

Licorice

Glycyrrhiza spp.

Glycyrrhiza glabra L. (syn. *G. glandulifera* Walst. & Kit.), *G. uralensis* Fisch. Ex DC.

[Fam. *Fabaceae*]

OVERVIEW

Licorice root is one of the most widely used medicinal herbs worldwide and is the single most used herb in Chinese medicine today. In a recent survey of Western medical herbalists, licorice ranked as the 10th most important herb used in clinical practice. While licorice root is commonly taken in combinations for treatment of catarrhs of the respiratory tract, cough and sore throat, as well as for dyspepsia, a few clinical studies have investigated its effects on aphthous, duodenal, and gastric ulcers.

PRIMARY USES

Crude Preparations

- Catarrh of upper respiratory tract

Deglycyrrhized Licorice Extract Preparations

- Aphthous, stomatitis (oral ulcers)
- Gastric ulcers
- Duodenal ulcer

NOTE: The Commission E also approved licorice preparations containing glycyrrhizin for gastric and duodenal ulcers.

OTHER POTENTIAL USES

- Prevention of radiation complications in lungs during radiotherapy
- Chronic hepatitis
- Sore throat
- Cough with viscid expectoration
- Dyspepsia

Purified Licorice Derivatives

- Hepatic failure, subacute
- Reduced risk of liver carcinogenesis in hepatitis C patients

Uses in Traditional Chinese Medicine (TCM)

- Bronchitis, pharyngitis, laryngitis, bronchial asthma, chronic hypocorticism

PHARMACOLOGICAL ACTIONS

Anti-inflammatory; expectorant; demulcent; adrenocorticotropic; antioxidant; protection of LDL against lipid peroxidation; accelerates healing of gastric ulcers.



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DOSAGE AND

ADMINISTRATION

Licorice should not be ingested for longer than 4 to 6 weeks without medical advice, although licorice root may be used as a flavoring agent up to a maximum daily dosage equivalent to 100 mg glycyrrhizin. A diet rich in potassium (eg., bananas) is recommended during the period of treatment with licorice.

Crude Preparations

DECOCTION: 1.0–1.5 g licorice root placed in approximately 150–250 ml cold water. Boiled, simmered for 10–15 minutes, then strained; 2–3 times daily.

INFUSION: Approximately 150 ml boiling water poured over 4.5 g licorice root and steeped 10–15 minutes; 2–3 times daily.

FLUID EXTRACT: 2–5 ml, 3 times daily.

POWDERED ROOT: Approximately 5–15 g root daily; equivalent to 200–600 mg

glycyrrhizin, 2–4 g single dose.

Deglycyrrhized Licorice (DGL) Preparations

DGL NATIVE DRY EXTRACT: 0.4–1.6 g, 3 times daily.

DGL CHEWABLE TABLETS: For acute cases of gastric or duodenal ulcers; 2–4 tablets chewed before each meal. For chronic cases, 1 to 2 tablets chewed before each meal.

Standardized Preparations

FLUID EXTRACT: 5–15 ml daily, (or 2–5 ml, 3 times daily) corresponding to German Commission E dosage of 5–15 g of root daily.

NATIVE DRY EXTRACT: 0.33–0.8 g, 3 times daily, after meals.

CONTRAINDICATIONS

Patients with cholestatic liver disorders, liver cirrhosis, hypertension, hypokalemia, severe kidney insufficiency, and possibly diabetes (unconfirmed contraindication) should consult a healthcare provider before using licorice.

PREGNANCY AND LACTATION: Not recommended during pregnancy. Heavy exposure to glycyrrhizin (<500 mg/wk) did not affect birth weight, but did double the risk of birth before 38 weeks. No known restrictions during lactation.

ADVERSE EFFECTS

No adverse effects have been associated with licorice when used appropriately. Prolonged use (longer than six weeks) and higher doses (greater than 50 g/day) may lead to sodium and water retention, and to potassium loss accompanied by hypertension, edema, hypokalemia, and, in rare cases, myoglobinuria. Side effects are less likely with aqueous licorice root extract than with isolated glycyrrhizin. In two separate cases, pulmonary edema and life-threatening ventricular tachycardia due to hypokalemia occurred as a result of overdoses of black licorice-flavored candy.

DRUG INTERACTIONS

Licorice may potentiate the side effects of potassium-depleting thiazide diuretics (eg., chlorothiazide, chlorthalidone, hydrochlorothiazide, and metolazone). With potassium loss, sensitivity to digitalis glycosides increases. Licorice should not be combined with corticoid treatment.

