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.

The present study shows the influence of the Keap1-Nrf2 pathway on the development of Alzheimer's disease and the influence of isoeugenol on this. I would like to congratulate the authors on their hypothesis, the conduction of assays, and the relevance of their findings. Here are some thoughts about the study in order to improve it:

1 - Refer to Alzheimer's disease as AD throughout the manuscript, including in the abstract;

2 - In the BBB permeation study, the concentrations must be in micromolar for better comparisons.

3 - Cells were pre-treated with isoeugenol. In a translational way, wouldn't it be better to use a post-treatment with eugenol, seeking a substance that impairs the progression of AD?

4 - There is no reference for the in vivo dose of isoeugenol (mg/kg). Are there previous results of toxicity? Were metabolic parameters measured with animal samples used for toxicity evaluation? The same for the histological analysis.

5 - In the histological analysis, the alterations referred to in the text must be presented in images.

7 - Include in the discussion more natural products that modulate the Keap1-Nrf2 pathway in AD or other neurodegenerative disorders.

8 - What advantages would intranasal administration offer for AD patients when compared to oral administration?

Congratulations on the excellent study!