REVIEW OF GLYCYRRHIZA GLABRA (YASTIMADHU) - A BROAD SPECTRUM HERBAL DRUG

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ABSTRACT

Glycyrrhiza glabra commonly known as Yashtimadhu, which has been used worldwide in various systems of medicine viz, Ayurvedic, Allopathic and other traditional systems of medicine. It is mainly used for the treatment of peptic ulcer, hepatitis C, and pulmonary and skin diseases, although clinical and experimental studies suggest that it has several other useful pharmacological properties such as anti-inflammatory, antiviral, antimicrobial, antioxidative, anticancer, immunomodulatory, hepatoprotective and cardio protective activities. A large number of components have been isolated from liquorice, including triterpene saponins, flavonoids, isoflavonoids and chalcones, with glycyrrhizic acid normally being considered to be the main biologically active component. This review attempts to highlight the available literature on Glycyrrhiza glabra with respect to its Ayurvedic aspects, pharmacognostical characteristics, phytochemical constituents, pharmacokinetics, pharmacological aspects with the clinical and adverse effects, toxicology and precautions of liquorice and its bioactive components are also discussed. This will be helpful to create interest towards liquorice and may be useful in developing new formulations with more therapeutic and economical value.

Keywords: Glycyrrhiza glabra, Yastimadhu, Liquorice.

INTRODUCTION

Glycyrrhiza glabra, also known as liquorice and sweet wood, is native to the Mediterranean and certain areas of Asia. They have been used medically since at least 500 BC and liquorice has been described as ‘the grandfather of herbs’ [1]. The Roman writers referred to it as Radix dulcis [2]. 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 [3]. It is the most prescribing herb after Ginseng in Chinese medicine [4] used for ailments related spleen, liver and Kidney [5]. Historically, the dried
rhizome and root of this plant were employed medicinally by the Egyptian, Chinese, Greek, Indian, and Roman civilizations as an expectorant and carminative\textsuperscript{[6]}. Liquorice has been used in medicine for 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 (2000 BC). Hippocrates (400 BC) mentioned its use as a remedy of ulcers and quenching of thirts. The drug was also mentioned by Theophrastus and Dioscorides. In traditional Siddha system of medicine, liquorice is used as a demulcent, expectorant, anti-tussive, laxative and sweetener\textsuperscript{[7]}.

MATERIALS AND METHODS
There are number of review articles are available on \textit{G. glabra} (Yastimadhu), though a few of them establish the relationship amongst classical and modern aspects. Thus, attempt has been made to review the classical Ayurvedic treatises to derive a detailed account of properties, action and uses mentioned in \textit{Charak Samhita}, \textit{Susruta Samhita}, \textit{Astang hridaya}, \textit{Astanga Sangraha} and \textit{Bhavprakasha} of Bhavmishra, etc. Contemporary research evidences have been reviewed to establish ancient- modern concordance for Yastimadhu.

RESULTS AND DISCUSSION
Ayurvedic aspects:
Yastimadhu (\textit{Glycyrrhiza glabra}) is considered as one of the popular drugs of Ayurvedic classics. Although it is not native to India, it was mentioned in all the Ayurvedic classics with the synonyms like \textit{Madhuyashtyaahvaa}, \textit{Madhuli}, \textit{Madhuyastikaa}, \textit{Atirasa}, \textit{Madhurasaa}, \textit{Madhuka}, \textit{Yastikahva}, \textit{Yastyahva}, \textit{Yasti}, \textit{Yastika}, \textit{Yastimadhuka} and \textit{Klitaka}\textsuperscript{[8]}. Charaka includes Yastimadhu in following groups.
TABLE 1: YASTIMADHU IN PHARMACOLOGICAL CLASSIFICATION OF CHARAKA

