Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Cognitive-enhancing effects of a herbal combination on D-galactose-induced memory impairment

Junyan Ran[1,2], Qiwen Wei[1,2], Tao Lu[1,2], Xingjiang Liao[1,2] , Xiuqing Pang[1] , Qinfeng Zhu[1,2,3,4*], Hanni Zhou[1,2*], Xun He[1,2,3,4*]

[1] State Key Laboratory of Functions and Applications of Medicinal Plants & School of Pharmaceutical Sciences, Guizhou Medical University, Gui-an New District, 561113, Guizhou, China

[2] University Engineering Research Center for the Prevention and Treatment of Chronic Diseases by Authentic Medicinal Materials in Guizhou Province, Gui-an New District, 550025, Guizhou, China

[3] Engineering Research Center for the Development and Application of Ethnic Medicine and TCM, Ministry of Education, Guiyang, 550004, Guizhou, China

[4] Guizhou Provincial Engineering Technology Research Center for Chemical Drug R&D, Guizhou Medical University, 550014, Guiyang, China

Article Info

Article history:

Received: February 25, 2026
Accepted: April 23, 2026
Published: May 31, 2026

Use your device to scan and read the article online

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, for which effective pharmacological interventions remain limited. This study investigated the cognitive-enhancing effects of an optimized six-herbal combination (HC) comprising Polygonati Rhizoma (PR), Lycium barbarum polysaccharides (LBPs), Green Tea (GT), Jujube Seeds (JS), Fructus hippophae (FH), and Mori Folium (MF). Using the Ellman method, we evaluated the acetylcholinesterase (AChE) inhibitory activities of individual herbs and HC. An $L_{25}(4^6)$ orthogonal design was employed to determine the optimal proportions of the six herbs, with AChE inhibition as the evaluation index. The optimal HC composition (PR 9 g, LBPs 6 g, GT 3 g, JS 3 g, FH 3 g, MF 5 g) exhibited 88.11% AChE inhibition at 2000 μg/mL, which was significantly higher than that of any individual herb ($p < 0.05$). Network pharmacology analysis revealed 682 common targets between HC and AD, with significant enrichment in the PI3K-Akt signaling pathway, lipid metabolism, and chemical carcinogenesis-receptor activation pathways, suggesting multi-target mechanisms of action. In a D-galactose-induced subacute aging mouse model (3.5 $g \cdot kg^{-1}$, 70 days), HC treatment (0.75, 1.5, and 3.0 $g \cdot kg^{-1}$, 28 days) significantly improved spatial learning and memory in the Morris water maze. Specifically, HC at 1.5 $g \cdot kg^{-1}$ significantly reduced escape latency ($p < 0.01$ vs. D-galactose group), increased superoxide dismutase (SOD) and glutathione (GSH) levels ($p < 0.05$), and decreased malondialdehyde (MDA) and monoamine oxidase (MAO) levels ($p < 0.01$), while ameliorating hippocampal neuronal damage, as confirmed by hematoxylin and eosin staining. These findings demonstrate that HC exhibits potent anti-cholinesterase activity, modulates oxidative stress, and protects against neuronal injury, positioning it as a promising multi-target botanical candidate for further development in the prevention and management of AD.

Keywords: Herbal Combination, Alzheimer's disease, Acetylcholinesterase, D-galactose, Cognitive Impairment

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder primarily affecting the central nervous system, leading to cognitive decline and memory loss. It predominantly manifests in individuals of middle to old age. Clinically, AD is characterized by deficits in memory, language, orientation, emotions, and behavior, ultimately resulting in an inability to perform self-care tasks and posing a threat to the patients' lives[1-3].The etiology of AD remains incompletely understood, with primary contributors including oxidative stress, neuronal apoptosis, neurotransmitter dysregulation, accumulation of β-amyloid (Aβ), and hyperphosphorylation of Tau protein, among other factors[4, 5]. Furthermore, its pathological hallmarks include neuroinflammation within the central nervous system, selective neuronal and synaptic loss in specific brain regions, and the presence of abundant senile plaques in the cerebral cortex[6-8].Currently, AChE inhibitors, anti-glutamate drugs, calcium channel blockers, and other symptomatic treatments are frequently utilized in clinical practice, despite their associated adverse reactions, which impose certain constraints[9]. Modern pharmacological studies indicate that traditional Chinese medicine (TCM) has progressively assumed a pivotal role in both the prevention and

