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Review

Evaluation of Glycyrrhiza Species as Medicinal Plant

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Abstract

In this study, *Glycyrrhiza* species cultivated in Turkey assessed in terms of their chemical composition, morphological features and therapeutic activities. Potassium and calcium salts including licritic acid, gylcertatol and glycyrrhic acid have been found in the roots. Glycyrrhizin, a cough suppressor and natural antioxidant, has been determined as major triterpenoid saponin found in roots. Studies revealed that leaves contain flavonoids which have antioxidant and anti-inflammatory effect. *Glycyrrhiza* species have economic value due to their compounds with different bioactivities such as antioxidant, anti-inflammatory, antimicrobial activity. In recent studies, besides of known therapeutic effects of active compounds obtained from *Glycyrrhiza* species, it has been investigating whether they have a neuroprotective effect for Alzheimer's disease therapy. In the light of the data in the literature, it has also been revealed side effects of active compounds in this plant species. On the other hand, the side effects of active compounds isolated from these species have been manifested with various data. To find their new bioactive compounds against different diseases, studies on *Glycyrrhiza* species should be increased.

Keywords: Glycyrrhiza; Therapeutic Agent; Phenolic Compounds; Antiviral; Antioxidant.

1. Introduction

People have interacted with nature in the past for various reasons, including shelter, clothes, and food. In ancient times, gatherers who consumed the plants discovered different beneficial and toxic effects. They also began hunting with the tools they had made from the toxic plants they had found and the wood from the plants. Herbs have been thought to be effective in the treatment of a variety of diseases and, used for therapeutic purposes. After the discovery of writing, knowledge, and information has been passed on to future generations.

Since ancient times, people have ensured the development of science and technology by conducting research in line with their needs. In the past, people have used various plants and potions derived from these plants, thinking that they can be useful in the treatment and prevention of diseases. Along with the use of plants by trial and error and the accumulation of knowledge from past to present, many plants with high therapeutic effects have been identified. The components in plants are not equally present in all of the plant's parts. Therefore, these determined plants are categorized by separating them according to their parts. In the following years, these studies have been used in the field of medicine and pharmaceuticals.

Glycyrrhiza species have been first described in written sources around 2500 B.C. It has been used for cough relief, according to Assyrian clay tablets and Egyptian papyri [1]. From ancient times to the present, it has been used to treat respiratory disorders in many cultures. *Glycyrrhiza* species and herbal teas made with them are still used today to treat a variety of health problems among the people in our country [2].

2. General Characteristics of *Glycyrrhiza* Species

Glycyrrhiza species are in the Fabaceae family. *Glycyrrhiza* species are best known for *Glycyrrhiza glabra*. It has been observed that various extracts are frequently used in the treatment since the past due to their high therapeutic efficacy. They are coniferous perennial herbaceous plants, usually one meter tall. The plant has flowers in shades of blue and white. The roots are sweet, and the reason for this is glycyrrhizinic acid

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in it. The roots and leaves of plants are often used as crude drugs. The plant grows frequently in the west of Asia and the south of Europe. *Glycyrrhiza glabra*, a *Glycyrrhiza* species found in our country, grows along the banks of streams in the Aegean, Marmara, and Southeastern Anatolia regions. *Radix Liquiritiae* extract has been produced in two factories in Turkey, one in Siirt another one in Izmir. After those have been closed only one active extract factory exists in our country and it is located in Kahramanmaras [3].

Leaves, roots, and rhizomes of *Glycyrrhiza* species are used for treatment. The glycyrrhizin, flavone and coumarin contained in the crude extracts obtained from these parts of the plant differ in their proportions. This situation leads to the emergence of different therapeutic effects on each part of the plant. Tea obtained from the roots of the plant have been used predominantly [4].

Scientific Classification of The Genus *Glycyrrhiza*:
Realm: Plantae
Division: Magnoliophyta (Angiosperms)
Class: Magnoliopsida (Dicotyledons)
Order: Fabales
Family: Fabaceae (Legumes)
Subfamily: Polygonoideae
Genus: *Glycyrrhiza*

3. Past to Present Use of *Glycyrrhiza* Species

Glycyrrhiza species is a plant with a high economic value and therapeutic efficacy that has been used as a preservative and therapeutic purpose in the past. The first written sources for the use of *Glycyrrhiza* species date back to 2500 B.C. It is mentioned in Assyrian clay tablets and Egyptian papyrus that it has been used for cough relief [1].

Aristotle's student, Theophrastus, used *Radix Liquiritiae* in cough and respiratory problems associated with asthma. In his work, Theophrastus gave the plant; the name "*Glycyrrhiza*", meaning sweet root [5]. The Romans used it to suppress hunger and thirst. In addition, Roman people thought that tea made from the plant's roots was effective in the treatment of asthma and infertility [6].

