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.

Minor comments

Abstract. Include in the last paragraph, the source of the isoeugenol (plant species).

Introduciton.

Pg. 3. 1st paragraph, AChE inhibitors, please include IC50 to compare dosages with those found in this isoeugenol study.

Pg. 4. Any clinical study avaialable in clinicaltrials.gov or in literature about the potential of isouegenol to investigate effects in AD context?

Materials.

Isoeugenol, purity ok, and supplier is Sigma, please include the species of origin.

Results.

No major comments. Very interesting results on adipose tissue, liver enzymes, cholesterol etc.,

Discussion

Pg. 36. Is it possible to include a figure of the mechanistic study possibilities? to enrich the discussion and to compare isoeugenol with other NRF2 activators (e.g. Isothiocyanates) in the AD context?

Conclusions.

The conclusive remarks are very positive (rewordy anyway) and the physiological relevance or potencial dosages to be

used in human trials it should be also included.

Evidence on absorption, distribution, metabolism, and excretion of isoeugenol in humans is sparse and limited to dermal exposure. In rodents, after oral and dermal exposure, isoeugenol is rapidly absorbed and excreted predominantly in the urine as glucuronide or sulfate conjugates, with little retention in tissues. The high dosages tried in the animals (100mg/kg), how can we express that in mg/kg human adult? Is it possible to extrapolate? safety/tox issues?

In B6C3F_1 mice and F344 rats exposed by oral administration (gavage), isoeugenol caused hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in male mice; a significant increasing trend in histiocytic sarcoma (multiple sites) in female mice; and a significant increasing trend in mammary gland carcinoma and benign or malignant thymoma in male rats (*Natl Toxicol Program Tech Rep Ser.* 2010; **551**: 1-178). How risky is to test this compound in human subjects with these potential carcinogenicity and at such high dosages?