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AYUSH-64 as an adjunct to standard care in asymptomatic, mild, and moderate COVID-19: A systematic review and meta-analysis

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The study was planned to systematically review the available evidence from randomized controlled trials on the efficacy and safety of AYUSH-64 in managing COVID-19. Electronic databases such as PubMed, Ayush Research Portal, DHARA, Cochrane CENTRAL, etc. were searched from December 2019 to October 2021, and updated in February 2022. The risk of bias was assessed through the RoB2 tool. Meta-analysis was done with the Review Manager 5.4 tool. The quality of cumulative evidence was evaluated through the GRADE approach. This study includes five RCTs with 420 participants. The risk of bias was assessed as low for most of the studies. The results demonstrated that AYUSH-64 administration as an adjunct to standard care was significantly better compared to standard care alone for asymptomatic, mild, and moderate COVID-19 in terms of clinical recovery (OR= 2.35; 95% CI= 1.33 to 4.16; p=0.003), and mean time to clinical recovery (SMD= -0.67; 95% CI= -1.16 to -0.18; p=0.007). There was no statistically significant difference between groups in SARS-CoV-2 clearance assessed by RT-PCR assay (OR= 1.21; 95% CI= 0.51 to 2.88; p=0.66). The overall incidence of adverse events showed no significant difference between groups (p=0.65). The quality of evidence was assessed as moderate for clinical recovery and low for SARS-CoV-2 clearance. Meta-analysis of five RCTs demonstrated that AYUSH-64 as an adjunct to standard care hastens clinical recovery and is safe in asymptomatic, mild, and moderate COVID-19. However, more robust RCTs would be required to generalize the results of this systematic review.

Keywords: Ayurveda, AYUSH-64, COVID-19, Pandemic, SARS-CoV-2, Systematic review

IPC Code: Int Cl.[23]: A61K 36/00, A61K 9/00

Since the first case of COVID-19 was identified in China in December 2019, it has afflicted more than 768 million people worldwide; with 6.95 million deaths reported to date[1]. As per the World Health Organization, about 80% of the COVID-19 patients are asymptomatic or mild to moderate, 15% develop the severe disease and 5% progress to the critical stage with complications[2]. Despite numerous clinical trials being conducted to evaluate potential strategies to reduce the risk of clinical progression, a consensus on the standard of care for patients with mild or moderate disease is not yet established[3].

Many phytoconstituents are identified and found effective against SARS-CoV-2 through molecular docking, *in-vitro* and *in-vivo* studies[4-6]. Several clinical studies have also been conducted to explore the therapeutic efficacy of traditional medicines in COVID-19 across the world. Systematic reviews of the clinical studies on traditional medicines for managing COVID-19 as an adjunct to the conventional treatment has shown significant effects of the combined therapy and highlighted the potential of traditional medicines in the treatment of COVID-19[7-11]. In India, until June 2020, out of 122 trials on COVID-19 registered in the clinical trial registry of India, the majority were registered in the traditional medicine category (n=67) compared to conventional medicine (n=42)[12].

AYUSH-64, an Ayurveda poly-herbal intervention, consisting of *Saptaparna* (*Alstonia scholaris* R. Br.), *Kiratatikta* (*Swertia chirata* Pexbex. Karst), *Kuberaksha* (*Caesalpinia crista* L.) and *Katuki* (*Picrorhiza kurroa* Royle ex. Benth), is indicated for infective febrile disease conditions such as malaria,

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microfilaremia, chikungunya, and influenza[13]. Molecular docking studies demonstrated that the constituents of AYUSH-64 inhibit replication of SARS-CoV-2 main protease enzyme[14,15]. Different clinical trials were conducted to evaluate the therapeutic efficacy of AYUSH-64 in asymptomatic, mild, or moderate COVID-19 in diverse populations across India[16-20]. Government of India recommended AYUSH-64 for managing asymptomatic and mild COVID-19 in the national guidelines for COVID-19 management through Ayurveda[21].

Therefore, this systematic review and meta-analysis was planned to provide objective evidence for the clinical efficacy and safety of AYUSH-64 as standalone or adjunct to conventional standard care in managing asymptomatic, mild, or moderate COVID-19. Although, few systematic reviews on Ayush interventions in COVID-19 are available[22,23], but to the best of our knowledge, the present study is the first systematic review to explicitly analyze the evidence on the efficacy and safety of AYUSH-64 in COVID-19.

Material and Methods

This systematic review was performed in concordance with the Cochrane Handbook of Systematic Review of Interventions guidelines[24]. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement has been followed to report the outcomes of this systematic review[25]. The PRISMA checklist is provided as Supplementary file. The study protocol was registered prospectively with PROSPERO, the International Prospective Register of Systematic Reviews (PROSPERO 2021: CRD42021267844) and published[26].

