Identification of Herbal Molecules for the Treatment of Alzheimer's Disease Through a Combination of Molecular Docking and In-Vitro Analysis

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Currently, there is a lack of therapeutic interventions that can modify the development and progression of Alzheimer's Disease (AD). The thorough pathology of AD remains unclear, creating ample opportunities for research aimed at developing innovative therapeutic approaches for managing the disease. The present research involved a literature survey to identify 100 herbal molecules that could potentially be beneficial in inhibiting Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE), β-Secretase, and mitigating oxidative and inflammatory stress, as well as neurodegeneration. The herbal molecules were screened against AChE, BChE, and β-Secretase using AutoDock Tools-1.5.6 docking software with Protein Data Bank (PDB) ID 1B41, 1P0I, and 1FKN, respectively. After assessing the docking parameters, it was determined that quercetin, rutin, vitisinol-C, dihydrotanshinone-I, and β-carotene exhibited the strongest potential against their respective protein receptors. Additionally, our in-vitro AChE and BChE assay results showed that quercetin and rutin have the ability to modulate cholinergic pathways associated with AD, thus providing potential therapeutic benefits. Our in-vitro studies on neurodegeneration revealed that quercetin and rutin exhibit a neuroprotective effect against neurodegeneration induced by HgCl₂, which suggests that they may have a potential role in protecting against neurodegeneration in AD. Nonetheless, additional preclinical investigations are essential to validate the potential effects of these molecules on AD pathogenesis.

Keywords: Acetylcholinesterase, Alzheimer’s disease, Butyrylcholinesterase, Quercetin, Rutin

Introduction

Alzheimer’s Disorder (AD) is one of the major healthcare concerns that is characterized by dementia and marked cognitive decline.¹ Recent time has witnessed a significant increase in the population affected by this lifestyle disorder, especially in developed and developing nations.² World Health Organization has raised serious concerns regarding the increasing global population of AD. As per the World Alzheimer Report 2021, AD and dementia were reported to be the 7th leading cause of global mortality. It was estimated that 57 million people suffered from AD in 2019, besides, it is estimated that the global burden of AD and dementia will increase to 153 million by the year 2050.³⁴ AD results from progressive neurodegeneration and thereby loss of normal physiological functioning of the brain, especially in the region of the hippocampus and cortex that are associated with learning, memory, and cognitive functions.⁴ Numerous identified pathways are supposed to be openly intricate in the development in addition to progression of AD, however, none of them is capable of fully explaining the underlying pathogenesis of AD. Some of these prominent pathways include neurodegeneration, impaired Acetylcholine, and cholinesterase functioning, oxidative stress, neuroinflammation, etc.² Accumulated evidence suggests that the brain's levels of the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes are dropped down in AD patients that upshots in impaired memory and other clinical implications of AD.⁵ Likewise, reduction in the levels of β-Secretase in the brain has been linked to the development of senile plaques, which is the hallmark of AD. These pathological pathways work in harmony to collectively form a complex interconnected network that contributes to the development and progression of AD.⁶ These pathways are the targets of the currently available AD therapeutic strategy. The majority of the currently available drugs target a single pathway of AD pathogenesis and are aimed at slowing down the progression rate and providing symptomatic relief from AD with negligible effect on the root cause of AD.

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therefore, AD continues to progress throughout life. Considering the current global burden of AD and future estimates along with the lack of an efficient therapeutic strategy to completely halt the development and progression of AD, we need to identify better therapeutic interventions that can target multiple pathways leading to the development and progression of AD at once to get better management of AD.

In traditional medicine, leaf, stems, roots, flowers, fruits, and seeds were used as an alternative and complementary therapy. Some derived components from herbs such as resveratrol, curcumin, ginsenoside, polyphenols, triptolide, etc. have neuroprotective effects. Herbal products contain numerous active components or phytochemicals like flavonoids, alkaloids, isoprenoids, etc., which make it difficult to determine which component of the herb is responsible for the biological activity, which limits the utilization of the bioactive molecule to its full potential. There is a vast potential for natural sources to provide therapeutic solutions for a range of disorders including cancer, diabetes, and CNS-related diseases. Herbal interventions such as Rivastigmine, Bacopa monnieri, nicotine, atropine, muscarine, physostigmine, among others, have demonstrated clinical presentations in managing CNS problems for instance AD. Therefore, in the present study, we used these tools to screen the potential of herbal molecules against neurodegeneration and prime targets of AD like AChE, BChE, and β-Secretase.

