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AYUSH-64 as an adjunct to standard care in mild to moderate COVID-19: An open-label randomized controlled trial in Chandigarh, India

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ABSTRACT

Objective: To determine the therapeutic efficacy and safety of AYUSH-64 as an add-on to standard care in mild to moderate COVID-19.

Design setting, and interventions: This open-label randomized controlled parallel-group trial was conducted at a designated COVID care centre in India in 80 patients diagnosed with mild to moderate COVID-19 and randomized into two groups. Participants in the AYUSH-64 add-on group (AG) received AYUSH-64 two tablets (500 mg each) three times a day for 30 days along with standard conventional care. The control group (CG) received standard care alone.

Main outcome measures: Proportion of participants who attained clinical recovery on day 7, 15, 23 and 30, proportion of participants with negative RT-PCR assay for COVID-19 at each weekly time point, change in pro-inflammatory markers, metabolic functions, HRCT chest (CO-RADS category) and incidence of Adverse Drug Reaction (ADR)/Adverse Event (AE).

Results: Out of 80 participants, 74 (37 in each group) contributed to the final analysis. Significant difference was observed in clinical recovery in the AG ($p < 0.001$) compared to CG. Mean duration for clinical recovery in AG (5.8 ± 2.67 days) was significantly less compared to CG (10.0 ± 4.06 days). Significant improvement in HRCT chest was observed in AG ($p = 0.031$) unlike in CG ($p = 0.210$). No ADR/SAE was observed or reported in AG. **Conclusions:** AYUSH-64 as adjunct to standard care is safe and effective in hastening clinical recovery in mild to moderate COVID-19. The efficacy may be further validated by larger multi-center double-blind trials.

1. Introduction

COVID-19 is the third known epidemic caused by highly pathogenic human coronavirus in the last two decades after Middle East Respiratory Syndrome (MERS) in 2012 and Severe Acute Respiratory Syndrome (SARS) in 2003. It has afflicted more than 315 million people worldwide

till date.¹ It can present as asymptomatic or mild to moderate illness to a severe pneumonia leading to a potentially fatal acute respiratory distress syndrome.² As per World Health Organization, about 80 per cent of the COVID-19 cases are asymptomatic or mild to moderate; 15 per cent cases have severe disease; and 5 per cent progress to a critical stage with complications.³ Elderly population, individuals with co-morbidities and

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frontline healthcare workers are at the highest risk for developing COVID-19. Recently, increasing incidence of COVID-19 in younger adults and children has also been observed.⁴ The physical, psychological, social, and economic consequences of the pandemic along with the considerable morbidity and mortality have affected the world in the most unprecedented manner and has challenged the healthcare systems globally. Several countries across the globe again witnessed a rise in COVID-19 cases in 2021, comparable to or worse than the peak touched during 2020. Apart from vaccines, significant efforts have been made to develop prophylactic and therapeutic interventions against COVID-19. As of now, very few approved therapeutic options are available for the management of COVID-19, though their clinical impact is under debate in different scenarios. The current strategy of conventional medicine is broadly based on the repurposing and repositioning of existing medications and recommends them for symptomatic support. On the basis of published empirical evidence, several therapeutic interventions such as anti-viral, anti-malarial, anti-inflammatory, and monoclonal antibodies have been proposed, however, the clinical outcomes observed in clinical trials are not very promising.⁵⁻⁷

Traditional Chinese Medicine and other complementary herbal medicines have been found to be effective in the management of SARS-CoV-2 infection.⁸⁻¹⁰ There is growing interest in scientifically exploring the potential of Indian traditional medicine systems such as Ayurveda to manage COVID-19.¹¹ Further, integrating Ayurveda with conventional medicine could offer a novel and cost-effective approach to reduce the disease burden and assist the over-burdened healthcare infrastructure. Repurposing Ayurveda interventions for early-stage COVID-19 is felt needed, given that their traditional use has established safety; and experimental studies have demonstrated their immunomodulatory, anti-inflammatory, anti-oxidant properties, and anti-viral activity.¹²⁻¹⁹ The Government of India has also supported the use of Ayurveda interventions in early-stage COVID-19 considering practice-based evidence and preliminary studies while underscoring the need for more studies on these interventions.²⁰

The trial drug, AYUSH-64, is a polyherbal formulation with proven efficacy in infective febrile conditions such as malaria, microfilariemia, chikungunya, and influenza with no safety issues observed in published clinical studies.²¹⁻²⁵ Furthermore, previous experimental studies suggest that the constituents of AYUSH-64 might exert immunomodulating, anti-inflammatory, and antioxidant activities.²⁶⁻³¹ These effects could halt the intense inflammatory responses in COVID-19 that cause progression to significant morbidity. AYUSH-64 was repurposed for COVID-19 in this study based on a previous clinical study that showed AYUSH-64 was effective in Influenza like Illness (ILI) and a molecular docking study that revealed 35 phytoconstituents isolated from AYUSH-64 demonstrated anti-viral activity against SARS-CoV-2.^{21,32} This study was designed to assess the efficacy and safety of AYUSH-64 as adjunct to standard care in improving the clinical outcomes of patients with mild to moderate COVID-19.