CLINICAL REVIEW

Ten studies that included a total of 2,544 participants had variable research designs and evaluated a wide cross-section of therapeutic uses. Eight showed positive effects for indications including the effects of licorice or its active constituents on pulmonary metabolism, pseudohyperaldosteronism, aphthous ulcer, benign gastric ulcer, chronic duodenal ulceration, LDL cholesterol, subacute hepatic failure, and chemoprevention. Three studies were conducted on licorice root extract, four studies on DGL extract, and two on isolated glycyrrhizin preparations. One study on birth outcome found that licorice did not affect birth weight but did double the risk of birth before 38 weeks.



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OVERVIEW

Licorice root is one of the most widely used medicinal herbs worldwide and is the single most used herb in Chinese medicine today. In a recent survey of Western medical herbalists, licorice ranked as the 10th most important herb used in clinical practice. While licorice root is commonly taken in combinations for treatment of catarrhs of the respiratory tract, cough, sore throat, and dyspepsia, a few clinical studies have investigated its effects on aphthous, duodenal, and gastric ulcers.

PRIMARY USES

Catarrh of the upper respiratory tract; oral ulcers; gastric and duodenal ulcers.

OTHER USES

Sore throat; cough with viscid expectoration; dyspepsia; prevention of lung complications during radiation therapy; reduction of risk of liver cancer in hepatitis C; chronic hepatitis.

TRADITIONAL CHINESE MEDICINE USES

Bronchitis; pharyngitis; laryngitis; bronchial asthma; chronic hypocorticism.

DOSAGE

Licorice should not be ingested for more than 4 to 6 weeks without medical advice. Licorice root may be used as a flavoring agent up to a maximum daily dosage equal to 100 mg glycyrrhizin. A diet high in potassium-rich foods such as bananas is recommended while being treated with licorice.

Crude Preparations

DECOCTION: 1.0–1.5 g licorice root placed in approximately 150–250 ml cold water. Boiled, simmered for 10–15 minutes, then strained; 2–3 times daily.

FLUID EXTRACT: 2–5 ml, 3 times daily.

POWDERED ROOT: Approximately 5–15 g root daily, equivalent to 200–600 mg glycyrrhizin, 2–4 g single dose.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Deglycyrrhized Licorice (DGL) Preparations

DGL NATIVE DRY EXTRACT: 0.4–1.6 g, 3 times daily.

DGL CHEWABLE TABLETS: For acute cases of gastric or duodenal ulcers; 2–4 tablets chewed before each meal. For chronic cases, 1 to 2 tablets chewed before each meal.

Standardized Preparations

FLUID EXTRACT: 2 to 5 ml, 3 times daily [standardized minimum 7% glycyrrhizin].

NATIVE DRY EXTRACT: 0.33–0.8 g, after meals, 3 times daily [standardized minimum 20% glycyrrhizin].



CONTRAINDICATIONS

Patients with cholestatic liver disorders, liver cirrhosis, high blood pressure, hypokalemia, severe kidney insufficiency, and possibly diabetes (unconfirmed contraindication) should consult a healthcare provider before using licorice.

PREGNANCY AND LACTATION: Not recommended for use during pregnancy. No known restrictions during lactation.

ADVERSE EFFECTS

No adverse effects have been associated with licorice when used appropriately. The prolonged use of licorice in high doses (greater than 50 g/day) and for more than six weeks may lead to sodium and water retention, and to potassium loss accompanied by high blood pressure, water retention, and potential cardiac complications. Aqueous licorice root extracts are less likely than isolated glycyrrhizin to produce side effects.

DRUG INTERACTIONS

Licorice may increase the side effects of potassium-depleting thiazide diuretics, including chlorothiazide, chlorthalidone, hydrochlorothiazide, and metolazone. With the loss of potassium, sensitivity to digitalis glycosides (heart medications) increases. Licorice should not be combined with corticosteroid drug treatment.



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[Fam. *Fabaceae*]

OVERVIEW

Licorice root is presently one of the most widely used medicinal herbs, and has been used therapeutically for several thousand years in Western and Eastern medicine (Gibson, 1978; Leung and Foster, 1996; Wang *et al.*, 2000). Licorice ranks as the 10th most important herb for Western medical herbalists and in Unani traditional medicine clinics in Pakistan (Bergner, 1994; American Institute of Unani Medicine, 1999). In Traditional Chinese Medicine (TCM), licorice root is the most commonly-used herb, though it is almost always used in combination with other herbs (Leung, 1999).

