



**Research Article**

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## Safety and efficacy of Ayush 64 tablets as an adjunct therapy and its effect on bio- markers in mild to moderate covid-19 patients

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### ABSTRACT

**Background:** COVID-19 has emerged as the latest pandemic that erupted in the Wuhan City of People's Republic of China in December 2019, which is affecting human health and economy across the world. The ongoing COVID-19 outbreak in developed countries also highlights the fact that developed countries and rich populations are not immune to infectious disease outbreaks. Coronaviruses (CoVs) are enveloped, single-stranded, positive-sense RNA viruses that belong to the Coronaviridae family. SARS-CoV-2 is a member of the beta CoV genus, which also includes SARS-CoV-1 and MERS-CoV. The lack of approved effective drug therapeutic protocols for CoVs would make treating newly emerged COVID-19 infections globally difficult. **Objective:** A clinical study was conducted to evaluate the safety and efficacy of AYUSH 64 a poly herbal drug as an adjunct therapy to standard of care in mild to moderate Covid 19 patients **Materials and methods:** A prospective, open-label, randomized, parallel assignment, single-center clinical study with pre-test and post-test design was conducted at Covid hospital, Hassan institute of medical sciences between September 2020 to December 2020. A total 60 diagnosed cases (22-75 years of age) of Covid 19 were randomly allocated to both the groups. Control group received standard of care (SOC) as prescribed by the ICMR/WHO and state government, Trial Group received one week intervention of AYUSH 64 tablets at the dose of 2gm/day along with standard of care. Assessment of parameters viz. improvement in the symptoms, hematology, liver function, kidney function tests, acute phase reactants, Serum ferritin, Di dimer, LDH, and hsCRP were analyzed on day zero, day three and day seven. **Results:** One-week intervention of AYUSH-64 along with SOC helped to recover from Covid 19 symptoms. The intervention was safe on blood and biochemical parameters. Trial group has shown significant reduction in acute phase reactants viz hsCRP, LDH, Di dimer and Ferritin compare to the control group. No serious drug adverse effects were observed during the study. **Conclusion:** AYUSH-64 along-with standard care in mild to moderate covid 19 patients is safe and efficacious and this may be used as add-on to standard care for early recovery and better outcome.

**Keywords:** Ayush 64, Acute phase reactants, Covid 19, Covid bio markers.

### INTRODUCTION

COVID-19 has emerged as the latest pandemic that erupted in the People's Republic of China's Wuhan City in December 2019, affecting human health and the global economy. According to the WHO Coronavirus disease 2019 (COVID-19) Situation Report, approximately 158,651,638 cases are reported globally, with 3,299,764 deaths as of May 11th, 2021. The ongoing COVID-19 outbreak in developed countries also highlights the fact that developed countries and rich populations are not immune to infectious disease outbreaks.

Coronaviruses (CoVs) are enveloped, single-stranded, positive-sense RNA viruses that belong to the Coronaviridae family. SARS-CoV-2 is a member of the beta CoV genus, which also includes SARS-CoV-1 and MERS-CoV. The lack of approved effective drug therapeutic protocols for CoVs would make treating newly emerged COVID-19 infections globally difficult.

Drug repurposing, defined as identifying alternative uses for approved or investigational drugs outside of their defined indication, could be a possible way to overcome the time constraints of research and development required to design a therapeutic drug to combat the pathogen. As a result, drug repurposing or repositioning can facilitate faster clinical decisions at a lower cost than de novo drug development [1]. Though drug repurposing is sometimes based on chance observations, target-based drug repurposing is dependent on prior knowledge of the precise molecular or cellular element recognized by the proposed drug [2, 3]. Ayurveda and traditional systems of medicine in India have been treating infectious and

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non-infectious diseases equally with high success rates, treating patients through an individualized person-to-person approach based on the patient's needs. The Central Council for Research in Ayurvedic Sciences, India's apex body for Ayurvedic research and development under the Ministry of AYUSH, has developed a poly-herbal drug called AYUSH 64 after extensive pharmacological, toxicological, and clinical studies. AYUSH 64 was found to be safe and non-toxic in experimental studies at a dose of 500 mg/kg weight for 12 weeks. Aside from its anti-malarial activity, it has been shown to be effective in fevers of unknown a etiology, filarial lymphangitis, and liver function derangement [4, 5, 6].

