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# Effect of an Ayurvedic Intervention (Ayush-64) as a Stand-Alone Treatment in Mild to Moderate COVID-19: An Exploratory Prospective Single-Arm Clinical Trial

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## Abstract

An Ayurvedic polyherbal formulation (Ayush-64) was repurposed for use in mild to moderate COVID-19 cases based on the supportive evidence obtained from a pilot study on its effect on Influenza like illness (ILI) and molecular docking study which revealed that several compounds isolated from Ayush-64 demonstrated antiviral activity. The study aims at evaluating the effect of an Ayurvedic intervention (Ayush-64) in mild to moderate COVID-19 patients. A prospective single arm, pilot study in mild to moderate COVID-19 patients. The study was conducted at Chaudhary Brahm Prakash Ayurved Charak Sansthan (CBPACS), New Delhi, India. A total of 37 COVID-19 participants confirmed through RT-PCR were included in the study. The proportion of participants with negative SARS-CoV-2 on nasal or throat swab in a 2-day consecutive real-time RT-PCR test was evaluated as the secondary outcome. In the study, 86.1% of participants demonstrated clinical recovery with 14 days of use of Ayush-64 as stand-alone treatment without any other conventional medicines, out of which 75% clinically recovered within 8 days. Further, 69.4% of participants turned negative by the $15^{th}$ day, out of which 50% became COVID-19 negative on the $8^{th}$ day. No AE/ ADR was observed during the study. Ayush-64 may significantly facilitate clinical improvement in terms of duration for clinical recovery and attaining negative conversion in mild to moderate COVID-19 cases.

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## INTRODUCTION

COVID-19 disease is an influenza like illness caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2) that was declared as Public Health Emergency of International concern on $30^{th}$ January and a pandemic on $11^{th}$ March 2020 by the World Health Organization. The search for effective therapeutic agents to tackle it has led to probing the existing drugs with antiviral potential and repurposing them. Available drugs repurposing for the management of several disease conditions is increasingly becoming a popular strategy as it uses

de-risked compounds with known preclinical, pharmacokinetic, Pharmaco-dynamic profiles which can directly enter phase III or IV clinical trial making the drug development process relatively rapid [1].

Ayurveda and other traditional systems of Medicine in India have been treating diseases of infectious and non-infectious origin equally with expansive success rates. Central Council for Research in Ayurvedic Sciences, under Ministry of AYUSH, Government of India has developed a poly-herbal drug 'Ayush-64' through pharmacological, toxicological, and clinical studies. The Ayush-64 tablet is prepared from a combination of four Ayurvedic herbal drugs, *Alstonia scholaris (*L.*)* R.Br. [2, 3], *Swertia chirayita* (Roxb. ex Flem.) Karst [4], *Picrorhizakurroa* Royle ex Benth [5] and *Caesalpinia crista* L [6].

Considering the positive response of Ayush-64 against Influenza like Illness (ILI) [7], the same was repurposed for use in COVID-19. The ingredients of this drug have been reported to have several pharmacological activities including anti-malarial, anti-viral, anti-inflammatory, and immunomodulatory activity. Currently, there are no standard treatments available against the disease so drug repurposing may be considered an effective strategy.

The study aims to evaluate the effect of Ayush-64 as a stand-alone therapy in mild to moderate COVID-19 patients.

## METHODS

### Study Design, Participants and Screening

This is a single arm, single centre, prospective, interventional pilot study executed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization – Good Clinical Practice guidelines. The study was done at Chaudhary Brahm Prakash Ayurveda Charak Sansthan (CBPACS), New Delhi, India which was designated as a COVID care centre by the Government. A total of 37 COVID-19 patients, confirmed through RT-PCR testing, fulfilling the selection criteria were enrolled in the study between $20^{th}$ June 2020 to $11^{th}$ August 2020. The study was approved by the Institutional Ethics Committee (IEC) of CBPACS (F1(553)/13/CBPACS /Adm/IECII/ 1068) and was registered prospectively in the Clinical Trials Registry of India (CTRI/2020/05/025335). Informed consent was obtained from all the participants who fulfilled the selection criteria.

