Liquorice

Species (Family)

Glycyrrhiza glabra L. (Leguminosae)

Synonym(s)

Licorice

Part(s) Used

Root, stolon

Pharmacopoeial and Other Monographs

BHC 1992[G6]
BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO volume 1 1999[G63]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G2,G6,G41,G48,G64]

Coumarins Glycyrin, heniarin, liqcoumarin, umbelliferone, GU-7 (3-arylcoumarin derivative).[1]

Flavonoids Flavonols and isoflavones including formononetin, glabrin, glabrol, glabrone, glyzarin, glycyrol, glabridin and derivatives, kumatakenin, licoflavonol, licoisoflavones A and B, licoisoflavanone, licoricone, liquiritin and derivatives, phaseollinisoflavan;[2] chalcones including isoliquiritigenin, licuraside, echinatin, licochalcones A and B, neolicuroside.[3]

Terpenoids Glycyrrhizin glycoside (1–24%) also known as glycyrrhizic or glycyrrhizinic acid yielding glycyrrhetinic (or glycyrrhetic) acid and glucuronic acid following hydrolysis;[4] glycyrrhetol, glabrolide, licoric acid, liquiritic acid and β-amyrin.

Volatile oils 0.047%.[5] More than 80 components identified including anethole, benzaldehyde, butyrolactone, cumic alcohol, eugenol, fenchone, furfuryl alcohol, hexanol, indole, linalool, γ-nonalactone, oestragole, propionic acid, α-terpineol and thujone[5]

Other constituents Amino acids, amines, gums, lignin, starch, sterols (β-sitosterol, stigmasterol), sugars and wax.

Other plant parts Components documented for the leaves of *G. glabra* include flavonoids (kaempferol and derivatives, isoquercetin, quercetin and derivatives, phytoalexins), coumarins (bergapten, xanthotoxin), phytoestrogen, β-sitosterol and saponaretin.[6]

Food Use

Liquorice is widely used in foods as a flavouring agent. Liquorice root is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that liquorice can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product.[G16] In the USA, liquorice is listed as GRAS (Generally Recognised As Safe).[G41]

Herbal Use[G2,G6,G7,G8,G10,G64]

Liquorice is stated to possess expectorant, demulcent, antispasmodic, anti-inflammatory and laxative properties. Traditionally, it is also reported to affect the adrenal glands. It has been used for bronchial catarrh, bronchitis, chronic gastritis, peptic ulcer, colic and primary adrenocortical insufficiency.

Dosage

Powdered root 1–4 g or by decoction three times daily.[G6,G7]

Liquorice Extract (BPC 1973) 0.6–2.0 g.

Pharmacological Actions

The pharmacological actions of liquorice have been reviewed.[7,8]

In vitro and animal studies

Much has been documented regarding the steroid-type actions of liquorice (*see* Side-effects, Toxicity). Both glycyrrhizin and glycyrrhetinic acid (GA) have been reported to bind to glucocorticoid and mineralocorticoid receptors with moderate affinity, and to oestrogen receptors, sex hormone-binding globulin and corticosteroid-binding globulin with very weak affinity.[9–11] It has been suggested that glycyrrhizin and glycyrrhetinic acid may influence endogenous steroid activity via a receptor mechanism, with displacement of corticosteroids or other endogenous steroids.[9]

The anti-oestrogenic action documented for glycyrrhizin at relatively high concentrations has been associated with a blocking effect that would be caused by glycyrrhizin binding at oestrogen receptors.[9] However, oestrogenic activity has also been documented for liquorice and attributed to the isoflavone constituents.[8] Liquorice exhibits an alternative action on oestrogen metabolism, causing inhibition if oestrogen concentrations are high and potentiation when concentrations are low.[8]

