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PHARMACOLOGICAL EVALUATION OF ISOXANTHOHUMOL IN ALCL3 INDUCED ALZHEIMER DISEASE

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, synaptic dysfunction, and neuronal loss, with limited disease-modifying therapeutic options available. The present study investigated the neuroprotective potential of isoxanthohumol in an aluminium chloride induced AD-like mice model using an integrated approach involving in silico, in vitro, and in vivo evaluations. Blood–brain barrier (BBB) permeability was predicted using SwissADME, confirming favorable physicochemical properties and potential central nervous system penetration. Molecular docking studies demonstrated strong binding affinity of isoxanthohumol toward acetylcholinesterase and moderate interaction with brain-derived neurotrophic factor, indicating dual involvement in cholinergic and neurotrophic pathways. In vitro cholinesterase assays revealed significant inhibitory activity against both acetylcholinesterase and butyrylcholinesterase, supporting its role in enhancing cholinergic neurotransmission. These effects were comparable, although slightly lower, than those observed with donepezil treatment. In vivo, cognitive performance was assessed using the novel object recognition test, where isoxanthohumol-treated mice showed significant improvement in recognition memory compared to the disease control group. The $AlCl_3$-induced model successfully replicated AD-like behavioral deficits, confirming oxidative and neurotoxic impairment. Collectively, the findings suggest that isoxanthohumol exerts multi-target neuroprotective effects through modulation of cholinergic activity and neurotrophic signaling, potentially supported by antioxidant and anti-inflammatory mechanisms. This study provides preliminary evidence that isoxanthohumol may serve as a promising natural therapeutic candidate for the management of AD. However, further mechanistic and translational studies are requires to validate its clinical applicability

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by gradual cognitive decline, memory impairment, and behavioral disturbances. It is the most common cause of dementia, contributing to approximately 60–70% of total dementia cases worldwide. Pathologically, AD is marked by amyloid-β plaque deposition, neurofibrillary tangles, synaptic dysfunction, and neuronal loss, ultimately leading to irreversible brain damage (World Health Organization., 2025). AD represents a multifactorial disorder with a complex etiology involving genetic, environmental, and lifestyle-related factors. The risk of developing AD increases significantly with advancing age, which is considered the strongest non-modifiable risk factor. Additional non-modifiable risk factors include genetic predisposition and family history, whereas modifiable factors such as hypertension, diabetes mellitus, obesity, smoking, physical inactivity, and social isolation contribute substantially to disease progression. Emerging evidence highlights neuroinflammation as a central unifying mechanism linking multiple risk factors, characterized by microglial activation and release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α . Furthermore, traumatic brain injury, depression, and metabolic disorders are increasingly recognized as contributors to AD pathogenesis (Weawer et al., 2023) The global burden of Alzheimer's disease is rapidly increasing, posing a significant public health challenge. According to the World Health Organization, approximately 57 million people were living with dementia globally in 2021, with nearly 10 million new cases reported annually. A major proportion of these cases is attributed to Alzheimer's disease, particularly in low- and middle-income countries. The socioeconomic impact is profound, with dementia ranking among the leading causes of disability and dependency in the elderly population . Projections suggest that the number of affected individuals will continue to rise dramatically in the coming decades, emphasizing the urgent need for effective therapeutic interventions.

Experimental models play a crucial role in understanding AD pathogenesis and evaluating potential therapeutic agents. Among these, aluminium chloride ($AlCl_3$)-induced neurotoxicity is widely used to mimic Alzheimer-like pathology in animal models. $AlCl_3$ is an environmental neurotoxin commonly found in food, water, and industrial products. Its administration leads to cognitive deficits, oxidative stress, neuroinflammation, and neuronal degeneration, closely resembling key features of AD. Mechanistically, $AlCl_3$ promotes the accumulation of reactive oxygen species (ROS), disrupts cholinergic transmission, enhances amyloidogenic pathways, and induces inflammatory signaling cascades, thereby contributing to neurodegeneration . Additionally, aluminium accumulation in brain tissues has been associated with impaired learning and memory, further supporting its relevance in AD research models (Alzheimer's Association., 2024). Currently, several pharmacological agents are available for the management of Alzheimer's disease; however, they provide only symptomatic relief rather than disease modification. The commonly used drugs include cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, which enhance cholinergic neurotransmission, and the NMDA receptor antagonist memantine, which regulates glutamatergic excitotoxicity. Despite their clinical utility, these drugs exhibit limited efficacy and are often associated with adverse effects, including gastrointestinal disturbances, dizziness, and hepatotoxicity. Moreover, recently developed monoclonal antibodies targeting amyloid-β have shown promise but remain limited by high cost, accessibility issues, and safety concerns. Therefore, there is a pressing need to explore novel therapeutic agents with multitargeted mechanisms and improved safety profiles (Rahman & Banu et al., 2024).

