Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research Article

A methodological analysis of CTRI registered clinical trials on ayurveda interventions for COVID-19 management

Swapnali S. Chaudhari [a, c, 1, *], Pramod R. Somvanshi [b]

[a] Savitribai Phule Pune University, Pune, Maharashtra, India
[b] Department of Systems and Computational Biology, School of Life Sciences, University of Hyderabad, Hyderabad, India
[c] Indian Institute of Public Health Hyderabad, Public Health Foundation of India, India

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ABSTARCT

Background: Clinical trial protocols provide important methodological information and are expected to be detailed. During COVID-19 pandemic several studies has been registered on CTRI regarding ayurveda for COVID-19. However, there is accumulating evidence that many protocols do not address important study elements. Therefore it is critical to analyze the clinical trial protocols and methodology of ayurveda clinical trials regarding COVID-19 registered on CTRI.

Objective: To assess the methodological aspects of CTRI registered ayurveda trial for COVID-19, based upon available trial protocols, during 2020 and 2021.

Materials and methods: We searched the CTRI database for interventional trials protocols regarding ayurveda for COVID-19, during the year 2020 and 2021. We assessed the protocols for several methodological aspects such as study design, sample size, randomization, blinding, intervention (duration and type) and outcomes.

Results: Total 140 clinical trial protocols were analyzed. The highest numbers of studies were registered in May, June, and July 2020 with steady decline thereafter despite rising COVID-19 cases. Total 90 trials were randomized and only 29 are blinded, however majority of the trials did not mention methods of randomization and blinding. Sample size in hospital-based studies ranged from 30 -500 and in community-based studies from 500-80000, however, sample size calculation details were not mentioned in the protocol. Most common intervention used were guduchi, ashwagandha, yashtimadhu, AYUSH-64, curcumin and chyavanprash.

Conclusion: Although there was a surge of clinical trials on CTRI regarding ayurveda for COVID -19, the methodological quality is not up to the mark with large scope for improvement.

1. Introduction

The unexpected emergence of the coronavirus disease-19 (COVID-19) pandemic has become a serious threat and a challenge to the entire world. In the last few months, several clinical trials evaluating Ayush systems, especially ayurveda, have been initiated in India [5,6] there are more number of ayurveda trials for COVID -19 compared to other AYUSH systems on Clinical Trials Registry - India (CTRI) (113 out of 197 Until Aug 2020) [1]. The clinical trial protocol provides guidance to individuals conducting the study, serves as the basis for study registration, and facilitates study appraisal by participants and external reviewers, including institutional review boards, regulators, funders, and journal editors. However, there is accumulating evidence that many protocols do not address important study elements [2]. Therefore, it is critical to analyze the emerging clinical trial protocols (datasets of protocols available) on CTRI regarding the use of ayurveda for the prevention and/or treatment of COVID-19. The present study attempts to assess the characteristics of ayurveda studies regarding COVID-19 registered on CTRI, and to understand the types and methodological aspects of these studies, using datasets available on CTRI. We analyzed 140 clinical trials registered on CTRI during 2020 and 2021.

* Corresponding author.
E-mail: drshrikrupa@gmail.com
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[1] Current address: Indian Institute of Public Health Hyderabad, Public Health Foundation of India.

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2. Methods

We searched the CTRI database from the website www.ctri.nic.in, an official Clinical Trials Registry-India website. We searched all the interventional trials' datasets regarding ayurveda for COVID-19, registered between 1st Jan 2020 and 31st Dec 2021, using keywords: *COVID-19, SARS-COV-2, Coronavirus, and Ayurveda, Ayurvedic intervention, Ayurvedic medicine*. All interventional trials independent of their status were included (Complete/incomplete, recruiting/not recruiting, published/unpublished, single-arm/double arm/triple arm, phase I/II/III). Information regarding the following characteristics was extracted from the datasets:

CTRI number, name of principal investigator, title, place/site of the trial, centre, trial status, study design, type (prophylactic/therapeutic), number of arms, inclusion/exclusion criteria, population, gender/age, randomization, method of generating random sequence, method of allocation concealment, intervention, duration of intervention, duration of the study, control/comparator details, blinding details, target sample size, primary outcome, secondary outcome, type and name of a sponsor.