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of the group</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Jivaneeya (Invigorator)</td>
</tr>
<tr>
<td>2.</td>
<td>Sandhaneeya (Wound healer)</td>
</tr>
<tr>
<td>3.</td>
<td>Varnya (Complexion promoter)</td>
</tr>
<tr>
<td>4.</td>
<td>Kanthya (Voice promoter)</td>
</tr>
<tr>
<td>5.</td>
<td>Kandughna (Itching reliever)</td>
</tr>
<tr>
<td>6.</td>
<td>Snehopag (Adjuvant of unctuous)</td>
</tr>
<tr>
<td>7.</td>
<td>Vamanopag (Adjuvant for emesis)</td>
</tr>
<tr>
<td>8.</td>
<td>Chhardinigrahan (Antiemetic)</td>
</tr>
<tr>
<td>9.</td>
<td>MutavrArnjiniya (Urinary antiseptic)</td>
</tr>
<tr>
<td>10.</td>
<td>Angamardaprasaman (cures malaise)</td>
</tr>
<tr>
<td>11.</td>
<td>Sonitsthapana (Haemostatic and blood purifier)</td>
</tr>
</tbody>
</table>

The root of Yastimadhu is usually preferred for therapeutic purpose, but charaka suggests its fruit for purgative activity. Its inclusion in eleven groups out of fifty (50) clearly projects the importance attributed to this drug by charaka. He further crystallized the properties and actions (activities) while furnishing the prime list of drugs [9] viz, Chakshushya (eye sight promoter), Vrishya(Aphrodisiac and fertility promoter), Keshya(Hair growth promoter), Kanthya(Voice promoter), Varnya(Complexion promoter), Virajaneeya(Antiseptic) and Ropana(healing) actions. Charaka suggested Yastimadhu in the management of Hridroga with Katuki.

Susruta[10] included Yastimadhu under Sarivadigana, Anjanadigana, Ambashthadigana, Nyagrodhadigana, Utpaladigana. Yastimadhu has not been included in the list of Samsamana group indicated in the management of each vitiated dosha. Out of 5 groups mentioned above Sarivadi, Anjanadi, Utpaladi and Nyagrodhadi ganas are incorporated and indicated for pittasansamana varga[11] (palliative to vitiated pitta).
Vagbhatt \[12\] enumerated Yastimadhu along with Jivanti, Jivaka, Madgaparni, Mashaparni etc.

**TABLE 2: AYURVEDIC PHARMACOLOGICAL ACTIVITIES OF YASTIMADHU**

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of the Pharmacological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Invigorator</td>
</tr>
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<td>2.</td>
<td>Wound healer</td>
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<td>11.</td>
<td>Spermatopoietic</td>
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<tr>
<td>12.</td>
<td>Hair growth promoter</td>
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<tr>
<td>13.</td>
<td>Anti inflammatory</td>
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<tr>
<td>14.</td>
<td>Analgesic</td>
</tr>
<tr>
<td>15.</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>16.</td>
<td>Aphrodisiac</td>
</tr>
<tr>
<td>17.</td>
<td>Galactogogue</td>
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<tr>
<td>18.</td>
<td>Beneficial for Eyes (Eye tonic)</td>
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</table>

Bhavmishra referred Yastimadhu with a synonym Klitaka and mentioned two of its varieties basing on the ecological distribution. He attributed Sukrala (Spermatopoietic) activity in addition to Chakshushya, Balya, Vrishya, Keshya, Swarya, Vranasothahara properties. Bhavmishra recorded analgesic activities of Yastimadhu on administration in...
the form of nasyakarma to relieve all types of headaches. He also describes that Yastimadhu relives cough immediately\cite{13}.

Vangasen \cite{14} has reported antiepileptic activity in combination with Kushmanda Swarasa. Sodhala \cite{15} describes its aphrodisiac activities, while author of Vaidya manorama confirms the galactogogue activity of yastimadhu\cite{16}. Chakradutta\cite{17} suggested its application on ulcers due to injury for relieving pain (Analgesic).