* Corresponding author.
E-mail address: hexun224@gmc.edu.cn (X. He); 15085968736@163.com (H. Zhou); zhuqinfeng@gmc.edu.cn (Q. Zhu).
Doi: http://dx.doi.org/10.14715/cmb/2026.72.5.1

management of AD. TCM may modulate the pathogenesis of AD through several mechanisms, including mitigating oxidative stress, impeding neuronal apoptosis, decreasing Aβ production, restraining Tau protein hyperphosphorylation, and alleviating neuroinflammatory responses, all while exhibiting minimal adverse effects[10, 11].

The concept of "medicine and food homology" has its roots in traditional Chinese medicine, which underscores the interconnectedness of food and medicine. Dating back to the Tang Dynasty, the text "Huangdi Nei Jing Tai Su" introduced the notion that food serves the purpose of nourishment, while medicine is employed for therapeutic interventions[12]. This concept highlights the distinct advantage of dietary interventions in promoting long-term health by addressing ailments. Contemporary investigations have revealed that *Lycium barbarum* polysaccharides, Fructus hippophae, and *Polygonati Rhizoma* are abundant in polyphenols, polysaccharides, and triterpenes, which exhibit anti-inflammatory, antioxidant, and neurotrophic properties[13]. Nonetheless, the majority of current studies predominantly focus on individual herbs, neglecting a comprehensive exploration of the synergistic mechanisms based on the holistic principles of TCM.

We utilized the Ellman method to assess the efficacy of individual herbs, various herbal combinations (HC), and different ratios within these combinations, with the aim of identifying the most effective herbal ratio within the HC. Furthermore, guided by the principles of systems biology, we applied network pharmacology to investigate the primary biological targets of the herbal combinations and to explore their underlying molecular mechanisms.

2. Materials and methods

2.1. Reagents

AChE, Huperzine A, 5,5'-dithiobis(2-nitrobenzoic acid, DTNB), Acetylthiocholine iodide (ATCI), and D-galactose (lot number: 101888658) were purchased from Sigma-Aldrich. SOD (lot number: 20191215), MDA (lot number: 20211124), GSH (lot number: 20191213), MAO (lot number:20191129), and GSH-Px (lot number: 20191220) kits were purchased from Nanjing Jiancheng Bioengineering Institute. Morris water maze analysis system (WMT-100, Chengdu Taimeng Software Co., Ltd.); tissue-cell homogenizer (Bullet Blender, Next Advance, USA); visible spectrophotometer (V-1100, Shanghai Metash Instrument Co., Ltd.).

2.2. Inhibitory effects of individual herbs and HC on AChE

Plant Material: *Polygonati Rhizoma* (PR), *Lycium barbarum* polysaccharides (LBPs), Green Tea(GT), Jujube Seeds (JS), Fructus hippophae (FH), Mori Folltfm (MF) purchased from JinshaTraditional Chinese Medicine Marketin Bijie,Guizhou, has been identified by Professor Liu Shao huan from Guizhou Medical University.

Preparation of Extract: Add water at a material-to-liquid ratio of 1:10, then decoct the mixture for 1 hour. Perform the extraction process twice, filter the resulting liquid after each decoction, and combine the filtrates. Concentrate the combined filtrates into an extract, and obtain the final water extract through freeze-drying. Prepare solutions of each water extract at a concentration of 2000 μg/mL in phosphate-buffered saline (PBS) containing 6% dimethyl sulfoxide (DMSO). Subsequently, dilute these solutions to prepare sample stock solutions at concentrations of 500 μg/mL and 31.25 μg/mL, respectively.

The inhibitory activity of each extract on AChE was evaluated using the Ellman: In this assay, the absorbance values were measured at 405 nm to determine the enzyme inhibition. The experimental setup included several control groups: the blank group, which contained phosphate-buffered saline (PBS) in place of the sample solution; the positive control group, where huperzine A (HupA) was used instead of the sample solution; and the sample blank group, in which PBS replaced AChE. These controls were essential for accurately assessing the specific inhibitory effects of the extracts on AChE activity.

