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Root/Stem Extracts of *Glycyrrhiza glabra*; As a Medicinal Plant Against Disease Forming Microorganisms

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Abstract

Nature is one of the major sources of medicines since the beginning of human civilization. Different counties around the globe have been used different plant materials to overcome varieties of ailments from simple cough to hepatitis to more complexes like SARS and most recently Covid 19. This review is an effort to emphasis the phytochemical and chemical constituents of *G. glabra* and their mechanisms against disease forming microorganisms. This traditional plant which is well known in Sri Lanka as "Welmi" is belongs to family Leguminosae/ Fabaceae. Chemical constituents of *G. glabra* like isoliquiritine, isoflavones, glycyrrhetic acid, saponin and their derivatives have been examined for their pharmacological activities. Most critical chemical compounds which isolated from the root/stem extract of the *G. glabra* are Glycyrrhizin and Glycyrrhetic acid. Glycyrrhizin is a prominent triterpenoid contain in *Glycyrrhiza glabra* which is responsible for the sweet taste of its roots. Glycyrrhizin act as anti-viral compound in two ways. It is able to inhibit the replication process of some RNA viruses such as SARS like corona type virus. Another process is acting as an immunostimulator. It has been used to treat patients suffering from chronic hepatitis C virus and HIV-1 patients owing to its capability of stimulating endogenous viral defense mechanisms.

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Another important phytochemical called Glycyrrhizic acid is a natural saponin composed of hydrophilic part, hydrophobic fragment, two molecules of glucuronic acid and glycyrrhetic acid. Apart from that some other isolated compounds like hispaglabridin B, 40-methylglabridin, glabridin, gabrin, 3-hydroxyglabrol and glabrene exhibits serious anti-bacterial actions. In addition, plant extract's chemicals have antidiabetic, antibiotic, antiviral, anti-inflammatory, anticancer, antiulcer and anti-demulcent activities as well. Finally, the phytochemicals present in *G. glabra* will perform a promising role in the development of new herbal drugs against disease forming virus and bacteria species as well as their derivatives are being generated to evaluate their pharmacological purposes for future drug use.

Keywords: pharmacology; phytochemical; medicinal plant; Glycyrrhiza glabra.

1. Introduction

Glycyrrhiza glabra has long been well-known in pharmacy. It was considered first-class drugs in the old Chinese pharmacy and the rejuvenating quality was attributed to it when ingested for long periods. Licorice was widely used in ancient Egypt, Greece and Rome. Theophrastus had alluded to this. The use from that time on, until now, proves the effectiveness. Trade content comes from wild plants and "semi-wild" plants grown in the former Soviet Union, Turkey, Iran, China, India, Pakistan, Afghanistan, Syria, Italy and Spain [1]. Crude plant-based drugs in Pakistan cost around Rs. 120 million per year. That is a good indicator of medicinal plants ' potential economic value. Aromatic and medicinal plants have regional and international markets of significant scale [2]. The Egyptian, Chinese, Greek, Indian, and Roman cultures also used the dried rhizome and root as expectorant and carminative. The Materia Medica referred to as bronchitis, emollient, emmenagogue, demulcent expectorant, diuretic, hemoptysis, laryngitis, laxative etc. Sore throat, soreness, cough, influenza, cold, bronchodilator, opthalmia, anti-syphilitic is beneficial [3]. The ethno botanical studies regarding the *G. glabra* also reported. The white and sweet yellowish decoction that was produced and used as purgative and for cough and this was sometimes used as a purgative for the pigs, goats and cows. It increased the production of milk in both cows and goats. *G. glabra* uses as a cough suppressant, throat dryness and as a tonic as well [4]. *G. glabra* plant can be used orally for gastric, duodenal, and esophageal ulceration, inflammation, cathartics, mouth ulcer, spasmolytic, anti-tussive, demulcent, expectorant, and components making it a suitable herb for respiratory disorders [5]. Apart from that Licorice helps improve memory, plays an antidepressant role and reduces cholesterol levels in the blood [6]. According to World Health Organization 80% of the world population depends upon indigenous medicinal plant remedies. The medicinal value of these plants lies in some chemical constituents that produce a definite physiological action on the human body. The most important of these bioactive substances of plants are saponin, flavonoids, triterpenoid, tannins, alkaloids, and phenolic compounds. *G. glabra* is native to Europe and Asia. The plant is classified as a weed in very ancient time. The early Egyptians frequently utilized *G. glabra* root. They used it in tea as a cure-all concoction. Later plant was imported to China where it became an important herb in Chinese medicinal tradition. In China this plant is known as gan-cao which means “sweet herb” [7]. *G. glabra*, commonly known as Licorice is one of the important medicinal plant. *Glycyrrhiza* is derived from the ancient Greek term glykos, meaning sweet, and rhiza, meaning root. *Glycyrrhiza glabra* is commonly known as, “Welmi” in Sri Lanka, “Mulaithi” in north India, “Licorice, liquorices, and sweet wood” in England, “Aslussiesa” in Arab, “Ausareha mahaka” in Persia,

