

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Traditional, Complementary, and Integrative Medicine therapies for the treatment of mild/moderate acute COVID-19: protocol for a systematic review and network meta-analysis

Authors

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VERSION 1 - REVIEW

Reviewer	1
Name	Li, Xuhao
Affiliation	Shandong University of Traditional Chinese Medicine, School of Acupuncture-Moxibustion and Tuina
Date	11-Jul-2024
COI	I have no potential Competing interests at the time of reviewing the paper.

We are making good progress in the fight against COVID-19 and there is no doubt that complementary and alternative medicine/therapies have an important role to play. Further refinement of this study will provide new evidence and ideas for complementary and alternative medicine/therapies to combat COVID-19. Therefore, I believe that the research in this article has some scientific significance and value, and I endorse and recommend the publication of this article.

Of course, I also have two suggestions:

1. it is recommended that the researcher add a flow chart for literature screening;
2. there are so many search terms that it seems a bit cumbersome , and the authors might consider revising how to further streamline and ensure accuracy.

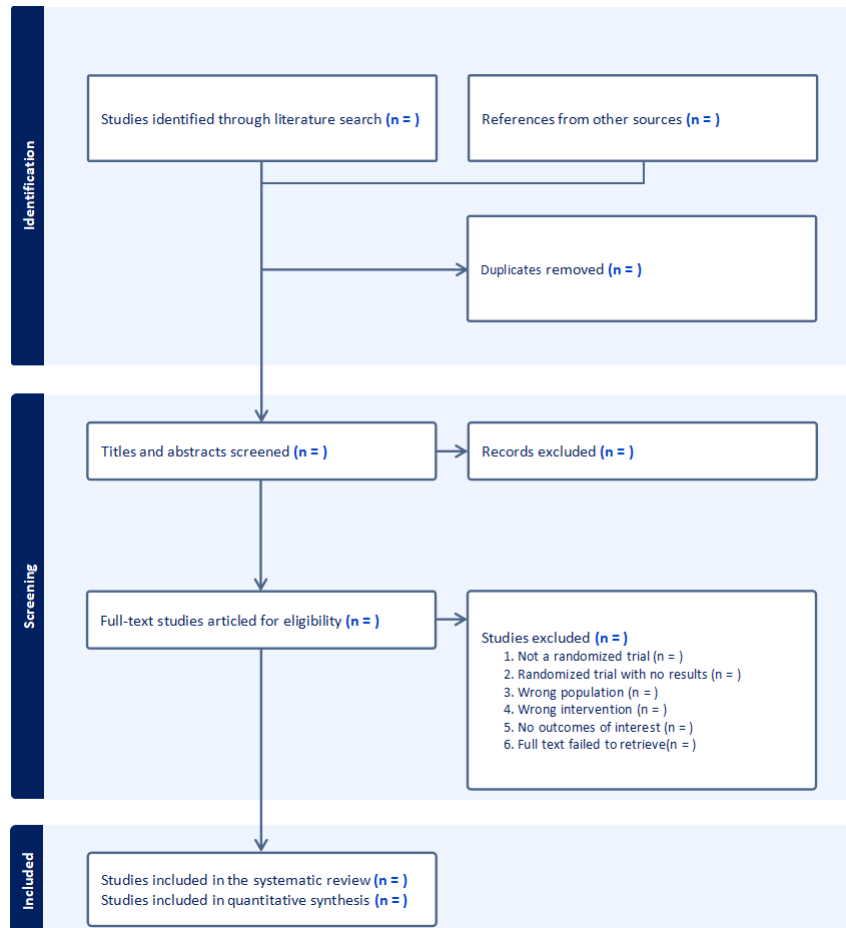
VERSION 1 - AUTHOR RESPONSE

Reviewer 1

1. It is recommended that the researcher add a flow chart for literature screening.

Reply: Thanks for the comment. We have added a flow chart in the manuscript:

“Figure 1 Flow diagram of the study screening process.”



