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Glycyrrhiza glabra: A phytochemical and pharmacological review

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Abstract: The phytochemical screening of the *Glycyrrhiza glabra* root revealed the presence of alkaloids, glycosides, carbohydrates, starches, phenolic compounds, flavonoids, proteins, pectin, mucilage, saponins, lipids, tannins, sterols and steroids. It showed memory enhancement, antidepressant, antimicrobial, anticancer, antioxidant, protective, antiinflammatory, antiulcer, antidiabetic, hypolipidemic and many other pharmacological effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Glycyrrhiza glabra*.

Keywords: *Glycyrrhiza glabra*, chemical constituents, pharmacology

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I. PLANT PROFILE:

Introduction:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plant derivates had been employed by population to prevent different kind of diseases for centuries. The knowledge of plant properties was acquired by ancient civilization that passed down from generation to generation until today. Plant showed wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects[1-33]. The phytochemical screening of the *Glycyrrhiza glabra* root revealed the presence of alkaloids, glycosides, carbohydrates, starches, phenolic compounds, flavonoids, proteins, pectin, mucilage, saponins, lipids, tannins, sterols and steroids. It showed memory enhancement, antidepressant, antimicrobial, anticancer, antioxidant, protective, antiinflammatory, antiulcer, antidiabetic, hypolipidemic and many other pharmacological effects. This review will highlight the chemical constituents and pharmacological effects of *Glycyrrhiza glabra*.

Synonyms:

Glycyrrhiza brachycarpa Boiss., *Glycyrrhiza glabra* var. *caduca* X.Y. Li, *Glycyrrhiza glabra* var. *glabra*, *Glycyrrhiza glabra* subsp. *glandulifera* (Waldst. & Kit.) Ponert, *Glycyrrhiza glabra* var. *glandulifera* (Waldst. & Kit.) Regel & Herder, *Glycyrrhiza glabra* var. *glandulifera* (Waldst. & Kit.) Boiss., *Glycyrrhiza glabra* var. *glandulosa* X.Y. Li, *Glycyrrhiza glabra* var. *laxifoliolata* X.Y. Li, *Glycyrrhiza glabra* var. *typica* L., *Glycyrrhiza glabra* var. *violacea* (Boiss. & Noe) Boiss., *Glycyrrhiza glandulifera* Waldst. & Kit., *Glycyrrhiza hirsuta* Pall., *Glycyrrhiza pallida* Boiss. & Noe, *Glycyrrhiza pallida* Boiss and *Glycyrrhiza violacea* Boiss. & Noe[34].

Common names:

The genus name Glycyrrhiza was derived from the Greek glykys, for (sweet), and rhiza, for (root). The species name glabra was derived from the Latin glaber, which means (smooth) or (bald) and refers to the smooth husks. The plant common names were: **Arabic**: Sus, Irik Sus, rib el-sus; **English:** licorice, licorice-root, liquorice; **French**: réglisse; **German**: Lakritze, Süßholz; **Hindi**: Mulhatti, Jethimadh, Mithilakdi; **Italian**: liquirizia; **Portuguese**: alcaçuz, pau-doce; **Spanish:** alcazuz, licorice, orozuz, regaliz; **Swedish**: lakritsrot[35-36].

Distribution:

Glycyrrhiza glabra was native to Eurasia, northern Africa and western Asia. It was distributed in **Africa** (Libya); **Asia** (Armenia, Azerbaijan, Georgia, Russian Federation, China, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Mongolia, Iran, Iraq, Afghanistan, Palestine, Jordan, Lebanon, Syria, Turkey, India, Pakistan); and **Europe** (Moldova, Albania, Bulgaria, Russian Federation-European part, Ukraine, Former Yugoslavia, Greece, Italy, Romania, France)[35].

Traditional uses:

The dried rhizome and root have been used as expectorant and carminative by the Egyptian, Chinese, Greek, Indian and Roman civilizations**.** Licorice was known in Chinese medicine as early as 2800 B.C. In Tibet, it was considered a classical medicine. In the tomb of the Egyptian pharaoh Tutanchamon (1350 B.C.), the healing power of licorice roots was described. The use of licorice preparations to alleviate throat and bronchial infections was known for more than 2000 years[(36)].

Leaves were used externally for the treatment of wounds. Rhizome and root were used orally to treat cystitis, kidney stones, lung ailment, diabetes, cough, stomachache, gastric ulcers, tuberculosis, Addison's disease, it was also used as mild laxative, contraceptive and to improve sexual function[(37)].

In addition, it was also used in sore throat, influenza, cold, bronchodilator, opthalmia, anti-syphilitic, antidysenteric, gastric imbalance, indigestion, vomiting, diarrhea, swollen abscesses and as diuretic[(38)].

Furthermore, licorice was also used as a flavoring agent in the tobacco and candy industries and to some extent in the pharmaceutical and beverage industries today[(39)].

Pats used medicinally: Leaves, root and rhizomes[(37-38)]**.**

Physicochemical characteristics:

Physicochemical analysis of *Glycyrrhiza glabra* roots revealed that extractive values were (petroleum ether 4.67 ± 0.23%, chloroform 10.56 ± 1.53%, *n*-butanol, 6.54 ± 0.84% and methanol 13.89 ± 2.42%); ash values were (total ash 4.67 ± 0.35%, acid insoluble ash 0.56 ± 0.34% and water soluble ash 6.54 ± 0.22%); loss on drying 5.87 ± 0.65%, moisture contents 0.56 ±0.054%, pH of the extract (1% solution) 5.04 ± 0.65, pH of the extract (10% solution) 6.26 ± 0.54[(40)].

Chemical constituents:

The preliminary qualitative phytochemical screening of the ethanolic extract of *Glycyrrhiza glabra* root revealed the presence of alkaloids, glycosides, carbohydrates, starches, phenolic compounds, flavonoids, proteins, pectin, mucilage, saponins, lipids, tannins, sterols and steroids[(40-41)].

Liquorice root contained triterpenoid saponins (4–20%), mostly glycyrrhizin, a mixture of potassium and calcium salts of 18β-glycyrrhizic acid (which was the major bioactive compound in the underground parts, which also called glycyrrhizic or glycyrrhizinic acid and a glycoside of glycyrrhetinic acid), it was 50 times sweeter than sugar. Liquorice root also contained other triterpenes included liquiritic acid, glycyrretol, glabrolide, isoglaborlide and liquorice acid. 18β-glycyrrhizic acid (3-*O*-(2-*O*-β-d- glucopyranuronosyl–α-d-glucopyranurosyl)-3-β-hydroxy-11-oxo-18β,20β-olean-12-en-29-oic acid) was isolated from the roots of *Glycyrrhiza glabra*[(42-43)].

The total phenolic contents of the ethanolic extract of *Glycyrrhiza glabra* root was 7.47 ± 0.05 mg/ gm of Gallic acid equivalent (GAE), while the total flavonoids contents was 2.25 ± 0.03 µg/gm quercetin equivalents (QE)[(40)].