Taking cues from the clinical experiences of physicians who had successfully used AYUSH-64 for the treatment of Influenza-like illness (ILI), the Central Council for Research in Ayurveda and Siddha conducted a pilot study (CCRAS). This sparked the idea of repurposing AYUSH 64 for use in the management of Covid-19 positive cases who also present with influenza-like symptoms due to respiratory tract affliction. *Saptaparna* (*Alstonia scholaris* R. Br.), *Katuki* (*Picrorhiza kurroa* Royle ex. Benth), *Kiratatikta* (*Swertia Chirata* Pexbex. Karst), and *Kuberaksha* (*Caesalpinia crista* Linn.) are among the Ingredients of AYUSH 64. Anti-inflammatory and immunomodulatory activities have been demonstrated in studies on the ingredients of AYUSH-64. Total alkaloids from *Saptaparna* have been shown in animal studies to inhibit the production of inflammatory cytokines TNF- and IL-8 in the BALF and lung [7]. *Swertia chirata* inhibited the expression of Vpr in Hela cells harbouring the TReX plasmid encoding full-length Vpr, and crude

extract of the whole *Swertia chirata* plant inhibited the expression of Vpr in Hela cells harbouring the TReX plasmid encoding full-length Vpr (TReX-HeLa-Vpr cells) [8, 9].

## OBJECTIVES

### Primary Objective

To compare the efficacy and safety of a combination regimen of Standard of Care (SOC) plus a selected standardised Ayurvedic drug (AYUSH 64 as adjuvant) in the treatment of mild to moderate COVID-19 to that of a standalone SOC regimen (active control).

### Secondary Objective

To determine the therapeutic effect of a combination of SOC plus a standardized Ayurvedic drug (AYUSH 64) on surrogate markers of COVID-19 disease severity and complications, and recovery pertaining to broad based domain of acute phase reactants.

## OUTCOMES

### Primary Outcomes

1. Improvement in selected laboratory parameters: blood hemoglobin, differential and total leukocyte counts, liver enzymes, renal functions, acute phase reactants, serum ferritin.

## STUDY DESIGN

**Table 1:** Study design

Study Type	Interventional (Clinical Trial)
Enrollment size	60 (30 Patients in each group)
Allocation	Randomized
Intervention Model	Parallel Assignment
Intervention Model Description	The main trial was an open label, randomized, Controlled trial which was conducted in the patients of COVID-19 in selected site Hassan institute of Medical sciences Hassan. Randomization was 1:1, stratified by severity of illness, to either with or without AYUSH-64 for 7 days. All patients were also received a supportive care/treatment according to ICMR/WHO guidelines for COVID-19
Purpose	Treatment
Masking	None (open label)
Control	Controlled
Timing	Prospective
No. of Groups	Two

## Interventions

**Group I:** (Ayurveda as add-on to standard care as per guidelines)

AYUSH 64

Dose	2 Tablets (500 mg each) twice daily
Dosage form	Tablets
Route of Administration	Oral
Time of Administration	Twice a day after food
Anupana	Water
Duration of therapy	7 days

**Group-II:** Conventional standard therapy as per ICMR/WHO guidelines

### ASSESSMENT PARAMETERS

**Clinical assessment:** Daily monitoring of Symptoms like Fever, breathless ness, Loss of taste and smell, headache, Myalgia, General Debility, Vomiting, Diarrhea, Headache

Daily monitoring of Body temperature, SPO2, Blood pressure

### Clinical Laboratory Parameters

The following laboratory tests were performed on the day of admission, day three and day seven in both the groups

Confirmatory Diagnostic Test: Nasal and/or Throat swab for real time RT-PCR for SARS-CoV-2, Haemogram, Liver function test, Kidney Function, Blood Sugar Level, Urine Routine, C-Reactive protein titer, LDH, Ferritin, D-Dimer, Serum Electrolytes

were screened, out of which 60 were enrolled in the study (Fig 1). Eligible subjects were allocated to two groups using simple randomization after obtaining the consent. In Group one the patients were given AYUSH 64 for 7 days only along with Standard of care and in group two only standard of care was administered and response was recorded on Day one and Day 7 in both the groups.

