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Short Communication

# Efficacy of Madhav Rasayan Plus as adjuvant in moderate COVID-19 patients: Preliminary outcomes of randomized controlled trial

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ABSTRACT

Apart from all the gloominess, the COVID-19 Pandemic has a silver lining of bringing a renaissance as Ayurveda and integrated medicine are becoming a choice for acute as well as infective diseases. Here we report outcomes of a preliminary work, the randomized controlled trial (CTRI/2021/02/031256) of Madhav Rasayan Plus, an Ayurveda formulation as adjuvant in moderate COVID-19 patients. Madhav Rasayan Plus is a herbomineral formulation beneficial for respiratory, coagulative and other systemic complements of COVID-19. Forty patients with moderate COVID-19 disease were included in two parallel groups (n = 20/group). The Intervention group (Treatment) received Madhav Rasayan Plus tablets (250 mg) twice a day for 15 days, along with standard care (SOC), while the control group received SOC alone. The intervention group significantly improved symptoms of COVID-19 like cough, breathlessness, fatigue and gastric disturbances. There was also statistically significant reduction in inflammatory markers like CRP and Ferritin. Tissue level markers like creatinine phosphokinase and NT- Pro BNP were found restored after treatment. The requirement of supplemental oxygen in the control group (6 days) was reduced by 2.5 times compared to the intervention group (2.4 days). There was also reduced hospital stay and reduced requirement of ICU in comparison with the control group. Also, the indices of fatigue severity score, disturbed sleep cycle score and quality of life revealed better and holistic recovery in the intervention group. This study reveals that COVID-19 and such infective diseases with vital complications can be better dealt with integrated management as immunomodulation and protection of tissues and vital organs are strengths of Ayurveda.


## 1. Introduction

The world is experiencing a health emergency during this pandemic of COVID-19. SARC-CoV-2 is the third coronavirus in the family which has caused severe disease in humans in the past 2 decades. The first two corona epidemics were severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2002–2003 and 2012 respectively [1]. Patients with comorbidities are at high risk of infection with SARS-CoV-2. It is demonstrated by several studies that elevated levels of cardiac troponin and brain natriuretic peptide (BNP) are found in patients with greater disease severity. Increased cardiac troponin levels can be correlated to other inflammatory markers like CRP, ferritin and IL-6. This leads to primary myocardial injury. The cytokine release directly affects the cardiomyocytes as well as leads to endothelial cell reprogramming and dysfunction, causing a role in COVID-19 cardiovascular manifestations [2]. In addition to cardiovascular damage, renal involvement is frequently observed in COVID-19, varying from mild proteinuria and minor serum creatinine elevations to acute kidney injury (AKI) and renal failure [3]. This underlines the importance of host response modification and protection of vitals as a management principle in COVID-19. A combination of antiviral, antimalarial, and antibiotic medicines is now being utilized to treat COVID-19 with focus on lowering the

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cytokine storm and increasing the benefits of COVID-19 treatment in terms of immune building.

By modifying host response and lowering complications and prognosis of disease into less severe phases, the integrated Ayurvedic method can provide a twofold benefit of developing immunity to combat the infection phase. Amidst the COVID-19 pandemic, there is a need for hours to find a potential treatment which can improve the clinical recovery and protect vital organ damage. Ayurvedic medicines have been used for the prevention and treatment of viral infections for years with favorable efficacy and insignificant toxicity. The Ministry of AYUSH, Government of India, and fraternity of Ayurveda has responded constructively to the health emergency of COVID-19 [4].

Many of the Ayurveda-based medications can prove effective as protease inhibitors, immunomodulators, and can alter host dynamics toward spike proteins, among other therapeutic targets investigated from SARS and MERS. Well before the first wave of COVID-19, prominent interdisciplinary scientists proposed use of Ayurvedic immunomodulator (Rasayana) medicines for COVID-19 [5]. Ayurveda scholars also interpreted COVID-19 pathophysiology and disease understanding in Ayurvedic terms [6,7]. In Ayurvedic perspective, immune mechanism is not sovereign entity but a resultant of multiple phenomenona including Endocrino-Metabolic factors. Agni (metabolic fire) remains pivotal in ayurvedic contemplation as weakened Agni is reported to be associated with decreased immune surveillance [8,9]. Psychiatry experts also endorsed use of Ayurveda for COVID-19 as Ayurveda herbs and formulations work on 'psychoneuroimmune' mechanism as a whole and thus not only modulate immune response but are beneficial for psychological quality of life and cognitive components [10].

