



## STUDY PROTOCOL

# **REVISED** Impact of AYUSH interventions on COVID-19: a protocol for a living systematic review and meta-analysis [version 2; peer review: 2 approved, 1 approved with reservations]

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## Abstract











**Background:** The coronavirus disease 2019 (COVID-19) pandemic has created a great burden on governments and the medical fraternity globally. Many clinical studies from the Indian system of Traditional Medicines [Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy (AYUSH)] have been carried out to find appropriate solutions. Through a living systematic review and meta-analysis, this study aims to determine the effectiveness of the Traditional System of Indian Medicine (AYUSH system) in lowering the incidence, duration, and severity of COVID-19.




**Methods:** We will search the following databases: Pubmed; the Cochrane central register of controlled trials (CENTRAL); the Clinical Trials Registry - India (CTRI); Digital Helpline for Ayurveda Research Articles (DHARA); AYUSH research portal; Google scholar and World Health Organization (WHO) COVID-19 database. Clinical improvement, WHO ordinal scale, viral clearance, incidences of COVID-19 infection, and mortality will be considered as primary outcomes. Secondary outcomes will be use of O2 therapy or mechanical ventilator, admission to high dependency unit or emergency unit, duration of hospitalization, the time to symptom resolution, and adverse events. Data will be synthesized, with RevMan 5.4 tool and the risk of bias will be assessed with RoB 2 (for RCTs) and ROBINS I (for NRSIs). Certainty of evidence will be assessed through the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool. The review will be updated bi-monthly with two updates.

**Conclusion:** This living systematic review will be the first to address AYUSH interventions in COVID-19, synthesizing the full spectrum of Indian Traditional System of Medicine against COVID-19. It will facilitate professionals, guideline developers, and authorities with up to date synthesis on interventions periodically to make health-care decisions on AYUSH therapies in the management of COVID-19.

## Open Peer Review

Approval Status   

	1	2	3
<b>version 2</b>			
(revision)			
08 Mar 2022			
<b>version 1</b>			
28 Jul 2021			

1. **Rohit Sharma** , Banaras Hindu University, Varanasi, India
2. **Ram C. Bajpai** , Keele University, Keele, UK
3. **Dr. Galib Ruknuddin** , University of Delhi, New Delhi, India

Any reports and responses or comments on the article can be found at the end of the article.

## Keywords

Ayurvedic medicine, AYUSH, Complementary therapies, COVID-19, Systematic review and meta-analysis

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**Author roles:** **Thakar A:** Funding Acquisition, Project Administration, Resources, Writing – Review & Editing; **Panara K:** Formal Analysis, Investigation, Writing – Original Draft Preparation; **Goyal M:** Conceptualization, Investigation, Writing – Original Draft Preparation; **Kumari R:** Investigation, Writing – Original Draft Preparation; **Sungchol K:** Conceptualization, Project Administration, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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**REVISED Amendments from Version 1**

We have added 'Google scholar' as an additional database for search in the abstract section as suggested by the reviewer. Global and Indian disease burden and chemoprophylaxis or therapeutic treatments for COVID-19 that are being used by conventional medicines have been added in the introduction section of the revised manuscript.

Definition of the outcome selected (clinical improvement) has been added in the revised manuscript.

Explicit data syntheses plan as "Meta-analysis of the data of individual drugs will be done if sufficient number of studies reported the particular outcome, if a single study will report the particular outcome, we will report the measure of effects. We anticipate scarce RCTs for each intervention, hence analytical observational studies will be included for data synthesis. As clinical heterogeneity is anticipated random effect model has been selected for meta-analysis." has been added in the data synthesis section of the revised manuscript.

In the revised article eligibility criteria of control have been added as "All the trials with the appropriate control as Standard of care or placebo or no treatment was included in this review. Uncontrolled studies or AYUSH drugs as control were excluded" in the intervention section.