Pharmacognosy:

Glycyrhiza glabra Linn is a hardy perennial shrub is a member of the pea family, Leguminosae; the word, Glycyrhiza is derived from the ancient Greek term glykos, meaning sweet, and rhiza, meaning root\cite{18}.

It grows in subtropical climates in rich soil to a height of four or five feet (2.5 m.). The leaves are compound, imparipinnate, alternate, having 4-7 pairs of oblong, elliptical or lanceolate leaflets. The flowers are white to purplish clusters, narrow, typically papilionaceous, born in axillary spikes, lavender to violet in colour. The calyx is short, campanulate, with lanceolate tips and bearing 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. Below ground, the liquorice plant has an extensive root system with a main taproot and numerous runners. The taproot is approximately 1.5 cm long and subdivides into 3-5 subsidiary roots, about 1.25 cm long, from which the horizontal woody stolons arise. These may reach 8 m and when dried and cut, together with the root, constitute commercial liquorice. It may be found peeled or unpeeled. The pieces of root break with a fibrous fracture, revealing the yellowish interior with a characteristic odour and sweet taste. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior.\textsuperscript{[19]}

Cultivation:

It is native to Mediterranean regions. Now, it is grown at Punjab, Jammu and Kashmir and south India.\textsuperscript{[20]}

The plants usually grow well in deep, sandy but fertile soil, near streams. The usual method of propagation is by replanting young pieces of stolon, but it can be grown from seed. The underground organs are sufficiently developed by the end of the third or fourth year at which stage they are dug up and washed. Enough always remains in the ground to renew itself during the ensuing three years. A great deal of it is peeled and cut up into short lengths before drying, but it is also used unpeeled.\textsuperscript{[21]}

Varieties for cultivation:

The genus Glycyrrhiza consists of about 30 species including G. glabra, G. uralensis, G. inflata, G. aspera, G. korshinskiiy and G. eurycarpa. G. glabra has different varieties growing at different regions viz; also includes three varieties Persian and Turkish liquorices are assigned to G. glabra var. violacea, Russian liquorice is G. glabra var gladulifera, and Spanish and Italian liquorices are G. glabra var. typical.\textsuperscript{[22]} All the three varieties were brought to Kashmir for cultivation. Its cultivation is being done at Ceria, Iran, Turkey, Greece and Russia. Similarly it is also in trade at Barcelona, Spain, Iraq, Italy, Aleczandreta, Ceria, Egypt, Belgium, France, and Germany. It is cultivated as major crop in Spain. Chinese liquorice is considered of good quality.\textsuperscript{[23]}
Haryana Mulhati No.1 (HM No.1), EC 111236, EC 124587, EC 21950, Mishree is a high yielding variety released by Central Institute of Medicinal and Aromatic Plants (CIMAP) [24].

Yield:
The crop gives an average yield of 2 - 3 tones of dried roots and a net profit of more than Rs. 25,000 per hectare [25].

Herbal trade:
Yastimadhu is amongst the significant medicinal plant species in high trade sourced largely through imports to India [26]. It is fourth highest (amongst 141 formulations available in market) used medicinal substance ranked for frequency of occurrence of medicinal plants in herbal formulations in India [27]. Liquorice is imported from Iran, Afghanistan, and China to India [28]. In India, every year approximately 5000 Tones of Yastimadhu is (i.e. 100% of Indian requirements) imported from Pakistan, Iran, Afghanistan [29] and UAE [30]. It is top selling herbal extracts (standardized) in world market [31]. There was demand of 873.4 in tones in 2001-02 reaching to 1359.8 tones in 2004-05 with an annual growth rate of 15.9 amongst 32 prioritized medicinal plants of India [32]. It is traditionally said that it has shelf life up to 10 years [33].

Substitute:
Dhataki (Woodfordia fruticosa L.) is suggested as a substitute for Yastimadhu [34,35].