2. Material and methods

2.1. Study design

This was a single center, open-label randomized controlled parallel group study with participants randomized in 1:1 ratio to either receive standard conventional care alone or standard care along with AYUSH-64.

2.2. Setting and participants

The study was conducted at Shri Dhanwantry Ayurvedic College and Hospital, Chandigarh, India. At the time of this study, the hospital was designated to provide medical care to patients with asymptomatic or mild to moderate COVID-19 and with a lower risk of severe COVID-19.

After obtaining written informed consent in their native language,

patients with asymptomatic, mild, or moderate COVID-19 admitted at the designated COVID care centre were screened for eligibility to participate in this study. Patients of either sex aged between 18 and 75 years, who tested positive for COVID-19 through RT-PCR and categorized as mild to moderate cases as per the Ministry of Health and Family Welfare (MoHFW), Government of India guidelines,³³ willing to provide written informed consent and agreeing to comply with planned study procedures were included in the study.

Patients with co-morbidities such as diabetes mellitus, hypertension, cardiovascular disease, liver disease, chronic kidney disease, pulmonary disease, active carcinoma; history of immune suppression (solid organ or bone marrow transplant, use of immunosuppressive anti-metabolic and biologic agents, intrinsic immunodeficiency, HIV infection); history of bleeding, hemorrhoids, hemoptysis and acid peptic diseases were excluded. We also excluded patients on any Ayush medications for COVID-19 like symptoms; on parenteral nutrition; who had known sensitivity or contraindication to any of the ingredients of study intervention or had participated in a clinical trial in the preceding three months or if they were pregnant or lactating.

The enrolled participants were admitted in the in-patient department and discharged as per the guidelines of the MoHFW.³⁴ At the time of discharge on day 15, patients were advised to isolate themselves at home and self-monitor their health condition. We invited study participants for a follow-up visit at the study hospital on days 23 and 30.

2.3. Study intervention

AYUSH-64 procured from Indian Medicines Pharmaceutical Corporation Limited (IMPCL), a GMP certified company under the Ministry of Ayush, Government of India (Batch no.:19-APM-LDA-175; Manufacturing date: April 2020; Expiry date: March 2023) was administered in the dose of two tablets (500 mg each) thrice daily with water after meals to the participants for 30 days along with standard conventional care in the AYUSH-64 add-on group (AG). The control group (CG) received conventional care suggested by MoHFW guidelines on clinical management of COVID-19³⁵ that included Paracetamol 500 mg SOS, Cetirizine 10 mg OD, Vitamin C 500 mg BD, and Azithromycin 500 mg OD (for 5 days) as per the clinical status of the patient. Standard infection prevention and control practices were followed in both the groups.

AYUSH-64 is a patent polyherbal formulation consisting of *Saptaparna* (*Alstonia scholaris* R. Br.), *Katuki* (*Picrorhiza kurroa* Royle ex. Benth), *Kiratatikta* (*Swertia chirata* Pexbex. Karst) and *Kuberaksha* (*Caesalpinia crista* L.). The composition details and quality standards of the trial drug were compliant with the Ayurvedic pharmacopoeia of India and are provided in the [Supplementary file 1 \(Tables 1 and 2\)](#).

2.4. Outcome measures

2.4.1. Primary outcome

The proportion of participants who attained clinical recovery was the primary outcome measure. The clinical recovery was defined as the absence of any clinical symptoms of COVID-19. The duration of clinical recovery was determined on the basis of case records for the inpatient duration of 15 days. The mean duration for clinical recovery was calculated on the basis of the daily recorded symptoms of each participant till day 15, after which they were discharged following the existing guidelines.

2.4.2. Secondary outcomes

The proportion of participants with negative RT-PCR assay for SARS-CoV-2 (on day 7, 15, 23, and 30) and change in laboratory parameters such as total and differential leukocyte count, inflammatory markers such as Interleukin-6 (IL-6), D-dimer, C-reactive protein (CRP), Serum ferritin, Pro-calcitonin, Lactate dehydrogenase (LDH), Brain-type natriuretic peptide (BNP), Creatine kinase, Troponin I, Troponin T on

day 30 compared to baseline were included as secondary outcome measures. Change in level of pulmonary involvement in COVID-19 assessed by HRCT chest on day 30 when compared to the baseline was also included as a secondary outcome measure. Scoring details (CO-RADS category for HRCT findings) are provided in [Supplementary file 2](#).

Safety assessment: Safety of the trial drug was evaluated through recording incidence of ADR/AE and change in liver function test and kidney function test on day 30, compared to the baseline. All adverse events during the study were recorded and monitored as per Good Clinical Practice (GCP-ICH) guidelines.

