

# Neurologic Effects of Licorice: A Review

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## ABSTRACT

Licorice (*Glycyrrhiza glabra*) is an herbal medicine with several pharmacologic properties in ancient traditional medicine. Studies have provided evidence on its clinical efficacy in variety of medical conditions. There are evidences implying the neuroprotective role of licorice extract and its pharmacologically active ingredients in acute and chronic neurodegenerative processes. In the present study, we made a thorough search on existing publications on neuroprotective effects of licorice both in molecular/cellular and human/animal *in vivo* studies. There is strong evidence on both molecular and functional animal/human levels that suggest licorice extract or its pharmacologically active ingredients assert neuroprotective effects in acute and chronic neurologic disorders including ischemic stroke, Alzheimer's disease, and Parkinson's disease. Licorice extract can be used safely in therapeutic doses for optimizing the treatment of a variety of neurodegenerative disorders as well as decreasing the extent of neural tissue damage and neurologic deficits after cerebrovascular accidents.

**Key words:** Licorice, neurologic, review

## INTRODUCTION

Licorice plant scientifically known as *Glycyrrhiza glabra* is an herbaceous perennial cultivated in Southern Europe and parts of Asia. The commercial products commonly known as licorice are extracted from the stoloniferous root of this plant and are used in tobacco flavoring, food industries, and herbal medicine.<sup>[1]</sup> Traditionally, in several regions including the Middle East, China, India, and Japan, licorice has been anciently used for medicinal purposes.<sup>[2]</sup> Its use has been indicated in various medical conditions such as viral diseases,<sup>[3]</sup> peptic ulcer disease,<sup>[4]</sup> and psychiatric disorders.<sup>[5]</sup>

Recent studies have scientifically evidenced several therapeutic properties for licorice. These findings have been contributed to three major families of chemical compounds which are isolated from licorice root; flavonoids, isoflavonoids, and triterpenes. Triterpenes include glycyrrhizic acid (GA) and glycyrrhetic acid monoglucuronide (GM) which are the main pharmacoactive agents in licorice responsible for antioxidant,<sup>[6]</sup> antiallergic, antiviral, and antineoplastic<sup>[7]</sup> characteristics of licorice.<sup>[8,9]</sup> GA is the ingredient responsible for sweet taste of licorice. Flavonoid compounds of licorice include liquiritin (LQ), LQ-apioside, liquiritigenin, and isoliquiritigenin (ISL) which have been associated with antiulcer, antimicrobial, antispasmodic, and antioxidation effects.<sup>[10]</sup> Dehydroglyasperin C (DGC) is an isoflavonoid isolated from licorice root. DGC has been less focused in existing studies compared to previously mentioned ingredients. Recent studies have revealed antineoplastic effects of DGC in mouse epidermal cells.<sup>[11]</sup> DGC has

been also shown to accelerate phase 2 detoxification enzymes in hepatic cells.<sup>[12]</sup>

We encountered studies reporting the efficacy of licorice extract or its purified ingredients in inhibition of a number of molecular pathways playing role in both acute and chronic neurodegeneration. Acute neurotoxic processes are responsible for neural tissue loss during episodes of ischemic stroke. After an ischemic event, a core of infarction forms in the center of the hypoperfused zone. A larger sphere (ischemic penumbra) around the core develops in which hypoperfusion is not severe enough to cause immediate cell death but results in inflammation and initiation of delayed pathways of programmed cell death. If protected from neurotoxicity and inflammation, this penumbral zone can survive and retrieve its normal physiologic and functional status.<sup>[13]</sup> Chronic neurotoxicity is the hallmark of pathogenesis in neurodegenerative diseases such as Alzheimer's disease (AD), and Parkinson's disease. Both whole extract of licorice and purified specific compounds derived from licorice including GA, GM, ISL, liquiritigenin, and DGC have been studied and documented as effective neuroprotective agents.<sup>[14-16]</sup> In the present study, we reviewed existing evidences on therapeutic effects of licorice and its major active compounds related to neurologic system and its disorders.