Adulterants:
Manchurian liquorice is obtained from Glycyrrhiza uralensis. It is chocolate brown in colour [36]. 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 [37]. Wild liquorice, also called as the Indian liquorice 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 liquorice. 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\textsuperscript{[38]}.

**Phytochemistry and Active Constituents:**

A number of components have been isolated from liquorice, including a water-soluble, biologically active complex that accounts for 40-50 percent of total dry material weight. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances\textsuperscript{[39]}. Glycyrrhizin, a triterpenoid compound, accounts for the sweet taste of liquorice root. This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2-25 percent range. Among the natural saponins, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid. The yellow color of liquorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone), and other compounds\textsuperscript{[40]}. The isoflavones glabridin and hispaglabridins A and B have significant antioxidant activity\textsuperscript{[41]}, and both glabridin and glabrene possess estrogen-like activity\textsuperscript{[42]}. The main chemical constituent of liquorice is glycyrrhizin (about 2-9 %), a triterpene saponin with low haemolytic index. Glycyrrhetinic (glycyrrhetic) acid (0.5-0.09%), the aglycone of glycyrrhizin are also constituents of liquorice include isoflavonoids and sterols, lignans, amino acids, amines, gums and volatile oils\textsuperscript{[43]}. 

**Pharmacokinetics**

After oral administration of liquorice in humans, the main constituent, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria possessing a specialized β-glucuronidase\textsuperscript{[44,45]}. Glycyrrhetic acid is 200-1,000 times more potent an inhibitor of 11-β-hydroxysteroid dehydrogenase (involved in corticosteroid metabolism) than glycyrrhizic acid; therefore, its pharmacokinetics after oral intake are more relevant. After oral dosing, glycyrrhetic acid is rapidly absorbed and transported via carrier molecules to the liver. In the liver it is metabolized to glucuronide and sulfate conjugates, which are subsequently rehydrolyzed to glycyrrhetic acid. Glycyrrhetic acid is then
reabsorbed, resulting in a significant delay in terminal clearance from plasma. After oral administration of 100 mg glycyrrhizin in healthy volunteers, no glycyrrhizin was found in the plasma but glycyrrhetic acid was found at < 200 ng/mL. In the 24-hour period after oral administration, glycyrrhizin was found in the urine, suggesting it is partly absorbed as an intact molecule.

Modern scientific validation

The various pharmacological activities attributed to Yastimadhu are demulcent, expectorant, anti-allergic, anti-inflammatory, spasmolytic, mild laxative, anti-stress, anti-depressive, anti-ulcer, liver protective, estrogenic, emanogogue, and anti-diabetic. It is widely used in bronchitis, dry cough, respiratory infections, catarrh, tuberculosis; genitourinary diseases, urinary tract infections; abdominal pain, gastric and duodenal ulcers, inflamed stomach, mouth ulcer; and for adrenocorticoid insufficiency.

The British Herbal Compendium indicates the use of liquorice for bronchitis, chronic gastritis, peptic ulcer, rheumatism and arthritis, adrenocorticoid insufficiency and to prevent liver toxicity. Indian Herbal Pharmacopoeia recognizes its use as an anti-inflammatory and anti-ulcer agent. German Commission E, ESCOP and WHO indicates its key application in catarrh of upper respiratory tract, gastric and duodenal ulcers.

Ulcer healing activity:

There is considerable amount of pharmacological research on the possible therapeutic value of roots extract as an anti-gastritis and anti-ulcer agent. Significant inhibition of experimental ulcer (ulceration by ligation of pylorus in albino rats; cinophen-induce peptic ulcer in dogs; acetic acid- induce chronic ulcer in rats) was observed by administration of herbal extract or herbal powder by various methods. Both glycyrrhizin (and related acids), and glycyrrhizin- free flavanoids have been shown to have anti-ulcer activity and synergism between this has been demonstrated. In controlled clinical trials therapeutic value of glycyrrhizinic acid, and its aglycon (and some synthetic derivatives) total herb (root) powder or its extract have been established.
Mechanism of action has been investigated\(^{[58]}\). In this connection it should be noted that glabridin, a flavonoid constituent of the herb has inhibitory activity (in vitro) against Helicobacter pylori, which is now known to be involved in the pathogenesis of some cases of gastritis and peptic ulcer\(^{[59]}\). Another contributing factor towards the therapeutic effect of G. glabra products in the anti-spasmodic action of the herb action as well as that of the glycyrrhizin- free total flavanoids fraction (specially isoliquiritigenin)\(^{[60]}\).

