

## Editorial Queries and Requests:

### Reviewer#1 Reports:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Comments to the Author:

1. This meta-analysis is well written. The authors describe that Chinese herbal medicine was associated with improved symptoms of functional constipation. This was evaluated by several outcomes, such as score on the Bristol Stool Scale, bowel movements, stool characteristics, recurrence rate, and efficacy rate. I congratulate the authors; this study has interesting findings with low heterogeneity (except bowel movements) that allow extrapolation of their findings to clinical settings.

**Reply:** Thank you for taking the time to review our submission and for these supportive and constructive comments.

2. However, they included studies with a high risk of bias that must be evaluated by a sensibility analysis.

**Reply:** The studies with a high-quality methodology have been evaluated as a subgroup analysis.

"Three studies evaluated as high quality with a low risk of bias in their methodology. They compared CHM with western medicine and reported efficacy rate (ER). Results showed the treatment for FC was significantly in favor of CHM (OR 2.89, 95% CI 1.29-6.46,  $p < 0.01$ ) (Table 2 and Figure 6). There was no significant heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.94$ )."

3. -Abstract-Aim: The authors must provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

**Reply:** The aim of the Abstract section has stated the questions about participants, interventions, comparisons, outcomes, and study design (PICOS).

"Functional constipation (FC) is a common and chronic gastrointestinal disease, and its treatment remains challenging. This review aimed to evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements, and the Bristol Stool Scale score in patients with FC by summarizing current available randomized controlled trials (RCTs)."

4. -Abstract-Results: the  $I^2$  must be included in this section.

**Reply:** The  $I^2$  has been included in this section.

"Ninety-seven studies involving 8,693 patients were included in this work. CHM was significantly associated with a higher efficacy rate (OR 3.62, 95% CI 3.19-4.11,  $p < 0.00001$ ) less severe global symptoms (OR 4.03, 95% CI 3.49-4.65,  $p < 0.00001$ ) compared with control treatment, with the low heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.76$ )."

5. -Introduction: As described above, the aim also must provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) in the introduction.

**Reply:** Thank you for the comment. The aim in the Introduction section has stated the questions about participants, interventions, comparisons, outcomes, and study design (PICOS).

"Therefore, the purpose of the review was to evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements, and the Bristol Stool Scale score in patients with FC by summarizing current available RCTs."

6. A meta-analysis evaluated the efficacy and safety of CHM in the treatment of constipation. The authors must describe the difference that has that meta-analysis with their study, this would add value to their study.

**Reply:** Thank you for the comment. The reference has been revised and shown as red words of the updated manuscript.

7. -Methods: The eligibility criteria must be described before the search strategy, as recommended by the PRISMA guideline.

**Reply:** Thank you for the comment. The order of eligibility criteria and search strategy has been revised.

8. -Methods: The authors must state that MD was used because the outcome measurements in all studies are made on the same scale.

**Reply:** Thank you for the comment. It has been revised.

9. -Results: Could a sensibility analysis based on methodological quality perform?

**Reply:** Thank you for the comment. The discussion section has been revised.

10.-Results: the statement "Five studies compared CHM with western medicine

and reported the recurrence rate (RR). The results showed the treatment for functional constipation was no sign in favor of CHM” must be corrected.

**Reply:** Thank you for the comment. This sentence has been revised.

“Five studies compared CHM with western medicine and reported the recurrence rate (RR). The results showed CHM was not superior to western medicine in controlling the recurrence rate of FC (OR 0.47, 95% CI 0.22-0.99,  $p = 0.05$ ) (Table 2 and Figure 5). There was no significant heterogeneity between studies ( $I^2 = 9\%$ ,  $p = 0.35$ ).”

11. Some references must be improved. These don't have pages number.

**Reply:** Thank you for the comment. The reference section has been revised.

**Reviewer #2:**

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Comments to the Author:

1. Scientifically, from what I can tell, this is well done. This is limited by poor writing/English and the fact that many of the cited studies are not in English.

**Reply:** Thank you for taking the time to review our submission and for these supportive and constructive comments. Native English speakers have been invited to read the manuscript and make revisions based on suggestions, and red fonts indicate the revisions

2. The major limitation here is that subgroup analyses by CHM ingredients are missing. Lumping all CHM into one intervention could be misleading. Both of these could be corrected, as well as the minor comments below, and this paper has the potential to be a great publication.