## ACTIVE COMPOUNDS OF LICORICE EXTRACT

Licorice root contains multiple active ingredients with biologic activity. High-performance liquid chromatography of licorice root extract has been successful in identification of several chemical compounds mostly belonging to major groups, triterpene saponins GA and flavonoids.<sup>[17,18]</sup> Other minor substances from coumarin family include glycoumarin, DGC, glycyrol, licoflavonol, and glycyrin. These substances are relatively insignificant to the topic of this study.<sup>[19]</sup>

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## TRITERPENES

Triterpenes isolated from licorice root extract include glycyrrhizin, 18  $\beta$ -glycyrrhetic acid, GA, and alpha and beta-liquiritic acid.<sup>[20,21]</sup>

In 2006, GA and GM were found to exert neuroprotective functions through inhibition of glutamate-mediated excitotoxicity in rat's neural tissue.<sup>[22]</sup> During the same year, another animal study revealed significant neuroprotective effect of roasted form of licorice compared with control group and subjects which had received raw form of licorice. High liquid pressure chromatography of roasted and raw licorice extracts revealed significantly higher concentrations of nonpolar agents such as GA and GM in the former. Based on this finding, authors concluded that these compounds can be responsible for this novel pharmacological effect of licorice.<sup>[23]</sup> These two pioneer investigations brought GA and GM to the center of attention as new natural neuroprotective compounds. In 2009, Kao *et al.* investigated several steps of mitochondria-induced apoptosis and reactive oxygen species (ROS)-modulated cytotoxicity pathways in hypoxic-damaged PC12 cell line tissues with and without the presence of GA. Results revealed significantly lower production of ROS in GA-treated group as well as decreased reactants involved in mitochondria-induced apoptosis cascade.<sup>[24]</sup> Anti-inflammatory effects of GA through inhibition of lipopolysaccharide (LPS)-mediated nitric oxide production, prostaglandin E<sub>2</sub>, ROS, nuclear factor-kappa B, tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin 6 (IL-6), and IL-1  $\beta$  were approved in the report by Wang *et al.*<sup>[25]</sup> In 2011, an animal study showed significantly smaller size of infarction zone in brains of rats who received intravenous GA injection after temporary occlusion of the middle cerebral artery.<sup>[26]</sup> Reduction of postischemic infarct volume was reassessed and confirmed later in an animal study along with molecular confirmation of significant inhibition of high-mobility group box 1 (HMGB1) protein expression which plays the key role in glutamate-N-Methyl-D-aspartic acid (NMDA) excitotoxicity.<sup>[14]</sup> Same results confirming neuroprotective activity of GA were achieved by both biomolecular and postischemic rat brain studies in 2014. The most important mechanisms through which GA can assert its neuroprotective effect were inhibition of HMGB pathway and glutamate-NMDA cytotoxic cascade.<sup>[27,28]</sup>

## FLAVONOIDS

There are several flavonoid and isoflavonoid compounds in licorice roots and rhizomes. Flavonoids have been shown to play protective role against stroke, coronary artery disease and cancer.<sup>[29]</sup> Flavonoid family is constituted from several compounds. Flavonoids present in licorice roots include ISL, liquiritigenin, LQ, and glabridin. In 2006, Zhan *et al.* reported the results of their study which showed preischemic treatment of rats with ISL for 7 days resulted in smaller infarction volume and neurologic deficit after 2 h of the middle cerebral artery occlusion compared to untreated controls. Authors also performed molecular investigations to clarify the mechanism of this effect. Results showed a significant decrease in malondialdehyde content and increase in brain endogenous antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase activity.<sup>[29]</sup> In confirmation of neuroprotective effect of ISL, Yang *et al.* stated that ISL effectively inhibits glutamate-induced cell damage in HT22 hippocampal neuronal cells.<sup>[30]</sup> LQ and liquiritigenin are two other flavonoids in licorice root and have both been found to possess neuroprotective effects through inhibition of glutamate-induced neurotoxicity.<sup>[15,31]</sup> It has also been reported that LQ significantly promotes neurite overgrowth which is a key process in neural tissue repair and axonal regeneration.<sup>[32]</sup> Asserting its neuroprotective effect in a similar manner to ISL, glabridin, another major flavonoid present in licorice root, reduces malondialdehyde

activity in neural cultured tissue with staurosporine-induced damage. The efficacy of glabridin in decreasing postischemic infarct size has also been approved.<sup>[16]</sup> A recent study showed that glabridin can significantly inhibit microglial LPS-induced inflammatory activities which results in decreased production of nitric oxide, TNF- $\alpha$ , and IL-1.<sup>[33]</sup>

