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.

The article deals with MD (in silico/computational) studies of BACE-1 inhibitors, which could lead to newer avenues of AD treatment, considering that the current drug candidates have been stopped at phase-3 clinical trials. This is to say that the reports of new potential targets of BACE-1 are highly important for the treatment of AD, the major neurodegenerative disease to date. However, we need to keep in mind that new avenues of effective treatment will most likely be reached by a combination of safe drugs targeting all possible pathways leading to AD. In this regard, in silico studies must be completed by in vitro studies, and the findings confirmed in vivo (animal models of disease) before translating a possible breakthrough discovery to humans.

Thus, the present article provides just an overview of potential BACE-1 inhibitors; it is, however, comprehensive, overall well-written, and presented. The pertinence, albeit the methodological strategy and idea are not too original, therapeutic strategy, is highlighted. Some figures and tables could be, however, improved. The conclusions are supported by the data, the methodology has been fairly used, although advanced tools could have been used, including to assess ADMET. Also, it will be valuable to mention (in the article) updates about recent AD therapeutics and also specify in which foods the selected compounds (potential BACE-1 inhibitors) are mostly found. I did not notice any ethical issues. The references should be updated, including with the following key articles:

1- Althobaiti NA, Menaa F, Dalzell JJ, Albalawi AE, Ismail H, Alghuthaymi MA, Aldawsari RD, Iqbal H, McAlinney C, Green BD. Ethnomedicinal Plants with Protective Effects against Beta-Amyloid Peptide (Aβ)1-42 Indicate Therapeutic Potential in a New In Vivo Model of Alzheimer's Disease. Antioxidants (Basel). 2022 Sep 21;11(10):1865. doi: 10.3390/antiox11101865. PMID: 36290588; PMCID: PMC9598277.

2- Althobaiti NA, Menaa F, Dalzell JJ, Green BD. *Globodera pallida*, a non-transgenic invertebrate as a new model for investigating Alzheimer's disease (and other proteinopathies)? Neural Regen Res. 2023 Jan;18(1):113-114. doi: 10.4103/1673-5374.341042. PMID: 35799520; PMCID: PMC9241411.

3- Althobaiti NA, Menaa F, Albalawi AE, Dalzell JJ, Warnock ND, Mccammick EM, Alsolais A, Alkhaibari AM, Green BD. Assessment and Validation of *Globodera pallida* as a Novel In Vivo Model for Studying Alzheimer's Disease. Cells. 2021 Sep 19;10(9):2481. doi: 10.3390/cells10092481. PMID: 34572130; PMCID: PMC8465914.

4- Chennai HY, Belaidi S, Bourougaa L, Ouassaf M, Sinha L, Samadi A, Chtita S. Identification of Potent Acetylcholinesterase Inhibitors as New Candidates for Alzheimer Disease via Virtual Screening, Molecular Docking,

Dynamic Simulation, and Molecular Mechanics-Poisson-Boltzmann Surface Area Calculations. Molecules. 2024 Mar 10;29(6):1232. doi: 10.3390/molecules29061232. PMID: 38542869.

5- Conti Filho CE, Loss LB, Marcolongo-Pereira C, Rossoni Junior JV, Barcelos RM, Chiarelli-Neto O, da Silva BS, Passamani Ambrosio R, Castro FCAQ, Teixeira SF, Mezzomo NJ. Advances in Alzheimer's disease's pharmacological treatment. Front Pharmacol. 2023 Jan 26;14:1101452. doi: 10.3389/fphar.2023.1101452. PMID: 36817126; PMCID: PMC9933512.

6- https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(22)00298-8/abstract

7- Nguyen, TD., Dang, L.N., Jang, JH. *et al.*Recent advances in Alzheimer’s disease pathogenesis and therapeutics from an immune perspective. *J. Pharm. Investig.***53**, 667–684 (2023). https://doi.org/10.1007/s40005-023-00631-0

Decision: considering the importance of the topic, the journal, and the overall presentation of the article, I would recommend the article with Minor Revisions.

Best,

The Reviewer