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Exploring Liquorice's Role in Neuroprotection: A Natural Ally Against Neurodegeneration

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Abstract: Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, present significant challenges due to their complexity and progressive nature. Recent research suggests that liquorice (*Glycyrrhiza glabra*) may serve as a promising natural compound with neuroprotective potential. Experimental studies have demonstrated that liquorice can protect neurons, primarily due to its bioactive constituents such as glycyrrhizin, flavonoids, and saponins. This book chapter compiles the current knowledge on liquorice's therapeutic potential in neuroprotection, emphasizing its mechanisms of action, safety profile, and potential as a complementary or adjunct therapy for neurodegenerative disorders. While liquorice shows considerable promise as a natural neuroprotective agent, further clinical studies are required to validate its efficacy and establish guidelines for safe and effective use.

Keywords: Neurodegenerative diseases, Liquorice extract, Pharmaceutical, Nutraceutical, Flavonoids.

1. Introduction

Over a century ago, it was discovered that *Glycyrrhiza glabra* root extract served as an affordable and effective remedy. Numerous studies have since investigated how liquorice extract and its bioactive compounds exhibit novel therapeutic properties. Glabridin, in particular, has shown promise as a neuroprotective agent, potentially offering breakthroughs in the treatment of neurological disorders, including acute and chronic brain injuries, Alzheimer's disease, Parkinson's disease, and other cerebral conditions. Three major active constituents of liquorice extract—glabridin, glycyrrhizin, and isoliquiritigenin—have been shown to protect neurons, reduce inflammation, and promote cell survival by inhibiting tau phosphorylation, mitigating neuroinflammation, and enhancing cognitive function. These compounds support neuronal activity by modulating neurotransmitters and other cerebral factors. Previous studies have demonstrated that liquorice and its multiple constituents can block harmful neuronal pathways at the cellular level [1]. Ongoing research on liquorice-based therapies offers hope for patients suffering from severe neurological disorders, suggesting that liquorice extract may preserve cognitive function and provide novel treatment opportunities for neurological conditions worldwide.

2. How Neurodegenerative Diseases Develop: Exploring Their Causes and Mechanisms

The onset and progression of neurodegenerative diseases result from a variety of processes associated with neuronal degeneration, influenced by genetic, environmental, and cellular factors. Dysregulation of protein structure, mitochondrial dysfunction, oxidative stress, and chronic inflammation are common features of disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease, as illustrated in **Figure 1** [2].

