JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/44205

SHORT REVIEW

A Systematic Review Investigating the Impact of *Glycyrrhiza glabra* on Cognitive Function and Memory: A Comprehensive Analysis

Mrudul Y. Chitrakar[1*], Vinay Pawar[2], Mangala Wange[1] and Vedvati K. Bhapkar[3]

[1]Department of Swasthavritta and Yoga, D.Y. Patil Deemed to Be University School of Ayurveda, Nerul, Navi Mumbai - 400706, Maharashtra, India; mrudulmlonkar@gmail.com

[2]Department of Sanskrit Samhita Siddhant, D.Y. Patil Deemed to Be University School of Ayurveda, Nerul, Navi Mumbai - 400706, Maharashtra, India

[3]Department of Rasshastra, D.Y. Patil Deemed to Be University School of Ayurveda, Nerul, Navi Mumbai - 400706, Maharashtra, India

Abstract

Introduction: This systematic review investigates the role of *Glycyrrhiza glabra* in cognitive function and memory enhancement. It focuses on gathering and synthesizing existing evidence published from September 2020 onwards to comprehensively evaluate the potential cognitive benefits associated with the consumption of *Glycyrrhiza glabra*. **Methodology:** A systematic literature search conducted in electronic databases included variations of "*Glycyrrhiza glabra*", "liquorice", "cognitive function", "memory" and related terms. Total 31 manuscripts were included in the study published from the year 2004 to 2020 onwards. The inclusion criteria comprised peer-reviewed articles from reputable scientific journals, encompassing diverse age groups of human subjects. The investigation considered research employing various forms of *Glycyrrhiza glabra*, including extracts, supplements, or dietary consumption, to evaluate cognitive impacts. To maintain linguistic consistency, studies not published in English were excluded, along with animal studies, reviews, and conference abstracts, ensuring a focused and rigorous analysis of pertinent literature. Two independent reviewers screened the titles and abstracts of identified articles based on the inclusion and exclusion criteria. Full-text articles of potentially relevant studies were then assessed for eligibility. **Results:** The analyses revealed that major mental impairment is caused due to various oxidative damages, neurodegenerative damages leading to the damage of the hippocampus region, HMGP1, neural damage, increase in the inflammatory cytokines production, and many others. Studies have shown that *G. glabra* and the components extracted from it have a great therapeutic potential for the treatment and stop these cognitive impairments as they can breach the blood-brain barrier, lower the above-mentioned damages and enhance the activity of the nervous system in a desired way. **Conclusion:** In the presented study, *G. glabra* was found to be effective for the treatment of cognitive impairments. However, this study reinforces the importance of classic Ayurvedic plants like *G. glabra* for the treatment of these neuro-cognitive disorders.

Keywords: Glycyrrhizin, *Medhya,* Nootropic, Neuroprotective, *Yashtimadhu*

1. Introduction

Medhya Rasayana, encompassing nootropic agents, constitutes a venerable domain within *Ayurvedic* pharmaceutics dedicated to enhancing cognitive functions. This category includes renowned medicinal plants such as *Centella asiatica (Mandukaparni)*, *G. glabra* (*Yashtimadhu)*, *Tinospora cordifolia* (*Guduchi)*, and *Convolvulus pluricaulis (Shankhapushpi)*, each historically acknowledged

*Author for correspondence

Article Received on: 24.05.2024 Revised on: 11.11.2024 Accepted on: 19.11.2024

for their cognitive enhancing properties[1]. One such plant, *G. glabra*, commonly referred to as liquorice and belonging to the Fabaceae family, holds a global reputation not only as a natural sweetener but also as a potent medicinal plant[2]. The dried root and rhizome of liquorice are particularly esteemed for their purported positive effects on the brain, often utilized in the treatment of depression and as a memory-stimulating agent.

Key bioactive components within *G. glabra*, including Glabridin, Glycyrrhizic acid, glycyrrhizin, isoliquiritigenin, liquiritigenin, and licochalcone (A/E), have been associated with diverse therapeutic effects. Notably, these components are linked to the inhibition of Aβ secretion and the amelioration of cognitive deficits. Glycyrrhizic Acid (GA), a prominent constituent, showcases a spectrum of biological activities, functioning as an antioxidant, anti-tumour agent, and anti-inflammatory compound[3,4]. Studies further underscore GA's neuroprotective activities, particularly in postischemic brain conditions, where it effectively suppresses proinflammatory and inflammatory cytokines. Additionally, GA demonstrates efficacy in mitigating neural death induced by glutamate, thus conferring neuroprotection.

Despite these promising findings, a comprehensive exploration of *G. glabra's* impact on neuroinflammation, cognitive function, and anti-neuroinflammatory impairments remains limited[5]. This study aims to bridge this research gap by systematically investigating the nuanced role of *G. glabra* in enhancing cognitive brain functioning. The ultimate objective is to contribute valuable insights that refine our understanding of the neuroprotective potential of this ancient herbal remedy, potentially paving the way for future therapeutic applications in the realm of neurological disorders[6].

2. Materials and Methods

2.1 Search Strategy and Data Collection

The present meta-analysis adhered to the guidelines outlined in the Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA statement)[7]. Utilizing the PubMed database, a comprehensive literature search was conducted from April 2022 to November 2022 using the search string: "*Glycyrrhiza glabra* or *glycyrrhizin*" and "cognitive function" OR cognition and memory". This search strategy aimed to identify relevant articles investigating the effects of *G. glabra* on cognitive function and memory. Unpublished data were not considered for analyses, and no contact with study investigators was made during the selection process.

2.2 Study Selection

The selection process involved screening titles, abstracts, and full-text articles by independent researchers. Articles were thoroughly reviewed to determine their relevance to the study objectives. Inclusion criteria encompassed articles related to memory, cognitive function, or cognition in English-language publications. No temporal restrictions were imposed on the search. After applying the exclusion criteria, a total of 31 articles were included in the systematic review, as presented in Table 1. The PRISMA flowchart for the process is presented in Figure 1.

