“Ayurveda formulation AYUSH 64 in asymptomatic and mild COVID 19 infection-A prospective, open label Clinical Study”

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Ayurveda formulation AYUSH 64 in asymptomatic and mild COVID 19 infection- A prospective, open label Clinical Study

Abstract

Background

COVID 19 pandemic has evolved as a unique unprecedented global health crisis that has affected severely the economies and daily lives of people. Despite the diligent worldwide efforts to contain it, there is an exponential rise in cases. Associated serious morbidity and mortality has continued the efforts towards a clinically proven prophylaxis and therapeutic strategy. In the absence of any effective approved treatment, drug repurposing of available drugs are underway across the globe for treating COVID 19 patients. AYUSH 64 is an antimalarial Ayurveda formulation repurposed in COVID 19 management due to its proven efficacy in malaria and influenza like illness.

Trial Design: This was a prospective, open-label, single-arm, pilot study conducted at Ayurveda and Unani Tibbia College(A&U Tibbia) and Hospital, Designated COVID-19 Health Center under Govt. of NCT of Delhi.

Objective: The primary objective of the study was to assess the efficacy of AYUSH 64 in the management of asymptomatic, mild to moderate COVID-19 cases .However the secondary objectives were to assess clinical safety and to describe the clinical profile of COVID-19 with special reference to early symptoms, severity of disease, complications, course of disease, diagnostic investigations, biochemical & imaging abnormalities and patterns of clinical recovery.

Methods:

The study was conducted on 40 patients out of which maximum were asymptomatic and mild COVID-19 cases of either sex aged above 18 years admitted in the hospital with positive naso-pharyngeal swab test for SARS-CoV-2 (RT-PCR) or Rapid antigen test. Ayush- 64 tablets in the dose of two tablets (500 mg) thrice a day after food with warm water was given to the participants for the period of 7 to 14 days but once the patient got RtPCR negative ,medicine was discontinued. The primary outcome of the

study was negative status of SARS-CoV-2 on nasal or throat swab after 07 days or 14 days of intervention in a 2-day continuous real time RT-PCR test and changes in liver enzymes & renal functions. The secondary outcome of the study included the mean time (days) for clinical recovery as per clinical recovery criteria defined, number of symptomatic patients showing clinical recovery and improvement in selected laboratory parameters: differential and total leukocyte counts, acute phase reactants, serum IL-6, Serological Protective Antibody Assay (IgE, IgM and IgG).

Results

Out of 40 participants who were enrolled in the study, 36 (90%) completed the trial. Out of 36 participants, 69.44% participants after 07 days of AYUSH 64 intervention in the study became RT-PCR negative until 8th day and the rest 30.55 % participants completed the study in 14 days and they turned RT-PCR negative on 15th day. Out of 36 participants, 28 participants were symptomatic. 39.28% participants clinically recovered in 7 days of AYUSH-64 intervention and 53.5% participants clinically recovered in 14 days. Mean time for clinical recovery was 7.04 days ($\pm$ 2.88 days standard deviation). No adverse drug reaction was found in any of the participants. Serious adverse event (SAE) was reported in two participants (5%) just another day after enrolment in the study, which was not related, to the trial drug and the same was informed to the sponsor.

Conclusion

Among asymptomatic and mild COVID-19 cases, the repurposing of AYUSH 64 was found efficacious and quite safe to alleviate infection with significant clinical improvement within 14 days. Subsequent research on larger scale is warranted for statistically robust evidences in the treatment of COVID-19.

Trial Registration: CTRI/2020/05/025338- Clinical Trials Registry-India

Key words: Ayurveda, AYUSH 64, COVID-19, SARS-CoV-2

Introduction:

The COVID-19 outbreak has been unprecedented since the cases were first reported in China in December 2019 and has affected **220 countries and territories** around the world¹. COVID-19 has a wide range of symptoms reported ranging from mild symptoms to severe illness, which may appear 2-14 days after exposure to the virus. The symptoms include fever or chills, sore throat, shortness of breath or difficulty in breathing, cough, fatigue, headache and muscle or body aches, loss of taste or smell, nausea or vomiting, nasal congestion and diarrhoea².

Individuals of any age are at risk for COVID 19 infection. However, the probability of severe COVID-19 disease is maximum in people aged above 60 years, or having chronic diseases. The incubation period of COVID-19 from the time of exposure is up to 14 days. The period of infectiousness, onset and viral shedding duration are not completely defined. Common laboratory findings of COVID-19 include lymphopenia, leukopenia, elevated levels of aminotransferase, D-dimer, C-reactive protein; lactate dehydrogenase and ferritin³. Molecular diagnostics of the viral genome is by Reverse transcription polymerase chain reaction (RT-PCR), chest x-ray or CT scan, and serology blood tests⁴.

Although many therapies have been proposed but no effective treatment to cure COVID-19 has been reported and mainly antiviral drugs and respiratory therapies are being used to treat the disease. With the number of COVID-19 cases surpassing every day, its socio-economic impact necessitates an urgent need for effective treatment modality. Developing new drug in a time-critical fashion is impractical seeing the immediate global challenge. Drug repurposing is an emerging strategy where existing medicines, having detailed information on their pharmacology, formulation and potential toxicity and tested safe in humans are redeployed to combat difficult-to-treat diseases⁵. It confers reduction in risk failure where a failure rate of approximately 45% is mainly associated to safety or toxicity issues in drug discovery with an additional benefit of saving average drug development time up to 5–7 years. The therapeutic value of a drug is maximized and consequently the success rate increases⁶. Since repurposing is based upon previous research and development efforts, hence the drug repurposed

could easily be ready for clinical trials quickly like Ayush 64 which was meant for Malaria & flue like illness.