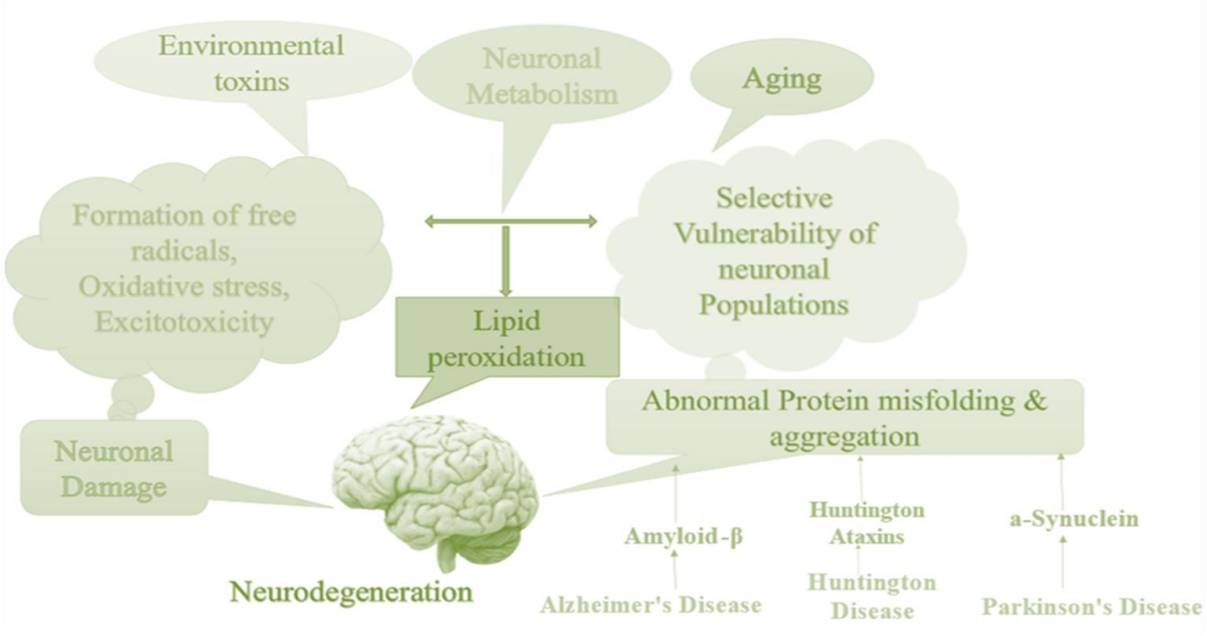

Figure 1: Various interconnected mechanisms contribute to the onset and progression of neurodegenerative diseases, playing a key role in neurodegeneration.

2.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia and represents a significant and growing global health concern. Current research has identified multiple factors contributing to its pathogenesis, including disruptions in the cholinergic system, accumulation of amyloid plaques, tau protein abnormalities, chronic inflammation, oxidative stress, imbalances in metal ions, glutamate excitotoxicity, gut-brain axis dysfunction, and impaired autophagy [2].

2.2 Parkinson's and ALS

Parkinson's disease primarily affects motor function, causing rigidity, tremors, and impaired facial expressions and posture. These symptoms can significantly impact daily activities and reduce overall independence. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that involves both upper and lower motor neurons, resulting in muscle weakness, paralysis, and ultimately respiratory failure.

2.3 Huntington's disease (HD)

In Huntington's disease (HD), the basal ganglia are primarily affected, leading to elevated dopamine activity, involuntary movements, and impairments in cognition and memory. Neurotransmitter imbalances contribute to these abnormal brain functions, which manifest as the clinical symptoms of HD. The disease is caused by an abnormal expansion of trinucleotide repeats in the Huntingtin (HTT) gene on chromosome 4, which disrupts normal cellular processes [2].

3. Therapeutic Approaches for Neurodegenerative Diseases (NDs)

The molecular pathways underlying neurodegeneration involve complex interactions among apoptotic cell death, excitotoxicity, mitochondrial dysfunction, neuroinflammatory processes, and oxidative stress. These interconnected mechanisms collectively contribute to neuronal loss, ultimately driving neurodegenerative disease progression. Therapeutic strategies for neurodegenerative disorders often target multiple pathways simultaneously, employing agents with antioxidant, anti-apoptotic, anti-inflammatory, and mitochondria-stabilizing properties, as well as interventions that mitigate excitotoxicity. Effective neuroprotection requires a comprehensive approach that engages several mechanisms of action concurrently. Researchers continue to investigate these intricate cellular processes to develop effective treatments for patients with

neurodegenerative conditions [3]. Potential therapeutic targets addressing various mechanisms of neurodegeneration are illustrated in **Figure 2**.

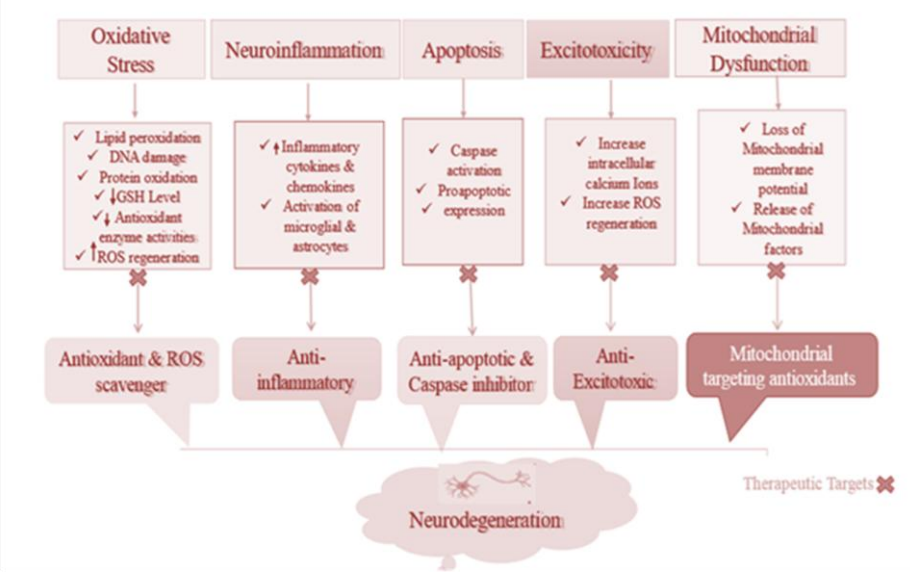

Figure 2: Potential therapeutic targets on various mechanisms of neurodegeneration.