2.5. Sample size

The sample size for the study was calculated based on the assumption that 80% of the participants in the AYUSH-64 group and 50% in the control group will attain clinical recovery on day 30. In the absence of any previous data on duration of clinical recovery using the trial interventions at the time of study design, our assumptions were based on the clinical experience of the investigators. With 95% confidence level ($\alpha = 0.05$), power of 80%, and assuming an attrition rate of 20%, 40 participants were estimated to be enrolled in each group. Hence, 80 participants were enrolled in the two groups of the study.

2.6. Randomization

Eighty eligible participants were randomized into two parallel groups in the ratio of 1:1 as per a statistician generated random number sequences using the Statistical Package for Social Sciences version 15.0 (SPSS 15.0 for Windows, 233 South Wacker Drive, 11th Floor, Chicago, Illinois, U.S.A.). Concealed allocation was done using sequentially numbered, opaque, sealed envelopes. The serial numbers matching the enrollment number of the participants was labeled on the outside of the envelopes. The sealed envelope with the eligible patient's enrollment number was provided to the participant after eligibility was ascertained.

2.7. Statistical analysis

The categorical variables are summarized as numbers (percentage) and compared using the chi-square test. Continuous data is represented as mean (standard deviation), except for data not following a normal distribution that is presented as median (Min, Max). Within group analysis was done using paired sample t-test for normal data, while Wilcoxon signed rank test was used for comparison of non-normal data. Comparisons between groups were done using independent sample t-test or Mann-Whitney Test for normal and non-normal data respectively. Kaplan-Meier curves were used for comparison of time to clinical recovery between the two groups and the significance of the differences was tested by a log rank test.

Effect sizes for parametric and non-parametric data have been computed using the methods as suggested by Cohen and Fritz et al.^{36,37} Effect sizes between group have been denoted as d_s and effect sizes within group have been reported as d_z . Effect size for non-parametric data has been denoted as r . A $p < 0.05$ was considered statistically significant. The result of per-protocol analysis of the study data is presented. Data analysis was done using the STATA version 16.1 (Stata/MP 16.1 for Windows, Stata Corp, 4905 Lakeway Drive, College Station, Texas, US).

2.8. Ethics and monitoring

The study was conducted in accordance with Indian Council of Medicinal Research (ICMR) National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017). The Institutional Ethics Committee of the host institute approved the study. The trial was registered prospectively at the Clinical Trial Registry of India (CTRI/2020/05/025214) dated May 15, 2020. Data and Safety Monitoring

Board (DSMB) monitored the study.

2.9. Compliance

All the study participants were closely monitored until discharge as per the existing guidelines. Further, participants assigned to the AG continued the use of trial drug till day 30 of the study. The format for reporting drug compliance was shared with all the study participants at the time of discharge. During the follow-up visits on day 23 and 30, filled drug compliance report forms and drug containers were collected from the participants in order to measure drug compliance. Participants in the CG were instructed not to take any additional medications without the knowledge of the investigators; this was enquired and confirmed at each follow up visit.

3. Results

3.1. Characteristics of participants

Participants flow from screening to analysis is depicted in [Fig. 1](#). Total of 90 RT-PCR confirmed COVID-19 patients were screened for their eligibility as per the selection criteria during the period from June 5, 2020 to July 16, 2020. After excluding ten patients (reason: not willing to provide written informed consent or comply with the requirements of the study protocol), 80 participants were enrolled on the next day of a positive RT-PCR test result. Two participants from each group dropped out from the study (reason: did not attend the scheduled follow-up). One participant in each group was withdrawn from the study (reason: conception in the AYUSH-64 group and referral to higher medical care in the control group). Therefore, 37 participants in each of the two study groups were included in the final analysis.

The baseline characteristics such as age, gender, and clinical severity were comparable in both the groups ([Table 1](#)). The majority of participants were young males (mean age of 36.8 years in the AG and 34.92 years in the CG). Majority of the participants (94.59% in the AG and 97.29% in the CG) were with mild symptoms and normal oxygen saturation level.

3.2. Clinical recovery

The proportion of participants who attained clinical recovery on day 15 was significantly higher in the AG (62.2%) compared with the CG (13.5%) ($p < 0.001$). The clinical recovery recorded on day 23 was 100.0% and 32.4% respectively ([Table 2](#)). On the day 30, all 37 participants in the AG had recovered clinically, compared to 54.1% in the CG. Headache, sore throat and cough were the persistent symptoms in the participants of CG even after 15 days. The mean duration for clinical recovery in the AG (5.8 ± 2.67 days) was significantly less compared to the CG (10.0 ± 4.06 days) on day 15. The Kaplan-Meier curve shows a steep fall in proportion of participants with persistent symptoms in the AG group compared to the CG ([Fig. 2](#)). At day 15, the cumulative proportion of patients with persistent symptoms was 37.8% in the AG group and 86.5% in the CG and these difference were statistically significant ($p < 0.001$).