We have added eight new references as required.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19) has expanded over the globe, affecting most countries in the world, and led to significant morbidity and mortality. Globally, more than 428 million cases had caused about 6 million COVID-19 deaths by end of the February 2022. In India, casualties crossed 5 lakhs, out of 42 million confirmed cases.<sup>1</sup> Mutation in SARS-CoV-2 within its transmissible form has been detected in some continents leading to increased public health distress.<sup>2</sup> Scientists throughout the world are rigorously engaged in the development of effective vaccines and therapeutics for the prevention and cure of this novel coronavirus. Statistics indicate that despite efforts undertaken by various health care professions and authorities, cases are still on the rise.<sup>3</sup> For inpatient, Remdesivir, Dexamethasone, and certain monoclonal antibodies are advocated<sup>4</sup>; nevertheless, efficacy has been revealed to be limited. To expedite the discovery, hydroxychloroquine and azithromycin were repurposed for the prevention or cure of COVID-19, but the outcomes were not encouraging.<sup>5-8</sup> Pre-exposure chemoprophylaxis therapies are still unavailable.<sup>4</sup>

People are turning to alternative treatments for prevention or cure because there is no promising medication accessible. Research on COVID-19 from Alternative and Complementary Medicines are being carried out in many countries.<sup>9</sup> Countries including India, China, and South Korea, have issued guidelines on traditional medicines for the prevention and management of COVID-19.<sup>10</sup> Several initiatives have been launched to support ongoing research in the Traditional, Integrative, Complementary and Alternative Medicine (TICAM) to utilize available traditional knowledge in an integrated manner.<sup>11,12</sup> Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy (abbreviated as AYUSH)<sup>13</sup> are five alternative and complementary therapies prevalent in India that are widely used in COVID-19 management. At inception of the pandemic, ministry of AYUSH (regulatory body of Indian system of medicine) issued advice based on an advisory panel of AYUSH experts and primitive evidence that recommended the use of some herbs and measures to enhance immunity.<sup>14</sup> In this advice, traditional herbs and measures, which have already been in use for decades for various ailments like fever, cough, and respiratory distress, and as a non-specific immunity enhancer, possessing anti-viral, anti-bacterial and anti-microbial properties, were recommended.<sup>15</sup> Among recommended formulations, some have undergone scientific investigations, such as Ayush 64, Chyawanprash, Guduchi Ghanavati, Arsenica Album, Kabasur Kudineer, Nilavembu Kudineer, for their possible preventive or therapeutic impact.<sup>16</sup> Some trials on AYUSH interventions are already completed and published<sup>17-20</sup> or in press. Findings of such studies need to be appraised and summarized carefully through syntheses of evidence to determine the strength of the evidence. Further, it is time for AYUSH health policy makers to examine and revise the guidelines recommended for COVID-19 using an evidence-based tactic, involving the best research existing till date. This study aims to assess the effectiveness of the Traditional System of Indian Medicine (AYUSH systems of Medicine) on reducing the incidence, duration, and severity of COVID-19 through systematic review and meta-analysis. Traditional systematic reviews provide an overview of the relevant evidence at a specific time only, whereas living systematic reviews address this limitation through periodical updates. A living systematic review provides a thorough and current appraisal of the evidence that may help to develop and update recommendations and clinical guidelines time to time.

**Protocol**

This protocol has been registered in PROSPERO (CRD42021244831) prospectively.

## Eligibility criteria

All clinical trials, observational (analytical) researches on any interventions of the AYUSH systems published in English language only, regardless of publication status, will be included in our study.

Protocol, pre-clinical, cross-sectional, case reports, case series, single-arm or not having appropriate control will be excluded. Articles published in a language other than English will also be excluded.

## Participants

Person with risk of COVID-19 exposure or with suspected, probable, or confirmed COVID-19 will be included independently of the severity of their symptoms, gender, age, or ethnicity.

## Interventions

Any type of intervention or exposure from any of the AYUSH system of medicine aimed at prophylaxis or treatment either stand-alone or add-on to the comparator (standard of care or placebo or no treatment control) will be included in our study. There will be no restriction regarding dose, dosage form, duration of treatment or number of medicines used. All the trials with the appropriate control as Standard of care or placebo or no treatment were included in this review. Uncontrolled studies or AYUSH drugs as control were excluded.

## Outcome measures

Studies done on AYUSH interventions intended for both prophylaxis and therapeutic purposes. Therefore, we will divide our outcome measures in two categories.

- Primary outcomes for therapeutic studies will be clinical improvement (defined as 'achieving health status of an absence of symptoms attributed to COVID-19 and saturation of Peripheral Oxygen ( $SpO_2$ ) > 93%'), **ordinal scale for disease severity**, mortality and viral clearance; and for prophylaxis studies will be incidence of COVID-19 infection and mortality.
- Secondary outcomes for therapeutic studies will be use of  $O_2$  therapy, use of ventilator, admission to high dependency unit or emergency unit, duration of hospitalization, the time to symptom resolution, and adverse events; and for prophylaxis studies will be symptomatic SARS-CoV-2 infection, disease severity and adverse events.