As indicated by existing reports, AD is caused by a complex interchange of various pathological pathways that works together. Therefore, the most effective way to discover an improved therapeutic strategy for AD would be to pinpoint molecules capable of targeting multiple pathways. The objective of the current research was to identify molecules capable of targeting multiple pathways leading to AD through the use of in-silico and in-vitro procedures by taking into consideration the major pathways that contribute to the pathogenesis of AD, which include AChE, BChE, β-Secretase, oxidative stress, inflammatory stress, and neurodegeneration.

**Materials and Methods**

**Material**

All the chemicals and reagents used in the present study were of analytical grade. All the chemicals, reagents, and enzymes used in the present study were procured from Sigma Aldrich until mentioned specifically.

**Preparation of the Ligands and Receptors**

For the current molecular docking investigation, a total of 100 herbal molecules were chosen from the literature examination considering their potential to modulate various pathways associated with AD such as AChE, BChE pathway, Tau protein phosphorylation, oxidative stress pathway, inflammatory stress pathway, etc. (Table 1). The 2D and 3D structures of selected ligands and receptors were created and validated in Maestro. The detail of ligands and receptors was listed on Table 1.

**Table 1 — Binding energies (Kcal/mol), RMSD values, and Inhibition constant (Ki) of selected ligands with PDB: 1B41 (Acetylcholinesterase), 1P0I (Butrylcholinesterase), and 1FKN (β-Secretase)**

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Docking Score (Kcal/mol)</th>
<th>Reference RMSD</th>
<th>Estimated Inhibition Constant (Ki)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1B41</td>
<td>1P0I</td>
<td>1FKN</td>
</tr>
<tr>
<td>β Carotene</td>
<td>-11.45</td>
<td>-9.66</td>
<td>-9.14</td>
</tr>
<tr>
<td>Dihydrotanshinone-I</td>
<td>-0.13</td>
<td>-9.08</td>
<td>-8.28</td>
</tr>
<tr>
<td>Donepezil</td>
<td>-9.44</td>
<td>-10.20</td>
<td>-8.97</td>
</tr>
<tr>
<td>Glibridin</td>
<td>-9.40</td>
<td>-9.20</td>
<td>-8.08</td>
</tr>
<tr>
<td>Liriodenine</td>
<td>-8.51</td>
<td>-8.26</td>
<td>-7.83</td>
</tr>
<tr>
<td>Morin</td>
<td>-7.65</td>
<td>-8.57</td>
<td>-7.05</td>
</tr>
<tr>
<td>N-Formylalanine</td>
<td>-2.65</td>
<td>-2.88</td>
<td>-2.91</td>
</tr>
<tr>
<td>Quercetin</td>
<td>-7.98</td>
<td>-8.24</td>
<td>-7.03</td>
</tr>
<tr>
<td>Quercitin</td>
<td>-7.80</td>
<td>-8.89</td>
<td>-7.23</td>
</tr>
<tr>
<td>Rutin</td>
<td>-7.97</td>
<td>-11.36</td>
<td>-7.64</td>
</tr>
<tr>
<td>Vitisinol C</td>
<td>-9.63</td>
<td>-10.59</td>
<td>-10.05</td>
</tr>
</tbody>
</table>
herbal molecules were generated through Chemdraw Ultra 7.0 software and Marvin sketch software. To analyze all the herbal molecules against AChE, BChE, and β-Secretase, we utilized the AutoDock tools-1.5.6 docking software with Protein Data Bank (PDB) ID 1B41, 1P0I, and 1FKN, respectively, with a resolution of 2.7, 2.5, and 1.9 Å. Selected molecules were converted to .pdbqt format by adding gasteiger charges to the ligands. Receptor preparation was performed according to the method described previously by Trott and Olson  in which atomic charges, fixed bond, Kolman charges, and hydrogens were added to the proteins and converted to a .pdbqt format, which stores the partial charges for further docking studies.