In a clinical study it was found that five cases of pemphigus patients, who had been kept free of blisters with prednisolone medication, the dose of prednisolone could be drastically reduced by co-administration of powdered root of G. glabra\(^{[61]}\).

A special liquorice extract known as DGL (deglycyrrhizinated liquorice) is used in the treatment of various types of ulcers especially peptic ulcer. A glycoside from liquorices root found to have safe and effective ulcer healing properties. Use of Carbenoxolone (a derivative of Liquorice root) should be considered when antacids fail to give relief in ulcer patients\(^{[62]}\). Topical liquorice preparations have been used to sooth and heal skin eruptions, such as psoriasis and herpetic lesions\(^{[63]}\).

**Hormonal effects:**

Oral administration of aqueous extract of rhizome and roots improve male sexual function\(^ { [64] }\). Components of liquorice root have both estrogenic and anti-estrogenic activity. It is thus an important herb for treating hormone-related female problems\(^ { [65] }\).

This drug has received significant attention from modern scientific researchers, chiefly because it is also an important herbal medicine in Europe, and is official in several Pharmacopoeias. The most important finding of the modern research on this drug has been that glycrrhizin and glycyrrhetic acid have corticoid-like (both glucocorticoid and mineralcorticoid) activity. For example, glycyrrhizin caused atrophy of thymus gland and increased the weight of adrenal gland, suggestive of corticotrohin-like action. It is now generally agreed that the action of glyrrhizin and related compounds is essentially by inhibition of the action of the enzyme \(4\)-5\(\beta\)-reductase, which plays an important role in human liver in modulating the cortisone and aldosterone metabolism. This, in turn
enhances the biological half life of cortisone and aldosterone. Thus in a way, these compounds act synergistically with endogenous hormones. This activity of glycyrrhizin and related compounds has bearing on their therapeutic action in the treatment of rheumatoid arthritis, inflammation, oedema, ulceration, allergy etc [66,67].

In experimental animal studies glycerrhizin (10 mg/kg i.m., once daily for 5 days) was shown to have anti-lipidemic activity in hyperlipidaemic rabbits [68].

**Antitussive activity:**

Extract of the drug taken by mouth was shown to have antitussive action (animal studies). The herb also promoted pharyngeal and bronchial secretions leading to a good expectorant action [69].

Liquiritigenin, a flavanoid component of G. glabra roots, has been demonstrated to exhibit anti-asthmatic activity [70]. Glycyrrhetic acid protected guinea pigs against bronchospasms induced by histamine [71]. besides, the glucocorticoid- like activity of the triterpenoid constituents of the herb has a positive role to play in allaying asthmatic condition.

**Antimicrobial activity:**

The active compounds are the triterpene saponins, particularly glycyrrhizinic acid, which also has antiviral and bacteriostatic activity; besides, several flavanoids present in the drug have anti microbial activity. Alcoholic extract of the herb, as well as sodium salt of glycyrrhizinic acid, shows in vitro antimicrobial action against a range of organisms (Staphylococcus aureus, Mycobacterium tuberculosis, Escherichia coli, Entamoeba histolytica protozoa, and Trichomonas) [72]. Several of the flavanoid constituents (hispaglabridin-A, hispaglabridin-B, glabridin, methylglabridin, glabrol, and 3-hydroxyglabrol) of the extract have been identified as active agents [73,74].

