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.

In the article “Targeting Alzheimer´s disease hallmarks with the Nrf2 activator Isoeugenol,” the authors have demonstrated the beneficial effect of Isoeugenol (Iso) in Alzheimer's disease. They have shown its effect on the N2A cell line and subsequently in a mouse model of Alzheimer's disease. The authors have used various experiments to determine the inflammatory, antioxidant, pharmacokinetic, and pharmacodynamic properties of Iso. The authors also show its effect on the activation of proteins that are beneficial in disease models. They also showed a reduction of Aβ peptides in cell ($A\beta_{40}$) and animal ($A\beta_{40}$ and $A\beta_{42}$) models. The changes suggested below will help to further improve the quality of the manuscript.

1. In section 3.3: The authors should mention the phosphorylated residue in the GSK3β phosphorylation antibody either in the Materials and Methods or in the Results section.

2. On page 17: Citoplasmatic/cytoplasmatic – both words are incorrect and can be replaced with cytoplasmic in the figure and text.

3. In figure 4: In figures 4C and 4D blots, the bands for HMOX1 are not properly visible to me. If the authors have any other good quality representative blots, they should substitute this figure with a better one or enhance the quality of the existing blot.

4. Figures 8A, 8B, and 8C are not described in the Results section.

5. For figure 11B, the authors can elaborate and describe in the Results section what they mean by “increased cell activation in the brain.”

6. After Figure 12, the consecutive figures are not labelled in the correct order.

7. On page 29: In the text of the results, Fig 10A-C is not labelled correctly. It should be labeled as figures 13A-C after the correct numbering order, and other similar mistakes in numbering should be checked and corrected.

8. In Figure 15 (which should be corrected to figure 16): The bar for the Vehicle treatment in the APP/PS1 group is not shown/visible in the graphs. The authors can recheck the graph.

9. On page 35: In the sentence “These Nrf2 activators are electrophilic molecules…,” the words “an undissociated Nrf2-Keap1 complex” can be replaced by “the dissociation of the Nrf2-Keap1 complex.”

10. On page 36: A few spelling mistakes to correct

a. “Investigates” should be written as “investigated.”

b. “animal’s” should be written as “animals.”