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Review article

Phytochemistry, pharmacological activity, and potential health benefits of *Glycyrrhiza glabra*

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ABSTRACT

Nature has always been an excellent source for many therapeutic compounds providing us with many medicinal plants and microorganisms producing beneficial chemicals. Therefore, the demand for medicinal plants, cosmetics, and health products is always on the rise. One such plant from the Leguminosae family is licorice and the scientific name is *Glycyrrhiza glabra* Linn. It is an herb-type plant with medicinal value. In the following article, we shall elaborately look at the plants' phytochemical constituents and the pharmacological impact of those substances. Several compounds such as glycyrrhizin, glycyrrhizinic acid, isoliquiritin, and glycyrrhizic acid have been found in this plant, which can provide pharmacological benefit to us with its anti-cancer, anti-atherogenic, anti-diabetic, anti-asthmatic, anti-inflammatory, anti-microbial, and antispasmodic activity. Alongside, these products have a different role in hepatoprotective, immunologic, memory-enhancing activity. They can stimulate hair growth, control obesity, and have anti-depressants, sedatives, and anticoagulant activity. This review examines recent studies on the phytochemical and pharmacological data and describes some side effects and toxicity of licorice and its bioactive components.

1. Introduction

From the beginning of human civilization, humans used plants for food, shelter, and treatment. Before the invention of modern medicine and the unprecedented advancement of science and technology, people entirely relied on certain plants with medicinal value. The biochemical study of plants and their natural compounds was extensively studied then, which still prevails in many corners of the world. Among the 250000–400000 plant species, only 6% have been studied for biological activity [1]. Many people in developing countries especially in Africa and Asia still depend on herbal extract to treat several human and animal diseases [2]. Several compounds such as triterpenoids, saponins, tannins, phenols, flavonoids, and alkaloids have been proven to have a positive effect on many physiochemical processes [3]. Since then, humans have developed several medicines with the help of natural products obtained from such medicinal plants. Ayurvedic, a particular type of therapeutic study initiated in India, is still prevalent in many developing countries [4]. Their easier availability, low cost of production, satisfying efficacy, and fewer adverse effects made it popular. *Glycyrrhiza glabra* is one such plant widely used in ayurvedic medicine [5]. This medicinal plant is found in Asia and parts of southern Europe [6]. It is believed that licorice was originated in Iraq [7]. But today, Italy, France, Spain, Greece, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, and China commercially cultivate several *Glycyrrhiza* species [8]. Table 1 tells about the taxonomy of *Glycyrrhiza glabra*. *Glycyrrhiza* genous is consists of about 30 species including *G. glabra, G. uralensis, G. aspera,* etc. Among them, *Glycyrrhiza glabra* has N_2 fixing ability from the atmosphere through symbiosis with the help of N_2 fixing bacteria [9]. It has a plethora of vernacular names such as jaishbomodhu (Bengali), mulaithi (Hindi), licorice (English), aslussiesa (Arab) [10]. Bangladesh, India, China, Spain, Russia, Iran, Italy, etc. countries are the natural habitats of the *Glycyrrhiza* plant where the soil is fertile, sandy, and having river or other water bodies around making the place accessible to sufficient water [5]. The licorice shrub that belongs to the pea family generally grows in subtropical soils [11]. The average height of its pinnate leaves is 7–15 cm comprising 9–17 leaflets each. Flowers are narrow, born in axillary spike and the calyx is short and campanulate [12]. The flowers are approximately 1 cm long and purple to pale whitish blue. The perennial herb itself can grow up to 2.5 cm in height. The fruit is a compressed legume, 1.5 cm in length and usually contains 3–5 brown reniform seeds [12].

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Table 1. Scientific classification of *Glycyrrhiza glabra*.

Taxonomy	
Kingdom	Plantae
Division	Angiospermae
Class	Dicotyledoneae
Order	Rosales
Family	Leguminosae
Genus	*Glycyrrhiza*
Species	glabra Linn

The root system has a fibrous and soft taproot with a bright yellow interior [13]. The taproot has 3–5 subsidiary roots from which the horizontal woody stolon grows [12]. Each of the subsidiary roots is about 1.25 cm long [12]. The licorice root is thick and it has multiple branches that are red or lemon color outside and yellowish or pale yellow color inside [14]. The bark of the roots and rhizomes is brownish green to dark brown [15]. The Indian, Egyptian, Chinese, Greek, Roman use the roots and rhizomes as carminatives. The roots, peeled or unpeeled roots, and rhizomes are used in treating many respiratory tract disorders such as cough, hoarseness, sore throat, bronchitis, asthma, tonsillitis, etc [16]. Besides, licorice has been used for the management of flatulence, stomach ulcer, colic, hyperdipsia, etc. digestive system disorders [16]. It is also used to cure epilepsy, fever, sexual debility rheumatism, paralysis, psoriasis, and jaundice [16]. In addition, it is useful in gout, swelling, acidity, leucorrhoea, bleeding, hiccough, and harmful conditions of vata dosha, gastralgia, cephalalgia, ophthalmology, and pharyngodnia [16]. *Glycyrrhiza* root is used as a medicine and flavoring agent in the food industries for more than 400 years. Licorice extracts are used as flavoring agents in baked food, ice cream, chewing gums, candies, and soft drinks [17]. Moreover, *Glycyrrhiza* is widely used in biomass, bioenergy as well as pulp production [18].

This review focuses on amalgamating experimentally isolated bioactive compounds from *Glycyrrhiza glabra*, their pharmacological role in combating different physiological ailments, and the potential promise of *Glycyrrhiza glabra* as a promising pharmaceutical product. Figure 1 tells about the workflow of this review.