### 1.1. Rationale of the study

The aim of the present preliminary research was to evaluate the safety and efficacy of the add-on Ayurveda intervention- Madhav Rasayan Plus tablets on patients of COVID-19.

### 1.2. Objectives of the study

The primary objectives of this preliminary study were to evaluate changes in clinical symptoms, inflammatory markers such as CRP, LDH and Ferritin, tissue level markers like Creatinine Phosphokinase and NT-Pro BNP. The secondary objectives of the study were to assess requirements of supplemental oxygen, admission to intensive care unit progression, duration of hospitalization, changes in sino-nasal complaints evaluated by modified SNOT questionnaire, improvement in sleep by disturbed sleep Questionnaire score, assessment of cognition and fatigue and quality of life by questionnaires. The safety assessment was done by evaluating changes in hematological and biochemical parameters along with the adverse event profile.

### 1.3. Trial design

This preliminary Trial was randomized and controlled trial with forty patients of moderate COVID-19 included in two parallel groups (n = 20/group). It was registered on CTRI (CTRI/2021/02/031256).

### 1.4. Inclusion criteria

Patients admitted to the research site aged between 18 and 60 years (both sexes) with positive RT-PCR confirmed COVID 19 were included in the study. The symptomatic patients with moderate to severe COVID-19 having no signs of ARDS (NEWS score <8) were included. Those patients willing to provide consent and follow up for study duration were considered for the study.

### 1.5. Exclusion criteria

Patients with autoimmune diseases or self-reports of HIV or syphilis infection were excluded from the study. The patients proving to be unfit for the study as per the investigator's discretion were not considered for the study. Patients requiring ICU admission, with comorbidity at critical stage at screening along with pregnant or lactating women were not considered in the study.

## 2. Methodology

This preliminary study was conducted at Lokmanya Hospital Chinchwad, Pune, after protocol approval from Institutional Ethics Committee, Lokmanya Medical Research Centre and after registration on Clinical Trial Registry of India i.e. CTRI (CTRI/2021/02/031256). The study was conducted prospectively after registering on the CTRI. The informed consent from every patient participating in the study was obtained before screening. In the current randomized controlled trial, 40 patients with moderate COVID-19 patients were included in two parallel groups (n = 20/group). The Intervention group (Treatment) received 250 mg tablets twice a day for 15 days along with standard of care (SOC) as per guidelines of ICMR (Indian Council of medical Research), while the control group received SOC alone. The outcome measures such as changes in inflammatory markers, tissue level markers and biochemical parameters were assessed on baseline and day 10 of treatment. All other outcomes including symptoms, questionnaire-based assessment and quality of life score were assessed on baseline, day 7 and day 15 [11–15].

### 2.1. Intervention details

Madhav Rasayan Plus tablet is a herbo-mineral composition depicted in Table 1. The dosage was 250 mg tablets twice a day with lukewarm water for 15 days. We asked study group patients not to consume bakery products, fermented food etc. as a part of dietary modification.

### 2.2. Randomization and allocation

We screened 45 participants based on the inclusion-exclusion criteria, of which 40 participants were found suitable and were

**Table 1**
Composition of madhav rasayan plus.

| SN | Name of ingredient | Botanical Name | Qty. |
|---|---|---|---|
| 1 | Tulasi (Leaf) | *Ocimum sanctum* | 30 mg |
| 2 | Vasa (Leaf) | *Adhathoda Vasica* | 30 mg |
| 3 | Yashtimadhu (Rhizome) | *Glycyrrhiza Glabra* | 30 mg |
| 4 | Manjishtha (Stem) | *Rubia Cordifolia* | 20 mg |
| 5 | Jatamansi Rhizome | *Nardostachys jatamansi* | 10 mg |
| 6 | Amruta (Stem) | *Tinospora cordifolia* | 30 mg |
| 7 | Erandmul (Root) | *Ricinus Communis* | 20 mg |
| 8 | Ashwagandha (Root) | *Withania somnifera* | 30 mg |
| 9 | Shatavari (Root) | *Asparagus recemosus* | 20 mg |
| 10 | Sunth (Rhizome) | *Zingibe Rofficinale* | 10 mg |
| 11 | Abhrak Bhasma Churna | Generic Medicine | 5 mg |
| 12 | Loha Bhasma Churna | Generic Medicine | 10 mg |
| 13 | Mouktik Bhasma Churna | Generic Medicine | 5 mg |
| 14 | Durva (Stem and leaves) | *Cynodon dactylon* | Q.S. (Quantum satis) |
| 15 | Dalchini (Bark) | *Cinnamomum zeylanicum* | Q.S. (Quantum satis) |
| 16 | Nagveli Patra (Leaf) | *Piper betele* | Q.S. (Quantum satis) |

