Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 4, 2011

Review Article

GLYCYRRHIZA GLABRA LINN COMMONLY KNOWN AS LICORICE: A THERAPEUTIC REVIEW

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Received: 15 Jun 2011, Revised and Accepted: 20 July 2011

ABSTRACT

Plants have been one of the important sources of medicines since the beginning of human cultivation. There is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. *Glycyrrhiza glabra* used as mild laxative, anti-arthritic, antiinflammatory,anti-biotic, anti-viral, anti-ulcer, memory stimulant (being MAOinhibitor), anti-tussive, aphrodisiac, anti-mycotic, estrogenic, anti-oxidant, anti-caries agent, anti-neoplastic, anti-cholinergic, anti-diuretic, hypolipidemic agent. It is reported to contain important phytoconstituents such as glycyrrhizin, glycyrrhizinic acid, glabrin A&B, glycyrrhetol, glabrolide, isoglabrolide, isoflavones,coumarins, triterpene sterols. A review of chemical constituents present in various parts of *Glycyrrhiza glabra* and their pharmacological actions is given in the present article.

Keywords: Glycyrrhiza glabra, Phytochemical constituents, Pharmacological actions, Toxicity

INTRODUCTION

Natural products are an important source of new structures leading to drugs in all major disease areas. They represent a pool of privileged structures that are optimized by evolution to interact with proteins and other molecules[1]. The starting materials for about one-half of the medicines we use today come from natural sources. The future of higher plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is also very promising [2].Natural products have provided us some of the important life saving drugs used in the armamentarium of modern medicine. However, among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity, and 15% have been investigated phytochemically. This shows a need for planned activity guided phyto-pharmacological evaluation of herbal drugs.

This article intends to provide an overview of the chemical constituents present in various parts of Glycyrrhiza glabra and their pharmacological actions.

Glycyrrhiza glabra, also known as licorice and sweet wood, is native to the Mediterranean and certain areas of Asia. 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. Licorice or Liquorice(*Glycyrrhiza glabra*), is a perennial herb which possesses sweet taste 3 Liquorice has extensive pharmacological effects for human being. The most Common medical use liquorice is for treating upper respiratory ailments including coughs, hoarseness, sore throat and bronchitis.([4,5].) The licorice shrub is a member of the pea family and grows in subtropical climates in rich soil to a height of four or five feet. It has oval leaflets, white to purplish flower clusters, and flat pods. Below ground, the licorice plant has an extensive root system with a main taproot and numerous runners. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior(.[6]) Glycyrrhiza is derived from the ancient Greek term glykos, meaning sweet, and rhiza, meaning root. Licorice 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. Deglycyrrhizinated licorice (DGL) preparations are useful in treating various types of ulcers, while topical licorice preparations have been used to sooth and heal skin eruptions, such as psoriasis and herpetic lesions.