In the first century A.D., Scribonius Largus, a Roman doctor, stated that *Radix Liquiritiae* is good for the voice. The famous medical writer Marcellus Empiricus recommended the use of licorice to treat lung diseases or pathologies. Abdullah bin Ahmed al-Baytar said that; Avicenna stated usage of licorine clarified the voice and reduced hoarseness. In addition, in his work *Canone*, Avicenna also stated that licorice could be used to treat respiratory tract diseases [4].
Nowadays, pharmaceutical companies and food industry widely use *Radix Liquiritiae* [7]. *Radix Liquiritiae*, which is used as a flavoring in the food industry, is also actively used in the pharmaceutical industry for the treatment of various health problems and for shaping tablets.

Glycyrrhiza glabra L. extracts made with different parts of the plant are used for hemorrhoids in different regions of Turkey [9].

Mixtures made with *Glycyrrhiza glabra L.* are used for treatment of kidney and urinary tract diseases in southern part of country [10].
In the treatment of diabetes, "*Glycyrrhiza glabra L.*" mixtures prepared as infusion with its roots are frequently used by the public [2].

4. Species of *Glycyrrhiza* In Monographs

Glycyrrhiza entered the European Medicines Agency monographs in 2007, as a traditional medicinal product for the treatment of digestive system problems such as burning and dyspepsia. In this monographs, two grams of ground herbs are suggested to be used in teas prepared in 150 ml of boiling water, two to four times a day [11].

It has been noted that *Glycyrrhiza* species, which entered the ESCOP monograph in 2003, may develop hypokalemia due to its excessive use and since it can increase the effect of cardiac glycosides, *Glycyrrhiza* plants can pose a great risk by interacting with antiarrhythmic drugs [12]. The plant entered the Monographs PDR in 2007 and FFD in 2011 [13].

5. Botanical Examination of *Glycyrrhiza* Species

Glycyrrhiza glabra is a typical perennial herbaceous plant, reaching up to one meter in height. Pinnate-type leaves are seven to fifteen centimeters long, and the flowers are purple to pale whitish blue. The fruit of the plant is a rectangular legume, two to three centimeters long and containing several seeds [14].

Genus *Glycyrrhiza* consists of about 30 species, such as; *G. glabra, G. uralensis, G. inflata, G. aspera, G. korshinskyi,* and *G. eurycarpa*. Although *Glycyrrhiza glabra*, like other Fabaceae plants, prefers moist soils, it is suitable for sandy and clay soils; due to symbiosis with Rhizobium bacteria, it can stable nitrogen at the root level. The roots are the most commonly used parts, while the leaves are considered agricultural chemical waste. Different scientists have studied the phytochemical composition of *Glycyrrhiza glabra* leaves in recent years, finding that certain compounds present in the roots are also found in the leaves, although in smaller quantities [15].

6. Chemical Examination of *Glycyrrhiza* Species

Glycyrrhiza glabra of the *Glycyrrhiza* species has triterpene, saponin, polysaccharide, flavonoid, simple sugar, pectin, essential oil, protein, and starch in its structure [16]. The taste of *Radix Liquiritiae* is sweet because of glycyrrhizin, a triterpenoid compound. Glycyrrhizin contains a mixture of potassium, calcium,

and magnesium salts of glycyrrhizic acid, which varies in the range of 2-25%. The yellow color of *Radix Liquiritiae* is due to liquiritin, isoliquiritin, and other flavonoids in its content [17]. Among the isoflavones it contains, glabridin and hispaglabridins A and B which have antioxidant activity [18].

The roots of *Glycyrrhiza glabra L.* contain *Glycyrrhiza*, a saponin 60 times sweeter than sugarcane sugar. Rich in flavonoids, its roots include lycirtin, isolikirtin, liquiritigenin and ramnoliquirilin. Recently, glycolykirtine apioside, prenlycoflavone A, shinflavonone, shinpterocarpine and 1-methoxyphaceoline have been found from its roots. Glycyrrhizin and glycyrrhetic acid, a saponin compound, are found as calcium and potassium salts in *Radix Liquiritiae* [19].

In a research conducted on *Glycyrrhiza aspera* roots in Japan, glycerin K-N have been isolated [20].

The essential oil in *Glycyrrhiza glabra* leaves contains; benzoic acid, linalool, prasterone, iodoquinol, diethyltoluamide, and benzene. Isoniazid, diethyltoluamide, and benzoic acid are major constituents [21]. While 82 different compounds have been identified in the essential oil of *Glycyrrhiza glabra* derived from the roots, the main compounds identified from the roots are; hexanoic acid, hexanol, and octanoic acid [22].