**Table 2**
Demographic details of the subjects.

| Parameters | Madhav Rasayan Plus | Control |
|---|---|---|
| @ Age (Years) | | |
| Male | 42.87 (10.4) | 42.79 (9.145) |
| Female | 42.08 (14.66) | 42.55 (9.992) |
| # Gender (%) | | |
| Male | 14 (66.7%) | 12 (70%) |
| Female | 7 (33.3%) | 8 (30%) |
| Comorbidity % | 19% | 25% |

@ Analyzed by student t test and # analyzed by chi square test, non-significant $p > 0.05$.

randomized using a computer-generated randomization sheet to receive either the standard treatment (Control Group), or Madhav Rasayan Plus tablets along with SOC (Treatment Group). All the patients were provided with conventional care advocated by the Indian Council of Medical Research (ICMR), the Ministry of Health and Family Welfare, the Government of India. Fig. 1 presents the flow of events for the trial. The mechanism used to implement the random allocation sequence was sequentially numbered containers. As the trial is open label there is no blinding. We received a randomization schedule from a qualified statistician and the investigator enrolled the participants into respective study groups.

### 2.3. Sample size

The present study was the first attempt of the study team to conduct a preliminary clinical trial in COVID 19. Also, being a preliminary study, the sample size was decided to be forty. We intended to enroll 40 patients in two groups (1:1).

### 2.4. Statistical analysis

The efficacy analysis was performed on the per-protocol (PP) population. In this study, the percentage and population of patients relieved of symptoms were analyzed using the Chi square Test. Variables like inflammatory, organ level markers and safety parameters were evaluated by student's t test. Quality of life and other questionnaire scores were analyzed by the ANOVA test.