Besides hailing the immunity boosting measures of AYUSH systems of medicine in these pressing times, Government of India has backed their role in prevention and treatment of the COVID-19. Being an opportune time to evaluate the Ayurveda concepts of holistic approach towards disease management and its interventions for prevention and treatment of the disease, several initiatives have been implemented in addressing COVID 19 pandemic problem through clinical studies on AYUSH systems of medicine. One such initiative was taken by Central Council for Research in Ayurvedic Sciences, under Ministry of AYUSH, Govt. of India in which AYUSH 64 , a poly herbal drug (Table 1) developed for its anti-malarial activity through extensive safety and efficacy studies was repurposed in COVID 19 based on its antiviral, immuno-modulator and antipyretic properties. AYUSH 64 is an anti-malarial drug found clinically effective in *Plasmodium vivax*, and *P. falciparum* malaria^{7, 8, 9}but has also been found effective in fever of unknown aetiology and filarial lymphadenitis^{10, 11, 12}.An experimental study on AYUSH 64 has shown it to be safe in a dose of 500 mg/kg body weight for a duration of 12 weeks¹³. Many of the clinical studies besides efficacy have reported that the formulation is safe without any adverse drug reaction or serious adverse events on parameters like Liver function test, Kidney function test^{14,15,16}

As per a recent study on AYUSH 64, one-week intervention of AYUSH-64 in a dose of 3 gms/day helped to recover from Influenza like illness symptoms with reduced frequency of usage of acetaminophen and antihistaminic drug. The intervention was found safe and could be used in other viral infections with pyrexia for early recovery and better outcome¹⁷. At the same time in COVID Scenario, Council has conducted in-silico study in collaboration with the National Institute of Nutrition, Hyderabad on AYUSH 64.The results showed that about 35 of its phyto-constituents have high binding affinity in COVID 19 virus¹⁸. This lead to repurposing AYUSH 64 in COVID-19.

COVID 19 resembles the symptoms of *Vata Kaphaj Jvara* or *Sannipataj Jvara* (*pittanubandhi*) as per the Ayurvedic Classics¹⁹. The trial drug AYUSH 64 is made of herbs *Saptaparna* (*Alstonia scholaris*) *Katuki* (*Picrorhiza kurroa*), *Kiratatikta* (*Swertia Chirata*) and *Kuberaksha* (*Caesalpinia bonducella*). The constituents used in the drug AYUSH-64 are *Jwarghna* (useful in fevers), *Shwasa-Kaasaghna* (useful in breathlessness, cough), *Shothaghna* (anti-inflammatory) and have anti-inflammatory and immunomodulatory activity²⁰.

A pilot study on AYUSH 64 was specifically designed to determine an appropriate evidence-based treatment modality from Ayurveda. This pilot study intended to evaluate the efficacy and safety of AYUSH 64 in the management of mild to moderate cases of COVID-19.

Methods:

Study Design:

The study is a prospective, open-label, single-arm, pilot clinical trial in accordance with the principles of Declaration of Helsinki and National Ethical Guidelines for Biomedical and Health Research involving Human Participant, 2017 by Indian Council of Medical Research.

Study Setting:

This study has been conducted at Ayurvedic and Unani Tibbia College and Hospital, Designated COVID Health Center under Govt. of NCT of Delhi.

Study Participants:

COVID 19 cases with positive naso-pharyngeal swab test for SARS-CoV-2 on RT-PCR or Rapid antigen test fulfilling the selection criteria of the study and admitted to Ayurvedic and Unani Tibbia College and Hospital, Delhi were enrolled in the study.

Selection Criteria:

The participants with the following inclusion criteria were included in the study after taking informed written consent:

Inclusion criteria:

Participants of either sex age above 18 to 60 years admitted at Ayurvedic and Unani Tibbia College and Hospital, Delhi with positive RT-PCR test or Rapid Antigen test for SARS-CoV-2 diagnosed as asymptomatic, mild* to moderate case** of COVID 19 as per the prevailing government guideline who were able to take oral medications and voluntarily signed the informed consent form for participation were included in the study.

*Mild COVID -19 : Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache Without shortness of breath or Hypoxia (normal saturation (*Ref: 2 Revised guidelines for Home Isolation of very mild/asymptomatic COVID-19 cases* (<https://www.mohfw.gov.in/pdf/RevisedguidelinesforHomeIsolationofmildasymptomaticCOVID19cases.pdf>))

Moderate COVID 19: Pneumonia with no signs of severe disease Adults with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO₂ 90 to ≤93% on room air, Respiratory Rate more or equal to 24 per minute. (*Ref: 2 Revised guidelines for Home Isolation of very mild/asymptomatic COVID-19 cases* (<https://www.mohfw.gov.in/pdf/RevisedguidelinesforHomeIsolationofmildasymptomaticCOVID19cases.pdf>))

Exclusion Criteria:

Participants with severe vomiting who could not take oral drugs, respiratory failure and requiring mechanical ventilation, in critical condition or ARDS or NIAD 8 –point ordinal score 2 Hospitalized, on invasive mechanical ventilation or extra corporeal membrane oxygenation or liver enzymes Alanine Transaminase (ALT) or Aspartate Transaminase (AST)>2 times the upper limit of normal, pregnant or lactating women

or having any other condition which as per the investigator would jeopardize the outcome of the trial.

Study Intervention:

The study drug is a polyherbal Ayurveda formulation AYUSH 64 developed and patented by Central Council for Research in Ayurvedic Sciences, New Delhi (Table 1) for antimalarial activity and repurposed as trial drug against mild to moderate cases of COVID 19 on the basis of its antiviral, immuno-modulator and antipyretic properties. Central Council of Research in Ayurvedic Sciences procured the trial drug from Indian Medicines Pharmaceutical Corporation Limited, Almora, Uttarakhand. The quality control and safety parameters of the formulation and its ingredients was complied with API limits/ In-house limits. The trial drug was given to the participants in the dose of 2 Tablets (500mg each) thrice daily with warm water after food i.e 3gm/ day for 7 days or 14 days. The duration of therapy depended upon the COVID – 19 test done on 8th day and 9th day consecutive days. If the test was positive, the trial drug was continued for the next seven days, and if the test was negative on two consecutive days, treatment was discontinued. Participant with drug compliance more than or equal to 80% were continued in the study. The compliance was assessed at each follow-up.

Sample Size:

The study was conducted as a pilot study with sample size as 30 participants. Assuming attrition rate as 25% the sample size of 40 was fixed for the study²¹.