4. Advancements in Herbal Medicine for Neurodegenerative Diseases

Advancements in neurodegenerative disease therapies increasingly rely on scientific research involving various plant components, including flowers, fruits, seeds, roots, leaves, and bark. The historical use of herbal remedies has provided valuable insights into their neuroprotective properties, such as mitigating oxidative stress, enhancing cognitive function, and reducing inflammation. However, further studies are required to establish a comprehensive understanding of these substances and their applications in treating neurodegenerative disorders. Consequently, health organizations are focusing their drug discovery efforts on medicinal plants as potential treatments for neurological diseases [4].

5. Neuroprotection for Neurodegenerative Diseases

Neuroprotection is a critical process that preserves neural function and guards against neurological disorders. Medicinal herbs are believed to contain neuroprotective compounds that act through multiple mechanisms, including inhibition of proteinaceous deposits (such as amyloid-β in Alzheimer's disease), mitigation of oxidative stress, modulation of neuroinflammation, and regulation or repair of key neurotransmitters, including acetylcholine and dopamine. The neuroprotective properties of these plants make them promising candidates for the treatment and prevention of neurodegenerative diseases [5]. Furthermore, the study of natural compounds may help identify novel neuroprotective targets and promote overall brain health [6].

6. Medicinal Herbs Identified for Neurodegenerative Diseases

Several herbs have been traditionally used for their potential benefits in supporting brain health and managing neurodegenerative conditions. Notable medicinal plants include Gotu Kola (*Centella asiatica*), Turmeric (*Curcuma longa*) [7], Ginger (*Zingiber officinale*), Ginkgo biloba, Ashwagandha (*Withania somnifera*) [8], Brahmi (*Bacopa monnieri*), White Mulberry (*Morus alba*), Sesame (*Sesamum indicum*), Tobacco (*Nicotiana tabacum*) [5], and Liquorice (*Glycyrrhiza glabra*) [8]. These plants are rich in bioactive compounds that may enhance cognitive function and provide neuroprotective effects by safeguarding neuronal integrity.

• **Brahmi (*Bacopa monnieri*):** This herb is abundant in bacosides and alkaloids, which are reported to enhance memory, support learning, and exert a calming effect on the nervous system. Additionally, it promotes neuronal regeneration, making it a promising candidate for the management of Alzheimer's disease.

• **Gotu Kola (*Centella asiatica*):** Renowned for its calming and cognition-enhancing effects, Gotu Kola (*Centella asiatica*) contains triterpenoids and organic acids that support mental clarity and promote relaxation.

• ***Ginkgo biloba*:** Often called the Maidenhair Tree, *Ginkgo biloba* is rich in potent antioxidants, including flavonoids and terpenoids, which support memory and cognitive function. It is currently being investigated for its potential neuroprotective effects in Alzheimer's disease.

• ***Panax ginseng*:** This renowned adaptogenic herb contains ginsenosides and antioxidants that help alleviate stress and support cognitive function. It offers a dual benefit by enhancing mental performance while providing neuroprotective effects.

• **Turmeric (*Curcuma longa*):** The principal active compound in turmeric, curcumin, possesses potent anti-inflammatory and antioxidant properties. It contributes to neuroprotection by safeguarding brain cells, reducing neuroinflammation, and supporting overall brain health, making it a promising candidate for the prevention and management of Alzheimer's disease.

7. Liquorice (*Glycyrrhiza glabra*)

Medical records indicate that liquorice (*Glycyrrhiza glabra*) has been used for medicinal purposes for over 4000 years. Its name is derived from the Ancient Greek words "glykys" (sweet) and "rhiza" (root), reflecting both its sweetness and its origin from underground parts. The primary bioactive compound, glycyrrhizin, exhibits cortisone-like activity and is significantly sweeter than sugar. Across different regions, liquorice is known by multiple names, being utilized by both medical practitioners for therapeutic purposes and chefs as a flavoring agent. Although the plant originates from Iraq, it is now widely cultivated in countries such as Spain, Italy, and China [8]. Historical evidence shows that medicinal uses of liquorice extend back to ancient Assyrian medicine around 2000 BC and Egyptian medical practices. Research demonstrates that liquorice is effective in treating digestive and respiratory disturbances as well as certain skin conditions . Modern studies further support its medicinal value, highlighting its antibacterial, antioxidant, and anti-inflammatory properties [9].