2.2.1 Inclusion Criteria

All animal models for the study of cognitive function and memory, all species of animals irrespective of age and sex. Anti-inflammatory and antioxidant properties, scopolamine-induced amnesia, learning and memory parameters, neuroinflammation and neuro-oxidative stress, cholinergic transmission.

2.2.2 Exclusion Criteria

Clinical studies, *in vitro* and *in silico* studies. Rest criteria for the study of cognition and memory

2.3 Data Extraction

Data extraction was conducted in a standardized format, ensuring consistency and accuracy across studies. Key information extracted included details on animal models utilized, substances administered (e.g., *G. glabra* extracts, specific compounds such as glycyrrhizin), doses administered, and evaluation parameters employed to assess cognitive function and memory.

2.4 Methodological Quality Assessment

A systematic assessment of methodological quality was performed for each selected research article. This

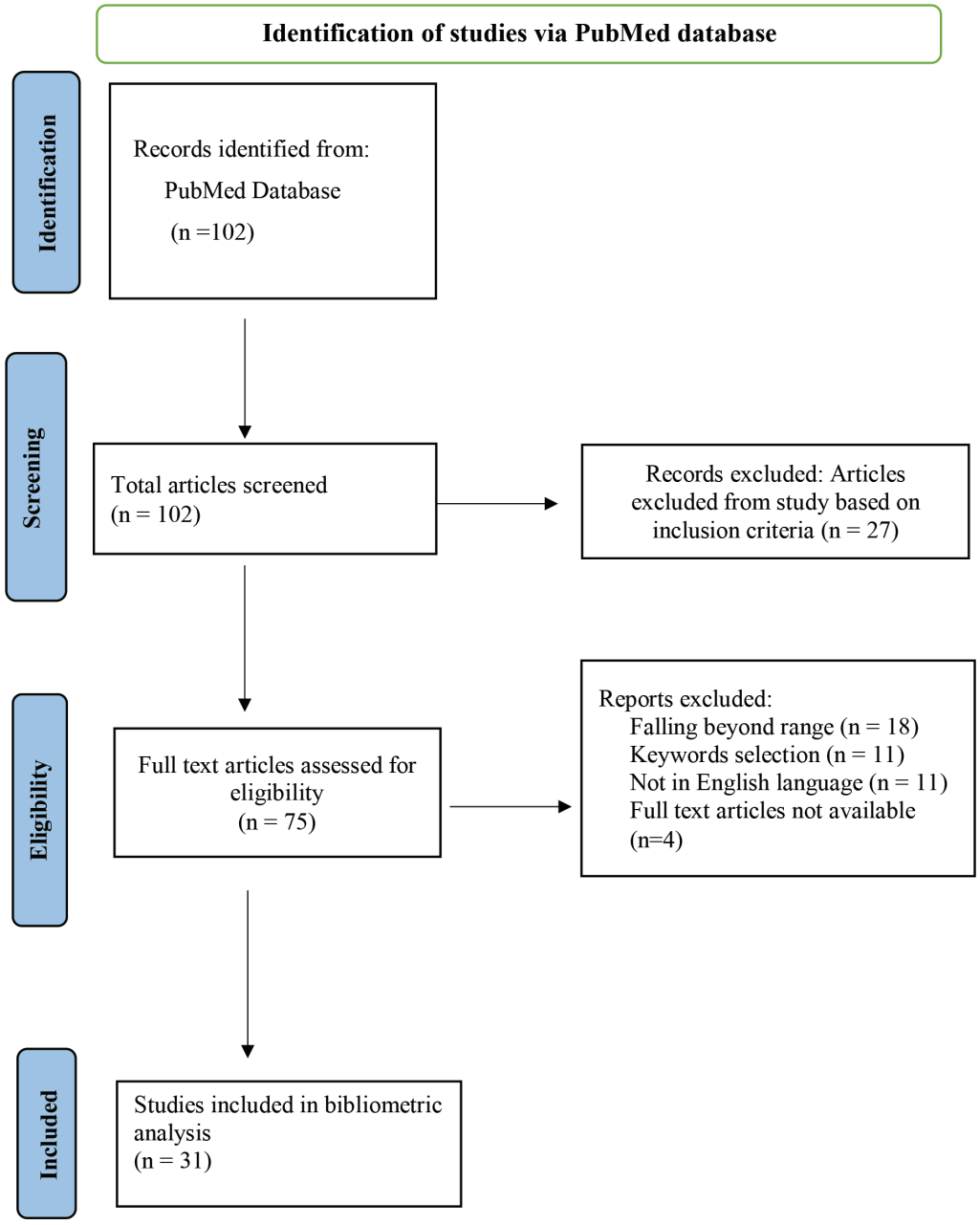


Figure 1. PRISMA flow diagram of the literature screening process.

evaluation encompassed various aspects, including the measures undertaken for randomization, the process of dosage administration, and the methods employed for outcome assessment. This comprehensive assessment aimed to gauge the robustness and reliability of the findings reported in the included studies.This study was enrolled in the PROSPERO-International Prospective Register of Systematic Reviews (registration no.CRD42022308966)[8]. This assessment is elaborated in Figure 2.