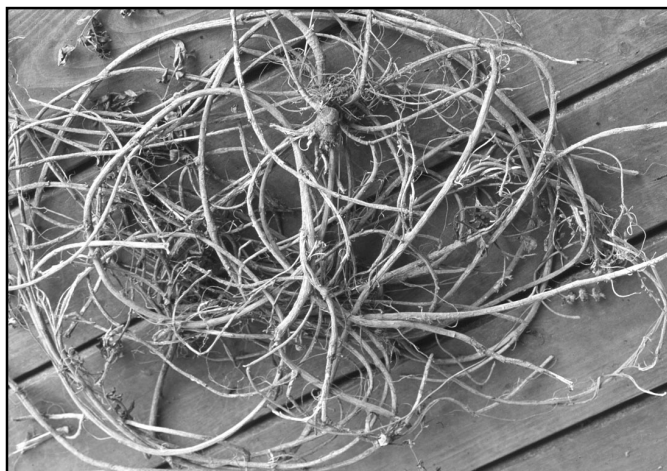


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DESCRIPTION

Licorice root consists of the dried roots and rhizomes of *Glycyrrhiza glabra* L. (syn. *G. glandulifera* Walst. & Kit.) and its varieties or *G. uralensis* (WHO, 1999; McGuffin *et al.*, 2001), or other species of *Glycyrrhiza* (US FDA, 1998), and contains no less than 4% glycyrrhizic acid (syn. glycyrrhizin) (Ph.Eur., 2001). Peeled roots contain no less than 20% water-soluble extractive, and unpeeled roots contain no less than 25% water-soluble extract (Blumenthal *et al.*, 1998), and no less than 25% dilute ethanol-soluble extract (JP XII, 1991; JSHM, 1993).

PRIMARY USES

Crude Preparations

- Catarrh of the upper respiratory tract (Blumenthal *et al.*, 1998)

Deglycyrrhized Licorice Extract (DGL) Preparations

- Aphthous, stomatitis (oral ulcers) (Das *et al.*, 1989)
- Gastric ulcers (Morgan *et al.*, 1985)
- Duodenal ulcer (Kassir, 1985; Larkworthy and Holgate, 1975)

NOTE: The German Commission E also approved licorice preparations containing glycyrrhizin for gastric and duodenal ulcers.

OTHER POTENTIAL USES

Miscellaneous Preparations

- Prevention of radiation complications in lungs during radiotherapy (Palagina *et al.*, 1999) [extract]
- Chronic hepatitis (Chang and But, 1986; Huang, 1999) [decoction]
- Sore throat, as a demulcent (IP, 1996; WHO, 1999) [form not specified]
- Cough with viscid expectoration (Schilcher, 1997) [extract, tea, or juice]
- Dyspepsia (WHO, 1999) [form not specified]

Purified Licorice Derivatives

- Hepatic failure, subacute (Acharya *et al.*, 1993) [NOTE: i.v. preparation]
- Reduced risk of liver carcinogenesis in hepatitis C patients (Arase *et al.*, 1997)

Uses in TCM

- Bronchitis, pharyngitis, laryngitis, bronchial asthma, chronic hypocorticism (PPRC, 1992)

Combination Preparations

- Infantile colic—with chamomile flower (*Matricaria* spp.), fennel seed (*Foeniculum vulgare*), vervain herb (*Verbena hastata*), and lemon balm leaf (*Melissa officinalis*) (Weizman *et al.*, 1993; Zand *et al.*, 1994)
- Productive cough in children—with marshmallow root (*Althaea officinalis*), anise seed (*Pimpinella anisum*), and cowslip flower (*Primula veris*) (Schilcher, 1997)

DOSAGE

Internal

Crude Preparations

DECOCTION: 1.0–1.5 g licorice root placed in approximately 150–250 ml cold water. Boiled, simmered for 10–15 minutes, then strained, 2–3 times daily (Meyer-Buchtela, 1999; ÖAB, 1991; Wichtl and Bisset, 1994).

INFUSION: Approximately 150 ml boiling water poured over 4.5 g licorice root and steeped 10–15 minutes; 2–3 times daily (Braun *et al.*, 1997).

FLUID EXTRACT BP [1:1 (g/ml), 16–20% ethanol (v/v)]: 2–5 ml, 3 times daily (BP, 1980; Bradley, 1992).

POWDERED ROOT: Approximately 5–15 g root daily, equivalent to 200–600 mg glycyrrhizin (Blumenthal *et al.*, 1998), 2–4 g single dose (API, 1989). NOTE: After decocting for 10 minutes, approximately 50% of the available glycyrrhizin, and approximately 45% of the liquiritin are released into the tea. After

30 minutes, approximately 80% of the glycyrrhizin, and 75% of the liquiritin are released, respectively (Meyer-Buchtela, 1999).

