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Research Article

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LICORICE - MULETHI (*Glycyrrhiza glabra L.*) Medication in Human Health

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Abstract

Glycyrrhizin is responsible for demulcent action of liquorice. Liquiritin apioside, an active compound present in the methanolic extract of liquorice which inhibits capsaicin induced cough. Ethanolic extract of G. glabrawas found to be responsible for inhibition of 35.62% SO2gas induced cough. High content of phenolic component in ethanolic extract of Liquorice (Glycyrrhiza glabra L) is responsible for its powerful antioxidant activity by means of significant free radical scavenging, hydrogen donating, metal ion chelating, and anti-lipid peroxidative and reducing abilities. The liquorice extract can be efficiently used to formulate cosmetic products for the protection of skin and hair against oxidative damage. Liquiritin present in liquorice extract disperse melanin, thereby inducing skin lightening. The antioxidants present in extract contribute to decrease in skin melanin content. The inhibition of tyrosinase enzyme and reduction in enzyme activity is caused due to modification of action site of the enzyme. Due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity. Ethanolic extract of Glycyrrhiza glabra is showed the improvement in the viscoelastic and hydration properties of the skin. Synergistic effect of UV protective, antioxidant and anti-inflammatory properties of liquorice extract might be responsible for giving beneficial effects on skin.

Antiviral activities of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid and glycyrrhizin proved that glycyrrhizin was the most efficient in controlling viral replication. Thus, it can be a good prophylactic measure. Glycyrrihizic acid down-regulates the expression of latency associated nuclear antigen (LANA) in B lymphocytes. This causes natural cell death (apoptosis) of the KSHV virus. Glabridin was found to be the active compound giving anti-fungal activity. In traditional medicine, liquorice has been recommended as a prophylactic agent for gastric and duodenal ulcers. It is employed in dyspepsia as an anti-inflammatory agent during allergenic reactions. It is used as a contraceptive, laxative, anti-asthmatic, emmenagogue, galactagogue, and antiviral agent in folk therapy. Glycyrrhiza roots are useful for treating cough because of its demulcent and expectorant property. It is also effective against anemia, gout, sore throat, tonsillitis, flatulence, sexual debility, hyperdypsia, fever, skin diseases, and swellings. Liquorice is effectively used in acidity, leucorrhoea, bleeding, jaundice, hiccough, hoarseness, bronchitis, vitiated conditions of Vata dosha, gastralgia, diarrhea, fever with delirium and anuria. Effectiveness of glycyrrhizin in the treatment of chronic hepatitis and liver cirrhosis is proved.

Phytochemical analysis of Glycyrrhiza glabra root extract showed that it contains saponin triterpenes (glycyrrhizin, glycyrrhetinic acid and liquirtic acid), flavonoids (liquirtin, isoflavonoids and formononetin) and other constituents such as coumarins, sugars, amino acids, tannins, starch, choline, phytosterols and bitter principles. Glycyrrhizin is habitually used as a vehicle in orally administered products, where it inhibits the growth of some bacteria, as well as dental plaque formation. In regards to its antibacterial action, inhibitory effects for licorice aqueous and ethanolic extracts on Staphylococcus aureus and Streptococcus pyogenes cultures, the first one showing the strongest inhibition with 10-15mm halo diameters.

1. Introduction

Glycyrrhiza glabra Linn is one of the most extensively used medicinal herb from the ancient medical history of Ayurveda. It is also used as a flavoring herb. The word Glycyrrhiza is derived from the Greek term glykos (meaning sweet) and rhiza (meaning root). Glycyrrhiza glabra Linn, commonly known as 'liquorice' and 'sweet wood' belongs to Leguminosae family. Vernacular names for liquorice are Jeshthamadh (Marathi), Jothimadh (Hindi), Yashtimadhu, Madhuka (Sanskrit), Jashtimadhu, Jaishbomodhu (Bengali), Atimadhuram, Yashtimadhukam (Telugu), Jethimadhu (Gujarati) and Atimadhuram (Tamil) [1,2].