**Molecular Docking**

The docking was performed with AutoDock tools-1.5.6 docking software in which three prepared protein targets, 1B41, 1P0I, and 1FKN, were docked with 100 herbal molecules along with an internal standard. Docking grids were created by adjusting the size of the grid box, which will pick the coordinates i.e. center x = 25.378, center y = 11.101, center z = 31.782, size x = 60, size y = 60 and size z = 60 within which the docking of ligand and protein was performed. The autogrid and AutoDock widgets were used to prepare the docking and grid files. Finally, docking parameter files and docking log files were generated by running the autogrid and AutoDock widgets to check the molecular interaction between ligand and protein molecules. The binding energy (Kcal/mol) was used as a measure to evaluate the outcomes of the docking study of the different conformations of ligands with the receptors, amino acid interactions, and bond length. To visualize results, PyMOL molecular graphics system and Protein-Ligand Interaction Profiler (PLIP) open-source web server were used.

**In-Vitro Evaluation**

We screened and identified quercetin, rutin, β-carotene, sumaflavone, and vitisinol-C to be most efficient in targeting 1B41, 1P0I, and 1FKN through docking studies. To narrow down the screening process, these molecules were then subjected to in-vitro testing on prominent pathways associated with the pathogenesis of AD. These pathways include neurodegeneration and cholinesterase activity in terms of AChE and BChE activity.

**In-vitro Neurotoxicity Assay**

The effect of the herbal molecules on the HgCl₂-induced neurotoxicity was evaluated on Neuro-2a cell lines in a 96-well plate by using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) as per the method described previously. Briefly, cells were incubated till 70% confluency in EMEM media. Growth media was replaced with serum-free EMEM media and 10 µl of different concentrations (300 µM) of the herbal molecules were added to each well. An equal volume of phosphate buffer saline (PBS; pH 7.4) was used for the control reaction well. Culture plates were incubated inside humidified CO₂ incubator at 37°C for 6 h. Incubated cells were then treated with 25 µM HgCl₂ to induce neurotoxicity. Cultures were allowed to grow for 24 h inside a CO₂ incubator at 37°C. Afterward, culture media was removed and cells were washed with PBS thrice. The culture was then incubated at 37°C for 3 h with 100 µl serum-free EMEM having 5 mg/mL MTT. This was followed by cell lysis with DMSO and the absorption of the formazan was recorded spectrophotometrically at 570 nm. The entire experiment was performed in triplicate and the percent neuroprotection was calculated.

### Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) Inhibitory Assay

Herbal molecules were further screened for their potential against AChE and BChE enzymatic activity as per the methods described previously, with slight modification. In both of these experiments, donepezil was used as a positive control. Briefly, the stock solutions of the herbal molecules (0.1M) and donepezil were prepared in PBS and stored at 4°C until used. The working dilutions were prepared from the stock solution by proper dilution with PBS. The inhibition of AChE and BChE activity was evaluated in a 96-well plate using 5,5'-Dithiobis-2-Nitrobenzoic acid (DTNB) or Ellman’s reagent. Each reaction mixture was composed of 25 µl enzyme solution (AChE or BChE) prepared as 25 mU enzyme in PBS, 75 µl DTNB prepared in PBS and stored at 4°C. Incubated cells were then subjected to 10 min after which 25 µl of 0.075 M HgCl₂ to induce neurotoxicity. The reaction mixture was incubated at 37°C for 10 min after which 25 µl of 0.075 M substrate (acetylthiocholine iodide for AChE and butrylthiocholine iodide for BChE) was added to initiate the reaction. Enzymatic activity was recorded spectrophotometrically at 412 nm over 4 min. Percent inhibition of AChE or BChE activity was calculated using the following equation:

\[
\% \text{AChE or BChE inhibition} = \frac{(\text{Abs of control} - \text{Abs of test})}{\text{Abs of control}} \times 100
\]
Inhibiting AChE which provides symptomatic relief from AD and results in increasing the ACh levels in the synapse, enhancing ACh levels by inhibiting AChE which lowered and clinical management of AD includes avoiding any variations in the standard for comparison. Donepezil as an internal standard for all receptors to respectively) by using AutoDock tools. We used the 10 best molecules based on the outcome. The molecules include β-carotene, dihydrotanshinone I, glabridin, liriodenine, morin, N-formylanonaine, quercetin, quercitrin, rutin, and vitisinol C. To get more prominent and confirmatory data for these molecules, these herbal molecules were subjected to molecular docking screening against AChE, BChE, and β-secretase (PDB ID: 1B41, 1P0I, and 1FKN respectively) by using AutoDock tools. We used Donepezil as an internal standard for all receptors to avoid any variations in the standard for comparison.

