

Research Article

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Complementary and alternate therapies (CAM) in the management of novel Corona virus (COVID-19): protocol for systematic review and meta-analysis

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Abstract: Background: In December 2019, a new coronavirus (COVID-19) infection broke out in the Chinese province of Wuhan. With the rampant spread of virus around the world, COVID-19 was declared as a global pandemic in the following year. Many complementary and alternate therapies (CAM) were used experimentally alongside conventional treatments for effective management of COVID-19.

Aim: This paper presents a protocol for the systematic review and meta-analysis of the studies with various CAM therapies for the management of COVID-19 pneumonia.

Methods: Electronic databases such as PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) could be used for searching the relevant trials and studies with keywords related to COVID-19 and CAM therapies. Two independent reviewers would screen a list of all the trials and extract the relevant variables. Additionally, we would also evaluate the risk of bias of the selected studies. Review Manager software (RevMan; version 5.3.5) and R statistical software (version 3.6.1) would be used for the data analysis.

Results: Risk ratio (RR) would be estimated for dichotomous outcomes, and the mean differences (MD) would be measured for continuous outcomes. Heterogeneity with the help of I^2 statistic would be used for the assessment of inconsistency across studies with the level of significance at $P < 0.10$. We would also assess publication bias using funnel plots and Egger's test for the selected studies.

Conclusion: The protocol for systematic review and meta-analysis would investigate the beneficial and possible adverse effects of various CAM therapies in the prevention and management of COVID-19 associated pneumonia.

Keywords: coronavirus, COVID-19, meta-analysis, systematic review

1 Introduction

The novel coronavirus 2019 (COVID-19) pandemic outbreak is a major challenge to public health with increased morbidity and mortality rates [1, 2]. The pneumonia associated with COVID-19 elicits influenza-like symptoms such as fever, dry cough, severe acute respiratory illness and even death [3]. The scale and magnitude of the number of patients being infected and the countries that are affected by COVID-19 is huge, when compared to the two recent epidemics, namely, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [4,5]. On the other hand, notable variants of SARS-CoV-2 are important factors that allow the virus to escape from the host immune system causing drug resistance and affecting virus transmission and disease severity [6]. Beyond being a public health crisis, the pandemic has had a significant impact on the global economy, due to factors

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such as an increase in the disease burden on treating this pandemic and lock-down measures.

Complementary and alternate medicine (CAM) therapies are widely used in the management of non-communicable diseases (NCDs) [7]. It has also been documented that CAM therapies are effective in reducing viral load, improving lung functions, reducing complications induced by the antibiotics and antiviral treatments, improving overall immunity and quality of life and reducing depression and anxiety associated with the pandemic [8]. The efficacy of CAM therapies in the management of communicable diseases has been observed during the outbreak of SARS and MERS [9,10]. CAM therapies might also play a crucial role in combating this pandemic of COVID-19, not just as a clinically effective measure to control the outbreak but also as a cost-effective measure [11]. In India, there is current surge in the application of the AYUSH (Ayurveda, Yoga, Unani, Siddha and Homeopathy) system of medicine; the Ministry of Health and Family Welfare has brought out several scientific guidelines to implement these CAM therapies and is encouraging the appropriate scientific application of these modalities for both communicable and non-communicable diseases [11].

There should be a seamless transfer of knowledge between CAM therapy practitioners and the conventional medicine practitioners in the management of COVID 19. The synergy of minds and integration of knowledge would help humanity in this time of crisis. However, global disease outbreaks like these might also lead to many unscientific claims as a cure for the disease. Therefore, it is important for the scientific community to assess the quality of studies conducted in the management of COVID 19 with solid scientific credibility, in which systematic review and meta-analysis play a pivotal role. The objectives of this report are to present a protocol for systematic review and meta-analysis of studies conducted in the area of CAM therapies in the management of COVID 19 and to examine the empirical evidence on the effect of CAM therapies in COVID-19 pneumonia and associated co-morbidities.

2 Methods

This protocol for the systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) guidelines (see figure 1 for details) [12]. We registered in PROSPERO on 21st May 2020 (CRD42020187532), and any

essential amendments will be updated in the PROSPERO records.

3 Eligibility criteria

Randomised and quasi-randomised trials or prospective controlled clinical trials on CAM therapies, with or without modern medicine for COVID-19 patients, would be included. Studies conducted on patients with a severe stage of COVID-19 and studies that included patients with life-threatening co-morbidities that might possibly have led to death within the follow-up period would be excluded.

