OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00014
Title: Neuroprotection by Dendrobium nobil Lindl. alkaloid in Alzheimer’s disease
Reviewer’s Name: Paulina Carriba
Reviewer’s country: UK

COMMENTS TO AUTHORS
Review about the potential beneficial use of Dendrobium nobil Lindl. alkaloid (DNLA) in Alzheimer's disease. DNLA is the main compound of a plant used traditionally in Chinese and Indian cultures with several health benefits. Although the topic is quite interesting, especially in cultures without tradition in using this plant, this review does not develop coherently the objectives and does not reach the quality to be published. In my opinion, it should be rewritten with a description of the findings with all relevant data and then a brief explanation of the meaning of these findings, not just their exposition.

The manuscript needs major changes. There are too many issues to cite all of them.

- Title: Because it has not been yet demonstrated, the authors cannot claim that DNLA neuroprotects against AD. They can mention that is a promising compound, or that several data suggest it might protect or be beneficial in AD.

- Because this manuscript will be read by people with different cultural backgrounds, the use of specific cultural terminology, such as YIN, is not recommended. Instead of the use of this word, it would be better to describe what refer to.

- "The chemical constituents of Dendrobium nobil Lindl. include alkaloids, glycosidic class, phenanthrene, dibenzyl, etc.". What glycosidic class is? Moreover, it sounds a bit unspecific in a paragraph dedicated to the chemical composition, mention "etc". You can replace "etc" with "and others". Similar unspecificity as "other information" in "The chemical structures and other information of these compounds were shown in Table. 1". Another way to write this: "Chemical structures, name, formula and percentage of the total in plant or from all alkaloids (to me, this is not clear in the text) are shown in Table 1".

- Some of the sentences should be redacted again:
  "Dendrobium nobile Lindl. alkaloids (DNLA) is an active ingredient extracted from Dendrobium nobile Lindl".
  "In in vitro studies, the same ability of DNLA was also observed in hippocampal neurons
and DNLA (35, 350 and 700 ng/mL) ....".

"In detail, DNLA showed that DNLA (20,40 mg/kg for 6 months) down-regulated...". Besides the grammatical mistakes, were the animals treat for 6 months or were the animals 6 months old? And which animals were?

- DNLA refers to dendrobium nobile Lindl. alkaloids, therefore how to interpret this sentence: "Alkaloids accounted for 79.8% of DNLA"

- "It has been reported that Dendrobium nobil. contains "the most" dendrobium alkaloids in the genus Dendrobium(Piccinelli AL et al., 2013)." the largest amount of

- Use the past tense to explain results, but use the present for describing the process of obtaining alkaloids, because this is the process not a description of any result.

- Authors have to choose carefully what they claim, for example, "Several reports have demonstrated the neuroprotective effects of DNLA against memory deficit(Li Y et al., 2011), neuronal and synaptic loss(Li LS et al., 2016), inhibition of tau protein hyperphosphorylation(Liu B et al., 2020) and apoptosis(Chen JW et al., 2008) in the hippocampus." Have been all these results demonstrated in the hippocampus?

- Some sentences are introduced by connectors and linkers without any sense: "Traditionally, AD has two major characteristics: Aβ plaques and NFTs".

- In vivo, in vitro in cursive.

- In the bibliography, I found more nobile rather than nobil. Is it correctly spelled?

- Pharmacokinetics and Tissue Distribution has to be rewritten again because it is really complicated to follow. In addition, what is the meaning of this section?
One of the important things of this part is that "The distribution in the brain suggested that Dendrobine could penetrate the blood-brain barrier", but how it was determined? Moreover, it is indicated the administration via for rats, but what about the administration for mice?
What does "phase I" mean? in "Beside, the metabolites of Dendrobine for phase I in human liver microsomes were similar to the mouse and dog liver microsomes incubation system". And what does this sentence mean? or this one "Based on the results of Dendrobine metabolism in vitro, mouse and dog would be selected for the further metabolism study (Lu YI et al., 2018)."
Is the last paragraph of this section misplaced and formed part of the introduction?

- In section 3, but general for the whole text. It is relevant to mention the models used in each experiment, in the case of animals, they were rats or mice, whether they were wild type or specific model, the age and via of treatment, and for how long were treated. Similar for cells, are cell lines or primary cultures? If not relevant, it is not necessary to put all doses used, maybe a range of doses.
Try to be as clear as possible. It would be desirable a kind of digest of the data presented to give a conclusion or a take home message, rather than a disjointed exposition of the bibliographic data. 

- On page 8, line 50, do you mean synaptes? or is it an increase in the number of neurons?
- SAMP8: Mention that is Senescence-Accelerated Mouse (SAM) and therefore a good model for studying age-related disorders as AD because those animals have learning and memory defects.
- "Glial cells (microglia and astrocytes(Gonzalez-Reyes RE et al., 2017)) are the main cells involved in..." Why is this reference in here? Moreover, this is incorrect. Microglia and astrocytes are the main types of glial cells, but oligodendrocytes are also glial cells.
- "The accumulation of these inflammation factors could further stimulate immune reactions and contributes to the degeneration of neurons, including the progressive loss of neurons or dead neurons, resulting in cognitive decline and dementia."

Among several pathological abnormalities in AD, inflammatory processes and Aβ deposition trigger neuroinflammatory responses, leading to the loss of neurons and the decline of cognitive functions." These two are consecutive paragraphs. But, is it the same? And, what is the difference between loss of neurons and dead neurons?

- "LPS, an inflammation inducer, has been reported to influence Aβ deposition and LPS injection to the mouse brain ventricle caused memory deficiency and Aβ accumulation." Reference for this. And as mentioned before, is this a wild type mouse or a model?
- Apoptosis is programmed cell death not preprogrammed. And it is not an essential "compound", it is an essential biologic process.
- Several research lines in AD try to inhibit apoptosis, therefore it is not a "novel approach" as the authors mention.
- "Moreover, DNLA was verified to attenuate neuronal apoptosis, with evidence of the increased cell viability and decreased cell morphologic impairment in vitro." "Furthermore, DNLA could improve cognitive ability and decrease Aβ plaque in vivo." Any ref for these two sentences?
- Figure 1 does not have enough resolution to identify the proteins involved. And a brief description would be desirable.

References:
- Wrongly written the following references in the reference list: Hebert LE et al., 2003; Tarozzi et al., 2013; and Uéda K et al., 1993.
- There are 2 references for Liu B 2020, but in the text it is not clear which one they refer to. Could you please use "a" and "b" to differentiate between these two references?
- What is the [55] reference?
- In the text "... and caspase-12(Wang Q,Gong Q,Wu Q and Shi J, 2010)."
- Reference Yang S et al., 2014 has been written twice in the reference list.
- As a reference for apoptosis, the authors cite (Barnes DG et al., 2013). Barnes DG, Vidiassov M, Ruthensteiner B, Fluke CJ, Quayle MR, McHenry CR (2013), Embedding and publishing interactive, 3-dimensional, scientific figures in Portable Document Format (PDF) files. PLoS One 8:e69446. In what is this related to apoptosis?
- Some bibliographies are not found in Pubmed. This could be a problem to trust the documents on which this review is based. The journals are: Chin J Pharmacol Toxico; Journal of Zunyi Medical
University; Nat Prod Res Dev; Chinese Journal of Experimental Traditional Medical Formulae; Chinese Pharmacological Bulletin.