Inclusion and exclusion criteria

Only randomized controlled trials (RCTs) investigating the effects of AYUSH-64 in patients with COVID-19 were included. RCTs in which AYUSH-64 was administered along with any other Ayush interventions, non-randomized trials, case series, case reports, and pre-clinical studies were excluded. The study participants include patients of any gender and age group diagnosed with COVID-19, with or without any co-morbidities. RCTs on AYUSH-64 alone or in combination with conventional standard care as intervention in managing COVID-19 were included. Studies where conventional standard care (including anti-virals, antibiotics, corticosteroids, and multi-vitamins) was taken as control were included. The language was restricted to English due to resource constraints.

Outcome measures

The primary outcomes were efficacy demonstrated in terms of clinical recovery, mean time to clinical recovery, and SARS-CoV-2 clearance assessed by negative RT-PCR assay. The secondary outcomes include the change in the levels of pro-inflammatory markers, chest imaging findings and quality of life (QoL) parameters, the average duration of hospitalization, clinical deterioration (progression to the severe or critical stage), and incidence of death. The safety outcomes were incidence of adverse events (AE) and change in hematological and biochemical parameters.

Information sources

Different online databases such as PubMed, Ayush Research Portal (National Repository on Ayush COVID-19 Clinical and other R&D Initiatives), Cochrane Central Register of Controlled Trials (CENTRAL), DHARA, COVID-19 Evidence Alerts from McMaster PLUS™, Epistemonikos, TRIP database, National Collaborating Centre for Methods and Tools (NCCMT) database of COVID-19 studies and Google Scholar were searched from December 2019 to October 2021. The search was subsequently updated in February 2022 to include the most up-to-date data. The Clinical Trial Registry of India and WHO dashboard for clinical trials related to COVID-19 were also screened to identify ongoing and completed trials. Lists of references of eligible RCTs revealed by the database search were screened for additional potentially relevant studies.

Search strategy

The search strategy was based on the combination of MeSH terms and free-text terms, adjusted for each database. The search strategy for PubMed is shown in Table 1.

Study screening and selection

The titles and abstracts of all the search results were screened by two authors independently (AKR and AA), where in the duplicates were also removed. In case of any disagreement between these two authors, it was resolved by discussing it with the third author (PM). Subsequently, the full text of the shortlisted studies was retrieved, and the two authors then independently reviewed them for inclusion in the systematic review. The RCTs fulfilling the inclusion

Table 1 — Search strategy

"AYUSH-64" OR "Ayurveda"* OR "Ayurvedic therapy" OR "Ayurvedic treatment" OR "Ayurveda intervention" OR "Ayurvedic management" OR "Polyherbal formulation"
"COVID-19" OR "COVID" OR "Coronavirus Disease" OR "Coronavirus Infections" OR "2019 novel coronavirus infections" OR "2019-nCoV" OR "SARS-CoV-2" OR "SARS coronavirus 2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "severe acute respiratory syndrome" OR "corona virus 2" OR "new coronavirus" OR "novel coronavirus"
"Disease Outbreaks" OR "Epidemics" OR "Pandemics"
"RCT" OR "Randomized controlled trial" OR "Randomized controlled study"
(1 AND 2 AND 3) (Under Title/Abstract)