6.1 Saponins

Saponins in licorice are usually found as a mixture of potassium and calcium salts. Licorice contains lycyritic acid, glycirretol, glabrolide, isoglabrolide and licorice acid [23].

Glycyrrhizic acid is the main triterpenoid saponin in *Radix Liquiritiae* and often used as a means to identify the plant. This saponin has also been called glycyrrhizin or glycyrrhizinic acid obtained from G. glabra, G. uralensis, G. infiata, G. aspera, G. korshinskyi, and G. eurycarpa [24,26].

The dried roots of Glycyrrhiza uralensis Fisch have been extracted with 70% ethanol and the concentrated extract has been suspended in water, and then passed through ethyl acetate and N-Butanol. A total of 28 triterpenoid saponin, including 13 new compounds and 15 known compounds, have been detected in N-Butanol extract [27]. Triterpenoid saponins have been isolated from European Radix Liquiritiae extract (Glycyrrhiza glabra). In addition to the predominant saponin glycyrrhizin in it; 30-hydroxy-glycyrrhizin, glycyrrhizin-20-methanoate, 24-hydroxy-gluco-glycyrrhizin, 20α-galacturonic-glycyrrhizin and galacto-glycyrrhizin have been found [28].

6.2 Coumarins

Glycyrrhiza glabra contains lycukumarin, glabrocumarone A and B, herniarin, glycine, glycocoumarin, lycofuranocoumarin, and lycopyranocoumarin [29].

6.3 Flavonoids

Licorice extract contains flavonoids and chalcones such as liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones isoliquiritin, isoliquiritigenin, glabrolide and licoflavonol [23].

Genistein, pinocembrin, prunetin, 6-prenylnaringenin, lycoflavanone, wighteone, and lupiwighteone have been found from the leaves of *Glycyrrhiza glabra* [30].

6.4 Isoflavonoids

Among the isoflavonoid derivatives found in *Radix Liquiritiae*; glabridin, galbrene, glabrone, shinpterocarpin, lycoisoflavones A and B, formononetin, glyzarin, and kumatakenin[23]. Recently, glabroizoflavanone A and B, and glabroisoflavanone B has been found [31].

7. Therapeutic Use of *Glycyrrhiza* Species

7.1 Antitussive Activity

Cough is one of the most important defense mechanisms of the respiratory tract. Cough prevents the closure of the airways, preventing infected mucus from landing in bronchitis and lungs. Cough seriously affects the quality of life of patients. It is known that antitussive agents are used to relieving coughing. There are many side effects of these cough-relieving drugs. For example, due to the use of codeine, the viscosity of mucus increases and becomes difficult to expectorate.

The antitussive effect of *Glycyrrhiza glabra* has been known since the past. In ancient Arabic medical books, its effectiveness as a cough suppressant and anti-constipation is mentioned [1]. Currently, it is believed that *Glycyrrhiza glabra* can be used as cough suppressant as an alternative to opioids due to their side effects such as sedation and constipation.

In a study of the antitussive activity of *Glycyrrhiza glabra*, a cough model has been created with sulfur dioxide gas in mice. Plant has been extracted with 70% ethanol using a soxhlet extractor for 24 hours. Within an hour, extract has been observed to show 35.62% activity. Codeine sulfate, a standard antitussive agent, has been observed at 32.98% activity per hour at 15 mg/kg according to body mass. This study showed that *Glycyrrhiza glabra* may be an alternative to standard antitussive agents [32].

It is thought that the antitussive activity of *Radix Liquiritiae* may be due to the 18β-glycyrretinic acid in it. In the study conducted on this, it has been observed that it has approximately the same power as codeine when given subcutaneously to guinea pigs. Dicholine glycyrrhetinic acid hydrogen succinate has been observed to exhibit the same degree of activity after oral administration. This study suggests that the antitussive activity may be due to 18β-glycyrrhrinic acid [33].

Glycyrrhiza species contain *Glycyrrhiza*, which relieves upper respiratory tract blockages and

accelerates the secretion of tracheal mucus because of its high antitussive activity [34].

In another study on the antitussive effect of *Radix Liquiritiae*, the activities of 14 main compounds of *Radix Liquiritiae* and raw licorice extract have been evaluated, using the classic ammonia-induced cough model and phenol red secretion model in mice. In this study, liquiritin apioside, liquiritin and liquiritigenin showed strong antitussive and expectorant activity. It has been concluded that liquiritin apioside and liquiritin are the main cough suppressant and expectorant compounds of *Radix Liquiritiae* [35]. These studies show that *Glycyrrhiza glabra* can be used for antitussive purposes.

7.2. Antioxidant Activity

Antioxidants are known to prevent cell damage by destroying damaging free radicals inside the cell. Tumor formation is prevented by antioxidants, which have great importance for human body. They also delay the process of aging. Studies on *Glycyrrhiza* species have shown that they have a high level of antioxidant activity. It is believed that due to the phenolic compounds derived from isoflavone, coumarin, and chalcone in plants content [36].

