

Glycyrrhiza glabra (1)

Licorice

Indications

Adrenal-related fatigue and hypotension.

Mechanism of Action

Glycyrrhiza contains steroidal saponins credited with many of the supportive effects on the adrenal glands and hypothalamic–pituitary–adrenal (HPA) axis. Many adaptogenic plants possess steroidal saponins shown to exert immunomodulating and anabolic activities.¹ As a general group of plant steroid-like compounds, saponins have been shown to promote neurogenesis, restore monoaminergic tone, enhance neurotrophic factors, and protect the HPA axis from acute and long-term stress.²

One of the most studied compounds in *Glycyrrhiza* is the steroidal saponin glycyrrhizin (synonymous with glycyrrhizic acid), which acts directly on the adrenal cortex and increases blood corticoids in patients with suppressed pituitary adrenocorticotropin (ACTH).³ Glycyrrhizin administered at a dose of 75 mg/kg/day for 5 days in rats resulted in inhibition of 11 β -hydroxysteroid dehydrogenase (HSD) activity and also a significant reduction in steady-state 11 β -HSD mRNA levels in both mineralocorticoid (kidney and distal colon) and glucocorticoid (liver and pituitary) target tissues.⁴

A similar group of steroidal saponins found in *Glycyrrhiza* are referred to collectively as glycyrrhizinates. Glycyrrhizinates inhibit 11- and 17 β -HSDs, a group of steroid-specific dehydrogenase enzyme responsible for catalyzing the interconversion of active and inactive corticosteroids, such as cortisol to cortisone. Inhibition of these enzymes will prolong the life of cortisol in general circulation and may support a weak adrenal gland by boosting the tissue cortisol levels when adrenal output is insufficient.

Glycyrrhizinates can induce mineralocorticoid-like effects in both animals and humans.⁵ Elevated cortisol, both endogenous and exogenous pharmaceutical, leads to elevated aldosterone due to agonism of the renal corticoid receptors, which triggers the release of aldosterone. *Glycyrrhiza* steroidal compounds elicit a similar phenomenon to what is called pseudoaldosteronism, whereby the steroids promote the release of renal aldosterone.⁶

Other steroid-like compounds in *Glycyrrhiza* have also been shown to inhibit 11 β -HSD enzymes, including glycyrrhetinic acid⁷ and the metabolic product of glycyrrhizin, carbenoxolone.^{8,9,10} Doses of 500 mg or less of glycyrrhetinic acid inhibit the enzymes only transiently, whereas 1000 and 1550 mg may cause long-lasting cortisone-like effects.¹¹ These compounds may also reduce new releases of cortisol by inhibiting the conjugation of the metabolic precursors deoxycorticosterone and dehydroepiandrosterone in the adrenal gland.⁷

Carbenoxolone is a glycyrrhetic acid derivative with a steroid-like structure. It has also been found to support mitochondrial function contributing to the adaptogenic actions of *Glycyrrhiza*, such as improving energy and stamina. Carbenoxolone promotes mitochondrial functions stimulating phosphorylation via specific effects on mitochondrial membranes.¹² This may help improve general cellular energy metabolism without the need to rely on greater adrenergic stimulation or stress on the HPA axis.

Adrenoreceptors on vascular smooth muscle fibers help regulate vascular resistance and blood pressure. Vascular adrenoreceptors are linked to pannexin channels involved in the release of ATP from smooth muscle cells, leading to vasoconstriction.¹³ Pannexin proteins are increasingly being shown to be involved in many physiological and pathological processes, amplifying ATP release, Ca(2+) signals, or both. Carbenoxolone inhibits pannexin channels.¹⁴ In adrenal chromaffin cells, pannexin channels play a role in the release of the catecholamine adrenaline and noradrenaline.¹³

Evidence-Based Research

Glycyrrhiza can normalize adrenal responsiveness as well as help mitigate stress affecting the HPA axis, as evidenced by its effects on adrenal hormones. *Glycyrrhiza* supports adrenal function, in part, by effecting cortisol-metabolizing dehydrogenase enzymes,¹⁵ as evidenced by increased blood levels of cortisol and decreased urinary excretion demonstrated with both animal and human studies. Human laboratory investigations show that *Glycyrrhiza* can lower cortisol in some subjects,¹⁶ yet raise it in Addison's disease patients where serum cortisol is low,¹⁷ exemplifying the definition of an adaptogen, which are herbs with many nonspecific actions on the hormonal regulation, adrenal response, and HPA axis feedback, capable of optimizing tone, response, and circadian rhythms of hormones whether excess or deficient.