"Boisdoux" in France and "Sussholz" in Germany [8, 9].

1.1 Taxonomical hierarchy

Kingdom: Plantae

Division: Angiospermae

Class: Dicotyledoneae

Order: Rosales

Family: Leguminosae

Genus: *Glycyrrhiza*

Species: *glabra Linn*

G. glabra is herbaceous perennial, growing to 1 m in height, with pinnate leaves about 7–15 cm long, with 9–17 leaflets. Usually flowers are of 0.8–1.2 cm long, purple to pale whitish blue color, and it is produced in a loose inflorescence. The fruit is an oblong pod, length of 2–3 cm, consists of several numbers of seeds [10]. The *Glycyrrhiza* shrub is a member of the pea family and grows in subtropical climates in rich soil. Below ground, the *G. glabra* plant has an extensive root system with a main taproot and numerous runners. The main taproot which is soft and fibrous has a bright yellow interior color and harvested for medicinal use [11]. Glycyrrhizin is the major bioactive compound in the *Glycyrrhiza* plant root which possesses a wide range of pharmacological properties and it is commonly used worldwide as a natural sweetener. Because of this it gives an economic value to the plant and biosynthesis of glycyrrhizin has received considerable attention. Glycyrrhizin is most likely derived from the triterpene β-amyrin, an initial product of the cyclisation of 2, 3 oxidosqualene. The subsequent steps in glycyrrhizin biosynthesis are believed to involve a series of oxidative reactions at the C-11 and C-30 positions, followed by glycosyl transfers to the C-3 hydroxyl group. Although glycyrrhizin is considered much sweeter than sucrose, the associated flavor limits its commercial value as a sweetener. Because glycyrrhizin also gives an undesirable brownish color to foods, and the sweetness is lost in acidic solutions, as occurs in most beverages, glycyrrhizin remains of little value to the food and beverage industries. *G. glabra* is recommended to treat respiratory problems by taking it as an oral supplement. It can help the body to produce healthy mucus. Increasing phlegm production may seem counterintuitive to a healthy bronchial system. But the production of clean, healthy phlegm keeps the respiratory system functioning without old, sticky mucus clogging it [12]. Main intension of this review article is to investigate the phytochemical and pharmacological importance of *G. glabra* and Properties such as antimicrobial, antiviral, anti-carcinogenic, antidiabetic etc. It is important to study the chemistry behind these properties of the constituents of this plant as it can be useful as remedy for the future drug production.

2. Methodology

Literature searches were done using the words "*Glycyrrhiza glabra*" or Licorice in PubMed, PMC and in science direct. Furthermore "*Glycyrrhiza glabra*" and "availability of *Glycyrrhiza glabra*" was searched in some popular search engines like Google, Google Scholar, to gather secondary data and to find items that are currently available to purchase in the world. All material, regardless of sources, was reviewed, and the review frame work was developed to represent the information available.

3. Results and Discussion

3.1 Photochemistry

G. glabra consists of numerous components that can be extracted from its roots and stem which are water soluble as well as biological active [13]. Some of those compounds include pectin, simple sugars, saponins, flavonoids, polysaccharides, triterpenes, essential oil, fat, female hormone estrogen, gum, resins, starches, sterols, volatile oils, glycosides, asparagins, amino acids and various other substances [14]. Glycyrrhizin (Figure 1) is a prominent triterpenoid present in *G. glabra* which is responsible for the sweet taste of its roots.