During AD, the levels of ACh in the brain are lowered and clinical management of AD includes enhancing ACh levels by inhibiting AChE which results in increasing the ACh levels in the synapse, which provides symptomatic relief from AD and slows down the disease progression.7 Inhibiting AChE in the brain is one of the most common therapeutic strategies employed in clinical settings to enhance cholinergic signaling during AD.7 The docking interaction results of 1B41 (AChE) are represented in Table 1 and Fig. 1. In our study, β-Carotene and Vitisinol C demonstrated the least binding energy with the target protein with docking scores of −11.45 Kcal/mol and −9.63 Kcal/mol respectively. These molecules interacted with various amino acids like ARG 292, SER 199, VAL 278, and GLY 117, suggesting their potential to modulate the activity of AChE. The docking score of the standard drug, donepezil, was observed to be −9.44 Kcal/mol, which was comparable to dihydrotanshinone I (−9.13 Kcal/mol) and glabridin (−9.40 Kcal/mol). Interestingly, the binding energy of quercetin with the target receptor was observed to be on the slightly lower side (−7.98 Kcal/mol), but it demonstrated interaction with PRO 286, ARG 243, and THR 234, suggesting its strong potential to modulate receptor activity. RMSD values of the herbal molecules were observed in the range of 0.00 to 1.0 and were comparable to donepezil, suggesting good interaction. Moreover, Ki values of the herbal molecules were observed in the range of 4.07 nm to 11.39 mM, and β-carotene (4.07 nM) and vitisinol C (87.14 nM) demonstrated better Ki values than donepezil (202.11 nM).

Along with AChE, recent findings suggest that BChE also plays a crucial role in regulating ACh levels in the brain.17 Along with this, BChE is associated with other AD pathways such as β-amyloid plaque deposition, etc.18 The docking interaction results of 1P0I (BChE) are represented in Table 1 and Fig. 2. In this study, the best results were observed for rutin and vitisinol C, which demonstrated a docking score of −11.36 Kcal/mol and −10.59 Kcal/mol, respectively. These results were better than the internal standard which demonstrated a docking score of −10.20 Kcal/mol. Moreover, rutin and vitisinol C demonstrated strong interaction with amino acids like SER195, GLY 114, THR 117, TYR 125, GLU 194, TYR 329, and GLY 436. Docking interaction of β-carotene, dihydrotanshinone I, glabridin, and quercitrin was observed in the range of −8.89 Kcal/mol to −9.66 Kcal/mol, which was comparable to the standard drug. RMSD values of the herbal molecules were observed in the range of 0.00 to 0.94, suggesting good interaction. Ki values of the herbal molecules were observed in the range of 4.73 nM to 7.79 mM. Rutin (4.73 nM) and vitisinol C (4.73 nM) demonstrated better Ki values than donepezil (33.18 nM), suggesting that these molecules can efficiently inhibit BChE to impart their beneficial effects.

The docking interaction results of 1FKN (β-Secretase) are represented in Table 1 and Fig. 3. β-secretase enzyme majorly involves the cleavage of amyloid precursor protein which ultimately forms the β-amyloid plaques.19 β-amyloid plaque deposition is the key factor that leads to AD progression.20 Our
results demonstrated the best docking interaction for viticinol C (−10.05 Kcal/mol) and β-carotene (−9.14 Kcal/mol) that was better than the donepezil (−8.97 Kcal/mol). Moreover, the docking interaction of dihydrotanshinone-I and glabridin was comparable to the standard and was observed to be −8.28 Kcal/mol and −8.08 Kcal/mol, respectively. RMSD value and Ki values for the herbal molecules were observed in the range of 0.00 to 1.00 and 42.94 nM to 7.35 mM, respectively, suggesting efficient ligand-protein interaction.
Overall, the results of the docking study suggest that viticinol C, β-carotene, rutin, dihydrotanshinone-I, and glabridin are having a strong potential to interact with AChE, BChE, and β-secretase and thereby could exploit these pathways to impart beneficial effects during AD pathogenesis.

