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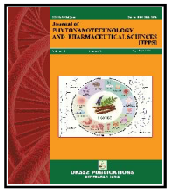

Review Article : Open Access

Licorice: A review on phytochemical insights and therapeutic potential

Shivani Jaswal, Sachin Sharma, Manoj Kumar, Rakesh Sharma and Abhimanyu Thakur◆

Department of Food Science and Technology, Dr. Yashwant Singh Parmar University of Horticulture and Forestry, Nauni, Solan-173230, Himachal Pradesh

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Abstract

Nature has long been a great source of therapeutic compounds, giving us access to a wide variety of medicinal plants and microbes that produce advantageous molecules. As a result, health products, medicinal plants and the market for cosmetics are constantly expanding. The scientific name for licorice, which belongs to the Leguminosae family, is *Glycyrrhiza glabra* Linn. It is a medical plant that resembles an herb and its roots/rhizomes are in wide use as it is having huge medicinal and therapeutic potential due to presence of various bioactive compounds, including glycyrrhizin, glycyrrhizinic acid, isoliquiritin, and glycyrrhizic acid. The root extracts of this plant has anticancerous, antiatherogenic, antidiabetic, antiasthmatic, anti-inflammatory, antimicrobial, and antispasmodic properties that can provide beneficial health effects by prevention of various diseases. The plant licorice exhibits a wide range of pharmacological properties, including antidepressant, sedative, and anticoagulant effects, and is also known to promote hair growth and regulate weight. Alongside the discussion of its diverse bioactive ingredients responsible for its therapeutic potential, recent studies have also highlighted some toxicity and adverse effects associated with licorice and its components. This comprehensive review delves into the phytochemical constituents, pharmacological activities, as well as the safety considerations necessary for the effective and responsible use of licorice in medicinal and food applications.

1. Introduction

Humans have used plants for sustenance, shelter, and medicine since the dawn of civilization. People relied solely on specific plants with therapeutic properties prior to the development of modern medicine and the extraordinary progress of science and technology. Back then, a lot of research was done on the biochemistry of plants and their natural chemicals, a practice that is still widely used today. Only a small fraction of the world's immense plant diversity has been scientifically explored. Out of the estimated 250,000-400,000 plant species on earth, merely about 6 per cent have undergone systematic investigation for their biological activity. This means that the vast majority of plants remain untapped reservoirs of potential medicinal compounds, nutritional resources, and ecological benefits (Sadeghi *et al.,* 2014). Many people in developing nations, particularly in Africa and Asia, still rely on herbal extracts to cure many human and animal disorders (Mahomoodally, 2013). Several chemicals, including triterpenoids, saponins, tannins, phenols, flavonoids, and alkaloids, have been shown to improve a variety of physiological processes (Mujeeb *et al.,* 2014). Since then, humanity has produced a variety of medications using natural compounds derived from medicinal plants. Ayurveda, a sort of therapeutic study that originated in India, is still popular in many developing countries (Chauhan *et al.,* 2015). Its popularity stemmed from its ease of availability, low production costs, satisfactory efficacy, and minimal side effects. *G. glabra* is one such plant that is commonly utilized in Ayurvedic medicine (Sharma *et al.,* 2016). This medicinal plant grows in Asia and portions of southern Europe (Fiore *et al.,* 2005). It is thought that licorice originated in Iraq (Mamedov and Egamberdieva, 2019). However, Italy, France, Spain, Greece, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, and China now commercially cultivate many *Glycyrrhiza* species. It has many vernacular names, including jaishbomodhu (Bengali), *mulaithi* (Hindi), licorice (English), and *aslussiesa* (Arab).

Licorice roots and rhizomes are the most important parts of the plant used for medicinal and commercial purposes. The rootstock consists of thick, cylindrical, woody, and branched roots along with long, horizontal, subterranean rhizomes that grow close to the soil surface. While both roots and rhizomes serve as raw materials popularly traded as "licorice root," the licorice root is robust, with numerous branches that are red or lemon outside and yellowish or pale-yellow inside (Ishtiyaq *et al.,* 2019). The bark of the roots and rhizomes ranges from brownish green to dark brown (Carvalho *et al.,* 2014). Roots and rhizomes are used as carminatives in India, Egypt, China, Greece, and Rome. The roots, peeled or unpeeled, and rhizomes are used to treat a variety of respiratory tract problems, including cough, hoarseness, sore throat, bronchitis, asthma, tonsillitis, and so on (El-Saber Batiha *et al.,* 2020). Licorice has also been used to treat flatulence, stomach ulcers, colic, hyperdipsia, and other digestive system issues (Batiha *et al.,* 2020). It is also used to treat epilepsy, fever, sexual dysfunction, rheumatism, paralysis, psoriasis, and jaundice (El-Saber Batiha *et al.,* 2020). It is also effective for gout, edema, acidity, leucorrhoea, hemorrhage, hiccough, and vata dosha-related illnesses such as gastralgia, cephalalgia, ophthalmology, and pharyngitis. *Glycyrrhiza* root has been used as a medicinal and

Corresponding author: Dr. Abhimanyu Thakur
Assistant Professor, Department of Food Science and Technology, Dr. Yashwant Singh Parmar University of Horticulture and Forestry, Nauni, Solan-173230, Himachal Pradesh
E-mail: abhimanyuthakurprashar@gmail.com
Tel.: +91-9882239719

flavoring additive in the food industry for over 400 years. Licorice extracts are used to flavor baked goods, ice cream, chewing gum, candy, and soft drinks (Rizzato *et al.,* 2017). Furthermore, *Glycyrrhiza* is extensively employed in biomass, bioenergy, and pulp manufacturing (Pastorino *et al.,* 2018).