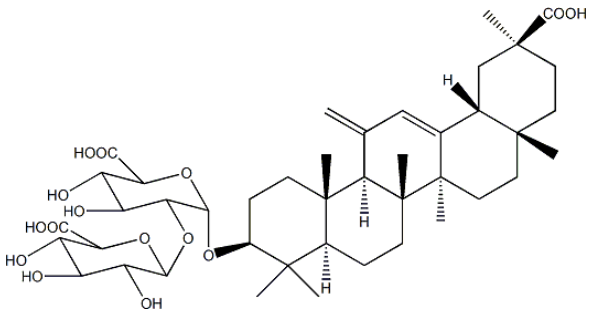

Figure 1: Chemical structure of the Glycyrrhizin exists as prominent triterpenoid present in *G. glabra* root/ stem extract.

This compound consists of potassium calcium-magnesium salts that vary between 2-25% ranges. Flavonoid content which includes a chalcone, liquiritin, and isoliquiritin gives the yellow color to the plant [15]. Glycyrrhizic acid is a natural saponin composed of hydrophilic part, hydrophobic fragment, two molecules of glucuronic acid and glycyrrhetic acid (Figure 2) [16]. The glabridin and hispaglabridins A and B are flavones that have significant antioxidant activity [17] and both glabridin and glabrene possess estrogen-like activity [18].

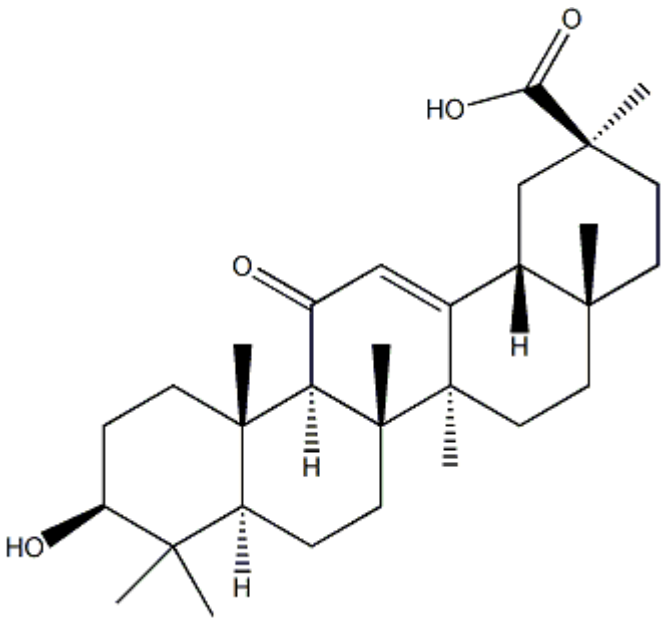

Figure 2: Chemical structure of the Glycyrrhizic acid is a natural saponin composed in *G. glabra* root/ stem extract.

3.2 Pharmacological activity

3.2.1 Antitussive and expectorant

G. glabra powder and its extracts were found to be helpful in curing ailments like cough, sore throat and bronchial catarrh. Due to the presence of glycyrrhizin and demulcent, antitussive and expectorant loosing activities can be seen. Therefore, it helps to expel congestion in the respiratory tract as it accelerates tracheal mucus secretion [19]. According to recent findings methanolic extract of *G. glabra* contain liquiritin apioside which has the ability to inhibit capsaicin- induced cough [20].

3.2.2 Antiviral

By preventing the binding of virus cell, Glycyrrhizin which is common in *G. glabra* shows antiviral activity. Glycyrrhizin is more effective in controlling viral replication and it can be used as a prophylactic measure and also it has been used to inhibit the replication of Severe Acute Respiratory Syndrome (SARS) associated coronavirus [21]. Recently antiviral activities of ribavirin, 6-azauridine, pyraziofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of SARS virus, i.e., FFM-1 and FFM-2 were evaluated and also previously it has been used to treat patients suffering from chronic Hepatitis C virus and HIV-1 patients [22, 23]. According to the studies of Utsunomiya and his colleagues 1997 it suggest that anti-viral activity of glycyrrhizin is basically due to the stimulation of β-interferon which is produced by T- cells. In this study BALB/c mice were selected who are infected with Influenza virus A2 (H2N2). They were unable to resist and survive 10 times the lethal dose (LD50) of virus. When they treated with 10 mg glycyrrhizin/kg in different time

periods such as, on the day prior to, the day after, and on the fourth day after infection complete survival was able to observe. And also it confirmed 70% of infected mice were survived with 50 times the viral lethal dose. Accordingly, to this study anti-viral mechanism of glycyrrhizin could be indirect and possibly stimulating endogenous viral defense mechanisms [24].