**Reply:** Thank you for the helpful comment. The CHM ingredients of each study were shown as supplement 1 and the subgroup analysis based on them has been added in this updated version.

“Method-Subgroup analyses were used to explore and interpret the sources of heterogeneity; to evaluate whether the effects were modified by treatment characteristics and study quality, we specified it based on CHM ingredients, western medicine treatment, and high-quality study.

Results-Two CHM ingredients commonly used in the treatment of functional constipation, Cannabis Fructus and Cistanche, were analyzed in a subgroup by measuring efficacy rate (ER). In the Cannabis Fructus subgroup, the results

showed Cannabis Fructus had no significant effect compared with western medicine (OR 1.88, 95% CI 0.97-3.65,  $p = 0.06$ ). There was significant heterogeneity between studies ( $I^2 = 61\%$ ,  $p = 0.08$ ) (Supplement 1 and Figure 7). In the Cistanche subgroup, the results showed Cistanche had a significant effect compared with western medicine (OR 3.49, 95% CI 2.76-4.41,  $p < 0.0001$ ). There was significant heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.71$ ) (Supplement 1 and Figure 8)."

3. In the supplementary documents, both the biostatistical review and non-native Speakers of English documents are just repeats of the PRISMA guidelines. Please upload these documents correctly.

**Reply:** Thank you for mentioning the concern. The two supplementary documents, both the biostatistical review and non-native Speakers of English documents, have been uploaded correctly.

4. This is especially true because the use of English is suboptimal in several places in this manuscript.

**Reply:** Native English speakers have been invited to read the manuscript and make revisions based on suggestions, and red fonts indicate the revisions.

5. In the version I received, it noted this was submitted to the "World J of Clinical Cases", but the Title page notes it is submitted to "World J of Gastroenterology". It is much more suited for the latter. I suspect this is a system error and not an error on the part of the authors.

**Reply:** Thank you for your kind reminder that the original intention of our manuscript is indeed to submit to the World Journal of Gastroenterology. But combined with the conclusions of our meta-analysis, the main reader group of the World Journal of Clinical Case Research is clinicians, we finally decided to submit the paper to the World Journal of Clinical Case Research, hoping that more clinicians can be inspired.

6. ABSTRACT: Scientifically, describes the study well from what I can understand apart from the many grammar, formatting, word choice errors.

**Reply:** Native English speakers have been invited to read the manuscript and make revisions based on suggestions, and red fonts indicate the revisions.

7. In methods, typically would say it was a search "of" six databases not "over" six databases. This sentence makes no sense as worded: "Meta-analyses were

performed to odds ratio (OR), mean differences (MD), and 95% CI using random-effects models." The sources of heterogeneity were not "discussed" using the mentioned methods. There are better word choices. Several missing spaces between words and parens make results hard to read.

**Reply:** Thank you for your kind reminder. The sentences have been corrected and red fonts indicate the revisions.

"Randomized controlled trials with CHM to treat FC were identified by a systematic search of six databases from inception to October 20, 2020. Two independent reviewers assessed the quality of the included articles and extracted data. Meta-analyses were performed to odds ratio (OR), mean differences (MD), and 95% CI using random-effects models. Subgroup analyses and sensitivity analyses were used to explore and interpret the sources of heterogeneity. The funnel plot, Begg's test, and Egger's test were used to detect publication bias.

Results: Ninety-seven studies involving 8,693 patients were included in this work. CHM was significantly associated with a higher efficacy rate (OR 3.62, 95% CI 3.19-4.11,  $p < 0.00001$ ) less severe global symptoms (OR 4.03, 95% CI 3.49-4.65,  $p < 0.00001$ ) compared with control treatment, with the low heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.76$ ). And CHM also associated with more frequent bowel movements (MD 0.83, 95% CI 0.67-0.98,  $p < 0.00001$ ), a lower score on the Bristol Stool Scale (OR 1.63, 95% CI 1.15-2.32,  $p < 0.006$ ), and a not significant recurrence rate (OR 0.47, 95% CI 0.22-0.99,  $p = 0.05$ ). No serious adverse effects of CHM were reported."

8. INTRODUCTION: Well written. A good summary of relevant literature.

Appropriately brief. Reference 3 notes "direct costs". This does not necessarily mean what patients pay. I would clarify.