**Antifungal activity:**

Glycyrrhizin has been shown to protect mice from systemic candidiasis, and it was concluded that glycyrrhizin may prove to be a useful adjuvant drug in the treatment of severe fungal infections [75].
Anti-viral activity:
Oral liquorice preparations, containing glycyrrhetinic acid, are used for the treatment of viral infections—viral hepatitis and common cold. Topical preparations, containing glycyrrhetinic acid, are used for herpes, eczema, and psoriasis. In Japan, a preparation of glycyrrhizin, cysteine and glycine is used by injection for the treatment of acute and chronic hepatitis. Liquorice extracts have been used for more than 60 years in Japan to treat chronic hepatitis, and also have therapeutic benefit against other viruses, including human immunodeficiency virus (HIV), cytomegalovirus (CMV), and Herpes simplex. Triterpenoid saponins from G. glabra roots have been shown to have antiviral activity. Thus, these saponins inhibit the growth of influenza A virus in hen embryos. Glycyrrhizinic acid inhibits the growth and cytopathology of several unrelated DNA and RNA viruses. It also inactivated Herpes simplex virus particles irreversibly.
Glycyrrhizin inhibited plaque formation in three different strains of Japanese encephalitis virus at a concentration of 500 mg/ml at 96 hours. In connection with its antiviral activity, it should be noted that glycyrrhizin has been shown, in invitro experiments, to induce and enhance gamma – interferon in human peripheral lymphocyte macrophage cultures developed by the lactin concanavalin A. Interferons regulate the immune system against infections.

Anti-inflammatory activity:
Anti-inflammatory activity of G. glabra root extract has been established in several experimental animal models as well as clinical trials. Action resembles that of phenylbutazone, hydrocortisones. Glycyrrhizinic acid as well as its aglycon glycyrrhetic acid are clearly the active agents, and this has been established in several animal models (formaldehyde- induced paw swelling, cotton pledget-induced granulation, etc.; albino rats). The flavanoid liquiritin and its genin liquiritigenin also displayed anti-inflammatory action. Mode of action of glycyrrhizinic and glycyrrhetic acid has been investigated, and it has been shown that these compound do not inhibit prostaglandin synthesis, but rather operate by moving leucocytes towards the inflamed spots.
Glycyrrhizin also has anti-thrombin activity, and this has been suggested as one of the contributors towards its anti-inflammatory action \cite{88}.

In a clinical trial of 32 cases of allergic conjunctivitis, a preparation containing glycyrrhetic acid as the active agent, therapeutic value was established both in acute and long standing cases \cite{89}. Eye drops containing 5% sodium glycyrrhizinate or the 8-12% suspension of glycyrrhetic acid or 10-30% herb extract, three or four times daily for 2-7 days, were effective in other eye inflammatory conditions such as Herpetic keratitis, keratoconjunctivitis and fascicular keratitis. In case of scleritis and episcleritis, treatment for 6-34 days was essential to cure the patients \cite{90}.

**Anti pyretic activity:**

Glycyrrhetic acid showed anti-pyretic activity similar to that of sodium salicylate on rectal temperature of normal and pyretic rat. In a clinical trial of traumatic inflammation, it was noted that \textit{G. glabra} possess more potent anti-pyretic effect than oxyphenylbutazone\cite{91}.

**Antioxidant activity:**

Flavanoids from the root have potent antioxidant activity. Six compounds with this activity have been characterized; these are hispaglabridin A and B, glabridin, methylgrabridin, isoliquiritigenin, and an isoprenylchalcone derivative. Of these, glabridin is the major (11% of the total extract) component. These compounds have been evaluated as an antioxidants towards LDL oxidation (a contributing factor to atherosclerosis) and glabridin was found to be highly effective \cite{92,93}. Some of these compounds have also been investigation for their ability to protect liver mitochondria against oxidative stress \cite{94}.