Data Variables:

Data variables recorded in the study included demographic details like age, gender, marital status, educational status, occupation, socio-economic status, habitat, religion ; vital signs viz. temperature, respiration rate, pulse rate, blood pressure- systolic & diastolic, SPO2; clinical signs and symptoms such as fever at evaluation, history of fever, cough, breathlessness, sore throat, sputum, nausea, body ache (muscle pain), abdominal pain, vomiting, nasal discharge (nasal congestion), chest pain, anorexia, headache, wheeze, nasal flaring, stridor, crepitation, lower chest in drawing and accessory muscle use; laboratory investigations namely Haematology, Absolute

lymphocyte Count, ESR, Blood Sugar : Fasting,HbA1c, Renal Function Test, Liver Function Test, Hs-CRP,IL-6,Ig-E,Ig-G,Ig-M and Urine Pregnancy Test , previous medication data, current medication data, comorbidity, travel & exposure history i.e history of travel to overseas (COVID affected areas), travel / residence in COVID hotspots/ endemic areas, workplace exposure to COVID 19 cases and Direct / indirect Contact with COVID 19 cases (Except workplace exposure) The participants were also assessed for Ayurvedic parameters of fever namely laziness, watering of eyes, burning sensation in eyes, excessive yawning, heaviness in body, exhaustion without exertion, exhaustion with minimal exertion, fatigue, frequently changing affection and aversions for sound, heat, sunlight, wind, water etc, no desire for food, indigestion, tastelessness, depletion in strength, feeling fatigued, depletion of skin lustre, slight change in behaviour, agitated eyes, excessive sleep, restlessness, bending of body/feeling as if muscles and body are contracting, tremors, Giddiness/ vertigo, excessive and irrelevant talking, insomnia, horripilation, hyperaesthesia teeth or tingling in teeth, weakness, generalized body ache, slowness in activities], taking comparatively longer time for a routine work, inability to do regular functions, difficulty in deglutition/ingestion of food, aversion for sweets and sudden affection for sour, salty and pungent tastes.

Outcome:

Primary Outcome measures:

Primary outcome measures included negative status of SARS-CoV-2 on nasal or throat swab after 07 days or 14 days of intervention in a 2-day continuous real time RT-PCR test

Secondary Outcome measures:

Mean time (days) for clinical recovery as per clinical recovery criteria defined, number of symptomatic patients showing clinical recovery [time frame: 7th day, 14th day if RTPCR positive-on 8th or 9th day] and improvement in selected laboratory parameters; differential and total leukocyte counts, acute phase reactants, serum IL-6, Serological Protective Antibody Assay (IgE ,IgM and IgG) assessed at 8th or 15th day time frame were the secondary outcome measures. The clinical recovery was defined as normal

forehead temperature by thermal scanner, absence of cough (infrequent, short episodic, non-wheezy, relieved by minimal or no medication, not interfering with routine speech and not related to lying in bed, mild sore throat or nasal congestion), absence of breathlessness on routine daily self-care chore or respiratory rate less than 30 breaths per minute without any supplemental oxygen, normalization of SpO₂ by standard peripheral oximetry device (above 95%), recovery sustained for at least 48 hours under physician observation and absence of any other symptom/sign attributed to COVID-19 illness which were assessed on 7th day and/or 14th day from baseline. and changes in the safety parameters viz liver and renal function assessed on 8th day if the rtPCR was negative and or 15th day.

Statistical Analysis:

The data has been analysed in two subgroups. Subgroup I for the participant who became RT-PCR negative for SARS-CoV-2 on nasal or throat swab after 07 days of intervention in a 2 day continuous real time RT-PCR test and subgroup II for the participants who became RT-PCR negative after 14 days of intervention in a 2 day continuous real time RT-PCR test. The data was analysed through Statistical package for Social Sciences (SPSS) version 15. The data on continuous variables are expressed as the mean $\pm$ standard deviation / Median (Min-Max) and categorical variables are expressed as numbers and percentages. A *p* value of less than 0.05 has been considered as significant. The assessment parameters have been compared for the participants who continued until 8th day with baseline by using paired sample t test or Wilcoxon signed rank test for data not distributed normally. The assessment parameters of the participants who continued in the study till 15th day was compared at baseline, 8th and 15th day using Repeated Measures ANOVA/ Friedman test.

Result:

Total 46 COVID 19 cases admitted at Ayurvedic and Unani Tibbia College and Hospital, Designated COVID Health Centre under Govt. of NCT of Delhi were screened on the basis of inclusion criteria, out of which 40 participants fulfilling the

inclusion criteria were enrolled in the study. Out of 40 participants enrolled, 04 participants were dropped out from the study as 02 discontinued the treatment while Serious Adverse Event (SAE) was reported in 02 participants who were referred to higher centre. Hence, outcome assessment was done on 36 participants. Among 36 participants, 08 participants were asymptomatic and 28 participants were mild COVID 19 cases. The CONSORT diagram of Study participants is shown in fig. 1.

All participants were found to be in the age group of 18-48 years with a mean age of 28.80 ± 8.94 . Among them male participants were 28 (78.4%) and female participants were 08 (21.6%). 59.5% participants were unmarried. In education status, maximum number of participants were graduate 12 (32.4 %). Maximum numbers of participants have fieldwork 16 (43.2%) followed by 9 (24.3%) participants involved in field work with physical labour. Among the total participants, 20 (56.8%) were above the poverty line. The majority of the participants 22 (62.2%) were from urban area followed by rural 03 (29.7%) area. 02 (5.55 %) participants had Hypertension as Co-morbidity condition. The participants who had history of travel / residence in COVID hotspots/ endemic areas were 13 (36.1%), workplace exposure to COVID 19 cases were 18 (50.0%) and remaining COVID 19 cases informed that they have no direct contact with COVID patient (Table 2.)