2. Traditional uses

G. glabra has various traditional uses like it is mixed with butter and used in burns and wounds, *Glycyrrhiza* mixed with cow's milk is used to encourage lactation, the blended root of *Glycyrrhiza* is used as a wash for greying of hair, and a decoction of *Glycyrrhiza* is used for erysipelas. A solution of rice milk produced with *Glycyrrhiza* is used for hoarseness of voice; a paste of yashti, milk, and *Sesamum indicum* combined with butter is used to cure oedema; *Glycyrrhiza* mixed with honey is supplemented right after the intake of milk as a tonic to boost intelligence (Kumar and Dora, 2012) and it is also applied for the treatment of intrinsic hemorrhage (Zhang *et al.,* 2021). In traditional and veterinary medicine, licorice root extract is widely utilized for diverse therapeutic applications. In India, licorice root extract is employed as an eye drop treatment for conjunctivitis, leveraging its anti-inflammatory and soothing properties to alleviate symptoms and promote recovery. Additionally, powdered licorice mixed with honey is traditionally used to combat anaemia, reflecting its nutritional and restorative benefits. A cardiotonic paste combining *Glycyrrhiza* and *Picrorrhiza kurroa* with sugar water is also employed to support heart health. In Pakistan, licorice root paste is administered to livestock such as cows, goats, buffaloes, and sheep, mixed with wheat and oil to enhance milk production and improve fertility. These varied uses underscore licorice's significance as a multifunctional herbal remedy with broad applications in human and animal health (Aziz *et al.,* 2018). The root sap of *Glycyrrhiza* is used in wine making in Turkey's middle region (Kargýoðlu *et al.,* 2010). In Italy, root decoction is used as a mild laxative (Motti, 2021), while juice from the root and stem is used as a stimulant, astringent, and tonic in Nepal (Luitel *et al.,* 2014). It is used with tea to treat sore throats in Egypt (Dissanayake *et al.,* 2020).

3. Phytochemistry or bioactive compounds

Many physiologically active chemicals have been reported from various portions of licorice, the majority of which are water-soluble and account for around 40-50 percent of total dry weight (Sharma *et al.,* 2016). The various biologically active compounds including their groups presented in licorice have been listed in Table 1.

Table 1: Major groups and bioactive compounds in Licorice

Groups	Bioactive compounds	References
Triterpenoids	Glycyrrhizin	Yu *et al.,* 2015
Saponins	Glycyrrhizic acid, 18-β-glycyrrhizinic acid	Obolentseva *et al.,* 1999
	Liquiritin, isoliquiritin, liquiritigenin,	Rizzato *et al.,* 2017
	Glabridin, glabrene, rhamnoliquiritin	Vaya *et al.,* 1997
Flavonoids	Glucoliquiritinapioside, prenyllicoflavone A, shrinflavonone, shrinpterocarpin, 1-methoxy-phaseolin	Fenwick *et al.,* 1990
	Glisoflavone, kanzonol R	El-Saber Batiha *et al.,* 2020
	Licochalcone A	Zhang and Ye, 2009
	Hispaglabridin A and B, licuraside, glyzaglabrin	Zhang and Ye, 2009
	Licocoumarin	Sharma *et al.,* 2016
Coumarins	Glycycoumarin, licopyranocoumarin, glabrocoumarone A and B	Kinoshita *et al.,* 2005
Isoprenoid substituted phenol	Semilicoisoflavone B, 1-methoxyficifolinol, isoangustone A, licoriphenone	Fenwick *et al.,* 1990
Alcohols (Volatile)	Pentanol, hexanol	Fenwick *et al.,* 1990
	2,3 Butanediol	El-Saber Batiha *et al.,* 2020
Acid (Volatile)	Propionicacid, benzoic acid, ethyl linoleate, Acetic acid, malic acid, butyric acid fumaric acid, citric acid	Tamir *et al.,* 2001
Terpenoids	Alpha terpineolGeraniol	El-Saber Batiha *et al.,* 2020
Aldehydes	Furfuraldehyde	El-Saber Batiha *et al.,* 2020

4. Pharmacological activity

The great potential of bioactive compounds from fruits and their by-products in promoting health is driving interest in discovering new products with beneficial pharmacological effects, including antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties Kaushal *et al*., 2022. Nowadays, the consumption of foods having phytochemicals has increased due to their role in human health as they have pharmacological potential which helps in the prevention of various diseases (Sharma *et al.,* 2019; Hamid *et al.,* 2022). The extracts collected or the powder prepared predominantly from the roots and rhizomes usually hold pharmacological importance. The various bioactive compounds present in licorice along with their health benefits have been illustrated schematically in the Figure 1. These bioactive compounds increase an individual's immune response by acting as immunomodulators and assisting our defence system.