Deglycyrrhized Licorice (DGL) Preparations

DGL NATIVE DRY EXTRACT BP [0.5–2.0% total flavonoids, calculated as liquiritigenin]: 0.4–1.6 g, 3 times daily (BP, 1986; Bradley, 1992).

DGL CHEWABLE TABLETS [380 mg DGL 4:1]: For acute cases of gastric or duodenal ulcers; 2–4 tablets chewed before each meal. For chronic cases, 1–2 tablets chewed before each meal (Pizzorno and Murray, 1999).

Standardized Preparations

FLUID EXTRACT DAB [2.0–4.0% glycyrrhizin, 52–65% ethanol (*v/v*): 5–15 ml daily, (or 2–5 ml, 3 times daily) corresponding to Commission E dosage of 5–15 g of root daily (Blumenthal *et al.*, 1998).

FLUID EXTRACT PPRC [minimum 7.0% glycyrrhizin, 20–25% ethanol (*v/v*): 2–5 ml, 3 times daily (PPRC, 1992).

NATIVE DRY EXTRACT [4–5:1 (*w/w*), minimum 20% glycyrrhizin]: 0.33–0.8 g, after meals 3 times daily.

DURATION OF ADMINISTRATION

No longer than four to six weeks internally without medical advice. There is no objection to using licorice root as a flavoring agent up to a maximum daily dosage equivalent to 100 mg glycyrrhizin (Blumenthal *et al.*, 1998). A diet rich in potassium (e.g., bananas) is recommended during treatment period (Bruneton, 1999).

CHEMISTRY

Licorice root contains triterpenoid saponins, mainly glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) (Tang and Eisenbrand, 1992; Ph. Eur. minimum 4%) with the sapogenin glycyrrhetic acid (glycyrrhetin, glycyrrhetic acid). Glycyrrhetic acid is a triterpene with an oleanan skeleton (Tang and Eisenbrand, 1992). Licorice also contains approximately 1% flavonoids, mainly flavanones (e.g., liquiritin), chalcones (e.g., isoliquiritin), and isoflavonoids (e.g., formononetin); polysaccharides (arabino-galactans); and sterols (β -sitosterol, stigmasterol) (Bradley, 1992; Tang and Eisenbrand, 1992).

PHARMACOLOGICAL ACTIONS

Human

Crude Preparations

Anti-inflammatory; expectorant; demulcent; adrenocorticotropic (Bradley, 1992); reduces serum testosterone in men (Armanini *et al.*, 1999); antioxidant (Fuhrman *et al.*, 1997).

Deglycyrrhized Licorice (DGL) Preparations

Protects LDL against lipid peroxidation (Fuhrman *et al.*, 1997).

Purified Licorice Derivatives

Accelerates the healing of gastric ulcers in controlled clinical studies of glycyrrhizic acid and the aglycone of glycyrrhizic acid (Blumenthal *et al.*, 1998).

Animal

Secretolytic and expectorant effects in rabbits; antispasmodic action in isolated rabbit ileum has been observed (Blumenthal *et al.*, 1998); antioxidant and oxygen radical-scavenging in rats (Yokozawa *et al.*, 2000); may have cancer chemopreventive effects (Wang *et al.*, 2000); induces liver microsomal cytochrome P450 in mice (Hu *et al.*, 1999); inhibits decline in immune complex (IC) clearance in carrageenan-injected mice (Matsumoto *et al.*, 1996); prevents gastric mucosal damage in rats (Goso *et al.*,

1996); protects mitochondrial function against oxidative stresses (Haraguchi *et al.*, 2000); anti-arrhythmic action of total licorice flavonoids (e.g., liquiritigenin and isoliquiritigenin) in mice and guinea pigs (Hu *et al.*, 1999); protects liver (Nose *et al.*, 1994; Shim *et al.*, 2000); inhibits generation of suppressor T-cells in thermally injured mice (Kobayashi *et al.*, 1993). Phytosterols, β -sitosterol, and stigmasterol are estrogenic in castrated mice (Van Hulle, 1970).

In vitro

Binds estrogen receptors (Zava *et al.*, 1998); antimicrobial (Li *et al.*, 1998; Okada *et al.*, 1989); antioxidant (Okada *et al.*, 1989); decreases arylamine N-acetyltransferase (NAT) activity in *Helicobacter pylori* cultures from peptic ulcer patients (Chung, 1998); anti-tumor necrosis factor (TNF) activity (Yoshikawa *et al.*, 1997).

