Journal of Biotechnology and Crop Science
Vol. 10, No. 15, January-December, 2022, 35-45

doi: 10.5958/2582-5089.2022.00005.6

Review Article

Pharmacology of *Glycyrrhiza glabra* (Mulhatti): The grandfather of herbs

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ABSTRACT

Glycyrrhiza glabra (am: Fabaceae), commonly known as liquorice, is one of the most widely used medicinal herbs and has been described as 'the grandfather of herbs. Various metabolites such as glycyrrhetinic acid and glycyrrhizic acid from this plant are mainly responsible for the pharmacological effects. Glycyrrhizin, the active constituent, is responsible for the root's sweet taste, as well as its antioxidant, anti-inflammatory, and antimicrobial properties. Liquorice extract also stimulate tracheal mucus secretions producing demulcent and expectorant effects. The glycyrrhizin acid has antiulcer effect by increase in the level of concentration of prostaglandins, enhance cell proliferation in stomach and mucous secretions. However, glycyrrhizin acquires an outstanding antiviral activity, as it prevents the binding of virus cell and it has been used to treat HIV-1 & chronic hepatitis C virus suffering patients.

Keywords: Liquorice, mulhatti, glycyrrhizin, glycyrrhizic acid, flavonoid, antioxidant

INTRODUCTION

Many plants are being used as spices and medicines because of their various pharmacological benefits over the centuries (Srivastava & Singh, 2017). These plants possess many functional properties because of being an enriched source of several bioactive compounds (Noreen et al., 2021). Wealth of India (1956) reported that *Glycyrrhiza glabra* is one of the most widely used herb belonging to the family of Fabaceae from the ancient medical history of Ayurveda, both as a medicine and also as a flavouring herb (Figure 1). *G. glabra* is commonly known as Madhuka, yashti-madhu in Sanskrit, Mulhatti, Jethi-madh in Hindi and Licorice, Liquorice and Sweet wood in English. It is native to the Mediterranean and certain areas of Asia (Sharma et al., 2021; Wealth of India, 1956). They have been used in several human ailments since 500 BC and liquorice has been described as 'the grandfather of herbs (Jitendra et al., 2020). Sharma et al. (2021) updated that Hippocrates (400 BC) mentioned its use as a remedy of ulcers and quenching of thirst and in traditional Siddha system of medicine, liquorice is used as a demulcent, expectorant, anti-tussive, laxative and sweetener. Wealth of India (1956) also reported that in India, every year approximately 5000 Tons of Yastimadhu is imported from Pakistan, Iran, Afghanistan and UAE and is top selling herbal extracts in world market. Chen et al. (2020) noted that various metabolites such as glycyrrhetinic acid and glycyrrhizic acid are mainly responsible for the pharmacological effects of licorice. Kwon et al. (2020) described that lycyrrhizic acid converted to glycyrrhetic acid, a triterpenoid aglycone conjugated to glucuronide and sulfate, which is 200–1000 times more integral inhibitor of 11b-hydroxysteroid dehydrogenase. The biologically active compound of licorice, glycyrrhizic acid,

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is being used as a plant-based medicine in many health issues conditions due to its neuroprotective, anti-inflammatory, antiviral, and anticarcinogenic properties (Sun et al., 2021). Murray (2020) suggested that glycyrrhizin is responsible for the root's sweet taste, as well as its antioxidant, anti-inflammatory, and antimicrobial properties. In this review, we have compiled comprehensive and updated view about the phytochemistry composition and pharmacology activities of *G. glabra*.

Phytochemistry

Licoricey is the source of polysaccharides, simple sugars, proteins, amino acids, and mineral salts like calcium, sodium, potassium, iron, zinc, copper, phosphorous, magnesium, manganese, silicon, and selenium and also contains vitamins like B1, B2, B3, B5, E and C (Wealth of India, 1956). The principal constituent of liquorice to which it owes its characteristics sweet taste is glycyrrhizin which is present in different concentration of 2-14% in different varieties (Wealth of India, 1956). Sharma et al. (2018) reported that different components have been isolated from liquorice, including triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances. This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2-25% range (Sharma & Agrawal, 2013). Murray (2020) also noticed that the main chemical constituent of liquorice is glycyrrhizin (about 2-9%), a triterpene saponin with low haemolytic index. Sharma et al. (2016) confirmed that the yellow color of liquorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin and other compounds. They also reported that glycyrrhizin acid (0.5-09%), the aglycone of glycyrrhizin are also constituents of liquorice include isoflavonoids and sterols, lignans, amino acids, amines, gums and volatile oils and among the natural saponins, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhizin acid.