In this context, natural compounds have gained considerable attention due to their diverse pharmacological activities and favorable safety profiles. Isoxanthohumol (Figure 1) a prenylated flavonoid derived from hops (*Humulus lupulus*), has been reported to exhibit multiple biological activities, including antioxidant, anti-inflammatory (Negrão et al., 2013) and anticancer effects (Girisa et al., 2021) . Studies have demonstrated that isoxanthohumol can modulate oxidative stress

pathways, inhibit pro-inflammatory cytokine production, and regulate signaling pathways such as NF-κB and MAPK, which are critically involved in neurodegeneration. Additionally, its ability to cross the blood–brain barrier and exert neuroprotective effects makes it a promising candidate for neurodegenerative disorders. Despite these promising pharmacological properties, there is currently limited evidence regarding the role of isoxanthohumol in aluminium chloride ($AlCl_3$)-induced Alzheimer's disease models. To the best of current knowledge, no comprehensive study has been reported evaluating its therapeutic potential specifically in $AlCl_3$-induced neurodegeneration. Therefore, investigating isoxanthohumol in this experimental model may provide novel insights into its neuroprotective mechanisms and potential application as a therapeutic agent for Alzheimer's disease.

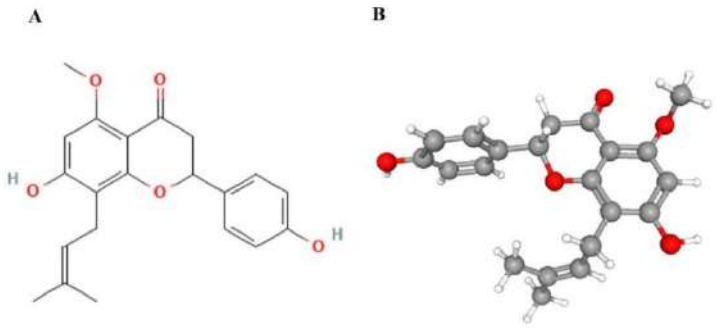

Figure 1: A and B represent 2D and 3D structures of Isoxanthohumol.

Materials and Methods

Chemicals

Isoxanthohumol and aluminium chloride ($AlCl_3$) were procured from Shanghai Macklin Biochemical Co., Ltd., ensuring a high degree of purity appropriate for experimental applications. Additional reagents, including dimethyl sulfoxide (DMSO) and chloroform, were obtained from a certified local pharmaceutical supplier and were used as received without further purification. All chemicals and reagents employed in the present study were of analytical grade, thereby ensuring the reliability and reproducibility of the experimental results.

Animals

Healthy adult mice, weighing between 30–40 g, were obtained from the National Institute of Health Islamabad. The animals were acclimatized prior to experimentation and housed in standard polypropylene cages, with five animals per cage to maintain appropriate social conditions. They were maintained under controlled environmental conditions, including a temperature of 25 ± 1 °C, relative humidity of 50 ± 10%, and a 12-hour light/dark cycle. A standard laboratory diet and clean drinking water were provided *ad libitum* throughout the study duration.

Blood Brain Barrier Permeability

The ability of isoxanthohumol to cross the blood–brain barrier (BBB) was assessed using the SwissADME web-based platform. Key physicochemical parameters, including lipophilicity, molecular size, and polarity, were systematically evaluated to estimate its potential for central nervous system (CNS) penetration. Furthermore, the BOILED-Egg predictive model integrated within SwissADME was employed to

assess both gastrointestinal absorption and the likelihood of BBB permeation, providing a comprehensive in silico estimation of the compound's pharmacokinetic behavior (Antoine Daina & Vincent Zoete, 2016).

Docking Study

The three-dimensional structure of the selected ligand was retrieved and subsequently visualized using BIOVIA Discovery Studio Visualizer. Protein targets associated with neurodegenerative and depressive pathways were selected for docking analysis, and their crystallographic structures were obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank. The selected targets included acetylcholinesterase (PDB ID: 4MOE) and brain-derived neurotrophic factor (PDB ID: 1BND). Prior to docking, protein structures were carefully prepared by removing co-crystallized ligands and water molecules, followed by the addition of polar hydrogen atoms to stabilize the system. The processed protein structures were then saved in PDB format for subsequent analysis. Molecular docking simulations were carried out using AutoDock and PyRx. The binding interactions between the ligand and target proteins were evaluated based on atomic contact energy (ACE) values expressed in kcal/mol. The most energetically favorable binding conformation, corresponding to the lowest ACE value, was selected for further structural and interaction analysis (Noman et al., 2022).

