

Dear Editor,

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "**Irritable bowel syndrome and functional constipation management with Integrative Medicine: Systematic review**". Those comments are all valuable and very helpful for revising and improving our paper. We have carefully read the comments and made relevant modifications marked in red in the manuscript. The point-to-point response to reviewers' comments are as following:

Reviewer 1#

This manuscript is clearly well-researched and the topic is clinically relevant. However, I found several areas of the manuscript considerably underdeveloped and the writing requires a close edit (ideally by a native speaker of the language) for language and grammar.

R: Thank you for your suggestion. The revised manuscript has already been modified by professional institute. And we also provided language certificate.

Specific comments: - Please change "Irritable bowel syndrome (IBS) and functional constipation (FC) are two common functional gastrointestinal disorders in clinical practice" to "Irritable bowel syndrome (IBS) and functional constipation (FC) are two commonly-encountered functional gastrointestinal disorders in clinical practice".

R: Thank you for your suggestion. We have already revised related contents.

- When you say they are "usually managed in cooperation with Traditional Chinese Medicine (TCM)", do you refer to TCM methods or TCM physicians?

R: Thank you for your question. We meant the TCM interventions. We also revised the related content to avoid misunderstanding.

- Please change "Although continuous clinical practice guidelines (CPGs) are developed to assist clinicians with their decisions, there is still blank in management recommendation

with Integrative Medicine (IM)" to "Although clinical practice guidelines (CPGs) have been developed to assist clinicians with their decisions, there are still gaps in management with regard to Integrative Medicine (IM) recommendations."

R: Thank you for your suggestion. We have already revised related contents.

- If the authors have a review protocol, and if it can be accessed (web address), include this and also provide the registration information including registration number. Ideally, the authors are required to register with PROSPERO for example, prior to carrying out the systematic review.

R: Thank you for your suggestion. We understand that protocol registration is an ideal process in developing a systematic review. We did try to register our systematic review in PROSPERO. However, considering that our work did not have a traditional structure like interventional or diagnostic systematic review, the PROSPERO website do not a suitable category for our work. Hence, we directly finished our systematic review without publishing our protocol.

- I am unsure how the methods answer the intended research question of this article. Although the authors presented a detailed review of current CPGs, they do not help guide the integration of TCM therapies into WM practice. The many TCM formulations provided in Table 6 and 7 are also mostly unavailable outside of China, hence limiting interest in the article and also an understanding of how clinicians could integrate these with current WM drugs. Unlike Western treatment approaches to specific pathologies, treatment in TCM is based on the general constitution of an individual. Hence, diagnosis is based upon identification of disease patterns and translating the pattern of symptoms manifested into specific TCM syndromes that reflect the pathogenesis of the disease, e.g. Qi or blood stagnation and consequently, herbs with properties of promoting blood circulation and eliminating stasis are often used to treat these syndromes. What is therefore the complementary approach to IBS and FC management?

R: Thank you for your question. First of all, integration of TCM and WM is still challenging in clinical practice, like you pointed out, factors including the pattern differentiation system, herb-drug interaction and treatment intervals would all impact its implementation. However, in this

systematic review, we gave a comprehensive view of current management using TCM and WM, and aimed to provide a possible direction for integration of TCM and WM, namely by using TCM interventions to fill up the circumstances which could not be fully dealt with WM. Secondly, the formulas in Table 6 and 7 may not be available outside China, but they could be considered as targeted interventions for further IM researches. After establishing corresponding evidences, the application may not be impossible. In addition, TCM has been listed in ICD-11 recently, which may also be a symbol that TCM has potential to be utilized internationally. Thirdly, the core tip of complementary approach to IBS and FC management is to recognize the population with specific TCM pattern and decide corresponding formula along with conventional interventions, no matter for researches or clinical treatment. We understand that TCM interventions are based on individualized pattern differentiation. It is not a simple work to let a practitioner with WM background understand and prescribe TCM interventions. Hence, under the table 4 and 5, we listed the pattern differentiation criteria for each pattern according to the guidelines. These criteria are on the foundation of symptoms, and hopefully in this way, it could help WM practitioners and researchers confirm suitable patient population. We also supplement corresponding pattern differentiation explanation in relevant section.