Total 25 participants were found to be RT-PCR negative on 9th day confirmed by two consecutive RT-PCR tests on 8th and 9th day and were considered in Subgroup I. Out of these 25 participants, 20 participants were symptomatic. The analysis of the clinical assessment data of symptomatic cases showed that symptoms like fever, breathlessness, sputum, nausea, abdominal pain and chest pain and Ayurveda parameters of *Jawara* like watering of eyes, burning sensation in eyes, exhaustion without exertion, indigestion, depletion in strength, depletion of skin lustre, slight change in behaviour, agitated eyes, excessive sleep, bending of body/feeling as if muscles and body are contracting, slowness in activities, taking comparatively longer duration for a routine work, inability to do regular functions, difficulty in deglutition/ingestion of food, aversion for sweets and sudden affection for sour, salty and pungent tastes were absent on 7th day. The symptoms like cough persisted in 7

(35%) , sore throat 3 (15%), body ache 2(10.0%), nasal discharge 2 (10.0%), anorexia 1 (5.0%), vomiting 1 (5.0%), headache 4 (20.0%), laziness 3 (12.0%), excessive yawning 2 (8.0%), heaviness in body 3 (12.0%), exhaustion with minimal exertion 2 (8.0%), fatigue 8 (32.0%), frequently changing affection and aversions for sound, heat, sunlight, wind, water etc, 1 (4.0%) no desire for food 1 (4.0%), tastelessness 1 (4.0%), feeling fatigued 1 (4.0%), restlessness 1 (4.0%), , Giddiness/ vertigo 1 (4.0%), insomnia 1 (4.0%), , weakness 4 (16.0%) and generalized body ache 4 (16.0%) on 7th day.

The other 11 participants who were found to be RT-PCR positive had completed the trial by 14th day and were found to be RT-PCR negative in two consecutive RT-PCR test done on 15th and 16th day. The data of these 11 participants was considered under Subgroup II for analysis. Out of the 11 participants, 08 participants were symptomatic. All the sign and symptoms at baseline were resolved in the participants except cough which was persisted in one case only .The percentage of relief in sign and symptoms may be seen in Table 3 & Table 4.as the tables are reflecting the details of presence of symptoms only in few cases.

Out of 28 participants who were symptomatic, mean time for clinical recovery was 7.04 days $\pm$ 2.88 days.. The number of participants who clinically recovered till 7th day were 11 (39.2%) and the number of participants who clinically recovered till 14th day were 15 (53.5%). (Table 5).

Reduction in the levels of Hs-CRP, IgG and Ig M was observed in Subgroup I, though it was statistically insignificant. Reduction in levels of Hs-CRP, IL-6, IgE and IgM was observed in Subgroup II which was statistically insignificant. There was statistically insignificant increase in level of IgG from mean value 1615.04to 1635.73on 15th day in subgroup II. (Table 6)

Invasive or non-invasive oxygen therapy was not required during the intervention period for any of the participants who completed the trial. Oxygen therapy was given to one of the participant who was withdrawn from the trial due to SAE on 2nd day of enrolment in the study and referred to higher health centre.

The haematological tests, liver and renal function tests were found within the normal limits at the baseline and during the intervention period in the study. Statistically insignificant increase in haematological parameters within normal range was observed in Subgroup I and II (Table 6). Statistically significant reduction in level of Total protein (p value 0.015) and Serum Globulin (p value 0.043) was observed in Subgroup I. Reduction in levels of other laboratory parameters of liver and kidney function tests was also observed which was statistically insignificant in Subgroup I. Reduction in laboratory parameters of liver and kidney function test was observed in Subgroup II except SGPT from mean value 37.73 at baseline to 43.36 on 15th day and Serum Alkaline phosphate from mean value 112.00 at baseline to 120.45 on 15th day which were statistically insignificant. (Table 7). The vitals such as temperature, respiratory rate, pulse rate, blood pressure or SPO2 were recorded within the normal limits during the intervention period in the participants (Fig.2 and Fig.3). Temperature, Respiration rate, Pulse rate, Systolic and Diastolic Blood pressure and SPO2 were within the normal range in subgroup I on 8th day and subgroup II on 15th day.

Concomitant medications were taken by two participants during the study. One participant was on tab. thyroxine in the dose of 150 mcg once daily for the past ten years for hypothyroidism and other participant was taking Tab. Telmisartan in the dose of 40 mg and Tab Torsemide in the dose of 5 mg once daily for the past one year for hypertension. The rescue medications were given to six participants of the study (Table 8).

Adverse drug reaction or adverse event was not reported in any of the participant who completed the study. Only 02 participants (5%) which do not have any existing co-morbidity condition were withdrawn from the study due to Serious adverse event (SAE) reported just another day after enrolling in the study, which probably may not be due to trial drug intake. Out of the two, One participant progressed towards severe stage with chief complaint as giddiness along with tingling sensation in left arm just after two days of trial drug initiation and another participant progressed towards moderate stage with breathlessness and pain in chest just next day of initiating trial intervention. Both the participant were given oxygen therapy and subsequently referred to higher centre.

Considering the onset of SAE in both the participants, it may be ascertained that the trial drug may be seemingly unrelated to SAE.

Discussion:

Scientific community across the globe are exploring an effective COVID 19 therapeutic intervention to contain the pandemic. In this study, the results of the administration of repurposed Ayurvedic formulation AYUSH 64 in patients with mild COVID 19 infection have been reported. The findings of the study showed the mean time for clinical recovery as 7.04 days (± 2.88). 39.2% have clinically recovered in 7 days and 53.5% recovered in 14 days. Outcome of a study on ivermectin in mild to moderate COVID 19 cases showed the total recovery time from the onset of symptoms as 10.09 ± 3.236 days for intervention arm while 11.50 ± 5.32 days for control arm with no significant difference in recovery time for fever, cough, shortness of breath and resolution of symptoms between the two arms. The study reported mean recovery time in the intervention arm as 5.31 ± 2.48 days which did not differ significantly from the control arm where mean recovery time was 6.33 ± 4.23 days²². Hydroxychloroquine administration in mild to moderate covid-19 patients admitted to hospital showed that negative conversion was not significantly higher than standard of care alone. Moreover, higher adverse events were reported in hydroxychloroquine recipients than the non-recipients²³.