3. Results and Discussion

3.1 Study Selection

A total of 102 records were identified from searching the PubMed database. After removing duplicates, 102 records remained for screening. The titles and abstracts of these 102 records were screened for relevance to the research topic. This initial screening excluded 27 records based on not meeting the pre-defined inclusion criteria i.e. disqualified after being subjected

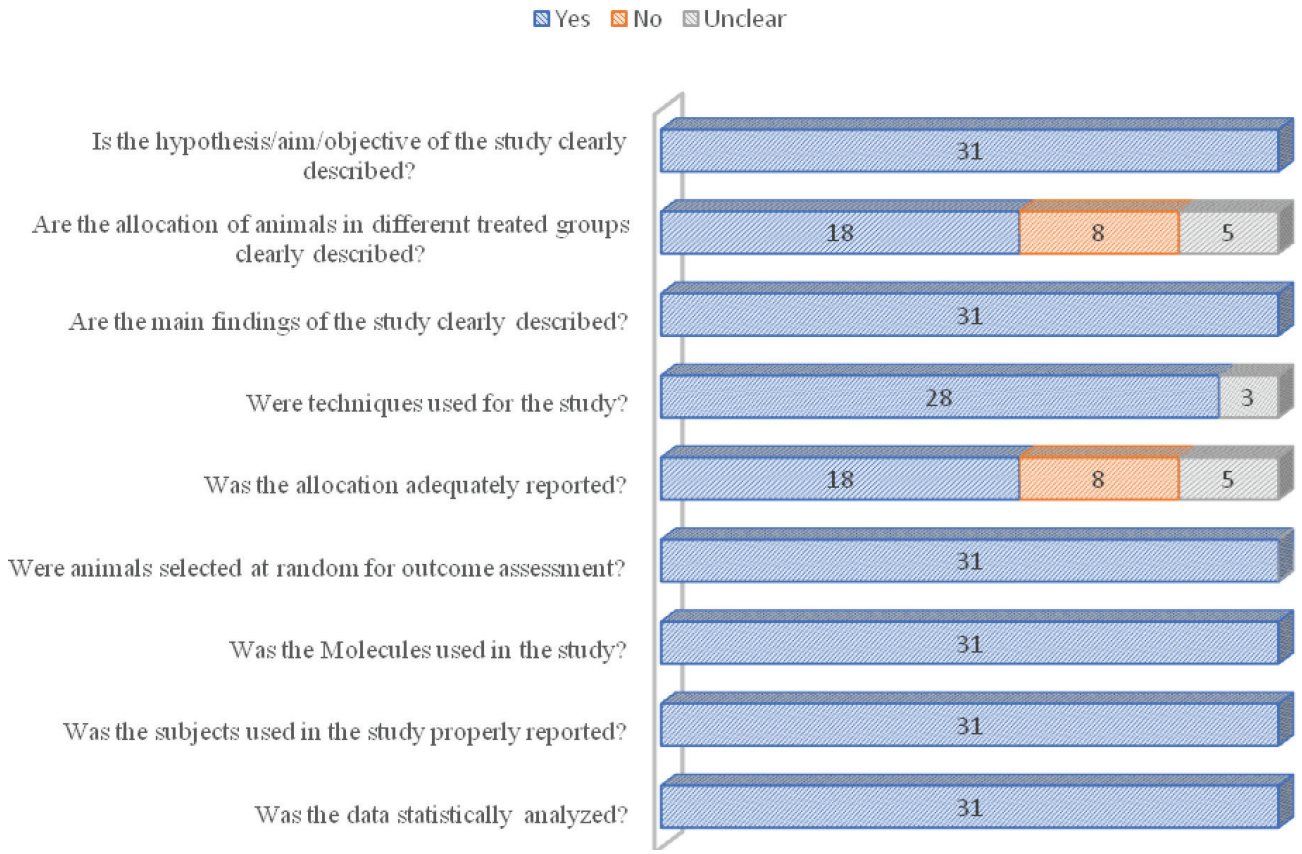


Figure 2. The methodological quality of included studies.

Table1. Studies selected for systematic review

Sr. no.	Authors, Year, Country	Subjects used in the study	Molecules used in the study	Techniques used for the study	Allocation of the animals in different treated groups
1	Parle M, 2004, India[9]	Mice	Liquorice	Interoceptive behavioural models. Three amnesia models were used: (a)scopolamine-induced amnesia; (b)diazepam-induced amnesia; and (c)ethanol-induced amnesia. (2) Exteroceptivebehavioral models. Two models were used: (a) elevated plus-maze and (b) passive avoidance	well-defined
2	Dhingra D, 2004, India[10]	Mice	Extract of *Glycyrrhiza glabra*	Laboratory models for testing learning and memory (i) Scopolamine-induced amnesia (Interoceptive Behaviour Model). (ii) Diazepam-induced amnesia (Interoceptive Behaviour Model). (iii) Elevated plus-maze (Exteroceptive Behaviour Model)	well-defined

Table1. Continued...

Sr. no.	Authors, Year, Country	Subjects used in the study	Molecules used in the study	Techniques used for the study	Allocation of the animals in different treated groups
3	Cui YM, 2008, China[11]	Mice	Glabridin	LC-MS analysis, Elevated plus maze, Passive avoidance test, Cholinesterase activity	not well defined
4	Sharifzadeh M, 2008, Iran[12]	Rat	Glycyrrhizin	Morris water maze task, HPLC	not well defined
5	Zhu Z, 2010, China[13]	Mice	2,2′,4′-trihydroxy chalcone	MWM, Congo red and Thioflavin S staining, Western blot, real-time quantitative PCR	not well defined
6	Hasanein P, 2011, Iran[14]	Rat	Glabridin	no information	no information
7	Song JH, 2013, Korea[15]	Mice	Glycyrrhizin	Real-Time PCR, western blotting, MWM, Immunohistochemistry	not well defined
8	Chakravarthi KK, 2013, India[16]	Rat	Root extract	Elevated plus maze, Hebb-William maze, and Morris water maze tests, Diazepam-induced amnesia	well-defined
9	Zhao H, 2013, China[17]	Mice	Diammonium glycyrrhizinate	MTT Assay, Western Blot, Real-time PCR, Morris Water Maze Test,Immunostaining	not well defined
10	Ma X, 2015, China[18]	Mice	Isoliquiritigenin	Morris Water Maze (MWM) test, peripheral insulin resistance, ELISA, western blot	not well defined
11	Madhavadas S, 2015, India[19]	Rat	Glycyrrhizin	behavioural assessment trials by Barnes maze task,ELISA,AChE Activity	well-defined
12	Singh P, 2016, India[20]	Mice	Root extract	DPPH free radical scavenging activity,Nitric oxide radical scavenging activity, Hydrogen peroxide scavenging assay	well-defined
13	Wang W, 2016, China[21]	Rat	Glycyrrhizin	WB, ELISA,MWM, Blood gas analysis	well-defined
14	Pang H, 2016, China[22]	rat	Glycyrrhizic acid	Phosphotungstic Acid Hematoxylin Staining, Western Blot, Immunohistochemistry, Immunofluorescence. TUNEL Staining, BBB Permeability Assay, Neurological Assessment brain water content	well-defined
15	Guo J, 2016, China[23]	Rat	Glycyrrhizinic acid (GA)	Morris water maze test, Histopathological studies, whole-cell patch-clamp analysis	
16	Kong ZH, 2017, China[24]	Mice	Glycyrrhizin	HMGB1, TLR4, NF-κB, p-Tau, and pro-inflammatory cytokines were determined by Western blot assay. The hippocampal level of β-amyloid (Aβ) was assessed by ELISA assay.	well-defined
17	Ko YH, 2017, Korea[25]	mice	Liquiritigenin	Novel object recognition test. Acetylcholinesterase activity assay, Thiobarbituric acid reactive substance activity assay,Western blot, Y-maze, passive avoidance test	not defined
18	Ong WY, Singapore, 2018[26]	Review on PD, AD humans	Liquorice	N/A	
19	Wang J, 2018, China[27]	Mice	Formononetin	Morris water maze test and Y maze test, levels of blood glucose, SOD, MDA, TNF-α, IL-1β, IL-6.	well-defined

