



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Licorice root

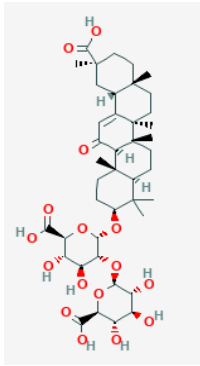
Evidence Summary

Licorice-derived glycyrrhizin may protect against liver disease through anti-viral and antioxidant properties, but excessive consumption can lead to hypertension and mineralocorticoid side effects.

Neuroprotective Benefit: Combined with other medicinal herbs in the form of yokukansan, licorice root may reduce dementia-related agitation, but small clinical studies suggest there is no benefit for reducing cognitive decline.

Aging and related health concerns: Antioxidant, anti-inflammatory and anti-viral effects may drive the protective effect of glycyrrhizin in hepatitis. Aside from hepatoprotection, licorice extract may protect against skin aging and dental cavities.

Safety: Safe for healthy people to consume in small doses. Should be avoided by anyone at risk for hypertension or cardiovascular disease due to its mineralocorticoid effects.

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| <p>Availability: OTC</p> | <p>Dose: Therapeutic dose for licorice root has not been established.</p> <p>Glycyrrhizin administered in an IV formulation (SNMC) and includes 0.2% glycyrrhizin, 0.1% cysteine, 2% glycine</p> | <p>Glycyrrhizin</p> <p>Chemical formula: C₄₂H₆₂O₁₆</p> <p>MW: 822.9 g/mol</p>  <p>Source: PubChem</p> |
| <p>Half-life: 6 to 10 hours (glycyrrhizin)</p> | <p>BBB: Glycyrrhizin and glycyrrhetic acid are penetrant</p> | |
| <p>Clinical trials: Licorice extract has been tested for Parkinson's disease, stroke, dental cavities, and post-operative sore throat. Also tested for dementia in the form of yokukansan. Glycyrrhizin has been tested for hepatitis, liver disease, and liver injury.</p> | <p>Observational studies: One retrospective study (n=193) found lower rates of hepatocellular carcinoma in hepatitis patients treated with glycyrrhizin.</p> | |

What is it?

Licorice is derived from the roots of the plant species *Glycyrrhiza*, which is native to Mediterranean areas. There are approximately 30 species in the *Glycyrrhiza* genus, three of which are commonly used to produce licorice root extract, *G. glabra* (European licorice), *G. inflata*, and *G. uralensis* (Chinese licorice) [1]. There are up to 300 biologically active components in licorice root, and the compound profile varies based on species, geography, harvesting, and processing. The triterpenoid glycyrrhizin is the major component of the roots, generally making up around 10% of the root by dry weight, but can be as high as 15% in some Mediterranean varieties. Glycyrrhizin content is used to assess quality and validate licorice root identity, such that a licorice root must contain at least 4% glycyrrhizin to qualify to be used as a medicinal herb [2]. Licorice root also contains a variety of flavonoid compounds, from which it derives its yellow color. Licorice has long been used in Eastern traditional medicine for its antioxidant, anti-inflammatory, and anti-microbial properties. Glycyrrhizin has been used clinically in China and Japan for liver disease, primarily hepatitis. Glycyrrhizin is 50 to 100x sweeter than sucrose, so licorice has also been used as a flavoring for food and beverages, primarily confections.

Neuroprotective Benefit: Combined with other medicinal herbs in the form of yokukansan, licorice root may reduce dementia-related agitation, but small clinical studies suggest there is no benefit for reducing cognitive decline.

Types of evidence:

- 6 clinical trials [carbenoxolone for cognition (n=22); Licorice syrup for PD (n=39); Yokukansan for dementia (n=13, 29, 106); Licorice root extract for stroke (n=75)]
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Glycyrrhetic acid is a major active metabolite of licorice root (*Glycyrrhiza*). Glycyrrhizin (glycyrrhizic acid), a main active ingredient in licorice root, is hydrolyzed by intestinal bacteria into 18 β -glycyrrhetic acid. Carbenoxolone is a water-soluble synthetic analog of glycyrrhetic acid, which is used in the treatment of peptic ulcers (Drugbank.ca). Both carbenoxolone and glycyrrhetic acid are non-specific inhibitors of 11 β -hydroxysteroid dehydrogenases (11 β -HSD), which are involved in the interconversion between active cortisol and inactive cortisone [3]. 11 β -HSD type 1 converts cortisone to cortisol, while 11 β -HSD type 2 catalyzes the inverse reaction and converts cortisol to cortisone. Based on postmortem human tissue analysis, 11 β -HSD1 is the major type found in the brain, including in the hippocampus and frontal cortex [4]. Therefore, 11 β -HSD inhibitors may be expected to reduce brain levels of active cortisol, and dampen stress-associated damage. In a small, double-blind, placebo-controlled, cross-over RCT, treatment with carbenoxolone (100 mg 3x/day + 10mg/day amiloride) for 4 weeks improved verbal fluency based on the Controlled Word Association Test in healthy men (n=10 ages 55 to 75), but had no effect on memory, nonverbal reasoning or processing speed [4]. In patients with type 2 diabetes (n=12), carbenoxolone treatment for 6 weeks improved verbal memory based on the Auditory-Verbal Learning Test, but had no significant effects on other cognitive measures. A trend toward reduced anxiety was seen in both the healthy men and diabetics. Amiloride was included to counteract the mineralocorticoid effects associated with inhibition of 11 β -HSD2 in the kidney. It is not known whether these minor effects are clinically meaningful or whether carbenoxolone could slow cognitive decline. Additionally, it has not been established whether treatment with whole licorice root, or glycyrrhizin, has a similar effect on cognition.