2.3. Network Analysis

The chemical components of each herb were sourced exclusively from authoritative databases, including the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) and the Chemical Abstracts Service SciFinder database, structural information for each compound was obtained using the ChemSpider and PubChem databases. Chemical structures were drawn using InDraw 5.1.0 software and saved in sdf and mol file formats. The relevant targets of these compounds were predicted using the DrugBank (https://www.drugbank.com/), SwissTargetPrediction (www.swisstargetprediction.ch/), and PharmMapper (http://lilab-ecust.cn/pharmmapper/index.html,) platforms. Predicted target information was validated against the UniProtKB database (https://www.uniprot.org), specifying targets from "Homo sapiens" and converting all target names to official gene symbols. To identify PF-related targets, searches were conducted on OMIM (www.omim.org) and GeneCards (www.genecards.org,) databases, filtering results based on score values to exclude targets below the median score. Duplicate genes were removed, and Venn 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html) was used to generate a Venn diagram showing overlapping targets between compounds and PF-related targets. Intersection targets with a network confidence score > 0.9 shown by the STRING database (https://string-db.org/) were imported into Cytoscape 3.9.1 for network topology analysis and core target identification. GO and KEGG enrichment analyses of core targets ($p < 0.01$) were performed using the DAVID database (https://david.ncifcrf.gov/). Pathways were ranked based on p-values, and the top 20 pathways were visualized.

2.4. Animals Experiments

90 SPF-grade male KM mice (6-8 weeks old, body weight 20 ± 2 g) were obtained from the Experimental Animal Center of Daping Hospital, Third Military Medical University [SCXK (Jun) 2012-0011]. The animal experimental protocol was approved in accordance with the "Guizhou Medical University Animal Experiment Ethics Review Form" and followed the guidelines outlined in the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health. The mice were maintained under controlled environmental conditions, including a temperature of 25 ± 5°C, relative humidity of 60 ± 5%, and a 12-hour light/dark cycle, with ad libitum access to standard laboratory chow and drinking water. After a 7-day acclimation period, the mice were randomly assigned to six groups using a digital randomization method based on their body weights: Control

group (n = 15), D-galactose group (n = 15), HupA group (0.54 g·kg^{-1}, n = 15), and HC group at low, medium, and high doses (0.75, 1.5, and 3.0 g·kg^{-1}, respectively; n = 15 group). Except for the Cotntrol group, all other groups received subcutaneous injections of D-galactose (3.5 g·kg^{-1}) in the nape region daily for 70 consecutive days to establish a subacute aging mouse model, whereas the Control group was injected with an equivalent volume of saline. Starting from day 43, the HupA group and HC group mice were administered their respective treatments by oral gavage once daily for 28 consecutive days. The Control group and the D-galactose group were given an equal volume of distilled water by gavage as a control.

2.5. Morris Water Maze (MWM)

The spatial learning and memory abilities of experimental mice were evaluated using the MWM.The MWM trial spanned 5 days,consisting of a 4 day positioned sailing test, followed by one day spatial probe. Throughout the entire experiment, the water temperature was maintained at 25±0.5°C.To induce a cloudy aspect in the water,titanium dioxide was added,and the platform was positioned 2 cm below the water surface.The time when the mouse found the platform was recorded for measuring performance during the first 4 days,and their swimming route was recorded on the fifth day. After removial of the platform, spatial exploration experiments were conducted and the frequency and time of mice entering the escape and effective regions were recorded and the ratio of the distance to the total distance.

2.6. H&E Staining of HippocampusTissue

Three hippocampus tissue samples were randomly selected from each animal experimental group for pathological examination. The hippocampal tissue was fixed in 4% paraformaldehyde, embedded in paraffin, and then cut into 4μm sections. Subsequently, H&E staining were performed separately. When H&E staining was performed, after dewaxing and rehydrating, the tissue sections were stained with hematoxylin for 3-5 min, followed by dehydration in 85 and 95% ethanol for 5 min each. Before dehydration and mounting,eosin solution was used to stain for 5 min. A microscope was used to observe the pathological changes in the CA1 and CA2 regions of the mice hippocampus.

2.7. Tissue Determination of SOD, MDA, GSH, MAO, and GSH-PX content in mouse brain tissue

The content of SOD, MDA, GSH, MAO, and GSH-PX in the brain tissue of each group was detected using reagents provided by Nanjing Jiancheng Bioengineering Institute.

