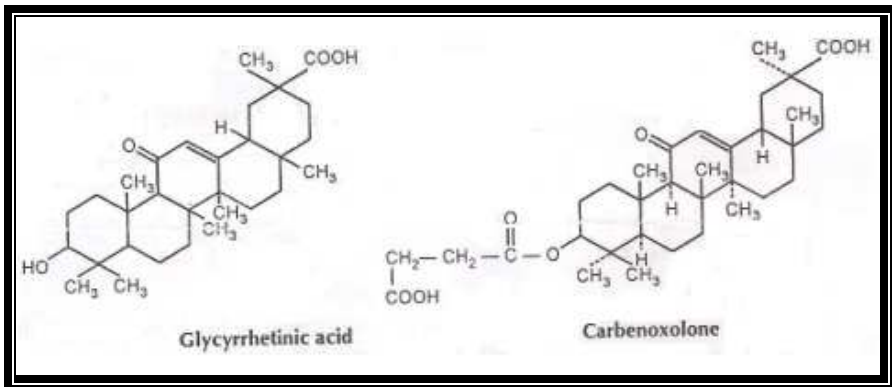

Figure 3
Structure of constituents in *Glycyrrhiza glabra*.

Glycyrrhizine, prenylated biaurone, licoagrone; 7- acetoxy- 2- methylisoflavone, 7- methoxy- 2- methylisoflavone and 7- hydroxyl- 2 methylisoflavone; 4- methyl coumarin, liqcoumarin; isoflavone, glyzaglabridin (7,2'- dihydroxy 3',4'- methylenedihydroxy isoflavone); quercetin, quercetin-3-glucoside, kaempferol, astragalin, liquiritigenin and isoliquiritigenin(root). Other constituents reported include a flavanone rhamnoglucoside, chalcone glucosides, trans- isoliquiritigenin- 4'- β- D- glucopyranoside (isoliquiritin) and trans- isoliquiritigenin-4'-β- D- glucopyranoside (neoisoliquiritin); 7-hydroxy-4'- methoxyisoflavone (formetin), licuraside, liquiritoside, rhamnoliquiritin, triterpenoid, liquoric acid, 11- deoxoglycyrrhetic acid, liquiritic acid, isoglabrolide, glabrolide, deoxoglabrolide, glycyrrhizic acid, glycyrrhetol, 21α- hydroxy- 11-deoxyglycyrrhetic and 24- hydroxyglycyrrhetic acids, 18 α- hydroxyglycyrrhetic acid olean-12-en-3β-ol-30 oic, olean- 11, 13 (18)-dien-3β-ol-30 oic acid, glabranine(5,7- dioxy-8-3(3',3'-dimethylallyl- flavonone),pinocembrin, prunetin, 4- hydroxyl chalcone, liquiritigenin, licoflavonol (6-γ- γ- dimethylallylkaempferol), kumatakenin, glycerol, licoricone, glabridin, glabrol, liqurazid, liquiritin, 3-hydroxyglabrol, 4'-0-methyl glabridin, 3'-methoxyglabridin, glycyrrhetinic acid; methyl olean-11,13 (18)-diene-3, 24-diol-30-oate, glabranine, formononetin, glabrene, saponaretin (isovitexin), 24-hydroxy-11-deoxyglycyrrhetic acid, methyl olean 11, 13(18) diene-3, glycerrhetol, 21α- hydroxy isoglabrolide, licoflavonol, glyzarin, glyzaglabrin, licoisoflavonones A, B and licoisoflavon, glycyrin, sugars and aspargin (root and other parts). [17]

QUANTITATIVE STANDARDS: [3, 12]

Total ash: Not more than 10.0%
Acid insoluble ash: Not more than 2.5%
Alcohol soluble extractive: Not less than 10.0%
Water soluble extractive: Not less than 20.0%

ADULTERANTS

Manchurian liquorice is obtained from *Glycyrrhiza uralensis*. It is chocolate brown in colour. [1] The distinguishing peculiarities are that the medullary rays are curved and presence of lacunae can be seen in the wood. It contains the active principle glycyrrhizin, but in very less quantity and that too free of sugars. [9] Wild licorice, also called as the Indian licorice is a common adulterant. It is derived from the roots of Abrus precatorius (Leguminosae). Its roots are very toxic due to an alkaloid abrine and therefore should not be used in place of licorice. The distinguishing property is that it possesses a disagreeable odour and bitter acrid flavour leaving faintly sweet after-taste. Microscopically the adulterant is characterized by stone cells. [3]

USES

Licorice roots are used for its demulcent and expectorant property. [22] It is useful in

anaemia, gout, asthama, sore throat, tonsillitis, flatulence, sexual debility, epilepsy, hyperdypsia, fever, coughs, skin diseases, swellings, acidity, leucorrhoea, bleeding, jaundice, hiccough, hoarseness, bronchitis, vitiated conditions of vata dosha, gastralgia, cephalalgia, ophthalmopathy and pharyngodnia. [7]