## Information sources

We will search the following databases: **Pubmed**; the Cochrane Central Register of Controlled Trials (**CENTRAL**); **WHO COVID-19 database**; the Central Trial registry - India (**CTRI**); Digital Helpline for Ayurveda Research Articles (**DHARA**); Google scholar; and **AYUSH research portal**. These databases will be searched from 1st December 2019. We will restrict our studies to the studies published in English only without any publication restrictions. Hand searches will be conducted on the reference lists of eligible primary studies. Preprints (**SSRN**, **OSF**, **medRxiv**), grey literature (**ayurCASERxiv**) and unpublished literature will be searched.

## Search strategy

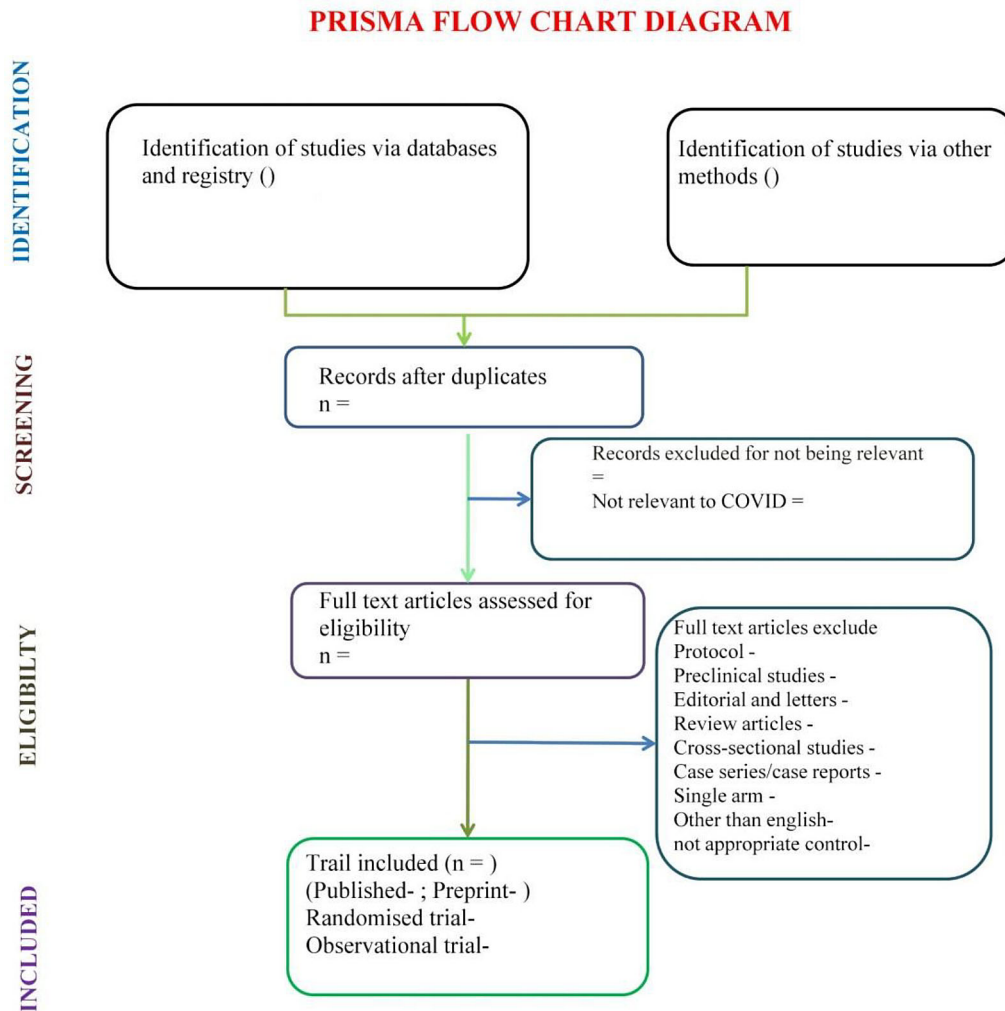
Search terms will be as follows: "COVID - 2019" OR "SARS-CoV-2" OR "NCP" OR "Corona Virus Disease-19" OR "COVID-19" AND "Indian Traditional Medicine" OR "AYUSH" OR "Ayurveda" OR "Yoga Naturopathy" OR "Unani" OR "Siddha" OR "Homeopathy". A combination of medical subject headings [MeSH] terms and other text words will be used. Full search strategies with preliminary results are summarized in the *Extended data*.<sup>21</sup>

## Data collection

Endnote X9 software will be used to manage the citations searched from the various databases. Two reviewers will independently screen all titles and abstracts. Of those articles selected by at least one of the reviewers, each of them will independently apply an inclusion and exclusion criteria checklist to decide if the study meets our selection criteria.