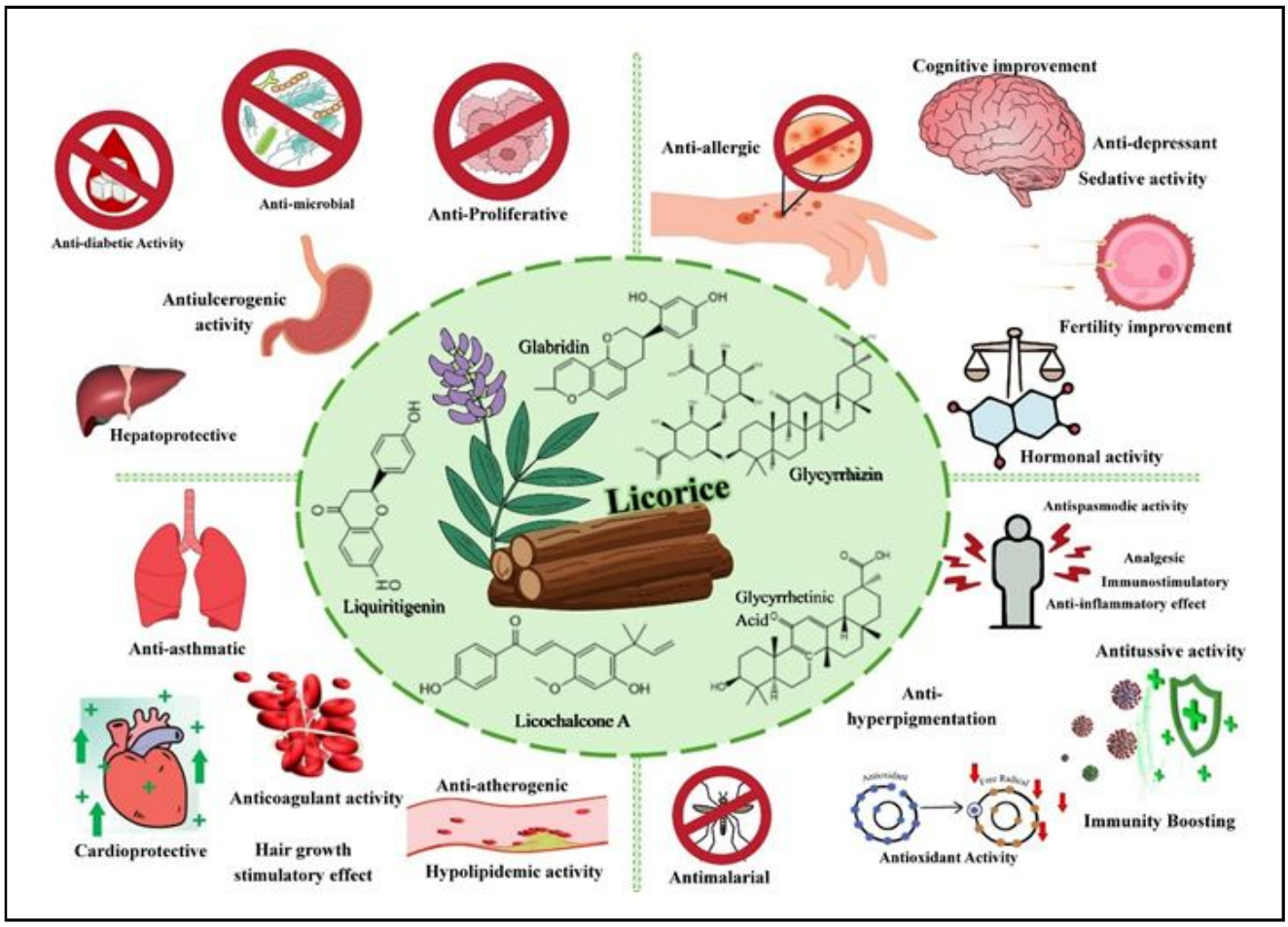

Figure 1: Major bioactive compounds and health benefits of Licorice (*G. glabra*).

4.1 Antitussive activity

Licorice powder and extract are highly effective for treating sore throats, coughs, and bronchial catarrh (Pastorino *et al.,* 2018). Glycyrrhizin, an active component found in *G. glabra*, provides antitussive, demulcent, and expectorant loosening properties. Glycyrrhizin reduces congestion in the upper respiratory tract and enhances tracheal mucus secretion. Liquiritinapioside, an active component found in methanolic extracts of licorice, can block capsaicin, which causes coughing (Pastorino *et al.,* 2018). Furthermore, an ethanolic extract of licorice can prevent sulfur dioxide gas-induced coughing in experimental mice (Damle, 2014). Licorice reduces inflammation and works as well as codeine to treat sore throats. Carbenoxolone, a semisynthetic substance produced from *G. glabra*, promotes stomach mucus secretion (Pandey *et al.,* 2017).