The relatively low affinity of glycyrrhizin and glycyrrhetinic acid for binding to mineralocorticoid receptors, together with the fact that liquorice does not exert its mineralocorticoid activity in adrenalectomised animals, indicates that a direct action at mineralocorticoid receptors is not the predominant mode of action.[12] It has been suggested that glycyrrhizin and glycyrrhetinic acid may exert their mineralocorticoid effect via an inhibition of 11β-hydroxysteroid dehydrogenase (11β-OHSD).[12] 11β-OHSD is a microsomal enzyme complex found predominantly in the liver and kidneys which catalyses the conversion of cortisol (potent mineralocortoid activity) to the inactive cortisone. Deficiency of 11β-OHSD results in increased concentrations of urinary free cortisol and cortisol metabolites. Glycyrrhetinic acid has been shown to inhibit renal 11β-OHSD in rats.[12] It has also been proposed that glycyrrhizin and glycyrrhetinic acid may displace cortisol from binding to transcortin.[13]

Antiplatelet activity *in vitro* has been documented for a 3-arylcoumarin derivative, GU-7, isolated from liquorice.[1] GU-7 was thought to inhibit platelet aggregation by increasing intraplatelet cyclic AMP concentration.

Isoliquiritigenin has been reported to inhibit aldose reductase, the first enzyme in the polyol pathway which reduces glucose to sorbitol.[14] Isoliquiritigenin was subsequently found to inhibit sorbitol accumulation in human red blood cells *in vitro*, and in red blood cells, the sciatic nerve and the lens of diabetic rats administered isoliquirigenin intragastrically.[14,15] Many diabetic complications, such as cataracts, peripheral neuropathy, retinopathy and nephropathy have been associated with the polyol pathway and have shown improvement with inhibitors of aldose reductase.[14,15]

Significant anti-inflammatory action is exhibited by glycyrrhetinic acid against UV erythema.[16] 18α-Glycyrrhetinic acid has exhibited stronger anti-inflammatory action compared to its stereoisomer 18β-glycyrrhetinic acid.[17] Chalcones isolated from *G. inflata* Bat. have been reported to inhibit leukotriene production and increase cyclic AMP concentrations in human polymorphonuclear neutrophils *in vitro*.[18] Glycyrrhetinic acid derivatives, but not glycyrrhetinic acid, have exhibited inhibitory effects on writhing and vascular permeability tests and on type IV allergy in mice.[19] The dihemiphthalate derivatives were especially active with respect to the two former activities and have previously been found to inhibit lipoxygenase and cyclooxygenase activities, and to prevent formation of gastric ulcer.[19]

Glycyrrhetinic acid is known to inhibit Epstein–Barr virus activation by tumour promotors.[20]

Antimicrobial activity versus *Staphylococcus aureus*, *Mycobacterium smegmatis* and *Candida albicans* has been documented for liquorice and attributed to isoflavonoid constituents (glabridin, glabrol and their derivatives).[2] Antiviral activity has been described for glycyrrhetinic acid, which interacts with virus structures producing different effects according to the viral stage affected.[21] Activity was observed against vaccinia, herpes simplex 1, Newcastle disease and vesicular stomatitis viruses, with no activity demonstrated towards poliovirus 1.[21]

In vitro hepatoprotective activity against CCl_4-induced toxicity has been reported to be greater for glycyrrhetinic acid compared to glycyrrhizin.[22] Glycyrrhetinic acid is thought to act by inhibition of the cytochrome P450 system required for the metabolism of CCl_4 to the highly reactive radical CCl_3.[22] *Glycyrrhiza uralensis* Fisch is used to treat hepatitis B in China, with a success rate reported to be greater than 70%.[23] Other activities documented for *G. uralensis* are anti-inflammatory and anti-allergic, treatment of jaundice, inhibition of fibrosis of the liver, corticosteroid-like immunosuppressing effect and a detoxifying effect.[23]

Screening of several plant extracts for antifertility activity reported liquorice to be ineffective following oral administration to rats in days 1–7 of pregnancy.[24]

Clinical studies

Carbenoxolone, an ester derivative of glycyrrhetinic acid, has been used in the treatment of gastric and

oesophageal ulcers. It is thought to exhibit a mucosal-protecting effect by beneficially interfering with gastric prostanoid synthesis, and increasing mucous production and mucosal blood flow.[25]