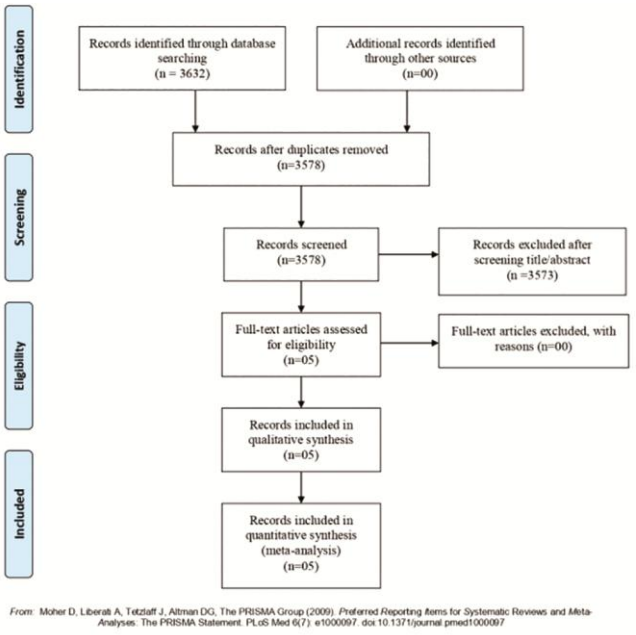

Fig. 1 — PRISMA Flow Diagram

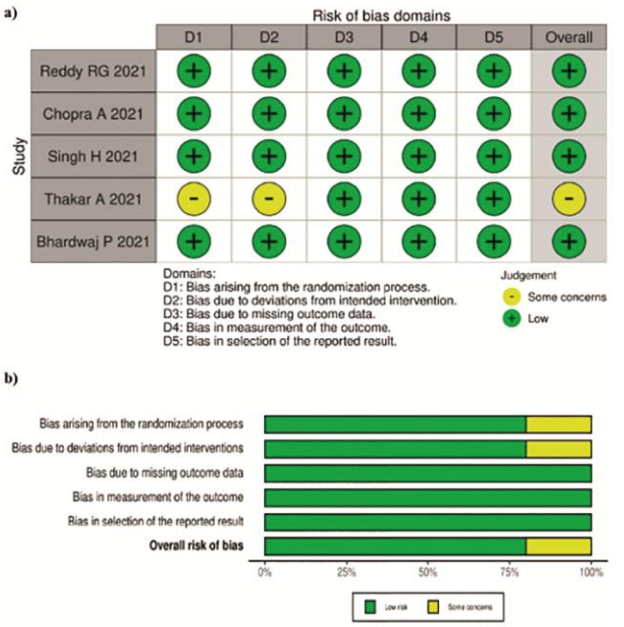

Fig. 2 — (a) Risk of Bias Graph (b) Risk of Bias Summary

criteria were included in the review. The screening and selection process is summarized as a PRISMA flow diagram (Fig. 1).

Data extraction from the included studies

The following data was extracted from the RCTs included in the systematic review for further analysis: publication-related information (first author and publication year), sample size, participants (age, gender, clinical stage of COVID-19), intervention details (route of administration, dose, frequency, duration), comparator details (name of the intervention, route of administration, dose, frequency, duration), follow-up period and outcome details (clinical efficacy and safety). If required, the authors of eligible studies were contacted through email for any incomplete or missing information.

Risk of bias (quality assessment) of individual studies

The risk of bias assessment of the included RCTs was carried out by two authors independently (AKR and AA) using the revised Cochrane risk of bias tool for randomized trials (RoB2) available online. Five domains, *viz*., randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results, were assessed with the help of pre-defined algorithms and were represented as traffic light plots and weighted summary plots (Fig. 2). A low risk of bias in all five domains was interpreted asa 'low' overall risk of bias. The study protocols of the included RCTs were accessed from the clinical trial registry to evaluate the reporting bias, if any.

Statistical analysis

Review Manager (RevMan) 5.4 software was used to carry out the meta-analysis. Standard mean difference (SMD) was used to measure the treatment effect for continuous data, and the odds ratio (OR) was used for dichotomous data with 95% confidence intervals (CI). Heterogeneity among trials was assessed using the chi-square test and the I^2 statistic.

The value of I^2 >30% and <75% was interpreted as moderate heterogeneity and I^2>75% as considerable heterogeneity[15]. The random-effects model was used. The subgroup analysis for clinical recovery was performed by follow-up period *viz.*, within 7 and 14 days.

Publication bias

Evaluation of publication bias of the summarized evidence within the individual studies was planned if at least ten RCTs were available for the particular study outcome.

Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the strength of the cumulative evidence. A summary of outcome measures and their associated GRADE ratings are presented as a summary of findings table generated using GRADEpro (GRADEpro GDT, McMaster University and Evidence Prime, 2021). The quality of evidence was classified as high, moderate, low, or very low.

Results

Literature search

A total of 3,632 records were identified from nine online databases, as shown in Figure 1. After removing the duplicates and other irrelevant results, 3,578 records were available. After the initial screening of titles and abstracts, five RCTs were identified and subjected to full-text screening as per the selection criteria. After the screening, five studies were included in qualitative synthesis and meta-analysis.

Characteristics of the included studies

All the five selected RCTs were conducted in India with a total sample size of 420 participants[16-20]. Among the five selected RCTs; one was a multi-center trial[18], and others were single-center trials[16,17,19,20]. All the RCTs were open-label and assessed the efficacy of AYUSH-64 as an adjunct to standard care in asymptomatic, mild, or moderate COVID-19. AYUSH-64 tablets/capsules were administered in the dose of 1.0 g three times daily except for one study where it was given two times daily. The intervention period ranged from seven days to 12 weeks. The conventional standard care, including vitamins, zinc, paracetamol, antibiotics, hydroxychloroquine was provided in the control group in all these studies. The mean time (in days) to attain clinical recovery and the proportion of participants who attained clinical recovery were the primary outcome measures in two studies[16,18] and secondary outcome in one study[17]. The mean time (in days) to negative RT-PCR assay for COVID-19 and the proportion of participants with negative RT-PCR assay at scheduled follow-up visitswere considered primary outcome measures in two studies[17,20] and secondary outcomes in one study[16]. Clinical improvement assessed by the WHO ordinal scale was taken as the primary outcome measure in one study[19]. Other outcome measures in these RCTs include the change in pro-inflammatory markers- IL-6, D-dimer, CRP, serum ferritin, etc.[16-20], change in HRCT chest findings[16], incidence of progression to severe stage of COVID-19 or need of oxygen therapy/ mechanical ventilation[17,19]. Change in metabolic functions- liver enzymes, renal function, and incidence of AE were assessed in all the selected studies. Any of the included studies did not report the average duration of hospitalization. Key data points from the included RCTs are presented in Table 2 and 3.

