

Peer Review File

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Reviewer A

The manuscript presents an interesting analysis, however, there are far too many figures and it makes reading/reviewing the paper very difficult. Most of these figures can be explained in text and some tables. Since authors considered randomized controlled trials evaluating OM-85 add-on therapy in 23 asthma patients up to December 2021, did any of the patients ever suffer from COVID-19?

Reply 1: We apologize for using so many figures and tables. To make it easier to read, we have combined several related figures and put them into the supplementary appendix.

Changes in the text: We have merged the contents of the original Figures 4–10 (Forest map of asthma-related clinical examinations) into the supplementary Figures S1-S4. We have modified the corresponding text (see page 6, lines 231, 238, 249, 263; page 7, lines 271, 274, 285; page 15, lines 639–660; page 16, lines 662–678, 683–687).

Reply 2: Most of the studies cited are clinical studies that were conducted in China. Because the Chinese government implemented a strict zero clearance policy for COVID-19 during the period of this study, COVID-19 patients who tested positive for nucleic acid were isolated and only patients who tested negative for COVID-19 were admitted to the hospital. For that reason, this work was less likely to include COVID-19 patients, and included only a few at most.

Reviewer B

Comment 1: There is some ambiguity in the methodology that the authors need to clarify.

The authors provide the following inclusion criteria: “(3) intervention group: patients who received at least one course of OM-85 alone...”, and then in the exclusion criteria they state: “(4) trials using OM-85 as intervention”.

Reply 1: We would like to thank the reviewer for drawing our attention to this error. “(4) trials using OM-85 as intervention” mentioned in our original exclusion criteria should be expressed as “Animal experiments using OM-85 as intervention.”

Changes in the text: We have modified our text accordingly (see page 3, lines 136–137).

Comment 2: Each time the authors give a different number of studies included in their meta-analysis - sometimes it is 36, sometimes 37 or 38.

E.g. “Finally, 38 eligible publications were included in this review”; “Of these 36 eligible publications, 35 were published in Chinese[11-45] and three in English[46-48]”; in turn, Figure 1 shows that there were 37 studies.

Reply 2: We are really sorry for our careless mistakes. We regret that there was indeed a low-level error in the data. We have confirmed the relevant data in the corresponding position in the paper. The number of included studies should be 36.

Changes in the text: We have modified our text as advised (see page 2, line 57; page 4, lines 174–176).

Comment 3: In the discussion, the authors mention: “OM-85 is non-viable bacterial extracts obtained by either chemical or mechanical lysis of bacterial cultures and lyophilization”. However, OM-85 is a polyvalent CHEMICAL bacterial lysate.

Reply 3: We feel great thanks for your reminding. We carefully searched the relevant literature to correct and improve the text. Bacterial lysates are classified as either alkaline or mechanical bacterial lysates, depending on the method of preparation. Commercial products based on both types are available. OM-85 and Luivac are alkaline bacterial lysates and Ismigen is a mechanical bacterial lysate.

Changes in the text: We have modified our text as advised (see page 8, lines 310–311), and we have added a reference.

Comment 4: In the discussion, the authors list 4 possible mechanisms of action of OM-85, where they cite a paper from 1994 [56. Mauël, J., Stimulation of immunoprotective mechanisms by OM-85 BV. A review of results from in vivo and in vitro studies. Respiration; international review of thoracic diseases, 1994: p. 8-15]. However, more recent articles in this area are available, e.g. doi: 10.3389/fimmu.2022.907149

Reply 4: We sincerely appreciate these valuable comments. We believe the original citations are appropriate, but many of the ideas they describe are out of date. We have added the references you recommended and updated some of the outdated references in our paper.

Changes in the text: We have replaced the outdated reference as advised (see page 8, line 338).

Comment 5: In the discussion, the authors make the following conclusion: “Hence, OM-85 may be administered to children who present with wheezing symptoms, but have not been diagnosed with asthma, in order to control or reduce wheezing”. Why? After all, studies involving children and adults with asthma were included in this meta-analysis.

Reply 5: Thank you for drawing our attention to the confusion caused by our lack of clarity. What we mean actually mean is that children who develop wheezing symptoms may be too young to cooperate with clinical tests such as lung function and bronchial dilation tests, and they cannot be accurately diagnosed with asthma or ruled out other diseases. OM-85 may be a suitable empirical medication for these patients; it has been shown to be effective, safe, and capable of controlling wheezing in children.

Changes in the text: We have revised this conclusion in case the reader is confused (see page 9, lines 363–367).

Comment 6: Also in the discussion, the authors mention that: “Bacterial lysates can be composed of validated probiotics, metabolites of certain bacteria, or combinations of these compounds, and can be used as a type of vaccine against gut-harming flora or as narrow-spectrum antibiotics”. The reviewer does not understand this sentence. Bacterial lysates and probiotics are completely different preparations.

Reply 6: We would like to thank the reviewer for their careful attention to detail. We did confuse bacterial lysates with probiotics, and we have decided to delete the following sentence: “Bacterial lysates can be composed of validated probiotics, metabolites of certain bacteria, or combinations of these compounds, and can be used as a type of vaccine against gut-harming flora or as narrow-spectrum antibiotics.”

Changes in the text: We have deleted the above sentence (see page 8, lines 374–377).

Comment 7: The studies included in the meta-analysis differ significantly in the duration of treatment. OM-85 was administered for 10 days in one study and 360 days in another. Could this affect the clinical effect? Please raise this issue in the discussion.