To get additional data regarding some other important variables based on SPIRIT and PICOT [3], we prepared google form questionnaires to be sent to principal investigators of the studies, which included the following characteristics:

Study setting, rationale of the study (here we enquired about ayurvedic rationale), sample size calculation details (such as any statistical or clinical assumption), type of randomization (simple/stratified/block, etc.), unblinding criteria, data analysis plan, stopping guidelines for trial, post-trial care, plan to record/manage adverse events, rationale for inclusion and exclusion criteria, intervention as an adjunct or stand-alone treatment, sponsor (government/private/pharmaceuticals), presence of comorbidity, method of disease diagnosis, involvement of ayurvedic physician in the trial. Additionally, to assess the quality of the included trials, we used the 'modified Jadad scale' (Details shown in Table 1) [4].

3. Results

Total clinical trial datasets analysed from year 2020 and 2021 are 122 and 18 respectively.

3.1. The month-wise distribution

The month-wise distribution of these trials revealed that there were no studies registered until March 2020, the highest number of studies were registered in May, June, and July 2020, after which there was a decline in the number of studies registered. Geographical mapping of the study sites revealed that the maximum number of studies were conducted in the state of Maharashtra (n = 31).

Table 1
Modified Jadad scale.

Question	Response	Possible score
Was the study described as randomized?	Yes/No	1/0
Was the method used to generate random sequence appropriate?	Yes/No	1/0
Was the study described as double-blinded?	Yes/No	1/0
Was the method of double-blinding appropriate?	Yes/No	1/0
Was there allocation concealment present?	Yes/No	1/0
Was the method for allocation concealment appropriate?	Yes/No	1/0
Total possible score:6		
Interpretation: Total score </ = 3: Not satisfactory and Total score >3: Satisfactory		

3.2. General characteristics of the studies

Investigators' background suggests that the majority of the trials (n = 87) involved ayurvedic physician in the study, while other (n = 35) trials did not have an ayurvedic physician involved. A major number of trials (n = 58) were sponsored by the Government of India and governmental funding agencies such as the Ministry of Ayush, as compared to investigator-initiated/academic studies (n = 37). There were 27 studies funded by pharmaceutical industries. Seventy nine studies included a population aged between 18 and 70 years, while 29 studies included participants above the age of 70 (Maximum 99 years). The studies that included a population below age of 18 years was 11, one study even included an age group of 1 day–80 years. Three studies included both sets of the population that is below 18 years and above 70 years.

4. Characteristics of hospital-based/COVID centre-based studies (n = 106)

These studies can be further divided into prophylactic (n = 39) and therapeutic (n = 83) studies. The majority number of the therapeutic studies included mild to moderate (N = 75), followed by asymptomatic to mild (N = 7) and severe (N = 1) COVID-19 patients. The study that included severe COVID-19 patients was carried out on patients admitted at an indoor department of multispeciality dedicated COVID-19 hospital, while the study drug was a herbo mineral combination that was administered for 12 days duration, along with standard treatment. The majority of the studies were having 2 arms (n = 80), while others were having a single arm (n = 25). One study included 3 arms. The most common method used for generating random sequences was computer-generated randomization (n = 44). Amongst 79 randomized studies, 57 studies mentioned having allocation concealment present, while 2 studies did not have allocation concealment. Eighteen studies mentioned allocation concealment either as "not applicable" (n = 16) or 'Other" (n = 2). 'Open list of random numbers' was the most frequently used method for allocation concealment (n = 21). Out of 106 trials, 24 trials were blinded and 75 trials were open-label studies. Seven studies mentioned blinding as "Not applicable". The major number of trials (N = 63) involved 'conventional/standard care' as a control group/comparator. Duration of intervention for therapeutic trials was 7–15 days for a major number of the studies (N=47), while for prophylactic trials it was up to 3 months. The most common range of sample size included was 50–100 participants and the maximum sample size was 500. Primary outcomes in these studies were time for clearance of infection either confirmed clinically or by laboratory tests or progression of the disease or incidence of infection, depending upon the aim of the study. Modified jadad score: Studies with modified Jadad score of and only 36 studies had a score of >**3**.