4.2 Antiulcerogenic activity

G. glabra extract inhibits two enzymes: 15-hydroxyprostaglandin and delta 13-prostaglandin reductase (Baker, 1994), and has been used as an anti-ulcerogenic agent. The inhibition of these two enzymes causes a rise in prostaglandin levels (Bakr *et al.,* 2022), since 15-hydroxyprostaglandin turns prostaglandin E2 and F2 alpha into inactive 15-ketoprostaglandins, while delta 13-prostaglandin reductase converts prostaglandins into 13, 14-dihydro, 15-ketoprostaglandin (Dissanayake *et al.,* 2020). Carbenoxolone is another molecule that can be derived from *Glycyrrhiza* extract. It can reduce gastrin secretion, resulting in an anti-ulcerogenic effect (Malek and Ghazvini, 2007). It is used to treat gastric and duodenal ulcers with a dose of 100 mg three times per day. Licorice demonstrates anti-ulcerogenic activity through multiple mechanisms. It elevates prostaglandin concentrations in the digestive tract, which stimulates mucus secretion from the stomach and helps prolong the survival of stomach surface cells, ultimately providing a protective effect against gastric damage and exhibiting anti-pepsin properties. Additionally, extract from licorice roots has been shown to suppress gastrin secretion, which leads to reduced gastric acid production further contributing to its antiulcer effects. These combined actions make licorice a potent natural agent in supporting gastrointestinal health and preventing ulcer formation (Ram *et al.,* 2010).

4.3 Anticancerous activity

Glycyrrhiza's bioactive components have demonstrated anti-cancer activities in both *in vivo* and *in vitro* tests (Sharma *et al.,* 2016). *Glycyrrhiza* contains 18-β-glycyrrhetinic acid and glycyrrhizic acids, which cause mitochondrial permeability, leading to tumor cell death (Lee *et al.,* 2008). The cytotoxicity of *Glycyrrhiza* methanolic extract was determined using the brine shrimp lethality assays. The cytotoxicity was sufficient, with an LC_{50} value of 0.77 µg/ml (Dang *et al.,* 2024). The anticancerous activity of licorice methanolic extract at 0, 12.5, 25, 50, and 100 µg/ml was investigated against intestinal

carcinoma cell line (Caco 2) and prostate carcinoma cell line (PC-3). Methanolic extract inhibited growth in Caco-2 and PC-3 cells. Licorice extract includes a large number of phytoestrogen components, making it an effective chemopreventive agent. As a result, it may exhibit anti-tumor effect against breast cancer, ovarian cancer, and stomach tumor. One trial shown that combining licorice extract with cisplatin helped reduce cisplatin-based toxicity (Icer *et al.,* 2017). Glycyrrhizinic acid can stimulate AKT/mTOR signaling in endometrial and breast cancer cells, inhibiting their growth (He *et al.,* 2015). Licorice's antineoplastic action has also been used successfully to treat cancer (Hamad *et al.,* 2020). *Glycyrrhiza* extracts can also suppress cancer cell proliferation by interfering with angiogenesis, one of the disease's hallmarks. This property was demonstrated in an *in vivo* test (Sheela *et al.,* 2006). The ethanolic extract has antiproliferative effects on MCF-7 cells in an adipose-dependent manner. In albino mice, a hydromethanolic extract of licorice demonstrated antimutagenic activity by inhibiting micronuclei development and chromosomal abnormality in bone marrow cells. Additionally, it inhibited thromboxane A2 in lung cancer cells (Deng *et al.,* 2017). It uses paclitaxel, an antimicrotubule drug, to block the G2/M transition in the cell cycle and stimulate BCL2 phosphorylation. The 70 per Kaurcent methanol soluble fraction of licorice extract can cause apoptosis in human monoblastic leukemia U937 cells. Both *in vivo* and *in vitro* studies show that glycycoumarin prevents cancer in human hepatocellular carcinoma cells such as HepG2, Huh7, human prostate cancer DU-145 cells, and male BLAB/c athymic nude mice by binding and inactivating oncogenic TOPK, which activates the p53 pathway (Song *et al.,* 2016).