4 Types of participants (P)

Patients diagnosed with COVID-19 viral infection, with or without co-morbidities (except for life-threatening comorbidities), would be included. No specific restrictions would be applied with respect to age, gender, country of origin or ethnicity. Surveillance case definitions could not be used by treating clinicians to diagnose the cases. Clinical criteria for case definition: patients with at least two of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorders or patients with at least one of the following symptoms: cough, shortness of breath or difficulty breathing or radiographic evidence of pneumonia. Laboratory criteria for case definition: confirmed laboratory evidence of detection of severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen via a molecular amplification detection test or any other approved serological test. In case of any substantial clinical heterogeneity in case definition, a sensitivity analysis would be conducted.

5 Type of interventions (I)

CAM therapies involving yoga practices (postures, breathing techniques, meditation practices), other mind-body interventions such as aromatherapy, acupuncture or acupressure, taichi, art or music therapy, psychotherapies, naturopathy and (non-pharmacological) interventions such as sun exposure, water therapies, including steam inhalation and hot-water gargling, regardless of their variations or forms. CAM therapies, either as a single

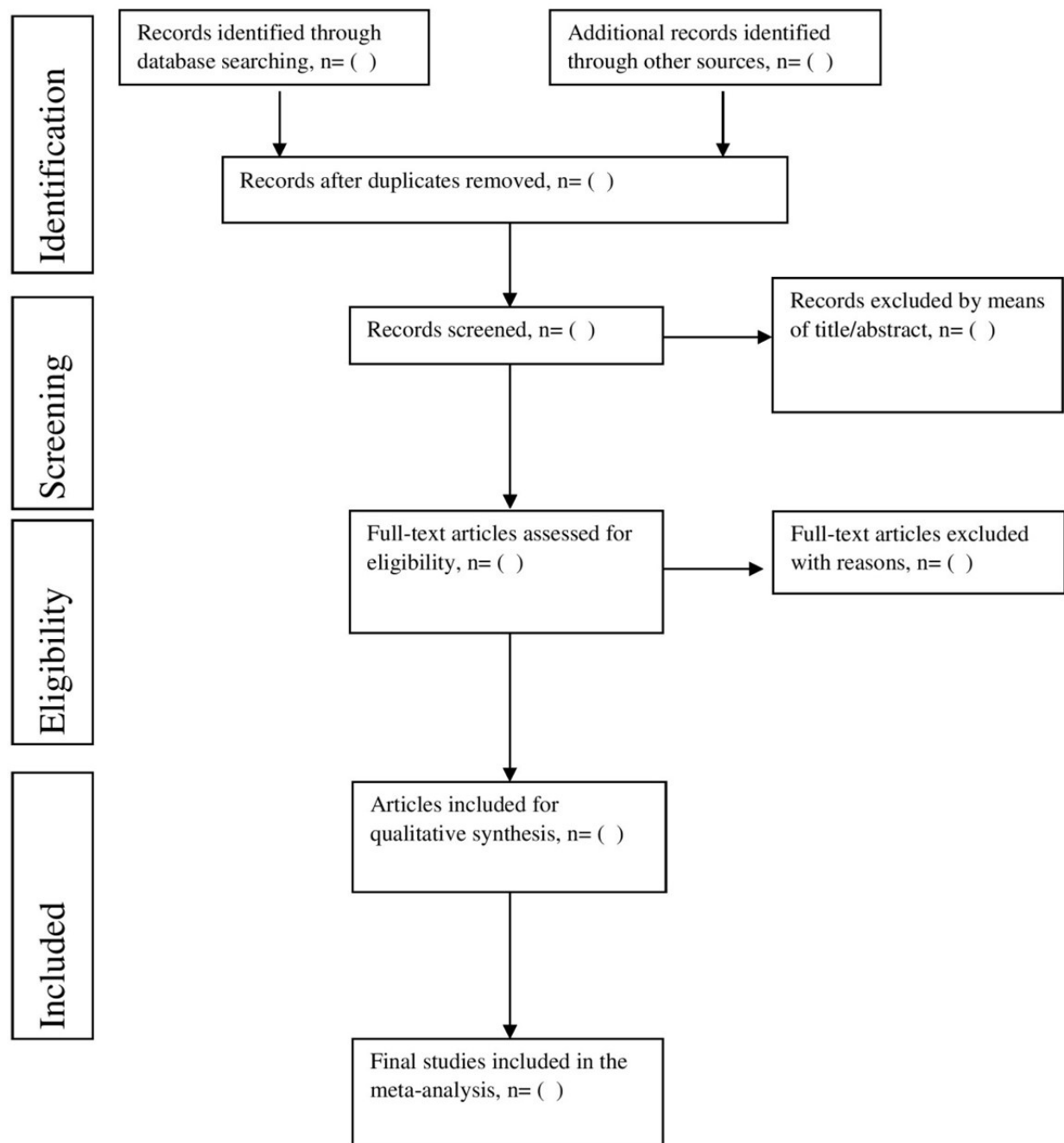


Figure 1: PRISMA flow diagram of the study selection process.

therapy or paired with other interventions, would also be included. There would be no limitations to the frequency, dosage or duration of the intervention. In addition, strategy used to support the CAM therapy implementation, such as a reminder system and motivation of the patient to practice yoga by the clinician, would also be included in the factors affecting intervention. Subgroup analyses would be conducted on all these variables to understand

the contribution of any or all of these factors in deciding the effectiveness of the intervention.

6 Type of control group (C)

The control group could be COVID-19 patients on conventional medical therapies, supportive treatments or other

standard treatment regimens; there are no specific limitations with respect to the nature of control group.

7 Type of outcome measurements (O)

The primary outcome of interest would be a change in the symptoms score and time period for the patient to become COVID-19-negative either at the end of intervention or after the follow-up. For scoring, we would use typical symptoms of COVID-19, primarily based on fever, cough, breathing difficulty, and loss of appetite. We would also evaluate other secondary outcomes, such as quality of life, mental health, stress and depression scores, cardiorespiratory function, inflammation index, duration of stay in hospital, and unfavorable events, if any.

8 Information sources, databases and search strategy