MECHANISM OF ACTION

- Glycyrrhizin is metabolized to its aglycone 18- β -glycyrrhetic acid in the intestine by human intestinal bacteria, which is then absorbed into the blood
- Protects liver through 18- β -glycyrrhetic acid and glycyrrhizin (Shim *et al.*, 2000)
- Relieves gastric inflammation, possibly by inhibiting prostaglandin synthesis and lipoxygenase (Inoue *et al.*, 1986; Tamura *et al.*, 1979)
- Antigastric ulcer activity is due to the FM 100 fraction (licorione), which lowers gastric acidity, reduces pepsin activity, and inhibits gastric secretion (Huang, 1999)
- Inhibits human 11- β -hydroxysteroid dehydrogenase, the enzyme that catalyzes the conversion of cortisol to cortisone, and bacterial 3- α , 20- β -hydroxysteroid dehydrogenase (Duax *et al.*, 2000)
- Inhibits 11- β -hydroxysteroid dehydrogenase, which minimizes the binding of cortisol to mineralocorticoid receptors, creating a mineralocorticoid-like effect (Farese *et al.*, 1991)
- Inhibits peripheral metabolism of cortisol, which binds to mineralocorticoid receptors in the same way as aldosterone (Heikens *et al.*, 1995)
- May also inhibit both 17- β -hydroxysteroid dehydrogenase and 17,20-lyase, which catalyzes conversion of 17-hydroxyprogesterone to androstenedione (Armanini *et al.*, 1999)
- Modulates the cell-mediated immune system, which may be due to glycyrrhizin stimulating the induction of contrasuppressor cells (Kobayashi *et al.*, 1993)
- Demulcent and expectorant actions due to stimulating tracheal mucous secretion (Hikino, 1985)
- Antioxidant action may be related to absorption and binding of licorice's flavonoids (e.g., glabridin) to the LDL particle, thereby protecting the LDL from oxidation (Fuhrman *et al.*, 1997)

CONTRAINDICATIONS

The German Commission E states that licorice is contraindicated in cholestatic liver disorders, liver cirrhosis, hypertension, hypokalemia, and severe kidney insufficiency (Blumenthal *et al.*, 1998). Licorice is also contraindicated in diabetes by the Belgian Pharmaceutical Association (Van Hellemont, 1986), although this was not confirmed in a subsequent monograph by the World Health Organization (WHO, 1999).

PREGNANCY AND LACTATION: Not recommended during pregnancy (Braun *et al.*, 1997; McGuffin *et al.*, 1997; WHO, 1999). The effect of glycyrrhizin was studied on 1,049 Finnish women and their infants. Heavy exposure to glycyrrhizin (<500 mg/wk) did not affect birth weight, but did double the risk of birth before 38 weeks (Strandberg *et al.*, 2001). No known restrictions during lactation.

ADVERSE EFFECTS

No adverse effects have been associated with licorice used within proper dosage and treatment period limits (Schulz *et al.*, 1998; WHO, 1999). With prolonged use (longer than six weeks), and higher doses (greater than 50 g/day), sodium and water retention and a loss of potassium may occur, accompanied by hypertension, edema, hypokalemia, and in rare cases, myoglobinuria (Blumenthal *et al.*, 1998; WHO, 1999). With short-term treatment for cough, these mineralocorticoid effects did not develop (Schilcher, 1997). Within several weeks of discontinuing use, any symptoms of hyperaldosteronism should disappear (Mantero, 1981). Side effects are less likely with aqueous licorice root extract than with isolated glycyrrhizin, due to lower intestinal absorption when consumed as a component of the total extract (Cantelli-Forti *et al.*, 1994). There has been one case report of pulmonary edema following an acute overdose (approximately 1,020 g, containing ~3.6 g glycyrrhizic acid in three days) of Hershey Twizzlers® black licorice-flavored candy (Chamberlain and Abolnik, 1997). There is one case report of life-threatening ventricular tachycardia due to hypokalemia induced by overdose (approximately 40–70g daily for four months) of a licorice candy (Eriksson *et al.*, 1999), though the brand of the candy, and the actual quantity of licorice or licorice derivatives contained in the candy are missing from the report.

DRUG INTERACTIONS

Licorice may potentiate the side effects of potassium depleting thiazide diuretics (e.g., chlorothiazide, chlorthalidone, hydrochlorothiazide, and metolazone) (Austin *et al.*, 2000; Blumenthal *et al.*, 1998; Shintani *et al.*, 1992). With potassium loss, sensitivity to digitalis glycosides increases (Blumenthal *et al.*, 1998; Van Hellefont, 1986). The 1998 French Explanatory Note warns not to combine with corticoid treatment (Bruneton, 1999). When decocted in combination with toxic herbs such as prepared aconite root (*Aconitum carmichaelii* Debeaux), a detoxified preparation used in TCM, the yield of anti-arrhythmic licorice flavonoids is significantly higher than when decocted alone. This mitigated the toxic effects (e.g., arrhythmia) induced by aconitine (Hu *et al.*, 1999; Leung, 1999) in mice and guinea pigs.

AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 2B: Not to be used during pregnancy (McGuffin *et al.*, 1997).

CLASS 2D: Not for prolonged use or in high doses except under supervision of a qualified health practitioner (McGuffin *et al.*, 1997).

REGULATORY STATUS

AUSTRIA: Unpeeled dried root is official in the *Austrian Pharmacopoeia* (Meyer-Buchtela, 1999; Wichtl, 1997).

BELGIUM: Traditional Herbal Medicine (THM) permitted for specific indications (Bradley, 1992; WHO, 1998).

CANADA: Approved active ingredient in THM products and in Homeopathic products, both requiring pre-marketing authorization with Drug Identification Number (DIN) assigned (Health Canada, 2001). Food if no claim statement is made.

CHINA: Dried root and rhizome, prepared (stir-fried with honey) root and rhizome, alcoholic fluid extract and dry aqueous native extract, containing not less than (NLT) 20.0% glycyrrhetic acid, are official drugs of the *Pharmacopoeia of the People's Republic of China* (PPRC, 1997).

EUROPEAN UNION: Dried unpeeled or peeled, root and stolons containing NLT 4.0% glycyrrhizic acid and standardized ethanolic fluid extract containing NLT 3.0% and NMT 5.0% glycyrrhizic acid are official in *European Pharmacopoeia* (Ph.Eur. 2001).

FRANCE: THM permitted for specific indications, internal or locally (mouth and throat). Official in *French Pharmacopoeia* (Bradley, 1992; Bruneton, 1999; WHO, 1998).

GERMANY: Dried root or dry extract for infusion, decoction, liquid or solid dosage forms, are approved non-prescription drugs in the Commission E monographs (Blumenthal *et al.*, 1998). Licorice root tea is approved as an over-the-counter (OTC) drug in the *German Standard License* monographs (Braun *et al.*, 1997). Peeled dried root containing NLT 4.0% glycyrrhizic acid, and standardized ethanolic fluid extract containing NLT 5.0% and NMT 7.0% glycyrrhizic acid are official in *German Drug Codex* supplement to *German Pharmacopoeia* (DAC, 1990 & 1995). Standardized ethanolic fluid extract containing NLT 2.0% and NMT 4.0% glycyrrhizic acid are official in *German Pharmacopoeia* (DAB, 1999).

INDIA: Dried unpeeled roots and stolons containing NLT 4.0% glycyrrhizic acid are official in *Indian Pharmacopoeia* (IP, 1996). Dried unpeeled stolon and root are official in the Government of India *Ayurvedic Pharmacopoeia of India* (API, 1989). Prepared mature root (min. 4 years) is an official single-drug and/or component of multiple-ingredient drugs dispensed in Unani system of medicine (CCRUM, 1986 & 1997). A monograph for dried root occurs in the *Indian Herbal Pharmacopoeia* (IHP I, 1998).

ITALY: Listed in the *Italian Pharmacopoeia* (Newall *et al.*, 1996).

JAPAN: Traditional Kampo medicine. Dried peeled or unpeeled root and stolon are official in the *Japanese Pharmacopoeia* (JSHM, 1993).

RUSSIAN FEDERATION: Official in the *State Pharmacopoeia of the Union of Soviet Socialist Republics*, Ph.USSR X (Bradley, 1992; Newall *et al.*, 1996).

SWEDEN: Classified as foodstuff. As of January 2001, no licorice products are listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: Official in *Swiss Pharmacopoeia*, Ph.Helv.VII (Bradley, 1992; WHO, 1998; Wichtl, 1997). Licorice is an approved component of multi-ingredient phytomedicines listed in the *Swiss Codex* 2001/02 available in juice, syrup, tea infusion, and tincture dosage forms (Ruppanner and Schaefer, 2000) with positive classification (List D) by *Interkantonale Konstellation für Heilmittel* (IKS) and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001).