Articles identified via different databases, registry and other methods will be collected and processed through Endnote X9 software wherein duplicates and irrelevant articles will be removed. Remaining article will be reviewed full text. Articles published in language other than English will also be excluded. Included studies will be categorized according to publication status and methodology and processed for systematic review. Study selection process is displayed graphically in the PRISMA-P flow diagram (**Figure 1**). Disagreements will be resolved by discussion between the two reviewers, with a third person if consensus cannot be reached.

For the short listed articles two reviewers independently extract the data with reference to name of study, place of study, type of study, inclusion criteria, exclusion criteria, number of participants randomized, dose, frequency, route of



**Figure 1. PRISMA flow chart for study selection process.** Flow chart covers the plan of study selection process of living systematic review.

administration and duration for each intervention, number of participants who received each intervention, comparators, baseline data, mean age, percent male, severity of illness (mild, moderate, severe, critically ill), co-morbidities outcomes, duration of interventions, number of participants, and methodological characteristics. A pilot-tested standardized data extraction form with detailed instructions has been developed (*Extended data*<sup>21</sup>). Any disagreement will be resolved by consensus or the involvement of the third assessor.

**Assessment of risk of bias**

The risk of bias of the included studies will be done using the Cochrane Risk of Bias tool RoB 2.0,<sup>22</sup> which includes consideration of the following items: randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of reported results. Non Randomized Studies of Interventions (NRSIs) will be ranked for risk of bias using Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool<sup>23</sup> and domains are: bias due to confounding; bias in selection of participants; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of the outcome; and bias in selection of the reported result. Across these domains we will rate the risk of bias of studies at i) low risk of bias, ii) some concerns, and iii) high risk of bias. When there is a low risk of bias across all domains, overall risk of bias will rank as low risk; when at least one domain bears some concerns, overall risk of bias will rank as some concerns; and studies will be ranked as high risk when at least one domain falls into the high risk category or multiple domains fall into the some concern category. Any differing views will be discussed with another team member.

### Effect measures

We will analyze our data in accordance with the Cochrane Handbook for Systematic reviews of Interventions.<sup>24</sup> We will use the Risk Ratio or Odds Ratio to compute relative impacts for outcomes with dichotomous data. For continuous outcomes, we will utilize mean difference and standard deviation (with 95% confidence intervals). If the unit of any of the measures isn't consistent throughout the studies, we will convert it to a standardized value for analysis.

### Dealing with missing data

Whenever we find insufficient or any missing data then the authors of the studies will be contacted for clarification, with one follow-up email. If we do not receive satisfactory answers then we will assume data to be missing at random and analyze only the available data (i.e. ignoring the missing data).

### Data synthesis

The characteristics and findings of the included studies will be presented in tables that summarize the study design, intervention, study participants, and outcomes. Meta-analysis will be displayed in forest plot. RevMan software 5.4<sup>25</sup> will be used for various task of data analysis such as measurement of effects, assessment of heterogeneity, sub-group analysis, sensitivity analysis and for assessment of reporting bias. Meta-analysis of the data of individual drugs will be done if sufficient number of studies reported the particular outcome, if a single study will report the particular outcome, we will report the measure of effects. We anticipate scarce RCTs for each intervention, hence analytical observational studies will be included for data synthesis. As clinical heterogeneity is anticipated random effect model has been selected for meta-analysis.

### Assessment of heterogeneity

Testing for heterogeneity between the studies will be done by using Cochran's Q test and by  $I^2$  test statistics. Heterogeneity will also be assessed by visual assessment of forest chart.

### Subgroup analysis

The subgroup analyses will be carried out for age category (young, middle, old), disease severity (mild, moderate, severe) and dose of the interventions, if possible.

### Sensitivity analysis

Sensitivity analysis will be performed to test the robustness of findings that are not affected by the different decisions that could be made during the review process. Sensitivity analysis has been planned considering risk of bias and study designs.