## LICORICE IN STROKE

Ischemic stroke is one of the leading causes of death worldwide. Acute ischemic stroke causes irreversible brain tissue loss if blood supply compromise lasts longer than 4.5 hours. Currently, the mainstay of the treatment of acute ischemic is to recover blood supply to the ischemic brain tissue; however, reestablishment of blood supply usually does not occur during the golden time because of contraindications to thrombolytic and endovascular interventions or late arrival of patients to medical facilities.<sup>[34]</sup> A number of medications have been proposed to minimize ischemia-induced neural tissue damage through inhibition of neurotoxic pathways and inflammatory pathways in the brain.<sup>[35]</sup> Licorice has been reported to suppress neuroexcitatory damage pathways in neural tissues *in vivo*. *In vitro* experiment on hypoxia-induced cultured gerbil hippocampus neural tissue revealed decreased lactate dehydrogenase release. In live animals that underwent surgical occlusion of both common carotid arteries for 5 minutes, increased superoxide dismutase activity and larger percentage of undamaged neural tissue in cresyl violet staining microscopy were noted in gerbils which received both raw and roasted forms of licorice compared to control groups.<sup>[23]</sup> In an animal study, brain ischemia was induced by occlusion of the middle cerebral artery in rats. In the group of animals that received intravenous GA after the ischemia, size of infarction, microglial activation, production of pro-inflammatory cytokines, and severity of motor functions were significantly decreased compared to the control group.<sup>[14]</sup>

Glycyrrhizin is another chemical found in licorice root which is known to strongly block the action of HMGB1.<sup>[36]</sup> HMGB is a signaling molecule which has been shown to play a key role in postischemic inflammation in neural tissue. This signal is released in association with NMDA receptor activation. In a study by Kim *et al.*, intravenous administration of glycyrrhizin after middle cerebral artery occlusion resulted in significant decrease in size of infarction as well as greater improvement of neurologic deficits in mice.<sup>[26]</sup> A recent study investigated inhibition of both T-cell-mediated cytotoxicity and HMGB pathways in the presence of glycyrrhizin. There was a significant decrease in infiltration of CD68-positive macrophages into the ischemic brain tissue in rats treated with intraperitoneal glycyrrhizin injection compared to the controls. This affect was undetectable in nude mice and rats with severe combined immune deficiency which had no functional T-cells. However, after reconstitution of T-cells, the protection was offered again. The results of this study confirmed the previously mentioned finding regarding HMGB-mediated neurotoxicity.<sup>[37]</sup>

Decreased mitochondrial release of apoptosis signals in neural tissues has also been contributed to ISL isolated from *Glycyrrhiza uralensis*. ISL is also present in licorice root (*G. glabra*).<sup>[18]</sup> ISL was found to inhibit glutamate-induced ROS production and alters production of Bcl-2 and Bax (apoptosis mediators) in favor of decreased apoptosis.<sup>[30]</sup>

In the first human study of licorice root in patients with acute ischemic stroke, we found a significant clinical improvement of neurologic function in patients who consumed dried powder capsules of whole licorice extract early after onset of ischemic stroke symptoms.<sup>[38]</sup>

## LICORICE IN ALZHEIMER'S DISEASE

MS and AD are chronic neurological disorders characterized by progressive loss of neural cells through various molecular and

pathological pathways. The most-studied pathways through which licorice is believed to play its neuroprotective role are:

1. Necrosis factor-kappa B (NF- $\kappa$ B) pathway<sup>[39]</sup>
2. Glutamate pathway
3. PI3K/Akt pathway<sup>[24]</sup>