7.1 Taxonomic Descriptions

Liquorice is derived from the Glycyrrhiza genus, which comprises approximately 30 species, with *G. glabra* being the most widely cultivated. These plants are distributed across various regions of Asia, Europe, and the Middle East, and have been traditionally used both in medicine and as a flavoring agent in multiple industries [10].

7.2 Morphological Characteristics

Liquorice is a robust perennial plant that grows to a height of 1–2 meters. Its cylindrical rootstock extends approximately 1 meter deep, with stolons spreading horizontally. The root is covered by a dark reddish bark, while the internal tissue is a vibrant yellow. The leaves are alternately arranged, pinnate, and oval, with yellow-green leaflets [5].

7.3 Historical Significance and Medicinal Uses of Liquorice

Liquorice, a medicinal plant with over 4000 years of use, has long been a staple in traditional folk medicine, as depicted in **Figure 3**. It has been employed to treat respiratory, gastrointestinal, and skin disorders. Recognized as an important herb in traditional medicine, liquorice provides therapeutic benefits for a variety of serious health conditions. Its long-standing history and versatility have cemented its status as a valuable medicinal plant.

7.4 Liquorice's traditional usage

Liquorice (Yashtimadhu or Madhuka) has historically been used [11] for the following purposes:

- **Enhancing Breastfeeding:** Combined with cow's milk to increase milk production.

- **Menstrual Health:** Mixed with rice water and sugar to reduce excessive menstrual bleeding.
- **Sore Throat Relief:** Used as a sweet with rice milk to soothe throat discomfort and improve voice quality.
- **Sexual and Cognitive Health:** Combined with honey and milk to support sexual function and brain health.
- **Heart Health:** Mixed with Picrorhiza kurroa and sugar water to improve cardiovascular function.
- **Bleeding Disorders:** Combined with Santalum album and milk to address bleeding issues.
- **Prevention of Internal Bleeding:** Applied as a paste.
- **Reducing Edema:** Combined with Sesamum indicum, milk, and butter to minimize fluid retention.
- **Wound, Bruise, and Burn Care:** Applied with warm clarified butter for healing.
- **Skin Infections:** Used as a decoction for topical treatment.
- **Hair Care:** Applied as a decoction to promote hair growth and prevent premature greying.

Figure 3: Historical Contributions to Liquorice as an Ethnomedicine.

7.5 Chemical profile of Liquorice (*Glycyrrhiza glabra*)

Liquorice (Glycyrrhiza species) is a rich source of more than 400 bioactive compounds, among which triterpene saponins and flavonoids are the most prominent. These constituents contribute significantly to its broad spectrum of therapeutic effects [12]. Liquorice is well recognized for its anti-inflammatory, antioxidant, and antibacterial properties. In addition, emerging evidence suggests its potential role in cancer prevention, along with cardioprotective and neuroprotective effects [10]. Liquorice extract represents a complex mixture of biologically active compounds, primarily secondary metabolites and their derivatives, as summarized in **Table 1**.

Table 1: Major phytoconstituents of Liquorice.

Class	**Phyto-constituents**
Triterpenoid	Glycyrrhizin
Saponin	Glycyrrhizic acid, 18-β-glycyrrhetinic acid
Flavonoid	Liquiritin, shrinpterocarpin, liquiritigenin Glabrene, licuraside, prenyllicoflavone A, shrinflavonone, isoliquiritin, 1-methoxy-phaseolin, Glisoflavone, kanzonol R, Licochalcone A, Hispaglabridin A and B, licuraside, glyzaglabrin, glabridin Rhamnoliquiritin, Glucoliquiritinapioside

Coumarin	Glabrocoumarone A and B, licocoumarin, Glycycoumarin, licopyranocoumarin, Licocoumarin
Isoprenoid-substituted phenol	Isoangustone A, Semilicoisoflavone B, licoriphenone, 1-methoxyficifolinol
Alcohol (Volatile)	2,3 Butanediol Pentanol, hexanol,
Acid (Volatile)	Citric acid, Propionic acid, benzoic acid, fumaric acid, Acetic acid, malic acid, butyric acid, ethyl linoleate
Terpenoid	Alpha terpineol, Geraniol