Table1. Continued...

Sr. no.	Authors, Year, Country	Subjects used in the study	Molecules used in the study	Techniques used for the study	Allocation of the animals in different treated groups
20	Zhao F, 2018, China[28]	Rat	Liquorice	NMR,Biochemical assays,ELISA	well-defined
21	Kundu P, 2018, USA[29]	Rat	Isoliquiritigenin (ISL), liquorice root extract (LRE), and whole liquorice root powder	Behavioural testing, MCOL procedure, DOR procedure. ISL and LIQ concentrations,Organ weights	well-defined
22	Cho MJ, 2018, Korea[30]	Rat	Liquorice	Behavioural tests, including the T-maze, novel object recognition and Morris water maze, western blot	well-defined
23	Liu J, 2019, China[31]	rat	Iisoliquiritigenin	Measurement of Inflammatory Cytokines, Western Blot, MWM, Determination of Contusion Volume	well-defined
24	Sathyamoorthy Y, 2019, India[32]	Rat	Glycyrrhizic acid	novel object recognition (NOR) test,T-maze, g hole board (HB) test,Histology and histomorphometry,Biochemical analysis, WB	well-defined
25	Liu W, 2019, China[33]	Mice	Glycyrrhizinic acid (GA)	Micro-PET/CT imaging, Morris water maze test (MWM), Histological and immunohistochemical staining	not-defined
26	Zhu X, 2019, China[34]	mice	Isoliquiritigenin	MWM, Western blot, ELISA, quantitative real time-PCR,Immunofluorescence (IF), immunohistochemistry (IHC) and histology, Open field test	well-defined
27	Yu M, 2019, China[35]	Rat	Glycyrrhizin	Glucose tolerance test (GTT), insulin tolerance test, EMSA,Western blot,ELISA, Immunofluorescent staining and TUNEL staining, Novel objective recognition test (NORT), Y-maze test	well-defined
28	Zhu X, 2019, China[36]	Rat	Isoliquiritigenin	ELISA, fluoro jade B;immunofluorescence; immunohistochemistry;quantitative real time-PCR; Western Blot, MWM	not well defined
29	Lai S, 2020, China[37]	Rat	Glycyrrhizin	Plasma corticosterone measurement, Western blot, Microdialysis, Elevated plus maze test, Contextual fear extinction	not-defined
30	Ban JY, 2020, Korea[38]	Mice	Glycyrrhizic acid	Y-maze test, acetylcholinesterase activity, antioxidant enzymes' activity (superoxide dismutase, catalase). Western blot	N/A
31	Le K, 2020, China[39]	Mice	Glycyrrhizin	elevated plus-maze test. Western blot, tunnel staining, ELISA, real-time PCR	well defined

to a stringent screening procedure that was based on their relevance to memory and cognitive function. The full texts of the remaining 75 articles were assessed for eligibility. A further 44 records were excluded for the following reasons: 18 records had publication dates outside the target range, 11 records did not contain the required keywords, 11 records were not published in English, and 4 records had full-text unavailable. This screening process resulted in 31 studies that met all the eligibility criteria and were included in the study.

3.2 Global Distribution of Studies

The included studies represented research conducted globally, with China accounting for the largest share of publications. Of the 31 studies, 17 were conducted in China (55%), followed by 6 in India (19%), 4 in Korea (13%), 2 in Iran (6%), 1each in Singapore (3%), and 1 in the USA (3%) respectively.

China led global research output, contributing almost one-third of included studies. This indicates significant investigation in China on the neuroprotective effects of licorice-derived compounds. India accounted for the second-highest share of studies, reflecting steadily growing research activity. A fair number of studies also originated from other Asian countries like Korea, Iran, and Singapore. Beyond Asia, there was only a single study from the USA.

Furthermore, Asian countries dominated research output on this topic, contributing over 70% of included studies. China and India had particularly high research activity and production. The geographic distribution highlights extensive investigation in Asian regions while revealing potential gaps in research from other areas like Africa and South America. Expanding studies to underrepresented regions could provide valuable additional evidence. However, the current landscape is skewed towards high output from top producers China and India.