Butyrylcholinesterase (BChE) and Acetylcholinesterase (AChE) Assays

The activity of butyrylcholinesterase (BChE) was determined spectrophotometrically using a specific BChE substrate in the presence of 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) as a chromogenic indicator. The rate of reaction was monitored by measuring absorbance at 412 nm, and enzyme activity was calculated using the appropriate molar extinction coefficient. Inhibitory potential was evaluated by preincubating the enzyme with the test compound prior to substrate addition. The results were expressed as IC_{50} values (µg/mL or µM), defined as the concentration of the compound required to inhibit 50% of the enzyme activity. Acetylcholinesterase (AChE) activity was assessed using the Ellman's method, employing acetylthiocholine as the substrate. Upon enzymatic hydrolysis, the liberated thiocholine reacted with DTNB to form a yellow-colored chromophore, which was quantified spectrophotometrically at 412 nm (ε = 13,600 $M^{-1}cm^{-1}$). Enzyme activity was expressed as µmol/min/mg protein. The inhibitory effect of the test compound on AChE activity was determined following a preincubation step under controlled experimental conditions (Noman et al., 2026).

Induction of Alzheimer's Disease (AD) in Mice

An Alzheimer's disease (AD)-like model was established in mice through oral administration of aluminum chloride ($AlCl_3$) at a dose of 17 mg/kg body weight daily for four consecutive weeks.

Experimental Design

The animals were randomly divided into five groups (n = 4 per group) and treated for 21 days as follows:

- Group I (Normal Control): Healthy mice receiving no treatment, serving as the negative control group.
- Group II (Disease Control): Mice subjected to $AlCl_3$ administration to induce AD-like pathology, without further treatment.
- Group III (Treatment Group): AD-induced mice treated orally with isoxanthohumol at a dose of 50 mg/kg body weight daily for 21 consecutive days.
- Group IV (Reference Drug Group): AD-induced mice treated orally with donepezil at a dose of 3 mg/kg body weight per day for 21 consecutive days, following cessation of $AlCl_3$ administration (Borai et al., 2017).

Behavioral Analysis

The Novel Object Recognition Test (NORT) was performed to assess recognition memory in mice. The test consisted of three phases: habituation, familiarization, and test session, conducted in an open-field arena. During the familiarization phase, mice were exposed to two identical objects, and the time spent exploring each object was recorded. After a retention interval, one familiar object was replaced with a

novel object, and exploration time toward each object was measured. Recognition memory was evaluated based on the differential exploration time, with reduced time spent on the familiar object indicating improved cognitive performance (Labban et al., 2021).

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS software (version 25), and graphical representations were prepared using GraphPad Prism (version 9.5.0). Intergroup comparisons were analyzed using one-way analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) post hoc test. A p-value of less than 0.05 was considered statistically significant.

Results

Blood brain barrier

The in silico analysis using SwissADME indicated that isoxanthohumol possesses favorable physicochemical properties for blood–brain barrier (BBB) permeability. The compound exhibited optimal lipophilicity and molecular size, supporting its potential for passive diffusion across the BBB. Polarity parameters, including topological polar surface area (TPSA), were within the acceptable range for central nervous system (CNS) activity. The BOILED-Egg model predicted high gastrointestinal absorption along with a strong likelihood of BBB penetration. Collectively, these findings suggest that isoxanthohumol has promising pharmacokinetic characteristics for effective CNS targeting (Figure 2).