5. Characteristics of community-based studies (n = 16)

All of the community-based studies (n = 16) were prophylactic and open label studies. Eleven studies were single-centered, and 5 studies were multi-centered. Duration of intervention ranged from 1 month to 3 months. The sample size in these studies was in the range of a minimum of 500 to a maximum of 50,000 participants. An obvious primary outcome in these trials was 'incidence of infection'.

6. Intervention details for year 2020 studies

1. Guduchi (*Tinospora cordifolia*) was used most frequently in both hospital-based (*n = 20*) and community-based studies

(*n = 11)* followed by ashwagandha (*Withania somnifera)* (*n = 9*) and yashtimadhu (*Glycyrrhiza gabra*) (*n = 7*).

2. The second most frequently used herb was ashwagandha (n = 12). Ashwagandha has been used as a rasayana (rejuvenator), adaptogen, antioxidant, anxiolytic, anticancer, immunomodulating, and anti-inflammatory. It contains a range of constituents like withanolides, sitoindosides, and other alkaloids that protects cells from oxidative damage.
3. The third most used (n = 8) herb was yashtimadhu (*G. gabra*)/Licorice. This plant contains different phytocompounds such as glycyrrhizin, glabrin A and B, and isoflavones. It has anti-inflammatory, anti-viral, antioxidant properties,
4. AYUSH -64, a drug developed by CCRAS was used in hospital/COVID center-based studies. AYUSH -64 is a multi-herb formulation containing a combination of saptaparna (*Alstonia scholaris*), chirayata (*Swertia chiraita),* katuki (*Picorrhiza kurroo*), and kuberaksha (*Caesalpinia crista).*
5. AYUSH kwath, which is also recommended by the ministry of Ayush for prophylaxis and contains a combination of tulsi (*Ocimum sanctum*), dalchini (*Cinnamomum zeylanicum*), sunthi (*Zingiber officinale*), and marich (*Piper nigrum*) was used in 2 hospital-based studies and 1 community-based study.
6. Curcumin was used in different forms such as curcumin tablet, powder, or haridra khand in hospital-based studies (*n = 5*).
7. Chyavanprash as recommended by the ministry of Ayush as an immunity enhancer was used in hospital/COVID center-based studies *(n = 5*) and community-based studies *(n = 4)* as well.
8. There were different kwath/decoctions used which contains a combination of various herbs such as surasadi kwath, bharangyadi kwath, pathyadi kwath, etc*(n = 18*)
9. Anu tail Nasya (through nasal route) was used in 3 hospital-based studies and 2 community-based studies. Til tail (sesame seed oil) was used in 1 study.
10. There were other classical ayurveda formulations used such as malla chandrodaya, sudarshan Vati, pippali rasayana, etc. in some of the studies (*n = 18).*
11. Many of the studies (*n = 25*) used proprietary ayurveda formulations. Details of ingredients of most of these formulations could not be retrieved from the protocols.
12. 4 of the studies mentioned used personalized ayurveda medicine according to various patient parameters and disease stages according to the physician's judgment.

Total clinical trial dataset analysed from the year 2021 is 18.

Out of these 18 studies, studies that were for treatment/prevention purposes are 8. The studies related to the COVID-19 vaccine were 2, while the studies related to post COVID syndrome were 6. The studies in which the nasal route for medication is used were 2.