Licorice is an important ingredient in medicinal oils for epilepsy, paralysis, rheumatism, haemorrhagic diseases. It is also used in the treatment of diarrhoea, fevers, fever with delirium and anuria. [18]

Due to glycyrrhetinic acid present in licorice which has the minerocorticoid activity, it is used in place of corticosteroids for the treatment of rheumatoid arthritis, inflammations and Addison's disease. Glycyrrhizin is an established anti-inflammatory drug. [9]

Research shows that on being broken down in the gut, glycyrrhizin exerts an anti-inflammatory action similar to hydrocortisone and other corticosteroid hormones. It stimulates production of hormones by adrenal glands and reduces the breakdown of steroids by the liver and kidneys. Glycyrrhizin also proved effective in the treatment of chronic hepatitis and liver cirrhosis. [4]

For relieving pain, discomfort and other symptoms caused by acrid matter in the stomach, licorice is considered as one of the best remedies. It seems to remove the irritating effects of acids in a better way than alkalies. [1]

It is used by practitioners of the indigenous systems as a tonic, as a demulcent in catarrh of the genitor-urinary passages and as a mild laxative. [5]

Other uses: The powdered licorice root is used for various pharmaceutical purposes as in the preparation of pills, either to give due consistence or to cover their surfaces and prevent them from cohering and as a diluents of powdered extracts, etc. The chief role which licorice is playing in pharmacy is in covering the acrid taste of many nauseous drugs, particularly senna, aloes, chloride of aluminium, senega, hyoscyamus, turpentine, etc. [1] It is also employed in dyeing and tobacco industries. It is used as a flavouring agent for chewing tobacco and snuff tobacco. [23, 24] Ammoniated Glycyrrhiza is used as a flavoring agent in beverages, confectionery and pharmaceuticals. It is also consumed in a fair quantity by the candy industry. Residual matter of the root left after extracting licorice is used as a foam stabilizer in foam type of fire extinguisher and also used as a fertilizer for mushrooms. [1, 9]

PHARMACOLOGICAL/BIOLOGICAL ACTIVITIES:

Smooth muscle depressant, anti-microbial, hypolipidaemic, antiantherosclerotic, antiviral, hypotensive, hepatoprotective, anti-exudative, spasmolytic, antidiuretic, antiulcer, antimutagenic, antipyretic, antioxidant, anti-inflammatory, anti-nociceptive, expectorant. [7, 16, 17, 19, 22, 23]

Tests on rabbits have confirmed the secretolytic and expectorant effect of glycyrrhizic acid. In the isolated rabbit ileum an antispasmodic action has been observed at the concentration of 1:2500 to 1:5000. [4]

Spasmolytic activity of glycyrrhizin (8%) was 1/500 that of papaverine. [25]

Rats were given 2.5 g powder/kg/day orally for 3 months showed decrease in body weight gain, blood cell count and thymus weight; atrophic cortex and sporadic lymphofollicle formation also noted in medulla of thymus gland. [26]

Antidyslipidaemic activity of Glycyrrhiza glabra was seen in high fructose diet induced dyslipidaemic Syrian golden hamsters. [27]

A study carried out on shay rat showed significant repairing effect on acetic acid ulcer, when a fraction of root extract was administered. [25]

Glycyrrhetic acid aluminium salt and its esters or dicarboxilic acid derivatives showed protective effect in rats with experimental ulcers. [28]

Glycyrrhizin injected (75.0 or 150.0 mg/kg, i.p.) in mice increased weight of spleen and

thymus; white blood cell count and clearance rate of charcoal particles injected i.v. also increased. [29]

When mice that had been exposed to 10-50% lethal doses of influenza virus were treated intraperitoneally with 10 mg of glycyrrhizin per kg of body weight 1 day before infection and 1 and 4 days post infection, all of the mice survived over the 21-day experimental period.

FURTHER REPORTED ACTIVITIES:

Estrogenic, [30, 31] antimycotic, [32] antioxidant, [33] oncology adjuvant therapy, [34] protection of mitochondrial function, [35] tyrosineinhibitory, [36] antiasthamatic,[37] antimicrobial,[38] antiulcerogenic, [39-41] anti-inflammatory, [42] protection against cytotoxicity, [43] anxiolytic, [44] cytochrome p450A4 inhibitory.[45]

CLINICAL STUDIES:

Controlled clinical trial conducted on 92 cases of post-operative traumatic inflammation following tonsillectomy, 28 cases were given Yashtimadhu powder in a dose of 3 gm t.d.s. In another series of 24 cases, oxyphenbutazone 2 tablets t.d.s. were given. On sequential analysis, the anti-inflammatory response of Yashtimadhu was found to be equivalent to that of oxyphenbutazone. It appeared to possess a more potent anti-pyretic and anti-exudative activity as compared to oxyphenbutazone.