Assessment of methodological quality (risk of bias) of selected studies

In all the included trials, details related to the randomization process were provided. Four selected RCTs have used computer-generated simple random number sequences for randomization[16,17,19,20], whereas one study used the block randomization technique

Table 2 — Characteristics of included studies

Studies	Year	Sample size (n)		Gender (male/female) (n)		Age (in years)		Clinical classification (asymptomatic/ mild/moderate)	
		AYUSH-64 + SC	Standard Care	AYUSH-64 +SC	Standard Care	AYUSH-64 + SC	Standard Care	AYUSH-64 + SC	Standard Care
Chopra *et al.*	2020	69	70	54/15	58/12	42.87±12.6	42.7±12.0	0/56/14	0/58/12
Thakar *et al.*	2020	41	39	26/15	27/12	40±12.9	35.31±11.68	16/25/0	22/17/0
Reddy *et al.*[17]	2020	25	27	18/07	18/09	43.68±9.97	35.22±11.80	09/16/0	08/19/0
Singh *et al.*	2020	37	37	24/13	22/15	36.86±12.30	34.92±11.94	0/35/02	0/36/01
Bharadwaj *et al.*[20]	2020	30	30	29/01	29/01	-	-	0/30/0	0/30/0

Table 3 — Intervention details of included studies

Studies	Intervention		Course of treatment	Follow up	Outcome indicators
	AYUSH-64 + Standard Care	Standard Care			
Chopra *et al.*[18]	AYUSH-64 two tablets (500 mg each) twice daily with a glass of water soon after meals along with standard care	Concomitant use of hydroxychloroquine, azithromycin, corticosteroids, antibiotics, ivermectin, zinc, vitamin C, antiplatelet agents as per the national guidelines of India	12 weeks	-	①②③④⑥⑦⑧
Thakar *et al.*	AYUSH 64 as an add-on treatment to standard care in the dose of 2 tablets (500 mg each) thrice daily orally after food along with water	Standard care which included vitamin-C (500 mg), Tablet B complex, Tablet folic acid, Azithromycin and/ or tablet Augmentin (625 mg), HCQ (200 mg), Cetrizine (10 mg), Tab Pantoprazole (40mg), and Paracetamol (500 mg) as per the stage and condition of the patient.	14 days	14 days	①③⑤⑦⑧
Reddy *et al.*	AYUSH-64 two capsules (500 mg each) thrice daily after food with water along with standard care.	Standard conventional care which included Paracetamol, Vitamin C, Zinc, Hydroxychloroquine, Doxycycline, Azithromycin, Amoxycillin with Potassium Clavulanate, and Favipiravir as per the clinical condition of the patient along with the infection prevention and control practices.	30 days	-	①②③⑤⑦⑧
Singh *et al.*	AYUSH 64 two tablets (500 mg each) thrice daily after food with water along with standard conventional care	Conventional care that included Paracetamol, Cetrizine, Vitamin-C and Azithromycin.	30 days	-	①②③④⑤⑦⑧
Bharadwaj *et al.*	AYUSH 64 two tablets (500 mg each) thrice daily orally after food along with water as an add-on treatment to standard care.	Standard treatment as per the guidelines of the Ministry of Health and Family Welfare, Government of India.	07 days	-	①②③⑦⑧

①-Clinical recovery; ②-Negative RT-PCR assay for COVID-19; ③- Change in the levels of pro-inflammatory biomarkers; ④-Change in the chest imaging findings; ⑤- Clinical deterioration; ⑥- Change in the quality of life parameters; ⑦- Incidence of adverse events; ⑧-Hematological and biochemical safety parameters

(with blocks of 20 participants each)[18]. Randomization was concealed using sequentially numbered, opaque, sealed envelopes in two RCTs[16,17] and centrally done through telephone in two studies[18,20]. The remaining study did not provide any information regarding allocation concealment[19]. All the included trials were open-label, so neither the investigator nor the participants were blinded for the intervention. As far as blinding of outcome assessment was concerned, only one study described it as assessor blind[18]. Two studies mentioned that investigators/assessors were not blinded to the group allocation of participants[16,19], and the remaining two studies did not provide any information regarding this domain[17,20]. The risk for missing outcome data and bias in outcome measurement was low for all the selected studies. All the studies declared loss to follow-up among their participants except for one study in which there were no drop-outs[20]. The risk for selective outcome reporting was low for all the included RCTs. The overall risk of bias was 'low' for four selected studies[16-18,20] and 'some concerns' for one study[19]. The details of the quality assessment of selected RCTs are shown in Figure 2.

