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.

Alzheimer´s disease (AD) is a neurodegenerative disease characterized by the loss of homeostatic functions related to redox and energy metabolism, neuroinflammation, proteostasis, et al. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) regulates these functions and is compromised in AD. Since no cure or treatment for dementia, thus, Nrf2 has been considered an attractive molecular target for AD therapeutic research. Ana Silva et al showed that Isoeugenol (a low molecular weight skin allergen) activates Nrf2 and displays antioxidant and anti-inflammatory effects and reduced the levels of Aβ peptides. Moreover, Isoeugenol improved the memory deficits observed in APP/PS1 mice, which was more evident in older animals (11-month-old), reinforcing its potential in ameliorating AD hallmarks, even at a late stage. Isoeugenor is a well chose candidate for AD models and has the potential for treatments. This manuscript was well designed and executed.

Major comments:

1) If Isoeugenol has the potential for treatments, it is better comparing its effects with currently used drugs, dimethyl fumarate or others. If not for all experiments, at least for some.

Minor comments:

2) At Fig 1 (page 14).

It will be better to present all three experiments, not just one.

3) Isoeugenol was used at very high concentration (up to 500 μM) in both in vitro and in vivo experiments; its potential non-specific toxicity is a concern. For example, at Table I (page 15) isoeugenol (250 μM) is less effective as β-Secretase inhibitor IV (15 nM), even at more than 10000 times higher concentration. The inhibition may be related to its non-specific toxicity.

4) At Results section, 3.2. Isoeugenol reduces Aβ40 peptide levels in an AD cell model (page 15).

24 hr evaluation of toxicity is not enough, should be extended to 4 days. No specific toxicity usually takes longer time to show up.

5) At Fig 2 (page 15). Isoeugenol reduces Aβ40 level but not Aβ42 in vitro experiments. At Fig 7 (page 20). Isoeugenol reduces both brain Aβ40 and Aβ42 level in AD mice model. What’s explanation for this?

6) For western blot comparison (Fig 3, 4 and 5) (page 16-19), it is better to run the samples together at the same gel, not separately.

7) At Fig 6A (page 20).

Claim of “Isoeugenol decreased the body weight” may be not right because less body weight at APP/PS1+Iso group without Isoeugenol treatment (time 0) than APP/PS1 group.

8) At Fig 13 (page 30-31).

How the authors define the base line? For example: Fig 13A, h-APP mRNA level is below base line at WT group, but above base line at APP/PS1 group. Fig 13B, Bacce1 mRNA levels are above base line at both WT and APP/PS1 group. Fig 13C, Hmox1 mRNA levels are below base line at both WT and APP/PS1 group.

9) At Fig 2, 3, 4, 5, 7 8, 10, 12, 13, 14, 16, and 17.

There is a lot of data comparison. When indicate the statistical significance, it is better marked the comparison groups, not at one bar.

10) There is two Fig 12, I believe it is mislabeled.