Flavonoids and chalcones isolated from *Glycyrrhiza glabra* included liquiritin, liquiritigenin, hamnoliquiritin, neoliquiritin, chalcones isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide, licoflavonol, 5,8-dihydroxy-flavone-7-O-beta-D-glucuronide, glychionide A, and 5-hydroxy-8-methoxyl-flavone-7-O-beta-D-glucuronide and glychionide B. Flavonoids were responsible for the yellow colour of liquorice. Isoflavones: glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin, hispaglabridin A, hispaglabridin B, 4′-O-methylglabridin and 3′-hydroxy-4′-O-methylglabridin, glabroisoflavanone A and B glabroiso-flavanone B were also isolated from *Glycyrrhiza glabra*[(44-46)].

The essential oil of *Glycyrrhiza glabra* leaves was obtained by hydrodistillation and analyzed by GC and GC-MS, showed that the main hydrocarbon and oxygen containing compounds were: isoniazid (13.36 %) ; diethyltoluamide (6.56 %), benzoic acid (5.37 %), benzene (4.58 %), linalool (2.25 %), prasterone (5.63 %), warfarin (1.43 %), iodoquinol (1.90 %), phenol, 4-(2-aminopropyl) (1.30 %), while 82 compounds were identified in the root essential oil of *Glycyrrhiza glabra*, the main compounds identified from the root were included hexanoic acid 31.57%, hexadecanoic acid 3.30%, hexanol 1.71% and octanoic acid 1.44%. The aroma of this essential oil was considered to be a result of estragole (methyl chavicol), anethole, eugenol, indole accompanied with γ-nonalactone and cumic alcohol[(47-48)].

Glycyrrhiza glabra samples taken from Egypt, Afghanistan, Syria, China, Bonn and Kiel were differ in their types and quantities of volatile oils. However, the volatile oil identified in the *Glycyrrhiza glabra* species root were: (E)-2-heptenal, 5-methyl- furfural, (2E, 1E) heptadienol, (E)-2-octen-1-al, o-guaiacol, 2-phenylethanol, (Z)-pinene hydrate, lavandulol, terpinen-4-ol, (E)-linalool oxide, p-cymen-8-ol, α-terpineol, methyl chavicol, (4E)-decenal, decanal, (2E, 4E)-nonadienal, cumin aldehyde, carvone, piperitone, (E)-

cinnamaldehyde, (E)-anethole, (2E, 4Z)-decadienal, thymol, indole, carvacrol, (2E, 4Z)-decadienal, p-vinyl-guaiacol, eugenol, γ-nonalactone, methyl eugenol, β-caryophyllene, β-dihydro-ionone, himachalene epoxide, spathulenol, (1α, 10α)-Epoxy-amorph- 4-ene, β-caryophyllene oxide and humulene epoxide II[49].

The heavy metal residues in the ethanolic extract of *Glycyrrhiza glabra* root were: cadmium: 0.28 ± 0.03, lead: 0.48 ± 0.12, arsenic: 0.47 ± 0.05 and mercury: 0.33 ± 0.08 mg/ kg[40].

However, the percent of trace elements in the root powder of *Glycyrrhiza glabra* were: potassium: 0.66, calcium 1.87, sulphur 0.09, iron 0.14, aluminium 0.05, phosphorous 0.06, silicon 0.12, magnesium 0.17 and sodium 0.04%[50].

The chemical composition of raw, tea and infusion forms of licorice were: protein (%): 9.15 , 1.55 and 1.81; fat (%): 0.53, 0 and 0; moisture (%): 6.80 for raw; ash (%): 7.70, 0.02 and 0.15; fiber (%): 24.48, 0 and 0; silica (%) : 3.56 , 0 and 0; for tea form, raw herb and infusion respectively. Carbohydrate: 47.11 for raw; moisture: 6.80 for raw; calcium: 1720, 30 and 80 mg/100 ml; phosphorus: 78, 1 and 4 mg/100 ml; sodium(ppm): 18580, 455.2 and 550; potassium (ppm): 7276, 178.4 and 215.1; zinc (ppm): 17.08, 0.118 and undetectable; copper (ppm) 11.01, 0.076 and undetectable, for tea form, raw herb and infusion respectively. The plant contained many amino acids included aspartic, glutamic, threonine, serine, proline, glycine, alanine, valine, isoleucine, leucine, tyrosine, phenylalanine, histidine, tyrosine and lysine, it appeared that proline was found to be the major free amino acid in the raw herb, licorice tea and infusion with concentrations of 1.02 %, 7.60 mg/100 ml and 6.80 mg/100 ml, respectively. Following in the order is aspartic acid, glutamic, valine and the other amino acids. The major amino acids in the methanolic extract were aspartic (91.96 mg/100 ml) followed by proline (77.14 mg/100 ml) and glutamic acid (27.05). HPLC analysis of the organic acids in the licorice methanolic extract, tea and infusion forms revealed that the plant contained acetic, fumaric, butyric, propanoic, malic, citic and tartaric acids. Tartaric acid was the predominant acid in the licorice methanolic extract (3.5%), followed by butyric acid, malic acid, propanoic acid and citric acid. The tea form had butyric acid (38.4 %) as a main acid followed by propanoic acid (0.33 %) and tartaric acid (0.22 %). The infusion form had acetic acid (19.9 %) as a major organic acid[51].

Pharmacological effects:

Effect on memory and learning:

The effect of *Glycyrrhiza glabra* root extract (75, 150 and 300 mg/kg for 2 weeks) was evaluated on learning and memory in three months old male rats. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters as exteroceptive behavioral model and Diazepam induced amnesia as interoceptive behavioral model. The aqueous extract of root of *Glycyrrhiza glabra* showed improvement in learning and memory in a dose dependent manner. However, 150 mg/kg dose significantly ($P<0.01$) enhanced learning and memory[52-53] .

The beneficial effects of aqueous extract of *Glycyrrhiza glabra* root extract (75, 150, 225, and 300 mg/kg, for six successive weeks) on learning and memory were studied in 1-month-old male Wistar albino rats using the elevated plus maze, Hebb-William maze, and Morris water maze tests as exteroceptive behavioral model and Diazepam-induced amnesia as interoceptive behavioral model. Results revealed that all the doses of aqueous root extract of *Glycyrrhiza glabra* significantly enhanced the memory, the doses 150 and 225 mg/kg, possessed significant ($P < 0.01$) enhancement in learning and memory. Furthermore, diazepam-induced amnesia was reversed by the aqueous root extract of *Glycyrrhiza glabra* (150 and 225 mg/kg, po)[54].