Human research to suggest benefits to patients with dementia:

Parkinson's disease: Potential benefit for motor symptoms, but not cognition

Levels of the damage associated molecular pattern (DAMP) molecule, HMGB1, were shown to be increased in the serum and substantia nigra of patients with Parkinson's disease (PD), and levels were positively correlated with disease duration [5]. In the MPTP mouse model, treatment with glycyrrhizin (50 mg/kg i.p.) prevented the increase in HMGB1 and protected against the loss of dopaminergic neurons [5]. A double-blind, placebo-controlled RCT in Iran tested oral licorice syrup (136 mg of licorice extract with 12.14 mg glycyrrhizic acid and 136 µg of polyphenols; 5 mL 3x/day + standard of care pramipexol or L-dopa) in PD patients (Hoehn and Yahr ≤ 3 ; n=39) for 6 months [6]. The study found that the licorice syrup improved the Total UPDRS score, activities of daily living, and tremor. The improvement in the UPDRS was driven by motor improvements, and the **licorice treatment had no effect on cognitive measures** (Part 1 UPDRS). Additionally, since baseline measures were not provided, it is unclear whether the treatment and placebo groups had comparable baseline scores on the UPDRS measures.

Dementia: Potential benefit for agitation as part of yokukansan, no benefit for cognition

Licorice root (*Glycyrrhiza uralensis*) is one of the seven medicinal herbs in the traditional Japanese medicine, yokukansan. The six other herbs are Atractylodes lancea rhizome, poria sclerotium, Cnidium rhizome, Uncaria hook, Japanese angelica root, and Bupleurum root. Yokukansan, in the TJ-54 formulation (Tsumura Co, Japan), has been tested in open-label clinical trials for alleviating behavioral and psychological symptoms in dementia patients in Japan. In two small studies (n=29, n=106) treatment with yokukansan (7.5 mg 3x/day) led to significant improvements on the Neuropsychiatric Inventory (NPI) with estimated treatment effects of -5.8 (95% CI -11.0 to -0.5) and -5.2 (95% CI -10.1 to -0.3), respectively [7; 8]. In both studies, there were **significant improvements in the agitation/aggression and irritability/lability subscales**. In a separate study (n=13), treatment with yokukansan (5 to 7.5 mg/day) improved sleep quality, and actinograph data showed that yokukansan improved wake after sleep onset time [7]. The contribution of licorice to these effects cannot be ascertained from these studies, though a preclinical study examining the sleep-inducing effects of yokukansan found that the biological effects were dependent on interactions between all the herbs that occurred during the extraction process [9]. While yokukansan appears to have some beneficial effects on behavioral symptoms, all three studies found that **it had no effects on cognition**.



Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Memory impairment: Potential benefit related to anticholinesterase activity (preclinical)

Glycyrrhetic acid, the major active metabolite of licorice root, has been shown to exhibit anti-acetylcholinesterase activity, which may account for some the beneficial effects of licorice root in animal models of memory impairment [10]. Treatment with *Glycyrrhiza glabra* root extract (150 or 225 mg/kg) for 6 weeks improved spatial learning memory (Morris water maze) and reversed diazepam-induced amnesia in male rats [11]. Aqueous extract of *Glycyrrhiza glabra* (150 mg/kg= 5.2 g dried licorice root) protected mice against diazepam or scopolamine induced memory impairments [12].

Ischemic brain injury: Case reports of licorice overdose associated stroke; Potential minor benefit with use near time of injury

Licorice related neuroprotection is attributed to its antioxidant and anti-inflammatory properties, which are partially mediated by glycyrrhizin (and its active metabolite glycyrrhetic acid). The results from a placebo controlled RCT in acute ischemic stroke patients in Iran (n=75) (NCT02473458) support the notion that licorice may offer minor benefits in this population [13]. However, the groups treated with licorice root extract (450 or 900 mg containing 35.3 mg and 70.6 mg glycyrrhizin, respectively 3x/day for 7 days) had significantly higher baseline severity scores on the NIH stroke scale (NIHSS) than the placebo group, which makes it difficult to interpret the clinical significance of the results. Additionally, there are several reports describing cases where licorice root intake led to hemorrhagic stroke, cerebral microbleeds, or ischemic stroke [14; 15]. The lack of safety signals in this trial may have been due to the short duration of treatment, so the risk-benefit profile with respect to stroke is likely dependent on the licorice preparation, glycyrrhizin content, and duration of use.

Preclinical studies suggest that licorice could offer modest neuroprotective benefits if administered close to the time of injury. In the MCAO model of cerebral ischemia, male mice pretreated with a methanol extract of *Glycyrrhizae* radix et rhizome (500 mg/kg) for 3 days prior to ischemia or (300 mg/kg) up to 1 hour after reperfusion showed a reduction in infarct size and degree of neuronal loss, but did not improve acute neurological deficits [16; 17].

Glycyrrhizin (20 mg/kg orally) was protective against spatial memory deficits (based on Morris water maze), preserved synaptic plasticity (based on hippocampal LTP), and reduced oxidative stress (based on MDA and SOD levels) in a rat model of ischemia vascular dementia [18].



Intravenous infusion of glycyrrhizin (4 mg/kg) was protective in the context of traumatic brain injury in male rats when administered anytime from 5 minutes prior to injury to 3 hours after injury [19]. Glycyrrhizin reduced BBB permeability, expression of pro-inflammatory mediators (TNF α , IL-6, IL-1 β), and was associated with reduced motor and cognitive impairments 7 days after injury. The anti-inflammatory effects may be related to the ability of glycyrrhizin to bind to the DAMP HMGB1, which prevents HMGB1's ability to activate the receptor for advanced glycation end products (RAGE) and initiate inflammatory signaling cascades.

APOE4 interactions: Unknown

Ageing and related health concerns: Antioxidant, anti-inflammatory and anti-viral effects may drive the protective effect of glycyrrhizin in hepatitis. Aside from hepatoprotection, licorice extract may protect against skin aging and dental cavities.