4.4 Antidiabetic activity

Type 2 diabetes mellitus is a widespread metabolic disorder marked by elevated blood glucose levels due to insulin resistance and inadequate physical activity. Multiple transcription factors regulate both glucose and lipid metabolism in this condition, among which the peroxisome proliferator-activated receptors (PPARs) play a central role. PPARs are a family of nuclear receptor transcription factors that modulate the expression of genes involved in carbohydrate and fat metabolism, influencing insulin sensitivity, lipid storage, and energy balance. Disruption or alteration in the activity of these transcription factors contributes significantly to the metabolic disturbances seen in type 2 diabetes mellitus (Dissanayake *et al.,* 2020). These PPAR receptors are predominantly found in liver, muscle, and kidney tissues. This PPAR can be classed as alpha, gamma, or delta. The insulin-sensitizing medicines mostly target the PPAR gamma receptor. Several substances derived from *G. glabra* root and crude extracts, including glycycoumarin, glycyrin, glyasperin D, dehydroglyasperin, glyasperin B, and iso-glycyrol ethyl solution, can bind to PPAR gamma, resulting in reduced blood glucose levels (Petropoulos *et al.,* 2019). *Glycyrrhiza* chalcone and amorfrutin promote adipocyte differentiation while also improving glucose and lipid metabolism (Gaur *et al.,* 2014). Amorfrutin can improve insulin sensitivity and glucose tolerance. Glabridin reduces glucose intolerance and maximizes glucose consumption by translocating GLUT-4 *via* adenosine monophosphate protein kinase (AMPK) (Chong *et al.,* 2020). Glycyrrhizin increases glycohaemoglobin, cholesterol, and triglyceride levels while decreasing blood insulin levels and pancreatic islet cell counts (Ishtiyaq *et al.,* 2019). Thus, licorice may play an important role in insulin resistance-related disorders.

4.5 Hormonal activity

Licorice has been shown to impact cortisol and estrogen activity, as well as inhibit testosterone synthesis (Armanini *et al.,* 2002). *Glycyrrhiza* includes glycyrrhizin and 18-β-glycyrrhetinic acid, which have mineralocorticoid characteristics, inhibiting cortisol metabolism. Licorice can lessen the diuretic side effects of spironolactone in PCOS patients (Armanini *et al.,* 2007). 18-β-glycyrrhetinic acid effectively inhibits 11-β-hydroxysteroid dehydrogenases (HSD). Lower levels of 11-β-HSD can lead to greater cortisol levels in humans, which interact with mineralocorticoid receptors and promote sodium ion reabsorption. Glycyrrhizin inhibits the enzymes 3-β-hydroxysteroid dehydrogenase, 17-β-hydroxysteroid dehydrogenase, and 17, 20-lyase, which play a role in androgen and estrogen synthesis (Armanini *et al.,* 2004). Licorice extracts limit the activity of the 11-β-HSD enzyme, which converts androgenic steroids into testosterone hormone, resulting in lower serum testosterone levels (Josephs *et al.,* 2001). A 25 mg alcoholic extract of *G. glabra* may have good estrogenic activity through uterine retention and vaginal opening. Licorice contains isoflavones, which can influence sexual development, impair estrus cycles, and disrupt the correct functioning of the ovarian, hypothalamic, and pituitary glands (Kim and Park, 2012). It has also been shown that isoliquiritigenin and formononetin can enhance sperm during fertilization (Tung *et al.,* 2014).

4.6 Antiobesity and hypolipidemic activity

G. glabra raised the former while lowering the latter, and so played an important role in antiobesity (Icer *et al.,* 2017). In the laboratory trial, glabridin ethanolic extract, ethyl-acetate soluble, water-soluble, and hexane soluble fractions of *G. glabra* lowered total serum cholesterol and triglycerides while increasing serum HDL (Maurya *et al.,* 2009).

4.7 Antiasthmatic activity

Asthma is a common respiratory condition mostly caused by chronic airway inflammation. To treat these airway inflammations, several corticosteroid medications are typically administered. However, long-term usage of these corticosteroid medicines might result in a variety of adverse effects. Compared to that, *G. glabra* is a considerably safer alternative. Licochalcone A, discovered in the root extract of this plant, has antiasthmatic properties. It inhibits TNF-α-induced NF-κB activation by preventing IKB kinase complex activation (Kim *et al.,* 2015). Licorice flavonoids also reduce eosinophilic lung inflammation, Ig levels, IL-3, IL-5, and IL-13 levels, as well as increase INF-gamma activity (Kao *et al.,* 2014), making them potentially protective against asthma.

4.8 Hepatoprotective activity

Chronic hepatitis is a chronic liver condition that leads to cirrhosis, severe hepatocellular carcinoma, and potentially liver failure (Schuppan and Afdhal, 2008). *Glycyrrhiza* has been used to treat chronic hepatitis patients for over 50 years. In a laboratory investigation, it was found to enhance liver histology and lower serum aminotransferases when compared to placebo.18-β-glycyrrhetinic acid reduces P450E1 expression, hence protecting the liver (Jeong *et al.,* 2002). Glycyrrhetinic acid inhibits oxidative and hepatic damage caused by aflatoxin (Saxena, 2005). *G. glabra* extract at a daily dose of 2 mg/kg body weight has a significant influence on improving liver function in acute liver disorders (Al-Razzuqi *et al.,* 2012).