Anti-tussive and expectorant activity

Liquorice has been shown to work as efficiently as codeine in sore throat (Kuang et al., 2018).

Dimri & Kumar (2018) demonstrated that the tracheal mucus secretions are stimulated by liquorice extract which generally produces expectorant and demulcent effects. Agarwala & Singh (2022) updated in his article that it decreases irritation and produces expectorant effects. Hasan et al. (2021) recently described that

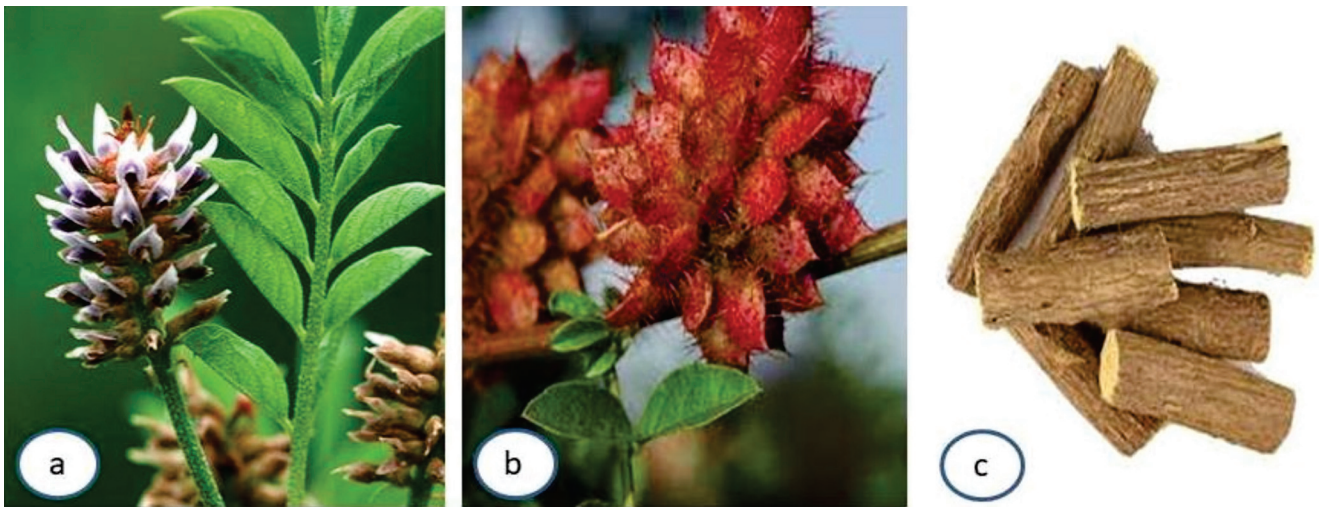

Figure 1: a. *Glycyrrhiza* Plant with flowers; b. *Glycyrrhiza* ripe fruits; c. *Glycyrrhiza* (Mulhatti) root sticks

carbenoxolone (a compound derived from *Glycyrrhiza*) stimulates gastric mucus secretion. Ahmed et al. (2021) reported that ethanolic extract of *G. glabra* was found to be responsible for inhibition of 35.62% SO_2 gas induced cough in experimental animals (mice).

Damle (2014) reported that liquorice extract may also be able to stimulate tracheal mucus secretions producing demulcent and expectorant effects. Michael & Murray (2020) suggested that glycyrrhizin is responsible for demulcent action of liquorice. Sharma et al. (2021) updated that liquiritin apioside, an active compound present in the methanolic extract of liquorice inhibits capsaicin induced cough.