2.8. Statistical analysis

All data wereanalyzed using Analysis of Variance (ANOVA).Theresults are presented as the mean ± standard error of the mean (mean ± SEM). Statistical significance was set at a p-value less than 0.05 ($p < 0.05$), and analyses were performed using SPSS 22.0 software (IBM, Armonk, NY, USA).

3. Results

3.1. Inhibition rates of AChE by various herbs and prescriptions

According to the measured absorbance values and the calculation formula described in Section 1.2.2, the AChE inhibitory activities of the six individual herbal medicines and the HC at three concentrations (2000, 500, and 31.25 μg/mL) in the reaction system were determined; the results are shown in Table 1. In addition, a general linear univariate ANOVA model was constructed with the AChE inhibition rate as the dependent variable and drug concentration as the independent variable. The results (Table 2) revealed that both the different herbal medicines and the different concentrations exerted significant effects on the AChE inhibition rate ($P < 0.05$). Across all three tested concentrations, HC demonstrated a stronger inhibitory effect on AChE than any of the individual herbs.

3.2. An $L_{25}(4^6)$ orthogonal design was adopted to screen the optimal proportion of each individual herb in HC

Based on the pharmacopoeial dosages of the individual herbs and preliminary experiments, an L25(46) orthogonal

Table 1. Inhibition rates of AChE by various herbs and prescriptions（Mean±S，n=3）.

Herb	AChE Inhibition rates (%)		
	2000 μg/mL	500 μg/mL	31.25 μg/mL
PR	61.22±2.19	53.68±1.80	31.83±1.80
LBPs	71.04±1.81	60.02±1.22	40.66±0.84
GT	75.54±2.03	63.10±2.84	54.57±0.92
JS	82.09±2.33	69.62±1.85	46.67±1.12
FH	67.46±1.34	48.36±1.11	40.87±1.17
MF	77.34±1.66	62.00±0.83	42.87±1.85
HC	88.11±2.19	73.75±0.55	66.01±1.65

Table 2. Univariate analysis of variance results of general linear model.

Source	III Sum of Squares	Degrees of Freedom	Mean Square	F-value	P-value
Modified Model	3622.001[a]	4	517.429	34.861	.000
Intercept	64562.618	1	64562.618	4349.759	.000
HC	1383.331	5	276.666	18.640	.000
Concentration	2238.670	3	1119.335	75.413	.000
Error	148.428	10	14.843	-	-

design was conducted to optimize the proportion of each single herb in HC, using the AChE inhibition rate as the evaluation index. The factor-level combinations are listed in Table S1. According to the P values in the ANOVA table, the optimal HCDE formulation was determined to be: PR 9 g, LBPs 6 g, GT 3 g, JS 3 g, FH 3 g, and MF 5 g.

3.3. Network analysis predicts potential targets and pathways of HC in improving AD

On the basis of database collection and analysis, a total of 1012 HC targets, and 5349 AD targets, were obtained. Figure 1A showed that there were 682 cross targets between HC and AD. From the intersection above, 109 targets were obtained, and the PPI network visualization was shown in Figure 1B, with the top 6 in degree order being SRC, TP53, PIK3CA, STAT3, and AKT1. They were mainly enriched in pathways such as Lipid and atherosclerosis, PI3K-Akt signaling pathway, and Chemical carcinogenesis-receptor activation (Figure 1C).

3.4. HC Alleviated D-galactose-Induced Spatial Memory Deficits in the MWM Test

The effect of HC on the learning ability and memory impairment in the D-galactose-induced mice AD model was assessed using the MWM test.The results of the place navigation test (Figure 2) showed that, in comparison to the Control group, the latency of the D-galactose group mice was prolonged and the latency of the HC group was shorter than that of the D-galactose group .The results of the spatial exploration experiment (Figure 2) showed that, in comparison to the Control group, the D-galactose group reduced the number of times entering the escape platform and effective area as well as the time in the effective area and target quadrant and the HC group showed improvement in all indicators compared to the D-galactose group.