Animal and human blood assays indicate that *Glycyrrhiza* at doses of 100, 250, and 500 mg/kg will acutely decrease serum cortisol, ACTH, aldosterone, and K and increase renin and Na concentration in a dose-dependent manner.^{16,18} *Glycyrrhiza* may double urinary cortisol excretion in some human subjects similar to the levels seen in Cushing's syndrome patients.¹⁹ Doses of 100 and 200 g/day will cause urinary cortisol to remain elevated for a week or more after *Glycyrrhiza* is withdrawn. A small pilot study showed serum cortisol levels in Addison's disease patients on prescription cortisone acetate to increase when *Glycyrrhiza* is added, and cortisol delivery to all tissues is improved.¹⁷ These polar effects of raising serum cortisol in Addison's patients and lowering it in other populations is evidence of the ability of *Glycyrrhiza*'s adaptogenic action on the HPA axis in a manner that optimizes tone and regulation, regardless of where the baseline cortisol lies—deficient or excess.

Blunting of responsiveness to glucocorticoids and the circadian rhythm of cortisol and dehydroepiandrosterone (DHEA) occurs in various diseases, as well as in general aging where weakness in the HPA axis amplifies age-related changes in the neuroendocrine system.^{20,21} Aging is associated with a progressive decrease in the DHEA:cortisol ratio and a shift from anabolic-to-catabolic dominance, which is also linked to atherosclerotic progression and loss of cognitive and immune competence.²⁰ One human clinical lab marker investigation found a low DHEA:cortisol to be associated with age in general, and in particular age combined with cognitive and mood disorders^{21,22} and a greater degree of anxiety and anger, depression and hostility, and age and age of onset/duration of illness in schizophrenic populations.²³ Subtle signs of adrenal weakness, or blunting of the HPA axis include easy fatigue, poor stamina, poor memory, depression, irritability, and frequent infections—the same set up symptoms that indicate the use of adaptogenic herbs.

Glycyrrhiza in moderate doses primarily affects cortisol metabolism, and the androgens to a lesser degree. Animal studies suggest that *Glycyrrhiza* can reduce elevated androgens,²⁴ and one human study showed *Glycyrrhiza* to decrease elevated serum testosterone in women as well;²⁵ yet, normal DHEA and testosterone levels in healthy subjects have not been shown to be significantly depressed or impacted. *Glycyrrhiza* at a dose of 100 g supplying 150 mg of glycyrrhetic acid was found to insignificantly reduce serum DHEA in men without affecting testosterone after 4 weeks.²⁶ Human studies assaying the effects of *Glycyrrhiza* on salivary cortisol also report that no changes in testosterone levels could be seen in healthy men.²⁷

Safety in Pregnancy and Breastfeeding

Glycyrrhiza is not considered to have the risk of inducing miscarriage or acting as an abortifacient, but it has been associated with an increased risk of preterm delivery. In general, *Glycyrrhiza* is demonstrated to have a spasmolytic action on the uterus.²⁸ Tissue studies suggest *Glycyrrhiza* to possibly inhibit oxytocin, prostaglandin, and KCl-induced uterine contractions²⁹ as well as those induced by calcium channel activation, nitric oxide synthase, or cyclooxygenase.³⁰ However, several outcome studies have reported a higher incidence of threatened miscarriages and preterm labors among regular users of *Glycyrrhiza* compared with those women not exposed to these herbs during pregnancy, although the sample size was small and the confounding factors numerous and complex.³¹ “Heavy” *Glycyrrhiza* exposure (>500 mg of glycyrrhizin per week) was associated with a greater risk of preterm delivery in one outcome study,³² without evidence of effects on birth weight or maternal blood pressure.³³ Another outcome study reviewed data on 185 pregnant women who used *Glycyrrhiza*-containing cough and cold formulas with a maximum dose of 2104 mg/day, anywhere between the 4th day and 25th week of gestation. The rate of stillbirths was marginally higher among women who took *Glycyrrhiza* than those who did not, and there was no evidence of teratogenic effects.³⁴

Synthetic glucocorticoids administered during pregnancy to improve fetal lung maturity in threatened preterm birth have been shown to reduce birth weight and head circumference, but they have not been linked to gross changes in long-term health to date. 11 β -HSD type 2 enzymes (11 β -HSD2), discussed above, are also active in the placenta and may become up-regulated during pregnancy if a woman is exposed to stress, as the enzymes promote glucocorticoid production.