In traditional medicine, liquorice has been recommended as a prophylactic agent for gastric and duodenal ulcers. It is employed in dyspepsia as an anti-inflammatory agent during allergenic reactions [3]. It is used as a contraceptive, laxative, anti-asthmatic, emmenagogue, galactagogue, and antiviral agent in folk therapy [4]. Glycyrrhiza roots are useful for treating cough because of its demulcent and expectorant property [5]. It is also effective against anemia, gout, sore throat, tonsillitis, flatulence, sexual debility, hyperdypsia, fever, skin diseases, and swellings. Liquorice is effectively used in acidity, leucorrhoea, bleeding, jaundice, hiccough, hoarseness, bronchitis, vitiated conditions of Vata dosha, gastralgia, diarrhea, fever with delirium and anuria [6,7]. Effectiveness of glycyrrhizin in the treatment of chronic hepatitis and liver cirrhosis is proved [8].

It is a saponin compound (60 times sweeter than cane sugar) comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone) conjugated to a disaccharide of glucuronic acid. Glycyrrhizin and glycyrrhetic acid can exist in the 18αand 18βstereoisomer forms [9]. Glycyrrhizin is considered to be the most common of the Asiatic folk medicines to be used as an anti-inflammatory agent on neutrophil functions including ROS (reactive oxygen species) generation [10].

The ammoniated salt of glycyrrhizin is manufactured from liquorice extracts. The specifications for this salt form have been established in the Food Chemicals Codex. This salt is used as a food flavoring agent [9,11]. An analog of glycyrrhetic acid, Carbenoxolone (18-βglycyrrhetinic acid hydrogen succinate) is useful in the treatment of alimentary tract ulcerative conditions like peptic ulcers [12]. Flavonoid rich fractions include liquirtin, isoliquertin, liquiritigenin and rhamnoliquirilin. Five new flavonoids- glucoliquiritin apioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1-methoxyphaseolin are isolated from dried roots [13]. Many volatile components are present in roots e.g. geraniol, pentanol, hexanol, terpinen-4-ol, α-terpineol. Isolation of various compounds like propionic acid, benzoic acid, furfuraldehyde, 2, 3 butanediol, furfuryl formate, maltol, 1-methyl-2-formylpyrrole, trimethylpyrazine etc from the essential oil is also reported [14]. The Indian variety of liquorice roots show 2-methyliso – flavones and C liquocoumarin, 6 - acetyl-5, hydroxy-4- methylcoumarin (unusual coumarin). Asparagine is also present [15].

Glycyrrhizin is responsible for demulcent action of liquorice. Liquiritin apioside, an active compound present in the methanolic extract of liquorice which inhibits capsaicin induced cough [16]. Ethanolic extract of G. glabrawas found to be responsible for inhibition of 35.62% SO2gas induced cough in experimental animals (mice) [17]. High content of phenolic component in ethanolic extract of Liquorice (Glycyrrhiza glabra L) is responsible for its powerful antioxidant activity by means of significant free radical scavenging, hydrogen-donating, metal ion chelating, and anti-lipid peroxidative and reducing abilities [18]. The liquorice extract can be efficiently used to formulate cosmetic products for the protection of skin and hair against oxidative damage [19]. It is derived from the sweet root of various species of Glycyrrhiza; however, the cultivation and harvesting practices modify the composition of various biologically important components of the Glycyrrhiza plant [20].

Liquiritin present in liquorice extract disperse melanin, thereby inducing skin lightening [21]. Also, the antioxidants present in extract may contribute to decrease in skin melanin content [22]. The inhibition of tyrosinase enzyme and reduction in enzyme activity is caused due to modification of action site of the enzyme. Due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity [23]. Ethanolic extract of Glycyrrhiza glabra is reported to show improvement in the viscoelastic and hydration properties of the skin. Synergistic effect of UV protective, antioxidant and anti-inflammatory properties of liquorice extract might be responsible for giving beneficial effects on skin [24]. This study on antiviral activities of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid and glycyrrhizin proved that glycyrrhizin was the most efficient in controlling viral replication. Thus, it can be a good prophylactic measure [25,26].