**Antitoxic activity:**

The drug extract have significant detoxicant action. This has been demonstrated by in vivo investigations on mice against strychnine, cocaine, arsenobenzene, mercurous chloride, and choral hydrate. Snake venom, tetrodotoxin, diphtheria toxin and tetanus toxin were also countered by glycyrrhizin \cite{95}. Glycyrrhizin is reported to be effective in
detoxifying the hepatotoxicity of parquet, a herbicide, in experimental animals. It appears that G. glabra root extracts / glycyrrhizin effect detoxification by a glucuronidation pathway.

New findings

Immunomodulating activity:
Extracts of roots of G. glabra have immunosuppressive activity. Thus, glycyrrhizin at 0.46 mM inhibited the degranulation of mast cell (elicited by a histamine liberation agent) in vitro, and thus suppressed the release of allergy mediators. Glycyrrhetic has also been shown to be a potent inhibitor (IC$_{50}$ = 35 mM) of the classical complement pathway. Crude extract devoid of glycyrrhizin at a dose of 2 mg/animal (I.V.) inhibited immune reaction in macrophages in mice.

Hepatoprotective:
Oral administration of G. glabra root extract to rats protected the animals from carbon tetrachloride induce liver injury. Hepatoprotective action was evident from abatement of hepatic degeneration and necrosis, recovery of hepatocellular glycogen, and from other indicators. Both glycyrrhizin and glycyrrhetic acid could decrease serum, billirubin and promote its excretion in urine in rabbit and rats with ligated common bile ducts. In a clinical trial on patients with sub acute hepatic failure a fraction derived from G. glabra (and termed interferon stimulator; vide supra) was demonstrated to be effective as the survival rose to 72.2%, as compared to 31.1% in patient who had received usual supportive therapy.

Hypolipidemic activity:
In experimental animal studies glycyrrhizin (10 mg/kg, i.m., once daily for 5 days) was shown to have antilipidemic activity in hyperlipidemic rabbits.

Radioprotection:
Extract of G. glabra root have been demonstrated to have radio protective action. This was inferred in the protection of microsomal members (reducing in lipid preoxidation in rat liver macromesomes), and rat plasmid DNA from radiation induced strand breaks.
Anticancer activity:
Products from G. glabra roots have both anticancer and cancer preventive activities. Thus, its extract showed antimutagenetic activity against ethyl methanesulphonate in the Salmonella / microsome revision assay \cite{105} Glycyrrhetic acid at 80 mg/kg, once daily, inhibited the transplanted oberling - guerin myeloma in rats. Glycyrrhizin also inhibited the subcutaneously transplanted jitan sarcoma in mice, and prevented the development of polyoxybenzidine-induced liver carcinoma in male mice\cite{106}. Oral ingestion (in drinking water) of glycyrrhizin to sencar mice lead to substantial protection against skin tumourigenesis induced by 7,12-dimethylbenz[a] anthracene and other carcinogens. Isoliquiritigenin, a flavanoid component of G. glabra root extract has been shown to have anticancer activity in vitro and in vivo models. New investigation have demonstrated that isoliquiritigenin significantly inhibited the proliferation of prostate cancer cells lines in a dose- dependent and time-dependent manner, and further work showed that isoliquiritigenin is a candidate for the treatment of prostate cancer\cite{107}.

Drug-Botanical Interactions:
There is an increased likelihood of cardiac arrhythmias, particularly in individuals with ischemic heart disease, when liquorice is used in conjunction with digoxin\cite{108}. Estrogen-based oral contraceptives may enhance the mineralocorticoid side effects of liquorice in susceptible individuals. This may be due in part to estrogens reacting with mineralocorticoid receptors or inhibition of 11β-hydroxysteroid dehydrogenase\cite{109}. Hypokalemia, commonly associated with metabolic acidosis, may co-present with essential benign hypertension in patients using diuretics and liquorice simultaneously\cite{110}.