3.5. HC Improved Histopathology of HippocampusTissue in AD Mice

The tissue morphology results of the hippocampus tissue of mice in each group were shown in Figure 3. On the basis of the H&E staining results the neurons in the Control group exhibited a well organized arrangement, clear outlines, and evenly stained nuclei. In contrast, neurons in the D-galactose group showed varying degrees of damage, such as a loose and chaotic arrangement, irregular shapes, pyknosis, and deeply stained nuclei, which significantly differed from normal tissues. In comparison to the D-galactose group, the pathological changes in the HC group were slighter, the cell pyknosis decreased, and the outline of some cells was clear.Thesefindings suggestedthat HC possessed a neuroprotective effect and could alleviate neuronal damage.

3.3. The Effect of HC on Oxidative Stress in the Brian Tissue of AD Mice

Oxidative stress responses are known to exacerbate the progression of AD.Superoxide dismutase (SOD) and Glutathione Peroxidase (GSH-PX) is an antioxidant enzyme playing a crucial role in mitigating oxidative stress, while malondialdehyde (MDA) is widely accepted to be a critical biomarker of oxidative stress. To evaluate the impact of HC on oxidative stress in the context of AD, the levels of SOD, GSH-PX, GSH and MDA in the brian tissue of the mice were determined. The results (Figure 4D,E) demonstrate that D-galactose significantly reduced the SOD, GSH-PX and GSH levels ($p < 0.01$ vs. Control group) and increased the MDA levels ($p < 0.01$ vs. Control group) of mice; conversely, treatments with HupA and HC significantly increased the SOD, GSH-PX and GSH levels and decreased the MDA levels ($p < 0.05$ or $p < 0.01$ vs. D-ga-

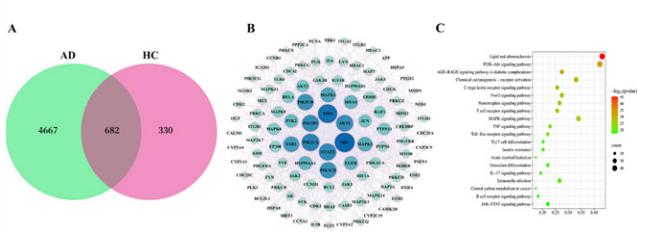


Fig. 1. Networkpharmacological analysis. A Intersection Venn diagram of the HC target and AD disease target. B PPI of the HC target and AD disease target. C KEGG pathway analysis.

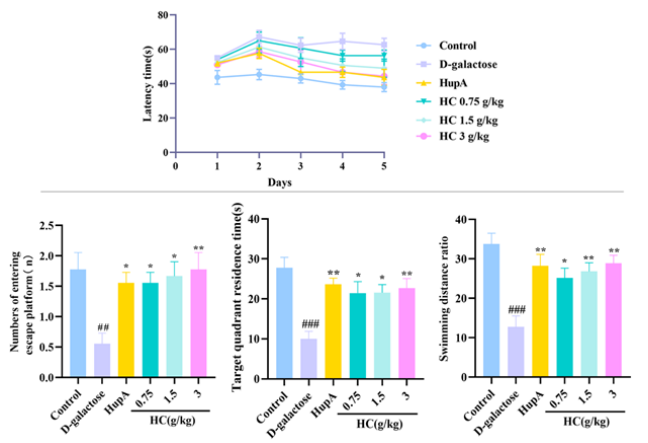


Fig. 2. Ameliorative effects of HC on learning and memory deficits in D-galactose treated mice.

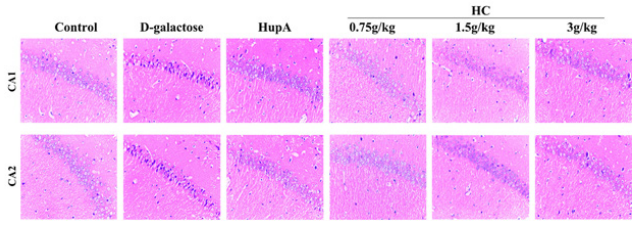


Fig. 3. HC Improved Histopathology of HippocampusTissue in AD Mice.