Glycyrrihizic acid down-regulates the expression of latency associated nuclear antigen (LANA) in B lymphocytes. This causes natural cell death (apoptosis) of the KSHV virus [27]. Glabridin was found to be the active compound giving anti-fungal activity [28]. Because of the presence of secondary metabolites such as; saponins, alkaloids, flavonoids in hydro-methanolic root extract of Glycyrrhiza glabra, the extract exhibits potent anti-bacterial activity [29]. In vivo studies against P. yoelii in mice with oral doses of 1000 mg kg-1 have shown to eradicate malarial parasite completely. Also, no toxicity was observed [30].

The study was conducted for 7 successive days in separate groups of animals. Significant improvement in learning and memory of mice was reported at the dose of 150 mg/kg. But, the exact mechanism of action is unknown and needs further investigation [31]. Alteration of membrane fluidity by the glycyrrhizin or inhibition of CCl4-induced membrane lipid peroxidation might be responsible for the activity. 18β-glycyrrhetic acid (an aglycone of glycyrrhizic acid)

shows hepatoprotective activity by inhibiting both free radical generation and lipid peroxidation [32]. Glycyrrhizin is useful in treating acetaminophen-induced hepatotoxicity. Liquorice extract is proved to show hepatoprotective activity against diclofenac – induced hepatotoxicity in rats [33].

Glycyrrhizin causes inhibition in thrombin induced platelet aggregation. But there was no effect of glycyrrhizin on Platelet Aggregating Factor (PAF) and Collagen induced agglutination [34].

Thus, after efficacy and safety analysis, it has been be concluded that, liquorice has a significant hair growth activity and it can be safely used in herbal formulations in treatment of various types of Alopecia [35]. Glycyrrhiza glabra Linn. commonly known as liquorice and sweet wood in english, Jothi-madh, Mulethi in Hindi, Yashti-madhuh, Madhuka in Sanskrit, Jashtimadhu, Jaishbomodhu in Bengali, Atimadhuranu, Yashtimadhukam in Telugu, Jethimadhu in Gujarati and Atimaduram in Tamil [2]. It is cultivated for its rhizomes (underground stems) that contain the compound glycyrrhizin, which is 50 times more sweetener than sugar. It is cultivated in the Mediterranean basin of Africa, in southern Europe, and in India, widely cultivated in Punjab and sub Himalaya tracts, Baramulla, Srinagar, Jammu, Dehradun, Delhi and South India [36,37].

The contents of these saponins and flavonoids may vary significantly due to different plant species and geographic sources [38]. Polysaccharides, pectins, Steroid hormones, sacharose, glucose, amino acids, mineral salts, Triterpenoid saponins Glycyrrhizin (2-15%) also known as Glycyrrhizic acid, present in the form of calcium and potassium salts. Glycyrrhetinic acid (18-beta-glycyrrhetinic acid, GA), bitter principle (glycymarin), Steroid hormone, Resinous oil, starch, glucose, asparagin, manitol, atropine, choline, betaine, progesterone, steroids, tannins etc [39-41].

It has also been used as antiallergic, demulcent, emollient, fungicide, respiratory, gastrointestinal, cardiovascular, eye, and skin disorders and for their antiviral effects [36,38]. The root extract produces mild estrogenic effects, and it has proven to be useful for some in treating symptoms of menopause, relieving menstrual cramps and regulating menstruation. the roots and rhizomes of Glycyrrhiza glabra has been in clinical use for centuries to treat liver diseases and is a major component of polyherbal formulations for the cure of hepatotoxicity, antiallergic, demulcent, emollient, fungicide, peptic ulcer [36,42].

Glycyrrhizin and glycyrrhizic acid have been shown to inhibit gro wth and cytopathology of numerous RNA and DNA viruses, a preliminary report which covers the isolation of licopyranocoumari and ant-HIV activity of licorice phenolics, inhibit the HIV-induced giant cell formation for molt-4 cells (, a major component of Glycyrrhiza, which exhibited higher anti -UV activity (SI=20.6) [43]. The roots and rhizomes of Glycyrrhiza glabra is an efficient brain tonic it increases the circulation into the CNS system and balance the sugar levels in the blood [44]. Aqueous extract of G. glabra were administered for 7 successive days in separate groups and observed in mice [45]. The protective effect of liquorice extract may be attributed to its antioxidant property by virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function thereby enhancing the memory [31]. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters and served as the exteroceptive behavioral models [46]. The roots and rhizomes of Glycyrrhiza glabra is an efficient brain tonic it increases the circulation into the CNS system and balance the sugar levels in the blood significant action an memory enhancing activity as dementia disorder [31,44].