2. Retrieval of published literature

To write this review article, all the previous works regarding this particular *Glycyrrhiza glabra* plant were taken into consideration. The works done from 1990 to 2021 have been studied intensively. Literature searches were done using the keywords such as "*Glycyrrhiza glabra* AND/OR licorice AND/OR Liquorice" in various available online scientific databases. Articles that represent phytochemistry AND/OR pharmacological activity AND/OR health benefits of *Glycyrrhiza glabra* are included in this review. All the articles available on phytochemical and pharmacological activities of *Glycyrrhiza glabra* in PubMed, Web of Science, PMC, Google Scholar, ScienceDirect, and ResearchGate were incorporated in this review. A total of 144 articles were selected for the final documentation. The chemical composition, the methods of biosynthesis, and metabolic reactions of *Glycyrrhiza glabra* were not within the scope of this review article and thus excluded. The screening language was strictly maintained as English.

3. Traditional uses

Glycyrrhiza glabra has versatile traditional uses- it is mixed with butter is used in burns and wounds, *Glycyrrhiza* mixed with Cow's milk is used to promote lactation, the blended root of *Glycyrrhiza* is used as a wash for greying of hair, decoction of *Glycyrrhiza* is used for erysipelas [19], A solution of rice milk prepared with *Glycyrrhiza* is used for hoarseness of voice; the paste of yashti, milk, *Sesamumindicum* mixed with butter are collectively used to treat oedema [19]; *Glycyrrhiza* mixed with honey is supplemented right after the intake of milk as a tonic to boost intelligence [19]; it is applied for the treatment of intrinsic hemorrhage as well [19], *Glycyrrhiza* root extract is used as an eye drop at times of conjunctivitis in India, the powdered form of licorice is mixed with honey as a treatment for anemia, the paste of *Glycyrrhiza* and *Picirrhizakurroa* with sugar water is used as cardiotonic, licorice and *Santalum album* powder mixed with milk is applied on haematemesis [19]. In Pakistan, root paste of licorice mixing with flour and oil is given to cow, goat, buffalo, and sheep to increase milk production and rate of fertility [20]. Root sap of *Glycyrrhiza* is utilized in wine production in the middle region of Turkey [21]. Decoction of root is used as a mild laxative in Italy [22] and juice from root and stem is used as a stimulant, astringent, and tonic in Nepal [23]. It is mixed with tea as the cure for sore throat in Egypt [11].

4. Phytochemistry or bioactive compounds

Many biologically active compounds have been extracted so far from different parts of licorice, most of which are water-soluble and are responsible for almost 40–50% of total dry weight [5]. The names of the biologically active compounds, including their groups, are presented in Table 2.

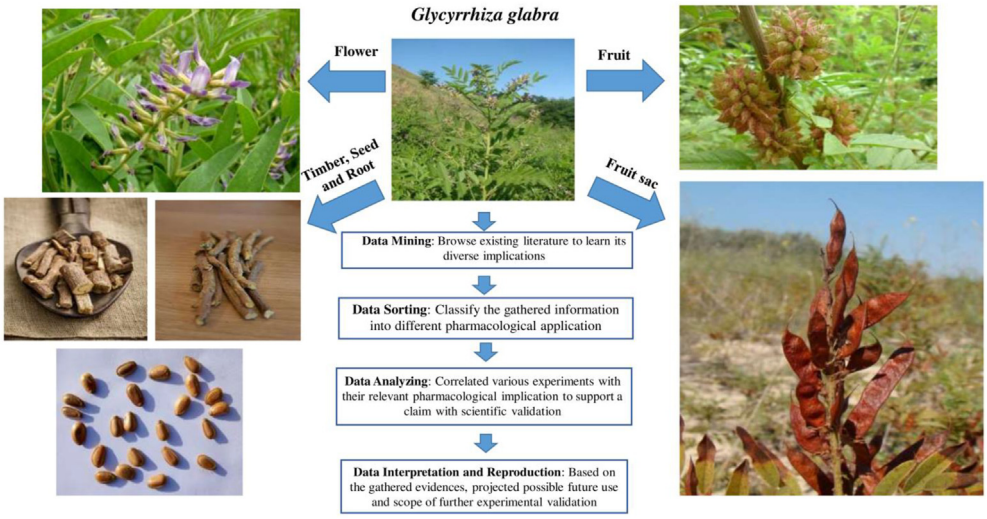

Figure 1. Workflow of the study.

5. Pharmacological activity

The extracts collected or the powder prepared predominantly from the roots and rhizomes usually hold pharmacological importance. Name of ailments and corresponding bioactive compounds are schematically presented in Figure 2.

5.1. Antitussive activity

The licorice powder and its extract are extremely useful in treating sore throat, cough, and bronchial catarrh [18]. The presence of glycyrrhizin, an active compound of *Glycyrrhiza glabra*, enables it to have antitussive, demulcent, and expectorant loosening activities. Glycyrrhizin helps to reduce congestion in the upper respiratory tract and increases tracheal mucus secretion [5]. Liquiritinapioside, an active compound of methanolic extract of licorice, can inhibit capsaicin, which induces cough [18]. Moreover, the ethanolic extract of licorice can inhibit sulfur dioxide gas-induced cough in experimental mice [33]. Licorice decreases irritation, and it works efficiently as codeine in sore throat. Carbenoxolone is a semisynthetic compound derived from *Glycyrrhiza glabra* that increases gastric mucus secretion [34].

5.2. Antiulcerogenic activity

Glycyrrhiza glabra extract can inhibit two enzymes, namely 15-hydroxyprostaglandin and delta 13-prostaglandin reductase [35], for which it is used as an anti-ulcerogenic agent since the 1070s. 15-hydroxyprostaglandin converts prostaglandin E2 and F2 alpha into inactive 15-ketoprostaglandins, and delta 13-prostaglandin reductase converts prostaglandins into 13, 14-dihydro, 15-ketoprostaglandin [11]. As a result of the inhibition of these two enzymes, the prostaglandin level, in turn, increases. Another chemical that can be obtained from *Glycyrrhiza* extract is carbenoxolone. It can inhibit gastrin secretion and ultimately play an anti-ulcerogenic role [36]. It is used as a treatment in gastric and duodenal ulcers at a dose of 100 mg three times a day. Licorice enhances prostaglandins' concentration in the digestive system and promotes mucus secretion from the stomach, prolonging the life span of surface cells in the stomach. As a result, an anti-pepsin effect is observed too [37]. Fraction FM-100 isolated from licorice roots inhibits gastrin's secretion, thus, licorice acts as an antiulcerogenic agent.