3.2.3 Antimicrobial

Currently one of the major problems is multidrug resistant microorganism that spread rapidly and also the chronic conditions that caused by them. *Glycyrrhiza* Linn and its species are recognized to have selective antimicrobial activity due to isoprenoid phenols present in it. Most recent studies have shown that there are significant antibacterial properties against gram positive and gram negative pathogens in hydromethanolic extracts of *G. glabra* [25]. Compounds such as hispaglabridin B, 40-methylglabridin, glabridin, gabrin, 3-hydroxyglabrol and glabrene which were isolated from *G. glabra* have shown *in vitro* antimicrobial properties. Specially chloroform, ethanol, methanol and diethyl ether extracts of *G. glabra* have been tested against number of species like *Salmonella typhimurium, Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtillus* by using agar well diffusion assay. Results obtained for *Pseudomonas aeruginosa* was really interesting because it was not inhibited by the antibiotics used but plant extracts tested was significantly inhibit the growth of *Pseudomonas aeruginosa* [26, 27]. Also *G. glabra* has used to treat cysts due to parasitic infestations of skin, pruritis and atopic dermatitis [28].

3.2.4 Antioxidant and Anti-inflammatory

Hydromethanolic root extract of *G. glabra* which consists of plenty of polyphenolic components can exhibit antioxidant activity and chemo preventive properties [28]. Retrochalcones is responsible for mitochondrial lipid peroxidation. This helps to prevent red blood corpuscles from oxidative hemolysis. Licochalcones B and D, Isoflavones such as glabridin and hispaglabridin A, 30 hydroxy-4- O-methylglabridin, hispaglabridin B isoliquiritigenin, and paratocarpin B also exhibit antioxidant activity. Apart from them current research has shown α-dihydro3, 5, 4-trihydroxy-4, 5-diiodopentenylstilbene which is a derivative of dehydrostilbene have the free radical scavenging activity [29, 30]. Due the metabolism of glycyrrhizin within the gut, it has the potential to act as hydrocortisone and other corticosteroid hormones [31].

3.2.5 Anticarcinogenic and Antimutagenic Activity

There is lot of *in vitro* and *in vivo* studies regarding the anticancer properties of several component of *G. glabra.* Glycyrrhetic acid can trigger proapoptotic pathway by inducing mitochondrial permeability transition. This feature can be used to induce the apoptosis of tumor cells [31, 32]. The *G. glabra* extract can arrest G2/M cycle in tumor cells and it induces the Bcl2 phosphorylation. Induction of the apoptosis in human monoblastic leukemia U937 cells can be enhancing by methanol: acetone (70:30) extraction of *G. glabra.* Basic compound which is responsible for this property is licocoumarone which is an antioxidant which shows antimicrobial activity as well [33]. A research was conducted by using albino mice stated that hydromethanolic extract of *G. glabra* root have ant mutagenic potential by aberration of chromosome in bone marrow cells and by inhibiting

micronucleus formation [34] It was found in TPA(12-O-tetradecanoylphorbal-13-acetate) treated cells, *G. glabra* extract can inhibit TPA inducing AP-1(activator protein-1) activity and also Glycyrrhizin can induce AP-1 activity in untreated cells. This mechanism can be used in the future for the development of chemo protective agents [35]. Compared to most common antitumor agents such as isoliquiritigenin and licochalcone A, compounds such as licochalcone E which can be extract from *G. glabra*, exhibit most potent cytotoxic effect [36].