Anti-ulcer activity

Lohar et al. (2020) reported that the most important component of licorice, is glycyrrhizinic acid that include antiulcer effect by increase in the level of concentration of prostaglandins, enhance cell proliferation in stomach and mucous secretions. Mohammed et al. (2020) found that, in vitro glycyrrhizic acid, works against *H. pylori* and therefore show its profitable effect on peptic ulcers. Dastagir & Rizvi (2016) reported 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. 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 (Brogden et al., 2012). Ingale et al. (2016) reported that significant inhibition of experimental ulcer in albino rats and dog by administration of herbal extract or herbal powder by various methods and concluded that both glycyrrhizin and glycyrrhizin-free flavanoids have been shown to have anti-ulcer activity and synergism between this has been demonstrated. Michael & Murray (2020) updated that therapeutic value of glycyrrhizinic acid, and its aglycon root powder action and noted that glabridin, a flavanoid 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. Hicham et al. (2020) 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.* Use of carbenoxolone should be considered when antacids fail to give relief in ulcer patients (Pinder et al., 1976).

Antioxidant activity

High content of phenolic component in ethanolic extract of [liquorice (*G. glabra*) is responsible for its powerful antioxidant activity by means of significant free radical scavenging, hydrogen-donating, metal ion chelating, anti-lipid peroxidative and reducing abilities (Jyothsna et al., 2016). Ahmad et al. (2021) reported in his experiment that antioxidant activity of liquorice flavonoids was found to be over 100 times stronger than that of antioxidant activity of vitamin E. A dose of 2.58 mg/ml liquorice flavonoids can scavenge more free radicals (20.6% scavenging) than 258 mg/ml of vitamin E (11.2% scavenging). Ciganovic et al. (2019) updated that liquorice extract can be efficiently used to formulate cosmetic products for the protection of skin and hair against oxidative damage. Shen et al. (2022) reported in his experiment that flavanoids from the root have potent antioxidant activity. They also noted that six compounds with this activity have been characterized; these are hispaglabridin A and B, glabridin, methylgrabridin, isoliquiritigenin, and an isoprenylchalcone derivative. Kaur et al. (2021) also reported that Flavonoids of liquorice have strong antioxidant property found in liquorice flavonoids and considered to be over 100 times stronger than antioxidant activity in Vitamin E. It is also found that glabridin has antioxidant activity towards oxidative lipoproteins of low density (Kaur et al., 2021).

Skin lightening and skin tightening activity

Lekshmy et al. (2021) updated that the extract of liquorice is an effective pigment lightening agent and it is the safest pigment-lightening agent known with least side effects. Liquiritin present in liquorice extract disperse melanin, thereby inducing skin lightening (Zaid & Ramahi, 2019). Pan et al. (2023) described in his article that glabridin in the hydrophobic fraction of liquorice extract inhibits tyrosinase activity in cultured B16 murine melanoma cells. They also reported that some other active compounds in liquorice extract like glabrene, licochalcone A, isoliquiritin are also responsible for inhibition of tyrosinase activity. Hasan et al. (2021) reported that *In vitro* tyrosinase enzyme inhibition studies has showed that 21.2 ìg/ml of methanolic extract of liquorice caused 50% tyrosinase enzyme inhibition and the inhibition of tyrosinase enzyme and reduction in enzyme activity is caused due to modification of action site of the enzyme. They also updated that due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity. Damle (2014) reported that synergistic effect of UV protective, antioxidant and anti-inflammatory properties of liquorice extract might be responsible for giving beneficial effects on skin.