8. Therapeutic Properties of *Glycyrrhiza glabra*

8.1 Antioxidant Activity

Leaves of *Glycyrrhiza glabra* (GL) contain dihydrostilbenoid compounds that exhibit potent antioxidant activity [13-14]. The antioxidant properties of licochalcones B and D present in GL effectively neutralize DPPH radicals and protect microsomal lipids from peroxidative damage. Owing to these strong antioxidant effects, liquorice extracts are widely incorporated into modern dermatological and cosmetic formulations. These extracts contribute to the protection and stabilization of skin homeostasis by safeguarding biological systems against oxidative stress–induced damage, thereby preventing skin injury [15-16].

8.2 Anti-inflammatory Activity

Administration of *Glycyrrhiza glabra* to male rats for four weeks resulted in statistically significant reductions in serum cholesterol, triglyceride levels, and liver enzyme markers [17]. GL also exhibits therapeutic effects in gastrointestinal and upper respiratory disorders by stimulating the production of serotonin and prostaglandins, thereby reducing gastric inflammation [18]. Furthermore, the anti-edematous and anti-inflammatory properties of GL enable its use in the management of various conditions associated with tissue swelling [19].

8.3 Anti-tussive and Expectorant

Liquorice is an effective therapeutic agent for the management of bronchial catarrh, cough, and pharyngitis. These beneficial effects are primarily attributed to glycyrrhizin, which enhances tracheal mucus secretion and facilitates the clearance of congestion in the upper respiratory tract [20]. Additionally, liquiritin apioside has been shown to suppress capsaicin-induced cough, further supporting the antitussive properties of liquorice [21]. The use of liquorice in the treatment of sore throat has also been compared to carbenoxolone, a steroidal derivative of glycyrrhetinic acid known to stimulate gastric mucus secretion [22].

8.4 Anti-ulcerative activity

Gastric ulcers benefit from Glycyrrhiza due to its ability to elevate prostaglandin levels, which in turn stimulate gastric mucus production [23]. This activity prolongs the lifespan of gastric epithelial cells and inhibits pepsin activity, thereby protecting the gastric mucosa [24]. Glycyrrhizinate, another active constituent of liquorice, also exhibits significant anti-ulcer activity [25]. Clinical trial data indicate that carbenoxolone, a glycyrrhetinic acid–based drug, enhances prostaglandin enzyme activity, leading to increased prostaglandin synthesis and improved healing of gastric and duodenal ulcers [22]. Additionally, *Glycyrrhiza glabra* extract supports ulcer healing by promoting cell regeneration and enhancing mucus secretion. However, the clinical use of carbenoxolone is limited due to its potential side effects, including pseudo-aldosteronism.

8.5 Sedative Activities

Glycyrrhizin exhibits both sedative and anxiolytic properties through its interaction with γ-aminobutyric acid type A ($GABA_A$) receptors. Glabridin, another key bioactive constituent of *Glycyrrhiza glabra*, activates $GABA_A$ receptors by enhancing GABA-mediated neurotransmission, thereby producing hypnotic and sedative effects [26]. Specific amino acid residues located on the β-subunit of $GABA_A$ receptors contribute to

this potentiation, resembling the mechanism of action of general anesthetics, although this effect is not antagonized by flumazenil [27]. Glabridin readily crosses the blood–brain barrier, which further enhances its hypnotic efficacy [28]. Collectively, these findings indicate that glabridin is a principal component responsible for the anxiolytic and sleep-modulating effects of *Glycyrrhiza glabra*, acting through the potentiation of $GABA_A$ receptor function.

8.6 Hepatoprotective activity

Glycyrrhizin and its related compounds exhibit significant hepatoprotective effects against a range of liver disorders, including hepatotoxicity, non-alcoholic fatty liver disease, and hepatocellular carcinoma. Both 18β-glycyrrhizic acid and glycyrrhizin protect hepatic tissue by reducing lipid peroxidation and limiting free radical generation. Experimental studies have demonstrated that *Glycyrrhiza glabra* extract effectively prevents carbon tetrachloride–induced liver damage in mice [29]. Furthermore, glycyrrhetinic acids and glycyrrhizin modulate bile acid metabolism and mitigate drug-induced liver injury, highlighting their therapeutic potential in liver protection [30].