Animal studies show long-term stress to alter the HPA axis and that *Glycyrrhiza*-like synthetic glucocorticoids can increase the occurrence of behavioral problems as a result.³⁵ Glycyrrhizin, a natural constituent of *Glycyrrhiza*, potently inhibits 11 β -HSD2, thereby reducing the fetoplacental barrier to the higher maternal cortisol levels. Maternal consumption of glycyrrhizin was shown to correlate to increased salivary cortisol levels in newborns, compared with newborns whose mother had zero exposure during pregnancy.³⁶ Another human outcome study reported that prenatal exposure to *Glycyrrhiza* exerted detrimental effects on cognitive performance, as determined by standardized neuropsychological assessment tests and the report of psychiatric symptoms. Those with zero to low exposure (0–249 mg/week) scored better than those with high exposure (\geq 500 mg/week).³⁷

One rat study reported *Glycyrrhiza* gavage at a dose of 100 mg/kg for 7 days to significantly increase the teratogenicity of cyclophosphamide by inducing cytochrome p450 enzyme conversion of the compound into toxic metabolites.³⁸ Other human outcome studies however have not observed *Glycyrrhiza* to have teratogenic activity.

Thus, it may be concluded that *Glycyrrhiza* be avoided in pregnancy in anything greater than an occasional cup of tea. High doses, concentrated products, and daily consumption of *Glycyrrhiza* should be avoided during pregnancy.

General Safety

Glycyrrhiza's side effect of hypertension has been widely publicized, although the actual occurrence of this side effect is quite rare. Studies indicate that *Glycyrrhiza* may aggravate high blood pressure more often in those with a preexisting complex adrenal disorder involving altered potassium levels^{39,40,41,42,43} or those with a particular isoform of the 11 β -dehydrogenase enzymes. Defects in the 11 β -HSD2 enzyme contribute to hypertension and may make some people more sensitive to the hypertensive effects of salt and *Glycyrrhiza* because the kidneys express high levels 11 β -HSD2 and are the principal source of cortisone in humans.⁴⁴

Interestingly, *Glycyrrhiza* has in fact been reported to *reduce* blood pressure in animal models with metabolic syndrome.⁴⁵ However, the side effect of elevated blood pressure remains unpredictable, so people using *Glycyrrhiza* supplements regularly should monitor their blood pressure. People with abnormally low potassium levels should avoid *Glycyrrhiza* due to the possibility of serious muscle weakness and high blood pressure. Do not consume more than 2 or 3 cups of *Glycyrrhiza* tea per day unless under a physician's guidance. One clinical study investigating the benefits of *Glycyrrhiza* on mineralocorticoids in women taking spironolactone reported no subjects to experience hypertension as a side effect.⁴⁶ There has been one anecdotal case report of acute urinary retention associated with severe hypokalemia possibly associated with *Glycyrrhiza* use in a pregnant woman.⁴⁷ Various genotoxic studies have indicated that glycyrrhizin is neither teratogenic nor mutagenic and may possess antigenotoxic properties under certain conditions.⁵

Glycyrrhizin/glycyrrhizic acid may induce edema, hypertension, and hypokalemia in patients treated with higher doses and long-term administration, all as a side effect of pseudoaldosteronism due to the 11 β -HSD inhibition. There are cases of *Glycyrrhiza* aggravating pseudohyperaldosteronism.⁴⁸ Hypokalemic periodic paralysis, a rare disorder consisting of sudden episodes of muscle weakness with areflexia involving all four limbs that spontaneously resolves in several hours to several days, may be associated with heavy *Glycyrrhiza* ingestion in some people.⁴⁹

Dosage

Traditional medicines include teas, syrups, and powders at a wide variety of dosages, depending on whether it is being used as a lead or supportive herb within the formula.

Modern encapsulations will use 250–1000 mg in a single dose that is repeated several times a day. As this herb has potential for toxicity symptoms, use caution if exceeding doses greater than 4 g/day continuously.

Based on the in vivo and clinical evidence, an acceptable daily intake of isolated glycyrrhizin, one that will not typically cause Na retention or hypertension, is 0.015–0.229 mg/kg body weight/day.⁵

Traditional Uses

Glycyrrhiza is a rhizome that has been used since ancient times in traditional Chinese medicine and in ancient Egyptian, Greek, and Roman healing traditions for numerous medicinal uses. In China it has been

referred to as “the great harmonizer” because of the belief that it can go everywhere in the body and pull together the actions of other herbs in botanical formulas. *Glycyrrhiza* seems to deserve this reputation because it can be used for ulcers, allergy, viral infections, fatigue, hepatoprotection, adrenal disorders, infertility, and numerous hormonal problems. Several *Glycyrrhiza*-based medicines have been introduced including a Japanese glycyrrhizin preparation used clinically as an antiallergic and antihepatitis agent and a remedy for gastric ulcer marketed in the Netherlands in 1940s. *Glycyrrhiza* also has a long-standing reputation as an emergency remedy in China for acute pituitary failure such as postpartum Sheehan’s syndrome.⁵⁰

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