Efficacy and Safety of Ayurveda Interventions as Standalone or Adjuvant Therapy in Management of COVID-19: A Systematic Review Protocol

Azeem Ahmad1, Amit K Rai2, Himanshu Negandhi3, Manohar S Gundeti4, BCS Rao5, Narayanan Srikanth6

ABSTRACT

Background: Coronavirus disease (COVID-19) is a highly infectious disease caused by the SARS-CoV-2 virus. World Health Organization (WHO) labeled it as a pandemic on March 11, 2020. Currently, there is no approved vaccine or treatment for the prevention and management of COVID-19, although multiple pharmacological/non-pharmacological options are being explored. Several clinical trials are going on in conventional as well as traditional medicines to find out an effective and safe treatment regimen.

Aim: To identify Ayurveda interventions for the management of patients with COVID-19 as a standalone or an adjuvant therapy in clinical practice.

Materials and methods: A systematic review protocol was developed based on the PRISMA-P statement. Articles for review will be selected from AYUSH Research Portal’s “National Repository on AYUSH COVID-19 Clinical and Other R&D Initiatives” and other electronic databases, i.e., PubMed, Cochrane Central Register of Controlled Trials, DHARA, IndMED, Google Scholar, etc. Readily accessible peer-reviewed full articles published in English or Hindi will be included. There will be no restrictions on the type of study or study setting or date of publication. Data from the included studies will be extracted independently by two review authors on study characteristics (i.e., authorship, publication-related information, methodology, participants, interventions, comparators, outcomes, and results) in a prestructured format for assessment of study quality and data analysis. The risk of bias in included studies will be assessed through suitable existing tools. We will conduct meta-analysis only when the included studies will be sufficiently homogeneous in terms of design, study population characteristics, interventions, and outcome measures. If it is not possible to conduct a meta-analysis, we will summarize the results of included studies as systematic qualitative synthesis.

Conclusion: The results generated from this review will be helpful in identifying the status of evidence regarding the efficacy and safety of Ayurvedic interventions for the management of COVID-19. It will also provide ideas for future research to generate good-quality evidence regarding the efficacy of Ayurvedic interventions in COVID-19.

Study registration: Registered with PROSPERO - [CRD42020206588].

Keywords: Ayurveda, COVID-19, SARS-CoV-2, Systematic review.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus.1 World Health Organization (WHO) labeled it a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and a global pandemic on March 11, 2020.2 At present, 213 countries and territories are having COVID-19 with total 21,260,760 confirmed cases and 761,018 confirmed deaths globally as per the information updated by WHO on August 16, 2020.3 The emergence of COVID-19 has highlighted weak health systems preparedness to respond to an infectious threat and the ineffective policy responses to emerging infectious disease pandemics.4 It is the third known instance of a coronavirus epidemic in the past two decades after severe acute respiratory syndrome in 2003 and Middle East respiratory syndrome in 2012. The global scale of transmission, a considerable number of deaths, infection, and mortality of healthcare providers, and a higher risk of death in vulnerable population have been the major concerns.5

This disease is believed to be predominantly transmitted by droplets through inhalation or physical contact with infected respiratory droplets. The most common symptoms of COVID-19 are fever, fatigue, dry cough, and dyspnea.6 Less common symptoms are nasal congestion, sore throat, diarrhea, nausea, vomiting, loss of taste and/or smell, headache, and dizziness.6

Patients who are elderly or with underlying comorbidities, such as hypertension, diabetes mellitus, cardiovascular disease, lung disease, renal disease, and on immunosuppressive drugs, are predisposed to adverse outcomes.6 The most common complications of COVID-19 are severe pneumonia, acute respiratory distress syndrome, arrhythmias, acute cardiac injury, septic shock,
venous thromboembolism, and acute kidney injury. Real-time reverse transcriptase polymerase chain reaction (rRT-PCR) of upper respiratory tract specimens (combined nasopharyngeal and oropharyngeal swab) is the recommended gold standard test for the diagnosis of COVID-19. Currently, there is no definite, proven vaccine or treatment for the prevention and management of COVID-19, although multiple pharmacological options are being explored. Several clinical trials are going on in conventional as well as traditional medicines to find out an effective and safe treatment regimen. So, the treatment of COVID-19 is mostly supportive and symptomatic till date. It makes prevention of this disease more crucial at this time, but it also seems difficult due to nonspecific clinical features, infectivity even before the onset of symptoms, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as conjunctiva, and transmission even after clinical recovery.