8.7 Antidiabetic

Further investigations into liquorice and its bioactive constituents are required to fully elucidate their potential role in diabetes management. Historically, liquorice has been widely used as a natural sweetener and flavoring agent [31-32]. Although liquorice consumption does not significantly reduce fasting blood glucose levels, it has been reported to alleviate diabetic symptoms such as polydipsia and polyuria [14]. Notably, glycyrrhizin, a major active compound in liquorice, has demonstrated antidiabetic potential. Experimental studies in diabetic rat models have shown that glycyrrhizin can reduce postprandial blood glucose levels, suggesting a possible supportive role in glycemic control [33].

8.8 Immunomodulatory Activity

Compounds derived from *Glycyrrhiza glabra* exhibit significant immunomodulatory activity, primarily attributed to the major bioactive constituent glycyrrhizin, which shows considerable promise for immune regulation and therapeutic applications. Experimental studies have demonstrated that aqueous extracts of *Glycyrrhiza glabra* roots possess notable immunomodulatory properties [34]. This activity is largely mediated by glycyrrhizin, the principal phenolic compound, which enhances immune function by stimulating human granulocyte activity and increasing the productivity of lymphocytes and macrophages.

8.9 Antimalarial

Liquorice-derived compounds, particularly licochalcone A and glabridin, have demonstrated potential antimalarial activity, suggesting their possible use as adjuncts in malaria treatment. Several constituents of liquorice, including 18β-glycyrrhetinic acid, glabridin, and licochalcone A, exhibit notable antimalarial properties. Among these, licochalcone A is one of the most extensively studied compounds and has been shown to inhibit the growth of both chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum in vitro*. Furthermore, glabridin has demonstrated anti-*Plasmodium falciparum* activity *in vitro*, potentially mediated through the induction of oxidative stress and apoptosis *via* the generation of reactive oxygen and nitrogen species [35].

8.10 Osteoporosis and Aging-related Bone Diseases

Compounds derived from *Glycyrrhiza glabra*, particularly glabridin, have demonstrated potential therapeutic benefits for bone health, especially in the context of osteoporosis and age-related bone disorders. Extracts of *Glycyrrhiza glabra* have been traditionally and experimentally used in the management of various bone-related conditions, including low bone mass, fractures, periodontal diseases, osteogenesis imperfecta, osteoporosis, and osteomalacia [36]. Glabridin, the principal bioactive constituent of *Glycyrrhiza glabra*, has been shown to inhibit bone resorption, thereby contributing to bone preservation [37]. Age-associated osteopathy is partly attributed to mitochondrial dysfunction, particularly disruption of the respiratory chain. Notably, glabridin has been reported to alleviate mitochondrial dysfunction and protect osteoblasts from age-related damage, highlighting its role in maintaining bone integrity during aging [38].

8.11 Antiallergic effects

Liquorice root (*Glycyrrhiza glabra*), particularly its active constituent 18β-glycyrrhetinic acid, exhibits potential therapeutic effects in the management of allergic conditions, inflammation, and asthma. Several compounds derived from liquorice, including 18β-glycyrrhetinic acid, glycyrrhizin, isoliquiritin, and liquiritigenin, have demonstrated notable antiallergic properties. Specifically, 18β-glycyrrhetinic acid has been shown to inhibit immunoglobulin E (IgE) production and alleviate pruritus [39]. Furthermore, experimental studies have reported that this compound effectively reduces airway inflammation in asthmatic mouse models, suggesting its potential as a therapeutic agent for allergic asthma [39]. Various chemical constituents responsible for the therapeutic properties of *Glycyrrhiza glabra* are depicted in **Table 2**.

Table 2: Therapeutic properties of *Glycyrrhiza glabra* (Liquorice).