To study urease inhibitor and antioxidant effects, *Glycyrrhiza glabra* roots have been extracted three times with methanol after drying in the sun. Then, the chemical content of the extract has been analysed. The antioxidant activity of 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) has been investigated. As a result, *Glycyrrhiza glabra* roots extract showed a high level of antioxidant activity. This study suggested that *Glycyrrhiza glabra* roots are a potential source of antioxidants and urease inhibitors and could be used as a precursor compound in drug models [37].

In an in vitro study conducted to investigate the antioxidant activity of *Glycyrrhiza glabra* root extracts, it has been stated that the extract with high phenolic compound content showed strong antioxidant activity. Furthermore, the data obtained suggest that suppressed human low-density lipoprotein (LDL) oxidation may be one of the powerful mechanisms explaining the anti-atherogenic properties of *Glycyrrhiza glabra* root. It is also thought that it can be used in the prevention of oxidative stress-related disorders such as atherosclerosis [38].

A study has been conducted on the effects of different plant extracts containing flavonoids on the physical stability of topical drug formulations. In this study, the antioxidant activity of plant extracts has been also evaluated using chemiluminescence and stable free radical DPPH experiments. As a result of this study, it has been shown that *Glycyrrhiza glabra* and ginkgo globa extracts can be used in topical formulations to protect the skin against damage caused by free radicals and reactive oxygen species [39]. This study showed also that *Glycyrrhiza glabra* extracts have high antioxidant activity and it has protective properties against damage caused by free radicals by using it in topical formulations. In a study conducted by Biondi et al., on *Glycyrrhiza glabra*, dihydrostilbene, which has a high level of antioxidant activity, has been found in leaves [40].

The free radical cleansing, antioxidant and immune system stimulating effects of licorice infusion (*Glycyrrhiza glabra*) has been studied. Antioxidant activity has been evaluated based on the beta carotene/linoleic acid model, in which the oxidation of β-carotene occurs in the presence of linoleic acid. Inhibition of bleaching in the presence of licorice infusion has increased as long as the concentration is high. It has also been observed that the infusion stimulates granulocyte and natural killer cells [41].

The antioxidant effect of glycyrrhizin, one of the main metabolites of glycyrrhizin, has been investigated in allergic rhinitis mice. Consumption of glycyrrhizin in allergic rhinitis mice reduces blood and nasal mucosa antioxidant enzyme activities, lipid peroxidation, and GSH levels, and increases IFN-levels, lowers IL-4 levels, thereby protecting nasal mucosa oxidative damage, and raising immune activity in allergic rhinitis mice. Inhibitory effects of glycyrrhizin against oxidative damage of the nasal mucosa have been observed to increase with increasing concentrations. In addition, glycyrrhizin increased IFN-γ and decreased IL-4 levels in glycyrrhizin-treated mice. This study observed that glycyrrhizin increased antioxidant activity, reduced the incidence of free radical-induced lipid peroxidation, and increased immune activities in the blood and nasal mucosa in mice [42].

In a study conducted on *Glycyrrhiza uralensis* in China, three polysaccharides have been isolated and purified from their roots. The physicochemical properties and antioxidant activities of the purified three polysaccharides have been investigated. These isolated heteropolysaccharides have been observed to have high antioxidant activity [43].

Recently, GPN, a water-soluble polysaccharide, has been isolated from *Glycyrrhiza glabra*. This isolated GPN is a glucose-weighted glucan. As a result of tests on GPN, it has been observed that it showed antioxidant activity [44].

7.3. Antiviral Activity

The first findings regarding the antiviral activity of licorice components have been found in 1979 as a result of a study conducted at the University of Cagliari in Italy. The presence of the compound called glycyrrhizic acid has been observed in *Glycyrrhiza glabra* extracts. It has been observed to have anti-viral activity, inhibiting the growth and cytopathic effect of various DNA and RNA viruses [45].

Glycyrrhiza, found in the roots of *Glycyrrhiza glabra*, shows activity against various viruses. The effects of glycyrrhizin on the Japanese encephalitis virus have been studied. Purified glycyrrhizin, at a concentration of 500 micrograms/mL for 96 hours, inhibited plaque formation on the Japanese encephalitis virus. Similar effects have been observed with the

ammonium salt of glycyrrhizic acid in *Radix Liquiritiae* at a concentration of 1000 micrograms/mL. As a result, naturally purified glycyrrhizin had stronger in vitro antiviral activity against the Japanese encephalitis virus than ammonium salt of glycyrrhizic acid and *Radix Liquiritiae* [46].