Effect of Herbal Molecules on HgCl₂-induced Neurotoxicity

Our research focused on HgCl₂, a widely recognized neurotoxin that can cause neuronal damage similar to the effects seen in AD, such as necrosis, apoptosis, and damage to the neuronal cytoskeleton. In our research, we used 25 μM HgCl₂.
to inflict neuronal damage in Neuro-2a cell lines and evaluated the neuroprotective effect of herbal molecules in terms of percent cell viability. The results are depicted in Fig. 4 and the results indicate that quercetin and rutin are the most promising molecules that are capable of rescuing neurons from neurodegeneration.

Our results of the MTT assay demonstrated marked neuronal destruction in the cells treated with HgCl₂ as suggested by the significantly (p < 0.001) reduced formazan formation in these cells when compared to the control. The cells treated with quercetin, and rutin showed significantly (p < 0.001) higher formazan formation in the MTT assay when compared to the control, which indicates a higher viable cell count in the cells treated with these molecules. Percent cell viability was observed to be 92.59 ± 2.00 for quercetin and 87.18 ± 0.92 for rutin. β-carotene,
sumaflavone, and vitisinol C also imparted significant (p < 0.001) neuroprotection against HgCl$_2$-induced neurodegeneration with the percent neuroprotection of 68.42 ± 2.87, 53.56 ± 1.94, and 39.95 ± 2.09, respectively, however, the results were not as promising as those observed for quercetin and rutin. These results are in line with the previous findings where quercetin and rutin have been reported to possess good neuroprotective effects. The findings indicate that quercetin and rutin are effective in shielding neurons from the neurodegenerative impact of HgCl$_2$ neurotoxin, which is similar to the degenerative pattern seen in AD, including, apoptosis, necrosis, and cytoskeletal loss, therefore, they could be considered as a potential measure to prevent neurodegeneration in AD. Previously, HgCl$_2$ has been demonstrated to impart neurodegeneration and is a valuable tool to screen drugs for their neuroprotective effects. Our results are in line with previous reports where quercetin and rutin have been demonstrated to rescue neurons from neurodegeneration and provide beneficial effects during AD.

Effect of Herbal Molecules on AChE Activity

Targeting AChE is one of the most promising approaches utilized in the clinical setting for the management of AD. In-vitro inhibition of AChE activity is one of the most widely used methods to screen molecules with the potential to target the AChE enzyme. It is based on the detection of the formation of 5-mercapto-2-nitrobenzoic acid spectrophotometrically as a result of the reaction between DTNB and thiocholine (formed as the result of the AChE-mediated hydrolysis of the substrate). The results of the effect of herbal molecules on AChE activity are demonstrated in Fig. 5 (A) in terms of IC$_{50}$ values. Our results demonstrated donepezil as the most potent molecule to inhibit AChE activity as indicated by the IC$_{50}$ value of 39.62 nM. Donepezil is a well-known inhibitor of AChE and our results agree with the previous findings where donepezil has demonstrated strong inhibition of AChE activity in in-vitro settings. Our results demonstrated quercetin and rutin to be the most potent herbal molecules to inhibit AChE activity and the IC$_{50}$ values for these...
molecules were observed to be 192.96 ± 17.54 µM and 335.07 ± 21.12 µM, respectively. Although the IC_{50} values for these molecules are significantly higher than donepezil, still having IC_{50} values in this range suggests these molecules be a strong inhibitor of AChE activity. These findings are in line with previous findings where quercetin and rutin have been reported to possess the good potential to inhibit AChE activity in in-vitro, pre-clinical settings, and clinical settings. β-carotene, sumaflavone, and vitisinol-C also resulted in a dose-dependent inhibition of AChE activity, and their IC_{50} values (508.60 ± 43.10, 694.18 ± 31.58, and 1009.87 ± 136.30, respectively) were observed to be higher than quercetin and rutin. These results suggest that quercetin and rutin could find an application in AD management by inhibiting AChE, as the inhibitors of AChE are known to slow down the progression of AD and are efficient in delaying AD onset. Further, both of these molecules are excellent antioxidants and therefore could impart additional benefits in AD pathogenesis by reducing oxidative stress, which is one of the critical pathways leading to neurodegeneration during AD.