***Glycyrrhiza glabra Linn* (Table 1)**

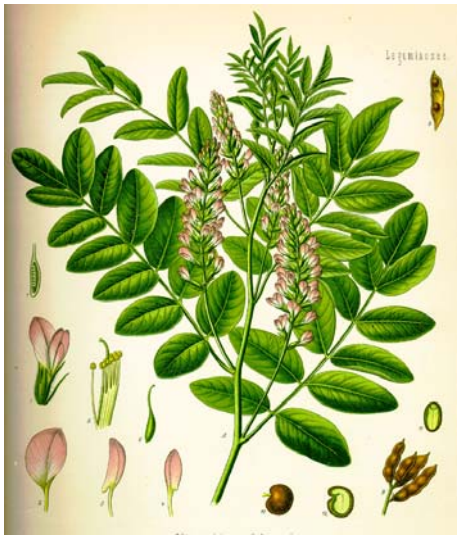

Fig. 1: Leaves and pods of *Glycyrrhiza Glabra*

Fig. 2: Leaves and flowers of *Glycyrrhiza Glabra*

Fig. 3: Leaves and Fruit of *Glycyrrhiza Glabra*

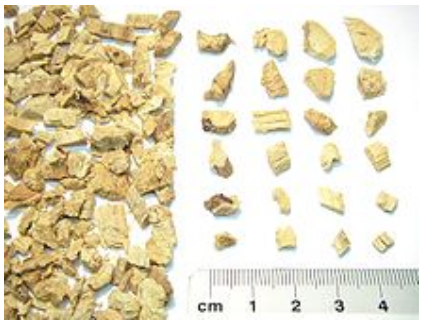

Fig. 4: Root of *Glycyrrhiza Glabra*

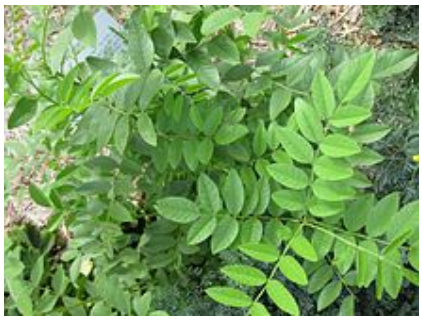

Fig. 5: Foliage of *Glycyrrhiza Glabra*

Vernacular Names

Sanskrit: Yashti-madhuh. Madhuka
Kannada: Yastimadhuka, atimaddhura
Hindi: Jothi-madh, Mulhatti
Malayalam: Iratimadhuram
Tamil: Atimaduram
Telugu: Atimadhuranu, Yashtimadhukam
English: Licorice, Liquorice, Sweet wood

Common Names

Lacrisse (German), Licorice Root, Liquorice, Reglisse (French), Regolizia (Italian), Suessholz, Sweet Licorice, Sweet Wood.

Origin

The roots are unearthed in the autumn of the fourth season. It is grown in India, Spain, Iran, Russia, China & Italy.

Morphology

Leaves stem and root: The plant is a herbaceous perennial. It is 1 to 2 m high and has a long sturdy primary taproot. The taproot is 15 cm long and subdivided into 3 to 5 subsidary roots, 1.25 m in length. There are several horizontal woody stolons which may reach 8 m. New stems are produced every year. They are sturdy, erect, branched either from the base or from further up, and are generally rough at the top. The foliage leaves are alternate, odd pinnate and 10 to 20 cm long. The leaflets are in 3 to 8 pairs.

The stipules are very small and drooping.Flower and fruit: The axillary inflorescences are upright, spike-like and 10 to 15 cm long. The individual flowers are 1 to 1.5 cm long, bluish to pale violet and short-pedicled. The calyx is short, bell shaped and glandular-haired. The tips of the calyx are longer than the tube, and are pointed lanceolate.Petals are narrow, the carina petals are not fused, and they are pointed but not beaked. The fruit is a pod, 1.5 to 2.5 cm long, and 4 to 6 mm wide. It is erect and splayed, flat with thick sutures, glabrous, somewhat reticulate-pitted, and usually has 3 to 5 brown, reniform seeds.

Geographical Distribution

Local: Bahariyah and Siwa oases

Regional: Mediterranean region and Middle East countries.

Global: Native to the Mediterranean region and parts of Asia.

It is cultivated worldwide.

Ecology

Liquorice enjoys fertile, sandy or clay soil near a river or stream where enough water is available for the plant to flourish in the wild, or under cultivation where it can be irrigated.