### Assessment of reporting bias

For a specific direct comparison, funnel plot assessment for publication bias will be done when there will be ten or more than ten studies available. Any asymmetry of funnel plot will signify possible small research effects and thus will enable us to be aware about the small study bias.

### Confidence in cumulative evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used for the assessment of evidence level of the results.<sup>26</sup> Factors that are considered to analyze the quality of the evidence include research limitations, effect consistency, imprecision, indirectness, and publication bias. The evidence quality will be categorized as high, medium, low and very low.

### Updates of living systematic review

We plan to run searches for new studies every month. This will also include screening abstracts of the recently retrieved reports. The monthly interval for screening was preferred as we expect a rise in appropriate publications. The review itself will be updated every two months, providing that a sufficient quantity of new records will be acknowledged for inclusion. We will adhere with the PRISMA 2020 guidelines for reporting systematic review and meta-analysis. Living review will be ceased after two updates, then its necessity will be reanalyzed. It may be only continued further if additional budget provided by funder.

This is living systematic review, so, there is no need for ethical approval. There is no direct involvement of human or animal participants. This review will be disseminated in a peer reviewed journal.

### Study status

Preliminary searches from databases and the study selection process have been completed, data are being analyzed and synthesized presently.

## Conclusion

This living systematic review will be first review addressing AYUSH interventions in COVID-19 in which the full spectrum of Indian Traditional System of Medicine against COVID-19 will be summarized. It will facilitate clinicians, guideline developers, and policymakers to take health care decisions on AYUSH interventions in COVID-19 management. The reliability and validity of the findings will mainly depend on the variability in Population, Intervention, Comparator, Outcome (PICO) of primary evidence included and methodological quality among them. We plan to include pre-prints due to the importance of the information and the fact that many studies will likely be first published in pre-print repositories. We can expect the possibility of publication bias as positive outcome studies are more likely to be published sooner than negative outcome studies; however, including pre-prints may reduce publication bias.

## Data availability

### Underlying data

No data is associated with this article.

### Extended data

Zenodo: Data set for AYUSH interventions for COVID-19- A Living Systematic Review and Meta-analysis, <https://doi.org/10.5281/zenodo.5091828>.<sup>21</sup>

This project contains the following extended data:

- Data extraction tool
- Search strategy

### Reporting guidelines

Zenodo: PRISMA-P Checklist of protocol – AYUSH interventions for COVID-19 – A Living Systematic Review and Meta-analysis, <https://doi.org/10.5281/zenodo.5109089>.<sup>27</sup>

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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# Open Peer Review

Current Peer Review Status:   

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## Version 2

Reviewer Report 04 April 2022

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 **Ram C. Bajpai** 

School of Medicine, Keele University, Keele, UK

Authors are planning to include all types of study designs (such as trials, cohort studies, and case-control studies) which is not recommended if you read the Cochrane Handbook carefully. A substantial methodological heterogeneity will make meta-analysis results useless and unreliable. Clinical trials and prospective observational can only be combined as their designs are similar. Authors must choose to do a systematic review of trials (may include prospective cohorts), or a systematic review of observational studies only (cohorts and other retrospective designs). High-quality evidence is solicited from any systematic review rather than low-quality evidence by colliding everything in an unexplained manner. Authors must think about it and make the right decision and modify the entire protocol here and in the PROSPERO.

I couldn't see the end date for the literature search in the information sources. It has to be a final date by which all databases will be searched.

The data synthesis section is too broad at the moment. Authors must write it according to the nature of outcomes variables (such as continuous and binary outcomes). They need to specify meta-analysis method by type of outcomes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology, Medical Statistics, Meta-analysis

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 28 March 2022

<https://doi.org/10.5256/f1000research.122040.r126658>

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**Rohit Sharma** 

Department of Rasa Shastra and Bhaishajya Kalpana, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

The authors have addressed my comments and I am satisfied with the improvements.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Ayurveda, Herbal Medicine, Traditional Medicine, Natural Products, Complementary and Alternative Medicine

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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Version 1

Reviewer Report 07 February 2022

<https://doi.org/10.5256/f1000research.58655.r122001>

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**Dr. Galib Ruknuddin** 

Department of Ras Shastra and Bhaishajya Kalpana, All India Institute of Ayurveda, University of Delhi, New Delhi, Delhi, India

A rational topic for systematic review. Evaluating the efficacy of AYUSH interventions by analyzing the best available evidence is the need of the hour. The outcome may significantly contribute to the suffering population. However, the present protocol may consider a few of the below:

1. Eligibility criteria for 'control' may be included.
2. Excluded studies may be mentioned in the eligibility criteria during the study design.
3. Detail planning on data synthesis methods is needed, focusing on how RCT and NRSI will be combined in meta-analysis and interpreted.
4. The author needs to clarify the selection of the model in data analysis and synthesis.