3.3 Bioactive Molecules in *Glycyrrhiza glabra*

Glycyrrhiza glabra, commonly known as liquorice, contains a variety of bioactive compounds that contribute to its pharmacological properties. Major constituents include glycyrrhizin, liquiritigenin, isoliquiritigenin, liquiritin, glycyrrhetinic acid, formononetin, glabridin, licochalcone A, and licochalcone B. Glycyrrhizin, a triterpenoid saponin, is considered the primary bioactive compound in liquorice root, comprising 1-9 % of the extract. It is 50 times sweeter than sugar and contributes to the sweet flavour of liquorice. Glycyrrhizin exhibits anti-inflammatory, antiviral, antimicrobial, antioxidative, antitumor, and neuroprotective properties. Other major bioactive like glabridin and liquiritigenin also demonstrate neuroprotective, antioxidant, anti-inflaatory, and estrogenic activities in pharmacological studies. Isoliquiritigenin shows anti-apoptotic, antioxidant and cholinesterase inhibitory effects relevant to neuroprotection. Overall, liquorice root contains a diverse mixture of hydrophobic and hydrophilic compounds with biomedical properties that make it a valuable therapeutic agent.

3.4 Evaluation Metrics

Animal studies on liquorice components have utilized a variety of behavioural, molecular, and histological evaluation metrics to assess neuroprotective effects. Common behavioural assessments include the Morris water maze to test spatial learning and memory, the novel object recognition test for visual memory, the Y maze for working memory, and the elevated plus maze to evaluate anxiety. Molecular metrics involve measuring neurotransmitters, inflammatory cytokines, antioxidant enzymes, and amyloid beta levels, among others, using techniques like ELISA, western blotting, and PCR. Histological analysis of neuronal morphology in the hippocampus and other brain regions is also performed using staining methods and microscopy. Advanced imaging techniques like PET have been applied to analyse neuroprotection too. The combination of behavioural studies, molecular analyses, and structural assessments provides a thorough evaluation of neuroprotective efficacy. However, additional metrics like EEG, MRI, and metabolomics could give further insights into functional and biochemical effects in the brain.

3.5 Animal Models

A variety of animal models have been utilized to investigate the neuroprotective potential of *G. glabra* components. Studies have tested liquorice extracts and bioactive constituents like glycyrrhizin and glabridin in mice and rat models of neurotoxicity induced chemically using drugs like scopolamine, diazepam and streptozotocin. Transgenic rodent models like APPswe/PS1dE9 mice and Kunming mice have also been used to study effects against amyloid beta pathology and memory impairment in Alzheimer's disease. Other studies have evaluated liquorice compounds in rat models of traumatic brain injury and cerebral ischemia using methods like middle cerebral artery occlusion. While findings have been promising, potential limitations exist in relying solely on animal models to predict efficacy in humans. Future

studies incorporating human cell lines, organoids, and bioinformatics approaches could help strengthen translational potential. However current evidence from various pharmacological, transgenic, and surgery-based rodent models provides important preliminary data on the neuroprotective properties of liquorice root constituents.

3.6 Combinatorial Approaches

Research has shown synergistic effects by combining *G. glabra* or its bioactive constituents with other natural compounds and drugs for neuroprotection. Co-administration with molecules like resveratrol, curcumin, or epigallocatechin gallate was found to potentiate the anti-inflammatory, antioxidant and memory-enhancing effects of liquorice flavonoids in rodent models. Combining glycyrrhizin or liquiritigenin with exogenous ketones also showed augmented benefits against cognitive impairment in mice. Additionally, glycyrrhizin improved the neuroprotective efficacy of memantine in a rat model of vascular dementia, indicating the potential for combinatorial therapy with Alzheimer's drugs. Such synergistic interactions highlight the opportunity to use liquorice extracts or compounds as adjuvants or complementary agents alongside pharmaceuticals, nutraceuticals, and other plant-derived molecules for multifaceted neuroprotective effects. Further research on optimal combinations is needed to translate these preclinical findings into clinically effective treatment strategies.

4. Conclusions

In conclusion, the included studies overwhelmingly utilized rodent models, primarily mice and rats, to investigate the neuroprotective potential of various *G. glabra*-derived molecules. The most commonly studied compounds were glycyrrhizin, liquiritigenin, isoliquiritigenin, and glabridin. While rodent models provide important preliminary evidence, future research should aim to incorporate human cell lines and organoid models to better translate the findings. Additionally, further bioactive constituents beyond the well-studied ones could be evaluated for neuroprotective properties. The studies demonstrated the beneficial effects of liquorice root extracts and compounds in enhancing cognitive function and memory in animal models. Spatial learning and memory improvements were frequently reported in Morris water maze tests after treatment with liquorice flavonoids. Positive effects on visual memory and working memory were also found in novel object recognition and Y-maze tasks respectively (Please refer to Figures 3 and 4). However, additional metrics like EEG, MRI, and metabolomics could give more objective insights into the neuroprotective mechanisms. Future studies should also evaluate long-term treatment regimens to determine the duration of cognitive benefits. While the included studies revealed promising results, methodological limitations existed in many studies, particularly regarding randomization, blinding, and statistical power. Future investigations