In this study, 90% participants completed the trial and turned RT-PCR negative till 15th day, out of which 69.44% participants became RT-PCR negative on 8th day with repeat RT-PCR on 9th day (Fig 5). A study on baloxavir marboxil, favipiravir showed that the percentage of COVID 19 patients who became viral negative after 14-day treatment was 70%, 77%, respectively and 100% for control group, with the medians of time to clinical improvement as 14, 14 and 15 days respectively²⁴. A short term study of remdesivir on 53 COVID 19 patients showed that after 18 days of treatment the clinical improvement was 68% with total 13% mortality and 47% patients were discharged from hospital. The study included cases of different stages of COVID 19 infection²⁵. A systematic review and network meta-analysis study on drug treatments for COVID 19 reported that ten randomized controlled trials on hydroxychloroquine,

lopinavir-ritonavir, remdesivir and standard care observed no convincing evidence that these interventions increased rate of viral clearance and reduced the time to viral clearance²⁶. A review study observed that the clinical outcomes of antiviral drugs are not consistent and found conflicting reports on oseltamivir. The study reported that eight trials on Lopinavir/ ritonavir and two randomized clinical trials on favipiravir failed in showing efficacy of the drugs in treating COVID 19 patients²⁷.

This study showed that most of the symptoms were resolved in the participants. Cough 1(12.5%), nasal discharge 1(12.5%), headache 1(12.5%) and sore throat 2(25.0%) was seen after 14 days of intervention in two participants. In a study on mild Covid-19 cases, the symptom resolution between nitazoxanide and placebo groups did not differ after 5 days of treatment²⁸.

WHO mentions that some patients might experience certain symptoms such as post viral cough beyond the period of infectivity on which further research is required²⁹. Urine output, bowel habit and appetite was normal in most of the participants. Disturbance in sleep was observed in a few participants. Results of a systematic review and meta-analysis study shows that SARS-CoV-2 may cause delirium in a significant proportion of patients in the acute stage and there is possibility of depression, anxiety, fatigue, post-traumatic stress disorder, and rarer neuropsychiatric syndromes in the longer term³⁰. The trial drug may be used effectively in mild to moderate cases of COVID 19 for quick recovery. As per WHO, SARS-CoV-2 RNA has been detected in patients one to three days before the onset of the symptoms and the viral load peaks in the upper respiratory tract within first week of infection which is followed by a gradual decline over a period. The patients may still test positive for weeks for SARS-CoV2 by RT-PCR even after resolution of symptoms³¹. As of now, discriminating positive RT-PCR test result due to COVID 19 infection recurrence or intermittent shedding of virus RNA fragments is not possible³². Given the fact, RT-PCR negative conversion of 69.44% participants on 9th day is quite encouraging for using AYUSH 64 as a standalone intervention in future for large scale trials on COVID 19 disease.

Though statistically insignificant but reduction in levels of Hs-CRP, IL-6, IgE, IgM, IgG was observed in the Study. IL6 expression is regarded as helpful in assessing the

risk of progression to severe condition, and higher CRP is an indicative of poor prognosis and severe disease³³. A meta-analysis and review studies have found that decreased S. Albumin, elevated CRP, LDH Lymphopenia and high ESR³⁴ along with increased D-dimer and low hemoglobin were most common laboratory features reported in COVID 19³⁵. The observations of reduction in levels of Hs-CRP, IL-6, IgE, in the trial have shown that AYUSH 64 as standalone intervention has effectively checked disease progression in asymptomatic and mild COVID 19 cases.

No Adverse event / Adverse drug reaction (AE/ADR) has been reported during the study period in any of the participants who completed this study. A study has reported 66% of adverse events due to Remdesivir treatment in comparison to 64% in placebo treatment³⁶. Another review study reported most common adverse events of remdesivir as gastrointestinal side effects (nausea, constipation, diarrhoea) and graded elevation in alanine transaminase and aspartate transaminase along with hepatic toxicity which lead to discontinuation of drug in 10% cases in a randomized control trial. The study reported adverse events of Lopinavir/ ritonavir as increase in alanine transaminase, gastrointestinal side effects such as diarrhoea, loss of appetite, nausea and vomiting and for favipiravir as diarrhoea, liver toxicity, hyperuricemia in some patients. Further, some studies on Lopinavir/ ritonavir were discontinued due to severe gastrointestinal side effects, hypokalemia, and skin eruptions³⁷. Adverse events were more commonly observed in the the hydroxychloroquine group (50.00%) and the chloroquine group (44.44%) compared to the control group (16.67%)³⁸. A Systematic Review and Meta-analysis showed that there was a higher risk of ECG abnormalities/arrhythmia with hydroxychloroquine / chloroquine³⁹.

Ayurvedic Clinical profile of COVID 19 based on a study is classified as agantuja jvara having vatakapha pradhana sannipata presentation with a consideration of dominance of Pitta at certain stages and some patients of COVID 19⁴⁰. Another study has proposed the Ayurveda protocol for treatment of COVID 19⁴¹. The constituents of AYUSH 64 have been reported to have antipyretic, hepatoprotective, anti-inflammatory, antioxidant, antiviral⁴²⁴³⁴⁴⁴⁵⁴⁶⁴⁷⁴⁸⁴⁹⁵⁰ and Immunostimulatory and immunomodulatory properties⁵¹⁵²⁵³⁵⁴⁵⁵⁵⁶⁵⁷⁵⁸ Ayurveda aims at digestion of *Ama* (toxic

by-products of partially digested food) for the treatment of *Jvara* for which *langhana* (fasting) along with Ayurveda single and polyherbal formulations having *tikta rasa* (bitter taste), *ushna virya* (hot potency), *katu* (pungent) *vipaka* and *amapachaka* (toxins alleviating/ anti-inflammatory) properties are described⁵⁹. The constituents of the trial drug are *tiktarasatmak*, which pacifies the vitiated *Kapha* and neutralize the *Amavisha* through its *Deepaniya* (stomachic), *Pachaniya* (digestant), and *shodhan* (purification) properties⁶⁰ and hence *Jvaraghana* (relieves fever), *Sannipatajwarahara* (relieves recurrent fevers), *Krimihara* (wormicidal), *Jantuhara* (anthelmintic), and *Shothahara* (anti-inflammatory). Ayurveda drugs strengthen *Agni* (digestive functions along with metabolic functions), *Bala* (innate strength) and restores balance among the *Doshas* and hence restores the overall functional integrity in order to overcome infection and recover from disease making this as potent therapy against COVID-19. About 81% COVID 19 cases are mild to moderate with mild symptoms up to mild pneumonia⁶¹. This study reflects the reasonable and plausible aspects that Ayurveda can provide management care for the patients diagnosed with asymptomatic, mild to moderate COVID 19.