Traditional and complementary medicine (T&CM) can make a significant contribution to the goal of universal health coverage through their preventive and curative strategies according to the World Health Organization. India has a well-established traditional medicine system, namely, Ayurveda having scientific, holistic, and time-tested principles to prevent such epidemics as well as their management. Ayurveda is probably the oldest system of medicine in which infectious diseases and epidemics have been described in the context of Aupasargaika Roga, Janpadodhvaamsa, Agantuja Vyadhi, etc. It is noteworthy that various modes of transmission of contagious diseases, such as Gatra-Samprasha (direct contact with an infected person or his body fluids), Nih-shvasa (inhalation of respiratory droplets), Saha-Bhojana (ingestion of infective micro-organisms while eating together), Saha-Shaiya (sleeping and/or lying alongside an infected individual), Saha-Asana (sitting along with infected individual), Vastra-Malya-Anulepana (use of contaminated articles), and sexual contact with an infected person are also elaborated in the classical texts of Ayurveda. It has been mentioned that vitiation of factors common to all inhabitants of a particular territory, i.e., Vayu (air), Jala (water), Desha (land), and Kala (season) may lead to the simultaneous manifestation of similar diseases leading to the societal collapse. Pragyaparada (imprudent conduct and unjust human actions), such as interference with the bio-ecology, pollution, etc., has been considered as the primary reason of vitiation of these factors. It has been clearly stated in Ayurveda classical texts that all the diseases cannot be named with specific nomenclature; instead, the physician tries to examine the factors involved in the pathogenesis, such as Samutthana-Vishesha (etiology of the disease), Adhishthana-Vishesha (site of disease manifestation), and Vikara-Prakriti (patho-physiology of the disease), for planning a rational line of management. As per Ayurveda, COVID-19 disease can be interpreted as Vata-Kapha Pradhana Sannipata Jvara caused by Bhutabhishanga (infective etiology). The line of management of Janapadodhvamsa (epidemics), Jvara (fever of infective origin), Pratishayaya (corzya), Kasa (cough), and Shvasa (dyspnea) described in Ayurveda can be adopted as per the stage and severity of this pandemic disease. Moreover, several Ayurveda medicines have been evaluated for their antiviral and immunomodulatory properties and found effective in flu-like illnesses. So, the prophylactic and therapeutic potential of Ayurveda needs to be explored in the search for effective management of the COVID-19 crisis. Ayurveda has time-tested strategies to improve the overall immunity of the patient, which may slow-down the pathogenesis of COVID-19 disease and may arrest the progression of confirmed mild cases into full-blown disease leading to complications and death. Thereby, Ayurveda interventions may be helpful in reducing morbidity and mortality associated with this pandemic. Ministry of AYUSH, Government of India, has also issued guidelines for the prevention of COVID-19 incorporating immunomodulating measures based on scientific principles of Ayurveda. In a recent development, Ministry of Health and Family Welfare, Government of India, has included various Ayurveda interventions in their post-COVID management protocol.

The present systematic review is an attempt to explore the role of Ayurvedic interventions in the management of COVID-19 as a standalone or adjuvant therapy along with conventional medicine.

**Review Question**

Are Ayurveda interventions effective and safe in the management of COVID-19 as a standalone system or adjuvant therapy along with conventional medicine?

**Objectives**

- To evaluate the efficacy of Ayurveda medicine as standalone or adjuvant therapy for management of COVID-19.
- To evaluate the safety of Ayurveda medicine as standalone or adjuvant therapy for management of COVID-19.