Newcastle disease is a highly contagious viral disease that caused huge economic losses worldwide. In the in-vivo trial, the effectiveness of extracts from *Glycyrrhiza glabra* leaves against the Newcastle disease virus (NDV) has been studied. Different plant extracts have been used in seven groups consisting of nine-day-old embryonated chicken eggs. Other eggs outside the control group have been injected with NDV. As a result, the extract obtained from the leaves of *Glycyrrhiza glabra* showed the highest antiviral activity [47].

In a study conducted at Tohuko University in 2001; in herpes simplex encephalitis, the effect of glycyrrhizin contained in *Radix Liquiritiae* extract has been studied on mouse models. Intraperitoneal administration of glycyrrhizin increased the survival rate of animals about 2.5 times. HSV-1 replication in the brain has been controlled by 45.6%. These data have shown that glycyrrhizin, found in *Radix Liquiritiae*, is effective against HSV-1 infection [48].

The effect of glycerine in the treatment of human immunodeficiency virus (HIV) in 42 hemophilia patients with HIV-1 infection has been studied. Improvement in patients' clinical symptoms, immunological function, and liver function has been observed [49].

Glycyrrhizin has been used in Japan for more than 20 years to treat chronic hepatitis C disease [50]. In addition, it acts by preventing the development of hepatocellular carcinoma in chronic hepatitis C [51]. Glycyrrhizin can also be used as a novel therapeutic method to control porcine epidemic diarrhea virus (PEDV) infection, inhibit infection of Vero cells, and lower mRNA levels of proinflammatory cytokines [52].

The effects of glycyrrhizin, one of the major compound of *Glycyrrhiza* species, on the hepatitis C virus have been studied. It has been observed that Hepatitis C Virus (HCV) inhibited the titer in a dose-dependent manner and showed a 50% reduction in HCV at a concentration of 14 ± 2 μg. Comparative studies have been conducted with interferon-alpha to investigate the synergistic effects between the antiviral compound and interferon-alpha 2a. Glycerine has been observed to exhibit a synergistic effect when combined with interferon. In addition, these results have been confirmed by temporarily transfecting liver cells with HCV 3A core plasmid. It has been observed to inhibit HCV full-length viral particles and HCV core gene expression or to function in a dose-dependent manner and have a synergistic effect with interferon. This study suggested that glycyrrhizin may be used to treat HCV infection in the future [53].

Triterpene glycyrrhizic acid (GRA), one of the major metabolite of *Glycyrrhiza glabra*, is known for its anti-inflammatory and antimicrobial activities. The induction of the autophagic process activator Beclin 1 in epithelial cells and how this property may affect its antiviral activity have been studied. After 24 hours of use, GRA induced more than twice the production of Beclin 1 of rapamycin, which has been used as a reference compound. Rapamycin activity has not been observed when the compounds have been added to HeLa cells along with viruses. As a result, GRA has been observed to be a potent inducer of the autophagy activator Beclin 1, which creates a state of resistance to HSV1 replication [54].

7.4. Immunomodulatory Activity

A study has been conducted in India in 2011 to determine the immunomodulatory properties of *Glycyrrhiza glabra* roots and to observe their effectiveness in combination with zinc. The effect of aqueous licorice extract and its combination with zinc on immunomodulatory potential, leukocyte count, and spleen weight has been analyzed. Leukocyte count and phagocytic index (carbon clearance) increased significantly compared to control with aqueous licorice extract treatment (1.5 g/kg). Zinc (45 mg/kg) in combination with aqueous licorice extract (0.75 g/kg) showed a significant increase in leukocyte count and phagocytic index compared to control. This study demonstrated the immunomodulatory activity of *Glycyrrhiza glabra*. *Glycyrrhiza glabra* in combination with zinc has been observed to increase immunomodulatory activity in all aspects of the study [55].

Glycyrrhizin plays a dual role in cellular immunity and humoral. Glycyrrhizin is an effective biological response modifier. It is complementary to immune regulation in immune-active cells. Glycyrrhizin can increase helper T lymphocyte proliferation and activity. It selectively inhibits complement system activation. It has also shown efficacy in psoriasis, chronic idiopathic urticaria, bronchial asthma, chronic liver disease, AIDS, cancer, and other diseases [56].

An in vitro study has been conducted on the immunomodulatory and antitumor potential of Chinese *Radix Liquiritiae* (*Glycyrrhiza uralensis Fisch*). *Glycyrrhiza uralensis* polysaccharides did not prevent the proliferation of IEC-6 cells even in high concentrations. Polysaccharides inhibited the proliferation of cancer cells (CT-26) at concentration lower than 50μg/ml. IEC-6 cells secrete IL-7 cytokines on average when treated with *Glycyrrhiza uralensis* polysaccharides. It has been stated that *Glycyrrhiza uralensis* polysaccharides, especially low molecular weight polysaccharides, can act as anticancer agents. The ability of polysaccharides to up-regulate the anticancer cytokine IL-7, which is important in the proliferation and maturation of immune cells and is associated with a better prognosis in cancer, has great

importance. For this reason, it is believed that immunomodulation can be used to treat cancer [57].