## RESULTS

Between September 2020 and December 2020, a total 78 participants

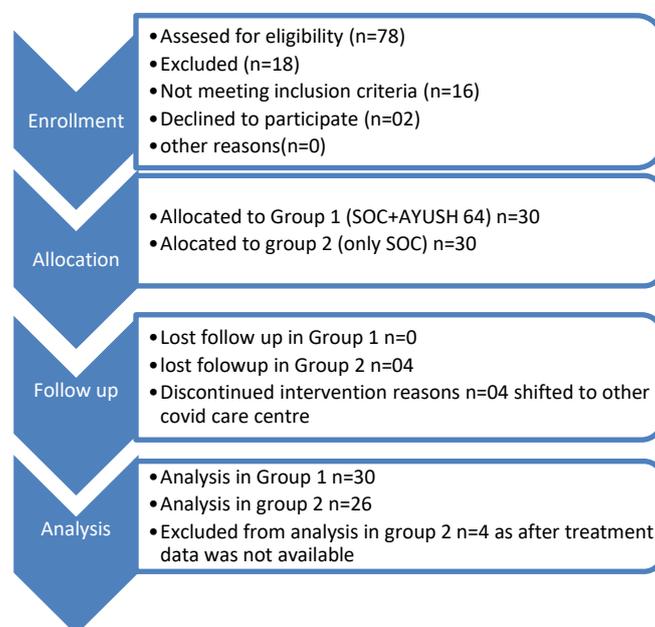


Figure 1: CONSORT 2010 Flow diagram

Table 2: Clinical features n=60

S. No	Symptoms	Frequency
1	Fever	18
2	Cough	23
3	Sore throat	13
4	Shortness of breath	14
5	Diarrhoea	04
6	Headache	11
7	Loss of taste	13
8	Tiredness	30
9	Skin rashes	00

Table 3: Trial group paired t test statistics

S. No	Assessment	BT	AT (Day7)	SD	SE	T test value	P value
1	SpO <sub>2</sub>	90.2	91.4	3.53	0.644	2.43	<0.05
2	Hb%	14.27	14.4	0.993	0.181	1.11	0.50
3	WBC	9686	11988	5.52	1.00	2.21	0.03
4	Platelet	1.91 lakh	2.66 lakh	76.08	13.89	8.54	0.001
5	RBC	4.88	5.22	0.5046	0.0921	7.24	0.009
6	LDH	419.66	287.86	152.60	27.86	4.731	0.000
7	Ferritin	766.85	432.19	414.52	75.68	8.23	0.0001

8	Hs-CRP	75.25	24.46	44.82	8.183	6.75	0.01
9	Trop-T	0.019	0.177	3.825	0.6984	1.65	0.23
10	D-DIMER	2094.9	1301.6	1849.28	337.6	6.78	0.001

**Table 4:** control group paired t test statistics

S. No	Assessment	BT	AT (Day 7)	SD	SE	T test value	P value
1	SpO <sub>2</sub>	88.88	89.15	3.86	0.757	0.43	0.34
2	Hb%	14.16	13.99	0.869	0.170	1.11	0.31
3	WBC	10918	11955	5.11	1.00	2.27	0.23
4	Platelet	2.32 lakh	2.49 lakh	85.59	16.78	8254	0.02
5	RBC	5.02	5.08	0.344	0.0674	4.24	0.053
6	LDH	407.4	388.8	186.04	36.48	0.508	0.61
7	Ferritin	628	640	344.07	67.47	8.23	0.03
8	Hs-CRP	48.51	33.08	53.21	10.43	5.75	0.01
9	Trop-T	0.026	0.007	2.671	0.5239	1.65	0.23
10	D-DIMER	1891.33	2007.27	1996.21	391.48	6.78	0.04

## DISCUSSION

Including both groups maximum subjects were males (80%), common age group 28-54 (70% of the subjects) all subjects tested negative for HCV, HBSAg, and HIV.

Among all the subjects (n=56) most common symptom observed is general tiredness (91%) followed by cough (60%), fever (51%), shortness of breath (48%), loss of taste (41%) and sore throat (37%) whereas diarrhea and headache were observed in least number of subjects. When compared with in the group both the groups have shown significant changes in terms of improvement in oxygen saturation levels in study duration. Statistically significant increase was observed in both groups in Hb%, RBC, and significant decrease was observed in LDH (p value 0.000), Ferritin (p value 0.0001), and hsCRP (p value 0.01) in trial group when compared to the control group. Highly significant increase in WBC (p value 0.03) and Highly significant decrease in Di dimer (p value 0.04) values observed only in trial group. Di dimer values are indicative of severe infection and altered coagulopathy and one of the associate indicators for the assessment of severity in covid19 patients which is complimented by decreased APTT in trial group on day seven. Decreased values of di dimer and hsCRP, LDH in trial group along with increased WBC values it evident that AYUSH 64 positively complimented along with SOC in reducing acute phase reactants and inflammatory markers in mild to moderate covid 19 patients.

Hematological parameters including liver function test and kidney function tests were within the normal limits during the treatment period and no significant change was observed in either of them in both the groups. Secondary complications of covid 19 were not observed in any participant during the study period in both the groups.

The ingredients in AYUSH-64 have been shown to have anti-inflammatory and immune modulatory properties. The aqueous extract of *A. scholaris* bark induced the cellular immune response in BALB/c mice at 50 mg/kg body weight once a day for 7 days, while 100 mg/kg

body weight inhibited the delayed type of hypersensitivity reaction<sup>[10]</sup>. Yun-Li Zhao *et al.* investigated the effects of *A. scholaris* indole alkaloids and total alkaloids on post-infectious cough in mice and airway inflammation in rats, respectively. Indole alkaloids suppressed inflammatory cells, cytokines (IL-6), and antioxidant balance. TNF- and IL-8 production in bronchoalveolar lavage fluid and lung was inhibited by total alkaloids<sup>[11, 12]</sup>.