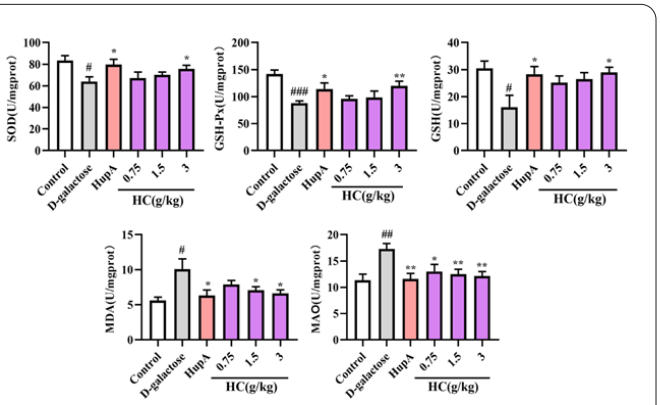


Fig. 4. C Improved Histopathology of HippocampusTissue in AD Mice.

lactose group).

Moreover, the abnormal changes of MAO not only reflect the imbalance of neurotransmitter metabolism, but also are related to key pathological processes (such as oxidative stress, neuroinflammation, etc.) in disease progress, it has become an important reference index for disease research and clinical evaluation.Accordingly, we also measured MAO levels in the brain tissue of each group. The results indicated that D-galactose markedly elevated MAO levels ($p < 0.01$ versus the control group), whereas HC significantly reduced MAO levels relative to the D-galactose group ($p < 0.05$ or $p < 0.01$).These findings suggest that the reduction in oxidative stress was involved in the anti-AD effect of HC.

4. Discussion

This study demonstrated that the optimized six-herb compound HC exhibited significantly greater AChE inhibitory activity across a defined concentration range compared to any of its individual constituent herbs. To identify the most effective combination of these herbs, we utilized an $L_{25}(4^6)$ orthogonal experimental design (Table S2), allowing us to systematically determine the optimal proportions of each herb within HC that maximized its anti-cholinesterase efficacy. Given that excessive AChE activity is a central pathological hallmark of AD and serves as the primary molecular target for most currently approved AD therapeutics, this finding carries substantial clinical relevance[14-16]. Consequently, HC presents itself as a promising natural, multi-target therapeutic agent capable of delivering therapeutic benefits while potentially minimizing the dose-dependent adverse effects commonly associated with synthetic cholinesterase inhibitors.

In addition, network pharmacology analysis provided deeper insights into the multifaceted mechanisms underlying HC's therapeutic actions, revealing that its effects extend well beyond simple cholinergic modulation. A total of 682 overlapping targets were identified between HC and AD-related pathways, among which SRC, TP53, PIK3CA, STAT3, and AKT1 emerged as the most interconnected hub nodes. These key proteins are integral components of the PI3K-Akt signaling pathway, lipid metabolism regulation, and receptor-mediated oncogenic signaling cascades-all of which are closely associated with neuronal survival, synaptic plasticity, and the processing of β-amyloid. These findings suggest that HC may concurrently suppress amyloidogenic pathways, promote neuroplasticity, and modulate vascular risk factors implicated in AD progression[17, 18].

Furthermore, using D-galactose-induced mouse model of AD, we observed that HC effectively ameliorated cognitive impairments. This improvement was demonstrated by a significant reduction in escape latency during the positioning navigation test and enhanced performance in the spatial exploration test, reflecting improved reference memory. Histopathological analyses also revealed that HC treatment alleviated neuronal loss, restored normal cellular morphology, and reduced nuclear pyknosis in the hippocampus-regions critically involved in learning and memory[19]. In addition, HC counteracted D-galactose-induced oxidative stress, as indicated by the normalization of antioxidant enzyme levels including SOD, GSH-Px, and GSH, MDA levels-a marker of lipid peroxidation[20, 21]. These results imply that the neuroprotective effects of HC are at least partly mediated through the restoration of redox balance.

Notably, HC also demonstrated the ability to downregulate MAO activity. Elevated MAO levels are known to contribute to the depletion of key neurotransmitters and to the increased generation of ROS[16, 22]. The dual regulatory action of HC on both AChE and MAO distinguishes it from conventional cholinesterase inhibitors, positioning it as a potential multi-modal, disease-modifying candidate with broader therapeutic implications for AD[23].