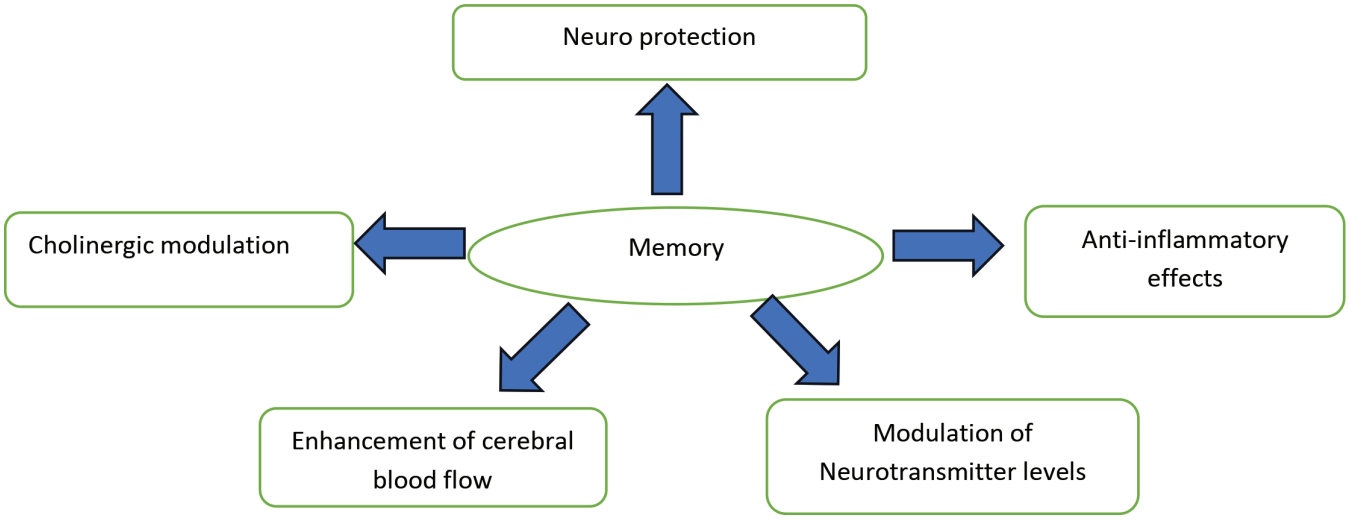


Figure 3. Possible mechanisms of impact of *Glycyrrhiza glabra* on cognitive function.

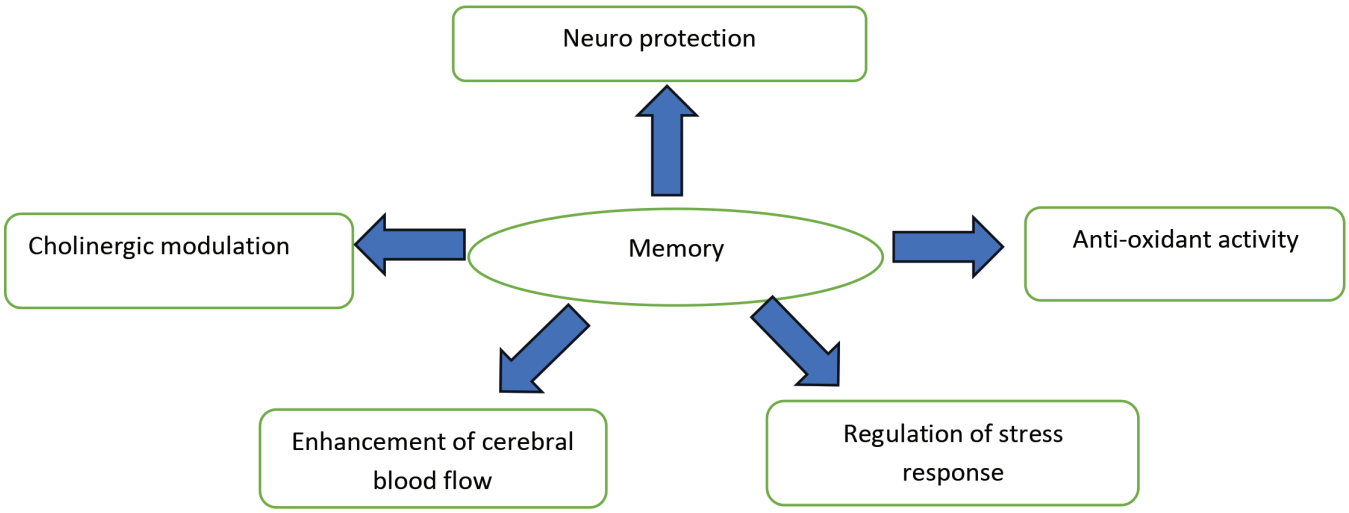


Figure 4. Possible mechanisms of impact of *Glycyrrhiza glabra* on memory.

should implement more rigorous methodologies including blinded experiments, randomized treatment allocation, well-powered sample sizes, and complete reporting following ARRIVE guidelines. Replication in multiple models and species will also strengthen the evidence base. High-qualitymulti-centre trials and the inclusion of both sexes are recommended before clinical translation.

5. Recommendations

Sustained long-term effects should be evaluated using chronic dosing regimens. Both sexes need to be assessed to improve translational potential. Testing in diverse species and multiple models is also advised to substantiate findings. Elucidating mechanisms using advanced multi-modal techniques including EEG, neuroimaging and metabolomics would provide additional insights. Determining optimal bioactive constituents, doses and formulations is imperative to progress towards clinical application. Furthermore, synergistic combinations with pharmaceuticals and nutraceuticals should be explored for multi-targeted benefits. Conducting collaborative multi-centre trials and independent replications will strengthen the existing evidence base. Finally, incorporating human cell lines and organoid models would enhance clinical predictive potential before planning human studies. Following these recommendations to optimize study methodology, expand characterization, and substantiate efficacy across models will help progress the most promising liquorice-derived neuro-protective compounds towards clinical evaluation.

6. Author Contributions

Conceptualization M. Y. C. and V. A. P.; methodology M. Y. C. and V. K. B.; data curation and review, M. Y. C., V. A. P. and V. K. B. M. W.; writing—original draft preparation, M. Y. C. and V. A. P., supervision, M. W. All authors have read and agreed to the published version of the manuscript.

7. References

1. Shukla V, Tripathi R. *Charaka Samhita with 'Vaidyamanorama' Hindi Commentary, Chikitsa Sthana; Rasayana Chikitsa: chapter 1/1, verse 8.* 2nd rev. ed. Delhi: Chaukhamba Sanskrit Pratishthan; 2004. p. 376.
2. Liu W, Huang S, Li Y, Zhang K, Zheng X. Suppressive effect of glycyrrhizic acid against lipopolysaccharide-induced neuroinflammation and cognitive impairment in C57 mice via toll-like receptor 4 signalling pathway. *Food Nutr Res.* 2019; p. 63. https://doi.org/10.29219/fnr.v63.1516 PMid:31073286 PMCid: PMC6495270
3. El-Saber Batiha G, Magdy Beshbishy A, El-Mleeh A, Abdel-Daim MM, Prasad Devkota H. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of *Glycyrrhiza glabra* L. (*Fabaceae*). *Biomolecules.* 2020; 10(3):352. https://doi.org/10.3390/biom10030352 PMid:32106571 PMCid: PMC7175350
4. Ramalingam M, Kim H, Lee Y, Lee YI. Phytochemical and pharmacological role of liquiritigenin and isoliquiritigenin from *Radix Glycyrrhizae* in human health and disease models.