Effect of Herbal Molecules on BChE Activity

BChE is another enzyme that is known to affect the cholinergic signaling in the brain and has been demonstrated to play a critical role in the pathogenesis of AD. Like the AChE assay, in-vitro inhibition of BChE activity is one of the most widely used methods to screen molecules with the potential to target the BChE enzyme. It is also based on the detection of the formation of 5-mercapto-2-nitrobenzoic acid spectrophotometrically as a result of a reaction between DTNB and thiocholine (formed as a result of BChE-mediated hydrolysis of butyrylthiocholine iodide). The results of the effect of herbal molecules on BChE activity are demonstrated in Fig. 5 (B) in terms of IC_{50} values. Our results demonstrated donepezil as the most potent molecule to inhibit BChE activity as indicated by the IC_{50} value of 142.52 ± 18.42nM. Although donepezil is a well-known inhibitor of AChE, it also has good potential against the BChE enzyme. Our results are in agreement with the previous findings where donepezil has demonstrated strong inhibition of BChE activity in in-vitro settings. Our results suggest that BChE activity is inhibited by donepezil, however, it has a significantly lower affinity for BChE than that observed for AChE. BChE and AChE are crucial for the normal functioning of the cholinergic system in the brain. According to studies, BChE functioning in the brain show gradual impairment with the progression of AD, suggesting its importance in the pathogenesis of AD. Our results demonstrated quercetin, rutin, and β-carotene to be the most potent herbal molecules to inhibit BChE activity in a dose-dependent manner, and the values in terms of IC_{50} for these molecules were observed to be 321.32 ± 6.44 µM, 355.61 ± 20.37 µM, and 411.46 ± 27.65 µM, respectively. Compared to donepezil, IC_{50} values for these molecules are higher, still, IC_{50} values in this range suggest these molecules to be a potential inhibitor of BChE activity. These findings are in line with previous findings where rutin, quercetin, and β-carotene have been reported to possess the good potential to inhibit BChE activity in in-vitro, pre-clinical settings, and clinical settings. Sumaflavone and vitisinol-C also resulted in dose-dependent inhibition of BChE activity, and their IC_{50} values (1299.95 ± 170.19 µM, and 1038.05 ± 119.37 µM, respectively) were observed to be on the higher side when compared to other molecules suggesting their lower potential to inhibit BChE activity. These results suggest that rutin, quercetin, and β-carotene could find an application in AD management by inhibiting BChE, as inhibitors of BChE are known to impart beneficial effects in the pathogenesis of AD. Further, rutin, quercetin, and β-carotene are excellent antioxidants and therefore could impart additional benefits in AD pathogenesis by reducing oxidative stress which is one of the critical pathways leading to neurodegeneration during AD.

Conclusions

The present study suggests that herbal molecules have the potential to target multiple pathways that contributes to the pathogenesis of AD and therefore could be beneficial in managing the development and progression of AD. Docking screening of the herbal molecules against AChE, β-secretase, and BChEsuggests that quercetin, rutin, sumaflavone, vitisinol-C, and β-carotene are having good affinity against these targets. These findings were further consolidated by the observed RMSD and Ki values of these molecules, which were comparable to the internal standard. These results suggest that these molecules could be beneficial in managing AD pathogenesis by interfering with AChE, BChE, and β-secretase pathways during AD. The results of the in-vitro neurodegeneration studies demonstrated quercetin and rutin to be the most potent molecules to rescue neurons against HgCl_{2}-induced
neurodegeneration. Moreover, quercetin and rutin were efficient in inhibiting AChE and BChE enzymatic activity in-vitro, suggesting that these molecules have the potential to regulate cholinergic pathways in AD, which may lead to beneficial effects in the treatment of the condition. Overall, based on the findings of the current study, we propose quercetin and rutin as promising molecules which could interact with multiple pathways of AD pathogenesis to impart their beneficial effects. However, the findings demonstrate in the present study are preliminary and need to be further justified extensively through preclinical investigation to reach a decisive conclusion about their potential against AD pathogenesis.

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References