Antioxidant may offer resistance against the oxidative stress by scavenging free radicals, inhibiting lipid peroxidation and by many other mechanisms and thus prevent disease, and today widely used as free radicals inhibitors in food for maintaining the freshness, flavor and odor for a longer period [47]. The roots of Glycyrrhiza glabra is a potential source of antioxidants and urease inhibitors. Extract of G.glabra was tested by studying the inhibition of radiation induced lipid peroxidation in rat liver microsomes [48]. Chemical constituents are glycyrrhizin, flavones, and coumarins. It shows its activity through free radical scavenging property [49]. The relative reducing activity in terms of antioxidant activity of extracts was determined by using individual extract (15mg) as well as its combination with equal amount of ascorbic acid [50]. Ethanolic extract of G. glabra possess considerable antioxidant activity and protective effect against the human lipoprotein oxidative system using in vitro models [18]. Maximum number of shoots/explants was produced on MS medium containing higher BAP (2.0 mg/l) level combined with NAA (0.05 mg/l). In vitro rooting was found better on full strength MS medium supplemented with IBA (0.5 - 1.0 mg/l) [51].

Sharma et, al., reported cost effective micro propagation protocol in selected plants for the conservation Artemisia annua L., Glycyrrhiza glabra L., Bacopa monnieri L. and Shoot tips, axillary buds and young leaf was used as explants. Yadav and Singh reported one protocol on micropropagation by manipulating growth regulators, culture conditions and other external factors influencing in vitro multiplication of G Glabra [52]. Shrivastava et al., studied in conserving shoot apices of Glycyrrhiza glabra L [53]. under slow growth conditions. Slow growth cultures were obtained by lowering incubation temperature and light intensity. A very low concentration of growth hormones (BAP and IAA) added to the conservation medium was beneficial for complete retrieval of the shoots. Different combinations of osmotic agents (sucrose, sorbitol and mannitol), used for increasing the s ubculture period, 20 gm/l of mannitol suited best for slow growth conservation with only subculture in a year [53]. The maximum induction rate was recorded as 96 % in MS medium with 0.5 mg/l 2,4 -D and 2 mg/l 6-BA with a light compact structure [54]. Fu et al

optimized embryogenic callus and embrygenesis and obsereved that the explants of hypocotyl give the highest calli formation frequency of 93.3% on Murashige and Skoog (MS) medium containing 2.0 mg/L 6 -benzylaminopurine (6-BA) and 0.5 mg/L 2,4- dichlorophenoxyacetic acid (2,4-D) [55].

Molecular tools are more reliable than phenotypic observation for evaluating tissue culture induced variations [56]. In plants regenerated via somatic embryogenesis, the quality of somatic embryos determines the production of true -to-type plants. Authors have reported that dedifferentiation of plant tissues leads to genetic modifications, but on the contrary, several reports also confirmed genetic integrity of tissue culture derived plants [57]. ISSR and RAPD based evaluation of genetic stability is reported encapsulated micro shoot of Glycyrrhiza glabra L. after 6-month storage. An experiment was conducted by Shirazi et al for Glycyrrhizin and isoliquiritigenin production by hairy root culture of Glycyrrhiza glabra L. by hairy root culture [58].