Types of evidence:

- 3 meta-analyses (Glycyrrhizin for hepatitis n=31 RCTs; Gegen Qinlian decoction for type 2 diabetes n=5 RCTs; Licorice root extract for post-operative sore throat n=5 RCTs)
- 7 clinical trials (Glycyrrhizin for NASH n=98; Aqueous licorice root extract for NAFLD n=66; Glycyrrhizin for hepatitis n=93; Glycyrrhizin for hepatitis and type 2 diabetes n=39; Glycyrrhetic containing creams in healthy women n=18; Licorice root extract for dental caries in children n=108, 60)
- 1 retrospective observational study for glycyrrhizin treatment and prevention of hepatocellular carcinoma in hepatitis patients (n=193)
- Numerous laboratory studies

Hepatoprotection

Non-alcoholic fatty liver disease: Potential benefit based on changes in liver enzymes

Two small clinical trials support a potential beneficial role for glycyrrhizin against fatty liver disease. Aqueous licorice root extract (2 g containing 20% glycyrrhizin) for 2 months in patients with NAFLD (n=66) decreased levels of the liver enzymes alanine aminotransferase (ALT 64.09 to 51.27 IU/ml) and aspartate aminotransferase (AST 58.18 to 49.45 IU/ml) [20]. However, liver histology was not examined and the clinical significance of this reduction in liver enzymes is not clear. Treatment with heparisin



(glycyrrhizin 40 mg, glycine 400 mg, L-cysteine hydrochloride 20 mg IV for 10 days then glycyrrhizin 25 mg, glycine, 25 mg, methionine, 25 mg tablet for 80 days) in patients with non-alcoholic steatohepatitis (NASH) and obesity (n=98) with or without chronic kidney disease led to a decrease in liver fibrosis by 1.5 to 2 times [21].

Preclinical rodent models of NAFLD and NASH have found that glycyrrhizin and its active metabolite 18 β -glycyrrhentic acid can protect against hepatic inflammation and lipotoxicity [22]. In these models, this protection has been attributed to a combination of effects including a reduction in oxidative stress, stabilization of lysosomal membranes, inhibition of mitochondrial cytochrome c release, reduction in pro-inflammatory cytokines, and restoration of bile acid homeostasis [23; 24; 25]. β

Liver Injury: Potential benefit based on changes in liver enzymes

Magnesium isoglycyrrhizinate, a salt of 18 β -glycyrrhentic acid, injection is used as a therapy for liver disease and injury in China, and has been shown to improve liver function in clinical trials based on changes in liver enzymes [22].

Hepatitis: Benefit using glycyrrhizin

Glycyrrhizin has been used as a treatment for chronic hepatitis in Japan for over 40 years, primarily in the form of Stronger Neo-Minophagen C (SNMC) which is an IV administered formulation containing 2 mg glycyrrhizin with 1 mg cysteine and 20 mg glycine, in order to prevent glycyrrhizin-induced pseudo-hyperaldosteronism [26]. In a meta-analysis of 31 RCTs (n=2753 patients) testing SNMC for chronic hepatitis B, treatment was **associated with improved hepatic function** including total response rate (Odds Ratio OR: 4.37, 95% Confidence Interval CI 2.62 to 7.28) and ALT normalization rate (OR: 3.77, 95% CI 2.46 to 5.79) [27]. SNMC was associated with significant reductions in ALT (Mean Difference MD: -31.63, 95% CI -51.57 to -11.70), AST (MD: -18.70, 95% CI -25.10 to -12.30), bilirubin (MD: -12.17, 95% CI -17.63 to -6.71), hyaluronic acid (MD: -94.89, 95% CI -125.19 to -64.60), as well as liver fibrosis markers LN (MD: -40.08, 95% CI -52.38 to -27.78), IV-C (MD: -50.61, 95% CI -63.40 to -37.81), and PC-III (MD: -49.71, 95% CI -71.72 to -27.69). A retrospective study (n=193) found that patients with chronic hepatitis C treated with SNMC (range of 2 to 16 years) had reduced 10th (7% vs 12%) and 15th (12% vs 25%) year rates of hepatocellular carcinoma relative to those treated with other herbal medicines [28]. A study examining liver histology (n= 93) found that SNMC treatment (100 ml/day for 8 weeks) improved histological measures of pathology in 44% and stabilized measures in 53%, but the degree of improvement relative to the control group was not indicated [29].

Diabetes/Metabolic effects: Mixed

Licorice derived glycyrrhizin has been found to exert a variety of anti-diabetic effects in pre-clinical models, including the downregulation of AGE and RAGE, glucose lowering effects, and increasing insulin sensitivity [30; 31; 32]. However, the clinical evidence to date regarding the metabolic effects of licorice is mixed.

A meta-analysis of 5 RCTs (n=499 patients) examining the effect of Gegen Qinlian decoction on normalizing hyperglycemia in type 2 diabetes found that it had a favorable effect (OR: 2.34, 95% CI 1.63 to 3.37), and acts synergistically with metformin [33]. The Gengen Qinlian decoction contains licorice root (*Glycyrrhiza uralensis*) along with lobed kudzuvine root, baical skullcap root, and golden thread, and it is not clear how much the licorice contributes to the glucose lowering effects in this preparation.

Licorice extract supplementation (1.5 g/day for 8 weeks) in combination with a low-calorie diet in overweight subjects (n=64) did not enhance the anti-obesity or insulin sensitizing effects of the diet alone in an RCT [34].

One small study (n=39) suggests that licorice may exacerbate insulin resistance and atherosclerosis in men by reducing testosterone levels [35]. In the study, men with type 2 diabetes and chronic hepatitis treated with glycyrrhizin (240 to 525 mg) for over a year showed a significant decline in serum testosterone (6.7 ± 3.8 vs. 11.1 ± 3.8 pg/ml, $P = 0.0009$), and increase in carotid plaque score (6.8 ± 3.1 vs. 3.7 ± 3.3 , $P = 0.0326$). The testosterone lowering effect of licorice has been supported in other studies [36; 37], but the degree is not thought to be clinically meaningful in healthy adults.

Some studies suggest that the metabolic effects of licorice are more pronounced in women [38]. One study (n=18) found that a cream containing 2.5% glycyrrhetic acid (80 mg/day) reduced the thickness of superficial fat on the thigh (16.8 ± 1.6 to 14.7 ± 1.4 mm) relative to the subjects treated with placebo cream (18.3 ± 1.9 to 17.6 ± 1.7 mm), though there was some variation in response rate at the individual level [39]. The mechanism is not known, but is hypothesized to stem from the inhibition of 11 β -HSD1 in adipose tissue.