Phytochemical Constituents of Licorice (*Glycyrrhiza Glabra***)** [9, 10]

- amino acids
- asparagin
- bitters
- essential oil
- fat
- female hormone estrogen
- flavonoids
- glycosides
- glycyrheticic acid
- glycyrrhizin (main constituent found in the root)
- gums
- mucilage (rhizome)
- protein
- resin
- saponins
- saponoids
- starches (30%)
- sterols
- sugars (up to 14%) when mixed with water or used in cough drops,
- tannin
- volatile oil
- yellow coloring matter

Medicinal Parts Used

Root, rhizomes (powder, teas, tonics, extracts, tinctures and decoctions)

Pharmaco kinetic study [11-14]

After oral administration of licorice in humans, the main constituent, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria possessing a specialized [beta]-glucuronidase. ([11,12]) Glycyrrhetic acid is 200-1,000 times more potent an inhibitor of 11-[beta]-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. ([13]) 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. [14]

Mechanism of action [15-30]

The beneficial effects of licorice can be attributed to a number of mechanisms. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A [15] and C, [16, 17] herpes zoster, [18] HIV, [19, 20] Herpes simplex, [21, 22] and CMV. [23]

Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5-[beta]-reductase, properties responsible for the well-documented pseudoaldosterone syndrome. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid. [24]

Licorice constituents also exhibit steroid-like anti-inflammatory activity, similar to the action of hydrocortisone. This is due, in part, to inhibition of phospholipase A2 activity, an enzyme critical to numerous inflammatory processes. ([25]) In vitro research has also demonstrated glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process. [25, 26]

Licorice constituents possess significant antioxidant and hepatoprotective properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation. ([27, 28]) In vitro studies have demonstrated licorice isoflavones, hispaglabridin A and B, inhibit [Fe.sup.3]-induced mitochondrial lipid peroxidation in rat liver cells. Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion. ([29]) Licorice constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients. [30]

Pharmacology [31]

Licorice contains the glycoside, glycyrrhizin which has a similar structure and activity as the adrenal steroids. Licorice has an anti-inflammatory activity similar to cortisone and has been found useful for arthritis and allergies. In addition licorice has been used for mild Addison's disease and other adrenal insufficiencies, such as hypoglycemia. Licorice also acts like the hormone, ACTH, causing sodium retention, potassium depletion, and water retention. Excess consumption of licorice can lead to the classic symptoms of hypertension, with edema, increased blood pressure, potassium loss, and muscular weakness. The Deglycyrrhizinated form is most often used to avoid the hypertensive side effects of the glycyrrhetinic acid in whole Licorice. Licorice and DGL have a mild laxative effect and can protect the intestinal lining by increasing the production of mucus, thus alleviating heartburn and ulcers. Licorice and DGL also have a demulcent action and have been used for coughs

Biological activity

Anti bacterial activity [32]

A study was conducted to determine the antibacterial activities of Licorice root extract in ether, chloroform, acetone on bacteria using the well diffusion method. The extracts showed significant antibacterial activities against two gram positive (*Bacillus subtili and Stapphylococcus aureus*) and two gram-negative (*Escherichia coli and Pseudomonas aeruginosa*) bacteria.The study concluded as It can be used in the folk medicine at different parts of the world to treat many diseases including bacterial infections.

Anti fungal activity [33]

Glycyrrhiza glabra possess good anti fungal activity. In the course of screening for antifungal compounds from various plant material, licorice (Glycyrrhiza glabra) extracts with 80% methanol (oil-based extract of licorice; OEL) was found to have high fungicidal effect against Arthrinium sacchari M001 and Chaetomium funicola M002,and its active compound was identified as glabridin (3-(2',4'-dihydroxyphenyl)-8-dimethylpyrano(8,7-e]chroman). OEL was effective against not only filamentous fungi but also some bacteria, especially thermo-resistant bacilli such as genera of Bacillus and Alicyclobacillus. Furthermore OEL reduced microorganism

contamination in polyethyleneterephthalate (PET) bottled tea based beverages. These results indicate that OEL has potential commercial applications for the prevention of beverage and food spoilage due to micro organisms.

