Reviewer's report

Title: Kihi-to, a herbal traditional medicine, improves Abeta(25-35)-induced memory impairment and losses of neurites and synapses

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Reviewer: Raymond Chang

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The manuscript entitled “Kihi-to, a herbal traditional medicine, improves Abeta (25-35)-induced memory impairment and losses of neurites and synapses” investigate the effect of a formulated herbal medicine, Kihi-to, on Abeta(25-35)-induced neurotoxicity. The authors demonstrate that Kihi-to can improve memory impairment in mice injected with Abeta. By using immunohistochemical staining, they found that administration of Kihi-to can attenuate neuritic, synaptic and myelin losses. They suggest that the protective effect may be partly mediated by inhibition of calpain and increase level of calpastatin.

The experimental design and interpretation are sound. The manuscript is written in a clear manner. There are a few points that I am concerning.

1. In the in vivo part, Kihi-to was administrated to mice 10 days after i.c.v. injection of Abeta. The author mentioned that in this stage, mice already show memory impairment. Since Kihi-to was given in a post-injury manner, it seems that the effect of Kihi-to is related to the regeneration of neurons. However, in the in vitro experiment, Kihi-to and Abeta were co-administrated for 4 days and then staining were performed. There was difference in the protective mechanism of Kihi-to between the in vivo and in vitro experiments. The author tried to explain the protective mechanism by using the in vitro experiment. It seems that the measurements of calcium influx, calpain and calpastatin were not directly correctly to the in vivo part where neurons had already been severely damage. It would be better if the author could explain the difference in protocol design.

2. Following the mechanistic experiment, I think it is important to show the effects of Abeta1-42 instead of Abeta25-35 in cell culture experiments.

3. The neuronal culture used in this study contained a high percentage of astrocytes and microglia. The measurement of calpain and calpastatin was only confined to neurons. Since many medicinal herbs were reported to have immune-modulation effect, the explanation would be more complete if immune response, such as activation of microglia and release of cytokine, could also be studied.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'