3.3. Markers of inflammation and disease progression

3.3.1. Negative RT-PCR assay for COVID-19

Majority of the participants (94.5%) tested negative for COVID-19 (RT-PCR assay) on day 15 in both groups. While all the participants in AG tested negative by day 23, this time to attain negative RT-PCR status was 30 days in CG ([Table 2](#)). However, these differences did not achieve statistical significance.

3.3.2. Pulmonary involvement in COVID-19

There was no significant difference in HRCT CO-RADS category score

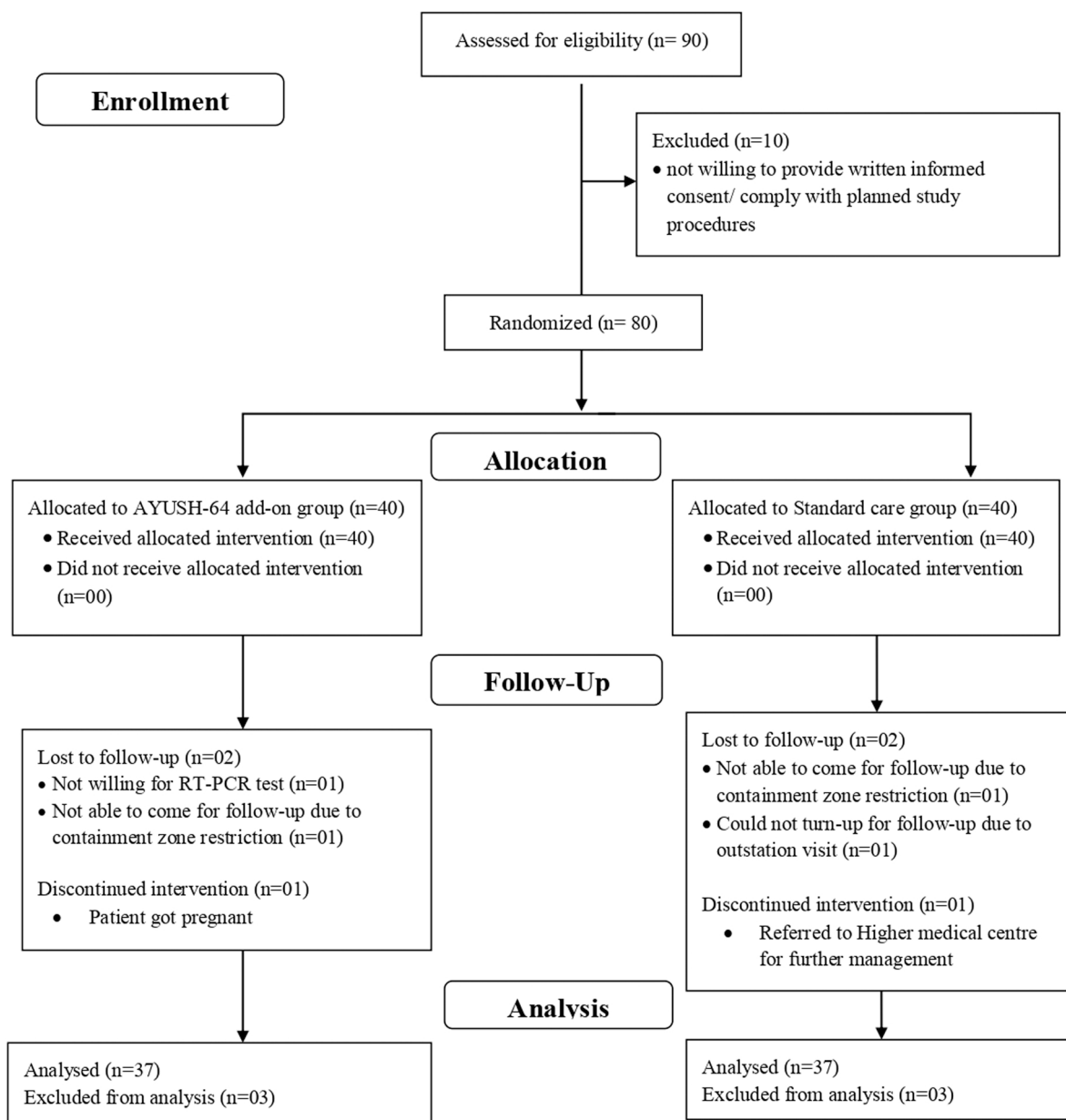


Fig. 1. CONSORT flow diagram.

Table 1
Demographic and clinical characteristics of the study participants.