Study limitations:

This is a pilot standalone intervention study with small sample size, non-blinded design, no comparator arm and conducted only in mild to moderate COVID 19 cases, which limits the data being generated on efficacy and safety profile of the trial drug. Preliminary clinical data is insufficient to elicit favourable risk/benefit profile for treatment of COVID-19. The effect of the trial drug on few more inflammatory and other laboratory parameters could have also been evaluated in the study which could not be realized due to logistical constraints.

Conclusion:

AYUSH 64 may be effectively used in asymptomatic, mild to moderate cases of COVID 19. The study provides the evidence of early clinical recovery with significant improvement in COVID-19 symptoms and the levels of inflammatory markers in asymptomatic, mild to moderate COVID 19 cases. AYUSH 64 has been well tolerated, no significant SAE/ADR was reported and no progression of the disease in

asymptomatic and mild COVID-19 cases to severe cases was seen. Repurposing the drug in COVID 19 could potentially offer a promising solution and rapid strategy in alleviating the infection and establishing an anti COVID-19 therapy in the country. AYUSH 64 has much broader spectrum of properties including antiviral, antipyretic, immune-stimulant and immunomodulatory activities, which could open new perspectives for effective and safe treatment in asymptomatic, mild to moderate cases of COVID-19.

However, statistical robustness of the results is limited to small sample size for which large-scale double blind Randomized Controlled Trial with better end-points may be designed to elucidate conclusive evidence on efficacy and safety profile of AYUSH 64 in COVID 19 treatment.

Ethics Approval and Trial registration

The study has been approved by institutional ethics committee and registered prospectively at Clinical Trial Registry India with registration no. CTRI/2020/05/025338

Conflict of Interest-Nil

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Ministry of Ayush, Government of India

Table 1: Composition of each 500 mg tablet of AYUSH 64

<i>Sr. No</i>	<i>Ingredients</i>	<i>Scientific name</i>	<i>Part used</i>	<i>Ratio</i>	<i>Actions as per Ayurveda</i>	<i>Pharmacological actions</i>
1	Saptaparna	Alstonia scholaris	Root Bark Aqueous Extract	100 mg.	Jvara, Swasa* (API Part I, Vol-I, pg-169)	Anti-inflammatory, Analgesic, Antioxidant, Immunomodulatory, Antimicrobial, Hepatoprotective, Antimalarial, Antifilarial (*Reviews on Indian Medicinal Plants, Vol-2, ICMR; Jian-Hua Shang et al. 2010; Arulmozhi.S et al. 2007)
2	Katuki	Picrorhiza kurroa Royle ex. Benth	Root Aqueous Extract	100 mg	Jvara, Vishamjvara, Swasa, Kaasa, Daaha, Krimiroga, Arochaka# (API Part I, Vol II,pg-93)	Immunostimulant, Immunomodulatory, Anti-inflammatory, Antipyretic, Antioxidant, Antiviral, Antihistaminic, Antimicrobial, Hepatoprotective, Renoprotective effects# (Reviews on Indian Medicinal Plants, Vol-20, ICMR; Umme Salma et al. 2017)
3	Kiratatikta	Swertia chirata Pexbex. Karst	Whole-plant Aqueous Extract	100 mg.	Sannipata jvara, Swasa, Kaasa, Daaha, Shotha, Trishna, Krimiroga, Kandū (API Part I, Vol-I, pg-127)	Antipyretic, Anti-inflammation, Anti-oxidant, Anti-viral, Hepatoprotective, Antibacterial, Antifungal activity (Vijay Kumar et al 2016, Sushil Bhargava et al.2009)

4	Kuberaaksha	Caesalpinia crista L.	Seed Powder	200 mg	Vishamajvara, Kasa, Shotha, Swasa, Agnimandya, Pravahika, Yakritpliharoga, Krimiropa (API Part I, Vol- V, pg-15)	Antiviral, Anti-inflammatory, Anti diarrhoeal, Antioxidant, Hepatoprotective, Antimicrobial activities, Immunomodulatory (Reviews on Indian Medicinal Plants, Vol-5, ICMR)
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Fig. 1 CONSORT Flow Diagram

Table 2: Baseline Characteristics:

Characteristics	
Age: Mean (SD)	28.80 (8.94)
Gender	
Male	28 (78.4%)
Female	08 (21.6%)
Marital Status	
Married	14 (40.5%)
Unmarried	22 (59.5%)
Educational status	
Illiterate	06 (16.7%)
Upto 10th	11 (30.6%)
Upto 12th	06 (16.7%)
Graduate	12 (33.3%)
Post graduate	01 (2.8%)
Occupation	
Desk work	1 (5.4%)
Field work with physical labour	9 (24.3%)
Field work	16 (43.2%)
House wife	2 (5.4%)
Student	8 (21.6%)
Habitat	
Urban	22 (62.2%)
Semi-urban	03 (8.1%)
Rural	11 (29.7%)
Economic status	
Above poverty line	20 (56.8%)
Below poverty line	16 (43.2%)
Co-morbidities	
COPD	0
Chronic Renal Disease	0
Bronchitis	0
Diabetes	0
Heart Disease	0
Hypertension	2(5.55%)
Asthma	0
Risk Factor	
Travel / residence in COVID hotspots/ endemic areas	13 (36.1%)
Workplace exposure to COVID 19 cases	18 (50.0%)
Direct/indirect Contact with COVID 19 Cases (Except workplace exposure)	16 (44.5%)
Values have been represented as n (%)	

Table 3: Observations for AYUSH 64 on clinical Symptoms and Signs (Present) at Baseline, 7th and 14th day

