Review of: "Targeting Alzheimer's disease hallmarks with the Nrf2 activator Isoeugenol"

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Potential competing interests: No potential competing interests to declare.

Overall, this is an extremely elaborate, generally well-written, and interesting study, though some shortening is needed in both the Introduction and Discussion parts. It will be a good idea to separate the materials into subgroups (experiment-wise) in the Materials subsection of the Material and Methods section. Otherwise, it may be confusing for non-specialist readers. The authors should also try to explain how isoeugenol as a potential therapeutic agent is different from several other proposed agents of the past. How is the Nrf2 pathway a standout among several alternative pathogenetic pathways proposed for AD? In other words, what will be the actual translatability of this treatment modality when a shift is made from preclinical to clinical studies.

1. In the Abstract, “in the past decades, recent reports” is repetitive, and any one may be used.
2. The authors mention skin allergen twice in the Abstract, while describing DMF and isoeugenol. Is there a link they want to emphasize between the two?
3. Since the authors focus on Nrf2, highlight points 1 and 2 may be swapped.
4. In the Introduction, “responsible for the transmission of information and movements,” is unclear.
5. In “in 2019 it was ranked as the sixth leading cause of death (Heron, 2021).”, a reference for 2019 should be provided.
6. “presence of allele 4 of the apolipoprotein E gene ” should be rephrased as “presence of the apolipoprotein E4 allele.”
7. In “As a consequence of the neurodegeneration process and synaptic dysfunction, neuroinflammation with activation of microglial cells and oxidative stress occurs”, is oxidative stress a cause or result of the neurodegeneration process? Accordingly, the sentence needs rephrasing.
8. In “Recently, the United States Federal Agency Food and Drug Administration (FDA) approved two antibodies designed to clear Aβ from the brain and block the formation of amyloid plaques (Song et al, 2022), ”, the original approval references of the FDA should be ideally given. The antibodies should also be named.
9. The Introduction is too long for an original research article. The authors may shorten it to the pathophysiological role of Nrf2 in AD and what they aim to show.
10. The last part of the Introduction is to be put in the Discussion and Conclusion. Findings are not to be discussed in the Introduction.
11. How were the “Amyloid beta 40 Human ELISA kit and the Amyloid beta 42 Human ELISA kit” human kits used for estimating animal levels of A beta?
12. “Moreover, Iso treatment significantly decreased Aβ40 peptide levels (Fig. 2A), compared to untreated cells (N2a-APPswe), although no effect was observed on Aβ42 peptide levels (Figure 2B).” This needs explanation.