**Reply:** Thank you for your kind reminder. The expression of this sentence has been corrected

"It is estimated that about 3.2 million FC patients in the United States visited medical centers in 2012, and the direct cost per patient for chronic constipation ranged from \$1,912 to \$7,522 per year [3]."

9. I would wonder if CHM is used by people outside of Asia. This intro is a little Asian-oriented. The study, reference 7, shows that patients in Taiwan use CHM often, but not that it is used by other patients. I would either find studies outside of Asia that support this statement or reword it to clarify that it is used often in Asia. Is there a specific hypothesis?

**Reply:** We found a study in the United States that proves that doctors use

traditional Chinese medicine to treat constipation outside of Asia, and cited this study to replace Reference 7.

10. Other PICO questions, i.e. outcomes?

**Reply:** Not sure which sections were pointed.

11. METHODS: There are several typographical errors, including missing spaces, commas, etc. PRISMA should be capitalized when spelled out Search Strategy can be in a supplement.

**Reply:** Thank you for the helpful comment. We have followed the suggestion to corrected these typographical errors and put the search strategy in the attachment as supplement 1.

12. The methods note databases were searched from the year of inception of Rome Criteria; whereas, abstract implies databases were searched from their inception. I also would write out and cite what year Rome Criteria was developed and what year was used.

**Reply:** Thank you for your useful suggestions. We have revised the expression about the search year to make it clearer

"An electronic search of the databases was performed from 1994, the year of the establishment of Rome criteria, up to June 2020"

13. It will be really important to clearly define what was considered CHM. Were all ages included, even children? All setting types (inpatient/outpatient)?

**Reply:**

14. The study selection process section skips right to extraction/data review and the study selection process is not described at all.

**Reply:** Thank you for your reminder. The selection process has described in the method section" Search Strategy and Study Selection"

"Two reviewers (LZP and BY) independently read the title and abstract to initially select the studies that meet the eligibility criteria. Further reading the full text to determine the included studies. If the reviewers had different opinions, the third researcher (ZLD) finally made a decision."

15. There needs to be a correction for multiple observations (i.e. Bonferroni) mentioned since there is no primary outcome identified. There are several outcomes, which means there is no primary (i.e., singular) outcome.

**Reply:** Thank you for this helpful comment. We have added the expression of the primary outcome and the secondary outcome.

"The efficacy rate (ER) was considered a primary outcome. The frequency of bowel movement (BM), the assessments of the global symptom (GS), the score of the Bristol Stool Scale (BSS), the recurrence rate (RR) within follow-up, and reported adverse effects (AEs) were considered to be the second outcome."

16. RESULTS: Again, several missing punctuations, spaces, etc. The first sentence is missing a subject, i.e. "studies".

**Reply:** We have made a correction

"There were 1,764 studies via electronic databases and 12 trials by supplementary retrieval of reference lists of relevant literature."

17. "Ninety-seven studies were retrieved base on selection criteria" – based on There is major limitations here that need to be addressed. Lumping "CHM" all into one intervention limits the analysis here. The interventions need to be separated by what ingredients. This would be much more helpful than knowing the outcomes compared to different controls (which is also helpful).

**Reply:** Thank you for the helpful comment. The CHM ingredients of each study were shown as supplement 1 and the subgroup analysis based on them has been added in this updated version. The detail can be found on page7-8 of the updated manuscript and No.2 reply.

18. I cannot assess nearly any of the original studies because they are in Chinese. Someone who is a native Chinese speaker needs to independently review these studies for accurate citations.

**Reply:** The majority of Chinese medicines are used in China. We also found through literature search that the 97 trials included were all conducted in China, and the results of 92 of these studies were only published in Chinese journals. We hope that through our research, more people can understand the efficacy and safety of Chinese medicine. And there are more excellent Chinese medicine researches published in English journals.

19. Outcomes for BM need to be specified to a time period. BM per day? Per week?

**Reply:** Outcomes for BM have been specified to BM per week.

"BM: to determine the efficacy of CHM on the frequency of bowel movement (BM) per week, e.g. 4 times/ week."

20. Subgroups for age, gender, outside China, only high-quality studies, etc. would be helpful. Perhaps in a supplement.

**Reply:** Method-Subgroup analyses were used to explore and interpret the sources of heterogeneity; to evaluate whether the effects were modified by treatment characteristics and study quality, we specified it based on CHM ingredients, western medicine treatment, and high-quality study.