GA has been shown to inhibit the activation of NF- $\kappa$ B pathway. NF- $\kappa$ B signaling pathway is one of the major key inflammatory pathways which plays role in pathogenesis of MS.<sup>[25]</sup> NF- $\kappa$ B is a pro-inflammatory protein complex which is activation by cell stress and inflammatory signals such as IL-1, TNF, and ROS. When activated, NF- $\kappa$ B results in propagation of multiple downstream inflammatory pathways. These pathways result is neural tissue loss seen in MS.<sup>[40]</sup> In the study by Cherg *et al.*, rat hippocampal cultured cells were treated with glutamate to induce apoptosis. Microscopic morphologic features of apoptosis were significantly decreased in a concentration-dependent fashion in present of GA. This study showed that GA causes a significant decrease in NMDA receptor mediated pathway of glutamate signaling as well as NF- $\kappa$ B which is a downstream signal in that pathway. GA was determined to significantly block the binding of factor- $\kappa$ B to its DNA sites which result in activation apoptotic pathways.<sup>[22]</sup> Another study confirmed the inhibitory effect of GA and GM on NF- $\kappa$ B pathway as well as multiple other inflammatory signals including nitric oxide, prostaglandin E<sub>2</sub>, ROS, TNF- $\alpha$ , IL-5, and IL-1, through LPS-induced inflammation.<sup>[25]</sup> GA and GM have also been shown to decrease the activity of mitochondrial Bcl-2 and increase phosphoinositide-3-kinase (PI3K) signal activity which result in inhibition of cell death mechanisms.<sup>[24]</sup> Another molecular pathway proposed to participate in GA neuroprotection is extracellular signal-regulated kinase (ERK) signal also known as mitogen-activated protein kinases pathway. The pathway starts with binding of an extracellular signal to a tyrosine-kinase protein. At the endpoint of this pathway, ERK molecule enters the nucleus and promotes transcription of signals and pathways which result in cell survival and protection against stress-induced apoptosis. Increased activity of ERK pathway was reported in neural cultures treated with GA.<sup>[27]</sup>

ISL and liquiritigenin are other active components present in licorice, which have been studied for neuroprotective properties.<sup>[41]</sup> The inhibitory effect of ISL on glutamate-mediated neurotoxicity is very similar to that of GA. ISL reduces stress mediators including ROS, lipid peroxidation, and Ca<sup>2+</sup> influx, decreases expression and activity of apoptosis signals such as apoptosis-inducing factor (AIF) and mitochondrial Bax, and also increases signals which inhibit apoptosis and promote cell survival including p53, ERK, Bcl-2, and c-Jun N-terminal kinase (JNK).<sup>[15,30]</sup>

Oxidative stress and mitochondrial dysfunction are common features of a large number of chronic and acute neurodegenerative disorders, including AD, Parkinson's disease, and Huntington's disease.<sup>[30]</sup> ISL abated glutamate-induced mitochondrial damage and hippocampal neuronal loss caused by glutamate, with the molecular mechanisms that ISL inhibited the release of AIF, Bcl-2 and Bax, from mitochondria into the cytosol, and suppressed glutamate-induced ROS production.<sup>[41]</sup>

Glabridin present in licorice root has also been shown to decrease microglial activation and resultant inflammation by blocking NF- $\kappa$ B and activator protein 1 (AP-1) transcription factor induced by LPS-mediated signaling pathways. This inhibition can suppress the neurotoxic processes in neuroinflammatory and neurodegenerative diseases.<sup>[33]</sup>

There are existing studies which investigated the effect of licorice components in specific neurotoxic processes in AD. Amyloid- $\beta$  peptide (25-35) (A $\beta$ (25-35))-induced neurotoxicity is major pathway which is known to play role in pathogenesis of AD.<sup>[42]</sup> ISL was found to significantly reduce the effects of neurotoxicity induced by