Activity	**Active Compounds**	**Mechanism of Action/Effects**
Antioxidant Activity	Licochalcones B and D	Scavenges DPPH radicals, reduces lipid peroxidation, protects biological systems from oxidative stress, supports skin health
Anti-inflammatory Activity	Glycyrrhizin	Reduces cholesterol, triglycerides, and liver enzymes; increases serotonin and prostaglandin for reduced gastric inflammation
Anti-tussive and Expectorant	Glycyrrhizin, Liquidritin apioside	Enhances tracheal mucus production, clears congestion, suppresses coughs, promotes mucus secretion
Anti-ulcerative Activity	Glycyrrhizin, Carbenoxolone	Increases prostaglandin levels, promotes mucus secretion, enhances ulcer healing, and prevents pepsin effects
Sedative Activities	Glabridin	Modulates $GABA_A$ receptors, exhibits anxiolytic and sedative effects, and helps in sleep and anxiety disorders
Estrogenic and Androgenic Effects	Glabridin, Glabrene, Isoflavones	Mimics estrogenic activity, impacts reproductive health, treats menopausal symptoms, potential therapeutic benefits for infertility
Hepatoprotective Activity	Glycyrrhizin, 18β-Glycyrrhizic Acid	Prevents liver damage, lipid peroxidation, and free radical production, aids in liver disease prevention
Antidiabetic Activity	Glycyrrhizin	Modulates blood glucose, reduces symptoms of diabetes (e.g., polydipsia, frequent urination), improves glycemic control post-meal
Immunomodulatory Activity	Glycyrrhizin	Enhances immune cell activity, increases macrophage and lymphocyte productivity
Antimalarial Activity	Licochalcone A, Glabridin	Inhibits the growth of *Plasmodium falciparum*, induces oxidative stress, leading to apoptosis
Osteoporosis & Aging-related Bone Diseases	Glabridin	Inhibits bone resorption, addresses mitochondrial dysfunction in osteoporosis, and prevents osteoblast damage
Antiallergic Effects	18β-Glycyrrhetinic Acid, Glycyrrhizin, Isoflavonoids	Inhibits IgE production, reduces airway inflammation, beneficial in treating allergic asthma and dermatitis

9. Neuroprotective Effects of Liquorice (*Glycyrrhiza glabra*) and Its Constituents

Numerous studies have investigated the neuroprotective potential of liquorice (*Glycyrrhiza glabra*) and its bioactive constituents. Available evidence suggests that liquorice exerts significant effects on key pathological processes such as oxidative stress, neuroinflammation, and cognitive dysfunction, and may be beneficial in the management of neurological disorders, including Alzheimer's disease, stroke, and epilepsy. Neuroprotective effects of liquorice (*Glycyrrhiza glabra*) and its active constituents in Alzheimer's disease are depicted in **Table 3**.

Table 3: Neuroprotective Effects of Liquorice (*Glycyrrhiza glabra*) and Its Active Constituents in Alzheimer's Disease

Active compounds	**Targeted Pathways/Effects**	**Studies/Findings**
Glycyrrhizic Acid (GA)	Inhibits the NF-kB pathway, reduces glutamate-induced apoptosis, and decreases inflammation.	Significantly decreases the morphological features of apoptosis in hippocampal cells treated with glutamate. - Blocks NF-kB DNA binding and prevents apoptotic pathways. - Reduces nitric oxide, ROS, IL-1, and TNF-α in LPS-induced inflammation.
Iso-liquiritigenin (ISL)	Reduces glutamate-induced neurotoxicity, inhibits oxidative stress, mitochondrial dysfunction, and apoptosis.	- Reduces ROS, lipid peroxidation, and Ca^{2+} influx. - Decreases apoptosis-inducing factors (AIF, Bax), increases cell survival signals (Bcl-2, ERK, JNK). - Abates mitochondrial damage and hippocampal neuronal loss.
Glabridin	Inhibits NF-kB and AP-1, reduces microglial activation, and decreases inflammation.	- Decreases microglial activation and inflammation via LPS-mediated signaling. - Inhibits neuroinflammatory processes, protective against neurodegenerative diseases.
Phenylflavonoids (DGC)	Antioxidant and anti-inflammatory properties.	- Significant antioxidant and anti-inflammatory effects. - Inhibits LPS-mediated inflammation and NF-kB activity in microglial cells.
Amyloid-β (Aβ(25-35))	Reduces neurotoxicity induced by Aβ(25-35), inhibits cell death signals.	- ISL significantly reduces neurotoxicity in cortical neural cells exposed to Aβ(25-35). - Decreases Bax, caspase-3, ROS, and Ca^{2+} levels.
Memory & Learning Enhancement	Potential anticholinesterase activity, cognitive enhancement.	- Liquorice water extract improved memory in mice, reversed amnesia induced by scopolamine and diazepam. - Glabridin improved learning and memory, reduced cholinesterase activity, similar to metrifonate.