The effects of aqueous extract of *Glycyrrhiza glabra* (75, 150 and 300 mg/kg po for 7 successive days) on learning and memory was also evaluated in mice. Elevated plus-maze and passive avoidance paradigm were employed to test learning and memory. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. This dose also significantly reversed the amnesia induced by diazepam (1 mg/kg ip) and scopolamine (0.4 mg/kg ip)[55].

The dose of 150 mg/kg of the aqueous extract of *Glycyrrhiza glabra* for 7 successive days, significantly improved learning and memory of mice and reversed the amnesia induced by diazepam (1 mg/kg p), scopolamine (0.4 mg/kg ip), and ethanol (1 g/kg ip)[56].

The effects of *Glycyrrhiza glabra* on learning and memory were evaluated using object recognition task (ORT) and elevated plus maze (EPM) models in mice. One dose level of aqueous liquorice extract 400mg/kg po, and two doses levels of glabridin rich extract 5mg/kg and 10mg/kg were administered orally in separate groups of animals. Aqueous liquorice extract and glabridin 10mg/kg treatment significantly improved learning and memory of mice by reversing the amnesia induced by scopolamine hydrobromide (2mg/kg, ip) and diazepam (1mg/kg, ip)[57].

The effect of glabridin isolated from the roots of *Glycyrrhiza glabra* was investigated on cognitive functions and cholinesterase activity in mice. Glabridin (1, 2 and 4 mg/kg, po) was administered daily for 3 successive days to mice. The higher doses (2 and 4 mg/kg po) of glabridin significantly antagonized the amnesia induced by scopolamine (0.5 mg/kg ip) in both the elevated plus maze test and passive avoidance test.

Glabridin (2 and 4 mg/kg po) also remarkably reduced the brain cholinesterase activity in mice compared to the control group[58].

The effect of *Glycyrrhiza glabra* oral supplementation was evaluated on the mental intelligence and memory function of the male students. *Glycyrrhiza glabra* tablets were formulated from the crude powder prepared from roots and subjected to dose standardization process. 123 students were divided into two group, treatment (1 tablet two times/ day) and placebo control (received starch powder) for the period of 60 days. Each group was further subdivided into two, based on low and high intelligence percentage in order to avoid biasness. Evaluation of improvement was judge by using NVIT (Non Verbal Intelligence Test) and memory test score before the start and at the end of treatment period and scored them accordingly into poor, moderate, good and, very good and expressed in percentage. The overall NVIT results indicated that oral consumption of *Glycyrrhiza glabra* tablets twice a day improved the intelligence level among the student compared to placebo treatment. *Glycyrrhiza glabra* treatment was found suitable without any side effects [59].

The deposition of senile plaque that is contributed mainly by amyloid-β (Aβ), whose production is initiated by beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is one of the typical hallmarks of Alzheimer's disease. Inhibition of BACE1 is thereby is an attractive strategy for anti- Alzheimer's disease drug discovery. The natural product 2,2′,4′-trihydroxychalcone (TDC) from *Glycyrrhiza glabra* functioned as a specific non-competitive inhibitor against BACE1 enzyme, and potently repressed β-cleavage of APP and production of Aβ in human embryo kidney cells. The amelioration ability of this compound against the *in vivo* memory impairment was further evaluated by APP-PS1 double transgenic mice model. 9 mg/kg/day of TDC decreased Aβ production and Aβ plaque formation, and efficiently improve the memory impairment based on Morris water maze test[60].

Antidepressant effect:

The effects of aqueous extract of *Glycyrrhiza glabra* on depression was investigated in mice using forced swim test (FST) and tail suspension test (TST). The extract of *Glycyrrhiza glabra* (75, 150, and 300 mg/kg) was administered orally for 7 successive days in separate groups of male mice. The dose of 150 mg/kg of the extract significantly reduced the immobility times of mice in both FST and TST, without any significant effect on locomotor activity of mice. The efficacy of extract was found to be comparable to that of imipramine (15 mg/kg ip) and fluoxetine (20 mg/kg ip). Liquorice extract reversed reserpine-induced extension of immobility period of mice in FST and TST. Sulpiride (50 mg/kg ip, a selective D_2 receptor antagonist) and prazosin (62.5 μg/kg ip, an α_1-adrenoceptor antagonist) significantly attenuated the extract-induced antidepressant-like effect in TST. On the other hand, *p*-chlorophenylalanine (100 mg/kg ip, an inhibitor of serotonin synthesis) did not reverse antidepressant-like effect of liquorice extract. It seemed that the antidepressant-like effect of liquorice extract mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin[61].

Antimicrobial effects:

The antibacterial effect of alcoholic extract obtained by percolation from roots of *Glycyrrhiza glabra* was tested against *Escherichia coli, Pseudomonas fluorescens, Enterococcus faecalis, Bacillus cereus,* and *Staphylococcus aureus*, the extract showed the strong antibacterial activity against all bacterial strains tested. The maximum inhibition diameter was 15 mm against *E. coli, E. faecalis, B.cereus*, whereas *P. fluorescens* showed the lowest sensitivity, with an inhibition zone of 9 mm[62].

The antimicrobial effect of the methanolic extract of *Glycyrrhiza glabra* was investigated against *B. megaterium, B. subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Pseudomonas aeruginosa, Salmonella paratyphi, S. typhi*, *Shigella boydii, S. dysenteriae, Vibrio mimicus* and *V. parahemolyticus*. *Glycyrrhiza glabra* methanolic extract showed potent antimicrobial activity against almost all the tested organisms except *Pseudomonas aeruginosa.* It exhibited highest activity against *Staphylococcus aureus* with a zone of inhibition of 22 mm[63].

The antimicrobial activity of methanolic extract and different fractions (*n*-butanol, ethyl acetate, chloroform and *n*-hexane) of *Glycyrrhiza glabra* root was studied against four bacterial strains *Escherichia coli, Bacillus subtilis, Staphylococcus aureus* and *Pasturella multocida* and three pathogenic fungi, *Aspergillus niger, Aspergillus flavus* and *Rhizopus solani* using disc diffusion and minimum inhibitory concentration methods. As general, plant extract and fractions were mildly potent antimicrobial agent. The results indicated that 100% methanolic extract showed good activity against *E. coli* and *B. subtilis*, showing the highest inhibition zones (33 and 27.5 mm) and the lowest MIC values (9.28 and 30.2 mg/ml), respectively. Least activity was exhibited against A. *niger* and *R. solani* with the smallest inhibition zones (16.5 and 16mm) and the highest MIC values (150 and 152 mg/ml). 80% methanolic extract showed strong activity against *B. subtilis* and *E. coli* with inhibition zones (30 and 28.5 mm) and the lowest MIC values (12.2 and 20.1 mg/ml), respectively. Least activity was exihibited against *S. aureus* with inhibition zone (19 mm) and the highest MIC value (110 mg/ml),

respectively. 80% methanolic fraction showed magnificent activity against *A. niger* as compared to standard drug fluconazole[64].