Photoaging: Potential benefit as ingredient in skin creams

Licorice root has become a popular ingredient in cosmetics and skin creams developed to reduce signs of skin aging.



Application of VEL-091604 (BSI Beauty Science Intelligence GmbH) 2x/day for 2 weeks significantly reduced inflammation and UV-induced erythema in a placebo-controlled RCT in healthy volunteers (n=42), with similar efficacy to 1% hydrocortisone acetate cream [40]. It also improved SCORAD severity score (from approximately 9 to 3) in patients with atopic dermatitis. VEL-091604 contains gentian root extract, willow bark extract, and licorice root extract. The licorice component was comprised of a CO₂ extract from *Glycyrrhiza uralensis* root enriched in flavonoids as well as 0.6% dipotassium glycyrrhizate. Since the cream contains a mixture of projected active ingredients, it is not possible to tease out the exact contribution of licorice to the protective effects, but preclinical studies suggest that licorice derived components can reduce oxidative stress damage and collagen loss.

In female mice, treatment with 18β-glycyrrhetic acid led to an upregulation of antioxidant enzymes (SOD, GSH-Px), and decreased levels of collagenases (MMP-1), leading to an increase in skin collagen content [41]. In human skin fibroblasts, glycyrrhizin treatment reduced UV-induced reactive oxygen species and inhibited collagenase and hyaluronidase enzymes, which preserved collagen levels [42].

Cancer: Unclear

Licorice root contains up to 300 active compounds, many of which have shown to have anti-cancer properties *in vitro* [43]. Since each species of *Glycyrrhiza* and method of extraction will produce a unique profile of active compounds with distinct biological activities [44], different preparations of licorice root will have different therapeutic potential.

Anti-viral and Anti-microbial activity: Benefit

Licorice root extract has been tested in clinical trials as an anti-microbial agent to protect against dental cavities and promote oral hygiene [45]. A sugar-free herbal lollipop used 2x/day for 10 days was found to reduce oral levels of the bacteria *Streptococcus mutans* in children (n=108) at high risk for cavities [46]. A mouthwash containing an ethanolic extraction of licorice (3.75%) was also able to reduce *Streptococcus mutans* oral bacteria levels in children (n=60) at a slightly better or comparable degree to standard aseptic mouthwash (0.156% chlorhexidine gluconate) [47]. A meta-analysis of 5 RCTs (n=609 participants) indicates that topical licorice is associated with reduced incidence of post-operative sore throat (Risk ratio RR: 0.44, 95% CI, 0.28 to 0.69; P < 0.001), but this is attributed to its analgesic properties [48].

Licorice-derived glycyrrhizin has been **shown to exert anti-viral** activity *in vitro*, and clinical studies [49], especially its use as a treatment for chronic hepatitis for over 40 years, support its anti-viral activity *in vivo*. A meta-analysis of 31 RCTs (n=2753 patients) using glycyrrhizin (in the form of SNMC) for chronic



hepatitis B found that glycyrrhizin treatment was associated with an increase in the seroconversion rate from positive to negative for hepatitis B antigen (OR: 2.23, 95% CI 1.70 to 2.94) and decrease of HBV DNA to undetectable levels (OR: 2.20, 95% CI 1.70 to 2.84) [27]. In cell culture, glycyrrhizin can inhibit cell entry of HIV and influenza A virus [50]. Glycyrrhizin or licorice extract has been used as an adjunct therapy for HIV in Southeast Asia, and there are reports that it can modestly reduce HIV- levels [51] and increase CD4+ T cell levels [52], which is suggestive of anti-viral activity. An herbal medicine containing licorice root (plus ephedra herb, apricot kernel, and cinnamon bark) was found to reduce influenza symptoms and viral persistence to a comparable degree as standardly used neuraminidase inhibitor antiviral drugs in a small RCT (n=28) [53]. Systemically administered glycyrrhizin showed protection against a mouse model of herpes simplex-1 encephalitis by reducing HSV-1 brain replication (by 46%) and increasing the survival rate (from 30 to 80%) [54]. Additionally, several clinical studies have found therapeutic benefits for the combination of glycyrrhizin with antivirals (valacyclovir, acyclovir) for the treatment of herpes zoster [49].

Safety: Safe for healthy people to consume in small doses. Should be avoided by anyone at risk for hypertension or cardiovascular disease due to its mineralocorticoid effects.

Types of evidence:

- 1 meta-analysis of safety outcomes from 18 clinical trials testing glycyrrhizin containing licorice
- 2 retrospective observational studies (Chronic glycyrrhizin use for hepatitis n=84; Yokukansan use and risk for hypokalemia n=389).
- Numerous laboratory studies

Licorice has generally recognized as safe (GRAS) status from the FDA, however, due to the mineralocorticoid effects associated with overconsumption, various government regulatory agencies have guidelines to limit daily intake of licorice [55]. The no-observed adverse effect level (NOAEL) for glycyrrhizin is 217 mg/day [38], but due to the increased sensitivity of certain populations, most recommendations are well below that level. In the Netherlands where licorice consumption per capita is relatively high, the recommended daily limit is 200 mg glycyrrhizin (150 g licorice), whereas the European Commission set the daily limit at 100 mg glycyrrhizin (60 to 70 g licorice) [55]. The FDA warns that eating 40 to 50 g of licorice per day for at least 2 weeks can increase the risk for heart arrhythmia, especially in men over age 40.

The primary safety concern associated with licorice is pseudo-hyperaldosteronism. While there are approximately 300 active compounds in licorice root, which could all potentially contribute to its safety profile [44], the **mineralocorticoid effects have been tied to the bioactivity of glycyrrhizin** (through its active metabolite 18 β -glycyrrhetic acid) [56], which is why licorice consumption limits focus on glycyrrhizin content. In the kidney, 18 β -glycyrrhetic acid inhibits the enzyme 11 β -HSD2, which converts active cortisol to inactive cortisone. As a result of the inhibition, there is an increase in cortisol levels which is then free to bind the mineralocorticoid receptor and induce hyper-mineralocorticoid effects, including the suppression of the renin-aldosterone axis [15]. The physiological result of this suppression is **an electrolyte imbalance including sodium retention (hyponatremia) and a reduction in plasma potassium (hypokalemia)**. This electrolyte imbalance can lead to a variety of adverse cardiovascular events, especially hypertension and arrhythmia. In healthy individuals the licorice induced changes are not expected to significantly affect cardiovascular function, however, in vulnerable populations, the impact could be clinically meaningful [57].