Clinical Sign & Symptoms present	Subgroup I (n=20)		Subgroup II (n=8)		
	Baseline	7 th day	Baseline	7 th day	14 th day
Fever at evaluation	5 (25.0%)	0	1 (12.5%)	0	0
Cough	13 (65.0%)	7 (35.0%)	4 (50.0%)	1 (12.5%)	1 (12.5%)
Breathlessness	8 (40.0%)	0	0	1 (12.5%)	0
Sore Throat	9 (45.0%)	3 (15.0%)	3 (37.5%)	3 (37.5%)	2 (25.0%)
Sputum	2 (10.0%)	0			
Nausea	1(5.0%)	0	3 (37.5%)	1 (12.5%)	0
Body ache	4 (20.0%)	2 (10.0%)	3 (37.5%)	1 (12.5%)	0
Abdominal Pain	2 (10.0%)	0	1 (12.5%)	0	0
Headache	5 (25.0%)	4 (20.0%)	3 (37.5%)	1 (12.5%)	1 (12.5%)
Nasal discharge	5 (25.0%)	2 (10.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
Chest pain	4 (20.0%)	0	2 (25.0%)	0	0
Anorexia	2 (10.0%)	1 (5.0%)	0	1 (12.5%)	0
Vomiting	1 (5.0%)	1 (5.0%)	1 (12.5%)	1 (12.5%)	0
Values have been represented as n (%) Subgroup I - Participants who completed the trial on 8th Day Subgroup II - Participants who completed the trial on 15th Day					

Table:4Ayurvedic Parameters of Jwara

Ayurvedic Parameters of Jwara	Subgroup I n=25		Subgroup II n=11		
	Baseline	7 th day	Baseline	7 th day	14 th day
Laziness	11 (44.0%)	3 (12.0%)	3 (27.3%)	4 (36.4%)	3 (27.3%)
Watering of eyes	4 (16.0%)	0	1 (9.1%)	0	0
Burning sensation in eyes	1 (4.0%)	0	1 (9.1%)	0	0
Excessive yawning	3 (12.0%)	2 (8.0%)	1 (9.1%)	1 (9.1%)	1 (9.1%)
Heaviness in body	4 (16.0%)	3 (12.0%)	2 (18.2%)	1 (9.1%)	1 (9.1%)
Exhaustion without exertion	7 (28.0%)	0	3 (27.3%)	1 (9.1%)	1 (9.1%)
Exhaustion with minimal exertion	6 (24.0%)	2(8.0%)	2 (18.2%)	0	1 (9.1%)
Fatigue	11 (44.0%)	8 (32.0%)	6 (54.5%)	7 (63.6%)	1 (9.1%)
Frequently changing affection and aversions for sound, heat, sunlight, wind, water etc	3 (12.0%)	1(4.0%)	0	0	0
No desire for food	3 (12.0%)	1 (4.0%)	2 (18.2%)	3 (27.3%)	1 (9.1%)
Indigestion	1 (4.0%)	0	3 (27.3%)	3 (27.3%)	1 (9.1%)
Tastelessness	9 (36.0%)	1(4.0%)	2 (18.2%)	3(27.3%)	1 (9.1%)
Depletion in strength	6 (24.0%)	0	1 (9.1%)	0	0
Feeling fatigued	6 (24.0%)	1(4.0%)	2 (18.2%)	0	0
Depletion of skin luster	2 (8.0%)	0	0	1(9.1%)	0
Slight change in behavior	3 (12.0%)	0	1(9.1%)	0	0
Agitated eyes	2 (8.0%)	0	1(9.1%)	0	0
Excessive sleep	4 (16.0%)	0	1 (9.1%)	1 (9.1%)	2 (18.2%)
Restlessness	5 (20.0%)	(4.0%)	3 (27.3%)	0	0
Bending of body/feeling as if muscles and body are contracting	1 (4.0%)	0	0	0	0
Giddiness/ vertigo	2 (8.0%)	1 (4.0%)	0	0	0
Insomnia	3 (12.0%)	1 (4.0%)	1 (9.1%)	0	1 (9.1%)
Weakness	13 (52.0%)	4 (16.0%)	6 (54.5%)	7(63.6%)	1 (9.1%)
Generalized body ache	8 (32.0%)	4 (16.0%)	6 (54.5%)	5 (45.5%)	1 (9.1%)
Slowness in activities], taking comparatively longer duration for a routine work	1 (4.0%)	0	0	0	0
Inability to do regular functions	1(4.0%)	0	1(9.1%)	0	0
Difficulty in deglutition/ingestion of food	1(4.0%)	0	0	0	0
Aversion for sweets	1(4.0%)	0	0	0	0
Sudden affection for sour, salty and pungent tastes	4(16.0%)	0	0	0	0
Values have been represented as Count(percentage) Subgroup I- Participants who completed the trial on 8th Day Subgroup II- Participants who completed the trial on 15th Day					

Table 5: Effect of AYUSH 64 on outcome measures

Primary outcome measures	Mean time (days) for clinical recovery as per clinical recovery		7.04 ± 2.88 days
	Number of patients showing ‘clinical recovery’ (n = 28)	7 th Day	11 (39.2%)
		14 th Day	15 (53.5%)
Secondary outcome measures	Percentage of patients with negative SARS-CoV-2 on nasal or throat swab in a 2 day continuous real time RT-PCR test	9 th Day	25 (69.44)
		16 th Day	11 (30.55)
	No of cases reporting any ADR/AE		0 (0%)
	Number of participants referred with onset of complications		2 (5%)
	Number of participants that required invasive or non-invasive oxygen therapy during the intervention.		0 (0%)
Values represented as n (%)			