Randomization: Out of these 18 studies, 11 studies were randomized.

Allocation concealment: 3 studies had 'sequentially numbered, sealed, opaque envelopes' and 2 studies had 'an open list of random numbers as a method of concealment. 4 studies involved 'an open list of random numbers' while 2 had 'centralized' and 1 had 'alternation'.

Blinding: Only 5 studies were double-blinded (participant and outcome assessor-blinded) while 1 study was single-blinded (outcome assessor blinded). All other studies (N = 13) were open labelled studies.

Primary outcome: In 8 studies, the primary outcome was 'time to recovery or time for negative RTPCR'. In 2 studies related to the COVID-19 vaccine, the primary outcome was 'antibody titre', while in the remaining 8 studies was 'time to symptomatic recovery'.

Secondary outcome: In these studies, the secondary outcome was either occurrence of adverse events, lab biomarkers, or quality of life.

Sample size: Minimum sample size included was 30 while the maximum was 80,000, which included a large cohort of Delhi Police.

Study duration: The duration of the study ranged from 1 month to 1 year.

7. Discussion

We considered ayurveda trials for COVID-19 registered on CTRI from January 2020 to December 2021.

A steady decline in the number of registered studies was contradictory to the steady rise observed in the number of COVID-19 positive cases until October 2020 (As shown in Fig. 1) [9]. State-wise distribution of the trials is in line with the fact of the presence of the highest number of cases in Maharashtra. The non-involvement of AYUSH experts in 35 studies was contradictory to the advisory by the ministry of Ayush released on 2nd April 2019, which recommends the involvement of AYUSH experts in AYUSH trials' planning and conduct [7,8]. Major funding by government and its agencies indicates a positive step towards ayurveda research. An almost equal number of trials conducted by allopathic medical colleges as ayurveda medical colleges point towards

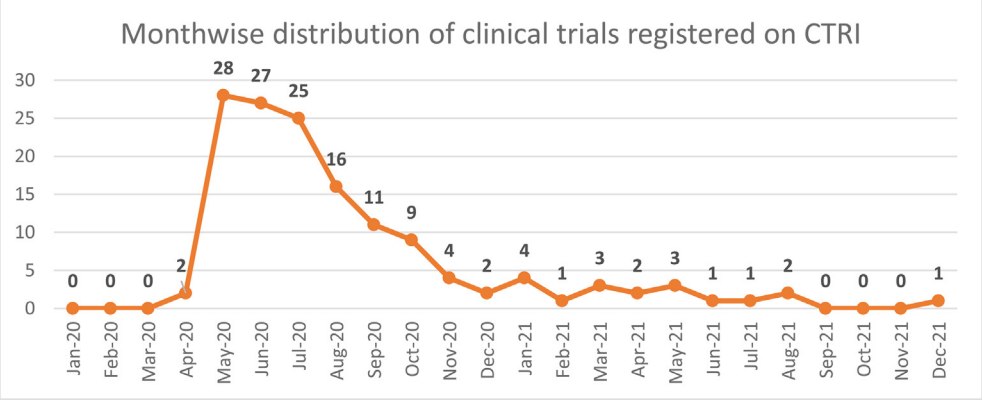

Fig. 1. Monthwise distribution of ayurveda trials for COVID-19 registered on CTRI till **December 2021**.

growing interest and recognition of the potential of ayurveda by modern medical researchers. There is a need for more collaborative efforts between ayurveda and other medical streams. The modified Jadad score of less than 3 of the majority of the trials suggests the need for improvement in the quality of these trials. Although ayurvedic medicines, when manufactured properly and prescribed in a proper therapeutic dose are considered safe even in children, the details of whether the dosages were adjusted according to the age of the participant were not mentioned in the protocols. Especially, caution should be considered when using ras aushadhi (herbo mineral formulations) in children. Although guidance by the Ayush ministry for management and use of specific ayurvedic formulations for COVID-19 cases with comorbidities such as diabetes, hypertension, and immunocompromised conditions has been provided, none of the studies included these populations in these trials. A personalized and holistic approach to treatment, which is a characteristic feature of ayurveda was used in only 4 of these trials. This approach should be encouraged in future studies. None of the registered trials mentioned any dietary restrictions or lifestyle modification advised. This might be because of the non-feasibility of these factors in hospitalized patients. However, it should be noted that not considering these factors can compromise the efficacy and success of ayurveda interventions.