5.3. Anti-cancer activity

The bioactive components of *Glycyrrhiza* have shown anti-cancer properties in both *in vivo* and *in vitro* studies [5]. 18-β-glycyrrhetinic acid and glycyrrhizic acids present in *Glycyrrhiza* are responsible for this property, which generally induces mitochondrial permeability transition causing tumor cell apoptosis [38]. The cytotoxicity of methanolic extract of *Glycyrrhiza* was tested by brine shrimp lethality bioassay. It exhibited sufficient cytotoxicity with an LC_{50} value of 0.77 μg/ml [39]. The anti-cancer activity of licorice methanolic extract of 0, 12.5, 25, 50, and 100 μg/ml was evaluated against intestinal carcinoma cell line (Caco 2) and prostate carcinoma cell line (PC-3). Growth inhibitory action of methanolic extract was observed against Caco-2 and PC-3 licorice extract contains a plethora of phytoestrogen compounds, making it a powerful chemopreventive agent. As a result, it could show anti-tumor activity against breast cancer, ovarian cancer, and gastric tumor. One experiment showed that the use of licorice extract with cisplatin could decrease the cisplatin-based toxicity [40]. Glycyrrhizinic acid can induce AKT/mTOR signals on endometrial and breast cancer cells and thus inhibit the proliferation of these cancer cells [41]. Antineoplastic activity of licorice has also been effectively utilized in the treatment of cancer [42]. The extracts of *Glycyrrhiza* can also inhibit cancer cells' growth by interfering in one of its hallmarks, angiogenesis. This property was proved *in vivo* assay [43]. The ethanolic extract exhibits antiproliferative effects against the MCF-7 in an adipose-dependent manner. In albino mice, hydromethanolic extract of licorice showed antimutagenic potential by suppressing the micronuclei formation and chromosomal aberration in bone marrow cells. Besides, it suppressed thromboxane A2 in lung cancer cells, too [44]. It can arrest the G2/M transition in the cell cycle and induces the BCL2 phosphorylation by using the anti-microtubule agent paclitaxel. 70% methanol soluble fraction of licorice extract can induce apoptosis in human monoblastic leukemia U937 cells. Both *in vivo* and *in vitro* study shows 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 because it can bind and inactivate oncogenic TOPK which leads to the activation of p53 pathway [45]. Another compound isolated from licorice is glycerol that can suppress IAPs, combined with butyrate-induced mitochondrial pathway, and can cause cell death in human colon cancer cells HCF116 and HT-29 [46]. Colorectal cancer is the fourth cause of cancer-related death worldwide [47].

Table 2. List of phytochemicals found in *Glycyrrhiza glabra*.

Groups	Bioactive compounds	Reference
Triterpenoid	Glycyrrhizin	[24]
Saponin	Glycyrrhizic acid, 18-β-glycyrrhetinic acid	[25]
Flavonoid	Liquiritin, isoliquiritin, liquiritigenin	[17]
	Glabrene, glabridin	[26]
	Rhamnoliquiritin	[27]
	Glucoliquiritinapioside, prenyllicoflavone A, shrinflavonone, shrinpterocarpin, 1-methoxy-phaseolin	[28]
	Glisoflavone, kanzonol R,	[16]
	Licochalcone A	[29]
	Hispaglabridin A and B, licuraside, glyzaglabrin	[29]
Coumarin	Licocoumarin	[5]
	Glycycoumarin, licopyranocoumarin, glabrocoumarone A and B	[30]
Isoprenoid substituted phenol	Semilicoisoflavone B, 1- methoxyficifolinol, isoangustone A, licoriphenone	[28]
Alcohol (Volatile)	Pentanol, hexanol	[28]
	2,3 Butanediol	[16]
Acid (Volatile)	Propionic acid, benzoic acid, ethyl linoleate	[31]
	Acetic acid, malic acid, butyric acid, fumaric acid, citric acid	[32]
Terpenoid	Alpha terpineol,	[16]
	Geraniol	[28]
Aldehyde	Furfuraldehyde	[16]

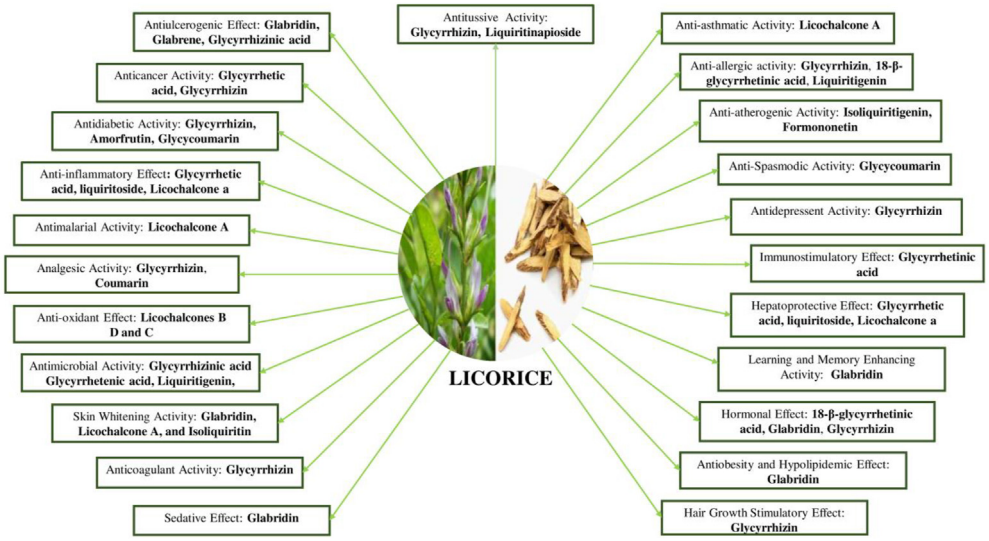

Figure 2. List of Bioactive compounds available in Licorice and their role in alleviating different physiological ailments.