Table 6: Effect of AYUSH 64 on Laboratory parameters in two Subgroups

	Subgroup I (n = 25)			Subgroup II (n = 11)			
Laboratory Parameters (Reference Range)	Baseline	8 th Day	p-value#	Baseline	8 th Day	15 th Day	p-value \$
Hemoglobin (g/dl)	13.80 (2.19)	13.90 (2.12)	0.449	14.32(1.87)	14.55(1.66)	14.73(1.54)	0.158
T.L.C(10 ³ /μL)	7.05(1.78)	7.25(1.82)	0.554	5.64(1.51)	6.61(1.67)	7.59(2.25)	0.001
N (%)	55.72(7.92)	55.88(9.85)	0.928	47.36(7.85)	48.55(6.27)	53.27(8.29)	0.071
E (%)	3.48(1.33)	3.32(1.60)	0.590	3.82(2.78)	4.91(3.36)	5.73(3.35)	0.153
B (%)	0.12(0.33)	0.16(0.37)	0.664	0.09(0.30)	0.36(0.50)	0.00(0.00)	0.067
L (%)	34.44(7.67)	34.36(7.98)	0.955	42.64(10.04)	39.91(6.55)	35.55(6.68)	0.064
M (%)	5.84(2.09)	6.28(2.91)	0.538	6.09(1.51)	6.27(2.05)	5.45(2.21)	0.475
Absolute lymphocyte (/cu.mm)Baseline	2360.96(592.51)	2405.24(658.67)	0.726	2381.73(788.22)	2605.36(616.67)	2553.82(533.83)	0.581
E.S.R. (mm/hour)	12 (8 – 28)	16 (8 - 22)	0.871	10 (5 – 12)	8 (6.5 – 8)	10 (10 -19.5)	0.378
Blood Sugar Fasting (mg/dL)	86.52(8.59)	91.04(14.58)	0.119	85.45(8.53)	82.18(5.29)	86.55(9.19)	0.256
HbA1c(%)	5.124(0.35)	5.208(0.47)	0.110	4.97(0.49)	5.06(0.64)	5.00(0.42)	0.726
Hs-CRP(mg/L)	4.68(9.77)	2.632(3.72)	0.348	2.25(3.95)	3.58(8.64)	1.03(1.52)	0.586
IL-6(pg/mL)	14.7 (4 – 111.3)	26.7 (12.8 – 120.75)	0.710	33.6 (11.15 – 151.47)	6.9 (0.8 – 229.5)	0.1 (0.06 – 26.82)	0.052
Ig E(IU/mL)	285 (51.8 -532.1)	332 (129 -1000)	0.158	392 (12.9 – 3000)	1392 (15.53 – 3000)	206.9 (4.8 - 3000)	0.347
Ig-G(mg/dL)	1494.62(319.16)	1447.99(335.97)	0.167	1615.04(338.76)	1631.09(502.75)	1635.73(386.50)	0.938
Ig-M(mg/dL)	126.128(55.59)	123.152(63.30)	0.717	99.715(58.97)	97.91(55.17)	98.11(56.99)	0.929

Sub group I: Participants who completed the study at 8th day
Sub group II: Participants who completed the study at 15th day
Values have been represented as Mean (SD) / Median (IQR)
#Compared using paired sample t – test / Wilcoxon sign rank test
\$Compared using Repeated Measure ANOVA / Friedman test
p-value of < 0.05 has been considered as significant

Table 7: Effect of AYUSH 64 on Safety Parameters Liver and Kidney Function in two subgroups

Safety Parameters (Reference Range)	Subgroup I (n = 25)			Subgroup II (n = 11)			
	Baseline	8 th Day	p-value#	Baseline	8 th Day	15 th Day	p-value \$
Serum Uric Acid (mg/dL)	5.01 (1.38)	5.18 (1.51)	0.582	5.15(1.38)	5.17 (0.96)	4.72 (0.92)	0.244
Serum Creatinine(mg/dL)	0.87 (0.158)	0.78 (0.207)	0.054	0.89(0.14)	0.88 (0.12)	0.78 (0.21)	0.261
S.G.O.T (A.S.T.)(U/L)	35.96 (12.52)	32.08 (15.85)	0.304	33.73(10.32)	49.82 (69.67)	28.00 (11.27)	0.359
S.G.P.T (A.L.T.)(U/L)	40.32 (19.31)	34.88 (17.61)	0.184	37.73(17.97)	75.64 (139.42)	43.36 (41.80)	0.393
Total protein(gm/dL)	7.95 (0.83)	7.37 (0.75)	0.015	7.67(0.64)	7.33 (0.43)	7.89(0.88)	0.197
S.Albumin(gm/dL)	4.53 (0.42)	4.46 (0.41)	0.460	4.35(0.36)	4.53 (0.14)	4.60(0.42)	0.174
S.Globulin(gm/dL)	3.42 (0.91)	2.91 (0.89)	0.043	3.32(0.79)	2.80 (0.46)	3.29(0.85)	0.146
Serum bilirubin total (mg/dL)	0.86 (0.55)	0.79 (0.41)	0.412	0.92(0.79)	0.77 (0.40)	0.84(0.49)	0.570
Conjugated bilirubin(mg/dL)	0.25 (0.16)	0.21(0.09)	0.059	0.26(0.15)	0.22 (0.09)	0.21(0.09)	0.307
Unconjugated bilirubin(mg/dL)	0.61 (0.40)	0.58(0.34)	0.668	0.66(0.65)	0.55 (0.33)	0.62(0.41)	0.632
Serum Alkaline Phosphatase(U/L)	127.24 (52.28)	111.72 (41.87)	0.128	112.0 (32.57)	107.09 (27.12)	120.45(38.18)	0.450

Sub group I: Participants who completed the study at 8th day
Sub group II: Participants who completed the study at 15th day
Values have been represented as Mean $\pm$ SD #Compared using paired sample t – test / Wilcoxon sign rank test
\$Compared using Repeated Measure ANOVA / Friedman test
p-value of < 0.05 has been considered as significant

Table 8: Details of Rescue Medicine

Assessment Visit	Total Participants	Participant Enrol No.	Rescue medicines	Dose	Duration of intake	Cause	Prescription/ Self Medication
7 th day	06	A 10	Diclofenac Rantac	75 mg 150 mg	1 Day	Headache	Prescription
		A 25	T.Azithromycin Syp. Diphenylamine	500 mg OD 1TSF BD	1 Day	Throat Pain Cough and Cold	Self medication from the medicine given to the participant by the referred center
		A 26	PCM Amlodipine Shitopladi Vasavleh	500mg g/2 gm 5 mg OD 1BD 1 TSF	3 days 1 day Continued 1 Day	Fever/ /Cough And Cold Hypertension	Prescription
		A28	Sitopaladi ch. Lavangadi vati	5 gm Tab 2BD	3 days 3days	Productive Cough & Cold , Sneezing	Prescription
		A30	PCM/ Shitopladi Ch.	500mg SOS 2 gm TDS	2 days 3 days	Headache & Feeling feverish Cold and Headache	Prescription
		A38	PCM + Rantac	500 mg 150 mg given Stat	1 Day (Once)	Fever, Body Pain	Prescription
14 th day	00	Nil					

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