Variable	Parameters	AYUSH-64 group (n = 37)	Control group (n = 37)	p-value ^a
Age: Mean (SD)		36.86 (12.30)	34.92 (11.94)	0.492
Gender: n (%)	Male	24 (64.9)	22 (59.5)	0.632
	Female	13 (35.1)	15 (40.5)	
Clinical Severity: n (%)	Mild	35 (94.59)	36 (97.29)	0.555
	Moderate	02 (5.41)	01 (2.71)	
SpO ₂ : Mean (SD)		97.49 (1.32)	97.14 (1.39)	0.270

SD: Standard deviation; SpO₂: Oxygen saturation by pulse oximeter.

^a Compared using chi-square test.

between the groups at baseline. Significantly more participants in the AG had lower CO-RADS score on day 30 than in CG (54% versus 27%, p-value = 0.017 for CORADS category 1). Within group comparisons revealed a significant difference in AG (p-value = 0.031) as compared to CG (p-value = 0.210) (Table 3).

3.3.3. Inflammatory markers

No significant difference at day 30 was observed between the groups in the levels of inflammatory markers viz. Interleukin-6 (IL-6), Serum ferritin, C-Reactive Protein (CRP), D-dimer, Pro-calcitonin, Lactate dehydrogenase, Creatinine kinase, Brain-type natriuretic peptide, Troponin I and Troponin T (Table 4, Supplementary file 1-Table 3). However, significant decrease in D-dimer level was observed in the AG (p = 0.007, d_z = 0.490) compared to CG (p = 0.129, d_z = 0.431). Statistically significant decrease was also observed in CRP level in both the groups; however, effect size was higher in AG as compared to CG (0.558 versus 0.465). Serum ferritin level also showed statistically significant reduction on within group comparison in both the groups, with AG showing larger effect size compared to CG (0.651 versus 0.565).

3.4. Safety parameters

No Adverse Drug Reaction (ADR) or Serious Adverse Event (SAE) was observed or reported in the AG. None of the participants required invasive or non-invasive oxygen therapy or developed complications

Table 2
Duration for clinical recovery and negative RT-PCR assay for COVID-19.

Outcome		AYUSH-64 group (n = 37)	Control group (n = 37)	p-value ^a
Proportion of participants clinically recovered	Day 7	14 (37.8%)	2 (5.4%)	< 0.001
	Day 15	23 (62.2%)	5 (13.5%)	< 0.001
	Day 23	37 (100.0%)	12 (32.4%)	—
	Day 30	37 (100.0%)	20 (54.1%)	—
	Day 7	27 (81.8) ^b	27 (79.4) ^c	0.803
Proportion of participants with negative RT-PCR	Day 15	35 (94.5)	35 (94.5)	0.999
	Day 23	37 (100.0)	36 (97.29)	0.314
	Day 30	37 (100.0)	37 (100.0)	0.999

^a Compared using chi-square test/fisher exact test.
^b Out of 33 participants (RT-PCR assay done on 33 out of 37 participants).
^c Out of 34 participants (RT-PCR assay done on 34 out of 37 participants).

such as pneumonia, acute respiratory distress syndrome, sepsis, and arrhythmia during the study period in the AG. Thus we did not find the use of trial drug to be associated with worsening of symptoms or disease progression. However, one participant in the CG needed hospitalization at a higher medical center due to progression of COVID-19 and hence withdrawn from the study. The liver function tests and kidney function tests were found to be within the normal limits throughout the study period in both the groups (Table 5).

4. Discussion

In this open-label randomized, active-controlled study, AYUSH-64 as an add-on to standard care in the management of mild to moderate cases of COVID-19 was found to be safe and leading to better clinical recovery.

Participants who received AYUSH-64 as adjunct to standard care demonstrated lower mean time for clinical recovery (5.8 days versus 10 days). On study day 15, around four times more participants had attained clinical recovery in AG, compared to CG (62% versus 13%, $p < 0.001$).

Clinical recovery in all participants in the AG observed on day 23 shows that compared with conventional medicine alone, combination therapy with AYUSH-64 could improve the clinical recovery in mild to moderate COVID-19 patients. The clinical outcomes perceived in the AG are supported by the observed improvement in several pro-inflammatory markers and CO-RADS scores for HRCT with the addition of AYUSH-64. Findings from the present study validates the evidence from the earlier studies on AYUSH-64 that reported early clinical recovery and reduction in the levels of pro-inflammatory markers in asymptomatic and mild COVID-19 cases.^{38,39} Immunopathological changes are marked as drivers of disease progression in COVID-19 and any medicine that can down regulate inflammatory cytokines and modulate immune response of host has better chances of improving patient prognosis in COVID-19. Reduction in the levels of pro-inflammatory markers indicates that AYUSH-64 could possibly down regulate the inflammatory cascade, thereby reducing the possibility of progression of the disease to severe or critical stage. Although pro-inflammatory markers decreased significantly in CG too, reduction in D-dimer and pro-calcitonin was seen only in the AG. Similarly, the improvement in CO-RADS score in the AG favors the add-on therapy. Although this was a single-center small-sized study, the finding that none of the participants required invasive or non-invasive oxygen support nor did any participant develop complications in the AG, unlike one participant in the CG who had progression of the disease suggests the need for further exploration of AYUSH-64 in preventing the disease progression. Moreover, no ADR or SAE was observed or reported by any of the study participants in the AG. This study furthers the findings of the established safety of AYUSH-64²¹⁻²⁵ by demonstrating its safety and tolerability when co-administered with conventional medicine and with less likelihood of drug-drug interactions.