Many of the other characteristic features of ayurveda such as panchkarma include gargles with herbal decoctions, mouth rinses, steam inhalation, consuming hot water/medicated water, which may have potential in the management of COVID-19 can be explored in future clinical trials. As COVID-19 is a public health concern, the interventions or drug formulations such as Guduchi, chyavanprash and ahwagandha, which are affordable to the general population, compared to conventional treatment should be investigated further.

12 of these trials had intervention duration </ = 7 days, (one of the trials with only 1-day intervention was also noted). It was not possible to establish either efficacy or safety of the intervention within this short interval. Although 75% of the studies are randomized, details of randomization were not clear. Out of 79 randomized studies, 57 studies mentioned having allocation concealment. open list of random numbers was the most common method to conceal allocation, by which it is not clear how the allocation was concealed. Only 25% of studies were blinded. Although it's difficult to implement blinding in AYUSH studies, the outcome assessor can still be blinded. Only 5 open-labeled studies followed this strategy. In these registered studies, a large amount of variability was seen in terms of sample size. In hospital-based studies, the sample size ranged from as low as 10 up to 500. There were 3 studies with a sample size less than or equal to 20. It is difficult to get unbiased estimates of meaningful differences between 2 groups with these small sample sizes [10,11]. Only 3 of the registered studies mentioned sample size calculation details in their protocols. We tried to retrieve data regarding sample size calculation and some other details by sending questionnaires and contacting 122 principal investigators of the trials via either email or phone calls, but unfortunately, we received less than 5% response rate from PIs, therefore it was not possible to collect this information.

In community-based studies, the sample size ranged from 500 to 50,000, with the maximum number of trials including sample size below 2000. Although these studies involved a larger group of the population as expected in community-based studies, it is critical to assess the compliance of the participants to the intervention. In these trials, healthy volunteers with a high risk of exposure such as in hotspots were involved and study drug was distributed among these populations. Mostly rasayana drugs such as guduchi, ashwagandha, yashtimadhu and chyavanprash were used in these studies. It is difficult to find out whether these people were consuming some other medicines or adjuvants or any other immunomodulators. In this situation of 'Infodemic' where huge information is available on public platforms, it was very obvious for the general public to try out various treatments/possible prevention interventions such as home remedies. Therefore, it is presumed that these confounding factors were taken care of by respective research teams.

There were only 18 studies meeting the eligibility criteria in the year 2021. This number is very less compared to the studies conducted in 2020(N = 122). Despite the second wave of the COVID-19 in 2021, the number of studies conducted was not increased. There were some studies related to the COVID vaccine, to assess the add-on effect of ayurveda intervention after the vaccine dose. Few studies also explored the effect of add-on ayurveda intervention in post COVID syndrome symptoms such as fatigue, cough, etc. The percentage of randomized studies in the year 2021 has decreased as compared to the year 2020 (75% vs 60%). In terms of blinding, there was still the same trend as the year 2020. Very few studies are blinded. The primary and secondary outcomes remained consistent. However, in some studies (N = 3) authors wrongly mentioned the expected impact of the study as the primary/secondary outcome. There is a large variation in sample size smallest being 30 while the largest cohort included 80,000 participants. Interventions/herbs used in these studies mostly focused on boosting

Table 2
Intervention details for year 2021 studies.