5. Conclusion

In conclusion, our findings offer robust preclinical evidence supporting the potential of HC as a safe, promising, and multi-target botanical therapeutic agent for the treatment of AD. Nevertheless, several critical aspects warrant further investigation. Firstly, it is essential to identify and quantitatively analyze the specific active components within HC that contribute to its observed synergistic therapeutic effects. Secondly, the direct impact of HC on tau protein phosphorylation and neuroinflammatory processes remains to be conclusively evaluated.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

The animal study was approved by the Animal Care Welfare Committee of GuiZhou Medical University (No. 1711020). This study was conducted in accordance with the local legislation and institutional requirements.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The datasets supporting the conclusions of this article are included within the article.

Authors' contributions

Danial Kahrizi: Research design and supervision; Samir. J. Bilal: Perform all laboratory procedures. Junyan Ran: writing-original draft, writing-review and editing. Qiwen Wei: writing-original draft, writing-review and editing. Shanggao Liao: conceptualization, data curation, writing-review and editing. Xingjiang Liao: data curation, project administration, writing-review and editing. Xiuqing Pang: resources, software, writing-review and editing. Qinfeng Zhu: supervision, writing-review and editing. Hanni Zhou: supervision, writing-review and editing. Xun He: supervision, writing-review and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This work was financially supported by the Guizhou Province College Students' Innovation and Entrepreneurship Training Program Project (202410660057 2X) and the Guizhou Province Science and Technology Program Funding Project (Qian Kehe Basic-2K [2024] No. 181.