Liquorice is thought to exert its mineralocorticoid effect by inhibition of the enzyme 11β-OHSD, which catalyses the conversion of cortisol to the inactive cortisone (*see* In vitro and animal studies). Administration of liquorice to healthy volunteers has resulted in a disturbance of cortisol metabolism and a significant rise in urinary free cortisol, despite there being no change in plasma concentrations. These changes are consistent with this hypothesis, being indicative of 11β-OHSD deficiency.[12] Liquorice has also been found to suppress both plasma renin activity and aldosterone secretion.[26–28]

The pharmacokinetic profile of glycyrrhizin in rats has been found to be similar to that observed in humans.[29] Glycyrrhizin is primarily (80%) excreted into the bile from the liver against a concentration gradient.[29] This process is saturable and can therefore affect the excretion rate of glycyrrhizin. In addition, enterohepatic recycling occurs with reabsorption of bile-excreted glycyrrhizin from the intestinal tract.[29] Subjects consuming 100–200 g liquorice/day have been reported to achieve plasma glycyrrhetinic acid concentrations of 80–480 ng/mL.[12]

Side-effects, Toxicity

Apart from confectionery, liquorice can also be ingested from infusions and by chewing tobaccos. Excessive or prolonged liquorice ingestion has resulted in symptoms typical of primary hyperaldosteronism, namely hypertension, sodium, chloride and water retention, hypokalaemia and weight gain, but also in low levels of plasma renin activity, aldosterone and antidiuretic hormone.[13,26,30]

Raised concentrations of atrial natriuretic peptide (ANP), which is secreted in response to atrial stretch and has vasodilating, natriuretic and diuretic properties, have also been observed in healthy subjects following the ingestion of liquorice.[13] Individuals consuming between 10–45 g liquorice/day have exhibited raised blood pressure, together with a block of the aldosterone/renin axis and electrocardiogram changes, which resolved one month after withdrawal of liquorice.[31] Individuals consuming vastly differing amounts of liquorice have exhibited similar side-effect symptoms, indicating that the mineralocorticoid effect of liquorice is not dose dependent and is a saturable process.[31]

Hypokalaemic myopathy has also been associated with liquorice ingestion.[32–36] Severe hypokalaemia with rhabdomyolysis has been documented in a male patient following the ingestion of an alcohol-free beverage containing only small amounts of glycyrrhetinic acid (0.35 g/day).[32] The patient had known liver cirrhosis due to alcohol consumption and it was suggested that cirrhotic patients may be more susceptible to the mineralocorticoid side-effects of liquorice.[32] In one case,[34] the myoglobinaemia led to glomerulopathy and tubulopathy but with no clinical evidence of acute renal failure (ARF). The latter was attributed to the volume expansion also caused by the liquorice ingestion.

Rhabdomyolysis without myoglobinuria has been described.[37] In addition, severe congestive heart failure and pulmonary oedema have been reported in a previously healthy man who had ingested 700 g liquorice over eight days.[30] Liquorice extract given orally has been reported to have a similar but longer lasting action to intravenous deoxycortone and it has been noted that sodium, chloride and water retention do not have to be accompanied by clinical oedema.[38] Amenorrhoea has been associated with liquorice ingestion (anti-oestrogenic action), with the menstrual cycle re-appearing following the withdrawal of liquorice.[31]

It has been noted that symptoms of hyperaldosteronism often resolve quickly, within a few days to two weeks, following the withdrawal of liquorice, even in individuals who have ingested the substance for many years.[28]

A case has been described where a patient presented with symptoms related to hyperglycaemia and myopathy secondary to liquorice-induced hypokalaemia. An inverse relationship was observed between the concentrations of fasting serum glucose and serum potassium.[39] Interestingly, animal studies have indicated that liquorice may reduce diabetic complications associated with intracellular accumulation of sorbitol.[19]

Contra-indications, Warnings

Numerous instances have been documented where liquorice ingestion has resulted in symptoms of primary hyperaldosteronism, such as water and sodium retention and hypokalaemia. Liquorice should therefore be avoided completely by individuals with an existing cardiovascular-related disorder, and ingested in moderation by other individuals. Hypokalaemia is known to aggravate glucose intolerance and liquorice ingestion may therefore interfere with existing hypoglycaemic therapy. Liquorice may interfere with existing hormonal therapy (oestrogens and antioestrogenic activities documented *in vivo*).