In colorectal cancer, several processes such as mutations in oncogenes, inactivation of tumor suppressors, the existence of various signaling pathways, dysregulation of apoptosis, morphological progression have been observed [48]. 18-β-glycyrrhetinic acid, a pentacyclic triterpenoid extracted from the licorice root, has potent inhibitory effects on colorectal cancer cell proliferation in a dose-dependent and time-dependent manner both in *in vivo* and *in vitro* experiment [49]. Glycyrrhetenic acid decreases the protein levels of p-PI3K, p-AKI, p-STAT3, p-JNK, p-P38, and p-NFkBP65. Among these, the phosphorylation of PI3K and STAT3 in LoVo, SW620, and SW480 cells decreases after 2 h of glycyrrhetinic acid treatment [49]. Activation of PI3K or AKI signaling pathway increases cell survival, outgrowth, and cell migration in cancer cells [50]. Inhibition of these pathways downregulates the expression of MMP 1, 2, 3, 9, 12, 13, and MTI-MMP and suppresses the proliferation and invasion of cancer cells [51]. Glycyrrhetenic acid also inhibits metastasis by impairing the p38-MAPK-AKI signaling axis [52], disrupts the actin cytoskeleton [53], and induces Fas or DNA fragmentation-mediated apoptosis [54]. Besides, it shows toxicity selectively against tumor cells. Its efficacy is more potent than many clinically available anti-tumor agents [53]. Glycyrrhetenic acid also reduces matrix metalloproteinase (MMP) expression [49].

5.4. Antidiabetic activity

Type-2 diabetes mellitus is a well-known metabolic disorder that manifests high blood glucose levels due to insulin insensitivity and inactivity. Several transcription factors are involved in glucose and lipid metabolism [11], out of which Peroxisome proliferation activated receptors (PPAR's) are one of them. These PPAR receptors are expressed mainly in liver, muscle, and kidney tissues. This PPAR can be classified into alpha, gamma, and delta. The insulin-sensitizing drugs mostly target this PPAR gamma receptor. Several compounds were obtained from *Glycyrrhiza glabra* root and crude extracts such as Glycycoumarin, glycyrin, glyasperin D, dehydroglyasperin, glyasperin B, and iso-glycyrol ethyl solution can significantly bind to PPAR gamma ultimately leading to lowered blood glucose level [11]. Chalcone and amorfrutin obtained from *Glycyyrhiza* helps in adipocyte differentiation and ameliorates glucose and lipid metabolism [55]. Amorfrutin can increase insulin sensitivity as well as enhance glucose tolerance. Glabridin prevents glucose intolerance and ensures maximum glucose utilization by translocation of GLUT-4 using Adenosine Mono Phosphate Protein Kinase AMPK [56]. Glycyrrhizin enhances the level of glycohaemoglobin, cholesterol, and triglyceride by reducing serum insulin level and pancreatic islet cell numbers [14]. Thus, licorice can play a crucial role in insulin resistance-related illnesses.

5.5. Hormonal activity

Licorice can influence cortisol and estrogen action and reduce testosterone synthesis [57]. *Glycyrrhiza* contains glycyrrhizin and 18-β-glycyrrhetinic acid, which have mineralocorticoid properties and thereby can inhibit cortisol metabolism. Licorice can reduce the side effects of spironolactone's diuretic activity in patients with the polycystic ovarian syndrome (PCOS) [58]. 18-β-glycyrrhetinic acid can be a potent competitive inhibitor of 11-β-hydroxysteroid dehydrogenases (11-β-HSD). A lowered level of 11-β-HSD can result in higher cortisol in humans, ultimately interacting with the mineralocorticoid receptors and promoting sodium ion reabsorption. Glycyrrhizin can block the 3-β-hydroxysteroid dehydrogenase, 17-β-hydroxysteroid dehydrogenase, and 17,20-lyase enzyme that basically takes the role in the metabolism and thus in the synthesis of androgen and estrogen [59]. Licorice extracts reduce the activity of the 11-β-HSD enzyme that catalyzes androgenic steroids into testosterone hormone and, therefore, ultimately decreases serum testosterone hormone level [60]. 25 mg alcoholic extract of *Glycyrrhiza glabra* could exhibit fine estrogenic activity through uterine retention and vaginal opening. Isoflavones present in licorice can influence sexual development, impair estrus cycling, and alter the proper functioning of the ovarian, hypothalamus, and pituitary glands [61]. For this, glabridin is used as a treatment for menopausal symptoms and shows an outcome similar to that of 17-β-oestradiol [62]. It has also been observed that isoliquiritigenin and formononetin can stimulate the sperm at the time of fertilization [63].

5.6. Anti-obesity and hypolipidemic effect

Acetyl CoA dehydrogenase and acetyl CoA carboxylase are two very important enzymes involved in lipid metabolism [64]. *Glycyrrhiza glabra* increased the former level while decreasing the later, subsequently played a crucial role in anti-obesity [40]. In the laboratory experiment, glabridin ethanolic extract, ethyl-acetate soluble, water-soluble, and

hexane soluble fractions of *Glycyrrhiza glabra* reduced total serum cholesterol, triglyceride, and increased serum HDL (High Density Lipoprotein) [65].