Assessment of study outcomes

Clinical recovery

The proportion of participants with clinical recovery was reported in three RCTs[16-18]. Overall, better clinical recovery was observed in patients treated with AYUSH-64 as an adjunct to standard care (AG) compared to the control group (CG) taking standard care alone (n=386; OR= 2.35; 95% CI= 1.33 to 4.16; p=0.003) (Fig. 3). No significant heterogeneity was observed in the included studies (I^2 = 18%; p=0.3). Further, better proportion of clinical recovery was observed in COVID-19 patients in AG within 7 days (n=260; OR= 2.75; 95% CI=

1.09 to 6.92; p=0.03) on subgroup analysis. The subgroup analysis results (I^2 = 0%; p=0.67) (Fig. 3) showed no statistical heterogeneity. One RCT that reported clinical improvement assessed by the WHO ordinal scale had no significant difference in the mean score between groups, although the proportion of asymptomatic participants progressing to the symptomatic stage was lower in the AG[19].

Mean time (in days) to clinical recovery

Three RCTs reported the mean time to clinical recovery in mild to moderate COVID-19 cases[16,18,19]. The meta-analysis revealed that the participants who received AYUSH-64 as adjunct demonstrated early clinical recovery compared to CG (n=264; SMD= -0.67; 95% CI= -1.16 to -0.18; p=0.007). Moderate heterogeneity was observed among the selected studies (I^2 = 71%; p=0.03) (Fig. 4).

SARS-COV-2 clearance (negative RT-PCR assay for COVID-19)

Three studies reported the proportion of participants with negative RT-PCR assay for COVID-19[16,17,20]. The time point to assess the SARS-COV-2 clearance through RT-PCR assay was day 07 onwards till clinical recovery. Better SARS-COV-2 clearance was observed in the AG within 14 days, although the results are not statistically significant (n=186; OR= 1.21; 95% CI= 0.51 to 2.88; p=0.66). No significant heterogeneity was observed among the studies considered for meta-analysis (I^2 = 10%; p=0.33) (Fig. 5).

Change in the levels of pro-inflammatory markers

Change in the levels of serum pro-inflammatory biomarkers, *viz.*, C-reactive protein (CRP), D-dimer, serum ferritin, Interleukin-6, Lactate dehydrogenase (LDH), and TNF-α was reported as outcome measure in all the five included RCTs[16-20]. No statistically significant difference was observed between groups in the levels of pro-inflammatory biomarkers, although a significant reduction in the levels of most of the biomarkers was reported within groups. One study reported the effect size of these parameters, which was higher for D-dimer (0.490 v/s 0.431), serum ferritin (0.651 v/s 0.565), and CRP level (0.558 v/s 0.465) in the AG as compared to CG[16].

Improvement in the chest imaging

Improvement in the chest imaging findings was reported in two studies[16,18]. One study reported HRCT