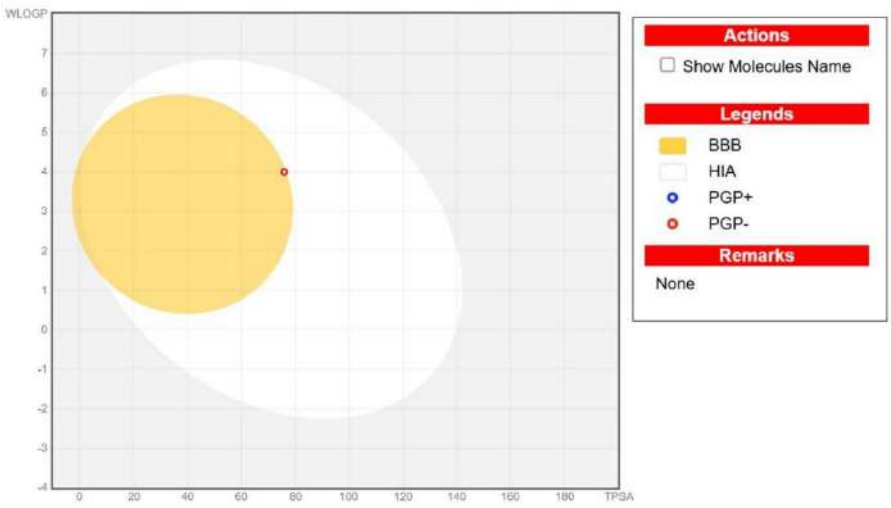

Figure 2: Blood brain barrier permeability of isoxanthohumol.

Computational study

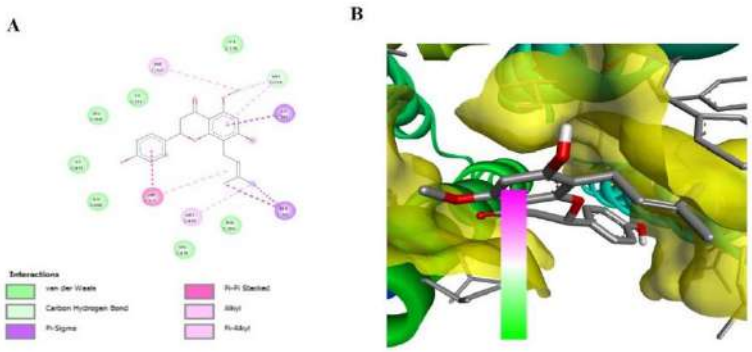

Figure 3: 2D and 3D interactions of isoxanthohumol against Acetylcholine.

Molecular docking analysis revealed strong binding affinity of isoxanthohumol toward the selected neurobiological targets. The ligand demonstrated a favorable interaction with Acetylcholinesterase, exhibiting a binding energy of −9.1 kcal/mol, indicating a highly stable ligand–protein complex. Similarly, docking with Brain-Derived Neurotrophic Factor showed a binding energy of −7.6 kcal/mol, reflecting moderate yet significant interaction (Table 1). The lower binding energy observed with acetylcholinesterase suggests a stronger affinity compared to BDNF. Interaction analysis further revealed stable binding conformations supported by key intermolecular interactions within the active sites. Overall, these findings highlight the potential of isoxanthohumol as a promising candidate for targeting both cholinergic and neurotrophic pathways (Figure 3,4).

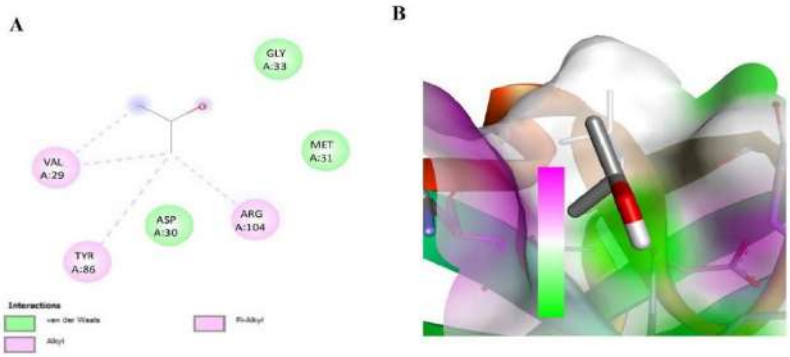

Figure 4: 2D and 3D interactions of isoxanthohumol against BDNF.

Table 1: Binding energy values of isoxanthohumol against acetylcholine and BDNF.

Compound	% Inhibition ± SD (BChE)	IC_{50} ± SEM (µM) (BChE)	% Inhibition ± SD (AChE)	IC_{50} ± SEM (µM) (AChE)
Isoxanthohumol	77.17 ± 1.78	9.3 ± 0.28	66.47 ± 1.69	11.78 ± 0.06
Donepezil	90.14 ± 1.19	4.4 ± 0.38	81.37 ± 1.19	3.38 ± 0.09

Table 2: BChe and AChe in vitro assay.

