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 manuscript entitled “Targeting Alzheimer's disease hallmarks with the Nr2 activator Isoeugenol” widely describes the preclinical evaluation of Isoeugenol both in vitro and in vivo in AD models. Particularly, special emphasis has been given to pharmacokinetic and metabolic investigations after intranasal administration. The work herein reported is impressive, and the results achieved are of interest for the community, but several improvements are needed to better clarify and present the most important experimental outcomes.

- Abstract and introduction are too long and should be more concise. Particularly, in the introductory section, a lot of details are given which are not essential for readers. Moreover, in the last part of the introduction, there is no need for listing the following experiments (the same thing happened at the beginning of the discussion) and major results (reported both in the discussion and conclusion thereafter).
- DMF should be included as a positive control for Nrf2 activation and in vivo evaluation to further confirm the potency and promising profile of isoeugenol in comparison with a proved Nrf2 activator.
- The concentration of isoeugenol exploited should be reported in every graph and caption for reasons of clarity.
- I suggest moving the BACE1 experiment to the supplementary material and avoiding correlations between the experimental outcomes and the BACE1 inhibitory potency since it's very low and at the concentrations used, a lot of other unexplored targets could be modulated and responsible for the observed biological results.
- In section 3.3 and the discussion, it is not clear if the proposed eugenol mechanism is through electrophilic addition to Keap1 or the AKT/GSK axis. Furthermore, it's better to clarify and only refer to AKT and GSK phosphorylation and not to “activation” or “overactivation” because they are not proved here.
- An important discrepancy occurs between Figure 6B and 12B. One is negative, and the other is positive, but throughout the manuscript, it is always referred to as the same decrease of body weight loss. These discrepancies should be better clarified.
- There are too many differences among the Aβ42 and Aβ40 experiments and the obtained results, which should be better described and justified, with a particular focus on Aβ42 because of its leading role in driving neurotoxicity: No variation in vitro after Iso treatment, reduction in the brain but not in plasma in 6-month-treated mice, reduction in plasma but not in the cortex and hippocampus in 11-month-treated mice. A tentative explanation should be reported for these significant differences.
- Differences of gender among the different in vivo experiments don't help in discussing the obtained results.