The antibacterial effect of flavonoid extract of *Glycyrrhiza glabra* was tested against four pathogenic bacterial strains: *Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis* and *Staphylococcus aureus.* The antibacterial effect of the extract appeared concentration dependent. Flavonoids possessed an inhibitory effect on both *Staphylococcus aureus* and *Enterococcus faecalis* but they showed less inhibitory effect against *Escherichia coli* and *Pseudomonas aeruginosa*[65].

The antimicrobial activities of licorice tea and infusion (0.05, 0.1, 0.2, 0.4, 0.6 and 0.8%) were studied against *Bacillus subtilis, Staphylococcus aureus, Escherichiea coli, Salmonella* and *Saccharomyces cerevisiae*. The results revealed that these concentrations didn't possess antibacterial activity[51].

The anti-bacterial activities of the methanol, ethyl acetate, acetone and chloroform extracts of *Glycyrrhiza glabra* plant roots were tested against six bacterial species (*Bacillus coagulans, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella typhimurium*) by the agar disc diffusion method. The results indicated that the extract of *Glycyrrhiza glabra* showed various antibacterial activities (9-14mm/20µl inhibition zone) against the tested bacteria. The methanol, ethyl acetate, acetone and chloroform extracts did not inhibit *Enterococcus faecalis, Pseudomonas aeruginosa and Staphylococcus aureus* but showed an inhibitory effect against *B. coagulans, E. coli* and *S. typhimurium*[66].

The antibacterial potency of 100%, 75%, 50% and 25% of methanolic and acetonic extract of root of *Glycyrrhiza glabra* was investigated against *Salmonella typhi, Escherichia.coli, Vibrio cholerae, Staphylococcus aureus, Bacillus cereus* and *Bacillus subtilis* strains. The 100% (w/v) concentration of both extracts showed maximum inhibition against *Bacillus subtilis* followed by *Escherichia coli, Staphylococcus aureus, Bacillus cereus, Salmonella typhi* and *Vibrio cholerae.* Maximum activity in acetonic extract was obtained against *Bacillus cereus* followed by *Salmonella typhi, Escherichia coli, Vibrio cholerae* and *Staphylococcus aureus* and minimum in *Bacillus subtilis.* A reverse pattern of inhibition activity was found in both extacts (methanolic and acetonic) against *Bacillus subtilis*. Maximum activity was found in methanolic extract against *Bacillus subtilis* (18.6 mm) and in acetonic extract against *Bacillus cereus* (16.3mm)[67].

The antibacterial activity of *Glycyrrhiza glabra* was investigated against oral pathogens [*Streptococcus mutans* (PTCC 1683), *Streptococcus sanguis* (PTCC 1449), *Actinomyces viscosus* (PTCC 1202), *Enterococcus faecalis* (ATCC 29212) as oral pathogens] and *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 29922) as controls. *Glycyrrhiza glabra* extract possessed inhibitory activity against the tested oral bacteria. No strain showed resistance to the extract. The inhibitory zone significantly increased in a dose dependent manner[68].

The diameter of the inhibitory zone of the aqueous extract and methanolic extracts of the root of *Glycyrrhiza glabra,* ranged between 10 - 22 mm against *Staphylococcus aureus*, *Streptococcus agalactiae* and *E. coli*. The methanolic extract was more effective than aqueous extract against *Staphylococcus aureus* (20 mm), *Streptococcus agalactiae* (22 mm) and *E. coli* (17 mm) at the concentration of 8 mg/disc. The MIC values of methanolic extract was 3.125 mg/ml for *S. aureus*, 1.56 mg/ml for *St. agalactiae* and 12.5 mg/ml for *E. coli*. Whereas the aqueous extract showed higher MIC values, 6.25 mg/ml against *S. aureus*, 3.125 mg/ml for *St. agalactiae* and the result was negative for *E. coli*[69].

Glycyrrhiza glabra root extracts (ether, chloroform, acetone) showed significant antibacterial activities against two Gram-positive (*Bacillus subtili* and *Stapphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. Acetone extract showed the highest antibacterial activity with diameter of inhibition of 32, 22, 22, 15 against *Stapphylococcus aureus*, *Bacillus subtili, Pseudomonas aeruginosa* and *Escherichia coli*[70].

The antibacterial effect of the glycoside extracted from *Glycyrrhiza glabra* was investigated against three bacterial strains, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It showed inhibitory effect on the Gram positive strain (*Staphylococcus aureus* ATCC23) and Gram negative strain (*Pseudomonas aeruginosa* ATCC53), but it possessed no effect on *Escherichia coli* ATCC22 strain[71].

The antimicrobial effects of roots extracts of *Glycyrrhiza glabra* was investigated against *Staphylococcus aureus, Salmonella typhi, Staphylococcus sciuri, Escherichia coli, Aspergillus awamorii* and *Rhizopus spp*. The methanolic extract of *Glycyrrhiza glabra* showed maximum antibacterial activity against *Staphylococcus aureus* at 500µg/ml (inhibition zone 13 mm) and maximum antifungal activity against *Rhizopus spp* at 500µg/ml (inhibition zone 11 mm)[50].

The antimicrobial activities of ethanolic and aqueous extracts from licorice leaves were studied compared to root extracts activities against *Bacillus subtilis, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli* and *Candida albicans*. The root and leave extracts showed activity against *Candida albicans* and the tested Gram-positive bacteria in a dose dependent manner. The ethanolic extract of the leaves was the most active extract against Gram-positive bacteria[72].

Glabridin exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria, the highest activity was recorded against Gram positive bacteria. Glabridin isolated from *Glycyrrhiza glabra* roots was potentially active against both *Mycobacterium tuberculosis* H37Ra and H37Rv strains at 29.16 µg/ml concentration[73].

The antimicrobial effect of root methanolic extracts of *Glycyrrhiza glabra* var. glandulifera was investigated against nine bacterial and two yeast strains: six Gram-positive bacteria [*Staphylococcus aureus* ATCC 6538, *Enterococcus faecalis* ATCC 51299, *Micrococcus luteus*, *Bacillus cereus* 7064, vancomycin-resistant *Enterococcus* (VRE) and methycilline resistant *Staphylococcus aureus* (MRSA)]; three Gram negative bacteria (*Escherichia coli* ATCC 11293, *Pseudomonas aeruginos* and *Klebsiella pneumoniae*) and two yeast species (*Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019)] using disc diffusion and minimum inhibitory concentration methods. The results indicated that the plant root extracts were more effective against Gram-positive bacteria than against Gram-negative ones. The plant methanolic extracts inhibited the growth of *B. cereus, E. faecalis, K. pneumonia*, MRSA *S. aureus*, VRE, *C. krusei* and *C. parapsilosis*. However, there was no activity against *E. coli, K. pneumoniae* and *M. luteus*. In addition, the extracts had higher antimicrobial effect against *Candida* species than against bacteria[74].