7.5. Antibacterial and Antimicrobial Activity

A study has been conducted to determine the antibacterial activity of licorice extracts prepared with ether, chloroform and acetone on bacteria by diffusion method. *Staphylococcus aureus, Bacillus subtilis, Escherichia coli*, and *Pseudomonas aeruginosa* microorganisms have been used in the study. Acetone extract showed the highest antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa,* and *Escherichia coli* with a diameter of 32, 22, 22, 15 inhibitions. As a result of the study, it has been observed that it showed antibacterial activity against these bacteria [58].

Lycocalcone A-D and echinatin isolated from the roots of *Glycyrrhiza inflata* show antimicrobial activity. Among these, lycocalcone A and C, have strong activity against some gram-positive bacteria. These retrocalcones inhibit oxygen consumption in susceptible bacterial cells and also inhibit the oxidation of NADH in bacterial membrane preparations [59].

The antimicrobial effect of the extract of *Glycyrrhiza glabra* has been tested on; *Bacillus megaterium, Bacillus subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Pseudomonas aeruginosa, Salmonella paratyphi, Salmonella typhi, Shigella boydii, Shigella dysenteriae boydii, Vibrio parahemolyticus*. *Glycyrrhiza glabra* extract showed strong antimicrobial activity against organisms tested, except *Pseudomonas aeruginosa* [60].

Antimicrobial effects of *Glycyrrhiza glabra* root extracts against; *Staphylococcus aureus, Salmonella typhi, Staphylococcus sciuri, Escherichia coli, Aspergillus awamori, and Rhizopus* spp. have been investigated. The methanolic extract of *Glycyrrhiza glabra* showed maximum antibacterial activity against Staphylococcus aureus at 500µg/mL (13mm inhibition zone) and maximum antifungal activity against Rhizopus spp. at 500µg/mL (inhibition zone 11mm) [61].

Licorice flavonoids show antimicrobial effects against methicillin-resistant Staphylococcus aureus. It shows antimicrobial activity against Micrococcus luteus ATCC 9341 and Bacillus subtilis PCI 219. It doesn't show an effect against Klebsiella pneumoniae PCI 602 and Pseudomonas aeruginosa IFO 3445 [62].

7.6. Antiulser Activity

Glycyrrhiza glabra extracts have an anti ulcerative effect due to the glycyrrhizin they contain. Glycyrrhizin can increase the concentration of prostaglandin in the digestive system and stimulate gastric mucus secretion [63]. In addition, *Radix Liquiritiae* has an anti pepsin effect by extending the life of stomach surface cells [64].

Using carrageenan-induced paw edema, when compared to diclofenac sodium (10 mg/kg), anti-inflammatory activities of both glycyrrhetinic acid (GA) and aqueous licorice extract (ALE) have been studied in male albino rats [65]. The anti-ulcer activities of ALE, famotidine (FT), and the combination of ALE and FT have been investigated using an indomethacin-induced ulceration technique in the stomach of rat(s). ALE and GA showed significant anti-inflammatory activity similar to diclofenac sodium (DS), and when taken concomitantly, no possible antagonism has been observed. The anti-ulcer activity of *Radix Liquiritiae* has been found to be similar to FT in the technique of indomethacin-induced ulceration in the rat stomach. When FT and licorice have been used together, the anti-ulcer activity of both has been higher than when they have been used seperately. Both GA and ALE have been found to have anti-inflammatory activity comparable to DS [66].

Hydroalcoholic extract of *Glycyrrhiza glabra* studied for its anti-ulcerogenic activity and acute toxicity profile in mice. As a result of the study, a significant decrease in the ulcer index has been observed compared to the control. The higher hydroalcoholic extract of *Glycyrrhiza glabra* and omeprazole showed a similar reduction in ulcer index compared to the control. In the control group, the ulcer index has been 15.33±0.19, while in the groups treated with lower doses, the ulcer index revealed a significant ($P<0.0001$) inhibitory effect. This study in mice models has shown that it can be used as a new approach in the treatment of ulcers [67].

7.7. Neuroprotective Activity

In a study conducted to investigate the effects of *Glycyrrhiza glabra* on learning and memory; three doses (75,150 and 300 mg/kg) of *Glycyrrhiza glabra* aqueous extract have been administered in individual groups of mice for seven consecutive days. It has been observed that the dose of 150 mg/kg of *Radix Liquiritiae* aqueous extract significantly improves the learning ability and memory of the mice. This effect on learning and memory has been thought to be due to the acceleration of cholinergic transmission in the mice's brain. As a result of the study; it has been thought that it can be used as a memory enhancer in external and perceptual behavioral memory models [68].