Pregnancy and lactation In view of the oestrogenic and steroid effects associated with liquorice, which may exacerbate pregnancy-related hypertension, excessive ingestion during pregnancy and lactation should be avoided. In addition, liquorice has exhibited a uterine stimulant activity in animal studies, and is traditionally reputed to be an abortifacient and to affect the menstrual cycle (emmenagogue).[G30]

Pharmaceutical Comment

The phytochemistry is well documented for liquorice and it is particularly characterised by triterpenoid components. Many of the traditional uses of liquorice are supported by documented pharmacological data although limited evidence of antispasmodic activity was found. Carbenoxolone, an ester derivative of a triterpenoid constituent in liquorice, is well known for its use in ulcer therapy. Much has been written concerning the steroid-type adverse effects associated with liquorice ingestion. Liquorice ingestion should therefore be avoided by individuals with an existing cardiovascular disorder and moderate consumption should be observed by other individuals.

References

See also General References G2, G3, G5, G6, G9, G12, G15, G16, G18, G21, G28, G30, G31, G32, G36, G37, G41, G43, G48, G50, G56, G63 and G64.

1 Tawata M *et al.* Anti-platelet action of GU-7, a 3-arylcoumarin derivative, purified from *Glycyrrhizae radix*. *Planta Med* 1990; 56: 259–263.

2 Mitscher LA *et al.* Antimicrobial agents from higher plants. Antimicrobial isoflavanoids and related substances from *Glycyrrhiza glabra* L. var. *typica*. *J Nat Prod* 1980; 43: 259–269.

3 Miething H, Speicher-Brinker A. Neolicuroside – A new chalcone glycoside from the roots of *Glycyrrhiza glabra*. *Arch Pharm (Weinheim)* 1989; 322: 141–143.

4 Takino Y *et al.* Quantitative determination of glycyrrhizic acid in liquorice roots and extracts by TLC-densitometry. *Planta Med* 1979; 36: 74–78.

5 Kameoka H, Nakai K. Components of essential oil from the root of *Glycyrrhiza glabra*. *Nippon Nogeikagaku Kaishi [J Ag Chem Soc Japan]* 1987; 61: 1119–1121.

6 Jimenez J *et al.* Flavonoids of *Helianthemum cinereum*. *Fitoterapia* 1989; 60: 189.

7 Chandler RF. Licorice, more than just a flavour. *Can Pharm J* 1985; 118: 421–424.

8 Pizzorno JE, Murray AT. *Glycyrrhiza glabra*. *A Textbook of Natural Medicine*. Seattle, WA: John Bastyr College Publications, 1985 (looseleaf).

9 Tamaya MD *et al.* Possible mechanism of steroid action of the plant herb extracts glycyrrhizin, glycyrrhetinic acid, and paeoniflorin: Inhibition by plant herb extracts of steroid protein binding in the rabbit. *Am J Obstet Gynecol* 1986; 155: 1134–1139.

10 Armanini D *et al.* Binding of agonists and antagonists to mineralocorticoid receptors in human peripheral mononuclear leucocytes. *J Hypertens* 1985; 3(Suppl.3): S157–159.

11 Armanini D *et al.* Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors. *Clin Endocrinol* 1983; 19: 609–612.

12 Stewart PM *et al.* Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. *Lancet* 1987; ii: 821–824.

13 Forslund T *et al.* Effects of licorice on plasma atrial natriuretic peptide in healthy volunteers. *J Intern Med* 1989; 225: 95–99.

14 Aida K *et al.* Isoliquiritigenin: A new aldose reductase inhibitor from *Glycyrrhizae radix*. *Planta Med* 1990; 56: 254–258.

15 Yun-ping Z, Jia-qing Z. Oral baicalin and liquid extract of licorice reduce sorbitol levels in red blood cell of diabetic rats. *Chin Med J* 1989; 102: 203–206.

