Author's response to reviews

Title: Effect of melilotus extract on lung injury by upregulating the expression of cannabinoid CB2 receptors in septic rats

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Author's response to reviews:

Dear Dr Anandjiwala

Re: No. MS: 2716823810275594

Please find attached a revised version of our manuscript “The effect of melilotus extract on lung injury by upregulating the expression of cannabinoid CB2 receptors in septic rats”, which we would like to resubmit for publication as a Research article in BMC Complementary and Alternative Medicine.

Your comments and those of the reviewers were highly insightful and enabled us to improve greatly the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow highlight for additions, and strikethrough font [example] for deletions. In accordance with reviewer Elif Cadirci and Niranjan Kanaki’s suggestions, we have added details regarding biologist identification, storage and preparation of Melilotus extract of M. Suaveolens, HPLC Fingerprint for analysis of the herb extract, survival curves, and revised the manuscript, especially the discussion, abstract and references.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Complementary and Alternative Medicine.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

Major Compulsory Revisions

The introduction says that the study aimed to investigate impact of M. Suaveolens Ledeb on the lung injury. However, they did not study directly the plant extract, they used a commercial product.

1) Is the product standard? Do the authors know the ingredients and also did any botanists identified that commercial product’s source. Namely I ask how authors can know the extract they used was M. Suaveolens Ledeb.

2) Another important point is, there are several compounds in a plant that can be effective. Extraction procedures are important in terms of obtaining different compounds from same plant. Is the extract they used standard?? The dose of extract “25 mg/kg q8h” is not clear. The animal model is appropriate for sepsis experiments. All analyses for biochemical; histopathologic and molecular evaluation is also ok.

3) However I could not understand how could the authors collected 5 ml blood sample from a mice. They can collect maximum 1-1.5 ml. Did they pool bloods of different animals?

4) Also another point is important: the survival of mice. Did all mice survived for 24 hours after clp application?? If not, present the survival data.

5) Overall the manuscript, especially discussion should be rewritten. There are many typografical mistakes. Also language should be edited.

Response: We have revised the text according to the reviewers suggestions to enable a better understanding of the biologists identification, storage and preparation of Melilotus extract of M. Suaveolens, HPLC Fingerprint Analysis of the herb extract, survival curves, and revised the manuscript, especially discussion, abstract and references. In the revised manuscript, some sentences have been revised as follows:

"the selective CB2 receptor--ANL241—can act on the CB2 receptors on the peripheral immune cells, inhibiting the release of inflammatory factors and play a role of analgesic" was modified to “the selective CB2 receptor stimulant AM-1241 can act on CB2 receptors on peripheral immune cells, inhibiting the release of inflammatory factors and easing pain”

“collected 5 ml blood sample from a mice” was revised to “Blood was extracted (1.5 ml)...”

“animals in the treatment group received melilotus extract (25 mg/kg) once every eight hours, and the normal control, sham and control groups were given the same volume of saline” was revised to “Two hours before surgery, animals in the treatment group received melilotus extract (25 mg/kg) once every eight hours, and the normal control, sham and control groups were given the same volume of saline”

"mice” was modified to "rat"
MPO and ALI have been added to the list of abbreviations. According to editor’s comments, we have revised the references according to the format of the journal.

2. Minor Essential Revisions

In discussion the sentence “For example, the selective CB2 receptor--ANL241—can act on the CB2 receptors on the peripheral immune cells, inhibiting the release of inflammatory factors and play a role of analgesic " is not clear.

Response: In the discussion the sentence "the selective CB2 receptor--ANL241—can act on the CB2 receptors on the peripheral immune cells, inhibiting the release of inflammatory factors and play a role of analgesic was modified to “For example, the selective CB2 receptor stimulant AM-1241 can act on CB2 receptors on peripheral immune cells, inhibiting the release of inflammatory factors and easing pain".

Responses to the comments of Reviewer #2

Major Compulsory Revisions

1) The title mentions rats but in the Materials and Methods section, the experiments are said to be done on mice.

2) The authors have used the Melilotus extract tablets purchased from a Japanese company, for their study. The label claim on the product does not mention anything about the identity of the plant species used to prepare the tablets. My question to the author is – How they have come to a conclusion that the tablets contain Melilotus suaveolens and not M. officinalis or any other species of Melilotus?

Response: 1) “Mice” was modified to "rat". 2) We have revised the text according to the reviewer’s suggestions to enable a better understanding of the biologist’s identification, storage and preparation of Melilotus extract of M. Suaveolens and HPLC Fingerprint Analysis of the herb extract.

Minor Essential Revisions

1) The article contains enormous typographical and grammatical errors. The writing is very poor. Some of the mistakes have been highlighted in the manuscript attached with the report.

2) The authors have not followed the general rules of writing such as:

The botanical name of the plant should always be in italics; The complete botanical name with genus and species should be mentioned at its first appearance in the manuscript; many of the abbreviations such as MPO and ALI are not mentioned in the list of abbreviations. These are not commonly used abbreviations, and hence, their full form should be given at their first appearance
Response: We have revised all the typographical and grammatical errors in the manuscript, including all the mistakes highlighted in the manuscript. The botanical name of the plant has been revised to italics. The complete botanical name with genus and species is now mentioned at its first appearance in the manuscript. Many of the abbreviations such as MPO and ALI have been added to the list of abbreviations and where they are first used in the text.