Anti-inflammatory activity

Rahnama et al. (2013) reported that *Glycyrrhiza* extract promotes the healing of ulcers of the stomach and mouth and they also reported that glycyrrhetinic acid in liquorice extract gives anti-inflammatory effect similar to glucocorticoids and mineralocorticoids. Sharma et al. (2021) described that *in vitro* studies, glycyrrhizic acid inhibits all factors responsible for inflammation. It inhibits cyclooxygenase activity and prostaglandin formation (specifically prostaglandin E2). Huang et al. (2020) updated that carbenoxolone, a glycyrrhetinic acid analog, is reported to inhibit two enzymes that are important in metabolism of prostaglandin, 15-hydroxyprostaglandin dehydrogenase and 13 prostaglandins thereby raising prostaglandin levels. Cohen (1987) also reported that prostaglandins stimulate mucous secretion and cell proliferation. Thus, ulcer healing is promoted. Carestia et al. (2022) reported that *Glycyrrhiza* is also responsible for indirectly inhibiting platelet aggregation. Ebanks et al. (2009) reported that the activity of glabridin is found to be efficient in inflammation and melanogenesis by preventing the tyrosinase property found in melanocytes. Kowalska et al. (2019) updated in his research article that β-glycyhrritinic acid, apprise anti-inflammatory property in different animal models by preventing the metabolism of glucocorticoid and β-glycyhrritic acid is considered as one of the major metabolite of glycyrrhizin. They also noted that it also inhibits the activation pathway of classical complement and its activity depends on its configuration. Yao et al. (2005) suggested that the *Glycyrrhiza* is useful in the treatment of inflammatory lung disease if its co-medication is done with hydrocortisone. A derivative of glycyrrhizic acid, glyderinine, also shows the anti-inflammatory effect and it plays an important role in reducing inflammatory myocardial edema in myocardial damage (Jitesh & Geeta, 2017). Mantelli et al. (2011) reported that 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. They noted that 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, kerato-conjunctivitis and fascicular keratitis.

Anti-viral effects

Lee et al. (2021) reported that glycyrrhizin does not allow the virus cell binding. Thus, it is capable of having a prominent antiviral activity and employed in the treatment of HIV-1 and chronic hepatitis C. Ghannad et al. (2014)

reported that liquorice extract inhibits the growth of viruses, including herpes simplex, Varicella zoster, and of Japanese encephalitis, influenza virus, vesicular stomatitis virus. Recent study on two clinical isolates of SARS virus (Severe Acute Respiratory Syndrome virus) [FFM-1 and FFM-2] gave valuable insight about anti-viral activity of glycyrrhizin (Zheng et al., 2020). Cinatl et al. (2003) experimented on patients with SARS, admitted to clinical center of Frankfurt University, Germany and concluded that antiviral activities of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid and glycyrrhizin proved that glycyrrhizin was the most efficient in controlling viral replication. Glycyrrhizic acid was found to have a distinctive effect against Kaposi sarcoma-associated herpes virus (KSHV) as found in in vitro studies (Curreli et al., 2005; Kang et al., 2011). KSHV also becomes latent in infected cells same as other herpes virus (Kang et al., 2011). Uppal et al. (2014) reported that glycyrrihizic acid down-regulates the expression of latency associated nuclear antigen (LANA) in B lymphocytes which causes natural cell death (apoptosis) of the KSHV virus. They also noted that glycyrrhizin, acquires an outstanding antiviral activity, as it prevent the binding of virus cell. It is found that glycyrrhizin is considered as most efficient to control viral replication and it has been used to treat HIV-1 and chronic hepatitis C virus suffering patients (Uppal et al., 2014). Murray (2020) demonstrated oral liquorice preparations, containing glycyrrhetinic acid and used for the treatment of viral infections- viral hepatitis and common cold. Topical preparations, containing glycyrrhetinic acid, are used for herpes, eczema, and psoriasis. Nose et al. (2017) reported, a preparation of glycyrrhizin, cysteine and glycine is used by injection for the treatment of acute and chronic hepatitis in Japan. Glycyrrhizinic acid inhibits the growth and cytopathology of several unrelated DNA and RNA viruses. It also inactivated Herpes simplex virus particles irreversible (Wang et al., 2013). Thangavelu & Geetha (2011) reported that 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*. Sharma et al. (2021) concluded that glycyrrhizin inhibited plaque formation in three different strains of Japanese encephalitis virus at a concentration of 500 mg/ml at 96 hours. They noted that in connection with its antiviral activity, in *in vitro* experiments, to induce and enhance gamma – interferon in human peripheral lymphocyte macrophage cultures developed by the lactin concanavalin A.