U.K.: Herbal medicine on the *General Sale List*, Schedule 1 (requires full Product License), Table A (internal or external use) (GSL, 1994). Dried unpeeled roots and stolons containing NLT

4.0% glycyrrhizinic acid, ethanolic fluid extract, and DGL dry aqueous extract containing 0.5–2.0% total flavonoids, calculated as liquiritigenin, are official in the *British Pharmacopoeia* (BP, 1986). U.S.: Dietary supplement or food depending on label claim statement (USC, 1994). Licorice root and derivatives are affirmed as Generally Recognized as Safe (GRAS) for use as a flavoring agent or flavor enhancer in vitamin or mineral dietary supplements, herb and seasoning products and nonalcoholic beverages, including tea (US FDA, 1998). Dried roots, rhizome and stolons, powdered root, and powdered dry extract are subjects of botanical monographs in development for the *US National Formulary*. Previews of the standards development were published in *Pharmacopoeial Forum* (USP, 2002).

CLINICAL REVIEW

Ten studies are outlined in the following table, “Clinical Studies on Licorice,” including a total of 2,544 participants. Eight studies including a total of 1,505 participants. All but one of these studies (Armanini *et al.*, 1999) demonstrated positive effects for indications such as treatment of various types of ulcers, chemoprevention, and use as an antioxidant. Three studies were conducted on licorice root extract (Armanini *et al.*, 1999; Armanini *et al.*, 1996; Palagina *et al.*, 1999), four studies were on DGL extract (Fuhrman *et al.*, 1997; Das *et al.*, 1989; Kassir, 1985; Morgan *et al.*, 1985), and two studies were conducted on isolated glycyrrhizin preparations (Arase *et al.*, 1997; Acharya *et al.*, 1993). These include an open (O) study on the effects of licorice root tablets on gonadal function (Armanini *et al.*, 1999), a comparison (Cm) study on pulmonary metabolism during radiotherapy (Palagina *et al.*, 1999), an O study on pseudohyperaldosteronism (Armanini *et al.*, 1996), a placebo-controlled (PC) study on LDL cholesterol (Fuhrman *et al.*, 1997), an O, uncontrolled study on aphthous ulcer (Das *et al.*, 1989), a Cm, randomized (R) study on chronic duodenal ulceration (Kassir, 1985), and a single-blind, controlled, R study on benign gastric ulcers (Morgan *et al.*, 1985). Isolated glycyrrhizin has been investigated as a chemopreventive in one retrospective Cm (Arase *et al.*, 1997) and one O study on the treatment of subacute hepatic failure (Acharya *et al.*, 1993). One study on birth outcome found that licorice did not affect birth weight but did double the risk of birth before 38 weeks (Strandberg *et al.*, 2001).

BRANDED PRODUCTS

Caved-S®: Tillots Pharma AG / Hauptstrasse 27 / CH-4417 Zeifen / Switzerland / Tel: +41-61-935-2626 / Fax: +41-61-935-2625. Each tablet contains 380 mg deglycyrrized licorice extract. This product is no longer available.

Saila Licorice Root Tablets: Saila S.p.A. / 83 Viale Garibaldi / Silvi Marina, Teramo / Italy. One tablet contains 500 mg glycyrrhizin.

Stronger Neo Minophagen-C (SNMC); Minophagen Pharmaceutical Co. / No. 3 Tomizawa Bldg. / 2-7, Yotsuya 3-chome / Shinjuku, Tokyo 160 / Japan / Tel: +81-3-3355-6561 / Fax: +81-3-3355-6565. Standardized to contain 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine in physiologic saline, intravenous. This product is no longer available.

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Clinical Studies on Licorice (*Glycyrrhiza* spp.)