The inclusion criteria were: COVID-19 positive participants diagnosed by RT-PCR test for SARS COV-2 of either sex aged between 18-65 years. The patients who fulfilled the criteria, were distributed patient information sheet and who expressed their willingness to participate in the study were recruited in the study.

Participants were excluded if they were in a critical condition due to COVID-19 in critical condition or Acute Respiratory Distress Syndrome (ARDS) or NIAID 8-point ordinal score 2, hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation, with severe vomiting which would make oral administration of medicine difficult, with alanine transaminase (ALT) or aspartate transaminase (AST) > 2 times the upper normal limit, were pregnant or lactating women.

### Study Intervention

The study drug Ayush-64 was given to participants in a dose of 2 tablets (500 mg each) thrice daily, after food with warm water for a minimum of 8 days and a maximum of 14 days (depending on whether the participant turned RT-PCR negative on 8th or 15th day).

The study drug (batch number 19-APM-LDA-187, manufacturing date- 05/2020) was procured from a GMP-certified manufacturer; Indian Medicines Pharmaceutical Corporation Limited (IMPCL), India. The individual drugs were extracted in an aqueous medium and were thoroughly mixed to obtain a homogenous blend and the drug was passed through a granulator to obtain granules and excipients were added as per requirements. The granules were subjected to compressing in a tablet punching machine.

All the individual herbs, their extracts, and the finished product were subjected to preliminary pharmacognostic, phytochemical screening, and HPTLC profiling to match the requirements of the Ayurvedic Pharmacopoeia of India (API). API is a regulatory document issued by the Government of India that defines the standards and narrates the quality of traditional drugs, that are manufactured, distributed, and sold in India. Particularly, the mechanism of action of medicinal formulations described in Traditional systems such as Ayurveda is often not amenable to the contemporary pharmacodynamic, pharmacokinetic and molecular profiling of herbal products and owing to which the trial drug was prepared as per the standards and quality requirements of in-house parameters.

### Outcomes

The primary outcome measure was the proportion of participants showing 'clinical recovery' which was defined as normal body temperature (using a thermal scanner) ($\leq$35.6°C), absence of cough, breathlessness on routine daily self-care, respira-

tory rate < 30 breaths per minute without supplemental oxygen, any other symptoms attributed to COVID-19 illness and normalization of SpO2 by standard peripheral oximetry device (above 95%).

The secondary outcome measures were the proportion of participants with negative SARS-CoV-2 on nasal or throat swab in a 2-day continuous real-time RT-PCR test. Improvement in differential and total leukocyte counts, hs-CRP, ESR, IgM and IgG, changes in liver enzyme and renal function, number of cases reporting any AE/ADR, participants referred with the onset of complications, and those who required invasive or non-invasive oxygen therapy were also evaluated as secondary outcomes.

RT-PCR test, clinical symptoms present, haematological and other relevant bio-chemical assessments were done on the $8^{th}$ day. Participants who turned COVID negative (after two consecutive negative RT-PCR tests done on the $8^{th}$ and $9^{th}$ day) were discharged and the treatment was discontinued. Participants who were COVID-19 positive continued in the trial as per the protocol and were again assessed on the $15^{th}$ day. The participants who turned negative after two consecutive negative RT-PCR reports on the $15^{th}$ and $16^{th}$ days were then discharged.

**Sample Size**

The study was taken up as a pilot study therefore sample size was set as 30 participants, assuming an attrition rate of 25%, the final sample size was set as 40 patients [8]. However, within the time frame of the study, we were able to recruit only 37 participants.