In a study conducted on albino rats, all doses of the aqueous root extract of *Glycyrrhiza glabra* significantly increased memory. However, at doses of 150 and 225 mg/kg, it showed a significant ($P<0.01$) increase in learning and memory. These findings suggested that memory enhancement effects may be due to their antioxidant and anti-inflammatory activity. For this reason, it is thought to be a promising drug to improve memory in the treatment of learning disorders, dementia, and other neurodegenerative disorders. Furthermore, these findings have shown that licorice may have a possible neuroprotective role in preventing diseases such as Alzheimer's. Because the basis of Alzheimer's is a chronic inflammation of certain brain regions, the anti-inflammatory activity of *Radix Liquiritiae* can have a memory-enhancing effect [69].

7.8. Anticarcinogenic and Antimutagenic Activity

Several studies are showing that *Glycyrrhiza glabra* extracts have potential anticancer properties. Anticancer activity is due to 18β-glycyrrhetinic and glycyrrhizic acids, which induce mitochondrial permeability transition leading to apoptosis of tumor cells [70]. In a study conducted in 2014 on mice, hydroethanolic root extract of *Glycyrrhiza glabra* has been noted to have antimutagenic potential by suppressing chromosomal aberration in albino mice. It has also been thought that chemotherapeutic agents can suppress side effects [71].

Isoliquiritigenin isolated from the root of *Glycyrrhiza glabra* prevented the incidence of 1,2-dimethylhydrazine-induced colon and lung tumors in mice when administered at a dose of 300 mg/kg. Isoliquiritigenin exhibited cytotoxic activity against cancer cells by acting as a monofunctional inducer of Phase II enzymes. Inhibitory effects of isoliquiritigenin have been reported in metastasis-related test systems [72].

Glycyrrhizin and glycyrrhizic acids are effective compounds in the treatment of stomach cancer, while glycyrrhizin suppresses thromboxane A2 in the lung cancer cell with low toxicity. This suggested that glycyrrhizin could be used to block the progression of the tumor. Furthermore, treatment with glycyrrhizin alone, or the combination of cisplatin and glycyrrhizin, significantly reduces the expression of thromboxane synthase (TxAS) and the expression of proliferating cell nuclear antigen (PCNA). It also reduces liver and kidney damage in tumor-bearing mice. Although it inhibited PCNA expression, it has not been able to significantly suppress TxAS expression. Due to the positive feedback loop between TPα and TxAS, glycyrrhizin is thought to exert its effects possibly through suppression of the TxA2 pathway [73].

The antiangiogenic and antitumor activity of *Glycyrrhiza glabra* has been investigated on VEGF and MTA1-induced angiogenesis. The angio-inhibitory activity of *Glycyrrhiza glabra* has been confirmed by inhibition of angiogenesis, peritoneal and chorioallantoic membrane testing. The decrease in the number of cytokine VEGF and microvessel density in the peritoneum of mice treated with *Glycyrrhiza glabra* decreased VEGF production of the plant extract. In addition, neovascularization in CAM induced by VEGF and MTA1 has been also inhibited [74].

In liver cancer, the compound inhibits the proliferation of HepG2 cells without affecting the normal liver cell line. 18β-Glycyrrhetinic acid in particular increases the generation of reactive oxygen species, nitric oxide production, and loss of mitochondrial membrane potential [75].

Glycyrrhizin is a promising anti-angiogenic therapeutic agent targeting the ERK pathway of glycyrrhizin by inhibiting carcinogenesis by reducing angiogenic activities such as migration, invasion, and tube formation of endothelial cells [76]. Glycyrrhizic acid has been proven to be blocking against human gastric carcinoma cell lines BGC823 and SGC-7901 by inducing apoptosis and cell cycle arrest in the G2 phase and inhibiting migration via the RoS/PKC-α/ERK pathway [77].

Licorice and its components have been studied to see whether licorice extract can induce cell death and apoptosis in prostate cancer cells, in order to validate previous findings showing the induction of cell cycle cessation or apoptosis in cancer cell sequences. Licorice has been observed to induce cell death in LNCaP cells depending on dose and time. Isoliquiritigen, a component of *Radix Liquiritiae*, has been observed to cause cell death through modulation of matrix metallopeptidase in human DU145 prostate cancer cells [78].

Glycyrrhiza enables apoptosis induction in human breast carcinoma MCF-7 cells through caspase activation and modulation of the 18β-glycirretinic acid AKT/FOXO3a pathway in its structure [80].

