Review of: "Design and Molecular Screening of Various Compounds by Molecular Docking as BACE-1 Inhibitors"

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Potential competing interests: No potential competing interests to declare.

Reviewer comment

In this study, the authors use molecular docking to study the interaction of quercetin, myricetin, & baicalein, ferulic acid, and donepezil with the BACE-1 protein and found that these compounds exhibit binding affinity, showing that they can fit better in the active site of BACE-1. According to the authors, these findings represent a major breakthrough in Alzheimer's disease research.

This paper appears to be interesting but needs a major revision. It cannot be accepted in its current form; therefore, further corrections are required following the comments listed below :

1. In the introduction, I understand that the authors want to clarify the β-amyloid hypothesis by using the colon; I would suggest the authors rewrite in their own words, removing the double colon in

β-amyloid hypothesis: The β-amyloid is a by-product of the protein Amyloid Precursor Protein (APP), whose function is believed to be involved in neuronal degradation.

1. The images in Figs.3-22 are not of good quality; the authors can revise or use another GUI that can provide beautiful images.
2. The authors can also present the molecular structures of the five US-FDA approved drugs, e.g., donepezil, rivastigmine, tacrine, galantamine, and memantine.
3. The authors should also correct several typos, as, for instance, leaving single spaces between words as illustrated in these sentences: "The drug most extensively researched and useful in all stages of AD isDonepezil", "The results of the enzyme inhibitions exhibit that electron-withdrawing groups like Cl, F can render the best effect at the ortho and para positions of the phenyl ring.Introduction of the basic nitrogen to the", "Natural compounds are an emerging approach for AD therapy.During the 90s,"" Future clinical trial efforts should instead focus on applying natural products to anti-amyloid treatment strategies for thepreclinical disease (the earlier the better).", " Ferulic acid (4-hydroxy-3-methoxycinnamic acid, FA) is a widely distributed constituent of plants. Ferulic acid (FA) is an antioxidant naturally present in plant cell walls with anti-inflammatory activities, and it is able toact as a free radical scavenger",

"Based on the above literature study and etiology of the disease,BACE-1 enzyme is selected as an important therapeutic target for AD in the development of inhibitor drugs for reduction of Aβ.Small molecules that may be inhibitors are designed

to be complementary to the target binding site."

1. Can the authors clarify this "On site 3 of the benzene ring, as mentioned in the above structure, modification in that part can lead to a strong acetylcholinesterase inhibitor"? Once again, the image is not of good quality.
2. Greater trial failures highlight the need for different approaches to AD therapy. Till date, amyloid-based therapeutics appear to be ineffective in modifying the disease course for AD. Future clinical trial efforts should instead focus on applying natural products to anti-amyloid treatment strategies for the preclinical disease (the earlier, the better).

This is a strong statement. If there are no references, the authors can clarify this by specifying that this is their opinion.

1. The authors mention that various flavonoids (galangin, myricetin, baicalein, quercetin), alkaloids (berberine), terpenes, curcumin, ferulic acid, etc., may exhibit potential BACE1 inhibition but select some from their study. If they can justify their choice in the text and why they did not consider galangin or curcumin, for instance.
2. References are needed for some sentences

e.g., The flavonoids like quercetin, myricetin, and baicalein contain considerable pharmacological effects (Fig. 6).

Myricetin (3,3′,4′5,5′,7-hexahydroxylflavone) is a common natural flavonoid found in many fruits, vegetables, and herbs.

Shimmyo et al. have reported that myricetin has dual activity, as it can directly inhibit BACE1 activity without affecting protein expression, and showed activation of α-secretase in a cell-free enzyme activity assay.

1. In silico drug design of various natural products like flavonoids (myricetin, baicalein, quercetin), ferulic acid, and donepezil (here taken as standard) was chosen as the lead molecule because they form hydrogen bonds and π-π interactions with our target. How can the authors know that these molecules form these types of interactions with their target without performing the docking calculations to justify their initial choice of these flavonoids?
2. The authors can explain the validity of their calculated ADMET scores to evaluate the chemical drug likeness of their compounds.
3. The authors should specify which kind of docking they performed, blind or flexible, and why.
4. The authors can also explain how they validated their docking results.
5. The authors should keep the same reference styles and add missing references in the section related to materials, molecular docking, and construction of a chemical library of compounds.
6. How were the initial geometries obtained before docking calculations were performed? Were the geometries used local or global minima, and which theory was used for optimization, and how and why? The sites 1-3 in Fig.9 are not clearly explained and elucidated.
7. Several sections contained repeating words which tend to annoy and distract the reader. The authors should take care with this and avoid redundancies.
8. The ligands exhibiting a cutoff score of 8.3 and above were selected. The authors should justify their choice of binding energy cutoff and also identify and provide explanations for the main weak interactions observed in different ligand-protein complexes.
9. I suggest the authors to run molecular dynamics calculations on some selected best ligand-protein candidates and add

a section before the conclusion where they can discuss the results obtained from different dockings.

10. The conclusion is not well written.