The *in vitro* activity of glycyrrhizic acid, glycyrrhetinic acid and a novel lipophilic derivative of glycyrrhetinic acid monoglucuronide acetylated GAMG was investigated against 29 *Helicobacter pylori* strains. Glycyrrhetinic acid was the most potent compound ($MIC_{50/90}$: 50/100 mg/l), inhibiting 79.3% of the strains at MIC <50 mg/l[75].

The antifungal potential of the hydroalcoholic extract prepared from rhizomes and roots of *Glycyrrhiza glabra* , was evaluated against 19 *Candida* strains, using the disc diffusion halo assay. The licorice extract was effective against all the tested *C. albicans, C. glabrata, C. parapsilosis* and *C. tropicalis* strains. The results for the inhibitory zones, at the tested concentration (50 mg/ml), after 24h, were 1.0 – 1.2 cm for *C. albicans* and *C. parapsilosis*, 1.0 – 1.3 cm for *C. tropicalis* and 1.2 cm for *C. glabrata*[76].

Glycyrrhiza glabra extracts and glycyrrhizic acid inhibited the replication of several viruses included Epstein-Barr virus, Herpes simplex virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Human cytomegalovirus, Human immunodeficiency virus, Influenza virus, SARS coronavirus and Varicella zoster virus[77-88].

Two coumarins of *Glycyrrhiza glabra*, glycocoumarin and licopyranocoumarin, inhibited giant cell formation in HIV-infected cell cultures without any cytotoxicity. lichochalcone A also had anti-HIV activity[89-90].

Glycyrrhizin was investigated as a therapy of human immuno-deficiency virus (HIV) in 42 hemophilia patients with HIV-1 infection. Patients showed improvement in their clinical symptoms (oral candidiasis, lymph node swelling and rash), immunological functions and liver functions[91].

Many studies have demonstrated that glycyrrhizin was responsible for the antiviral activity of licorice. The possible antiviral mechanisms of this compounds were (HCV): affected release step while infectious HCV particles are infecting cells. Inhibited HCV full length viral particles and HCV core gene expression. (HSV): reduced adhesion force and stress between CCEC and PMN. (CVB3): blocked the degradation of nuclear factor κB inhibitor IκB. (DHV): activated T lymphocyte proliferation. (H5N1): weakened H5N1-induced production of CXCL10, IL-6 and CCL5, and suppressed H5N1-induced apoptosis. (Influenza virus): reduced HMGB 1 binding to DNA, and inhibited influenza virus polymerase activity. (CVA16 EV71): inactivated CVA16 directly, while the effect of anti-EV71 was associated with an events during the virus cell entry. (HSV1): established a resistance state to HSV1 replication. (Rotavirus): reduced the levels of viral proteins VP2, VP6 and NSP2 at a step or steps subsequent to virus entry[92].

Anticancer effect:

The cytotoxic activity of the methanolic extract of *Glycyrrhiza* was tested using brine shrimp lethality bioassay methods. The extract possessed potent cytotoxic activity with LC_{50} value of 0.771µg/ml[63].

The antitumor activity of licorice methanolic extract (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). Licorice methanolic extract had a growth inhibitory action against Caco-2 and PC-3 with IC_{50} values of 40 and 40.6 µg/ml, respectively[51].

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[93].

The cytotoxic activity of different extracts of *Glycyrrhiza glabra* was tested on mice transformed cell line. The results showed that hot alcoholic extract possessed the greatest cytotoxic effect on the cancer cells ($P < 0.05$) after 72 hourse exposure[94].

The effects of an ethanol extract of *Glycyrrhiza glabra* extract (50,100,150, and 200 µg/ml) was investigated on the expression of HSP90, growth and apoptosis in the HT-29 colon cancer cell line. Results

showed that *Glycyrrhiza glabra* inhibited proliferation of the HT-29 cell line at a concentration of 200 µg/ml, this effect was confirmed by the highest rate of cell death as measured by trypan blue and MTT assays. RT-PCR results showed down-regulation of HSP90 gene expression which confirmed the ability of *Glycyrrhiza glabra* to induce apoptosis in HT-29 cells[95].

The antiangiogenic and antitumor activity of *Glycyrrhiza glabra* were investigated on VEGF and MTA1 induced angiogenesis. The angio inhibitory activity of *Glycyrrhiza glabra* was confirmed by its inhibition of angiogenesis, peritoneal and chorioallantoic membrane assay. Reduction in the levels of the cytokine VEGF and microvessel density count in the peritoneum of mice treated with *Glycyrrhiza glabra* indicated that the plant extract decreased VEGF production. It also inhibited the neovascularization in CAM induced by VEGF and MTA1[96].

Antioxidant effect:

Chalcone derivative, a novel group of neolignan lipid esters, and seven known phenolic compounds (formononetin, glabridin, hemileiocarpin, hispaglabridin B, isoliquiritigenin, 4‘-O-methylglabridin, and paratocarpin B) isolated from the roots and stolons of *Glycyrrhiza glabra* were tested in an authentic peroxynitrite anti-oxidant assay. Of these compounds, hispaglabridin B, isoliquiritigenin, and paratocarpin B were found to be the most potent anti-oxidant agents[93].

The antioxidant effect of root methanolic extracts of *Glycyrrhiza glabra* var. glandulifera was investigated using the DPPH (1,1-diphenyl-2-picrylhydrazyl) method. The extracts showed good antioxidant activity, with a median inhibitory concentration (IC_{50}) of 588 ± 0.86 to 2190 ± 1.73 mg/ml[74].

The free radical scavenging of the methanolic extract of *Glycyrrhiza glabra* was investigated using DPPH. The extract showed moderate free radical scavenging activity with IC_{50} value of 87.152 µg/ml[63].

The antioxidant activity of roots extracts of *Glycyrrhiza glabra* was investigated with DPPH scavenging assay. The results revealed that methanolic extract of *Glycyrrhiza glabra* was potent antioxidant with maximum scavenging effect of 67.22% at a concentration of 500µg/ml. The calculated IC_{50} for the methanol extract of *Glycyrrhiza glabra* was 359.45µg/ml[50].

Effect on respiratory system:

The bronchorelaxant effect of *Glycyrrhiza glabra* was studied in a clinical trial (54 patients) in comparison with *Boswellia carterii* (Olibanum) and prednisolone (18 patients each group) for 21 days. Pulmonary function tests and serum electrolytes: calcium, magnesium, potassium and selenium were done before and after the study. The results showed that the tested plants had significant elevation in the values of forced expiratory volume in first second (FEV1%) as (72.45±5.83 vs 61.33±6.04 and 81.10±11.07 vs 62.30±7.22) for olibanum and licorice respectively. Also, elevation in the values of forced volume capacity (FVC) with marked reduction in asthmatic attacks as (2.63±0.82 vs 0.72±0.16, 3.60±0.02 vs 1.08±0.08, and 2.25±0.16 vs 1.05± 0.15) for olibanum, licorice and prednisolone respectively, with better symptomatic improvement in licorice group as compared to olibanum. *Glycyrrhiza glabra* was significantly elevated Mg: from 0.66±0.17 to 1.02±0.10 , Se: from 28.19±3.72 to 51.70±8.63, Ca: from 1.90±0.06 2 to .30±0.08 and K: from 3.60±0.03 to 4.10±0.12[97].