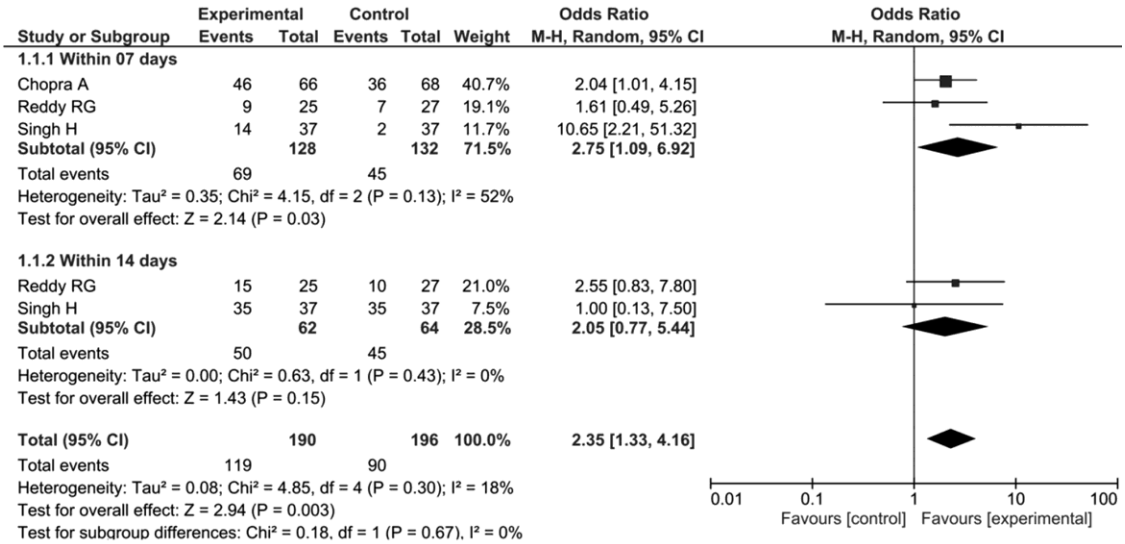

Fig. 3 — Forest plot of the Clinical Recovery

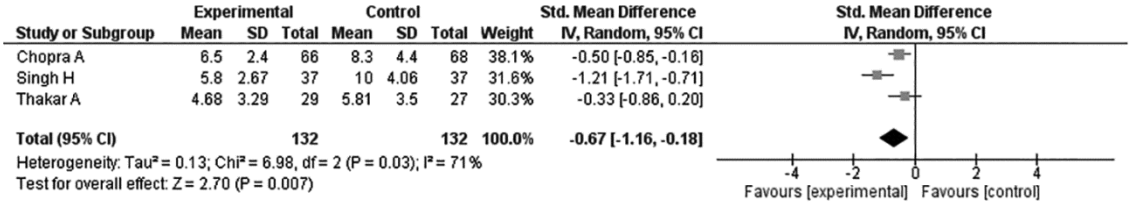

Fig. 4 — Forest plot of the mean time to Clinical Recovery

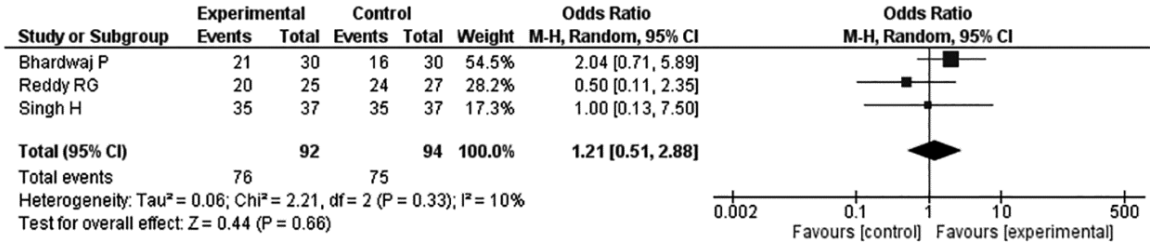

Fig. 5 — Forest plot of SARS-CoV-2 clearance

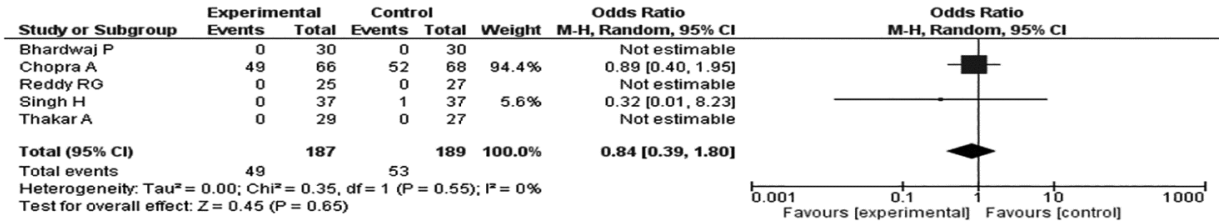

Fig. 6 — Forest plot of the incidence of adverse events

chest CO-RADS score and significant difference in the AG (p-value = 0.031) compared to the CG (p-value = 0.210) was reported[16]. Further, it was reported that more participants in the AG had a lower CO-RADS category 1 score on day 30 compared to the CG (p-value = 0.017). Another study reported chest skiagram findings, and the results were comparable in both groups, with no post-COVID lung complications at the end of the study period[18].

Progression to severe or critical stage/ clinical deterioration

Clinical deterioration was reported as an outcome measure in three RCTs[16,17,19]. Two studies observed that no participants required oxygen therapy or developed complications such as pneumonia, acute respiratory distress syndrome (ARDS), sepsis, arrhythmia, etc., during the study period in the AG[16,17]. One study reported that one participant in the CG discontinued from the study due to worsening of the disease[16], and another study reported that oxygen therapy was required for two and one participant in the AG and CG, respectively[19].

Incidence of adverse events (AE)

Incidence of AE was reported in all the RCTs included in this review. No Serious Adverse Event (SAE) was reported in the AG in any five studies, while two studies reported SAE in the CG[16,18]. One study reported that three participants in the CG developed SAE; nevertheless, these study participants recovered completely[18]. Another study reported disease progression in one participant in the CG and thereby withdrawn from the study[16]. Further, one study reported 49 AEs in the AG and 52 AE in the CG, including fever, myalgia, fatigue, breathlessness, loss of taste and loss of smell[18]. The overall incidence of AEs reported in the included studies was synthesized, and the result showed no significant difference between groups (n=376; OR= 0.84; 95% CI= 0.39 to 1.80; p=0.65) (Fig. 6). No significant heterogeneity was observed among the RCTs considered for meta-analysis (I^2 = 0%; p=0.55).

Safety parameters

Assessment of liver function tests and kidney function tests were reported in all five studies. Their levels were within normal limits in both the AG and CG at the end of the study period.

Incidence of mortality

No death was reported in either of the groups in the selected RCTs.