This study is one of the early attempts at repurposing Indian traditional medicine for a newer disease with a pandemic disposition, such as COVID-19. So far, clinical studies on repurposing existing medications for COVID-19 included studies on Hydroxychloroquine, Favipiravir, Remdesivir and corticosteroids such as Dexamethasone. The outcomes of the clinical trial on Hydroxychloroquine do not recommend its use in the COVID-19 management.⁴⁰ Clinical studies on Remdesivir have also shown mixed or inconclusive results.^{41,42} Dexamethasone has shown promising results in reducing mortality among severe COVID-19 patients.⁴³ Favipiravir has also been found effective in mild or moderate COVID-19 patients but has resulted in moderate elevation of hepatic transaminases.⁴⁴ Probably, Favipiravir, Remdesivir, and

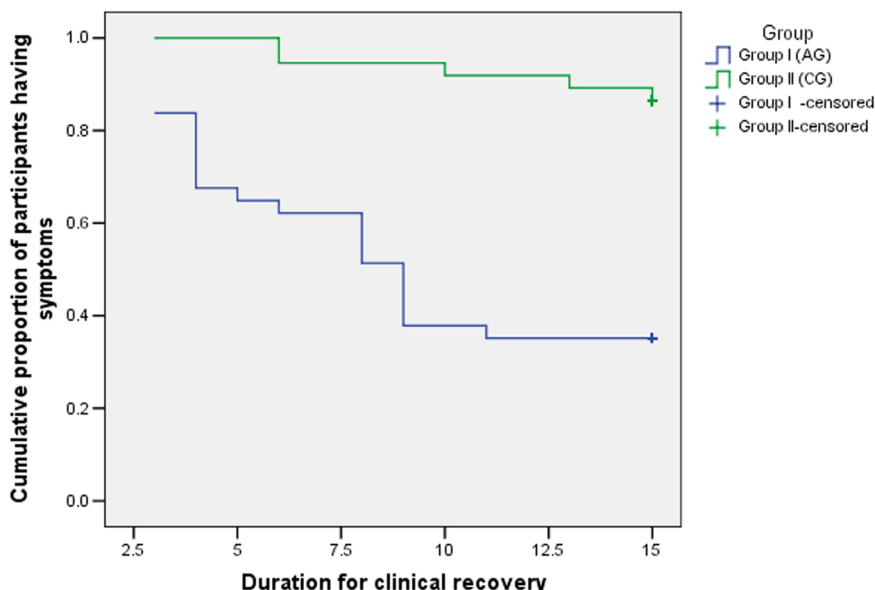


Fig. 2. Kaplan-Meier curve showing clinical recovery.

Table 3
Group comparison of HRCT chest CO-RADS category.

Grading		Baseline	30th day
CO-RADS 1	AG	13 (35.1%)	20 (54.1%)
	CG	8 (21.6%)	10 (27.0%)
	p-value^a	0.197	0.017 (*)
CO-RADS 2	AG	6 (16.2%)	5 (13.5%)
	CG	9 (24.3%)	13 (35.1%)
	p-value^a	0.385	0.030 (*)
CO-RADS 3	AG	4 (10.8%)	3 (8.1%)
	CG	5 (13.5%)	6 (16.2%)
	p-value^a	0.722	0.285
CO-RADS 4	AG	7 (18.9%)	4 (10.8%)
	CG	5 (13.5%)	2 (5.4%)
	p-value^a	0.596	0.394
CO-RADS 5	AG	7 (18.9%)	5 (13.5%)
	CG	10 (27.0%)	6 (16.2%)
	p-value^a	0.407	0.743

Within group *p-value* for AG (Compared using chi-square test) = 0.031 (*).
Within group *p-value* for CG (Compared using chi-square test) = 0.210.
(*) *p-value* < 0.05 has been considered as significant.

AG: AYUSH-64 Group; CG: Control Group; HRCT: High-resolution computed tomography; CO-RADS: COVID-19 Reporting and Data System. CO-RADS: A categorical assessment for chest CT in patients suspected for pulmonary involvement of COVID-19.

^a Between Group *p-value* compared using chi-square/Fisher exact test.