Reply 7: We would like to thank the reviewer for this suggestion. We have analyzed the improvement in clinical symptoms of asthma and its relationship to the duration of treatment as a subgroup. As shown in the following figure, there was no significant difference in the improvement clinical symptoms of asthma as OM-85 treatment continued. However, the issue still needs more study and data for each subgroup to increase the solidity of this conclusion.

Changes in the text: We now address this issue in the discussion (see page 9, lines 386–392).

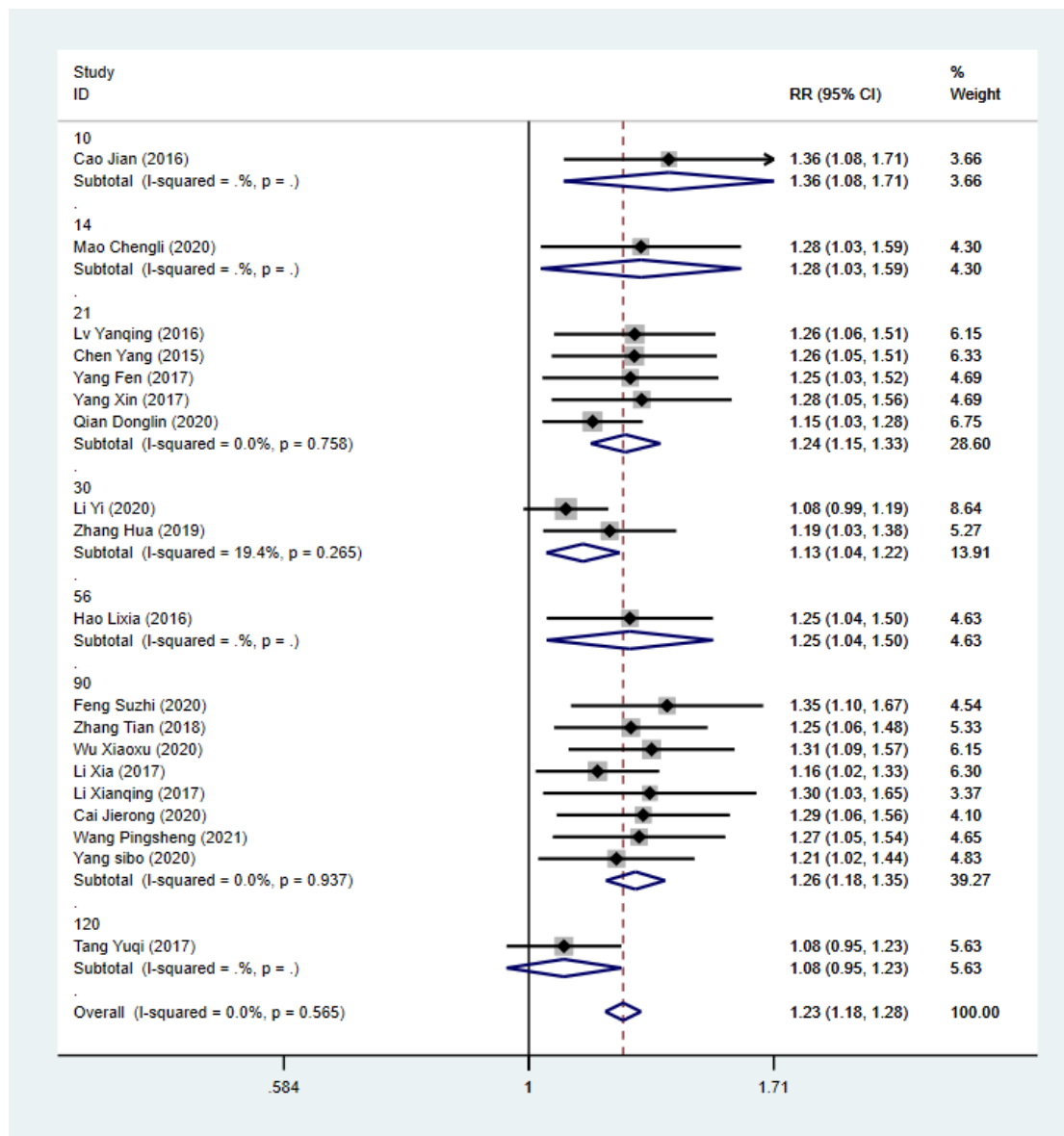


Figure 4. Proportion of improvement in clinical symptoms of asthma (subgroup analysis of treatment duration)

Comment 8: The information provided by the authors in Table 1 shows that: in the Yang Yong 2018 study, the intervention group received routine asthma therapy plus OM-85 plus Shenmai Injection, while the control group received only routine therapy. So how can you be sure that the effects obtained are the result of OM-85? and not the effect of Shenmai Injection?

Reply 8: We believe this issue is critical. We cannot be sure whether the therapeutic effect is from OM-85 or Shenmai injection. The Yang Yong 2018 study should not be included in our meta-analysis. To fix this error, we have removed the Yang Yong 2018 study and modified the figures, table, sensitivity analysis, funnel plot, and text.

Changes in the text: We have modified the original figures, table, sensitivity analysis, funnel plot (including Figures 1, 2, 3A, 4B, 4E, 5, 9A, S1, and S2 and Table 1), and text

(see page 5, lines 179–181, 188, 200–210; page 6, lines 226–228, 234–237, 258, 262)
affected by the Yang Yong study.