Change in quality-of-life parameters

Change in quality-of-life parameters was reported in one included study[18]. The study assessed quality of life through the WHOQOL-BREF scale. Significant improvement was reported in the physical health, psychological health, social relationship, and environmental well-being in the AG compared to the CG. One study reported Perceived Stress Scale score, and the results were comparable in both groups at the end ofthe study period[17].

Quality of evidence

The GRADE approach was used to assess the quality of cumulative evidence. The synthesized

AYUSH-64 as adjunct to standard care compared to Standard Care alone for COVID-19

Patient or population: COVID-19
Setting:
Intervention: AYUSH-64 as adjunct to standard care
Comparison: Standard Care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard Care	Risk difference with AYUSH-64 as adjunct to standard care
Clinical Recovery assessed with: Absence of clinical symptoms follow-up: range 7 days to 14 days	386 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	**OR 2.35** (1.33 to 4.16)	459 per 1,000	**207 more per 1,000** (71 more to 320 more)
Mean duration (days) for Clinical Recovery assessed with: Duration to resolve clinical symptoms follow-up: range 7 days to 14 days	264 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	-	-	SMD **2.38 SD lower** (4.11 lower to 0.65 lower)
Negative RT-PCR Assay for COVID-19 within 14 days assessed with: RT-PCR assay follow-up: range 7 days to 14 days	186 (3 RCTs)	⨁⨁◯◯ Low[a,b]	**OR 1.24** (0.57 to 2.70)	798 per 1,000	**32 more per 1,000** (106 fewer to 116 more)
Incidence of adverse events assessed with: Reported by the study participant follow-up: range 7 days to 12 weeks	376 (5 RCTs)	⨁⨁⨁◯ Moderate[a]	**OR 0.84** (0.39 to 1.80)	280 per 1,000	**34 fewer per 1,000** (148 fewer to 132 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded once for imprecision due to the small sample size(<400).
b. 95% CI overlaps no effect (OR of 1.0).

Fig. 7 — Summary of findings

evidence showed moderate confidence for clinical recovery and mean time to clinical recovery, whereas low confidence was observed for SARS-CoV-2 clearance assessed by RT-PCR assay with AYUSH-64 as an adjunct to standard care compared to standard care alone in patients with COVID-19. The evidence for clinical recovery and its mean duration was downgraded to moderate due to insufficient sample size. The evidence was downgraded to low for negative RT-PCR assay for COVID-19 due to inadequate sample size and 95% confidence interval overlapped no effect. A summary of findings is shown in Figure 7.

Publication bias

As the RCTs available for meta-analysis were very few (less than 10), a funnel plot was not employed to assess the publication bias.

Discussion

A total of five RCTs assessing the efficacy and safety of AYUSH-64 as an adjunct to standard care in asymptomatic, mild, and moderate COVID-19 were included in this systematic review.

The results of this review demonstrate with moderate confidence that combination therapy of AYUSH-64 and standard care hastens the clinical recovery in asymptomatic, mild, and moderate COVID-19. It was also observed that AYUSH-64 administered with standard care has a better effect on improving chest CT parameters and reducing the disease progression. Further, better SARS-CoV-2 clearance assessed by RT-PCR assay was observed in the AYUSH-64 group, although it was statistically not significant and the level of evidence is low. A significant reduction in the levels of several pro-inflammatory biomarkers was observed in both groups; however, the effect size of these parameters was larger in the participants who received AYUSH-64 as an adjunct to standard care. No significant difference was observed in the overall incidence of AEs between groups, and no death was reported in any of the included RCTs. Safety parameters such as liver function tests and kidney function tests were within normal limits in both groups. In one study, significant improvement in the QoL parameters was observed in the AG.

The prophylactic and therapeutic potential of Ayush systems needs to be explored in the search for effective options to mitigate the COVID-19 pandemic[27,28]. Several clinical studies have been conducted to evaluate the therapeutic efficacy of Ayush interventions in COVID-19 along with some systematic reviews. However, the authors of these systematic reviews have not performed the meta-analysis on the efficacy outcomes of separate Ayush interventions such as AYUSH-64 and have reported the outcomes of all the Ayush interventions as a whole[22,23]. Combining the efficacy of several heterogeneous interventions may only provide a broad overview of the Ayush interventions, but not intervention-specific efficacy. Further, these reviews have not included all the available RCTs on AYUSH-64 in COVID-19. One living systematic review on Ayush interventions in COVID-19 has included only

three RCTs, and another systematic review included only two RCTs on AYUSH-64 in COVID-19. However, the present study has included five RCTs and explicitly analyzed the evidence on the efficacy and safety of AYUSH-64 in COVID-19. However, the potential efficacy of AYUSH-64 against SARS-CoV-2 has been portrayed by the previously done systematic reviews on Ayush interventions.