In a clinical trial conducted on 32 cases of allergic conjunctivitis, glycyrrhetinic acid drops were found to be much efficacious in acute as well as long standing cases.

When a combination of Yashtimadhu and Ashwagandha (Withania somnifera Dunal) was given to 91 patients suffering from gastritis, hyperacidity, hypoacidity and peptic ulcer in a clinical trial, it proved to be much beneficial without any untoward side effects. [17]

Oral administration of deglycyrrhizinated licorice (380mg 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antacid or cimetidine treatments. Other unidentified constituents of the herb also contribute to its antiulcer activity. Controlled clinical studies show that glycyrrhizic acid and the aglycone of glycyrhhizic acid accelerate the healing of gastric ulcers. [4]

Its role is currently investigated in cancer protection and certain immune functions such as interferon production. [46]

MECHANISM OF ACTION FOR PEPTIC ULCER:

Glycyrrhiza glabra reduces stomach secretion, produces thick protective mucus for stomach lining which protects it from inflammations, gastritis and peptic ulcerations. [4]

The deglycyrrhized licorice is used in peptic ulcers due to the flavonoids present in it. This form has a reduced minerocorticoid activity and therefore used in the treatment of peptic ulcer for healing purposes. [9]

DOSAGE:

Root powder: 3-5 gm [23]

Licorice liquid extract: 2-4 ml [3]

MARKETED FORMULATIONS

Yashtyadi churna, Yashtyadi kwath, Swadishta virechan churna, Yashtimadhu churna, Yashtimadhvadya taila, Eladi gutika, Kalyanavleha, Angamaradaprashamana kashaya, Brihat ashwagandha ghrita, Brihachchhagaladya ghrita, Shatavaryadi ghrita, Nasika churna, Guduchyadi taila, Pippalyaditaila, Vyaghri taila, Kubjaprasarini taila, Vridhihara lepa. [17]

SUGGESTED COMBINATIONS

Root mixed with lime juice and linseed is used for coughs and colds. A compound powder which consists of licorice root and fennel fruit, senna, sublimed sulphur and refined sugar is useful as a gentle laxative. [5]

TOXICITY

The intake of higher doses of licorice (above 50 g/day) over an extended period may cause sodium retention, hypertension and cardiac complaints. [4, 47]

If taken in excessive amounts it can cause metabolic disturbances known as pseudoaldosteronism (due to mineralocorticoid effect of glycyrrhizin) leading to oedema, hypertension and weight gain. [3]

ACUTE TOXICITY: *[17]*

Glycyrrhizin (crude extract 48-58%):
LD50 values in rats and mice
LD50 s.c. 4-4.4 g/kg
LD50 i.p. 1.42-1.70 g/kg
LD50 oral 14.2-18.0g/kg

PRECAUTIONS

The drug is contraindicated in patients with a history of hypertension, renal failure and using digitalis preparations. [4] Pregnant or breastfeeding women should not take licorice. Use of any licorice product is not recommended for longer than 4 - 6 weeks. [50]

SAFETY

The drug when used within the recommended dosage and the treatment period is devoid of any adverse reactions. [3]
Interactions with drugs are mentioned in table no.1.

Table 1
Interaction with drugs *[48]*

DRUG	RESULT OF INTERACTION	COMMENTS
Prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC, increases plasma concentrations of prednisolone	11β-dehydrogenase converts endogenous cortisol to cortisone; orally administered glycyrrhizin is metabolized mainly to glycyrrhetinic acid.
Hydrocortisone	Glycyrrhetinic acid potentiates cutaneous vasoconstrictor response.	Glycyrrhetinic acid is a more potent inhibitor of 5alpha-5β-reductase and 11β-dehydrogenase than is glycyrrhizin
Oral contraceptives(OC)	HT, oedema, hypokalemia	OC use may increase sensitivity to glycyrrhizic acid.

CONCLUSIONS

Glycyrrhiza glabra is a widely used and potent medicinal plant used in many ailments of different systems. It is used as a single drug and also as a main content in many medicinal preparations like syrups, lozenges etc. It is in great demand internationally as medicinal and nutritional supplement. The plant has been used since centuries for asthma, bronchitis, ulcers, and an anti-inflammatory. It is reported to contain essential oil, coumarins, alkaloids and flavonoids. Extract of root can be found in various herbal preparations that are in market today. The pharmacologic and clinical studies reported in the present review confirm the therapeutic value of *Glycyrrhiza glabra*. It is an important source of various types of compounds with diverse chemical structures as well as pharmacologic properties. Presence of such a wide range of chemical compounds indicates that the plant could serve as a “lead” for the development of novel agents having good efficacy in various disorders in the coming years.

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