Receptor	PDB ID	Compound	Energy Values Kcal/mol
Acetylcholine	4 MOE	Isoxanthohumol	-9.1
BDNF	1 BND	Isoxanthohumol	-7.6

Butyrylcholinesterase (BChE) and Acetylcholinesterase (AChE) Assays

Isoxanthohumol showed notable inhibitory activity against both cholinesterase enzymes. For butyrylcholinesterase (BChE), it produced 77.17 ± 1.78% inhibition with an IC_{50} value of 9.3 ± 0.28 µM, indicating moderate potency. Against acetylcholinesterase (AChE), it exhibited 66.47 ± 1.69% inhibition with an IC_{50} value of 11.78 ± 0.06 µM, suggesting slightly lower activity compared to BChE. In comparison, Donepezil demonstrated significantly stronger inhibition for both enzymes, with 90.14 ± 1.19% (BChE) and 81.37 ± 1.19% (AChE). Its corresponding IC_{50} values (4.4 ± 0.38 µM for BChE and 3.38 ± 0.09 µM for AChE) confirm its higher potency than Isoxanthohumol (Table 2).

Novel Object Recognition Test

The Novel Object Recognition Test (NORT) results show clear differences in exploratory behavior across groups. The Alzheimer's disease (AD) disease control group spent significantly more time exploring the familiar object (~57 s) compared to the normal control group (~24 s), indicating impaired recognition memory, as reflected by the highly significant difference (###, $p < 0.001$ vs. control). Treatment with Isoxanthohumol (50 mg/kg) markedly reduced the exploration time (~24 s), bringing it close to normal levels and showing a significant improvement compared to the AD group (, *$p < 0.001$). Similarly, Donepezil (3 mg/kg), a standard anti-Alzheimer's drug, further reduced the exploration time (~18 s), also demonstrating a highly significant improvement* (, $p < 0.001$ vs. AD). Overall, these findings suggest that both Isoxanthohumol and Donepezil effectively ameliorate recognition memory deficits in the AD model, with Donepezil showing a slightly stronger effect (Figure 5).

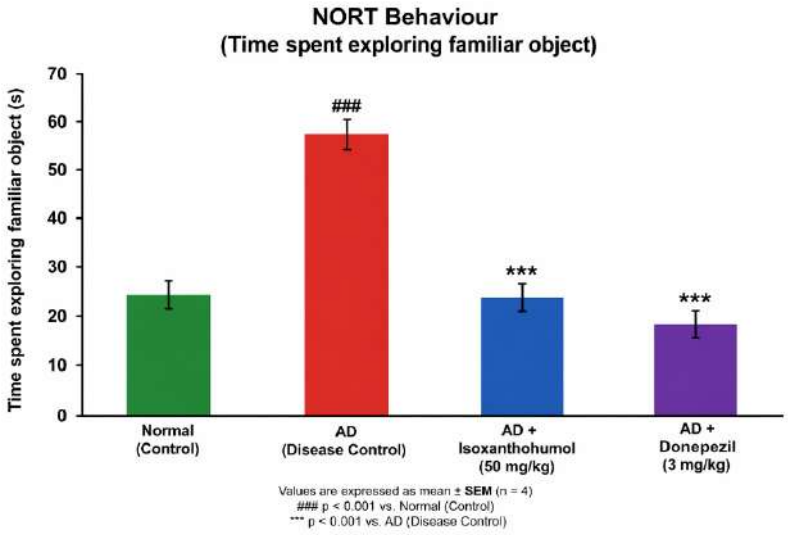

Figure 5: Novel object recognition test.