Glycyrrhiza decreased irritations in the throat and produced expectorant effects. It was assumed that *Glycyrrhiza* was able to stimulate tracheal mucus secretions and produce demulcent and expectorant effects[98-99].

Its powder and extract was useful for the treatment of sore throat, cough and bronchial catarrh. It also possessed antitussive and expectorant[100].

Protective effects:

The hepatoprotective potential of aqueous (QGG) and ethanol extract of *Glycyrrhiza glabra* (EGG) and their possible mechanism were studied in rats hepatotoxicity.For acute hepatopathy, rats were intraperitoneally injected with CCl_4 at a dose of 1.0 ml/kg as a 50% olive oil solution. The rats were orally given the aqueous and ethanol extract of *Glycyrrhiza glabra* at doses of 250, 500 mg/kg after 6 h of CCl_4 treatment. At 24 h after CCl_4 injection, samples of blood and liver were collected and then biochemical parameters and histological studies were carried out. The results revealed that both extracts inhibited significantly the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which elevated by CCl_4 and increased the activity of superoxide dismutase which decreased by CCl_4[101].

The hepatoprotective effect of aqueous extract (2gm/kg/day orally for 7 days) of *Glycyrrhiza glabra* roots was investigated in rabbit models with acute liver injury induced by carbon tetrachloride at a dose of 1.25 ml/kg. Aqueous extract of *Glycyrrhiza glabra* had a significant effect in amiolerating liver functions as well as restoring hepatic tissue in acute liver diseases[102].

The hepatoprotective and antioxidant potential of *Glycyrrhiza glabra* hydro-methanolic root extract were investigated against carbon tetra chloride induced oxidative-stress mediated hepatotoxicity in liver tissue of Swiss albino mice. The results suggested that, the crude extract of root of *Glycyrrhiza glabra* at the doses of 300 and 600mg/kg bw for 7 days possessed significant hepatoprotective potential against CCl_4 induced oxidative stress mediated hepatotoxicity ($P<0.05$) at dose dependent manner[103].

The protective effect of three medicinal plants, *Nigella sativa*, *Glycyrrhiza glabra* and *Zingiber officinale*, and their combination was studied against doxorubicin (DOX) -induced apoptosis and death in H9c2 cells. The cells were incubated with different concentrations of each extract or their combination for 4 hr and continued in the presence or absence of 5μM doxorubicin for 24 hr. Treatment with doxorubicin increased ROS generation, enhanced malondialdehyde (MDA) formation, and induced apoptosis. Co-treatment of the cells with each herb extract increased viability of cells dose-dependently with a maximum protection effect of about 30%, and their potencies were *Nigella sativa* > *Glycyrrhiza glabra* > *Zingiber officinale*. The combination of the threshold dose of each extract produced a similar effect, which was increased dose-dependently to a maximum protection of 70%. These effects were correlated with the effects of the combination on ROS and MDA[104].

The efficacy of intravenous glycyrrhizin in decreasing alanine aminotransferase level in the early stage of acute onset autoimmune hepatitis was studied clinically. Thirty-one patients defined as acute onset of autoimmune hepatitis based on a uniform criteria, were enrolled in study. 17 patients were treated with (100 ml/day) of intravenous glycyrrhizin at an early stage and 14 patients of severe disease were treated with intravenous glycyrrhizin and corticosteroids. Treatment response, clinical and biochemical parameters were evaluated. The alanine aminotransferase level could be controlled at an early stage using intravenous glycyrrhizin with no significant difference compared with glycyrrhizin and corticosteroids. Recovery rate was higher in the intravenous glycyrrhizin group than in the glycyrrhizin and corticosteroids group. The authors concluded that sufficient doses of intravenous glycyrrhizin might prevent disease progression in patients with acute onset autoimmune hepatitis[105].

The effect of *Glycyrrhiza glabra* on the metabolism of acetaminophen was examined in male rats. The pretreatment with the methanol extract of *Glycyrrhiza glabra* roots (1 g/kg, po) for 6 days significantly increased the cumulative biliary (156%) and urinary (132%) excretions of acetaminophen, glucuronide conjugate within 120 min after the administration of acetaminophen (150 mg/kg, iv) without affecting thioether and sulfate conjugates. In order to study the effect of *Glycyrrhiza glabra* on the glucuronidation in rat liver, the enzymatic activity of p-nitrophenol UDP-glucuronosyltransferase (UGT), and intracellular concentrations of hepatic UDP-glucuronic acid were examined upon the administration of *Glycyrrhiza glabra* (1 g/kg, po) or glycyrrhizin (23 mg/kg, po), for 6 days. *Glycyrrhiza glabra* and glycyrrhizin caused increases in specific activities of UGT1A by 111% and 96%, respectively. Concentration of UDP-glucuronic acid was increased 257% by *Glycyrrhiza glabra* and 484% by glycyrrhizin[106].

Anti-inflammatory effect:

The anti-inflammatory activity of hydro alcoholic extract of *Glycyrrhiza glabra* (HAEGG) root was evaluated against carrageenan induced rat paw oedema at dose levels of 100, 200, and 300 mg/kg orally. The hydro alcoholic extract of *Glycyrrhiza glabra* showed a maximum (46.86%) inhibitory action on carrageenan induced paw oedema at the dose of 200 mg/kg and inhibited the leukocyte migration in a dose dependent manner. The anti-inflammatory activity was comparable to indomethacin (10mg/kg)[66].

Several secondary metabolites isolated from rhizomes of *Glycyrrhiza glabra* were investigated for the COX-2 inhibitory activity using Cayman COX (ovine) inhibitory screening assay. A few molecules showed potent COX-2 inhibitory activity which may beneficial as anti-inflammatory agents[107]

Glycyrrhizin exhibited steroid-like anti-inflammatory activity, similar to hydrocortisone due to inhibition of phospholipase A2 activity, glycyrrhizic acid inhibited cyclooxygenase activity and prostaglandin formation (specifically prostaglandin E2), as well as indirectly inhibiting platelet aggregation[108-109].

Effect in gastric duodenal ulcers:

Carbenoxolone a glycyrrhizate analog was effective in clinical trials in the treatment of gastric and duodenal ulcer at the medium dose of 100 mg three times a day. Liquorice can raise the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach, it was also prolonged the life span of surface cells in the stomach and has an anti-pepsin effects[110-114].