Dexamethasone are not the choice for treating asymptomatic and mild to moderate COVID-19 patients, with their known side-effects, if an alternative intervention with no such side-effects is available. With this analysis and background, this study could pave the way to positioning AYUSH-64 as a potential adjunct to standard care in the management of COVID-19. AYUSH-64 has demonstrated that it has a positive role in reducing duration of clinical recovery, down regulating inflammatory cytokines, and reducing the progression to severity, which are important outcomes, especially in a developing country like India, where the burden of hospitalization due to COVID-19 has a major impact. The effect sizes we provide from this study should be helpful in the design of future multicentre studies with large sample size needed to strengthen the evidence to support combination therapy with AYUSH-64. In the then prevailing circumstances of the pandemic and evidence from the age-old practices and early studies like the present one, the Indian Ministry of Ayush launched a nation-wide campaign for mass distribution of AYUSH-64 to asymptomatic, or mild to moderate cases of COVID-19 in home isolation.⁴⁵ Further, AYUSH-64 has also been incorporated in the National COVID management protocol based on Ayurveda and Yoga by the Government of India.²⁰

4.1. Limitations of the study

Patients with mild to moderate COVID-19 were included in the study; therefore, the findings could not be extrapolated to patients with severe infection or with co-morbidities. Our finding needs to be interpreted keeping in mind that this was an open-label single center study.

Table 4
Comparison of change in inflammatory markers.

Parameters	Assessment stage	AG (n = 37)	CG (n = 37)	Difference between the groups: mean difference (95% CI)	ES (between group)	^a <i>p-value</i>
Interleukin-6 (0–7.00 pg/mL): Median (Min, Max)	Baseline	5.8 (0.04, 465.70)	4.4 (0.08, 38.29)			0.556
	7th day	5.0 (0.02, 380.0)	8.0 (0.05, 48.90)			
	15th day	4.3 (0.01, 45.0)	2.8 (0.01, 37.50)			
	30th day	4.7 (0.03, 40.0)	4.5 (0.03, 32.60)		0.236	0.538
	ES (Within group) ^bp-value (time effect)		0.142 0.017(*)	0.232 0.006 (*)		
C-Reactive protein (< 6.0 mg/dL): Median (Min, Max)	Baseline	5.0 (2, 30)	5.0 (2, 35)			0.392
	7th day	4.0 (2, 47)	4.0 (1, 22)			
	15th day	3.9 (2.4, 35.0)	4.0 (2.5, 28.8)			
	30th day	3.7 (2, 33)	3.8 (2, 19)		0.085	0.566
	ES (Within group) ^bp-value (time effect)		0.558 < 0.001	0.465 < 0.001		
Serum ferritin (4.6–204 ng/mL): Median (Min, Max)	Baseline	86.7 (9, 1500)	109.5 (6, 618)			0.685
	7th day	93.0 (6, 1500)	105.3 (6, 560)			
	15th day	73.4 (8, 1428)	81.4 (5, 489)			
	30th day	59.0 (4, 1400)	76.0 (6, 515)		0.089	0.433
	ES (Within group) ^bp-value (time effect)		0.651 < 0.001	0.565 0.009		
D-dimer (0–0.5 µg/mL): Mean ± SD	Baseline	0.35 ± 0.211	0.34 ± 0.176	0.006 (– 0.084 to 0.964)		0.484
	7th day	0.36 ± 0.301	0.33 ± 0.401			
	15th day	0.26 ± 0.115	0.35 ± 0.168			
	30th day	0.21 ± 0.115 (*)	0.24 ± 0.146	-0.026 (– 0.087 to 0.034)	0.228	0.134
	ES (Within group) ^bp-value (time effect)		0.490 0.007	0.431 0.129		

(*) *p-value* of < 0.05 has been considered as significant; ES–effect size; AG: AYUSH-64 group; CG: Control group.

^a *p-value* – Calculated between group using independent sample t-test for normal data/using Mann-Whitney test for non-normal data.

^b *p-value* (time effect) – Calculated within group using one way repeated measure Anova for normal data/using Friedman test for non-normal data.

Table 5
Group comparison of effect on the safety parameters.