exposure of cortical neural cells to A $\beta$ (25-35) *in vitro*. Downstream mediators of A $\beta$ (25-35) neurotoxicity including Bax and caspase-3 were decreased as well as inflammatory indicators such as Ca<sup>2+</sup> and ROS levels.<sup>[43]</sup> In a study on cultured rat pheochromocytoma cell line PC12, water extract of licorice was shown to significantly decrease neurotoxic effects of A $\beta$ (25-35) protein.<sup>[44]</sup> Aside from inhibition of molecular pathways involved in pathogenesis of AD, licorice has been shown to improve memory and learning in animal models. After 7 days of treatment with water extract of licorice, studied mice had increased learning and memory functions assessed by elevated plus maze and passive avoidance paradigm. Licorice was also found to reverse amnesia induced by scopolamine and diazepam in that study, indicating that licorice may have anticholinesterase activity. Anticholinesterase medications are one of the key treatments offered for patients with AD.<sup>[45]</sup> A similar study design was applied to purified glabridin from licorice root to investigate its effect on functional memory and learning as well as acetylcholinesterase activity. The results revealed enhancement of memory and learning in mice which received glabridin orally for 3 days. Cholinesterase activity was found to be significantly decreased in glabridin-treated group compared to controls. Inhibition of cholinesterase was comparable with the standard drug "metrifonate."<sup>[46]</sup> Glabridin has also been reported to reverse learning and memory dysfunction in rats caused by diabetes. Diabetic rats which received glabridin for 30 days revealed significantly higher memory and learning function compared to untreated diabetic rats. However, this finding was not seen at doses previously reported to enhance memory and learning in healthy mice (5 mg/kg daily) but at higher doses (25 and 50 mg/kg).<sup>[47]</sup>

We found two studies which investigated a less studied group of compounds present in licorice root, phenylflavonoids (isoflavonoids). There are three phenylflavonoids in licorice root, the most potent being DGC. DGC was found to have significant antioxidant and anti-inflammatory activities. DGC inhibited both LPS-mediated inflammation and NF- $\kappa$ B activity in microglial cells.<sup>[48,49]</sup>

There are no human studies available to investigate effectiveness of licorice or its components in patients with neurodegenerative disorders.

## LICORICE IN PARKINSON'S DISEASE

Similar to MS and AD, Parkinson's disease is another neurodegenerative disease in which neuronal loss and gliosis is seen in the substantia nigra as the hallmark of pathogenesis. In 2012, the first study on this issue investigated the cellular effect of ISL on 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in dopaminergic neurons. Mouse dopaminergic cell line cultures were treated with 6-OHDA which is known to induce stress and apoptosis signals in neurons. Addition of ISL extracted from licorice resulted in decreased generation of nitric oxide and ROS. Furthermore, significant inhibition of Bax, JNK, cytochrome c and caspase-3, intracellular signals, and mediators of apoptosis was noted in the cultures treated with ISL.<sup>[50]</sup> In a recent study, ISL and liquiritigenin were found to significantly inhibit deposition of  $\alpha$ -synuclein fibrils in cultured neural tissue. In addition, ISL disaggregated preformed deposits. Depositions of Lewy bodies made of  $\alpha$ -synuclein and the resultant inflammation and neurotoxicity is the major pathophysiologic process in Parkinson's disease.<sup>[51]</sup>

## SAFETY OF LICORICE

There are some safety considerations associated with chronic high-dose licorice intake. Adverse effects of high-dose licorice consumption have been contributed to glycyrrhizates (glycyrrhizin, GA and GM). Glycyrrhizin has been shown to inhibit 11  $\beta$ -hydroxysteroid dehydrogenase-2 enzyme in the kidney which is responsible for degradation of cortisol. This



inhibition can lead to hypermineralocorticoid states characterized by increased excretion of potassium and retention of sodium and water in the kidneys. This causes a mild reversible hypertension which resolves by discontinuation of licorice. Based on existing evidences of glycyrrhizin toxicity, a daily dose of 0.015–0.229 mg/kg body weight has been considered safe.<sup>[52,53]</sup> Since there is variability in concentration of glycyrrhizin and GA in different preparations and extractions of licorice,<sup>[54]</sup> we recommend that studies and producing companies measure exact concentrations of produced preparations to enable adjusting the dosage within safety limits. In the final toxicology report published in 2007, no teratogenic or carcinogenic effect by licorice was declared in animal studies. There is no relevant reproductive or developmental damage with licorice ingestion. Recommendation of toxicology studies on licorice consumption is that the therapeutic doses are generally safe in human.<sup>[55]</sup> In our human clinical trial, doses of 900 mg whole extract of licorice were prescribed three times daily for 7 days. No significant alteration in blood pressure and serum concentration of sodium, potassium, and glucose was not detected in serial measurements.<sup>[38]</sup> In the study by van Gelderen, healthy volunteers consumed variable doses of GA (0, 1, 2, and 4 mg/kg/day) for 8 weeks. The no effect dose was identified as 2 mg/kg, the authors by assuming a 0.2% content of GA in licorice preparations, suggested that 6 gr daily intake of licorice for a 60 kg individual would not lead to any of known adverse effects of licorice.<sup>[56]</sup>