The anti- *Helicobacter pylori* activity of glycyrrhizic acid, glycyrrhetinic acid and a novel lipophilic derivative of glycyrrhetinic acid monoglucuronide acetylated GAMG was tested against 29 *Helicobacter pylori*

strains. Glycyrrhetinic acid was the most potent compound (MIC $_{50/90}$, 50/100 mg/l), inhibiting 79.3% of the strains at MIC <50 mg/l[75].

Forty patients receiving either 3.0 or 4.5 g deglycyrrhizinated licorice (DGL) daily for eight weeks, were assessed for relief from epigastric pain, nausea, vomiting, x-ray of ulcer craters to determine changes in size of ulcer, and frequency of relapse. All patients showed significant improvement after 5-7 days[115].

In more larger trial carried out on 874 patients with chronic duodenal ulcers. Patients were received DGL, cimetidine, or antacids. No differences were recorded among groups in the rate of ulcer healing, but patients in the DGL group showed less occurance of relapses[116].

Effect on smooth muscles:

The effect of the hydro-alcoholic extract of licorice rhizome on mechanical activity of isolated colon, was studied in male rats. The mechanical activity of tissue in presence of extract and epinephrine was significantly decreased ($p \leq 0.05$) compared to the control group. While the mechanical activity in the presence of extract and propranolol was significantly increased ($p \leq 0.05$) compared to the control group. However, no significant modification was observed in the mechanical activity of the tissue in the presence of phenylephrine and extract compared to the control group. According to the result, it appeared that hydro-alcoholic extract of licorice had modifying effect on colon motility via synergist effect with beta adrenergic receptors and independent of the alpha adrenergic receptors[117-118].

Isoliquiritigenin isolated from an aqueous extract of licorice was a potent relaxant, it inhibited the contraction induced by various types of stimulants, such as CCh, KCl, and BaCl2 with IC_{50} values of 4.96±1.97 microM, 4.03±1.34 microM and 3.70±0.58 microM[119-120].

The mechanisms of action of licorice rhizome extract on duodenal motility *in vitro* were investigated in rats. Mechanical activity in response to extract 43µg/ml (most effective concentration based on concentration/response experiments) in the presence of acetylcholine (10-5 M) as the muscarinic receptor agonist, atropine (10-4 M) as the muscarinic receptor antagonist, epinephrine (10-6 M) as the β-adrenoceptor agonist, propranolol as β receptor antagonist, or N-w- nitro- L arginine methyl ester (L-NAME) (10-4 M) as the inhibitor of the NO synthase enzyme was measured. The results showed that the contraction force exerted on the isolated duodenum pieces by acetylcholine was remarkably reduced in the presence of licorice rhizome extract compared to that of the control group ($P<0.05$). However, this response in the presence of atropine, propranolol and (L-NAME) was not changed significantly. According to the results of the study, alcoholic extract of licorice rhizome decreases bowel motility. This inhibitory effect was independent of cholinergic, β-adrenergic and nitrergic pathways[121].

Effect on diabetes:

The effects of long-term glycyrrhizin treatment (2.7, 4.1 g/kg diet) on diabetic symptoms were studied using genetically non-insulin dependent diabetic model mice (KK-Ay). The elevation of blood glucose concentration was almost entirely suppressed in mice fed the 0.41% glycyrrhizin diet 7 weeks after the beginning of test feeding, although it was not suppressed in mice fed the control diet or the 0.27% glycyrrhizin diet. Water intake in the control and 0.27% glycyrrhizin diet groups increased gradually, whereas, this was not true in the 0.41% glycyrrhizin diet group. Glycyrrhizin treatment significantly lowered blood insulin level. It did not affect the food intake or body weight. 0.41% glycyrrhizin diet in mice also improved their tolerance to oral glucose loading 9 weeks after the beginning of test feeding[122].

The effect of glycyrrhizin was studied on streptozotocin (STZ)-induced diabetic changes and associated oxidative stress, including haemoglobin-induced free iron-mediated oxidative reactions. Glycyrrhizin treatment improved significantly the diabetogenic effects of STZ, it modulated blood glucose level, glucose intolerant behaviour, decreased serum insulin level including pancreatic islet cell numbers, increased glycohaemoglobin level and enhanced levels of cholesterol and triglyceride. The treatment significantly reduced diabetes-induced abnormalities of pancreas and kidney tissues. Oxidative stress parameters, serum superoxide dismutase, catalase, malondialdehyde and fructosamine in diabetic rats were reverted to respective normal values after glycyrrhizin administration. Free iron in haemoglobin, iron-mediated free radical reactions and carbonyl formation in haemoglobin were pronounced in diabetes, and were counteracted by glycyrrhizin. Effects of glycyrrhizin and glibenclamide treatments appeared comparable[123].

Hypolipidemic effect:

Ethanolic extract and its ethyl acetate soluble, water soluble and hexane soluble fractions decreased serum level of total cholesterol by 25.9, 38.0, 39.0 and 26.3%, respectively in high fructose diet induced dsyslipidaemic in Syrian golden hamsters. Furthermore, they also increased the serum HDL-cholesterol level by 14.8, 34.3, 27.3 and 17.2%, and decreased triglyceride level by 31.3, 37.2, 41.2 and 28.9%, respectively. The

reduction in LDL-cholesterol level by ethanolic extract, ethyl acetate soluble fraction and water soluble fraction were 43.9, 31.0, 33.4 and 24.6%, respectively[124].

Effect on body weight:

In studying of body weight changes of rats pre-treated with licorice in infusion and tea forms, the results showed that after 4-weeks, the mean values of body weight gains for control and pre-treated rats group with licorice infusion and tea were 118.5, 132.6 and 121.7 gm ($p < 0.01$) respectively. After 8-weeks, the group of male rats drank licorice infusion were increased in weight than that of the control[51].

Effect on metabolic syndrome:

Therapeutic potential of *Glycyrrhiza glabra* root extract incorporated diet at 300 mg/kg/day was evaluated in a rat model with high-fat diet-induced signs of metabolic syndrome. *Glycyrrhiza glabra* root extract significantly reduced the weight of epididymal tissue (19.0%, $p < 0.01$) and basal serum glucose level (19.4%, $p < 0.05$), decreased systolic blood pressure by 12.0% ($p < 0.05$), reduced serum IL6 and corticosterone levels induced by HFD and reduced triacylglycerol accumulation in the liver[125].

Reproductive and hormonal effects:

The aphrodisiac activity of aqueous extract of *Glycyrrhiza glabra* roots and rhizomes was investigated in rats. 150 mg/kg & 300 mg/kg/day were administered orally by gavage for 28 days. Mount latency, intromission latency, mounting frequency, intromission frequency observed before and during the study at day 0, 7, 10, 14, 21, and 28. The extract reduced significantly mount latency and intromission latency. The extract also increased significantly mounting frequency and intromission frequency[126].