5.7. Anti-asthmatic activity

Asthma is a common respiratory disorder mainly caused due to chronic airway inflammation. Usually, different corticosteroid drugs are used to treat these airway inflammations. But long-term use of these corticosteroid drugs can bring several side effects. Compared to that, *Glycyrrhiza glabra* is a much safer option. Licochalcone A found from the root extract of this plant has anti-asthmatic activity. It inhibits nuclear factor kappa B (NF-KB) activation caused by TNF-α by blocking IKB kinase complex activation [66]. Alongside, licorice flavonoids reduce eosinophilic lung inflammation, Ig levels, IL-3, IL-5, IL-13 levels and enhance INF- gamma activity [67] and thus can serve as a protection against asthma.

5.8. Hepatoprotective effect

Chronic hepatitis is a progressive liver disease that causes cirrhosis leading to severe hepatocellular carcinoma or even up to liver failure [68]. In the treatment of chronic hepatitis patients, *Glycyrrhiza* has been used for more than 50 years. In a laboratory experiment, it has shown improved liver histology and reduced serum aminotransferases compared to placebo. Hydromethanolic root extract of *Glycyrrhiza* at a 300 and 600 mg/kg dose for 7 days has shown hepatoprotective effect against CCl_4 induced oxidative stress in liver tissue of Swiss albino mice [69]. 18-β-glycyrrhetinic acid has also decreased the expression of P450E1 and thus protects the liver [70]. Glycyrrhetinic acid prevents oxidative and hepatic damage caused due to aflatoxin [71]. *Glycyrrhiza glabra* extract at a single dose per day of 2 mg/kg body weight shows a significant impact in improving liver function in acute liver diseases [72]. Aqueous and methanolic extracts of *Glycyrrhiza* inhibit the activity of Aspartate aminotransferase that was elevated by CCl_4 in rats to produce acute hepatotoxicity [73].

5.9. Antispasmodic activity

When licorice is hydrolyzed by heat and converted into isoliquiritigenin it exhibits strong solid spasmolytic activity [74]. Coumarin compounds isolated from licorice can help controlling abdominal cramping, fecal urgency, and postprandial lower abdominal discomfort associated with diarrhea [75]. Glycycoumarin showed an inhibitory effect on smooth muscle contraction induced by different types of stimulants such as carbachol, KCL, barium chloride, and calcium ionophore 3 by inhibiting phosphodiesterases increasing intracellular cyclic AMP when experimented in male ICR mice [76] Another study showed that (2.7 mmol/kg) glycycoumarin reduces tetanus induced contractions by suppressing calcium ion-induced concentrations and relieve muscle cramps by (15–22)%, but a higher dose of glycycoumarin (27 mmol/kg) glycycoumarin more rapidly reduces the amplitude of tetanus-induced contractions by (17–24) % [77]. Alcoholic extract of licorice has antispasmodic activity because it can reduce the contraction of the ileum that is independent of beta-adrenergic, opiodic, and NO receptors [18]. Another study again found that alcoholic extract of licorice rhizome decreases duodenum contraction independent of cholinergic acid, beta-adrenergic receptors, and NO pathway and increases the smooth muscle relaxation of intestinal cells [78].

5.10. Effect on fertilization

Water extract of licorice increases the rate of *in vitro* fertilization (IVF) [79]. Artificial insemination is an assisted reproductive technology in which pregnancy can be achieved by introducing semen into the female genital tract artificially. Artificial insemination is vital for cattle breeding as well as an infertility treatment for humans [80]. In this process, ejected sperm cell undergoes a maturation process after a definite period, then causes an acrosome reaction, and finally, an egg is fertilized. It is found that two water extracts of licorice, isoliquiritigenin, and formononetin improve the rate of IVF in the rodent model [79]. Estrogen influences the activation of sperm and acrosome reactions. Isoliquiritigenin possesses strong estrogen-like activity. Formononetin helps in sexual development, including pubertal timing, ovarian function, impaired estrous cycling, and functions of the pituitary and hypothalamus [61]. Isoliquiritigenin and formononetin affect sperm during fertilization yet the embryos are not affected [79].

5.11. Anti-atherogenic effect

The anti-atherogenic activity of *Glycyrrhiza glabra* has been found from *in vivo* and *in vitro* studies [81]. The alcoholic root extract of *Glycyrrhiza glabra* can act as a potential anti-oxidant in hypercholesterolemia patients and atherosclerotic apolipoprotein-E deficient mice when given in 0.1 g/day for 1 month [70]. It can also inhibit the oxidation of LDL (Low Density Lipoprotein) [82].

5.12. Anticoagulant activity

Pulmonary emboli, deep vein thrombosis, cardiovascular diseases are the major causes of death and disability that may arise from blood clotting [83]. Anticoagulant therapy such as vitamin K antagonists (warfarin), unfractionated heparin, and low molecular weight heparins are used as a treatment strategy but these can increase the bleeding risk [84]. Factor Xa (FXa); a trypsin-like serine protease enzyme helps in fibrin and clot formation and thus acts as a component of the coagulation cascade [84]. Recently, FXa inhibitors have been used as new oral anticoagulants (NOAC) [85]. The dose of 250mg hydromethanolic licorice extract exhibits FXa inhibitory effects in vitro [84]. Glycyrrhizin has been found in *Glycyrrhiza glabra*, which is well known as an inhibitor of thrombin. As a result, it can delay the thrombin-fibrinogen clotting time, enhances plasma recalcification duration, and inhibit thrombin-induced platelet aggregation [5]. However, Collagen-induced platelet agglutination is not affected by this process [5].