Study No.	Name of the intervention	Duration of intervention
1.	Tab Gorochanadi Vati	3 days
2.	SwasVimochan, SwasanRakshak, Swasamrite, Immune EnergyTablets	7 days
3.	Noxguard nasal spray	14 days
4.	CIM-Meg19 (kalmegh and minerals)	21 days
5.	Inhaler containing Cinnamomum Camphora and *Trachyspermum ammi*	28 days
6.	NOQ19 500 mg (Ashwagandha + Yashtimadhu)	28 days
7.	AEV01 (root extract of Kutki (*Picrorhiza kurroa*))	30 days
8.	Ayush 64 capsule, Sanshamani Vati, Vatashleshma Jwarhar Kwatha	30 days
9.	Vardhmana Pippali	30 days
10.	Chatushashti Prahari Pippali	8 weeks
11.	Zandu Chyawanprash, Zandu Pure Honey, Trishun Tablets and Immuzan Tablets	8 Weeks
12.	Ashwagandha Capsule	12 weeks
13.	Ashwagandha Tablet	24 Weeks
14.	Balchaturbhadrika Churna, Laghu Malini Basant Rasa	Not mentioned
15.	AYUR RAKSHA Kit	
16.	NF2 and NF4 (Ayurvedic medicine)	
17.	PulmoCard caps, Acalogen caps, Opthoxy eye drops and ZingiVir-H tablets	
18.	Sadangpaniya kwath, Viyosadi churn tablet, Vyasthapan kasay ghana tablet	

immunity, such as Ashwagandha, Guduchi, Yashtimadhu, Pippali, Chyavanprash and other proprietary products such as Immuzan tablets, Pulmocard capsules, etc. In some studies (n = 5) duration of the intervention was not mentioned (Refer to Table 2). This lack of reporting about details of the intervention in the protocol on CTRI can be overcome by providing structured intervention details template in the protocol format.

8. Limitation

The present study considered only available protocol datasets on CTRI, which are not complete protocols. Further detailed analysis may have been possible with complete protocols. Additional information regarding some characteristics of the studies could not be retrieved from respective Principal investigators, which may limit the analysis.

9. Conclusion

Although there was a surge of clinical trials on CTRI regarding Ayurveda for COVID -19, the methodological quality is not up to the mark and there is large scope for improvement. Assessing the methodological quality of CTRI registered ayurveda trials for COVID -19 was the main objective of this study. We found that although there was surge of registered trials, the quality was not upto the mark. Major flaws were in terms of lack of randomization, blinding, allocation concealment, less sample sizes and less intervention duration. Apart from the quality of the trials, we noticed that some major elements of the trials were not reported in some of the protocols. They were details of intervention (components of the formulations), sample size calculation, Type of randomization, and allocation concealment. In some places, the elements were mentioned as 'others' without specifying further. This lack of reporting makes the assessment challenging. In conclusion, there is a large scope for improvemnt in terms of quality ofthe trials and reporting on CTRI portal as well.

10. Recommendations

1. Randomization methods such as restricted randomization (especially in the case of a small sample) should be considered.
2. Maximum allocation concealment and appropriate methods of concealment should be taken into consideration.
3. Blinding should be implemented as much as possible.
4. Larger sample sizes with statistical sample size calculation by considering parameters such as expected power of the study, level of significance, effect sizes, should be considered. Further, follow-up studies with larger samples are needed.
5. There is a need to implement characteristic features of Ayurveda in clinical trials such as personalized approaches, dietary and lifestyle modifications, and panchakarma therapies as well.
6. CTRI dataset format can be improved further by including details of some sections such as randomization details, Sample size calculations, statistical analysis plan, Intervention details such as nature of the intervention (The whole herb, extract, etc) and duration, Specification of the terms such as 'Other' wherever mentioned.

Author contribution

SC has conceived the work and analysed the trials. SC and PRS wrote the manuscript. PRS contributed to the analysis.

Conflicts of interest

None.

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