A systematic search of published literature, unpublished (grey) literature, and trial registries including relevant accessible new evidence would be conducted. Adding both emerging literature and unpublished literature is crucial for researching pandemics like COVID 19. Electronic databases such as PubMed, Embase, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) would be used for searching potential studies. The search would be organized as per the research question and PICO (P = Patient, Population or Problem; I = Intervention or Exposure; C = Comparison or Control (if applicable) O = Outcome(s), which would include both MeSH (Medical Subject Headings) and key words for COVID-19 and CAM therapies. All possible keyword combinations for CAM therapies would be used for screening the eligible studies. A combination of search words, such as “Acupuncture” OR “Yoga” OR “psychotherapy” OR “Music therapy” OR “Aromatherapy” AND “COVID-19” OR “SARS-CoV-2”, would be used alone or in combination. The complete search strategy for other keywords in PubMed is explained in detailed in the additional file attached, and similar keywords and strategies would be used for searching other electronic databases, as well. Expert opinion would also be obtained on the possible studies for timely progression of the review (see Figure 2 for details).

9 Study selection

We would import the selected studies into EndNote X6 software and verify for the duplicate entries. All members of the research group would independently screen the citations as per the inclusion and exclusion criteria. After removing duplicates, two independent reviewers (SG and SP) would verify the retrieved records based on the title and abstract. The selected full text would be obtained and scrutinized independently by two reviewers (VV and KM) to identify eligible studies. Disagreements in the selection of studies, if any, would be discussed and resolved with the help of the third reviewer (RP). The eligibility criteria might have to be revised based on the information obtained from the studies as the entire spectrum of COVID 19 is still not clear.

10 Data extraction

Extracted records would be arranged by a predefined extraction template as follows: (1) general information—first author with year, title, journal, country, study design; (2) details of patients—age, sex, stage/type and disease severity, comorbidity; (3) nature of intervention—protocol of CAM therapies (types, dosage, frequency, duration) and characteristics of comparators (types); (4) characteristics of design —setting of the study (ambulatory /hospital sector), size of the sample (methods used for the recruitment, blinding and allocation concealment) and (5) outcome details—all outcomes, including adverse events, reported. Original authors of studies would be contacted in order to request any missing data if required. All information would be cross-checked by two reviewers (SG and SP), and any disagreements would be resolved after discussion, which would include the third reviewer (VV). The degree of agreement between the two independent data extractors would be computed with kappa statistics to indicate the difference between observed and expected agreements between the two extractors at random or by chance.