**Statistical Analysis**

Demographic profile and clinical characteristics evaluated as continuous variables have been shown as mean $\pm$ standard deviation (SD) if the data followed normal distribution and median (Q1, Q3) if it was non-normal. Nominal data has been expressed as number (%). Data on hematological and biochemical parameters were compared at the end of treatment to baseline by using paired sample t-test if the data followed a normal distribution, while Wilcoxon signed-rank test was used if the data was not normal. A *p-value* of <0.05 has been considered significant. The analysis was done using Statistical Package for Social Sciences (SPSS) 15.0.

## RESULTS

A total of 64 participants who were referred to CBPACS by the government of Delhi, India were screened for eligibility as per the selection criteria. Out of which, 37 participants fulfilling the eligibility criteria were enrolled in the study. However, the data of only 36 participants have been utilized for analysis as 01 participant was withdrawn from the study and referred to a higher centre, due to the onset of some symptoms unrelated to the study drug.

The baseline demographic characteristics of the participants revealed that the median age of participants was 43 years ranging from 20 to 65 years. Out of a total of 36 participants, the majority (52.8%) were male. Diabetes as co-morbidity was present in 8.3% of participants, while 16.7% were found to be hypertensive.

Out of a total of 36 participants who were considered for analysis, participants who showed clinical recovery on the $8^{th}$ day were 27 (75.0%), while 31 (86.1%) recovered by $15^{th}$ day. Participants who became RT-PCR negative on $8^{th}$ day were 18 (50.0%), while a total of 25 (69.4%) participants turned negative on $15^{th}$ day.

Median ESR levels reduced from 20.0 (10.5, 35.5) to 17.0 (10.0, 31.5). however the reduction was not statistically significant (*p-value* = 0.617). Reduction in median IL-6 levels was also observed, which reduced from 52.5 (13.0, 245.0) at baseline to 39.0 (7.25, 249.75) at the end of the treatment (*p-value* = 0.072). Median Ig-E levels although reduced significantly from 154.50 (35.25, 479.50) at baseline to 122.0 (33.0, 416.0) at the end of the treatment (*p-value* = 0.047) (Table 1).

The liver and kidney function tests were found to be within the normal limits throughout the intervention period. No abnormalities in vital signs such as blood pressure, heart rate or respiratory rate were recorded during the intervention period in any of the participants. Adverse event (AE) was not reported by any of the participants. None of the participants required invasive or non-invasive oxygen therapy. Only one (01) participant was referred to a higher center within 24 hrs of enrollment in the study due to the onset of some other symptoms unrelated to trial intervention and hence was excluded from the analysis.

## DISCUSSION

This study was carried out to evaluate the effect of Ayush-64 and its safety in mild to moderate COVID-19 cases. It was observed that Ayush-64 as a stand-alone therapy was effective in attaining clinical recovery and turning RT-PCR negative.

Results from a retrospective cohort study of COVID-19 patients in Qingdao, China demonstrate that the rate of RNA negative conversion within 7 days, 14 days, and 21 days among all patients were 10.2%

**Table 1: Effect of the Intervention on Bio-Chemical and Inflammatory Markers**

| Parameters | Baseline | After Treatment | p-value |
|---|---|---|---|
| Total Leukocyte Count (per) | $6.61 \pm 2.088$ | $7.69 \pm 1.704$ | $0.001(*)^a$ |
| Neutrophil (%) | $52.47 \pm 7.121$ | $54.50 \pm 6.814$ | $0.054^a$ |
| Lymphocyte (%) | $37.78 \pm 8.909$ | $35.53 \pm 6.734$ | $0.104^a$ |
| Absolute Lymphocyte Count | $2360.72 \pm 648.969$ | $2685.22 \pm 697.755$ | $0.003(*)^a$ |
| ESR (mm at the end of $1^{st}$hr) | 20.0 (10.5, 35.5) | 17.0 (10.0, 31.5) | $0.617^b$ |
| Hs-CRP | 2.0 (1.0, 6.0) | 1.5 (1.0, 4.0) | $0.405^b$ |
| IL-6 | 52.5 (13.0, 245.0) | 39.0 (7.25, 249.75) | $0.072^b$ |
| Ig-E | 154.50 (35.25, 479.50) | 122.0 (33.0, 416.0) | $0.047(*)^b$ |
| Ig-G | $1413.72 \pm 315.658$ | $1396.92 \pm 344.433$ | $0.719^a$ |
| Ig-M | $132.72 \pm 94.462$ | $131.64 \pm 69.460$ | $0.940^a$ |