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Ayurveda

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 02 Mar 2022

**Kalpesh Panara**, Institute of Teaching and Research in Ayurveda, Jamnagar, India

First of all, we are gratefully appreciating your invaluable suggestions in improving the quality of our research article. The responses to your observation and suggestion are as follows:

**Comment #1:** Eligibility criteria for 'control' may be included.

**Response:** As per the suggestion of the respected reviewer, eligibility criteria for the control has been added as:

*This review will include all the trials with the appropriate control as Standard of care or placebo or no treatment. Uncontrolled studies or AYUSH drugs as control will be excluded.*

**Comment #2:** Excluded studies may be mentioned in the eligibility criteria during the study design.

**Response:** We value the suggestion of the respected reviewer and added the type of study which will be excluded as:

*Protocol, pre-clinical, cross-sectional, case reports, case series, single-arm or not having appropriate control will be excluded. Articles published in a language other than English will also be excluded*

**Comment #3:** Detail planning on data synthesis methods is needed, focusing on how RCT and NRSI will be combined in meta-analysis and interpreted.

**Response:** We agree that RCTs and NRSIs are not combined routinely in meta-analysis except in exceptional circumstances. As limited RCTs on Ayush interventions are anticipated,

which may restrict us from performing a meta-analysis, we opted to add NRSI and RCT for meta-analysis. It may lead to induce clinical heterogeneity in the pooled outcome measure. Further, assuming heterogeneity due to different designs, we have planned a random effect model to compute the summary effect. Moreover, we will perform sensitivity analysis considering the study design to know the impact of the inclusion of NRSI on pooled estimates. Further, if sufficient RCTs will be available in subsequent updates, we may exclude NRSIs from data syntheses. The intent of this reply is added and highlighted with green colour in the revised manuscript.

**Comment #4:** The author needs to clarify the selection of the model in data analysis and synthesis.

**Response:** We thank our reviewer for their observation that the selection of the model in data analysis and synthesis should be more explicit.

Concerning the data analysis and synthesis, our submissions are as follows:

As the anticipated nature of studies may be diverse, heterogeneity may be observed.

Therefore, we have planned a random effect model to compute the summary effect.

Additionally, Sensitivity analysis based on the nature of the study will be done to explain the heterogeneity, if sufficient number of study available.

The intent of this reply has been added and highlighted in the manuscript for an easy review.

All the additional phases have been highlighted in green in the revised manuscript for easy review.

Finally, the authors are warm-heartedly admiring your invaluable comments/suggestions and believe that your kind contributions have undisputedly helped us to improve the quality of the research article.

**Yours sincerely**

**Authors**

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 24 November 2021

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? Ram C. Bajpai 

School of Medicine, Keele University, Keele, UK

Authors must be more specific about the study designs eligible for this systematic review. For example, it is completely unclear whether a large case-series study will be eligible or not. So, kindly elaborate on your inclusion in more detail.

Authors cannot ignore Google Scholar for searching eligible articles, as it is one of the biggest databases for grey literature and lots of Indian papers published in non-indexed journals. What do you mean by 'till current time' for searching different databases? There has to be an end date in the protocol.

How was clinical improvement defined for this systematic review? Kindly explain in more detail. The statement, "Protocol, pre-clinical, cross-sectional, case reports, case series, single-arm or not having appropriate control will be excluded. Articles published in a language other than English will also be excluded." Should be mentioned in the eligibility section.

Authors must adhere to the PRISMA 2020 reporting guidelines for the main systematic review and it should be cited in the protocol as well.

The data synthesis plan is not sufficiently explained in this protocol. For example, authors are planning to combine RCTs and observational studies in the meta-analysis that will add a huge clinical/methodological heterogeneity, and mean difference will be an appropriate measure. Similarly, what model will be used to combine data from different studies? All these important considerations must be incorporated with clarity in the protocol as a priority.

GRADE approach better suits randomised control trials so authors must distinguish from observational studies and present a proper plan. Add reference for GRADE.