References

1. Ibrahim AM, Pottoo FH, Dahiya ES, Khan FA, Kumar JS (2020) Neuron-glia interactions: Molecular basis of Alzheimer's disease and applications of neuroproteomics. Eur J Neurosci 52:2931-2943. doi: 10.1111/ejn.14838
2. Ma CJ (2024) Cognitive enhancing activity of cynaroside isolated from Lysimachia christinae on memory impairment insulted by scopolamine. Nat Prod Sci 30:175-181. doi: 10.20307/nps.2024.30.3.175
3. Ahmad S, Khan A, Ali W, Jo MH, Park J, Ikram M, Kim MO (2021) Fisetin rescues the mice brains against D-galactose-induced oxidative stress, neuroinflammation and memory impairment. Front Pharmacol 12:612078. doi: 10.3389/fphar.2021.612078
4. Martinez KL, Garcia de la Torre P, Serrano L, Gutiérrez E (2020) Citrulline supplementation modifies cognitive decline by changes in arginine and nitric oxide levels in a murine model for AD: Developing topics. Alzheimers Dement 16:e047305. doi: 10.1002/alz.047305
5. Song B, Yue D, Yan H, Feng L, Li M (2025) Traditional Chinese medicine natural products targeting shared mechanisms of T2DM and AD: Potential therapeutic insights. Drug Des Devel Ther 19:7681-7705. doi: 10.2147/DDDT.S484456
6. Zhang T, Kim BM, Lee TH (2024) Death-associated protein kinase 1 as a therapeutic target for Alzheimer's disease. Transl Neurodegener 13:4. doi: 10.1186/s40035-023-00395-5
7. Neuschmid S, Schallerer C, Ehrlich BE, McGuone D (2025) Pathological calcium signaling in traumatic brain injury and Alzheimer's disease: From acute neuronal injury to chronic neurodegeneration. Int J Mol Sci 26:9245. doi: 10.3390/ijms26199245
8. Rehman IU, Ahmad R, Khan I, Lee HJ, Park J, Ullah R, Choi MJ, Kang HY, Kim MO (2021) Nicotinamide ameliorates amyloid beta-induced oxidative stress-mediated neuroinflammation and neurodegeneration in adult mouse brain. Biomedicines 9:408. doi: 10.3390/biomedicines9040408
9. Loffredo G, D'Amelio M (2025) Disarming COX-1 to disrupt Alzheimer's inflammatory trajectory: Preclinical insights and translational promise. Transl Neurodegener 14:46. doi: 10.1186/s40035-025-00480-9
10. Li S, Yang J (2024) Pathogenesis of Alzheimer's disease and therapeutic strategies involving traditional Chinese medicine. RSC Med Chem 15:3950-3969. doi: 10.1039/d4md00660g
11. Wu Q, Wang W, Huang Z, Lin X, Yao M, Cai C, Weng G, Gu Y, Li H, Liu J (2024) Unveiling the molecular mechanisms of Danggui-Shaoyao-San against Alzheimer's disease in APP/PS1 mice via integrating proteomic and metabolomic approaches. Alzheimers Res Ther 16:251. doi: 10.1186/s13195-024-01651-4
12. Jiang J, Ou H, Chen R, Lu H, Zhou L, Yang Z (2023) The ethnopharmacological, phytochemical, and pharmacological review of Euryale ferox salisb.: A Chinese medicine food homology. Molecules 28:4399. doi: 10.3390/molecules28114399
13. He Y, Chen Z, Nie X, Wang D, Zhang Q, Peng T, Zhang C, Wu D, Zhang J (2022) Recent advances in polysaccharides from edible and medicinal Polygonati rhizoma: From bench to market. Int J Biol Macromol 195:102-116. doi: 10.1016/j.ijbiomac.2021.12.010
14. Bulacios GA, Cataldo PG, Naja JR, de Chaves EP, Taranto MP, Minahk CJ, Hebert EM, Saavedra ML (2023) Improvement of key molecular events linked to Alzheimer's disease pathology using postbiotics. ACS Omega 8:48042-48049. doi: 10.1021/acsomega.3c06805
15. Sikora J, Podsiedlik M, Pietras T, Kosmalski M, Matłoka M, Moszczyński-Petkowski R, Wieczorek M, Markowicz-Piasecka M (2020) Quetiapine and novel PDE10A inhibitors potentiate the anti-BuChE activity of donepezil. J Enzyme Inhib Med Chem 35:1743-1750. doi: 10.1080/14756366.2020.1817927
16. Walczak-Nowicka ŁJ, Herbet M (2021) Acetylcholinesterase inhibitors in the treatment of neurodegenerative diseases and the role of acetylcholinesterase in their pathogenesis. Int J Mol Sci 22:9290. doi: 10.3390/ijms22179290
17. Qu EK, Yang ML, Liu SJ, Li HY, Huang ZL, Yang LR, Luo R, Liang YN, Zhang DB (2025) Fritaipaines A−J, isosteroidal alkaloids with anti-neuroinflammatory activity from the bulbs of Fritillaria taipaiensis. Fitoterapia 183:106546. doi: 10.1016/j.fitote.2025.106546
18. Qu YJ, Zhen RR, Zhang LM, Gu C, Chen L, Peng X, Hu B, An HM (2020) Uncovering the active compounds and effective mechanisms of the dried mature sarcocarp of Cornus officinalis Sieb. Et Zucc. for the treatment of Alzheimer's disease through a network pharmacology approach. BMC Complement Med Ther 20:157. doi: 10.1186/s12906-020-02948-9
19. Yan MH, Cai H, Ding HX, Su SJ, Li XN, Xu ZQ, Feng WC, Wu QQ, Chen JX, Wang H (2025) Multifaceted mechanisms of Danggui Shaoyao San in ameliorating Alzheimer's disease based on transcriptomics and metabolomics. Zhongguo Zhong Yao Za Zhi 50:2229-2236. doi: 10.19540/j.cnki.cjcmm.20250110.701
20. Asgari Z, Iranzadeh S, Roghani M (2025) Myricetin alleviates learning and memory deficits in trimethyltin Alzheimer's phenotype via attenuating hippocampal endoplasmic reticulum stress and regulating inflammation and oxidative stress. Brain Res Bull 111382. doi: 10.1016/j.brainresbull.2025.111382
21. Patel Y, Solanki N, Dwivedi PS, Shah B, Shastry C, Azad S, Vejpara D, Patel M, Shah U, Patel S (2025) Integrating network pharmacology and in vivo study to explore the anti-Alzheimer's potential of Bergenia ligulata and Nelumbo nucifera. 3 Biotech 15:1-19. doi: 10.1007/s13205-024-04234-8
22. Jaisa-Aad M, Muñoz-Castro C, Healey MA, Hyman BT, Serrano-Pozo A (2024) Characterization of monoamine oxidase-B (MAO-B) as a biomarker of reactive astrogliosis in Alzheimer's disease and related dementias. Acta Neuropathol 147:66. doi: 10.1007/s00401-024-02723-7
23. Youdim MB (2022) Site-activated multi target iron chelators with acetylcholinesterase (AChE) and monoamine oxidase (MAO) inhibitory activities for Alzheimer's disease therapy. J Neural Transm 129:715-721. doi: 10.1007/s00702-022-02496-7