4.9 Anticoagulant activity

Anticoagulant therapy, which includes vitamin K antagonists (warfarin), unfractionated heparin, and low molecular weight heparins, is utilized as a treatment approach; however it can increase the risk of bleeding (Ibrahim *et al.,* 2020). Factor Xa (FXa) is a trypsin-like serine protease enzyme that aids in fibrin and clot formation and hence functions as a component of the coagulation cascade (Ibrahim *et al.,* 2020). 250 mg of hydromethanolic licorice extract inhibits FXa *in vitro* (Ibrahim *et al.,* 2020). Glycyrrhizin, a recognized thrombin inhibitor, has been identified in *G. glabra*. As a result, it can slow thrombin-fibrinogen clotting, increase plasma recalcification time, and prevent thrombin-induced platelet aggregation (Sharma *et al.,* 2016).

4.10 Antimicrobial activity

G. glabra includes isoprenoid phenols, which can prevent microbial development. Glycyrrhizinic acid is also effective in treating atopic dermatitis, pruritis, and cysts (Saeedi *et al.,* 2003). Licorice extract has been shown to prevent the proliferation of many viruses, including herpes simplex, influenza virus, and vesicular stomatitis virus (Wang *et al.,* 2015). Glycyrrhizic acid can terminate the latent infection of Kaposi sarcoma-associated herpesvirus (KSHV) by downregulating the expression of latency-associated nuclear antigen (LANA) in B lymphocytes, resulting in the KSHV virus's natural cell death (Curreli *et al.,* 2005). Glycyrrhizin and 18-β-glycyrrhetenic acid restrict viral gene expression and decrease HMGB1 binding to DNA (Wang *et al.,* 2015).

The antifungal activity of hydroalcoholic extracts derived from *G. glabra* roots and rhizomes was investigated. It was evaluated against 19 *Candida* strains utilizing a disc diffusion technique. It was found to be effective against *C. albicans, C. glabrata, C. parapsilosis*, and *C. tropicalis* strains. After 24 h of treatment, inhibitory areas were found (1-1.2 cm) for *C. albicans* and *C. parapsilosis*, 1-13 cm for *C. tropicalis*, and 1.2 cm for *C. glabrata* (Martins *et al.,* 2014).

4.11 Antimalarial activity

Malaria is one of the most important public health issues in Asia, Africa, and Latin America (Chen *et al.,* 1994). *G. glabra* is thought to be a malaria-reducing agent. An *in vitro* study found that 9.95 µg/ml water-methanol and 13 µg/ml ethyl acetate fractions isolated from the root extract of licorice possess good antiplasmodial activity against *P. falciparum* strain with low toxicity against HeLa cells. An *in vivo* study showed that administration of these fractions of licorice root extracts inhibited 72.2 per cent and 65 per cent growth of *P. berghei* in mice (Ramazani *et al.,* 2018). Licorice contains licochalcone, which has antimalarial properties. In mice, an oral dose of 1000 mg/kg totally eliminated malaria parasites (Schwikkard and van Heerden, 2002).

4.12 Anti-inflammatory activity

The anti-inflammatory effect of *Glycyrrhiza* extracts has been studied both *in vitro* and *in vivo*. Five flavonoids isolated from licorice extract have anti-inflammatory properties, reducing nitric oxide, interleukin-6, and prostaglandin E2 levels in lipopolysaccharide-induced macrophage cells (Fu *et al.,* 2013). Cytokines such as tumor necrosis factor-alpha, interleukin-6, and interleukin-10 were significantly reduced when macrophage cells were treated with licorice extract at a concentration of 0.2-0.5 mg/ml (Mueller *et al.,* 2010). Glycyrrhizic acid, an aqueous root extract of licorice, can suppress cyclooxygenase activity. It has steroid-like anti-inflammatory activity, similar to hydrocortisone, and inhibits phospholipase A2, which is responsible for a variety of inflammatory processes. Usually, the balance of angiogenic and antiangiogenic factors maintains corneal avascularity. When the balance shifts toward angiogenic factors, corneal neovascularization (CNV) develops (Cursiefen *et al.,* 1998). CNV affects around 4.14 percent of the global population (Chang *et al.,* 2012). CNV development exacerbates corneal transparency due to the ingrowth of new blood vessels from the eye's limbus region, resulting in visual impairment and blindness (Hosseini and Nejabat, 2007). Several pathogenic circumstances, including inflammation, infection, degeneration, and traumatic diseases, contribute to the development of CNV (Shah *et al.,* 2018). Among these, infectious corneal disorders are the leading cause of CNV (Zhang and Ma, 2007). However, nonsteroidal anti-inflammatory medications, steroids, laser therapies such as thermal argon laser photocoagulation (Jiang *et al.,* 2019) and limber transplantation (Shao *et al.,* 2004) have been utilized to cure CNV, but their drawbacks include high cost, minimal efficacy, and adverse effects. Licorice extract has been found to effectively halt CNV. Glycyrrhizin and various other licorice chemicals can decrease CNV but do not totally eliminate the disorder. The ophthalmic drop of crude licorice extract (2 per cent w/v methanolic extract of licorice) and 1 per cent w/v glycyrrhizin inhibits the growth of vessels in the corneal region, making it effective in the treatment of CNV (Treede, 2018).