Anti oxidant activity [34-37]

Glycyrrhiza has also been shown to have a Significant free-radical quenching effect [34-36] glabridin is reported to be a potent antioxidant towards LDL oxidation [37]

Anti tussive activity [38]

A study was carried out to evaluate anti-tussive activity of combination of herbal drugs as formulations in sulphur dioxide (SO2)-induced cough model in mice. Albino mice of either sex, weighing 25-30 g were divided into eight groups, (n = 6). Group 1 served as normal control, group 2 mice were given distilled water, group 3 was positive control and received codeine sulphate(10 mg/kg, p.o.) and group 4, 5, 6, 7 received coded l formulations 1, 2, 3and 4 respectively at a dose of 0.3 ml/mice, orally, while group VIII was the vehicle control. Thirty minutes later, the mice were exposed to sulphur dioxide again for 45 sec. The mice were then placed in an observation chamber for counting of cough bouts, by two independent observers, for five minutes. All the formulations used showed significant antitussive activity in sulphur dioxide induced cough model. Thus, these formulations can prove to be useful for alleviating cough.glycyrrthenic acid from liquoirice is present in that formulation.

Anti ulcer activity [39, 40]

Glycyrrhizinic acid, a major component of licorice, has antiulcer effect by raising the local concentration of prostaglandins that promote mucous secretion and cell proliferation in the stomach. In vitro activity of Extractum liquiritiae (EL), glycyrrhizic acid (GL), glycyrrhetinic acid (GA) and a novel lipophilic derivative of glycyrrhetinic acid monoglucuronide (GAMG), acetylated GAMG (aGAMG), against 29 Helicobacter pylori strains. The MIC of each compound was determined by the agar dilution method, and the killing kinetics were monitored in brain heart infusion broth (approximately 10(6)-10(7) cfu/mL) at 0, 4, 24, 48, 72 and 96 h. GA was the most potent compound (MIC(50 /90), 50/100 mg/L), inhibiting 79.3% of the strains at MIC < or =50 mg/L. Clarithromycin-resistant strains were susceptible at 12.5 and 25 mg/L, and metronidazole-resistant strains at 25-50 and at 200 mg/L. The MIC distribution (mg/L) of aGAMG was < or =6.25 (29.2%), 50 (4.2%), 100-200 (12.5%) and > or =400 (54.1%). EL and GL were less active (MICs >400 mg/L). GA exhibited rapid, concentration and strain-dependent bactericidal activity. The potent in vitro activity of GA against H. pylori provides a further explanation for its beneficial effect on peptic ulcers. Its effectiveness against clarithromycin-resistant strains provides hope that it can form the basis for an alternative therapeutic agent against H. pylori.

Hepatoprotective activity [41, 42]

Glycyrrhizin shows hepatoprotective effect by preventing

changes in cell membrane permeability, inhibiting phospholipase A2 (PLA2) and increasing survival rate of hepatocytes.

Anti inflammatoy acrtivity [25-27]

Glabridin has effect in melanogenesis and inflammation by inhibiting the tyrosinase activity of melanocytes. -glycyhrritinic acid exhibits anti-inflammatory activity by inhibiting glucocorticoid metabolism.

Estrogenic activity [43]

Glycyrrhiza glabra grown in Egypt proved to be a high estrogenic plant as proved by uterine response and vaginal opening.Based upon the mouse-uterine-weight method, three doses of 25 mg. each of the alcoholic extract showed an estrogenic activity which, in terms of estradiol monobenzoate, is 1:4716980. A higher dose of 50 mg. daily for 3 days proved to possess a lower estrogenic activity when compared with estradiol monobenzoate. Using this dose, Glycyrrhiza extract was 1: 8670520 the activity of estradiol monobenzoate. This suggests the presence of antihormone factor(s) in the alcoholic extract of the plant upon uterine motility, the extracted plant manifested an inhibitory influence upon the spontaneous movement of the organ at di-estrus, estrus and pregnancy.