16 Fujita H *et al.* Antiinflammatory effect of glycyrrhizinic acid. Effects of glycyrrhizinic acid against carrageenin-induced edema, UV-erythema and skin reaction sensitised with DCNB. *Pharmacometrics* 1980; 19: 481–484.

17 Amagaya S *et al.* Separation and quantitative analysis of 18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid in *Glycyrrhizae radix* by gas-liquid chromatography. *J Chromatogr* 1985; 320: 430–434.

18 Kimura Y *et al.* Effects of chalcones isolated from licorice roots on leukotriene biosynthesis in human polymorphonuclear neutrophils. *Phytother Res* 1988; 2: 140–145.

19 Inque H *et al.* Pharmacological activities of glycerrhetinic acid derivatives: Analgesic and anti-type IV allergic effects. *Chem Pharm Bull* 1987; 35: 3888–3893.

20 Tokuda H *et al.* Inhibitory effects of ursolic and oleandolic acid on skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate. *Cancer Lett* 1986; 33: 279–285.

21 Pompei R *et al.* Antiviral activity of glycyrrhizic acid. *Experientia* 1980; 36: 304.

22 Kiso Y *et al.* Mechanism of antihepatotoxic activity of glycyrrhizin, I: Effect on free radical generation and lipid peroxidation. *Planta Med* 1984; 50: 298–302.

23 Chang HM *et al.* *Advances in Chinese Medicinal Materials Research*. Singapore: World Scientific, 1985.

24 Sharma BB *et al.* Antifertility screening of plants. Part I. Effect of ten indigenous plants on early pregnancy in albino rats. *Int J Crude Drug Res* 1983; 21: 183–187.
25 Guslandi M. Ulcer-healing drugs and endogenous prostaglandins. *Int J Clin Pharmacol Ther Toxicol* 1985; 23: 398–402.
26 Conn J *et al.* Licorice-induced pseudoaldosteronism. Hypertension, hypokalaemia, aldosteronopenia and suppressed plasma renin activity. *JAMA* 1968; 205: 492–496.
27 Epstein MT *et al.* Effect of eating liquorice on the renin-angiotensin aldosterone axis in normal subjects. *BMJ* 1977; 1: 488–490.
28 Mantero F. Exogenous mineralocorticoid-like disorders. *Clin Endocrinol Metab* 1981; 10: 465–478.
29 Ichikawa T *et al.* Biliary excretion and enterohepatic cycling of glycyrrhizin in rats. *J Pharm Sci* 1986; 75: 672–675.
30 Chamberlain TJ. Licorice poisoning, pseudoaldosteronism, heart failure. *JAMA* 1970; 213: 1343.
31 Corrocher R *et al.* Pseudoprimary hyperaldosteronism due to liquorice intoxication. *Eur Rev Med Pharmacol Sci* 1983; 5: 467–470.
32 Piette AM *et al.* Hypokaliémie majeure avec rhabdomyolase secondaire à l'ingestion de pastis non alcoolisé. *Ann Med Interne (Paris)* 1984; 135: 296–298.
33 Cibelli G *et al.* Hypokalemic myopathy associated with liquorice ingestion. *Ital J Neurol Sci* 1984; 5: 463–466.
34 Heidermann HT, Kreuzfelder E. Hypokalemic rhabdomyolysis with myoglobinuria due to licorice ingestion and diuretic treatment. *Klin Wochenschr* 1983; 61: 303–305.
35 Ruggeri CS *et al.* L. Carnetina cloruro e KCl nel trattamento di un caso di rabdomiolisi atraumatica senza mioglobinuria da ingestione di liquerizia. *Minn Med* 1985; 76: 725–728.
36 Bannister B *et al.* Cardiac arrest due to liquorice induced hypokalaemia. *BMJ* 1977; 2: 738–739.
37 Maresca MC *et al.* Low blood potassium and rhabdomyolosis. Description of three cases with different aetiologies. *Minerva Med* 1988; 79: 79–81.
38 Molhuysen JA. A liquorice extract with deoxycortone-like action. *Lancet* 1950; ii: 381–386.
39 Jamil A *et al.* Hyperglycaemia related to licorice-induced hypokalaemia. *J Kwt Med Assoc* 1986; 20: 69–71.