Licorice represents a replacement candidate reported to be useful for its multiple beneficial health effects including immunomodulatory, antimicrobial, antioxidative, anti-inflammatory, antidiabetic, hepatoprotextive, antiviral, anti-infective, and radical-scavenging activities [59]. Licorice is also known as Radix Glycyrrhizae or Liquiritiae Radix. It is the root of Glycyrrhiza uralensis Fisch. ex DC., G. glabra L. or G. inflata Bat., Leguminosae [59,60]. Phytochemical analysis of licorice root extract exhibited that it contained flavonoids (isoflavonoids, formononetin, and liquiritin), saponin triterpenes (liquirtic acid and glycyrrhizin), and other components such as sugars, coumarins, amino acids, starch, tannins, phytosterols, choline, and vitamins (e.g., ascorbic acid) [1]. Previous reports have shown that more than 20 triterpenoids and 300 flavonoids have been procured from licorice. Glycyrrhizin constitutes up to 25% of the licorice root extract [61]. Glycyrrhizin consists of glucuronic acid (two molecules) and glycyrrhetinic acid (one molecule) [62]. Badr et al., analyzed the raw form of licorice chemically and summarized its contents as follows: carbohydrate (47.11%), fiber (24.48%), protein (9.15%), silica (3.56%) and low-fat content (0.53%) [63].

The licorice root color is yellow because of its flavonoid components such as hispaglabridins and glabridin [64]. Additionally, the dried aqueous extracts of licorice contain approximately 4–25% glycyrrhizinic acid [65]. The main active ingredients of licorice are liquiritin, isoliquiritigenin, liquiritigenin, and glycyrrhetinic acid, glycyrrhiza polysaccharide, and this herb is rich in flavonoids and syringic, abscisic, trans-ferrulic, 2,5-dihydroxy benzoic, abscisic, and salicyclic acids [7]. Licorice (Glycyrrhiza glabra L., Fabaceae) is a perennial plant, well-known for its sweet-tasting root. It contains a wide array of bioactive natural products. Glycyrrhizin, the sweet principle of licorice root is a triterpene-type saponin that displays antiviral, anti-inflammatory, antitumor, and antimicrobial properties [66]. Besides glycyrrhizin, phenolic components, such as chalcone isoliquiritigenin and isoflavonoid glabridin are also important for the observed biological activity of licorice root. G. glabra has been traditionally used for promotion of wound healing. Licorice root extracts protect the skin against oxidative stress injuries, accelerate wound epithelization, and ameliorate remodeling at the wound site, and efficiently reduce the symptoms of atopic dermatitis (AD) [67-69]. Furthermore isoliquiritigen in was also found to be beneficial for the treatment of AD-like skin lesions in mice, giving hope that it could be a potential therapeutic agent for the treatment of AD in humans [70]. Glabridin has many properties potentially beneficial in cosmeceutical products. It acts as antioxidant, estrogenic, anti-inflammatory, and skin-whitening agent [71]. It displays skin depigmentation activity and is being incorporated in topical products intended specifically for that purpose [72]. A medicinal use of licorice includes cough suppression, treatment of early Addison disease, treatment of liver disease and dyspepsia also in the prophylaxis and treatment of gastric and duodenal ulcers [73].

It may be noted that G. glabra is used in traditional medicine to treat liver diseases and is a major component of poly herbal formulations for the cure of hepatotoxicity, it was also reported to have hyporcholesterolemic and hypoglycemic activities and to have protective role against oxidative stress [42,74]. M. chamomillahas been used for centuries as a medicinal plant mostly for its anti-inflammatory, anaglestic, antimicrobial, antispasmic and sedative properties [75,76]. Phytochemical analysis of Glycyrrhiza glabra root extract showed that it contains saponin triterpenes (glycyrrhizin, glycyrrhetinic acid and liquirtic acid), flavonoids (liquirtin, isoflavonoids and formononetin) and other constituents such as coumarins, sugars, amino acids, tannins,starch, choline, phytosterols and bitter principles [39]. Presently, interferon (IFN) therapy is a predominant treatment for chronic hepatitis. Because its efficacy is limited, an alternative treatment is desirable. SNMC has profound effects on the suppression of liver inflammation and is effective in improving chronic hepatitis and liver cirrhosis. It also appears to have considerably fewer side effects than IFN [77]. Alonso J. had studied the glycyrrhizin is habitually used as a vehicle in orally administered products, where it inhibits the growth of some bacteria, as well as dental plaque formation. In regards to its antibacterial action, in vitro studies have demonstrated inhibitory effects for licorice aqueous and ethanolic extracts on Staphylococcus aureus and Streptococcus pyogenes cultures, the first one showing the strongest inhibition with 10-15mm halo diameters [19,78].

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