2. There are so many search terms that it seems a bit cumbersome , and the authors might consider revising how to further streamline and ensure accuracy.

Reply: Thanks for the comment. Through our scoping of the literature we have realized that there is a wide variety of descriptions of Traditional, Complementary, and Integrative Medicine (TCIM) in the literature, and not always described by broader terms such as “Traditional Medicine”. They are also not fully indexed in the databases. We therefore made a concerted effort to describe in detail as many groups of TCIM as possible. We used the Cochrane Taxonomy of TCIM, the indexed trees in both Emtree and Mesh, and further complemented with expert review of the terms used. While the search seems overwhelming to look at, we have a simple Excel list of all terms used (this can be shared if needed). This maintains clarity in adapting and using the searches as well as simplicity in reviewing the terms used.

Reviewer 2

3. Very interesting protocol, success in the development.

I suggest to include an Ayurvedic clinical trial base, for example: DHARA.

Reply: We appreciate the kind comments. While Dharaonline is a good resource, it is limited in its scope. It is focused on Ayurveda only, while our review encompasses many more types of TCIM. Unfortunately searching each therapy based repository would not be feasible for a project with such a wide scope. Furthermore, Dharaonline includes not only trials but also commentaries and reviews. Its interface is

limited to single key word searches and doesn't support the use of Boolean operators. Which makes this interface too limited for our use. It also sources it's data from most main stream databases such as Pubmed/Medline which we have searched. We have further searched the following databases and believe this is comprehensive and meets the criteria for searching good practice:

EMBASE (Elsevier), Medline (OVID), VHL TCIM database, Cochrane Central, Clinical Trials.gov and ICTRP.

4. Please review this hypothesis, is it based in previous research? - "We hypothesize, a priori, that treatments will yield larger effect in trials with high risk of bias, among unvaccinated patients, among suspect or probable cases, and in preprint publications."

Reply: Thanks for the comment. According to previous studies, studies with high risk of bias were observed to have larger effect sizes on average compared to studies with low risk of bias;[1] preprints may have a higher risk of bias and their results may change when they are eventually published in peer reviewed journals;[2] vaccination is associated with lower COVID-19 hospitalization and with lower disease progression to death or invasive mechanical ventilation,[3] as a complementary intervention, we hypothesized that TCIM therapies could bring more benefits to unvaccinated COVID-19 patients. Having said that, as mentioned in the Methods section, we will further assess the credibility of these moderators using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN).

Ref 1: Hartling L, Ospina M, Liang Y, et al. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ*. 2009;339:b4012. Published 2009 Oct 19. doi:10.1136/bmj.b4012

Ref 2: Bai AD, Jiang Y, Nguyen DL, et al. Comparison of Preprint Postings of Randomized Clinical Trials on COVID-19 and Corresponding Published Journal Articles: A Systematic Review. *JAMA Netw Open*. 2023;6(1):e2253301. doi:10.1001/jamanetworkopen.2022.53301

Ref3: Tenforde MW, Self WH, Adams K, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. *JAMA*. 2021;326(20):2043-2054. doi:10.1001/jama.2021.19499

5. In the annex I suggest to review the categories of interventions, maybe explain the rationality of the division.

Reply: Thanks for the comment. It is always a great problem to structure the TCIM therapies and there are various different approaches. Our categorization is mainly based on WHO global report on traditional and complementary medicine and the classification of National Center for Complementary and Integrative Health.[1,2] We have further modified Appendix 1 with the input of our Steering Committee. As well as TCIM interventions description in Methods section:

"TCIM interventions (Supplementary 1) include traditional medicine and practices, natural health products, mind-body therapies, physical therapies and manual therapies, and further complex non-traditional medicine treatments."

Ref 1: World Health Organization. WHO global report on traditional and complementary medicine 2019 [Available from: <https://www.who.int/publications/i/item/978924151536>.

Ref 2: National Center for Complementary and Integrative Health. Complementary, Alternative, or Integrative Health: What's In a Name? [Available from:

<https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name>