Anti-fungal activity

Pastorino et al. (2018) reported that methanolic extract of liquorice have fungicidal activity against *Arthrinium sacchari* and *Chaetomium funicola*. Fatima et al. (2009) updated that glabridin was found to be the active compound giving anti-fungal activity. Lee et al. (2021) described in his research article that *G. glabra* acquires excellent anti-fungal activity. Simmler et al. (2013) reported that isoflavonoids such as glabridin, glabrol and their derivatives are responsible for *in vivo* inhibition of *Mycobacterium smegmatis* and *Candida albicans.*

Anti-bacterial activity

Dwivedi et al. (2020) noted that the presence of secondary metabolites such as; saponins, alkaloids, flavonoids in hydro-methanolic root extract of *G. glabra*, the extract exhibits potent antibacterial activity. Malvania et al. (2019) proved that aqueous and ethanolic extracts of liquorice show inhibitory activity on cultures of *Staphylococcus aureus* and *Streptococcus pyogenes*. Ethanolic extracts of liquorice justifies, that the *Staphylococcus aureus* and *Staphylococcus pyogenes*, exhibits the inhibitory activity (Irani et al., 2010). Chopra et al. (2013) reported that the hydro-methanolic extract of roots of *G. glabra* includes some secondary metabolites like alkaloids, saponins 7 flavonoids, they shows antibacterial activity against *S.*

aureus and it is considered as an important drug and is able to fight against bacterial infection, scavenging of hydroxyl radicals.

Anti-malarial activity

Licochalcone A present in liquorice has reported to possess strong antimalarial activity (Mittal & Kakkar, 2021). Asl & Hosseinzadeh (2008) experimented *in vivo* against *P. yoelii* in mice with oral doses of 1000 mg kg^{-1} have shown to eradicate malarial parasite completely and concluded the *in vitro* growth of chloroquine-resistant (Ddz) and chloroquine-susceptible (3D7) strains of *Plasmodium falciparum* is inhibited by licochalcone A. Wahab et al. (2021) reported that all *Glycyrrhiza* species have licochalcone A compound in different amounts and showed strong anti-microbial activity.

Immunostimulatory effects

Lohar et al. (2020) showed high immunostimulatory effects of 100 µg/ml concentration of liquorice under *in vitro* condition and concluded that it increases production of TCD69 lymphocytes and macrophages from human granulocytes. Abraham et al. (2021) also updated that *in vivo* studies, liquorice root extract was found to prevent the increase in the amount of immune-complexes related to autoimmune diseases like systemic lupus erythematosus.

Memory enhancing activity

Kumar et al. (2017) updated that the effects of *G. glabra* on learning and memory was investigated in mice. They reported that elevated plus-maze and passive avoidance paradigm were used to test learning and memory. Three doses of aqueous extract of liquorice were administered (75, 150 and 300 mg/kg). The study was conducted for 7 successive days in separate groups of animals and concluded that significant improvement in learning and memory of mice was reported at the dose of 150 mg/kg (Kumar et al., 2017). The products of oxidative metabolism and oxygen free radicals found to be neurotoxin (Gomaa & Wadood, 2021). Akbar (2020) described in his research article that the roots and rhizomes found in *G. glabra* is considered as an effective brain tonic as it enhances the CNS system circulation and manage the level of sugar in blood.

Hepatoprotective activity

Liquorice extract is proved to show hepatoprotective activity against diclofenac–induced hepatotoxicity in rats (Damle, 2014). Gomaa & Wadood (2021) also reported that glycyrrhizin significantly inhibits the CCl_4- induced release of AST and LDH at concentrations of 25–200 µg/ml and concluded that alteration of membrane fluidity by the glycyrrhizin or inhibition of CCl_4-induced membrane lipid peroxidation might be responsible for the activity. 1-8-β-glycyrrhetic acid (an aglycone of glycyrrhizic acid) shows hepatoprotective activity by inhibiting both free radical generation and lipid peroxidation (Gomaa & Wadood, 2021). Glycyrrhizin is useful in treating acetaminophen-induced hepatotoxicity (Xu-ying, 2009). Kaur et al. (2021) updated that *Glycyrrhiza*, has been used for more than 60 years, so as to treat chronic hepatitis, clinically as antihepatitis & anti-allergic agent in Japan under the name of stronger Neo-Minophagen C (SNMC). Bailly and Vergoten (2020) discussed that an aglycone of glycyrrhizin, which is 1-8-β-glycyrrhizin acid (GA), is found to reduce the P450 E1 expression, and therefore protect the liver and they also suggested that GA contribute in the anti-carcinogenic activity of hepatotoxin by metabolic deactivation, and also inhibits the hepatic and oxidative damage caused due to a flatoxins by increase in the CYP1A1 and glutathione-S-transferase (GST) activities. Nassan et al. (2021) reported that oral administration of *G. glabra* root extract to rats protected the animals from carbon tetrachloride induce liver injury and hepatoprotective action was evident from abatement of hepatic degeneration and necrosis, recovery of

