Author’s response to reviews

Title: In vitro antioxidant and cholinesterase inhibitory activities of Elatostema papillosum leaves and correlation with their phytochemical profiles: a study relevant to the treatment of Alzheimer's disease

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To

The Editor-in-Chief

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Sub: Submission of Revised Manuscript (BCAM-D-17-00808R1)

Dear Editor and Reviewer

Thank you very much for your positive comments and giving me an opportunity to revise our manuscript entitled “In vitro antioxidant and cholinesterase inhibitory activities of Elatostema papillosum leaves and correlation with their phytochemical profiles: a study relevant to the
treatment of Alzheimer's disease”. We have made necessary changes (red colored) in the revised manuscript as the reviewer suggested. In the following, I have written a point-to-point response to address the reviewer’s concern.

We believe the manuscript has been improved substantially after necessary revisions. Therefore, it would be highly appreciated if you kindly consider our manuscript for publication in your journal.

Sincerely

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A response to reviewer’s comments

Jason Eriksen (Reviewer 2)

Comment-1: page 3, line 56: there is substantial loss of both cholinergic and cortical neurons, not just cholinergic neurons.. Furthermore, the term "associated cognitive deficits" is not entirely clear; this should be revised to reflect specific cognitive deficits.

Response: Thank you very much for your suggestion. In page 3, lines 55-56, we have revised accordingly. Moreover, we have replaced "associated cognitive deficits" by “cognitive deficits” in page 3, line 58.
Comment-2: Pg 3, ln 64: "The aberrant accumulation of ROS is 64 the causative agent for a range of chronic diseases, including AD, by inducing oxidative stress 65 [8, 9]." This statement that ROS is the triggering agent does not reflect current scientific consensus in the field of Alzheimer's disease. A variety of studies have looked at ROS and therapeutic interventions in this area exhibit no clinical impact on the progression of disease. While I think it's fine to stay to that ROS scavenging may positively impact the disease, the authors should revise their statements to reflect current scientific consensus.

Response: In page 3, lines 63-65, we have revised according to the comment of reviewer as follows: The aberrant accumulation of ROS has been found in several chronic diseases, including AD suggesting that ROS may contribute to the pathogenesis of these diseases by inducing oxidative stress.

Comment-3: Pg 11: in addition to a set of cholinesterase inhibitors, memantine (an NMDA blocker) is also used as a pharmacological agent. The authors should revise the wording in the discussion to reflect the pharmacological treatments that are currently available.

Response: In pages 11-12, lines 250-266, we have revised our manuscript according to reviewer’s suggestion. The revision was as follows: Currently, only three cholinesterase inhibitors such as donepezil, galantamine, rivastigmine and a patial NMDA receptor antagonist, memantine, are the Food and Drug Administration (FDA) approved drugs to treat AD. The purpose of cholinesterase inhibitors is to inhibit the degradation of acetylcholine within synapses, resulting in increased amount of acetylcholine. Memantine, which is a partial NMDA receptor antagonist, protects neurons from glutamate-induced excitatory damages (1). These strategies represent the only current treatments available for AD. The cholinesterase inhibitors employed in current treatments are limited and they show a wide variety of toxic effect including insomnia, anorexia, diarrhea, fatigue, nausea, gastrointestinal disorders and cardiovascular disorders (1, 2). Therefore, researchers have focused their attention towards the discovery of new drugs from natural sources such as plants, which have enormous potential for the treatment of AD. In this study, we have discovered the capacity of EPL-M80 to significantly inhibit AChE and BChE activities in a dose-dependent manner (Figure 1&2). The inhibition of cholinesterases
was found to be better compared to other medicinal plants including Andrographis paniculata, Nelumbo nucifera, Myristica fragrans, and Aegle marmelos (2, 7) suggesting EPL-M80 extract as an effective cholinesterase inhibitor and can be used in the treatment of AD [5].

Comment-4: Pg 12: The authors repeatedly imply that a benefit of EPL - M80 is potentially reduced toxicity compared to that reported with synthetic agents like Aricept. Typically the toxicity of current cholinesterase inhibitors is primarily due to the inhibition of acetylcholinesterase. Consequently, it is not clear why the Authors expect that EPL - M80 will have and improved toxicity profile over synthetic agents when given at therapeutic concentrations, particularly since this is not been assessed in animal studies. The IC50 of EPL-M80 appears substantially greater than that of synthetic compounds. While the current traditional use of EPL may not have toxicity, the extract is a highly concentrated form and if given in doses that are sufficient to inhibit acetylcholinesterase, there is likely to be a similar degree of toxicity. The authors should word their discussion carefully so as to not oversell EPL-M80.

Response: In page 13, lines 292-293 (The widespread traditional uses of EPL suggest there are no toxic effects on the human body as a result from therapeutic doses and it is primarily assumed that EPL is free from toxic hazards [21]) have been omitted from the text. In addition, “a multitude of degenerative” has been changed to “a multitude of degenerative diseases” in page 13, line 297.

Other necessary corrections were as follows:

1. In page 2, line 46, “an effective and safer treatment for AD” has been replaced by “an effective treatment for AD”.

2. In page 4, line 74, “for the development of novel cholinesterase inhibitors with reduced side effects” has been changed to “for the development of new cholinesterase inhibitors and antioxidants”.
3. In page 4, line 76, “the potential of plants as vital sources for cholinesterase inhibitors” has been changed to “the potential of plants as vital sources for cholinesterase inhibitors and antioxidants”.

4. In page 12, line 275, “OS contribute to the etiology of numerous human” has been changed to “OS contribute to the pathogenesis of numerous human”

5. In page 14, lines 307-308, “Further studies are necessary to evaluate the neuroprotective effects and the safety/toxicity profile of the plant in animal model” has been changed to “Further studies are warranted to isolate and characterize the active polyphenol compound that may be used a