5.13. Anti-microbial activity

Glycyrrhiza glabra contains isoprenoid phenols that can selectively inhibit microbial growth. Glycyrrhizinic acid can also be used to cure atopic dermatitis, pruritis, and cysts [86]. The growth of viruses including herpes simplex, influenza virus, and vesicular stomatitis virus has been seen to be inhibited by licorice extract [87]. Besides, Glycyrrhizin can interfere in viral binding and thus prevent viral replication. This has benefitted patients from SARS, HIV-1, and chronic hepatitis C virus [88]. 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 and thereby results in natural cell death of the KSHV virus [89]. Glycyrrhizin and 18-β-glycyrrhetenic acid inhibit virus gene expression and reduce HMGB1 binding to DNA [87]. These compounds increase host cell activities, including the propagation of the cellular response to inflammation, T lymphocyte proliferation, and suppression of host cell apoptosis by blocking the degradation of the enzyme IkB [87].

The hydroalcoholic extracts collected from the roots and rhizomes of *Glycyrrhiza glabra* have been checked for antifungal capacity. It was tested against 19 strains of *Candida* by using the disc diffusion assay. The effective activity was observed against *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* strains. After 24 h of application, inhibitory regions were observed [1–1.2 cm] for *C. albicans* and *C. parapsilosis*, 1–13 cm for *C. tropicalis,* and 1.2 cm for *C. glabrata* [90]. 80% methanolic extract *Glycyrrhiza glabra* can exhibit an inhibitory effect against Aspergillusniger, just like synthetic drug fluconazole [91]. Besides, *Glycyrrhiza*

glabra produces important secondary metabolites like alkaloids, flavonoids, and saponins those exhibit antibacterial effects [87]. Alcoholic extract of *Glycyrrhiza* has shown antibacterial activity against *Escherichia coli*, *Pseudomonas fluorescens*, *Enterococcus faecalis*, *Bacillus cereus,* and *Staphylococcus aureus,* etc. The maximum inhibition diameter observed was 15 mm against *E. coli*, *E. faecalis*, and *B. cereus* [92]. In *in vitro* analysis, *Glycyrrhiza* also affected membrane permeability, efflux activity, and biofilm formation of *Pseudomonas aeruginosa* and *S. aureus* can produce an exotoxin named α-haemolysin, which can cause myriad diseases such as skin infections and lethal pneumonia, etc. Liquiritigenin prevents the formation of α-haemolysin, which can protect human lung cells (A549) from α-hemolysin mediated injuries [92].

5.14. Antimalarial activity

Malaria is one of the most serious health problems in Asia, Africa, and Latin America [93]. In 2012, the World Health Organization (WHO) estimated the 219 million global incidences of malaria and 660000 deaths due to this disease [94]. *Glycyrrhiza glabra* is considered as a constituent that can reduce the risk of malaria. An *in vitro* study showed 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 whereas the *in vivo* study showed that administration of these fractions of licorice root extracts inhibits 72.2% and 65% growth of *P. berghei* in mice [95]. Licorice contains licochalcone, which has antimalarial activity. An oral dose of 1000 mg/kg in mice has completely eradicated malarial parasites [96].

5.15. Anti-inflammatory effect

The anti-inflammatory activity of *Glycyrrhiza* extracts has been tested both *in vitro* and *in vivo* [97]. Five flavonoids isolated from licorice extract exhibit anti-inflammatory potential by reducing nitric oxide production, interleukin-6, and prostaglandin E2 in lipopolysaccharide-induced macrophage cells [98]. Cytokines such as tumor necrosis factor-alpha, interleukin-6, and interleukin-10 were greatly reduced by treating the macrophage cells with licorice extract at a concentration of (0.2–0.5) mg/ml [99]. Glycyrrhizic acid, an aqueous root extract of licorice can inhibit cyclooxygenase activity. It has steroid-like anti-inflammatory activity just like hydrocortisone, which inhibits phospholipase A2 activity responsible for numerous inflammatory processes [100]. For this, *Glycyrrhiza* is used to treat allergies and other inflammatory diseases [100]. The outer tissue of the eye, the cornea, is avascular, transparent and this transparency is vital for clarity of vision. Usually, the balance between angiogenic and antiangiogenic maintain corneal avascularity. When the balance shifts towards angiogenic factors, corneal neovascularization (CNV) occurs [101]. About 4.14% of the world's population is affected by CNV [102]. CNV development exacerbates corneal transparency because of the ingrowth of new blood vessels from the eye's limbus region which eventually causes visual impairment and blindness [103]. Several pathological conditions such as inflammation, infection, degeneration, traumatic disorders are responsible for developing CNV [104]. Among these, infectious diseases of the cornea are the most critical cause of CNV [105]. Albeit, the use of non-steroidal anti-inflammatory drugs, steroids, laser therapies like thermal argon laser photocoagulation [106] and limber transplantation [107] has been used to treat CNV, the limitations of which are high cost, low efficacy, and side effects. It is found that the extract of licorice effectively halts CNV. Glycyrrhizin and several other compounds in licorice can inhibit CNV but not completely diminish the condition. The ophthalmic drop of the crude extract of licorice (2% w/v methanolic extract of licorice) and (1% w/v glycyrrhizin) inhibits the growth of vessels in the corneal region, thus effective in the treatment of CNV [104].

5.16. Analgesic activity

According to the International Association for the study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with the actual or potential tissue damage or described in terms of such damage [108]. Pain can be chronic or acute according to duration. Analgesics are substances that act on the central nervous system (CNS) and peripheral nervous system to reduce pain [109]. *Glycyrrhiza glabra* is a common natural analgesic [110]. It has been proved by using formalin and light tail-flick test, the hydroalcoholic root extract of licorice inhibits the immigration of white globules and the production of inflammatory mediators and neutrophils [111]. Moreover, the alcoholic extract of licorice produced of hydroglia aspirin C, dehydrogol aspirin D, glycaemia coumarin, glycerin [112], and glycyrrhizin in ammonium salt possess anti-inflammatory activity [113].