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

No

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology, Medical Statistics, Meta-analysis

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 02 Mar 2022

**Kalpesh Panara**, Institute of Teaching and Research in Ayurveda, Jamnagar, India

First of all, we are gratefully appreciating your invaluable suggestions in improving the quality of our research article. The responses to your observation and suggestion are as follows:

**Comment #1:** Authors must be more specific about the study designs eligible for this systematic review. For example, it is completely unclear whether a large case-series study will be eligible or not. So, kindly elaborate on your inclusion in more detail.

**Response:** The authors are thankful for the observation of the reviewer. We wish to clarify that large case-series will also be excluded as it does not have the control arm. As far as the Explicit exclusion criteria of the articles are concerned, the following is our submission:

*"Protocol, pre-clinical, cross-sectional, case reports, case series, single-arm or not having appropriate control will be excluded. Articles published in a language other than English will also be excluded."*

The intent of this reply is added and highlighted in the revised manuscript.

**Comment #2:** Authors cannot ignore Google Scholar for searching eligible articles, as it is one of the biggest databases for grey literature and lots of Indian papers published in non-indexed journals.

**Response:** In response to the reviewer's suggestion, Google Scholar has been added in the source of information section, the relevant section has been highlighted in the revised manuscript.

**Comment #3:** What do you mean by 'till current time' for searching different databases? There has to be an end date in the protocol.

**Response:** Here, we wish to clarify 'till current time' means the date on which the actual search will be done. However, considering the ambiguity of this phrase among the readers, we are deleting this in our revised article.

**Comment #4:**

How was clinical improvement defined for this systematic review? Kindly explain in more detail.

**Response:** We are very thankful for the reviewer's comment, and in response to the reviewer's suggestion, the definition of clinical improvement has been added as follows: Clinical improvement has been defined as 'achieving health status of an absence of symptoms attributed to COVID-19 and/or Saturation of Peripheral Oxygen (SpO<sub>2</sub>) > 93%'. The definition has been added and highlighted in the manuscript.

**Comment #5:** The statement, "Protocol, pre-clinical, cross-sectional, case reports, case series, single-arm or not having appropriate control will be excluded. Articles published in a language other than English will also be excluded." Should be mentioned in the eligibility section.

**Response:** The authors agree with the respected reviewer, and the statement mentioned

above has been mentioned in the eligibility section.

**Comment #6:** Authors must adhere to the PRISMA 2020 reporting guidelines for the main systematic review and it should be cited in the protocol as well.

**Response:** Reporting guideline suggested by the reviewer has been added.

**Comment #7:** The data synthesis plan is not sufficiently explained in this protocol. For example, authors are planning to combine RCTs and observational studies in the meta-analysis that will add a huge clinical/methodological heterogeneity, and mean difference will be an appropriate measure. Similarly, what model will be used to combine data from different studies? All these important considerations must be incorporated with clarity in the protocol as a priority.

**Response:** The authors raised important concerns about the data synthesis method, and we have clarified it by adding more details on data syntheses.

We agree that RCTs and NRSIs are not combined routinely in meta-analysis except in exceptional circumstances. As limited RCTs on Ayush interventions are anticipated, which may restrict us from performing a meta-analysis, we opted to add NRSI and RCT for meta-analysis. It may lead to induce clinical heterogeneity in the pooled outcome measure. Further, assuming heterogeneity due to different designs, we have planned a random effect model to compute the summary effect. Moreover, we will perform sensitivity analysis considering the study design to know the impact of the inclusion of NRSI on pooled estimates. Further, if sufficient RCTs will be available in subsequent updates, we may exclude NRSIs from data syntheses.

**Comment #8:** GRADE approach better suits randomized control trials so authors must distinguish from observational studies and present a proper plan. Add reference for GRADE.

**Response:** The authors are grateful to the reviewer for their observation.

We will adopt the GRADE approach to know the quality and strength of evidence. The current GRADE approach for a body of evidence relating to interventions accept observational studies (otherwise known as non-randomized studies, or NRS) also wherein certainty for observational study starts with low grade, unlike RCTs. We will follow the GRADE present guideline for an observational study to rate the evidence. Reference for GRADE has been added.

All the additional phases have been highlighted in green in the revised manuscript for easy review.

Finally, the authors are warm-heartedly admiring your invaluable comments/suggestions and believe that your kind contributions have undisputedly helped us to improve the quality of the research article.