Glabridin (for Diabetes)	Cognitive improvement in diabetic rats.	- Significant improvement in memory and learning with high doses of glabridin (25 and 50 mg/kg).

9.1 Ischemic stroke

Ischaemic stroke is among the leading causes of mortality worldwide. Acute brain injury develops when cerebral blood flow is interrupted for more than approximately 4.5 hours. Current treatment strategies primarily focus on restoring blood flow; however, therapeutic intervention is often delayed due to late hospital presentation or procedural constraints [40]. To minimize ischemia-induced neuronal damage, several pharmacological approaches aim to inhibit neurotoxic and inflammatory pathways in the brain. Experimental evidence suggests that liquorice possesses neuroprotective potential by attenuating damage signals in neural tissues [1]. In laboratory studies, hypoxic exposure of gerbil hippocampal tissue resulted in reduced lactate dehydrogenase release, higher superoxide dismutase activity, and improved tissue preservation in animals treated with raw or roasted liquorice compared to untreated controls following a 5-minute common carotid artery occlusion [41]. Additionally, studies using rat models of middle cerebral artery occlusion demonstrated that a single intravenous administration of glycyrrhizic acid significantly reduced infarct size, improved motor function, and suppressed microgliosis and neuroinflammation compared to control animals [42]. Furthermore, glycyrrhizin, a key bioactive constituent of liquorice, inhibits high-mobility group box 1 (HMGB1) activity, thereby reducing neurological deficits and limiting brain injury in rats subjected to middle cerebral artery occlusion [43].

9.2 Parkinson's disease

Ischaemic stroke is one of the leading causes of mortality worldwide. Acute brain injury develops when cerebral blood flow is interrupted for more than approximately 4.5 hours. Current treatment strategies primarily aim to restore blood flow; however, timely intervention is often hindered by delayed hospital presentation or procedural limitations. To minimize ischemia-induced neuronal damage, several therapeutic approaches focus on inhibiting neurotoxic and inflammatory pathways in the brain. Experimental studies indicate that liquorice exhibits neuroprotective potential by attenuating neural damage signals [44]. In laboratory investigations, hypoxic exposure of gerbil hippocampal tissue resulted in reduced lactate dehydrogenase release, elevated superoxide dismutase activity, and improved tissue preservation in animals treated with raw or roasted liquorice compared to untreated controls following a 5-minute common carotid artery occlusion. Furthermore, studies using rat models of middle cerebral artery occlusion demonstrated that a single intravenous administration of glycyrrhizic acid significantly reduced infarct size, improved motor function, and suppressed microgliosis and neuroinflammation compared to control animals. Additionally, glycyrrhizin, a major bioactive constituent of liquorice, inhibits high-mobility group box 1 (HMGB1) activity, thereby alleviating neurological deficits and reducing brain injury in rats subjected to middle cerebral artery occlusion [45].

9.3 Alzheimer's disease

Alzheimer’s disease (AD) is a chronic neurodegenerative disorder characterized by the progressive loss of neuronal cells through multiple molecular and pathological mechanisms [1]. The neuroprotective effects of liquorice in Alzheimer’s disease are primarily attributed to its modulation of several key molecular pathways, including the nuclear factor-κB (NF-κB) pathway, the glutamatergic signaling pathway, and the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway.

10. Conclusion

Over a century ago, it was discovered that *Glycyrrhiza glabra* (liquorice) root extract served as an affordable and effective medicinal remedy. Subsequent studies have demonstrated that liquorice extract and its bioactive compounds exhibit a wide range of therapeutic properties. Among these, glabridin has shown considerable promise as a neuroprotective agent, potentially offering breakthroughs in the treatment of neurological conditions, including acute and chronic brain injuries, Alzheimer’s disease, Parkinson’s disease, and other cerebral disorders. Three key active components—glabridin, glycyrrhizin, and isoliquiritigenin—protect neurons by reducing inflammation, supporting cell survival, and inhibiting tau phosphorylation,

thereby mitigating neuroinflammation and enhancing cognitive function. These compounds contribute to the maintenance of neuronal health by modulating cerebral neurotransmitters and biochemical pathways. Experimental evidence has shown that liquorice and its constituents can inhibit detrimental neuronal pathways at the cellular level. Ongoing research continues to explore the potential of liquorice as a therapeutic option, suggesting its ability to preserve cognitive function and provide novel treatment avenues for severe neurodegenerative disorders across global populations.

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