Ulcers

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Das <i>et al.</i> , 1989	Aphthous ulcer	O, U n=20	2 weeks	Mouthwash with 200 mg DGL extract solution, 4x/day	DGL powdered extract dissolved in 200 ml warm water (brand not stated)	15 of 20 (75%) experienced 50–75% improvement within 1 day followed by complete healing of ulcers by 3rd day.
Kassir, 1985	Chronic duodenal ulceration	Cm, R n=874 (169 in Caved-S® group)	3 months	380 mg tablet 3x/day	Caved-S® tablet (380 mg DGL extract) vs. antacid (AL-Mg hydroxide equivalent) vs. cimetidine vs. Gefarnate	At 6 weeks a highly significant difference ($p < 0.01$) in favor of antacid, but at 12 weeks no significant difference ($p > 0.05$) among the 4 groups. There were fewer relapses in the DGL group compared to the 3 other treatments.
Morgan <i>et al.</i> , 1985	Benign gastric ulcer	SB, C, R, Cm n=82	3 months healing study continued as 2-year maintenance study	Two, 380 mg DGL extract tablets plus antacid combination chewed between meals 3x/day vs. cimetidine (200 mg 3x daily and 400 mg at bedtime)	Caved-S® containing 380 mg DGL extract per tablet vs. cimetidine	No significant difference between 2 drug regimens. After ulcer healing, drug dosage was reduced. After one year of maintenance therapy, there were 4 ulcer recurrences in each group. After second year, recurrence rate was 29% in Caved-S® group and 25% in cimetidine group. Authors conclude that long-term maintenance therapy is safe and reasonably effective.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Strandberg <i>et al.</i> , 2001	Birth effects	O n=1,049 questionnaires distributed in the hospital and review of maternity records	9 months	Glycyrrhizin levels from licorice consumption grouped into 3 levels: low (<250 mg/week; n=751), moderate (250–499 mg/week; n=145) and heavy (≥ 500 mg/wk; n=110)	Brand not stated	Heavy exposure to glycyrrhizin (<500 mg/wk) did not affect birth weight, but did double the risk of birth before 38 weeks.
Armanini <i>et al.</i> , 1999	Gonadal function	O n=7 healthy men (ages 22–24 years)	1 week treatment followed by 4 days of no treatment	7 g licorice root extract/day (500 mg glycyrrhizin)	Saila licorice root tablets	Serum testosterone concentrations decreased and serum 17-hydroxy-progesterone concentrations increased during treatment period. Authors concluded that men with decreased libido or other sexual dysfunction should be cautioned about licorice ingestion.
Palagina <i>et al.</i> , 1999	Pulmonary metabolism during radiotherapy in women ages 20–40 years with breast cancer Stage I–II	Cm n=25 women with breast cancer Stage I–II	2 weeks	Not available	Ural licorice extract (brand not stated)	Administration of licorice promoted inactivation of lipid peroxidation and maintenance of most biochemical parameters on baseline level. It is speculated that this effect is due to licorice components with antioxidant and lung surfactant synthesis stimulant actions. Authors conclude that licorice extract is promising for prevention of radiation complications in lungs during radiotherapy in chest area.

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.

Clinical Studies on Licorice (*Glycyrrhiza* spp.) (cont.)

Other (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Arase et al., 1997	Chemo-prevention	RS, Cm n=453 patients with hepatitis C (84 in SNMC group)	16 years (median, 10.1 years)	100 ml/day intravenous first 8 weeks, followed by 2-7x/week for 2-16 years	Stronger Neo-Minophagen-C (SNMC) providing 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine in physiologic saline	After 10 years, cumulative incidence of hepatocellular carcinoma (HCC) was 7% in SNMC group and 12% for non-treatment group. After 15 years, cumulative incidences were 12% and 25%, respectively. Statistically significant reduction in serum alanine aminotransferase (ALT) levels was reported in 34 of 84 patients (35.7%) in treatment group. HCC in 30 patients with normal ALT levels was slightly lower than the 54 remaining patients with higher ALT scores (p=0.08). An increase in blood pressure was noted in 3 of 84 patients. Authors concluded that long-term administration of SNMC in patients with chronic HCC is effective in reducing risk of liver carcinogenesis.
Fuhrman et al., 1997	Antioxidant action	PC (ex vivo assay) n=20 healthy male volunteers	2 weeks	100 mg DGL extract/day	DGL extract in softgel capsule (brand not stated)	In licorice group, 44% reduction in lipid peroxides formed per mg of LDL cholesterol after exposure of plasma to copper sulfate ex vivo, and 36% reduction after exposure to water-soluble free radical generator, vs. no significant changes observed in plasma of placebo group.
Armanini et al., 1996	Pseudohyperaldosteronism	O n=6 male volunteers	1 week	7g licorice root extract/day (500 mg glycyrrhizin)	Saila licorice root tablets	Pseudohyperaldosteronism occurred during treatment period. Ratio of tetrahydrocortisol + allo tetrahydrocortisol to tetrahydrocortisone in urine increased in 5 cases after 3 days without increase of plasma mineralocorticoid activity. Authors concluded that pseudohyperaldosteronism is due to decreased activity of 11-β-hydroxysteroid-dehydrogenase and in some cases a direct effect on mineralocorticoid receptors.
Acharya et al., 1993	Subacute hepatic failure	O n=18	3 months	40 or 100 ml/day intravenous first 30 days, followed by 3x/week for 8 weeks	Stronger Neo-Minophagen-C (SNMC) providing 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine in physiologic saline	Survival rate was 72.2% compared to reported rate of 31.1% in 98 patients who received supportive therapy (p<0.01). Authors concluded that further studies are necessary to standardize the dose and duration of therapy with SNMC in subacute hepatic failure.

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.