Parameters		AG (n = 37)	CG (n = 37)	Difference between the groups Mean difference (95% CI)	[#] p-value
Blood Urea Nitrogen (5–25 mg/dl)	Baseline	13.40 ± 3.66	12.54 ± 3.27	0.862 (– 0.747 to 2.472)	0.922
	30th day	10.71 ± 2.47	10.72 ± 3.28	-0.008 (– 1.358 to 1.341)	0.233
	^a p-value	0.001	0.019		
Serum Uric Acid (3.4–6.2 mg/dl)	Baseline	5.23 ± 1.36	5.41 ± 1.39	-0.181 (– 0.819 to 0.457)	0.792
	30th day	5.64 ± 1.44	5.73 ± 1.38	-0.086 (– 0.742 to 0.569)	0.536
	^a p-value	0.019	0.050		
Serum Creatinine (0.7–1.2 mg/dl)	Baseline	0.77 ± 0.19	0.71 ± 0.14	0.595 (– 0.194 to 0.138)	0.229
	30th day	0.77 ± 0.13	0.72 ± 0.10	0.041 (– 0.014 to 0.097)	0.093
	^a p-value	0.786	0.637		
AST (0–35 U/L)	Baseline	30.0 (12, 157)	33.0 (16, 161)		0.762
	30th day	24.0 (14, 60)	27.0 (17, 59)		0.070
	^a p-value	0.002	0.008		
ALT (5–40 U/L)	Baseline	38.0 (12, 265)	49.0 (2, 257)		0.685
	30th day	32.0 (9, 106)	34.0 (10, 99)		0.489
	^a p-value	< 0.001	0.031		
Serum Alkaline Phosphatase (35–104 U/L)	Baseline	85.43 ± 30.68	83.43 ± 19.45	2.0 (– 9.945 to 13.945)	0.086
	30th day	85.51 ± 20.50	84.51 ± 22.65	1.0 (– 9.015 to 11.013)	0.788
	^a p-value	0.985	0.747		
Serum Albumin (3.2–5.0 gm/dl)	Baseline	4.18 ± 0.37	4.11 ± 0.32	0.676 (– 0.095 to 0.230)	0.956
	30th day	4.35 ± 0.29	4.32 ± 0.33	0.027 (– 0.120 to 0.174)	0.499
	^a p-value	0.013	0.005		
Serum Globulin (2.3–3.5 gm/dl)	Baseline	3.19 ± 0.56	3.19 ± 0.46	0.005 (– 0.235 to 0.245)	0.271
	30th day	2.96 ± 0.51	2.96 ± 0.50	-0.004 (– 0.242 to 0.233)	0.983
	^a p-value	0.043	0.010		
Conjugated Bilirubin (0–0.2 mg/dl)	Baseline	0.17 ± 0.09	0.15 ± 0.47	0.016 (– 0.017 to 0.051)	0.179
	30th day	0.16 ± 0.08	0.15 ± 0.06	0.015 (– 0.018 to 0.048)	0.675
	^a p-value	0.679	0.691		
Unconjugated Bilirubin (0–0.8 mg/dl)	Baseline	0.66 ± 0.28	0.60 ± 0.20	0.060 (– 0.055 to 0.175)	0.031
	30th day	0.61 ± 0.22	0.60 ± 0.22	0.008 (– 0.095 to 0.113)	0.910
	^a p-value	0.137	0.968		

(*) p-value of < 0.05 has been considered as significant; Values are reported as Mean ± SD/Median (Min, Max); SD: Standard deviation; AG: AYUSH-64 group; CG: Control group; AST – Aspartate aminotransferase; ALT – Alanine aminotransferase.

[#] Between group p-value, compared using independent sample t-test/Mann-Whitney test.

^a Within group p-value, compared using paired sample t-test/Wilcoxon sign rank test.

5. Conclusions

AYUSH-64 as an adjunct to standard conventional care is safe and hastens clinical recovery in COVID-19 patients with mild to moderate disease. The use of AYUSH-64 significantly reduced the levels of pro-inflammatory markers such as IL-6, D-dimer, CRP, LDH, serum ferritin and HRCT chest score. Hence, AYUSH-64 can be considered as a safe and effective add-on intervention for the management of mild to moderate COVID-19. The efficacy of AYUSH-64 in COVID-19 may be further validated by larger multi-center double-blind trials.

Trial Registration

Clinical Trial Registry of India – CTRI/2020/05/025214.

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CRediT authorship contribution statement

Harbans Singh: Conceptualization, Project administration, Validation. **Sumit Srivastava:** Investigation, Resources, Project administration. **Babita Yadav:** Conceptualization, Methodology, Writing – review & editing. **Amit K Rai:** Writing – original draft, Writing – review & editing, Visualization. **Sophia Jameela:** Conceptualization, Methodology, Writing – review & editing. **Sanuj Muralidharan:** Investigation, Resources. **Rijin Mohan:** Investigation. **Shikha Chaudhary:** Investigation. **Richa Singhal:** Formal analysis, Data curation, Writing – review & editing. **Rakesh Rana:** Methodology, Formal analysis, Data curation. **Shruti Khanduri:** Methodology, Writing – review & editing. **Bhagwan S Sharma:** Resources, Writing – review & editing. **Bhogavalli Chandrasekhararao:** Conceptualization, Methodology, Writing – review & editing. **Narayanam Srikanth:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Sarika Chaturvedi:** Writing – review & editing, Visualization. All authors read, provided feedback, and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing interests. The authors Harbans Singh, Babita Yadav, Amit K Rai, Sophia Jameela, Richa Singhal, Rakesh Rana, Shruti Khanduri, Bhagwan S Sharma, Bhogavalli Chandrasekhararao and Narayanam Srikanth work in Central Council for Research in Ayurvedic Sciences (CCRAS), Ministry of AYUSH, Government of India, New Delhi. AYUSH-64 is a proprietary formulation of CCRAS.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ctim.2022.102814](https://doi.org/10.1016/j.ctim.2022.102814).

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