hepatocellular glycogen, and from other indicators. Kumar et al. (2012) updated that both glycyrrhizin and glycyrrhetic acid could decrease serum, billirubin and promote its excretion in urine in rabbit and rats with ligated common bile ducts. Wu et al. (2021) tested in his experiment that in a clinical trial on patients with sub-acute hepatic failure a fraction derived from *G. glabra* 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.

Anticoagulant activity

Glycyrrhizin is the first plant-based inhibitor of thrombin (Sharma et al., 2016). Sharma *et al.* (2018) also reported in his book that it is found to prolong the thrombin and fibrinogen clotting time and also increases plasma recalcification duration. Ahmad et al. (2021) also reported that glycyrrhizin causes inhibition in thrombin induced platelet aggregation but there was no effect of glycyrrhizin on Platelet Aggregating Factor (PAF) and collagen induced agglutination.

Hair growth stimulatory activity

Lohar et al. (2020) also reported that the hydro-alcoholic extract of liquorice showed good hair growth promoting activity. Sharma et al. (2022) experimented on comparison between liquorice extract and the standard drug used (Minoxidil 2%) showed that, 2% concentration of liquorice extract showed better hair growth stimulatory activity than 2% minoxidil. Thus, after efficacy and safety analysis, it has been 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 (Sharma et al., 2022).

Anticancer activity

Oyenihi et al. (2021) reported that products from *G. glabra* roots have both anticancer and cancer preventive activities. Thus, its extract showed antimutagenatic activity against ethyl methanesulphonate in the *Salmonella* / microsome revision assay (Oyenihi et al., 2021). Ferdous et al. (2022) updated that glycyrrhizin also inhibited the subcutaneously transplanted jitan sarcoma in mice, and prevented the development of polyoxybenzidine-induced liver carcinoma in male mice. Oral ingestion (in drinking water) of glycyrrhizin to sencar mice lead to substantial protection against skin tumourigenesis induced by 7,12-dimethylbenz[a] anthrancene and other carcinogens (Ferdous *et al.*, 2022). Glycyrrhetic acid at 80 mg/kg, once daily, inhibited the transplanted oberling - guerin myeloma in rats (Murray, 2020). Shen et al. (2022) updated that isoliquiritigenin, a flavanoid component of *G. glabra* root extract has been shown to have anticancer activity *in vitro* and *in vivo* models. Prajapati et al. (2021) reported 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.

Antitoxic activity

Goorani et al. (2019) reported that glycyrrhizin is effective in detoxifying the hepatotoxicity of parquet, a herbicide, in experimental animals and noted that the drug extract have significant detoxicant action. Xu et al. (2020) demonstrated by *in vivo* investigations on mice against strychnine, cocaine, arsenobenzene, mercurous chloride, and choral hydrate and concluded that Snake venom, tetrodotoxin, diphtheria toxin and tetanus toxin were also countered by glycyrrhizin. Dissanayake et al. (2020) also updated that *G. glabra* root extracts / glycyrrhizin effect detoxification by a glucuronidation pathway.

CONCLUSION

The pharmacological and clinical studies reported in the present review confirm the therapeutic value of *Glycyrrhiza glabra*. This plant has been broadly used

as a traditional medicine and food industry ingredient, particularly as a flavour and sweetening agent. Presence of chemical compounds indicates that the plant could serve as "lead" for development of novel agents for disorders in the coming years. In this regard, further studies need to be carried out to explore *G. glabra* for its potential in preventing and treating diseases. There is also an immense scope to explore different combinations of liquorice preparations in a wide range of disorders.

Conflict of interest

The authors declare no conflict of interest.

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