Front Aging Neurosci. 2018; 10:348. https://doi.org/10.3389/fnagi.2018.00348 PMid:30443212 PMCid: PMC6221911
5. Ong WY, Wu YJ, Farooqui T, Farooqui AA. Qi Fu Yin: a Ming Dynasty prescription for the treatment of dementia. *Mol Neurobiol.* 2018; 55(9):7389–400. https://doi.org/10.1007/s12035-018-0908-0 PMid:29417476 PMCid: PMC6096952
6. Zhu X, Liu J, Huang S, Zhu W, Wang Y, Chen O, *et al.* Neuroprotective effects of isoliquiritigenin against cognitive impairment via suppression of synaptic dysfunction, neuronal injury, and neuroinflammation in rats with kainic acid-induced seizures. *Int Immunopharmacol.* 2019; 72:358–66. https://doi.org/10.1016/j.intimp.2019.04.028 PMid:31030091
7. Page MJ, Moher D, Bossuyt PM, *et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021; 372:n160. https://doi.org/10.1136/bmj.n160 PMid:33781993 PMCid: PMC8005925
8. PROSPERO-International prospective register of systematic reviews. Available from: https://www.crd.york.ac.uk/prospero/
9. Parle M, Dhingra D, Kulkarni SK. Memory-strengthening activity of *Glycyrrhiza glabra* flavonoids in rats. *J Ethnopharmacol.* 2004; 91(2–3):303–8. https://doi.org/10.1016/j.jep.2004.01.016 PMid:15120462
10. Dhingra D, Parle M, Kulkarni SK. The memory-enhancing activity of *Glycyrrhiza glabra* in mice. *J Ethnopharmacol.* 2004; 91(2–3):361–5. https://doi.org/10.1016/j.jep.2004.01.016 PMid:15120462
11. Cui YM, Ao MZ, Li W, Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. *Planta Med.* 2008; 74(4):377–80. https://doi.org/10.1055/s-2008-1034319 PMid:18484526
12. Sharifzadeh M, Shamsa F, Shiran S, Karimfar MH, Miri AH, Jalalizadeh H, *et al.* A time-course analysis of systemic administration of aqueous liquorice extract on spatial memory retention in rats. *Planta Med.* 2008; 74(5):485–90. https://doi.org/10.1055/s-2008-1074494 PMid:18404595
13. Zhu Z, Li C, Wang X, Yang Z, Chen J, Hu L, *et al.* 2,2',4'-trihydroxychalcone from *Glycyrrhiza glabra* as a new specific BACE1 inhibitor efficiently ameliorates memory impairment in mice. *J Neurochem.* 2010; 114(2):374–85. https://doi.org/10.1111/j.1471-4159.2010.06751.x PMid:20412384
14. Hasanein P. Glabridin as a major active isoflavan from *Glycyrrhiza glabra* (liquorice) reverses learning and memory deficits in diabetic rats. *Acta Physiol Hung.* 2011; 98(2):221–30. https://doi.org/10.1556/APhysiol.98.2011.2.14 PMid:21616781
15. Song JH. Neuroprotective effects of glycyrrhizinic acid on amyloid beta-induced cytotoxicity in primary hippocampal neurons. *Int J Mol Sci.* 2013;14(6):11113–26.
16. Chakravarthi KK, Avadhani R, Rao YV. A novel diterpenoid glycoside from *Glycyrrhiza glabra* enhances hippocampal neurogenesis in C57BL/6J and APP transgenic AD model mice. Curr Alzheimer Res. 2013; 10(6):646-61.
17. Zhao H, Wang SL, Qian L, Jin JL, Li H, Xu Y, *et al.* Diammonium glycyrrhizinate attenuates Aβ(1-42)-induced neuroinflammation and regulates MAPK and NF-kB pathways *in vitro* and *in vivo*. CNS Neurosci Ther. 2013; 19(2):117-24. https://doi.org/10.1111/cns.12043 PMid:23279783 PMCid: PMC6493378
18. Ma X, *et al.*Isoliquiritigenin ameliorates cognitive impairments induced by a high-fat diet in rats. Brain Res Bull. 2015; 112:31-8.
19. Madhavadas S, Subramanian S. Combination of spirulina with glycyrrhizin prevents cognitive dysfunction in aged obese rats. Indian J Pharmacol. 2015; 47(1):39-44. https://doi.org/10.4103/0253-7613.150327 PMid:25821309 PMCid: PMC4375816
20. Singh P, Singh D, Goel RK. Protective effect on phenytoin-induced cognition deficit in pentylenetetrazol kindled mice: A repertoire of *Glycyrrhiza glabra* flavonoid antioxidants. Pharm Biol. 2016; 54(7):1209-18. https://doi.org/10.3109/13880209.2015.1063673 PMid:26154520
21. Wang W, Chen X, Zhang J, Zhao Y, Li S, Tan L, *et al.* Glycyrrhizin attenuates isoflurane-induced cognitive deficits in neonatal rats via its anti-inflammatory activity. Neuroscience. 2016; 316:328-36. https://doi.org/10.1016/j.neuroscience.2015.11.001 PMid:26550949
22. Pang H, Huang T, Song J, Li D, Zhao Y, Ma X. Inhibiting HMGB1 with glycyrrhizic acid protects brain injury after DAI via its anti-inflammatory effect. Mediators Inflamm. 2016; 2016:4569521. https://doi.org/10.1155/2016/4569521 PMid:27041825 PMCid: PMC4799817
23. Guo J, Yang CX, Yang JJ, Yao Y. Glycyrrhizic acid ameliorates cognitive impairment in a rat model of vascular dementia associated with oxidative damage and inhibition of voltage-gated sodium channels. CNS NeurolDisord Drug Targets. 2016; 15(8):1001-8. https://doi.org/10.2174/1871527315666160527163526 PMid:27238153
24. Kong ZH, Chen X, Hua HP, Liang L, Liu LJ. Oral pretreatment of glycyrrhizin prevents surgery-induced cognitive impairment in aged mice by reducing neuroinflammation and Alzheimer 's-related pathology via HMGB1 inhibition. J Mol Neurosci. 2017; 63(3-4):385-95. https://doi.org/10.1007/s12031-017-0989-7 PMid:29034441
25. Ko YH, Kwon SH, Lee SY, Jang CG. Liquiritigenin ameliorates memory and cognitive impairment through cholinergic and BDNF pathways in the mouse hippocampus. Arch Pharm Res. 2017; 40(10):1209-17. https://doi.org/10.1007/s12272-017-0954-6 PMid:28940173
26. Ong WY, Wu YJ, Farooqui T, Farooqui AA. Qi Fu Yin—a Ming Dynasty prescription for the treatment of dementia. Mol Neurobiol. 2018; 55(9):7389-400. https://doi.org/10.1007/s12035-018-0908-0 PMid:29417476 PMCid: PMC6096952
27. Wang J, Wang L, Zhou J, Qin A, Chen Z. Protective effect of formononetin on cognitive impairment in streptozotocin