4.13 Analgesic activity

The international association for the study of pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with real or potential tissue injury, or described as such (Kirkpatrick *et al.,* 2016). *G. glabra* is a frequent natural pain reliever. The hydroalcoholic root extract of licorice inhibits the immigration of white globules as well as the production of inflammatory mediators and neutrophils, as demonstrated by the formalin and light tail-flick tests (Kim *et al.,* 2010). Furthermore, an alcoholic extract of licorice including hydroglia aspirin C, dehydrogol aspirin D, glycaemia coumarin, glycerin (Noori *et al.,* 2018), and glycyrrhizin in ammonium salt exhibits anti-inflammatory effect (Ahmad *et al.,* 1993).

4.14 Antiallergic activity

In most nations, allergic diseases such as asthma, rhinitis, and atopic dermatitis have become the most frequent health concerns (Shoormasti *et al.,* 2018). Mast cells and basophils are responsible for a variety of biological processes that contribute to allergic diseases. TNF-α induces MUC5AC protein and mRNA expression in cultured NCI-H292 cells. Glycyrrhizin suppresses the transcription of the MUC5AC gene, which reduces mucus hyperproduction (Nishimoto *et al.,* 2010). Furthermore, glycyrrhizic acid treats ovalbumin-induced allergic asthma by inhibiting OX40-OX40L and p38 MAPK activity, which modulates the Th1/Th2 balance (Wu *et al.,* 2016). The licorice doses of 50 mg/kg and 100 mg/kg inhibit scratching behavior by 18 per cent and 29 per cent, respectively (Shin *et al.,* 2007). Further they reported that 50 mg/kg of liquiritigenin and the same amount of 18-β-glycyrrhetinic acid reduced scratching frequency by 51 per cent and 52 per cent, respectively.

4.15 Antioxidant activity

Glycyrrhiza's antioxidant properties have been tested and shown in both *in vitro* and *in vivo* investigations (Dirican and Turkez, 2014). *In vitro*, *Glycyrrhiza* root extract was combined with DPPH (1, 1-diphenyl-2-picrylhydrazyl) to conduct a scavenging assay. Glabridin has antioxidant action against LDL oxidation. Licochalcones B and D found in *Glycyrrhiza* can prevent microsomal lipid peroxidation and protect biological systems from oxidative stress (Sharma *et al.,* 2016). Similarly, licochalcone C can inhibit superoxide radical generation and inducible nitric oxide synthase (iNOS) activity by acting as an antioxidant (Dirican and Turkez, 2014). Retrochalcone from *G. glabra* can shield red blood cells from oxidative hemolysis. As a result, it is estimated that *G. glabra* flavonoids have a 100-fold higher antioxidant capacity than vitamin E (Damle, 2014).

4.16 Immunostimulatory activity

The virus that causes this ailment is Influenza, an H1N1. *In vitro* studies have shown that N-Acetylmuramyl, an analog of glycyrrhizin, has the potential to inhibit virus replication (Baltina, 2003). *Glycyrrhiza* polysaccharide extracts activate macrophages and boost immunological responses. When neutrophils are combined with an alcoholic extract of *Glycyrrhiza*, the phagocytic capability increases (Vikhe *et al.,* 2013). Another *in vitro* investigation found that licorice at a dosage of 100 ìg/ml has an immunostimulant effect (Damle, 2014). It may stimulate the development of TCD69 lymphocytes and macrophages in human granulocytes. The root extract of *Glycyrrhiza* prevented the accumulation of excessive immune complexes associated with autoimmune diseases such as systemic lupus erythematosus (Damle, 2014).

4.17 Learning and memory-enhancing activity

Licorice contains antioxidant properties that help minimize brain damage by removing or using free radicals while boosting cognitive function and memory (Kim *et al.,* 2012). The cognitive-enhancing potential of *G. glabra* (licorice) root extract was evaluated using behavioural models such as the plus-maze and morris water maze tests. To translate these findings into a practical intervention, a tablet formulation was prepared using crude root extract powder and standardized for experimental use. A total of 123 healthy male students participated in a controlled study, wherein participants were randomly assigned to test and placebo groups. Both groups underwent assessment using the nonverbal intelligence test (NVIT). The results revealed that administration of *G. glabra* tablets, taken twice daily, significantly improved learning and memory performance compared to placebo. Moreover, the treatment was well tolerated and associated with minimal adverse effects, suggesting that licorice supplementation can serve as a safe and effective cognitive enhancer in student populations (Teltumbde *et al.,* 2013).

4.18 Antidepressant activity

Glycyrrhizin, a component of the aqueous *Glycyrrhiza* root extract, was found to have antidepressant effects in mice utilizing the forced swim test (FST) and tail suspension test (TST) (Dhingra and Sharma, 2006). In another study the extracts were given to male mice orally for 7 days at doses of 75, 150, and 300 mg/kg in independent groups. In both the FST and TST, a dosage of 150 mg/kg reduced immobility duration while maintaining locomotor activity (Teltumbde *et al.,* 2013).