**Materials and Methods**

The PRISMA-P (preferred reporting items for systematic review and meta-analysis protocol) statement guidelines have been followed for drafting this protocol. The Cochrane Handbook for Systematic Reviews of Interventions has also been referred for methodological considerations.

**Eligibility Criteria**

**Study Designs**

All randomized controlled trials, non-randomized controlled trials, quasi randomized controlled trials, and multi-arm parallel group comparative trials that assess the efficacy and safety of Ayurvedic interventions for the management of COVID-19 as a standalone system or adjuvant therapy along with conventional medicine.

**Participants**

Patients of both sex and all age-groups, diagnosed with COVID-19, with/without any preexisting comorbid conditions.

**Interventions**

Ayurvedic interventions (Shodhana or/and Shamana) with any drug, dosage form, dose, scheduled alone, or in combination with standard conventional care.

**Comparators/Control**

Ayurvedic interventions with any drug, dosage form, dose, schedule, non-Ayurvedic interventions, or combination of Ayurveda and non-Ayurvedic interventions, conventional treatment, placebo and/or sham therapy, waitlist controls, and no treatment.

**Outcomes**

**Primary Outcomes**

**Efficacy**

Mean duration to achieve “Clinical recovery” (normalization of Pyrexia (≤36.6°C axilla or ≤37.2°C oral temperature), relief
in cough or mild cough (infrequent, short episodic, non- wheezy, relieved by minimal or no medication, not interfering with routine speech and not related to lying in bed, mild sore throat or nasal congestion), respiratory rate <24 breaths per minute, SpO₂ >94% on room air by pulse oximetry, absence of any other symptom/sign attributed to COVID-19 illness, and recovery should be sustained for at least 48 hours under physician observation), serum cytokine levels, C-reactive protein, erythrocyte sedimentation rate, serum lactate dehydrogenase, and D-dimer, Immunoglobulins (IgM, IgG, IgE).

Safety
Incidence of adverse events (AEs) reported as hazard ratios (HRs), risk ratios (RRs), or odds ratios (ORs) at specific time points (as mentioned).

Secondary Outcomes
Mean duration to achieve disappearance of accompanying symptoms (such as myalgia, expectoration, nasal stuffiness, runny nose, chest distress, crackles, headache, nausea, vomiting, anorexia, diarrhea), average hospitalization time, recurrence rate, the conversion rate from mild to severe or critical stage of COVID-19 following treatment, and mortality.

Measures of Effect
The binary variable analyzed using the odds ratio (OR) with 95% confidence intervals (CIs). If the data is a continuous variable, we would choose the mean difference (MD) with 95% CIs.

Timings
No restrictions will be made to the length of follow-up assessment.

Setting
There will be no restrictions by type of setting.

Language
Studies published either in English or Hindi.

Information Sources
COVID-19–specific electronic database of AYUSH Research Portal namely—National Repository on AYUSH COVID-19 Clinical and Other R&D Initiatives—will be the primary source for the study selection. However, other electronic databases, i.e., PubMed, Cochrane Central Register of Controlled Trials, DHARA, IndMED, Google Scholar, etc., will also be searched for required clinical studies. The Clinical Trial Registry of India and WHO dashboard for clinical trials related to COVID-19 and reference list of the included studies will also be screened. Study authors will be contacted if any information is required regarding the study.

Search Strategy
Suitable search strategies will be adopted for different databases; however, common search terms are listed in the following table:

**Search Terms**

- (Ayurveda* OR “Ayurvedic therapy” OR “Ayurvedic treatment” OR “Ayurveda intervention” OR “Ayurvedic management” OR Herbal Medicine OR “Traditional Medicine” OR “Alternative Medicine” OR “Complementary Medicine” OR “Herbo-mineral” OR Polyherbal OR Rasashadhi OR Rasakalpa OR “Metallic preparation” OR Mercurial OR Medicinal Plants OR Immuno-modulators OR Panchakarma OR Shodhana OR Shamana OR “AYUSH Kwath” OR “AYUSH Kadha” OR “AYUSH-64” OR Rasayana OR Chyavanprash OR Chyawanprash OR Guduchi OR “Sanshamani Vati”) OR “Ayurveda’s immunity-boosting measures” OR Yashtimadhu OR Ashwagandha OR Guduchi Pippali OR Ginger OR Turmeric OR Shatavari
- (COVID OR COVID-19 OR “Corona Virus” OR “Corona Virus Disease” OR “2019 novel coronavirus infection” OR “2019-nCoV disease” OR “SARS-CoV-2” OR Pandemic OR “Severe acute respiratory syndrome” OR “RT-PCR” OR rRT-PCR OR “real-time reverse transcription-polymerase chain reaction”)
- (“Clinical trials” OR “Clinical trial” OR RCT OR “Randomized trial” OR “quasi-randomized trial” OR “Non-Randomized trial” OR “Parallel group trial” OR “Multi-arm trial”)
- (1 AND 2 AND 3)

**Study Records**

Data Management
The collected data from all the available sources will be kept secure. A duplicate copy will also be created and kept in an external data storage device; it will be accessible only to the authors of the present systematic review.

Selection of Studies
Two authors will independently screen all the results. If there will be any disagreement between these two authors, it will be resolved by a discussion with the third author. Where there will be still any doubt, the full article will be acquired for further inspection. Once the full article will be obtained, two authors will decide whether the study met the review criteria. If still any disagreement will persist, these trials will be added to the list of those awaiting assessment.

Data Collection Process
Two reviewers will assess the eligibility of the searched studies independently using the inclusion and exclusion criteria. We will make a predesigned format to extract data from the included studies for further data analysis. The following study items will be extracted: authorship, publication-related information, methodology, participants, interventions, comparators, and outcomes.

Data Items

**Participants**
Patients of both sex and all age-groups diagnosed with COVID-19, with/without any preexisting co-morbid conditions. We will also collect details such as patient characteristics (average age, gender, stage of the disease, etc.), study design, and sample size.

**Interventions**
Ayurvedic interventions (Shodhana or/and Shamana)/plant, mineral and/or metal-based medicines mentioned in Ayurveda classics with any drug, dosage form, dose, scheduled alone or in combination with standard conventional care.

**Comparators/Control**
Ayurvedic interventions with any drug, dosage form, dose, schedule, non-Ayurvedic interventions, or combination of Ayurvedic and non-Ayurvedic interventions, conventional treatment, placebo and/or sham therapy, waitlist controls, no treatment.
**OUTCOMES**

**Primary Outcomes**

**Efficacy**
Mean duration to achieve two continuous negative RT-PCR results or Criteria of “Clinical recovery,” serum cytokine levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase, and immunoglobulins (IgM, IgG, IgE).

**Safety**
Incidence of adverse event (AE) reported as hazard ratios (HRs), risk ratios (RRs), or odds ratios (ORs) at specific time points (as mentioned).

**Secondary Outcomes**
Mean duration to achieve disappearance of accompanying symptoms, average hospitalization time, recurrence rate, conversion rate from mild to severe or critical stage of COVID-19 after treatment, and mortality.

**RESULTS**
Mean duration to achieve negative RT-PCR results or clinical recovery, change in inflammatory markers, appearance of adverse drug reaction (ADR)/AE, average hospitalization time, recurrence rate, and mortality.

**Risk of Bias (Quality) Assessment**
The methodological quality of included randomized controlled trials (RCTs) will be assessed by using the revised tool to assess the risk of bias in randomized trials (RoB 2) which is available online.\(^{24}\) Five domains, namely, randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results will be assessed with the help of predefined algorithms.