A meta-analysis of 18 clinical trials (n=337 participants) testing licorice containing at least 100 mg glycyrrhizin (mean 377.9 mg) in healthy volunteers found that (glycyrrhizin containing) licorice was associated with significant decreases in plasma potassium (-0.33 mmol/L, 95% CI -0.42 to 0.23), renin activity (-0.82 ng/mL per hour, 95% CI -1.27 to -0.37) and aldosterone (-173.24 pmol/L, 95% CI -231.65 to -114.83) [57]. There were also **significant increases in systolic** (5.45 mm Hg, 95% CI 3.51 to 7.39) **and diastolic** (3.19 mm Hg, 95% CI 0.10 to 6.29) **blood pressure**, which were dose dependently related to changes in mineralocorticoid related measures. One study (n=24) using graded doses of aqueous licorice root extract containing 108, 217, 380, and 814 mg glycyrrhizin found changes in the renin-aldosterone axis and water retention related changes in body weight starting within one week of high dose licorice consumption [38]. In general, edema and hypertension changes were mild and transient in the healthy population. Notably, the two participants who discontinued due to cardiovascular adverse events were at higher risk due to pre-existing conditions and/or concomitant drug use. One subject had a family history of hypertension while the other was taking oral contraceptives.

Formulation of glycyrrhizin containing cysteine and glycine used primarily for liver diseases appear to be associated with lower incidence of mineralocorticoid effects, though this could potentially stem from a reporting bias. A retrospective study of people with chronic hepatitis using SNMC for a median of 10.1 years (n=84) found evidence of mild hypokalemia in 10.7% and hypertension in 3.6%, but both were readily reversible with administration of the aldosterone antagonist spironolactone, and were not associated with discontinuation [28].



The mineralocorticoid effects of glycyrrhizin can also occur in preparations of herbal mixtures that contain licorice root. In dementia patients, the consumption of yokukansan (TJ-54) was generally well-tolerated and only one trial reported a decline in serum potassium levels in 4 patients, only 2 of which had clinically meaningful changes, and resolved upon cessation [8]. A retrospective cohort study (n=389) examining yokukansan induced hypokalemia found several factors were associated with higher risk [58]. These included people who were simultaneously taking other K+ lowering drugs and/or had hypoalbuminemia at baseline.

The incidence of mineralocorticoid effects has typically been low in most clinical trials using licorice, which is likely related to the inclusion-exclusion criteria, as most exclude people with hypertension and other cardiovascular risk factors. Due to the increased risk for licorice toxicity, licorice **should be avoided by people with congestive heart failure, hypertension, or those taking K+ lowering drugs**. Licorice components have been shown to inhibit cytochrome P450 enzymes, indicating that licorice may interfere with the metabolism of some drugs, though the profile of potential interactions may vary with different licorice preparations [59]. Due to drug interactions, licorice should be avoided by people taking digoxin or warfarin. Licorice intake is also contraindicated in people taking the immunosuppressant cyclosporine, since it can decrease its bioavailability. Licorice has a food interaction with grapefruit ([Drugs.com](https://www.drugs.com)).

Sources and dosing:

Licorice is available in a variety of OTC forms including licorice root powder and licorice roots extracts. It can also be found as an ingredient in cosmetic creams, and as a flavoring for gum, beverages, and confections. Licorice supplements should contain the glycyrrhizin content, however, the glycyrrhizin content in food and beverages can vary widely depending on the amount and source of the licorice used, and is generally not indicated. The therapeutic dose for licorice has not been established, but chronic overconsumption of licorice containing products may increase the risk for mineralocorticoid side effects.

Glycyrrhizin has most frequently been used clinically in Japan in the form of SNMC, where glycine and cysteine are added to reduce the mineralocorticoid effects. For chronic hepatitis patients it is administered IV, most commonly at 100 mL/day.

The content of glycyrrhizin and other active compounds can vary greatly across samples of licorice root depending on the species, growing conditions, and extraction processes [1]. Glycyrrhizin content was found to be highest in *G. glabra* harvested in the Spring (May), which was associated with higher



superoxide scavenging capacity [60]. *G. uralensis* typically has the highest flavonoid content [61], and due to high solubility, alcohol-based extracts are enriched for flavonoids.

Research underway:

According to [Clinicaltrials.gov](https://clinicaltrials.gov), there are currently 16 active clinical trials for licorice, however, most involve Traditional medicines in which licorice root is used in conjunction with a variety of other medicinal herbs. Licorice itself is being tested for the prevention of dental caries and post-operative sore throat.

The pharmaceutical use of licorice extract has been hampered by the lack of standardization across batches of cultivated licorice root, due to the large degree of variation in the composition of bioactive compounds stemming from genetic and growing environment related factors [62]. There are numerous efforts underway to develop new methods to improve the extraction of the bioactive components.