5.17. Anti-allergic activity

In most countries, allergic disease like asthma, rhinitis, and atopic dermatitis has become the most common health problems [114]. Mast cells and basophils are responsible for the various biological process leading to allergic diseases. These cells and cell surface-bound IgE release histamine, cytokines, prostaglandins. Cytokines further stimulate chemotaxis and phagocytosis of neutrophils and macrophages which eventually create inflammation of the tissue. According to *in vivo* and *in vitro* studies, *Glycyrrhiza* has the potential to treat allergic diseases [115]. Glycyrrhizin, 18-β-glycyrrhetinic acid, isoliquiritin, and liquiritigenin isolated from licorice have anti-allergic such as anti-scratching properties and IgE production inhibitory activity [18]. Liquiritigenin and 18-β-glycyrrhetinic obtained from methanolic extracts inhibit the degranulation of RBL-2H3 cells induced by IgE and (DNP-HSA) antigen [97]. These also inhibit the anaphylactic reaction induced by the compound 48/80. Glycyrrhizic acid, liquiritigenin, liquiritin inhibit inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), TNF-α, IL-1 β, IL-4, IL-5 and IL-6, etc pro-inflammatory mediators in BV2 cells [24]. Glycyrrhizic acid helps to enhance the 60% cell membrane permeability and decreases the elasticity modulus of the cell membrane in human RBC [116]. In cultured NCI–H292 cells, TNF-α expresses MUC5AC protein and mRNA. Glycyrrhizin inhibits the transcription of the MUC5AC gene leading to attenuate the mucus hyperproduction [117]. Besides, glycyrrhizic acid has a therapeutic effect on ovalbumin-induced allergic asthma by suppressing OX40-OX40L and p^{38} MAPK activity that regulates the Th1/TH2 balance [118]. The 50 mg/kg and 100 mg/kg doses of licorice inhibit the scratching behavior by 18% and 29% respectively [97]. It has been proved that the 50 mg/kg dose of liquiritigenin and the same dose of 18-β-glycyrrhetinic acid inhibit 51% and 52% frequency of scratching behavior [97].

5.18. Anti-oxidant effect

The anti-oxidant property of *Glycyrrhiza* has been checked and proved in both *in vitro* and *in vivo* studies [119]. For *in vitro* analysis, *Glycyrrhiza* root extract was mixed with DPPH (1,1-diphenyl-2-picrylhydrazyl) to perform a scavenging assay. The methanolic extract was found to be a potent anti-oxidant with a maximum scavenging effect of 67.22% at a concentration of 500 μg/ml [120]. The IC_{50} calculated for it was 359.45 μg/ml [14]. Phenolic contents present in the ethanolic extracts such as glabridin, hispaglabridin A, and 30-hydroxy-40-methylglabridin- all have anti-oxidant activity through free radical scavenging,

hydrogen-donating, metal ion chelating, and reducing abilities. Glabridin provides anti-oxidant activity against LDL oxidation. Licochalcones B and D, present in *Glycyrrhiza* can inhibit microsomal lipid peroxidation and protect biological systems against oxidative stress [5]. Similarly, licochalcone C can reduce the production of superoxide radicals and the activity of inducible nitric oxide synthase (iNOS), due to functioning as an effective anti-oxidant [121]. Retrochalcone from *Glycyrrhiza glabra* can protect red blood corpuscles from oxidative hemolysis. Hence, it is estimated that the anti-oxidant capacity of *Glycyrrhiza glabra* flavonoids is 100 times more potent than that of vitamin E [33].

5.19. Immunostimulatory effect

Swine flu, one of the deadliest respiratory diseases of pigs, see an upsurge every autumn and winter in temperate regions every year [122]. The virus that is responsible for this disease is Influenza, an H1N1. In *in vitro* analysis, it has been seen that N-Acetylmuramyl, an analog of glycyrrhizin has the potential to restrict the virus replication [123]. Polysaccharide extracts of *Glycyrrhiza* stimulate the macrophages and increase the immune stimulations. Neutrophils, when mixed with alcoholic extract of *Glycyrrhiza*, increases the phagocytic capacity [124]. In another *in vitro* study, licorice at 100 μg/ml concentration exhibits an immunostimulatory effect [33]. It could enhance the production of TCD69 lymphocytes and macrophages in human granulocytes. The root extract of *Glycyrrhiza* prevented the accumulation of excessive immune complexes involved in autoimmune diseases like systemic lupus erythematosus [33].

5.20. Learning and memory-enhancing activity

Licorice has an anti-oxidant activity that can reduce brain damage by eliminating or utilizing the free radicals and improving neural function and memory [125]. A Plus-maze and Morris water maze tests were conducted to evaluate the learning and memory-enhancing ability of *Glycyrrhiza glabra* root extract. 150 mg/kg dose of aqueous extract root was enough to observe a significantly enhanced learning ability and memory [126]. Crude powder of the root extracts was used to prepare a *Glycyrrhiza glabra* tablet. After standardization, it was used in an experiment involving 123 male students. After dividing the candidate into the test group and placebo group, NVIT (Non-Verbal Intelligence Test) was conducted on either of them. It was seen that oral consumption of licorice twice a day could improve the student's intelligence level compared to placebo treatment with minimal side effects [127].

5.21. Anti-depressant activity

Glycyrrhizin, a component of the aqueous *Glycyrrhiza* root extract showed anti-depressant effects in mice using the forced swim test (FST) and tail suspension test (TST) in an experiment [128]. The extracts were administered orally for 7 successive days in male mice at a dose of 75, 150, and 300 mg/kg in separate groups. In both the FST and TST, the dose of 150 mg/kg showed reduced immobility time without compromising locomotor activity [128].

5.22. Sedative effect

GABA or Gamma Amino Butyric Acid is a well-studied inhibitory neurotransmitter in the central nervous system (CNS) [129]. Glabridin, a compound obtained from *Glycyrrhiza glabra* can induce GABA-induced receptors by positively modulating the GABA receptors and show sedative and hypotonic effects [130]. The mode of action is merely the same as other general anesthetics involving the amino acids N265 and M286, which are located in the second and third transmembrane domains on the beta subunit of GABA receptors [131].