The quality of non-randomized studies will be assessed with the help of ROBINS-I tool (risk of bias in non-randomized studies - of interventions) in which seven domains – Bias due to confounding, bias due to selection of participants, bias in the classification of intervention, bias due to deviation from intended interventions, bias due to missing data, bias in the measurement of the outcome, bias in the selection of the reported result and overall bias, will also be evaluated based on predefined algorithms and will be represented in traffic light plot and weighted summary plot shown in the Figures 1 and 2.\(^{25}\)

When disagreement will arise as to which category a trial will be allocated, again we will attempt to resolve it by discussion. When this will not be possible, we will enter the data and add the trial to the list of those awaiting assessment until further information will be obtained.

**Data Synthesis**
The study data will be quantitatively synthesized (meta-analysis) if sufficient studies are found with clinical and methodological similarities, with statistically similar treatment effects.\(^{26}\) For dichotomous data, risk ratio will be used, whereas the mean difference will be used for continuous outcomes to measure the treatment effect with 95% confidence intervals. Heterogeneity among trials will be assessed by applying the chi-square test and using the $I^2$ statistic. The study will not be considered to have heterogeneity if the $I^2 < 50\%$, whereas significant heterogeneity can be observed if $I^2 \geq 50\%$. If significant heterogeneity is detected and is still considered clinically meaningful to combine studies, then a random-effects model will be used. In case of no significant statistical heterogeneity, a fixed-effects model will be used. Meta-analyses will be completed using Review Manager 5.3.

If meta-analysis will not be conducive due to substantial heterogeneity, we will summarize and explain the results of the included studies as the systematic qualitative synthesis.

---

**Study ID**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Randomization process</th>
<th>Deviations from intended interventions</th>
<th>Missing outcome data</th>
<th>Measurements of the outcome</th>
<th>Selection of the reported result</th>
<th>Overall bias</th>
<th>Bias classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT_1_2002_Abc et.al.</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>Low risk</td>
</tr>
<tr>
<td>RCT_2_2009_Xyz et.al.</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>Some concerns</td>
</tr>
<tr>
<td>RCT_3_2010_Abd et.al.</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Fig. 1: RoB 2 traffic light plot plot
Analysis of Subgroups or Subsets
If significant heterogeneity exists, we will perform subgroup analyses to explore the possible causes. Preplanned categories for subgroup analyses are as following:

- Patient demographics (e.g., age, gender, race/ethnicity, preexisting co-morbidities like cardiovascular disease, diabetes mellitus, hypertension, and kidney function abnormalities, etc.)
- Types of interventions and controls (e.g., Ayurveda intervention standalone, Ayurveda intervention adjuvant to standard care, standard care alone, Placebo/Sham or no treatment, etc.)
- Study characteristics (e.g., study design, sample size, duration of follow-up, study quality, and geographical location, etc.)

Ethics and Dissemination
This review does not require formal ethical assessment and approval, as no confidential participant data will be included. The results of this systematic review will be reported per the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and will be published in an indexed, open-access journal as well as will be presented in national and/or international conferences to ensure wider dissemination.

Acknowledgments
Authors are thankful to Prof (Vd.) KS Dhiman, Director General, CCRAS, CCRAS, Ministry of AYUSH, Govt. of India for their support and valuable guidance.

Authors’ Contribution
Manohar S Gundeti and Azeem Ahmad conceived the study. Manohar S Gundeti, Himanshu Negandhi provided general guidance to the drafting of protocol. Azeem Ahmad and Amit Rai drafted the protocol, designed the search strategy, and prepared an initial draft of the manuscript. Manohar S Gundeti and Himanshu Negandhi reviewed and revised the manuscript. BCS Rao and Narayanan Srikanth performed critical revision of the manuscript and given the final approval; All authors have read and approved the final version of the manuscript.