The biopolymeric fraction RLJ-NE-205 derived from the rhizomes of *P. kurroa* improved the immune system of mice by increasing lymphocyte proliferation and cytokine levels (IL-4 and IFN-gamma) in serum, phagocytic index, and CD4/CD8 population<sup>[13]</sup>. Pretreatment with *P. kurroa* rhizome extract demonstrated anti-inflammatory activity by suppressing macrophage-derived cytokines (TNF-, IL-1, IL-6, IL-10) and mediators via NF-B signalling<sup>[14]</sup>. Picoside II, an active ingredient from *P. scrophulariiflora*, has been shown to have promising anti-inflammatory effects in cells and animals by lowering TNF-, IL-1, and IL-6 concentrations. When compared to lipopolysaccharide (LPS) stimulation, it inhibited the activation of the p65 NF-B signalling pathway. Pathologic changes in lung tissues had been alleviated, and the lung wet/dry weight ratio had been reduced<sup>[15]</sup>.

At  $IC_{50}$  concentrations, *Swertia chirata* inhibited NF-kB/DNA interactions and reduced pro-inflammatory IL-8 expression in cystic fibrosis cells<sup>[16]</sup>, the two main xanthones from *S. chirata*, bellidifolin and swerchirin, inhibit the production of the pro-inflammatory cytokines IL-6 and TNF-. Bellidifolin inhibited prostaglandin E2 (PGE2) production by suppressing cyclooxygenase-2 protein expression (COX-2)<sup>[17]</sup>. In HeLa cells harbouring the TReX plasmid encoding full-length Vpr (TReX-HeLa-Vpr cells), a CHCl<sub>3</sub> soluble crude extract of *S. chirata* inhibited the expression of Viral protein R (Vpr)<sup>[18]</sup>. A crude extract of the swertia plant was found to have antiviral properties against the Herpes simplex virus type-1<sup>[19]</sup>.

TNF-, IL-1, and IL-6 mRNA expression were reduced in the hippocampus and frontal cortex brain areas of rats after administration of methanolic extracts of *C. crista*<sup>[20]</sup>. *Caesalpinia bonducella* seed

extract increased antibody production and delayed type hypersensitivity in rats in a dose-dependent manner, indicating promising immune stimulant properties [21]. A water-soluble glucoside isolated from the alkaline extract of the endosperm of *C. bonducella* seeds demonstrated immune stimulant activity by activating splenocytes and thymocytes [22]. In experimental albino rats, whole ethanolic seed extract of *C. bonducella* seeds exhibited anti-inflammatory, antipyretic, and analgesic activities [23, 24].

According to Ayurvedic theory, weakened *agni* in *jvara* causes the formation of *ama* (proinflammatory undigested substance), which results in *amavastha* and a weakened immune system. The Ayurvedic treatment aims to correct *agni* status through *agnideepana* and *amapachana*, resulting in *niramavastha* (absence of *ama*), i.e. reversing the pathology and improving immune status. Tikta rasa (*Agnideepak* and *Amapachak*) is one of main *rasa* in the ingredients in AYUSH 64; hence AYUSH 64 takes on the role of *amapachaka* and changes the status of *agni* from *sama* to *nirama*. *Niramavastha* which has the effect of restoring normal metabolism and strengthening the immune system.

The seven-day treatment of AYUSH 64, combined with standard care, resulted in symptom reduction in the majority of patients. Symptoms such as fever, cough, and headache, as well as difficulty breathing and general debility, had significantly decreased by the seventh day of intervention. However, AYUSH 64 for a longer period of time may have produced better results in terms of metabolism restoration and immune system strengthening. In terms of herb–drug interactions, AYUSH 64 was used earlier in conjunction with standard antimalarial treatment. The seven-day administration of AYUSH 64 in conjunction with standard care was well tolerated in this study, and no adverse events were recorded.

### Limitations

This is pre and post-test design study with a small sample size and was focused on mild to moderate covid 19 patients only clinical safety related biochemical parameters. However, for substantial evidence, a larger multicentric study with a robust design with standard diagnostic investigations and cytokine response will be helpful to validate the efficacy of this drug.

### CONCLUSION

AYUSH 64 along-with standard care in mild to moderate covid 19 patients is safe and efficacious it may be used as an add-on to standard care for early recovery and better outcome

### Clinical Trial Registry

Clinical Trial Registry of India (CTRI), number: CTRI/2020/07/035245.

### Source of support

CCRAS, Ministry of AYUSH, Gol. Provided trial drug AYUSH 64 for the study.

### Conflict of Interest

None declared.

### Financial support

Nil.

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