Search terms:

Pubmed, Google: Licorice, Licorice root, Glycyrrhizin +

- Alzheimer's disease, Parkinson's disease, neurodegeneration, cognition, stroke, aging, cancer, hepatitis, diabetes, cardiovascular, anti-viral, safety, clinical trial, meta-analysis

Websites visited for Licorice:

- [Clinicaltrials.gov](https://clinicaltrials.gov) [Licorice](#), [Glycyrrhizin](#)
- [Examine.com](https://www.examine.com)
- [Drugs.com](https://www.drugs.com)
- [WebMD.com](https://www.webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [MSKCC](https://www.mskcc.org)

References:

1. Pastorino G, Cornara L, Soares S *et al.* (2018) Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. *Phytotherapy Research* 32, 2323-2339. <https://onlinelibrary.wiley.com/doi/abs/10.1002/ptr.6178>
2. Douglas JA, Douglas MH, Lauren DR *et al.* (2004) Effect of plant density and depth of harvest on the production and quality of licorice (*Glycyrrhiza glabra*) root harvested over 3 years. *New Zealand Journal of Crop and Horticultural Science* 32, 363-373. <https://doi.org/10.1080/01140671.2004.9514317>



3. Gomez-Sanchez EP, Gomez-Sanchez CE (2006) Central hypertensinogenic effects of glycyrrhizic acid and carbenoxolone. *American Journal of Physiology-Endocrinology and Metabolism* 263, E1125-E1130. <https://journals.physiology.org/doi/abs/10.1152/ajpendo.2006.263.6.E1125>
4. Sandeep TC, Yau JLW, MacLulich AMJ *et al.* (2004) 11Beta-hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci U S A* 101, 6734-6739. <https://www.ncbi.nlm.nih.gov/pubmed/15071189>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC404114/>
5. Santoro M, Maetzler W, Stathakos P *et al.* (2016) In-vivo evidence that high mobility group box 1 exerts deleterious effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model and Parkinson's disease which can be attenuated by glycyrrhizin. *Neurobiol Dis* 91, 59-68. <https://www.ncbi.nlm.nih.gov/pubmed/26921471>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4867789/>
6. Petramfar P, Hajari F, Yousefi G *et al.* (2020) Efficacy of oral administration of licorice as an adjunct therapy on improving the symptoms of patients with Parkinson's disease, A randomized double blinded clinical trial. *Journal of Ethnopharmacology* 247, 112226. <http://www.sciencedirect.com/science/article/pii/S0378874119311298>
7. Okahara K, Ishida Y, Hayashi Y *et al.* (2010) Effects of Yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 34, 532-536. <http://www.sciencedirect.com/science/article/pii/S0278584610000606>
8. Mizukami K, Asada T, Kinoshita T *et al.* (2009) A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *International Journal of Neuropsychopharmacology* 12, 191-199. <https://doi.org/10.1017/S146114570800970X>
9. Ogawa Y, Fujii Y, Sugiyama R *et al.* (2016) The role of the seven crude drug components in the sleep-promoting effect of Yokukansan. *Journal of Ethnopharmacology* 177, 19-27. <http://www.sciencedirect.com/science/article/pii/S0378874115302385>
10. Abdel Bar FM, Elimam DM, Mira AS *et al.* (2019) Derivatization, molecular docking and in vitro acetylcholinesterase inhibitory activity of glycyrrhizin as a selective anti-Alzheimer agent. *Natural Product Research* 33, 2591-2599. <https://doi.org/10.1080/14786419.2018.1462177>
11. Chakravarthi KK, Avadhani R (2013) Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. *J Nat Sci Biol Med* 4, 420-425. <https://www.ncbi.nlm.nih.gov/pubmed/24082744>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3783792/>
12. Dhingra D, Parle M, Kulkarni SK (2004) Memory enhancing activity of *Glycyrrhiza glabra* in mice. *Journal of Ethnopharmacology* 91, 361-365. <http://www.sciencedirect.com/science/article/pii/S0378874104000455>
13. Ravanfar P, Namazi G, Atigh M *et al.* (2016) Efficacy of whole extract of licorice in neurological improvement of patients after acute ischemic stroke. *Journal of Herbal Medicine* 6, 12-17. <http://www.sciencedirect.com/science/article/pii/S2210803315300130>
14. Shin H, Chung M, Rose D (2019) Licorice Root Associated With Intracranial Hemorrhagic Stroke and Cerebral Microbleeds. *Neurohospitalist* 9, 169-171. <https://www.ncbi.nlm.nih.gov/pubmed/31244975>

15. Omar HR, Komarova I, El-Ghonemi M *et al.* (2012) Licorice abuse: time to send a warning message. *Ther Adv Endocrinol Metab* 3, 125-138. <https://www.ncbi.nlm.nih.gov/pubmed/23185686>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3498851/>
16. Lim C, Lim S, Lee B *et al.* (2018) Licorice Pretreatment Protects Against Brain Damage Induced by Middle Cerebral Artery Occlusion in Mice. *Journal of Medicinal Food* 21, 474-480. <https://www.liebertpub.com/doi/abs/10.1089/jmf.2017.4044>
17. Au - Lee S-E, Au - Lim C, Au - Lee M *et al.* (2018) Assessing Neuroprotective Effects of Glycyrrhizae Radix et Rhizoma Extract Using a Transient Middle Cerebral Artery Occlusion Mouse Model. *JoVE*, e58454. <https://www.jove.com/video/58454>
18. Jie G, Chunxiao Y, Jiajia Y *et al.* (2016) Glycyrrhizic Acid Ameliorates Cognitive Impairment in a Rat Model of Vascular Dementia Associated with Oxidative Damage and Inhibition of Voltage-Gated Sodium Channels. *CNS & Neurological Disorders - Drug Targets* 15, 1001-1008. <http://www.eurekaselect.com/node/142599/article>
19. Okuma Y, Liu K, Wake H *et al.* (2014) Glycyrrhizin inhibits traumatic brain injury by reducing HMGB1–RAGE interaction. *Neuropharmacology* 85, 18-26. <http://www.sciencedirect.com/science/article/pii/S0028390814001749>
20. Hajiaghahmohammadi AA, Ziaee A, Samimi R (2012) The Efficacy of Licorice Root Extract in Decreasing Transaminase Activities in Non-alcoholic Fatty Liver Disease: A Randomized Controlled Clinical Trial. *Phytotherapy Research* 26, 1381-1384. <https://onlinelibrary.wiley.com/doi/abs/10.1002/ptr.3728>
21. Khukhlina O, Antoniv A, Kanovska L *et al.* (2018) Effectiveness of nonalcoholic steatohepatitis correction on the background of obesity with concomitant chronic kidney disease. *Georgian medical news*, 76-80. <https://www.ncbi.nlm.nih.gov/pubmed/30516498>
22. Li J-y, Cao H-y, Liu P *et al.* (2014) Glycyrrhizic acid in the treatment of liver diseases: literature review. *Biomed Res Int* 2014, 872139-872139. <https://www.ncbi.nlm.nih.gov/pubmed/24963489>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052927/>
23. Jung J-C, Lee Y-H, Kim SH *et al.* (2016) Hepatoprotective effect of licorice, the root of *Glycyrrhiza uralensis* Fischer, in alcohol-induced fatty liver disease. *BMC Complement Altern Med* 16, 19-19. <https://www.ncbi.nlm.nih.gov/pubmed/26801973>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4722619/>
24. Wu X, Zhang L, Gurley E *et al.* (2008) Prevention of free fatty acid–induced hepatic lipotoxicity by 18 β -glycyrrhetic acid through lysosomal and mitochondrial pathways. *Hepatology* 47, 1905-1915. <https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.22239>
25. Yan T, Wang H, Cao L *et al.* (2018) Glycyrrhizin Alleviates Nonalcoholic Steatohepatitis via Modulating Bile Acids and Meta-Inflammation. *Drug Metab Dispos* 46, 1310-1319. <https://www.ncbi.nlm.nih.gov/pubmed/29959134>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6081736/>
26. Rossum TGJV, Vulto, Man RAD *et al.* (1998) glycyrrhizin as a potential treatment for chronic hepatitis C. *Alimentary Pharmacology & Therapeutics* 12, 199-205. <https://onlinelibrary.wiley.com/doi/abs/10.1046/i.1365-2036.1998.00309.x>
27. Chen J, Wang J, Qin TQ *et al.* (2014) [Efficacy and safety of Stronger Neo-Minophagen C for treatment of chronic hepatitis B: a meta-analysis of randomized controlled trials]. *Nan fang yi ke da xue xue bao = Journal of Southern Medical University* 34, 1224-1229