References
हिंदी सारांश

कोविड-19 में प्रमुख या सहायक चिकित्सा के रूप में आयुर्विदिक चिकित्सा परिवार से प्रभावशीलता व सुरक्षितता: प्रणालीगत समीक्षा हेतु प्रोटोकॉल

अजीम अहमद, अमित कुमार राय, हिमांशु नेगंधी, मनोहर मुंडेटी, बी सी एस राव, नारायण श्रीकांत

पृष्ठभूमि: कोरोना वायरस रोग (कोविड-19) SARS-CoV-2 वायरस के कारण होने वाला एक अत्यधिक संक्रामक रोग है। विश्व स्वास्थ्य संगठन (WHO) ने इसे 11 मार्च, 2020 को वैश्विक महामारी घोषित किया है। दर्जनों में कोविड-19 की रोकथाम और प्रबंधन के लिए कोई अनुमोदित वैज्ञानिक या उपचार नहीं है। एक प्रभावी और सुरक्षित उपचार का पता लगाने के लिए पारंपरिक और परंपरागत चिकित्सा विज्ञान में कई चिकित्सा परीक्षण चल रहे हैं।

उद्देश्य: कोविड-19 महामारी के उपचार में प्रमुख या सहायक चिकित्सा के रूप में आयुर्विदिक चिकित्सा परिवार से संबंधित चिकित्सा अध्ययनों की एक व्यवस्थित समीक्षा करना और कोविड-19 में आयुर्विदिक उपचार की प्रभावशीलता और सुरक्षा के बारे में साक्ष्य उत्पन्न करना है।

विधियाँ और विशेषण: PRISMA-P स्टेटमेंट के आधार पर एक प्रणालीगत समीक्षा प्रोटोकॉल विकसित किया गया है। आयुर्विदिक पोर्टल तथा अन्य इलेक्ट्रॉनिक डेटाबेस (PubMed, Cochrane सेंट्रल रजिस्टर ऑफ़ कंट्रोल ट्रायल, DHARA, IndMED, Google Scholar, आदि) पर उपस्थित कोविड-19 में आयुर्विदिक चिकित्सा से संबंधित चिकित्सा अध्ययनों को समीक्षा के लिए संकलित कर विश्लेषण किया जाएगा। अंग्रेजी या हिंदी में प्रकाशित चिकित्सा अध्ययन से संबंधित पूर्ण लेख ही संकलित किए जाएंगे। अध्ययन के प्रकाश, अध्ययन स्थल या प्रकाशन की तारीख के आधार पर चिकित्सा अध्ययनों के संकलन को संक्षिप्त नहीं किया जाएगा। अध्ययन की गुणवत्ता और डेटा विशेषण के आकलन के लिए पूर्व-संचित प्रारूप में अध्ययन विशेषज्ञाओं (लेखक, प्रकाशन-संचित जानकारी, कार्यक्रमाली, प्रतिभागियों, चिकित्सकविद्या, आदि) पर दो समीक्षा लेखकों द्वारा स्वतंत्र रूप से डेटा निकाला जाएगा। दो लेखक स्वतंत्र रूप से शामिल अध्ययनों में पूर्वार्ड जोखिम का आकलन अपयुक्त मौजूदा उपकरणों के माध्यम से करेंगे। सम्मिलित अध्ययनों के डाइजाइन, उनमें सम्मिलित रोगियों की विशेषताएं, दी गई चिकित्सा और उसके परिणाम सरासरी होने की स्थिति में ही मेटा-विशेषण किया जाएगा। यदि मेटा-विशेषण अनूकुल नहीं होगा, तो इस शामिल अध्ययनों के परिणामों को व्यवस्थित गुणात्मक संस्करण के रूप में प्रस्तुत करेंगे।

निष्कर्ष: इस समीक्षा से उत्पन्न परिणाम कोविड-19 के उपचार में आयुर्विदिक चिकित्सा की प्रभावशीलता और सुरक्षा के बारे में साक्ष्य प्रस्तुत करने में सहायक होंगे। साथ ही इस प्रणालीगत समीक्षा द्वारा कोविड-19 में आयुर्विदिक चिकित्सा की प्रभावशीलता के बारे में उच्चकोटि प्रमाण उत्पन्न करने हेतु अभियंता में होने वाले चिकित्सा शोध के लिए अवधारणा भी प्राप्त होगी।