5.23. Hair growth stimulatory effect

The hydro-alcoholic extract of *Glycyrrhiza* possesses good hair growth-promoting activity [132]. In treating alopecia, *Glycyrrhiza glabra* has long been used as herbal medicine. A study [132] has shown better hair growth stimulatory effect than 2% minoxidil.

5.24. Skin whitening activity

The anti-oxidant and anti-inflammatory effects of Glycyrrhizin can protect the skin [133]. It can act as an effective pigment-lightening agent. Glabridin, licochalcone A, and isoliquiritin inhibit tyrosinase (an enzyme involved in the biosynthesis of melanin that is vital for skin pigmentation) in cultured B16 murine melanoma cells [134]. In an *in vitro* experiment, 21.2 μg/ml of methanolic extract of licorice could inhibit tyrosinase activity by up to 50% [134]. Ethanolic extract of licorice helped skin retain water more effectively and stay hydrated [33]. Human keratinocytes with 18-β-glycyrrhetinic acid and glabridin have prevented DNA damage and thus avoid apoptosis activation caused due to UVB radiation [132]. For all these, licorice is popular in treating dermatitis, pruritus, cysts, and eczema. It is also used for cosmetic formulation as a depigmenting agent to inhibit the tyrosinase enzyme [135].

6. Potential toxicity and possible side effects

The excess consumption of licorice is associated with elevated blood pressure due to its effect on the renin-angiotensin-aldosterone system. Sometimes overdose causes hypokalemia and sodium retention leading to edema. Saponins present in licorice can potentiate the aldosterone action in the kidneys while binding to mineralocorticoid receptors [5]. A high amount of glycyrrhizin consumption produces hyper-mineralocorticoid like effects [18]. As a result of inhibiting the enzyme 11-β-hydroxysteroid dehydrogenases, glycyrrhetic acid, and licorice saponin helps in the cortisol-induced mineralocorticoid effect. So, the level of sodium is increased and potassium level is decreased [136]. Prolonged use of glycyrrhizin leads to pseudoaldosterinism which makes a person hypersensitive to the hormone of the adrenal cortex. As a result of pseudoaldosterinism headaches, fatigue, high blood pressure, and even heart attack can occur. It is also responsible for water retention from which leg swelling and other problems may arise [137]. Licorice extract and glycyrrhizin change cytochrome P_{450} related activities and create cytotoxicity that can increase the metabolism of the co-administered drug and thus adversely affect our health [138]. The use of this plant may responsible for water retention and bloating during pregnancy [18]. The treatment with licorice extracts increases plasma renin and decreases the level of plasma cortisol, adrenocorticotropic hormone (ACTH), and aldosterone [139]. As the loss of potassium is associated with laxatives and diuretics, licorice should not use with stimulant laxatives or hypotensive diuretics [140, 141]. Insulin-dependent diabetes is predisposed to hypokalemia and sodium retention so licorice ingestion is contradicted by diabetes [136, 142]. Usually, people suffering from delayed gastrointestinal transit time experience these side effects more because of enterohepatic cycling and licorice metabolites reabsorption [143]. But with the discontinuation of licorice consumption, all of these side effects disappear [5]. Therefore, LD_{50}, LC_{50} of licorice has to be considered while using them in the medicinal industry for an animal trial followed by clinical trial to ensure how to have it in the right amount keeping minimum side effects.

7. *Glycyrrhiza glabra* as potential pharmacological product

From the above discussion, we have seen *Glycyrrhiza glabra* has numerous potential benefits that can be translated into pharmacological value. The plethora of medicines and drugs stay stuck at clinical trials to treat cancer, asthma, ulcer, diabetes, obesity, etc. *Glycyrrhiza glabra* can be used to help us in all of them. Ayurveda medicine makes use of its

health benefits. Glycyrrhizin has been intravenously used as a treatment in Japan and it has yielded remarkable liver improvement [144]. Biochemical evidence suggests that glycyrrhizinate inhibits 11-β-hydroxysteroid dehydrogenase, the enzyme that inactivates cortisol. Thus, this can have an impact on hormonal activity which can be used in pharmacology to treat and prevent hypertension and other stress-related conditions [136]. In China, Licorice is even used to treat Arthritis as a medicinal plant [7]. Extensive researches and experiments have been conducted on the pharmacological value of the active compounds of this plant *in vitro* and *in vivo*, both in rodents and humans-most of them gave substantial evidence to carry this on to the next step [135]. The principal ingredients of *Glycyrrhiza glabra* responsible for the therapeutic and pharmacological values are mainly glycyrrhizinic acid, glycyrrhizin, glabridin, isoliquiritin, glaciomarine, licochalcone A [18]. All of these active compounds can be utilized individually for obtaining their maximum effect.

8. Conclusion

In this review, we discussed the active biomolecules isolated from *Glycyrrhiza glabra* and outlined their biological functions. There are more than five key components that provide a lot of essential beneficial effects. We studied how in various ways the different parts of the plant can be processed and consumed to gain its maximum medicinal values. Moreover, clues on how its pharmacological properties can be capitalized in pharmaceutical industries to ensure its proper use in an appropriate controlled way are also discussed in this review. Thus, bringing a pharmaceutical product from it can pave the way to restrict inappropriate, undisciplined consumption while availing the potential benefits to the general mass. Further lab analysis and clinical trials are needed to be carried out to be certain about the alleged properties, but we conclude this paper with the hope of obtaining a natural herbal product in a medicinal form that can enhance the healthy living of people worldwide.

Declarations

Author Contribution Statement

Md. Kamrul Hasan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Iffat Ara: Performed the experiments; Wrote the paper.

Muhammad Shafiul Alam Mondal: Performed the experiments; Wrote the paper.

Yearul Kabir: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data; Wrote the paper.

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Declaration of interest statement

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Additional Information

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