28. Arase Y, Ikeda K, Murashima N *et al.* (1997) The long term efficacy of glycyrrhizin in chronic hepatitis C patients. *Cancer* 79, 1494-1500. <https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291097-0142%2819970415%2979%3A8%3C1494%3A%3AAID-CNCR8%3E3.0.CO%3B2-B>
29. Hino K (1987) Effects of glycyrrhizin therapy on liver histology in chronic aggressive hepatitis. New trends in peptic ulcer and chronic hepatitis. *Excerpta Medica*. <https://ci.nii.ac.jp/naid/10016177540/en/>
30. Cheng HS, Kong JMXF, Ng AXH *et al.* (2014) Novel Inhibitory Effects of Glycyrrhizic Acid on the Accumulation of Advanced Glycation End Product and Its Receptor Expression. *Nat Prod Bioprospect* 4, 325-333. <https://www.ncbi.nlm.nih.gov/pubmed/25369772>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4250570/>
31. Abo El-Magd NF, El-Mesery M, El-Karef A *et al.* (2018) Glycyrrhizin ameliorates high fat diet-induced obesity in rats by activating Nrf2 pathway. *Life Sciences* 193, 159-170. <http://www.sciencedirect.com/science/article/pii/S0024320517305829>
32. Sen S, Roy M, Chakraborti AS (2011) Ameliorative effects of glycyrrhizin on streptozotocin-induced diabetes in rats. *Journal of Pharmacy and Pharmacology* 63, 287-296. <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.2042-7158.2010.01217.x>
33. Ryuk JA, Lixia M, Cao S *et al.* (2017) Efficacy and safety of Gegen Qinlian decoction for normalizing hyperglycemia in diabetic patients: A systematic review and meta-analysis of randomized clinical trials. *Complementary Therapies in Medicine* 33, 6-13. <http://www.sciencedirect.com/science/article/pii/S096522991730119X>
34. Alizadeh M, Namazi N, Mirtaheri E *et al.* (2018) Changes of Insulin Resistance and Adipokines Following Supplementation with Glycyrrhiza Glabra L. Extract in Combination with a Low-Calorie Diet in Overweight and Obese Subjects: a Randomized Double Blind Clinical Trial. *Adv Pharm Bull* 8, 123-130. <https://www.ncbi.nlm.nih.gov/pubmed/29670847>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896387/>
35. Fukui M, Kitagawa Y, Nakamura N *et al.* (2003) Glycyrrhizin and Serum Testosterone Concentrations in Male Patients With Type 2 Diabetes. *Diabetes Care* 26, 2962-2962. <https://care.diabetesjournals.org/content/diacare/26/10/2962.1.full.pdf>
36. Armanini D, Mattarello MJ, Fiore C *et al.* (2004) Licorice reduces serum testosterone in healthy women. *Steroids* 69, 763-766. <http://www.sciencedirect.com/science/article/pii/S0039128X04001783>
37. Armanini D, Bonanni G, Mattarello MJ *et al.* (2003) Licorice consumption and serum testosterone in healthy man. *Experimental and clinical endocrinology & diabetes* 111, 341-343
38. Bernardi M, D'Intino PE, Trevisani F *et al.* (1994) Effects of prolonged ingestion of graded doses of licorice by healthy volunteers. *Life Sciences* 55, 863-872. <http://www.sciencedirect.com/science/article/pii/S0024320594900426>
39. Armanini D, Nacamulli D, Francini-Pesenti F *et al.* (2005) Glycyrrhetic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. *Steroids* 70, 538-542. <http://www.sciencedirect.com/science/article/pii/S0039128X05000577>
40. Seiwerth J, Tasiopoulou G, Hoffmann J *et al.* Anti-Inflammatory Effect of a Novel Topical Herbal Composition (VEL-091604) Consisting of Gentian Root, Licorice Root and Willow Bark Extract. *Planta medica* 85, 608-614. <https://www.ncbi.nlm.nih.gov/pubmed/30690691>