## CONCLUSION AND DISCUSSION

Licorice extract which is produced from roots of licorice plant (*G. glabra*) is an affordable and effective remedy known since 100 of years ago. Recent studies have been focused on revealing new pharmacologic properties of licorice extract and its active ingredients including GA, GM, ISL, and glabridin. One of the newly discovered pharmacologic activities of major components of licorice is their neuroprotective effect which can open a practice-changing paradigm in the treatment of neurologic diseases. This neuroprotective effect is suggested for both acute and chronic neural damage processes including MS, Alzheimer's and Parkinson disease, as well as acute ischemic stroke.

Present studies all agree that active compounds found in licorice roots including triterpenes and flavonoids have significant biomolecular effects in inhibition of cytotoxic pathways in neural tissues. These studies have also succeeded to reveal that administration of whole licorice extract or purified GA, GM, ISL, and glabridin can significantly reduce post-ischemic infarct volume in animal models. Major cellular pathways which have been reported to be inhibited by administration of licorice components include glutamate-induced toxicity, mitochondrial initiated apoptosis pathways, ERK, and HMGB nuclear expression.

Some of the existing studies report that preexposure administration of licorice can play remarkable protective role in neural tissue when exposed to certain neurotoxic agents and oxidative stressors. Findings of these types of studies suggest that licorice can minimize neurologic damage from a possible future threat or present ongoing damaging condition such as in neurodegenerative disorders. On the other hand, several studies investigated neuroprotective effect of licorice administration in postischemic neural tissue. These studies similarly reported that administration of licorice after an ischemic damage has occurred can reduce the volume of infarction through inhibition of inflammatory response and excitotoxicity neural damage.

Medications for chronic neurodegenerative diseases such as AD and Parkinson's disease which target the main pathophysiologic mechanisms are few and expensive. Similarly, for the management of acute ischemic stroke, the only Food and Drug Administration approved management is fibrinolysis approach which should be administered within a short duration after ischemic attack and triggers reperfusion cytotoxic neural

damage pathways. No medication has been approved for postischemic neuroprotection yet. Considering these limits in appropriate and effective treatment for both acute and chronic brain damage processes, introduction of licorice extract as a neuroprotective agent to the market can greatly improve management of patients with varieties of neurologic disorders.

Existing studies have been targeted to reveal the effectiveness of licorice and its bioactive components in inhibition of neurotoxic pathways and signaling mechanisms in cellular and molecular levels. Limited research on neuroprotection offered by licorice or its extracted ingredients in postischemic states and memory/learning functions also exists in animal models. All studies have reported promising results. However, human studies do not exist in any of diseases and conditions except for postischemic neuroprotection in stroke patients. It seems necessary that studies are held to investigate safety and efficacy of licorice in variety of acute and chronic neurodegenerative disorders.

## BRIEF SUMMARY

Licorice is a food and herbal medicine product from roots of *Glycyrrhiza glabra* plant. Medicinal use of licorice has been documented in ancient Greek and oriental civilizations. Recently, modern medical research studies have elaborated various medical properties of licorice root extract and its active ingredients. Many of these studies have investigated the effects of either licorice root extract or purified derivatives of this herbal plant on neurologic system in neural cultured tissues, animal models, and human studies. In the present study, existing literature regarding neurologic pharmacology of licorice was reviewed. Current evidence suggest that licorice extract or certain compounds found in licorice including flavonoids, isoflavonoids, and triterpenes have beneficial effects in neurodegenerative diseases such as Alzheimer's disease, and Parkinson's disease. In addition, it has been shown that licorice extract can reduce neuroinflammatory processes after an acute ischemic damage to neural cells. Licorice has been proven safe for human consumption in studied therapeutic dosages. These findings can lead to development and production of new drugs for neurodegenerative diseases as well as acute neural tissue damage

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## Conflicts of interest

There are no conflicts of interest.

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