Discussion

Alzheimer's disease (AD) remains a progressive and multifactorial neurodegenerative disorder, characterized by irreversible cognitive decline, synaptic dysfunction, and neuronal loss. In the present study, we investigated the neuroprotective potential of isoxanthohumol in an aluminium chloride ($AlCl_3$)-induced AD-like mouse model, integrating in silico, in vitro, and in vivo approaches. The overall findings demonstrate that isoxanthohumol exerts significant cholinesterase inhibitory activity, favorable blood–brain barrier (BBB) permeability, and measurable cognitive improvement in behavioral testing, suggesting its potential as a multi-target neuroprotective agent. The pathophysiology of AD is strongly associated with amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, and chronic neuroinflammation, all of which contribute to progressive synaptic failure (Selkoe & Hardy, 2016; Heneka et al., 2015). In addition, cholinergic dysfunction is a well-established hallmark of cognitive decline in AD, forming the basis for current symptomatic therapies such as acetylcholinesterase inhibitors. In this context, the significant inhibitory activity of isoxanthohumol against both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) observed in our study suggests a mechanistic relevance to cholinergic enhancement. Although its potency was lower than donepezil, the dual inhibition profile indicates a broader modulatory effect on cholinergic neurotransmission, which may be advantageous in multifactorial neurodegeneration. The molecular docking results further support the experimental findings by demonstrating strong binding affinity of isoxanthohumol toward acetylcholinesterase and moderate interaction with brain-derived neurotrophic factor (BDNF). The stronger binding to AChE aligns with its in vitro inhibitory activity, reinforcing the likelihood of direct enzyme modulation. Interestingly, interaction with BDNF suggests a possible neurotrophic regulatory role, which is particularly relevant given the well-documented reduction of BDNF signaling in AD and its association with impaired synaptic plasticity and memory formation (Zuccato & Cattaneo, 2009). Such dual targeting of cholinergic and neurotrophic pathways may provide a mechanistic advantage over single-target drugs. The in silico BBB permeability analysis using SwissADME indicated that isoxanthohumol possesses favorable physicochemical properties for central nervous system (CNS) penetration. Effective CNS drug candidates must satisfy strict requirements related to lipophilicity, molecular size, and polar surface area. The predicted BBB permeability suggests that isoxanthohumol is capable of reaching its central targets, which is a critical prerequisite for any neuroprotective agent. This finding is particularly important, as

many natural compounds fail in clinical translation due to poor CNS bioavailability.

The $AlCl_3$-induced neurotoxicity model used in this study is widely accepted for mimicking AD-like pathological changes, including oxidative stress, cholinergic dysfunction, and neuroinflammation. Aluminium exposure has been shown to enhance reactive oxygen species (ROS) generation and disrupt neuronal integrity, thereby accelerating cognitive deficits (Kaur & Gill, 2005). In our study, behavioural impairment in the disease control group in the Novel Object Recognition Test (NORT) confirmed successful induction of memory dysfunction. The significant improvement in recognition memory following isoxanthohumol treatment indicates its ability to reverse or attenuate cognitive deficits induced by neurotoxic insult. The behavioral outcomes observed in the NORT were strongly supported by biochemical evidence from cholinesterase assays. Isoxanthohumol significantly improved cholinergic enzyme profiles, suggesting enhanced synaptic neurotransmission. This improvement may be attributed to its antioxidant and anti-inflammatory properties, as oxidative stress and inflammation are key drivers of cholinergic neuron degeneration in AD (Perry et al., 2002). Natural flavonoids, in general, are known to modulate multiple signaling pathways including NF-κB and MAPK, which regulate inflammatory cytokine production (e.g., TNF-α, IL-6, IL-1β), further supporting their neuroprotective potential. Importantly, isoxanthohumol has previously been reported to exhibit antioxidant and anti-inflammatory activity (Negrão et al., 2013) and anticancer properties (Girisa et al., 2021). These pleiotropic effects may contribute to its observed neuroprotective efficacy in the present study. Neuroinflammation is now recognized as a central contributor to AD progression, with activated microglia releasing pro-inflammatory mediators that exacerbate neuronal damage (Heneka et al., 2015). Therefore, compounds that simultaneously modulate oxidative stress, inflammation, and neurotransmission may offer superior therapeutic benefits compared to conventional single-target drugs. When compared with donepezil, isoxanthohumol exhibited moderate but significant efficacy across enzymatic and behavioral parameters. While donepezil remains more potent as a cholinesterase inhibitor, it is primarily symptomatic and does not address upstream pathological mechanisms such as oxidative stress or inflammation. In contrast, isoxanthohumol demonstrated a broader mechanistic profile, suggesting potential disease-modifying properties rather than purely symptomatic relief. Overall, the integration of computational, biochemical, and behavioral data supports the hypothesis that isoxanthohumol exerts neuroprotective effects through multi-target modulation involving cholinergic enhancement, neurotrophic signaling, and likely antioxidant and anti-inflammatory pathways. However, further studies are required to validate these findings at the molecular level, particularly focusing on oxidative stress markers, inflammatory cytokines, and synaptic plasticity proteins in brain tissues.

Conclusion

In conclusion, this study provides preliminary but compelling evidence that isoxanthohumol may serve as a promising natural candidate for the management of Alzheimer's disease. Its ability to cross the BBB, inhibit cholinesterase enzymes, and improve cognitive performance in an experimental AD model highlights its therapeutic potential. Nevertheless, future investigations involving chronic models, detailed mechanistic studies, and pharmacokinetic profiling are essential to fully establish its clinical relevance.

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