

Name of journal: *World Journal of Methodology*

Manuscript NO: 73782

Title: Nature and mechanism of immune boosting by Ayurvedic medicine: a systematic review of randomized controlled trials

No	Reviewer comment	Author response
	Reviewer #1	
1	Vallish et al. reviewed the literature exploring the role of Ayurvedic medicine on immune cells. Most articles were published by Indian scientists and the research was mainly conducted in India.	We thank the reviewer for spending their valuable time in reviewing our work and providing feedback for improving our research findings.
2	Major points: 1. The authors collected information regarding the effects of Ayurvedic on immune cells. However, they did not introduce the Ayurvedic compounds; what are they and what have they been used for. Perhaps the second paragraph in the discussion should be expanded and used in the introduction instead. Also, Supplementary Table 3 should be expanded and placed in the beginning of this review.	We agree to this comment, though we have provided a brief glimpse about Ayurveda in the second paragraph that is relevant to the current research. We have expanded this paragraph and have provided additional details about Ayurvedic system of medicine, though we hope that the reviewer agrees with us that a detailed explanation of Ayurvedic medicines is beyond the scope of this research. The compounds mentioned in Supplementary Table 3 are only those of the innumerable Ayurvedic medicines that have been used in the different studies included in the present review: these represent only a small proportion of compounds used as Ayurvedic medicines. In fact, there are multiple compendia and dictionaries of Ayurvedic medicines (such as the one used by us as a reference: Khare CP. Indian medicinal plants: an illustrated dictionary. Berlin: Springer; 2007). Thus, we believe that neither the second para in the discussion, nor the supplementary table 3, should be altered.
3	2. In several parts of this review, the authors mentioned that various Ayurvedic compounds affect NK cell activity. No explanation was given whether this is detrimental or beneficial. NK cells are pleiotropic which have many biological activities, including anti-tumor and anti-viral effects, to being inflammatory secreting variety of inflammatory cytokines and chemokines. The authors should specifically indicate in each study described the functional activity of NK cells. Similar point regarding CD4 T cell	We agree to this assessment about the pleiotropic effects of both NK cells and CD4 T cells. Unfortunately, the explanation about the outcomes of enhancement of number and/ or activities of these cells are not described in the individual studies. This was also one of our major findings: that the explanation for immune enhancing effect by different Ayurvedic formulations has not been adequately explored in human clinical trials. Since our work is a review of the information available in these primary studies, we hope that the reviewer agrees with us that, it is not possible for us to evaluate whether the impact of modification of NK cell/ CD4 T cell activity has been detrimental or harmful in these

		individual studies. Also, information about the impact of different Ayurvedic preparations on NK cell activity was available in 5 studies, and we have compiled this information as the second paragraph of section 3.2.1.2.
	Reviewer #2	
4	<p>I liked reading the article since the topic is exciting and timely, and not just because of the covid pandemic but in general as well. I was really interested in the findings reported by the authors.</p> <p>The review article is thorough and clear, the steps made to accomplish the study are well explained, the search strategy, the eligibility criteria, and finally the details of the included works, the tables and figures are appropriate, too.</p> <p>The sections of the article are well-organized and are in line with the major components and functions of the immune system.</p> <p>The authors aim to be objective, impartial, and reasonable, but this purpose is not always achieved.</p>	We thank the reviewer for the encouraging words and providing constructive feedback to improve our research.
5	<p>I have the following remarks about the details of the article:</p> <p>1) Page 13, section 3.2.1.3. reference 18. IgA is doubled: "increase in serum levels of IgA and IgM, and also of IgA".</p>	This was supposed to be "...IgA and IgM, and also of IgG..."; this has been now rectified.
6	<p>2) Page 13, section 3.2.1.4. reference 26. "such pathogens" doesn't seem to make sense. What pathogens? Thus?</p>	This sentence has been edited to improve clarity.
7	<p>3) Page 14. section 3.2.1.5. The section is about the effects on total wbc counts, total lymphocyte counts, and neutrophil counts, phagocytic function by neutrophils, levels of eosinophils and basophils. I suggest that the title of this section be: "Impact on total WBC counts and granulocytes". (T and B lymphocytes, and NK cells have already been discussed in separate prior sections.)</p>	Thank you for this suggestion; the title has been modified.
8	<p>4) Page 15. section 3.2.1.6. "patients" in doubled: "infusion among patients GI cancer patients undergoing surgery".</p>	Thank you; the first mention of 'patients' is removed.
9	<p>5) Page 16. reference 36. Please explain this reference in a bit more details. "the number of COVID-19 patients with negative RTPCR results was zero" sounds weird; first I thought you mixed up positive to negative, and had to check the original work.</p>	Thank you for pointing this error; this has now been rectified
10	<p>6) Page 18. lower paragraph: "Perhaps the ongoing pandemic was a missed opportunity towards this end, wherein stakeholders were interested in profitmaking through sales of products with</p>	This sentence was inserted because there were attempts by some entities in India to market few medicines containing some Ayurvedic ingredients, supposedly targeting COVID-19, without producing

	dubious claims, rather than relevant and credible clinical evidence generation." Well, this double statement may be stretching credibility. On the one hand, the pandemic is not over; on the other hand, this review is about clinical evidence generated; finally, profitmaking with dubious claims might be an exaggeration, and not the task of a scientific paper to judge this (especially in a world journal). Please reconceive these lines or eliminate them.	evidence for the same. However, we now realise that inclusion of this point may not be entirely appropriate for a scientific paper, as rightly pointed out by the reviewer, and hence the entire sentence has been now removed.
11	7) Page 27. Table 1. 'Some concerns of bias' is marked with a question mark in a yellow circle in the table itself, while in the footnote it is an exclamation mark.	Thank you for this astute observation; the footnote is now updated
12	8) Page 28. Table 2. Notes are marked with 1,2,2,3 instead of 1,2,3,4 (like in the table).	The footnote is now updated with the appropriate superscripts
13	After revising the above points this nice review warrants publication in WJM.	We hope that our updated manuscript has satisfied all your queries; we once again thank you for the valuable comments.
	Science editor	
14	The authors conducted a systematic evaluation of a randomized controlled trial to elaborate the nature and mechanism of Ayurvedic drugs in enhancing immunity. Respected authors, this is a well written paper and covers an interesting topic. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. Language Quality: Grade C (A great deal of language polishing) Scientific Quality: Grade C (Good)	We thank the science editor for the encouraging comments. The present work is a systematic review in Ayurveda, and a targeted journal search was involved in the process. For this reason, we are unfortunately not in a position to comply with the requirement that there must not be more than 3 references from the same journal.
	Company editor-in-chief	
15	I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Methodology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or	We thank the company editor-in-chief for the decision. We have complied with all the instructions.

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