**Yours sincerely**

**Authors**

**Competing Interests:** No competing interests were disclosed.



Reviewer Report 20 September 2021

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? **Rohit Sharma** 

Department of Rasa Shastra and Bhaishajya Kalpana, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

The manuscript follows the PRISMA-P guidelines and is methodologically good and well written. The study covers two aims that encompass determining the Prophylactic effect of the AYUSH medicines on Sars-Cov-2 infection and evaluating the therapeutic effectiveness of AYUSH drugs to COVID-19 patients. As the study is living in nature, evidence will be updated from time to time and may guide stakeholders. However, there are a few concerns for authors to consider:

1. In the abstract author has written that 'Data will be synthesized, and the risk of bias will be assessed with RevMan 5.4 tool' that seems incomplete. RevMan tool has been designed for the synthesized and meta-analyzed data. The authors should mention the method used for the Risk of Bias assessment.
2. To give more impact on background, the author may include the COVID19 epidemics data of global and Indian tertiary.
3. In the introduction, there was no mention of chemo-prophylaxis or therapeutic treatments that are being used by conventional medicines that need to be added by authors.
4. The authors should provide additional information about the data synthesis methods used to analyse the various medicines in the AYUSH system, perpendicularly to whether it's evaluated together or separately?

I particularly value the fact that this is a good systematic review study protocol, possibly the first of its type to encompass the entire AYUSH system.

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Ayurveda, Herbal Medicine, Traditional Medicine, Natural Products, Complementary and Alternative Medicine

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 02 Mar 2022

**Kalpesh Panara**, Institute of Teaching and Research in Ayurveda, Jamnagar, India

First of all, we are gratefully appreciating your invaluable suggestions in improving the quality of our research article. The responses to your observation and suggestion are as follows:

**Comment #1:** In the abstract author has written that 'Data will be synthesized, and the risk of bias will be assessed with RevMan 5.4 tool' that seems incomplete. RevMan tool has been designed for the synthesized and meta-analyzed data. The authors should mention the method used for the Risk of Bias assessment.

**Response:** As far as the methods of risk of bias assessment are concerned, the following is our submission:

Revised Cochrane tool for assessing the risk of bias RoB-2 was used for RCTs, and Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) was used for Non-Randomized Studies of Interventions (NRSIs) to rate studies at outcome level.

The intent of this reply is added and highlighted in the abstract section of the revised manuscript.

**Comment #2:** To give more impact on background, the author may include the COVID-19 epidemics data of global and Indian tertiary.

**Response:** In response to the reviewer's suggestion, we have added the following line that represents the current COVID-19 epidemics data of global and Indian territory in the introduction section. "Globally, more than 428 million cases had caused about 6 million COVID-19 deaths by end of the February 2022. In India, casualties crossed 5 lakh, out of 42 million confirmed."

**Comment #3:** In the introduction, there was no mention of chemo-prophylaxis or therapeutic treatments that are being used by conventional medicines that need to be added by the authors.

**Response:** The authors are thankful for this observation and in response, chemo-prophylaxis or therapeutic treatments conventionally used have been added in the revised manuscript.

"For inpatient situations, Remdesivir, Dexamethasone, and certain monoclonal antibodies are advocated; nevertheless, efficacy has been revealed to be limited. To expedite the discovery, hydroxychloroquine and azithromycin were repurposed to prevent or cure

COVID-19, but the outcomes were not encouraging. Pre-exposure chemoprophylaxis therapies are still unavailable.”

**Comment #4:** The authors should provide additional information about the data synthesis methods used to analyse the various medicines in the AYUSH system, perpendicularly to whether it's evaluated together or separately?

**Response:** In response, we have clarified the data synthesis methods used to analyze the various medicines in the AYUSH system in our revised manuscript. Following is our submission:

We are intended to meta-analyse the outcome data of individual drugs when a sufficient number of studies reported the particular outcome. If a single study will report the particular outcome, we will only report the measure of effects. We anticipate scarce RCTs for each intervention, hence analytical observational studies will be included for data synthesis. As clinical heterogeneity is anticipated random effect model has been selected for meta-analysis.

All the additional phases have been highlighted in green in the revised manuscript for easy review.

Finally, the authors are warm-heartedly admiring your invaluable comments/suggestions and believe that your kind contributions have undisputedly helped us to improve the quality of the research article.

**Yours sincerely**

**Authors**

**Competing Interests:** No competing interests were disclosed.

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