

## OPEN PEER REVIEW REPORT 1

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**Title:** Natural products as potential therapeutic targets for Alzheimer's disease

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### COMMENTS TO AUTHORS

In the review, the authors introduced animal models of Alzheimer disease (AD) and described the usefulness of natural products acting on the mechanism of AD etiology. The review may provide readers and investigators with a good information, especially on their merits including low adverse effects.

However, the review is focused on the preventive mode rather than therapeutic (i.e., recovery) mode of action. Actually, there are recent reports on the regenerative activity of natural products, in which effects on neurite outgrowth (that is, axonal sprouting) and synaptogenesis as therapeutic modes have been demonstrated. Please refer to a reference: Kim, J., et al., Platycodon grandiflorus root extract improves learning and memory by enhancing synaptogenesis in mice hippocampus. *Nutrients* 2017, 9, 794.

Indeed, drugs which successfully inhibited the amyloid plaques in mice, failed to cure AD in humans (King, 2018), as the authors mentioned in the Introduction section. In fact, accumulation of amyloid peptides is a causative factor of neuronal death in AD. In mice and *Drosophila* with relatively-short lifespans, only a part of the neurons maybe dead or under dying progress during the amyloid accumulation, during which effective elimination of amyloids can restore the neural system. In comparison, in human AD patients, a large part of the neurons might be destroyed during a long-term (even longer than 10 years) challenge of amyloidosis. Thus, simple elimination of amyloids using antibodies, drugs, and natural products targeting amyloids produced or under production may not be effective. Therefore, recovery and regeneration of the damaged or lost neurons might be a practical strategy.

It is strongly recommended that review on the neuro-regenerative activities of natural products should be added.