Toxicity:
Crude drug, because of the mineralocorticoid activity of its main constituent glycyrrhizin, if ingested orally in larger dose (>50 g crude drug per day) over an extended period of time leads to hypocaemia, hypernatraemia, oedema, hypertension and cardiac disorder. These problems disappear in the course of a few days after stopping the drug. Preparations of liquorice should not be taken for longer than 6 weeks\cite{111}.
Hepokalemia is the greatest threat when liquorice preparations high in glycyrrhizin are prescribed for prolonged periods. Liquorice causes fluid retention. Patients should be placed on a high potassium and low sodium diet. Special precautions should be taken with elderly patients with hypertension or cardiac, renal or hepatic disease\cite{112}.

**Dosage:**

Because individual susceptibility to various liquorice preparations is vast, it is difficult to predict a dose appropriate for all individuals. Nevertheless, a daily oral intake of 1-10 mg of glycyrrhizin, which corresponds to 1-5 g liquorice (2% glycyrrhizin), has been estimated to be a safe dose for most healthy adults\cite{113}. Studies of DGL for peptic ulcers employed dosages ranging from 760 - 2280 mg DGL daily.

**Herb extract**\cite{114}:

\[
LD_{100}, 3.6 \text{ g/kg (mice subcutaneous injection)}
\]

Daily dose of 2 g orally to guinea pig for 45 days led to a slight increasing in body weight (not due to oedema).

**Glycyrrhizin-free extract**\cite{115}:

\[
LD_{50}, 760 \text{ mg/kg (mice, i.p.)}
\]

**Other uses:**

The powdered liquorice 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 liquorice is playing in pharmacy is in covering the acrid taste of many nauseous drugs, particularly senna, aloes, chloride of aluminium, senega, hyoscyamus, turpentine, etc\cite{116}.

It is also employed in dyeing and tobacco industries. It is used as a flavouring agent for chewing tobacco and snuff tobacco\cite{117}. 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 liquorice is used as a foam stabilizer in foam type of fire extinguisher and also used as a fertilizer for mushrooms\cite{118,119}.

**Regulatory assessment of glycyrrhiza glabra linn:**
Liquorice and liquorice derivatives, including ammoniated glycyrrhizin, are affirmed as generally recognized as Safe (GRAS) for use in foods by the U.S. FDA (21 CFR 184.1408). FDA assumes that glycyrrhizin levels in foods do not pose a health hazard, provided that these foods are not consumed in excess or by individuals who are sensitive to low levels of glycyrrhizin. Liquorice extract and its derivatives are also approved for use in some over-the-counter drugs (21 CFR 310.528; 310.544; 310.545), and liquorice is included as a GRAS ingredient in animal feeds (21 CFR 582.10; 582.20). Liquorice root, liquorice extract, liquorice extract powder and glycyrrhizin were included in the Flavor and Extract Manufacturers’ Association (FEMA) list of GRAS substances. At the 1977 meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a decision on an acceptable daily intake (ADI) for liquorice was held in abeyance. Glycyrrhizinic acid was evaluated during a more recent JECFA meeting[120]. Although a formal ADI was not established, the committee indicated that consumption of 100mg/day would be unlikely to cause adverse effects in the majority of adults and recognized that a subset of the population may be more susceptible to its physiological effects even at lower doses. Both the Council of Europe and the UK Food Additive and Contaminants Committee consider liquorice as a natural plant product intended for use in small quantities as a food additive with the intention that its consumption be limited by the glycyrrhizin levels and not to exceed those occurring naturally in foods[121]. A limit of less than 50 ppm glycyrrhizin was established by these organizations.

CONCLUSION
In summary, liquorice is used throughout the world as a traditional herbal remedy. As for the properties of liquorice and its active constituents, it is suggested that their potential roles are evaluated for their effects in the treatment of different kinds of disease such as cancer, atherosclerosis, immunodeficiency, hormone deficiency, and skin diseases. The specific aspects delineated in Ayurvedic classics still provides ample opportunity to carry on further research to understand therapeutic role of Yastimadhu.

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