Results-Two CHM ingredients commonly used in the treatment of functional constipation, Cannabis Fructus and Cistanche, were analyzed in a subgroup by measuring efficacy rate (ER). In the Cannabis Fructus subgroup, the results showed Cannabis Fructus had no significant effect compared with western medicine (OR 1.88, 95% CI 0.97-3.65,  $p = 0.06$ ). There was significant heterogeneity between studies ( $I^2 = 61\%$ ,  $p = 0.08$ ) (Supplement 1 and Figure 7). In the Cistanche subgroup, the results showed Cistanche had a significant effect compared with western medicine (OR 3.49, 95% CI 2.76-4.41,  $p < 0.0001$ ). There was significant heterogeneity between studies ( $I^2 = 0\%$ ,  $p = 0.71$ ) (Supplement 1 and Figure 8)."

21. DISCUSSION: Studies and patients were not "recruited" for this review. "But all reported adverse effects didn't need urgent treatment." Is repeated from the results. I would put in one or the other, probably the discussion and not the results (unless there was an objective assessment of this). I would consider rewording to "were not serious"

**Reply:** Thank you for the helpful comment. We have deleted the description of adverse events in the results section. And corrected the expression in the discussion section.

"For the safety of CHM, adverse effects were reported, such as abdominal pain or bloating, nausea, stomach discomfort, diarrhea, and passing of gas. But there were only 12.4% (12/ 97) of studies mentioned the safety of interventions or the AEs investigated as one of the main outcome indicators. In addition, many traditional Chinese medicines have been widely used by Chinese traditional medicine practitioners for nearly two millennia. This supports their security. Therefore, more attention should be paid to record and report the harmful effects of these interventions."

22. "subgroup analysis according to ages and so on" Did I miss the aging subgroup? What were the others? "But we acknowledged that it was difficult to conduct blind successfully due to the special smell of CHM. And with a specific



score criterion, it could reduce the possibility of bias." I know what the authors are trying to say, but these sentences make no sense.

**Reply:** Thank you for your reminder. "subgroup analysis according to ages and so on" was a mistake and we deleted it. Also, sentence- "But we acknowledged that it was difficult to conduct blind successfully due to the special smell of CHM. And with a specific score criterion, it could reduce the possibility of bias."- has been deleted to make the discussion clearer.

23. Limitation of missing potentially relevant articles is missing. Also, geographic bias is another limitation. I would recommend a separate, single limitation paragraph that is easy to identify.

**Reply:** Thank you for your helpful comment. Limitations have been separated as a solo paragraph to make it clearer. Also, the geographic bias has been added.

#### "LIMITATION

We searched main English and Chinese databases under well-designed searching strategies and made the comparison between CHM and different WM therapies more clear. There are several limitations to this systematic review. Firstly, missing articles that might be relevant. Although we searched through databases and did not limit the language of the article, we may still miss relevant articles in regional journals. Because the articles published in these regional magazines are not included in the database we searched. Secondly, most of the studies we included were published only in Chinese, which limited readers' review of the original research. This situation may be improved with the worldwide promotion of CHM. Thirdly, the studies we included were all conducted in the Asian region, so the extrapolation of these results is limited by geography. "

24. REFERENCES: The references are not formatted consistently. Please correct. As above, I could not verify the accuracy of most of the references due to them not being available in English.

**Reply:** Thank you for the comment. The reference section has been revised.

25. TABLES/FIGURES: All tables and figures need titles detailed enough to stand alone. That is some mention of the focus of this SR/MA.

**Reply:** The titles of figure 2 have been detailed about this SR/MA. The rest titles of the figure and table are not sure how to be more detailed of the focus of this SR/MA

"Figure 2. Risk of bias graph with the studies comparing CHM with PEG/ mosapride/ lactulose/ phenolphthalein/ probiotics/ placebo for the treatment of

FC.”

“Figure 3. Forest plot of randomized controlled trials in patients with functional constipation comparing CHM with PEG/ mosapride/ lactulose/ phenolphthalein/ probiotics/ placebo. Odds Ratio (95% CIs) for effective rate are shown.”

26. As above, I think scientifically, this is well done. Some different subgroup analyses, most importantly by ingredient of CHM would be helpful. There is a lot of room for writing/English improvement. But, I think these could be overcome with some work on the authors’ part to make this work a great publication.

**Reply:** Thank you for your useful comment. We have made corrections according to your suggestions to make our manuscript clearer and invited native English authors to correct the language errors in the manuscript to make it easier to understand.