- In clinical practice, drug-herb interaction is also an area of great concern for doctors and patients alike. However, while drug-drug interaction is well studied, the knowledge in drugherb interaction, especially TCM herbs (in contrast to herbs used in Western folk medicine), is seriously lacking. The usual advice of taking them “two hours apart” (or even four hours) instructed by most TCM practitioners addresses only interaction in the stomach. However, besides absorption, there are downstream processes of distribution, metabolism and excretion which are subjected to pharmacokinetic interaction with other drugs. In addition, pharmacodynamic interaction that may potentiate or antagonise the pharmacological activity needs to be considered too. These questions and more are essential to consider if TCM were to be integrated into WM practice.

R: We total agree your viewpoint. Herb-drug interaction is a vital question in IM implementation. However currently, both IM CPGs and TCM CPGs did not mention relevant contents. Therefore, we could not recognize certain recommendations. Following your suggestions, we have

supplemented some contents in the discussion section. The core tips contained impact of herb-drug interaction, current researches and future directions.

- Please change "It was recommended by 6 CPGs, while was regard as weak or insufficient evidence by 5 CPGs" to "It was recommended by 6 CPGs, while was regarded as weak or insufficient evidence by 5 CPGs".

R: Thank you for your suggestion. We have already revised related contents.

- Please change "there has been established a relatively comprehensive and practical management algorithm against IBS and FC" to "there are relatively comprehensive management algorithm for IBS and FC already developed."

R: Thank you for your suggestion. We have already revised related contents.

- What is "therapeutic choice for global symptom relieving"?

R: Thank you for your question. A mistyping of full stop was before this phrase. The revised sentence would be "herbal medicine, acupuncture and other external therapies could be supplemented as second-line interventions for certain symptoms, therapy intervals or special patients, and therapeutic choice for global symptom relieving in IBS." The concept of "global symptom" came from the 2014 ACG monograph, which indicates all aspects related to IBS, not only limited to abdominal pain.

Reviewer #2

Congratulation, very nice study. Be so kind to emphasize that the review is based on the 2 decades experience.

R: Thank you for your acknowledgement. We hope this systematic review could be a resource for researchers to further investigate the possibilities of IM in IBS and FC management. have already revised related contents.

Reviewer #3

This systematic review of clinical practice guidelines and traditional chinese medicine (TCM). * The originality of this manuscript is to reiew as well occidental drugs as traditional chinese therapeutic.

R: Thank you for your acknowledgement. In this systematic review, we aim to summarize the current available WM and TCM interventions for IBS and FC on the foundation of clinical evidences, and then hope to provide new insights for further IM researches and management.

* The quality of this review is the amptitude of drugs reported ib booth medicines

R: Thank you for your acknowledgement. We have reviewed available CPGs in recent two decades, and the systematic review indeed contained relatively large data size.

* The limitis of this review is to put at the same levels all these treatments despitet the proof of efficacy aried strongly according to the treatment and to neglect manipulative treatment as osteopathy or abdominal massage.

R: Thank you for your comments. We understand that the efficacy of intervoention could be influenced by multiple factors. Hence, the appraisal of recommendation level was based on study methodology. According to this mechanism, we believed that the different interventions could be evaluated fairly. In addition, the osteopathy and abdominal massage were not included in our review because available CPGs did not include relevant contents. Therefore, we could not summarize the related recommendations.

Based on the above comments we received, we tried our best to revise our manuscript. In addition, the revised manuscript has been further modified by professional institute to guarantee the language quality. We hope that the revision will meet the standard of *World Journal of Clinical Cases*. Once again, thank you for your supporting, and we are looking forward to your response.

Sincerely yours

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