Anti dysliipidaemic effect

In the present study ethanolic (95%) extract of root of Glycyrrhiza glabra and its fractions were investigated for its antidyslipidaemic activity on HFD induced dyslipidaemic hamsters. Ethanolic extract and its ethyl acetate soluble, water soluble and hexane soluble fractions decreased serum level of total cholesterol by 25.9, 38.0,

39.0 and 26.3%, respectively. On the other hand ethanolic extract, ethyl acetate soluble, water soluble and hexane soluble fraction increased the serum HDL-cholesterol level by 14.8, 34.3, 27.3 and 17.2%, respectively.Ethanolic extract, ethyl acetate fraction, aqueous fraction and hexane fraction decreased triglyceride level by31. 3, 37.2, 41.2 and 28.9%, respectively. The reduction in LDL-cholesterol level by ethanolic extract, ethyl acetate soluble fraction and water soluble fraction were 43.9, 31.0, 33.4 and 24.6%, respectively. The treatment with *Glycyrrhiza glabra* root ethanolic extract and its fractions significantly brought down LDL and VLDL in the HFD fed hamsters to various degrees.

Hepatocellular Carcinoma [44]

In a retrospective study, long-term licorice administration for hepatitis C infection was effective in preventing hepatocellular carcinoma (HCC). Four hundred fifty-three patients diagnosed with hepatitis C were divided into three groups and given either licorice, in the form of SNMC at a dose of 100 mL daily for two months, or other natural treatments, such as vitamin K. The remaining group of patients was treated with a wider number of agents, including SNMC, corticosteroids, and immunosuppressive agents; as a result of the mixed medication regimen, this group was excluded from the study. After 10 years, analysis of the results showed 30/84 patients (35.7%) employing SNMC had normalized AST levels, compared with seven patients (6.4%) not treated with IV SNMC. Moreover, the 10--and 15-year appearance rate of HCC was 7 and 12 percent in the treated group compared to 12 and 25 percent in the untreated group, respectively, A summary of the literature on HCC and the use of SNMC has confirmed that IV glycyrrhizin not only decreases ALT levels but also improves liver histology and decreases incidence of hepatic cirrhosis

Dental Implications

Oral lichen planus [45]

Patients with chronic hepatitis C often experience oral lichen planus, an inflammatory disease characterized by lymphocytic hyperkeratosis of the oral mucosa. It is rarely cured and effective treatments are limited. In an open clinical trial, 17 hepatitis C-positive patients with oral lichen planus were given either routine dental care or 40 mL IV glycyrrhizin daily for one month. Among nine patients taking glycyrrhizin, six (66.7%) noted improved clinical symptoms, such as decreased redness, fewer white papules, and less erosion of the mucosa. In the non-glycyrrhizin group of eight patients, only one (14.3%) reported any improvement.

Aphthous ulcer [46, 47]

In a double-blind, placebo-controlled trial, 24 patients with recurrent aphthous ulcers were randomly allocated to consume 2 g glycyrrhizin (carbenoxolone sodium) in 30 mL of warm water or a placebo three times daily following meals for four weeks. In contrast to the placebo group, the use of the oral licorice mouthwash significantly reduced the average number of ulcers per day, pain scores, and the development of new ulcers. ([46]) In a study of 20 patients instructed to use a DGL mouthwash four times daily, 15 experienced 50-75 percent clinical improvement after only one day, with complete healing of canker sores after three days. [47]

Other Therapeutic Considerations [48-56]

Armanini et al investigated the effect of licorice on serum testosterone in nine healthy women, ages 22-26, using the same licorice preparation as above, and found total serum testosterone decreased from 27.8 ([or -] 8.2) to 19.0 (or -] 9.4) ng/dL after one

month, and further decreased to 17.5 ([or -] 6.4) ng/dL after the second month of therapy. This is likely due to inhibition of 17-hydroxysteroid dehydrogenase, indicating licorice may be of benefit in treating women with hirsutism and polycystic ovary syndrome. [48]

Studies also show licorice constituents to be effective in the treatment of eczema, [49] melasma, [50] eosinophilic peritonitis. [51] postural hypotension, [52] erosive gastritis, [53] and as anti-malarial [54] and anti-Leishmanial agents. [55] More recently, animal studies indicate aqueous extracts of G. glabra may have memory-enhancing activity via reversal of chemically-induced amnesia, as measured by maze and passive avoidance testing in mice. [56]