4.19 Sedative Activity

GABA is a well-studied inhibitory neurotransmitter in the central nervous system (de Leon and Tadi, 2023). Glabridin, a compound derived from *G. glabra*, can activate GABA-induced receptors by positively modulating them, resulting in sedative and hypotonic effects (Jin *et al.,* 2013). The mechanism of action is the same as that of other general anesthetics involving the amino acids N265 and M286, which are found in the second and third transmembrane domains of the beta subunit of GABA receptors (de Leon and Tadi, 2023).

5. Potential toxicity and possible side effects

Licorice consumption in excess has been linked to high blood pressure due to its effect on the renin-angiotensin-aldosterone system. Overdose can produce hypokalemia and salt retention, which leads to edema. Saponins found in licorice can enhance aldosterone function in the kidneys by binding to mineralocorticoid receptors (Sharma *et al.,* 2020). A large dose of glycyrrhizin causes hypermineralocorticoid-like effects (Josephs *et al.,* 2001). Glycyrrhetic acid and licorice saponin inhibit 11-β-hydroxysteroid dehydrogenases, which contribute to the cortisol-induced mineralocorticoid effect. As a result, the sodium concentration rises while the potassium concentration falls (Isbrucker and Burdock, 2006). Licorice extract and glycyrrhizin alter cytochrome P450-related activities, causing cytotoxicity that can enhance the metabolism of the co-administered medicine and so negatively impact human health (Paolini *et al.,* 1998). The usage of this plant during pregnancy may cause water retention and bloating (Pastorino *et al.,* 2018). Licorice extracts increase plasma renin levels while decreasing plasma cortisol, adrenocorticotropic hormone (ACTH), and aldosterone (Al-Qarawi *et al.,* 2002). Licorice should not be used with stimulant laxatives or hypotensive diuretics because potassium loss is associated with these medications (Asl and Hosseinzadeh, 2008). Diabetes is predisposed to hypokalemia and sodium retention, so consuming licorice is contraindicated. People with delayed gastrointestinal transit time are more likely to experience these side effects due to enterohepatic cycling and licorice metabolite reabsorption (Størmer *et al.,* 1993). However, once licorice consumption is discontinued, all of these side effects disappear (Sharma *et al.,* 2016). As a result, the LD_{50} and LC_{50} of licorice must be evaluated when employing it in the medicinal business for an animal study followed by a clinical trial to guarantee that it is used in the appropriate amount while causing the fewest negative effects.

6. *Glycyrrhiza glabra* as potential pharmacological product

As discussed above, *G. glabra* has numerous potential benefits that can be translated into pharmacological value. Many treatments and drugs are still under clinical trials to treat cancer, asthma, ulcers, diabetes, obesity, and other conditions. *G. glabra* can benefit us in any of this situation (Hasan *et al.,* 2021). Ayurvedic medicine makes use of these health benefits. Glycyrrhizin has been utilized intravenously as a treatment in Japan, and it has resulted in significant liver improvement (Sato *et al.,* 1996). According to biochemical data, glycyrrhizinate inhibits 11-β-hydroxysteroid dehydrogenase, an enzyme responsible for cortisol inactivation. As a result, this can have an effect on hormone activity, which can be employed in pharmacology to treat and prevent hypertension and other stress-related disorders (Isbrucker and Burdock, 2006). In China, licorice is even utilized as a medicinal plant to cure arthritis (Noori *et al.,*

2018). *G. glabra*'s main medicinal and pharmacological components include glycyrrhizinic acid, glycyrrhizin, glabridin, isoliquiritin, glaciomarine, and licochalcone A (Pastorino *et al.,* 2018). All of these active chemicals can be used individually to achieve their full impact.

7. Conclusion

G. glabra, commonly known as licorice, is a medicinal plant rich in bioactive compounds that offer significant health benefits through their anti-inflammatory, hepatoprotective, antimicrobial, and antioxidant properties. This review highlights the key active molecules extracted from licorice and their diverse biological functions, emphasizing how different parts of the plant can be optimally prepared and utilized to maximize therapeutic value. The pharmacological potential of licorice presents promising opportunities for pharmaceutical development, aiming to deliver controlled, standardized products that ensure safe and effective use. Although further laboratory and clinical studies are necessary to fully validate these benefits, licorice holds strong promise as a natural herbal product capable of improving health outcomes globally.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Shivani Jaswal: Contributed to writing the original draft, reviewing and editing the manuscript, software handling, project administration, and methodology. **Sachin Sharma:** Contributed to data curation, formal analysis, investigation, and validation. **Manoj Kumar:** Contributed to resources, methodology, and visualization. **Rakesh Sharma:** Contributed to literature review, data analysis, and manuscript editing. **Abhimanyu Thakur:** Contributed to conceptualization, supervision, validation, and overall project administration

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

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