7.9. Antidepressant Activity

Glycyrrhiza glabra has a potential therapeutic effect in the treatment of depressive disorders. Recent studies have shown that licorice extract produces significant antidepressant effects during the mandatory swimming test (FST) and tail suspension test in mice. In the FST model, mice have been forced to swim in a limited area, causing a characteristic inactivity behaviour. This condition reflects a state of depression. The TST model also causes a state of inactivity, which is claimed to reproduce a condition similar to human depression. Both models are widely used to screen for antidepressant drugs. It has also been suggested that the extract may increase norepinephrine and dopamine levels in the mice's brain by interacting with α1-adrenoceptors and dopamine D2 receptors [81].

7.10. Cardiovascular Activity

Many studies have been conducted to show that *Radix Liquiritiae* may have cardiovascular effects. A study has been conducted in 1991 on the antiplatelet effect of isoliquiritigenin, an aldose reductase inhibitor in *Radix Liquiritiae*. Isoliquiritigenin 40000- and 20000-dalton significantly inhibited the phosphorylation of the protein. It inhibited the formation of 12(S)-hydroxy-5,8,10-heptadecatrienoic acid, 12-hydroxyeicosetraenoic acid, and thromboxane B2. Isoliquiritigenin's inhibitory effect on platelet aggregation in vitro has been observed to be comparable to aspirin. It has also been observed that isoliquiritigenin acts antiplatelet in vivo [82]. In addition, studies have shown that *Radix Liquiritiae* accelerates metabolism in bone marrow erythroid stem cells and increases resistance to stress in animals [83]. In studies on isoliquiritigenin, one of the phenolic compounds in *Radix Liquiritiae*, it has been observed to have a vascular relaxant effect [84].

The antioxidant property of *Glycyrrhiza glabra* protects heart cells from doxorubicin-induced toxicity.

It reduces oxidative stress and provides the regulation of mitochondrial functions [85].

Glycyrrhizin protects the rat heart against ischemia-reperfusion damage through blockade of the HMGB1-bound phospho-JNK/Bax pathway. Glycyrrhizin has been found to inhibit extracellular HMGB1 cytokine activity and protect the spinal cord, liver, and brain from I/R-induced injury in experimental animals [86].

8. Side Effects and Toxicity

There are misconceptions that plants have no side effects because they are natural sources. Plants have side effects as well as prepared medicines. Using herbs in high doses can cause serious side effects. *Glycyrrhiza* species have side effects like other plants with therapeutic activity.

Glycyretic acid and licorice saponins inhibit the enzyme 11-β-hydroxysteroid dehydrogenase, resulting in a cortisol-induced mineralocorticoid effect and causing increase in sodium and decrease in potassium levels [87]. High consumption of licorice can lead to a decrease in 11β-HSDPA activity, causing hypertension and hypokalemia [65].

Studies on rodents and humans have shown that glycyrrhizin is poorly absorbed by the gastrointestinal tract, but is largely metabolized by the intestinal microflora to glycyrrhizic acid and monoglucuronyl glycyrrhizic acid. Therefore, an enterohepatic circulation of glycyrrhizic acid may occur, requiring several days for complete elimination from the body [88].

Use during pregnancy should be avoided. *Radix Liquiritiae* exhibits estrogenic activity and has low-inducing effects. There is no clinical evidence to support the use of licorice tea as a galactagogue [89].

9. Conclusion

Being from the Fabaceae family, *Glycyrrhiza* species grown widely in the world and our country. In Turkey, *Glycyrrhiza glabra L.*, which has a high economic value, is grown in the Aegean, Marmara, and Southeast Anatolia regions.

As a result of studies on *Glycyrrhiza glabra* and *Glycyrrhiza uralensis*, it has been observed that it has antioxidant activity due to the phenolic compounds it contains.

18β-glycyrrhizic acid in the extract obtained from the roots of *Glycyrrhiza glabra* shows antibacterial and antifungal activity. 18β-glycyrrhizic and glycyrrhizic acids show anticancer activity on various types of cancer by inducing mitochondrial permeability transition leading to apoptosis of tumor cells. The extract obtained from its roots has an inhibitory effect against various types of viruses. Glycyrrhizin in *Radix Liquiritiae* extracts increases prostaglandin concentration and shows an anti-ulcerative effect by increasing gastric mucus secretion.

An overdose of *Glycyrrhiza* species, which has high reliability, can lead to a decrease in 11β-HS2 activity due to the saponins in its content, causing hypertension and hypokalemia. As with other phytotherapeutics, the structure of which is not fully enlightened, its use should be avoided in pregnant women.

The *Glycyrrhiza* species, which are generally used in the pharmaceutical sector for flavoring and shaping tablets, should be considered as an active compound sources, not neglecting their high pharmaceutical efficiency.

Conflict of Interest

The authors declare no conflict of interest.

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