11 Assessment of risk of bias (RoB)

Risk of Bias (RoB) will be judged as low, unclear or high. The parameters evaluated to assess RoB in the studies would be random sequence generation, allocation concealment, and similarities in groups for selection bias; blinding of participants and caregivers, co-interventions,

	2021		2022						
	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July
Conduct initial searches to refine protocol									
Complete searches and de-duplication									
Screening titles and abstracts reviewer 1									
Screening titles and abstracts reviewer 2 (test set only, plus 10%)									
Data extraction (Single reviewer, 10% double data extracted)									
Synthesis - identification of initial indicators									
Finalizing the studies for meta-analysis									
Statistical Analysis									
Writing up methods and findings									

Figure 2: Systematic review and Meta-analysis Gantt chart

compliance for performance bias; blinding of outcome assessor, timing of outcome assessments for detection bias; and selective reporting for reporting bias. To maintain the consistency (at least 80%) of risk of bias assessment, guidance from the latest version of the Handbook of Systematic Reviews of Interventions or randomized trials and non-randomized trials would be followed [13, 14]. Interventions with higher risk of bias or vague bias would be given less weight in our outcome reports.

12 Data analysis

RevMan software (version 5.3.5) and R statistical software (version 3.6.1) for data analysis would be used. Risk ratio (RR) would be estimated for dichotomous outcomes, and the mean differences (MD) would be measured for continuous outcomes with 95% confidence intervals. Heterogeneity with the help of I^2 statistic would be used for the assessment of inconsistency across studies with a significance level of $P < 0.10$. The Mantel-Haenszel and DerSimonian and Laird inverse variance method would be used for dichotomous outcomes and continuous outcomes. A random-effects model would be used to estimate overall pooled impact of the data. We would also assess publication biases with funnel plot, Egger's test and Begg's test for the selected studies.

13 Results

13.1 Subgroup and Sensitivity analysis

Subgroup analysis would be performed for the following variables: age, gender, types of intervention, duration and dosage of intervention and stages of COVID-19, if reported in the included studies. In addition, we would also do a sensitivity analysis to look into the consequence of studies with high risk of bias.

13.2 Quality of evidence

We would use the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for the assessment of quality of evidence for each of the outcomes. The assessment would be conducted by the two independent reviewers (SG and SP) [15] and would be graded accordingly as high, moderate, low or very low. The overall quality of studies would be rated as good, fair and poor and the rate would be included in the results of the meta-analysis.

13.3 Discussion – Implications of the protocol for systematic review and meta-analysis

The aim of this protocol generation (for the systematic review and meta-analysis) is to provide scientific evidence regarding CAM therapies in COVID-19. Heterogeneity of study population and methods could cause confounding and unrecognized effect modifications that could be minimized to a certain extent by following a standard method of systematic review and meta-analysis.

CAM therapies had a significant role in ensuring optimum public health outcomes in various disease conditions in the past, and their role could be crucial again in managing the current pandemic of COVID-19, which is very much similar to the more recent pandemics of SARS and MERS, in order to reduce morbidity and mortality arising due to COVID-19 [16, 17]. CAM therapies had a significant role in the management of the SARS during the outbreak in 2002, including reduction in the flu-like symptoms, corticosteroid dosage, improved absorption of pulmonary infiltration and quality of life (QoL) [18]. Similarly, CAM therapies were also widely used during the management of MERS [19]. Mind-body interventions such as yoga are documented as an effective complementary therapy in the management of respiratory conditions, [18] and they also improve psychological well-being, which could be of benefit in the management of COVID-19 [20,21].

The current systematic review would be the first of its kind to examine the available evidence on the effectiveness of CAM therapies in the management of COVID-19 pneumonia. The review is aimed at providing an overview of the application of CAM therapies in the management of COVID-19 and also assess the benefits and risks of these therapies. A meta-analysis would be conducted following a systematic review after an adequate number of scientifically conducted studies are published or available. The protocol we describe is based on the available empirical evidence, and any possible change in the methodology would promptly be updated in the PROSPERO database. We would disseminate the information to all the stakeholders periodically as publications, reports and in several knowledge-exchange platforms.

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Conflict of interest

The authors state no conflict of interest

Ethical approval

The conducted research is not related to either human or animal use.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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