Licorise showed mineralocorticoid properties due to the presence of glycyrrhizin and its metabolite 18β-glycyrrhetinic acid, which was an inhibitor of cortisol metabolism. It was suggest the mineralocorticoid properties of liquorice, agonist of mineralocorticoid receptors and mild inhibitor of androgen synthesis, can reduce the prevalence of side effects related to the diuretic activity of spironolactone in patients with PCOS (Polycystic Ovarian Syndrome)[127-128].

18β-glycyrrhetinic acid, was a potent competitive inhibitor of 11β-HSD (11β-hydroxysteroid dehydrogenase). Lowered 11β-HSD activity resulted in higher peripheral and intrarenal concentrations of corticosterone in experimental animals and cortisol in humans, which interacted with mineralocorticoid receptors and promote Na^+ re-absorption. Acute pretreatment of adrenalectomized male rats with the the water-soluble succinate derivative of 18β-glycyrrhetinic acid (carbenoxolone sodium) caused both cortisol and corticosterone to display significant mineralocorticoid-like activity, particularly Na^+ retention[129-130].

Glycyrrhiza glabra (25 mg alcoholic extract) showed high estrogenic activity reflected by uterine response and vaginal opening. Based upon the mouse uterine weight method, three doses of 25 mg of the alcoholic extract showed an estrogenic activity 1:4716980 of estradiol monobenzoate[131].

Six *Glycyrrhiza* phenols showed binding affinities for the bovine uterine estrogen receptor. The affinity of a dihydrostilbene with two 3-methyl-2-butenyl (prenyl) groups, gancaonin R, was higher than those of isoflavone phytoestrogens (genistein and daidzein) in dietary foods. The affinities of the other five phenols, a flavanone (liquiritigenin), two prenylflavanones (isobavachin and sigmoidin B), a prenylated coumestan (glycyrol), and a pyranoisoflav-3-ene (glabrene), were similar to that of the dietary isoflavone, genistein or daidzein[132].

Effect on oral health, aphthous ulcer and lichen planus:

In a double-blind, placebo-controlled trial, 24 patients with recurrent aphthous ulcers were randomly allocated to consume 2 g glycyrrhizin (carbenoxolone sodium) in 30 ml of warm water three times daily following meals for four weeks. Oral licorice mouthwash significantly reduced the average number of ulcers per day, pain scores, and the development of new ulcers compared with placebo. In another trial, 20 patients used DGL mouthwash four times daily. 50-75 percent clinical improvement was recorded in 15 patients after only one day, with complete healing of canker sores after three days[133-134].

In an open clinical trial, 17 hepatitis C positive patients with oral lichen planus (an inflammatory disease characterized by lymphocytic hyperkeratosis of the oral mucosa) were given either routine dental care or 40 ml iv glycyrrhizin daily for one month. 66.7% of patients showed general clinical improvement, decreased redness, fewer white papules, and less erosion of the mucosa[135].

Effect on the skin:

The extract of liquorice was reported to be an effective pigment lightening agent. Glabridin, in the hydrophobic fraction of liquorice extract inhibited tyrosinase activity in cultured B16 murine melanoma cells. Glabridin, licochalcone A and isoliquiritin were inhibited tyrosinase activity. *In vitro* tyrosinase enzyme inhibition studies has showed that 21.2 μg/ml of methanolic extract of liquorice caused 50% tyrosinase enzyme

inhibition. Due to good tyrosinase inhibition activity, liquorice extract can be used to formulate cosmetic formulations with depigmenting activity. Ethanolic extract of *Glycyrrhiza glabra* was reported to show improvement in the viscoelastic and hydration properties of the skin[136-138].

A double blind placebo controlled study was carried out on one hundred female volunteers suffering from melasma (93 completed the study). Half of the females were used 2.5% of *Glycyrrhiza glabra* extract cream and the other half were used placebo for 28 days. Comparison between the active treated cream and placebo on week intervals, indicated a non significant improvement for the first week of the treatment course (P=0.18). However, there was a significant difference in the improvement rate between the two treatment groups for week 2 (P=0.009), week 3 (P=0.005) and week 4 (P=0.001)[139].

Liquorice showed hair growth stimulatory activity. Comparison between liquorice extract and Minoxidil 2%, showed that, 2% concentration of liquorice hydro-alcoholic extract possessed better hair growth stimulatory activity than 2% Minoxidil[140].

Immunological effect:

Neutrophils treated with alcoholic extract of *Glycyrrhiza glabra* showed increase in phagocytic activity[141]. The effect of *Glycyrrhiza glabra* root extract (0.1, 0.2 and 0.3 mg/l drinking water) was investigated on the performance and some immunological parameters of broiler chickens. *Glycyrrhiza glabra* root extract had no significant (P > .05) effect on immunological parameters including antibody titers against Newcastle disease and Influenza viruses, heterophil and lymphocyte percentages and heterophil to lymphocyte (H/L) ratio as well as liver and lymphoid organ (bursa of Fabricius, thymus and spleen) weights[142].

Side effects and contraindications:

LD_{50} values of Glycyrrhizin (crude extract 48-58%) in rats and mice: LD_{50} sc 4-4.4 g/kg, LD_{50} ip 1.42-1.70 g/kg and LD_{50} oral 14.2-18.0 g/kg[143].

At lower dosages or normal consumption levels, few adverse reactions were evident. Ocular effects and hypersensitivity have been described. Hypertension and hypokalemia were recognized after excessive licorice consumption. Large doses of glycyrrhizinic acid and glycyrrhetinic acid can lead to hypokalemia and serious increases in blood pressure, a syndrome known as apparent mineralocorticoid excess. The majority of cases of hypertension caused by liquorice were caused by eating too much liquorice candy[39,144-145].

Licorice with glycyrrhizin may cause serious side effects. Too much glycyrrhizin causes a condition called pseudoaldosteronism, which can cause a person to become overly sensitive to a hormone in the adrenal cortex. This condition can lead to headaches, fatigue, high blood pressure, and even heart attacks. It may also cause water retention, which can lead to leg swelling and other problems. Although the dangerous effects mostly happen with high doses of licorice or glycyrrhizin, smaller amounts of licorice may cause side effects. Some people have muscle pain or numbness in the arms and legs[146].

Use during pregnancy should be avoided. Licorice exhibited estrogenic activity and possessed abortifacient effects. There was no clinical evidence to support the use of licorice tea as a galactogogue[6]. Glycyrrhizin interacted with prednisolone, hydrocortisone and oral contraceptives[143].

Dose:

Licorice root has been used in daily doses from 1 to 15 g (2% glycyrrhizin) for ulcer and gastritis. Higher doses given for extended periods of time may pose a risk of hyperkalemia. The acceptable daily intake for glycyrrhizin was 0.2 mg/kg/day[39,144].

II. CONCLUSION:

The review highlighted the chemical constituent, pharmacological and therapeutic effects of *Glycyrrhiza glabra* as promising source of drugs because of its safety and effectiveness.

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