41. Kong S-Z, Chen H-M, Yu X-T *et al.* (2015) The protective effect of 18 β -Glycyrrhetic acid against UV irradiation induced photoaging in mice. *Experimental Gerontology* 61, 147-155.<http://www.sciencedirect.com/science/article/pii/S0531556514003556>
42. Afnan Q, Adil MD, Nissar-UI A *et al.* (2012) Glycyrrhizic acid (GA), a triterpenoid saponin glycoside alleviates ultraviolet-B irradiation-induced photoaging in human dermal fibroblasts. *Phytomedicine* 19, 658-664.<http://www.sciencedirect.com/science/article/pii/S0944711312000918>
43. Bode AM, Dong Z (2015) Chemopreventive Effects of Licorice and Its Components. *Current Pharmacology Reports* 1, 60-71.<https://doi.org/10.1007/s40495-014-0015-5>
44. Li G, Nikolic D, van Breemen RB (2016) Identification and Chemical Standardization of Licorice Raw Materials and Dietary Supplements Using UHPLC-MS/MS. *Journal of agricultural and food chemistry* 64, 8062-8070.<https://www.ncbi.nlm.nih.gov/pubmed/27696846>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5378676/>
45. Sidhu P, Shankargouda S, Rath A *et al.* (2018) Therapeutic benefits of liquorice in dentistry. *Journal of Ayurveda and Integrative Medicine*.<http://www.sciencedirect.com/science/article/pii/S0975947617305107>
46. Almaz ME, Sönmez IŞ, Ökte Z *et al.* (2017) Efficacy of a sugar-free herbal lollipop for reducing salivary Streptococcus mutans levels: a randomized controlled trial. *Clinical Oral Investigations* 21, 839-845.<https://doi.org/10.1007/s00784-016-1827-y>
47. Jain E, Pandey R, Khanna R (2013) Licorice root extracts as potent cariostatic agents in pediatric practice. *Journal of Indian Society of Pedodontics and Preventive Dentistry* 31, 146-152.<http://www.ijsppd.com/article.asp?issn=0970-4388;year=2013;volume=31;issue=3;spage=146;epage=152;aulast=Jain>
48. Kuriyama A, Maeda H (2019) Topical application of licorice for prevention of postoperative sore throat in adults: A systematic review and meta-analysis. *Journal of Clinical Anesthesia* 54, 25-32.<http://www.sciencedirect.com/science/article/pii/S0952818018311334>
49. Zhi-Gang S, Ting-Ting Z, Na L *et al.* (2019) Research Progress of Glycyrrhizic Acid on Antiviral Activity. *Mini-Reviews in Medicinal Chemistry* 19, 826-832.<http://www.eurekaselect.com/node/169159/article>
50. Harada S (2005) The broad anti-viral agent glycyrrhizin directly modulates the fluidity of plasma membrane and HIV-1 envelope. *Biochem J* 392, 191-199.<https://www.ncbi.nlm.nih.gov/pubmed/16053446>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1317678/>
51. Hattori T, Ikematsu S, Koito A *et al.* (1989) Preliminary evidence for inhibitory effect of glycyrrhizin on HIV replication in patients with AIDS. *Antiviral Research* 11, 255-261.<http://www.sciencedirect.com/science/article/pii/0166354289900351>
52. Yao W-h, Zhao W, Wu Y *et al.* (2006) [Effect of compound glycyrrhizin on peripheral T-lymphocyte subset in AIDS patients]. *Zhonghua nan ke xue = National journal of andrology* 12, 598-601
53. Nabeshima S, Kashiwagi K, Ajisaka K *et al.* (2012) A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. *Journal of Infection and Chemotherapy* 18, 534-543.<https://doi.org/10.1007/s10156-012-0378-7>
54. Sekizawa T, Yanagi K, Itoyama Y (2001) Glycyrrhizin increases survival of mice with herpes simplex encephalitis. *Acta virologica* 45, 51-54

55. Deutch MR, Grimm D, Wehland M *et al.* (2019) Bioactive Candy: Effects of Licorice on the Cardiovascular System. *Foods* 8, 495. <https://www.mdpi.com/2304-8158/8/10/495>
56. Card WI, Strong JA, Tompsett SL *et al.* (1953) Effects of liquorice and its derivatives on salt and water metabolism. *The Lancet* 261, 663-668. [https://doi.org/10.1016/S0140-6736\(53\)91801-7](https://doi.org/10.1016/S0140-6736(53)91801-7)
57. Penninkilampi R, Eslick EM, Eslick GD (2017) The association between consistent licorice ingestion, hypertension and hypokalaemia: a systematic review and meta-analysis. *Journal of Human Hypertension* 31, 699-707. <https://doi.org/10.1038/jhh.2017.45>
58. Shimada S, Arai T, Tamaoka A *et al.* (2017) Licorice-induced hypokalaemia in patients treated with Yokukansan preparations: identification of the risk factors in a retrospective cohort study. *BMJ Open* 7, e014218-
e014218. <https://www.ncbi.nlm.nih.gov/pubmed/28619768>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5623453/>
59. Li G, Simmler C, Chen L *et al.* (2017) Cytochrome P450 inhibition by three licorice species and fourteen licorice constituents. *European Journal of Pharmaceutical Sciences* 109, 182-190. <http://www.sciencedirect.com/science/article/pii/S0928098717304335>
60. Cheel J, Tůmová L, Areche C *et al.* (2013) Variations in the chemical profile and biological activities of licorice (*Glycyrrhiza glabra* L.), as influenced by harvest times. *Acta Physiologiae Plantarum* 35, 1337-1349. <https://doi.org/10.1007/s11738-012-1174-9>
61. Zhang Y-J, Gong H-B, Zhu H-L (2018) A Systematic Review of the Comparison of Three Medicinal Licorices, Based on Differences of the Types and Contents about Their Bioactive Components. *J Chem Biol Pharm Chem* 1. <http://www.imedpub.com/articles/a-systematic-review-of-the-comparison-of-three-medicinal-licorices-based-on-differences-of-the-types-and-contents-about-their-bioac.php?aid=22030>
62. Yu F, Wang Q, Wei S *et al.* (2015) Effect of Genotype and Environment on Five Bioactive Components of Cultivated Licorice (*Glycyrrhiza uralensis*) Populations in Northern China. *Biological and Pharmaceutical Bulletin* 38, 75-81

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