$^a$Compared using paired sample t-test. Values are given as Mean $\pm$ SD; $^b$Compared using Wilcoxon Sign Rank test. Values are given as Median (Q1, Q3); (*) A p-value of <0.05 is considered as significant; Reference Range

(95% CI: 2.1%–17.5%), 62.7% (48.1%–73.2%), and 91.2% (80.4%–96.4%), respectively [9]. This would substantiate that the duration of negative conversion can range anywhere between 7 to 21 days or more Incidences of patients remaining RT-PCR positive for SARS-CoV-2 even 5-13 days after meeting the clinical cure and discharge criteria following treatment have been reported which would affirm that at least a proportion of recovered patients will remain positive even after they are clinically cured [10]. Therefore, obtaining a 50% negative conversion on day 7 and 69.4% in 14 days in this study is a comparably good response in COVID-19 positive cases.

None of the participants required invasive or non-invasive oxygen therapy which deems the intervention to be an effective choice in the management of mild to moderate COVID-19.

It has also been observed that inflammatory markers also decreased at the end of the treatment period. Therefore, it is evident from the trial that Ayush-64 has the potential for lowering acute phase reactants such as hs-CRP, ESR, IL-6, and Ig-E which is an indicator of reduced inflammation or decreased disease severity. Ayush-64 may be used as a safe treatment option in mild to moderate COVID-19 and is likely to significantly facilitate clinical improvement.

Single-arm pilot study without any control arm, small sample size, only mild to moderate COVID-19 cases are some of the limitations of this study. Being a pilot study without a comparative arm, the data generated may not be sufficient to generate a generalizable efficacy statement. Therefore, for conclusive efficacy and safety evidence, larger multicentre randomized control trials with a robust design could be explored.

## CONCLUSION

Currently, there is no specific effective antiviral treatment for COVID-19 and a vast majority of drugs are being used all over the world based on either in-vitro or extrapolated evidence or observational studies, which does not give priority to safety or risk-benefit assessment before being utilized for treatment or research. Likewise, often multiple drugs or cocktail of different drugs with different pharmacokinetics are being utilized to manage the situation. The observations from this pilot study demonstrate that Ayush-64 is a safe treatment option in mild to moderate COVID-19 and is likely to significantly facilitate clinical improvement in terms of duration for clinical recovery and attaining negative conversion, without any AE/ADR. Ayush-64 may be used as a single stand-alone drug for mild to moderate cases of COVID-19 and the supportive evidence for efficacy may be garnered through robust RCTs. However, future study designs may incorporate a flexible intervention duration depending upon the time taken for negative conversion and complete clinical remission on an individual basis.

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### Author Contributions

Study Conceptualization and Methodology: BY, AG, NRS. Data collection: AM. AG, VRW, Data analysis: RR, RS. Writing original draft: ND, SJ, RS. Review and

editing: SK, BS, BCSR. Supervision: BG, NS, KSD.

**Conflicts of Interest**

The authors declare no conflict of interest.

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**Ethical Statement**

The study was approved by the Institutional Ethics Committee (IEC) of CBPACS (F1(553)/13/CBPACS /Adm/IECII/ 1068) and was registered prospectively in the Clinical Trials Registry of India (CTRI/2020/05/025335).

**Trial Registry**

Study was registered prospectively in the Clinical Trials Registry of India (CTRI/2020/05/025335).

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