Traditional medicine as adjunct to conventional standard care has been utilized for the management of COVID-19 in several countries such as India, China, and Iran. Traditional medicine has shown promising outcomes in prevention as well as managing asymptomatic, mild and moderate COVID-19[7-11]. Government of India has also recommended Ayurveda interventions for prophylaxis, and management of COVID-19 and post COVID care[21]. AYUSH-64 has been suggested for managing asymptomatic and mild cases in the guidelines for COVID-19 management through Ayurveda[21]. AYUSH-64 was repurposed for managing COVID-19 considering the outcomes generated from a clinical study[29] showing efficacy of AYUSH-64 in Influenza like Illness (ILI) and a molecular docking study[30] in which phytoconstituents from AYUSH-64 demonstrated inhibitory activity against SARS-CoV-2. Preliminary pilot study[31] followed by randomized controlled trials[16-20] highlighted the efficacy of AYUSH-64 in improving the clinical outcomes in asymptomatic, mild and moderate COVID-19. Meanwhile, a community-based interventional study also reported good clinical outcomes in home-isolated cases of COVID-19 after the AYUSH-64 administration as stand-alone or add-on to conventional care[32]. Several experimental studies also highlighted the potential immunomodulatory, anti-inflammatory, and antiviral properties of the ingredients of AYUSH-64[33-37] which could down regulate the pro-inflammatory cytokines and modulate the immune response of the COVID-19 patients. This could potentially reduce the possibility of disease progression in patients with COVID-19.

The outcomes of the present study emphasize that the synergistic effect of AYUSH-64 along with conventional care is better than stand-alone conventional treatment in the management of asymptomatic, mild, or moderate cases of COVID-19.

Limitations of this study

Limited RCTs were available for meta-analysis, and all of them were designed as open-label. Most of the included studies are single-center studies with a small sample size. Further, most of the included studies reported the per-protocol analysis to estimate the efficacy of AYUSH-64. In addition, only Indian participants were included in the RCTs selected for this systematic review. Furthermore, the interventions for the standard care in the included studies were different as per the guidelines existing at each point of time.

This systematic review had several strengths, such as explicit eligibility criteria, comprehensive search of nine online databases, inclusion of preprints of unpublished RCTs, analysis of important clinical efficacy-related outcomes, and critical appraisal of the quality of evidence using the GRADE framework.

Implications for further research

So far, very few approved therapeutic conventional medicine options are available to manage COVID-19. AYUSH-64 as an adjunct to conventional standard care showed potential in managing asymptomatic, mild, and moderate COVID-19, as evident by the findings of this systematic review. Further good-quality RCTs may be undertaken to strengthen the evidence regarding the efficacy of AYUSH-64 in preventing the progression of COVID-19 to severe or critical stage. The positive outcomes demonstrated by AYUSH-64 also put forward to look at other options from the traditional medicine systems to manage COVID-19 and its long-term effects.

Implications for clinical practice

The findings of this study assert that AYUSH-64 as an adjunct to standard care in asymptomatic, mild, or moderate COVID-19 is associated with good clinical outcomes. It may be considered for managing non-critical and home-isolated cases of COVID-19.

Conclusions

The evidence synthesized from five RCTs demonstrated that AYUSH-64 as an adjunct to standard care hastens clinical recovery compared to conventional standard care alone, and is safe in asymptomatic, mild, and moderate COVID-19. The current meta-analysis provided an updated evaluation of the available scientific evidence. However, considering low to moderate certainty of synthesized evidence, more robust RCTs would aid in generating a strong evidence base for utilizing the AYUSH-64 in managing COVID-19.

Supplementary Data

Supplementary data associated with this article is available in the electronic form at https://nopr.niscpr.res.in/jinfo/ijtk/IJTK_22(03)(2023)526-536_SupplData.pdf

Appendix A

Supplementary file: PRISMA Checklist

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Conflict of Interests

Amit K Rai, Azeem Ahmad, Pallavi Mundada, Krishna Kumar V, Sophia Jameela, Babita Yadav, Shruti Khanduri, Bhogavalli Chandrasekhararao, and Narayanam Srikanth work in CCRAS, Ministry of Ayush, Government of India, New Delhi. Amit K Rai, Sophia Jameela, Babita Yadav, Shruti Khanduri, Bhogavalli Chandrasekhararao, and Narayanam Srikanth are authors in two RCTs included in this systematic review.

Author's Contributions

AKR: Conceptualization, Methodology, Investigation, Data curation, Formal Analysis, Validation, Writing – original draft. AA: Conceptualization, Methodology, Software, Formal Analysis, Project Administration, Validation. PM: Methodology, Investigation, Data curation, Writing – review & editing. KKV: Investigation, Data curation. SJ: Writing – review & editing, Visualization. BY: Resources, Writing – review & editing. SK: Resources, Writing – review & editing. BC: Conceptualization, Writing – review & editing. NS: Conceptualization, Supervision, Writing – review & editing. All authors read, provided feedback, and approved the final manuscript.

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