(STZ)-induced diabetic mice. Biomed Pharmacother. 2018; 106:1250-7. https://doi.org/10.1016/j.biopha.2018.07.063 PMid:30119194

28. Zhao F, Gao L, Qin X, Du G, Zhou Y. Intervention effect of liquorice in *D-galactose*-induced ageing rats by regulating the taurine metabolic pathway. Food Funct. 2018; 9(9):4814-21. https://doi.org/10.1039/C8FO00740C PMid:30131986
29. Kundu P, Korol DL, Bandara S, Monaikul S, Ondera CE, Helferich WG, *et al.*Liquorice root components mimic estrogens in an object location task but not an object recognition task. Horm Behav. 2018; 103:97-106. https://doi.org/10.1016/j.yhbeh.2018.06.002 PMid:29920269 PMCid: PMC6086590
30. Cho MJ, Kim JH, Park CH, Lee AY, Shin YS, Lee JH, *et al.* Comparison of the effect of three liquorice varieties on cognitive improvement via amelioration of neuroinflammation in lipopolysaccharide-induced mice. Nutr Res Pract. 2018; 12(3):191-8. https://doi.org/10.4162/nrp.2018.12.3.191 PMid:29854324 PMCid: PMC5974064
31. Liu J, Xiong X, Sui Y. Isoliquiritigenin attenuates neuroinflammation in traumatic brain injury in young rats. Neuroimmunomodulation. 2019; 26(2):102-10. https://doi.org/10.1159/000495467 PMid:30783039
32. Sathyamoorthy Y, Kaliappan K, Nambi P, Radhakrishnan R. Glycyrrhizic acid renders robust neuroprotection in a rodent model of vascular dementia by controlling oxidative stress and curtailing cytochrome-c release. NutrNeurosci. 2020; 23(12):955-70. https://doi.org/10.1080/1028415X.2019.1580935 PMid:30794076
33. Liu W, Huang S, Li Y, Zhang K, Zheng X. Suppressive effect of glycyrrhizic acid against lipopolysaccharide-induced neuroinflammation and cognitive impairment in C57 mice via toll-like receptor 4 signalling pathway. Food Nutr Res. 2019; p. 63. https://doi.org/10.29219/fnr.v63.1516 PMid:31073286 PMCid: PMC6495270
34. Zhu X, Liu J, Huang S, Zhu W, Wang Y, Chen O, *et al.* Neuroprotective effects of isoliquiritigenin against cognitive impairment via suppression of synaptic dysfunction, neuronal injury, and neuroinflammation in rats with kainic acid-induced seizures. Int Immunopharmacol. 2019; 72:358-66. https://doi.org/10.1016/j.intimp.2019.04.028 PMid:31030091
35. Yu M, Huang H, Dong S, Sha H, Wei W, Liu C. High mobility group box-1 mediates hippocampal inflammation and contributes to cognitive deficits in high-fat high-fructose diet-induced obese rats. Brain Behav Immun. 2019; 82:167-77. https://doi.org/10.1016/j.bbi.2019.08.007 PMid:31430517
36. Zhu X, Liu J, Chen S, Xue J, Huang S, Wang Y, *et al.* Isoliquiritigenin attenuates lipopolysaccharide-induced cognitive impairment through antioxidant and anti-inflammatory activity. BMC Neurosci. 2019; 20(1):41. https://doi.org/10.1186/s12868-019-0520-x PMid:31387531 PMCid: PMC6685153
37. Lai S, Shi L, Jiang Z, Lin Z. Glycyrrhizin treatment ameliorates post-traumatic stress disorder-like behaviours and restores circadian oscillation of intracranial serotonin. Clin Exp Pharmacol Physiol. 2020;47(1):95-101. https://doi.org/10.1111/1440-1681.13173 PMid:31494960
38. Ban JY, Park HK, Kim SK. Effect of glycyrrhizic acid on scopolamine-induced cognitive impairment in mice. Int Neurourol J. 2020; 24(Suppl 1):S48-55. https://doi.org/10.5213/inj.2040154.077 PMid:32482057 PMCid: PMC7285697
39. Le K, Wu S, Chibaatar E, Ali AI, Guo Y. Alarmin HMGB1 plays a detrimental role in hippocampal dysfunction caused by hypoxia-ischemia insult in neonatal mice: Evidence from the application of the HMGB1 inhibitor glycyrrhizin. ACS Chem Neurosci. 2020; 11(6):979-93. https://doi.org/10.1021/acschemneuro.0c00084 PMid:32073822