Drug-Botanical Interactions [57-59]

There is an increased likelihood of cardiac arrhythmias, particularly in individuals with ischemic heart disease, when licorice is used in conjunction with digoxin. [57]

Estrogen-based oral contraceptives may enhance the mineralocorticoid side effects of licorice in susceptible individuals. This may be due in part to estrogens reacting with mineralocorticoid receptors or inhibition of 11 [beta]-hydroxysteroid dehydrogenase. [58]

Hypokalemia, commonly associated with metabolic acidosis, may co-present with essential benign hypertension in patients using diuretics and licorice simultaneously. [59]

Side Effects and Toxicity [60- 62]

One of the most commonly reported side effects with licorice supplementation is elevated blood pressure. This is thought to be due to the effect of licorice on the renin-angiotensin-aldosterone system. It is suggested licorice saponins are capable of potentiating aldosterone action while binding to mineralocorticoid receptors in the kidneys. The phenomenon is known as "pseudoaldosteronism." In addition to hypertension, patients may experience hypokalemia (potassium loss) and sodium retention, resulting in edema. All symptoms usually disappear with discontinuation of therapy. Many studies report no side effects during the course of treatment. ([60], [61]) Generally, the onset and severity of symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility. Patients with delayed gastrointestinal transit time may be more susceptible to these side effects, due to enterohepatic cycling and reabsorption of licorice metabolites. The amount of licorice ingested daily by patients with mineralocorticoid excess syndromes appears to vary over a wide range, from as little as 1.5 g daily to as much as 250 g daily. ([62])

CONCLUSION

Glycyrrhiza glabra (GG) (licorice, Fabaceae/Papilionaceae) is a plant with a rich ethnobotanical history. The roots are used as a folk medicine both in Europe and in Eastern countries. The main components are the triterpene saponins, glycyrrhizin and glycyrrhetic acid, which are believed to be partly responsible for anti-ulcer, anti-inflammatory, anti-diuretic, antiepileptic anti-allergic and antioxidant properties of the plant as well as their ability to “fight” low blood pressure . Furthermore, GG extracts have been shown to possess antidepressant-like, memory-enhancing activities and produce antithrombotic effects.

On the other hand, the root extracts are reported to exhibit anti androgenic and antitumor activitiesand radio-protective effects. Besides, the isolates from GG roots viz. glabridin (an isoflavan) and isoliquiritigenin (a flavonoid), are known to be pharmacologically active compounds. Glabridin is reported to be a potent antioxidant towards LDL oxidation ,whereas isoliquiritigenin is known to exert vasore-laxant effect, anti-platelet, anti-viral, estrogenic activities and has the protective potential against cerebral ischemic injury .Antihyperlipilaemic and antihypertriglyceridaemic properties of GG root have also been reported *Glycyrhhiza* flavonoids provide protection to hepatocytes exposed to carbon tetrachloride, and galactosamine.

The researchers pointed to the antilipid peroxidation effect of *Glycyrrhiza* as the central mechanism contributing to its protective action against carbon tetrachloride-induced hepatotoxicity. The pharmacological and clinical studies reported in the present review confirm the therapeutic value of *Glycyrrhiza glabra* Presence of chemical compounds indicates that the plant could serve as “lead” for development of novel agents in disorders in the coming years. In this regard, further studies need to be carried out to explore *Glycyrrhiza glabra* Linn for its potential in preventing and treating diseases.

ACKNOWLEDGEMENT

The author is also thankful to Dr.N.DJayakumar , Principal,saveetha Dental college &Hospitals,Chennai.&Dr.M.Nallanayagam,H.O.D Of Pharmacology,Saveetha Dental college & Hospitals,Chennai-77 For their kind support.More over The authors are also grateful to the authors/editors of all those articles, journals and books from where the matter for this article has been reviewed and discussed.

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