3.2.6 Antiulcer Activity

As a result of the ability of *G. glabra* extract to inhibit delta13-prostaglandin reductase and 15-hydroxyprostaglandin dehydrogenase, *G. glabra* extract exhibit anti-ulcer effect. Conversion of prostaglandins E2 and F2alfa into inactive component of 15-ketoprostaglandins is done by 15-hydroxyprostaglandin dehydrogenase. Inactive an l3-prostaglandin is metabolized to 13, 14-dihydro, 15-ketoprostaglandin by Delta13-prostaglandin reductase. *G. glabra* extract has been used as an antiulcer agent from very early days of 1970. Glycyrrhizin and deglycyrrhizinated in *G. glabra* extract are well known as a treatment for ulcers. Antiulcer genic effect can be exhibit by Carbenoxolone which is present in *G. glabra* extract by inhibiting secretion of gastrin [29] and also it can raise the prostaglandin concentration in the digestive system to induce mucus secretion in the stomach [30].

3.2.7 Antidiabetic

Diabetes type 2 is a growing health problem in the world. Peroxisome proliferation activated receptors (PPAR's) are transcriptional factors that regulate the genes which are responsible for glucose and lipid metabolism. There are three types of such PPAR receptors as PPAR-α, PPAR-γ, and PPAR-δ. Among them PPAR-γ plays a major role in targeting insulin sensitizing drugs. With the help of several phenolic compounds like glycycoumarin, glycyrin, glyasperin D, dehydroglyasperin, glyasperin B and isolglycyrol ethyl acetate extract of *G. glabra* exhibit significant binding ability to PPAR-γ. This significant PPAR-γ ligand binding ability helps to reduce the blood glucose level. This has been tested in knockout diabetic mice. Since *G. glabra* extract has been used as artificial sweetener in the past this finding is more significant as it could help in insulin resistance syndrome which is common in modern world [37].

3.2.8 Immunomodulatory Activity

G. glabra roots consist of Glycyrrhizic acid has the ability to inactivate virus particles and inhibit the virus growth as a potent source of immunomodulatory. A species- specific disease known as the Swine flu is a respiratory disease of pigs with low mortality (1-4%). Outbreak of this disease takes place once in a year in between in autumn and winter mostly in temperate zone of the world. Influenza A H1N1 virus is one such virus which had the ability to cross species barrier and infect to human from pigs. This virus was spread throughout the world rapidly among humans. Fractions of polysaccharide extracted from *G. glabra* stimulate the microphages and assist and elevate the immune stimulations [38]. A peptide known as N-acetylmuramoyl is glycyrrhizin analogue which have the potential in *in vitro* immune-stimulation and it can mediate the virus by

restricting the virus replication. This was tested and confirmed in animal studies. Even in plants which contain Glycyrrhizic acid, can protect its self from virus due to the action of Glycyrrhizic acid as it inhibits the virus growth and inactivate virus particles as a source of immunomodulatory [39].

3.2.9 Antiatherogenic effects

G. glabra extract can possess antiatherogenic effects and can inhibit the oxidation of Low Density Lipoproteins. These results have been tested *in vitro* and *in vivo* studies. By administrating small amount of *G. glabra* root alcoholic extract (0.1 g/day for 1 month) which is free from glycyrrhizin can act as a potent antioxidant in atherosclerotic apolipoprotein E-deficient mice and hypercholesterolemia patients [40].

4. Conclusion

G. glabra is a medicinal herb which has numerous Ayurveda medicinal values. Most significant phytochemicals have been identified in *G. glabra* root and stem extracts. Glycyrrhizin is a prominent triterpenoid present in *G. glabra* which exhibits anti-viral activities against RNA based viral species such as SARS virus. Therefore, anti-viral mechanisms of Glycyrrhizin could be indirect and possibly stimulating endogenous viral defense mechanisms. Glycyrrhizin also can be considered as immunostimulant. It is described anti-viral activity of glycyrrhizin is basically due to the stimulation of β-interferon which is produced by T- cells. Even though root and stem extract of the *G. glabra* showed different pharmacological activities more research should be focused on mitigation of viral contaminations based on Glycyrrhizin chemistry against RNA based viruses. Further Due to the chemical composition of *G. glabra* not only in drug industry but also this will be a strong beneficial factor in food industry as well.

5. Limitations of the Study

Lack of researches on ethnomedicinal properties of the plant was observed. The research study has been limited to antibacterial, antifungal and antiviral effects of root extract of *G. glabra.*

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