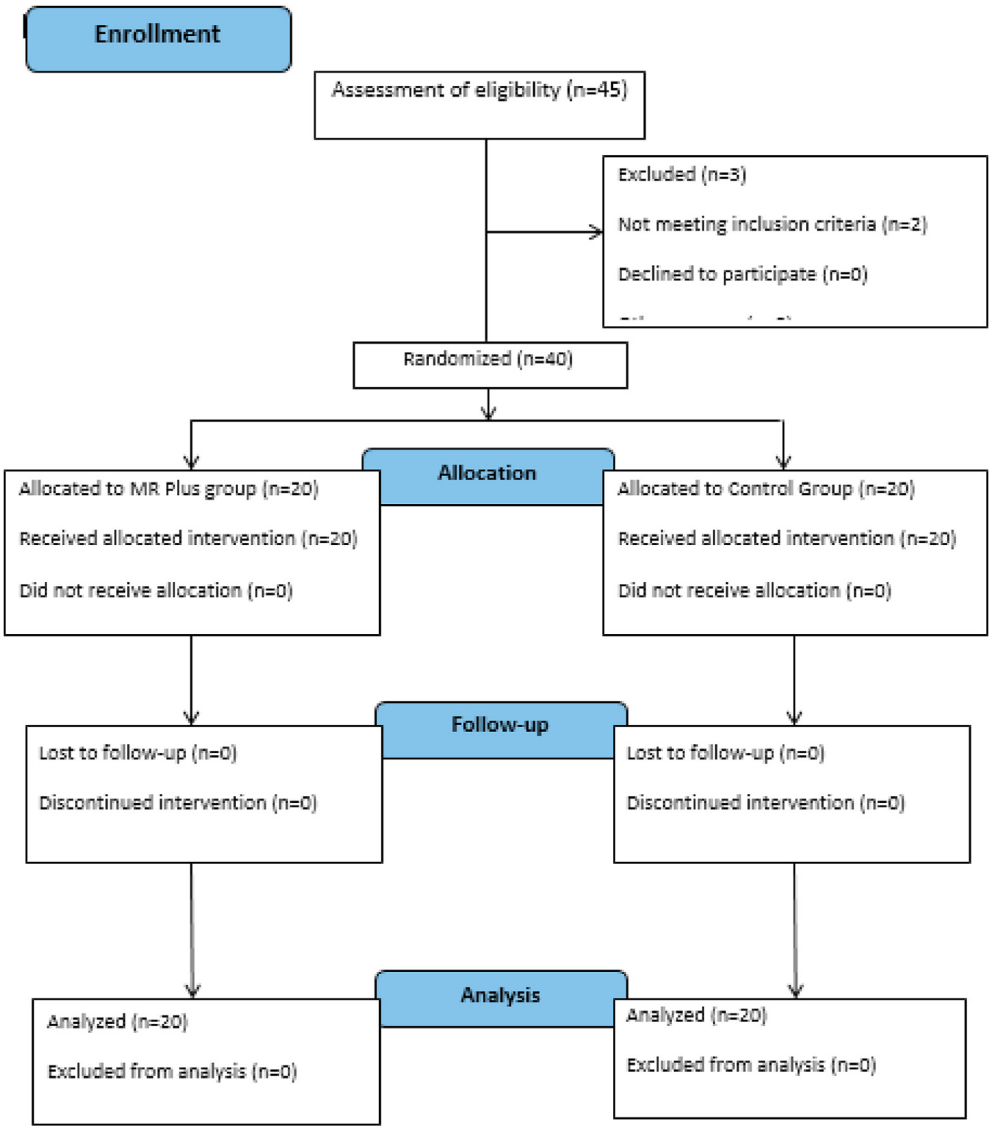


**Fig. 1.** CONSORT flow chart.

## 3. Results

All the primary outcome variables are mentioned below and in Table 3a–c. The secondary outcome variables are mentioned below and in Table 4a–c.

### 3.1. Demographic characteristics

In the present study, the mean age of male and female patients in the test and control group were comparable and the groups are described in Table 2.

### 3.2. Changes in symptoms of COVID 19

It was evident that there was faster relief of symptoms in the add-on MR Plus treatment group compared to control. There were more patients getting relieved of cough, breathlessness, fatigue and gastric disturbances on day 5, day 10 and day 15. The comparison was statistically significant. The data of patients getting relieved of symptoms is depicted in Table 3a.

### 3.3. Changes in modified fatigue severity score

Moderate to severe fatigue was a common complaint in patients of both groups on baseline. There was a 90.65% reduction in fatigue severity score in the add-on MR Plus group compared to 45.63% in the control group. The add-on MR Plus group significantly ($p < 0.05$) reduced fatigue (Table 3a).

### 3.4. Changes in inflammatory markers

All of the inflammatory markers were elevated in both groups. There was a 73.25 and 56.05% decrease in serum CRP levels in the intervention and the control group respectively. Add-on MR Plus treatment led to a significant decrease in CRP level ($p = 0.04$). Also treatment with add-on MR Plus led to a 48.12% reduction in serum ferritin, which was statistically significant ($p = 0.04$). On the contrary, there was an 11.24% increase in serum levels of ferritin in the control group. Results are displayed in Table 3b.

### 3.5. Changes in tissue level markers

The tissue level markers like creatinine phosphokinase and NT-Pro BNP were raised in patients on screening day. As expressed in Table 4a–d, there was a 42.94 and 42.46% decrease in creatinine phosphokinase and NT- Pro BNP respectively GFR was within the normal range for patients on screening as well as on day 10 (Table 3c).

### 3.6. Changes in sino-nasal complaints evaluated by modified SNOT (sino nasal outcome test) questionnaire

There was a 67.22% decrease in SNOT questionnaire score in the add-on MR Plus group vs 57.75% decrease in the control group at the end of the study. The difference was statistically significant on day 7 as well as day 15. Refer to Table 4d.

### 3.7. Changes in disturbed sleep cycle score

There was reduced disturbed sleep cycle score (Table 4d) in both treatment groups but the add-on MR Plus group demonstrated an around 80.55% decrease and the control group with 34.56% respectively. The between group analysis revealed the treatment group significantly ($p < 0.05$) reduced the disturbed sleep cycle score.

### 3.8. Changes in cognition score

There were cognition related symptoms portrayed by patients on screening day in both groups. The symptoms are eventually

**Table 3a**
Changes in subjects getting relieved of the symptoms from baseline to day 15 between groups.

| Groups | Baseline | Day 5 | Day 10 | Day 15 |
|---|---|---|---|---|
| Subjects relieved of cough | | | | |
| Test | 1 | 10 | 15 | 20 |
| Control | 2 | 2 | 7 | 10 |
| Subjects relieved of breathlessness | | | | |
| Test | 1 | 10 | 17 | 18 |
| Control | 2 | 5 | 8 | 10 |
| Subjects relieved of gastric disturbance | | | | |
| Test | 2 | 12 | 18 | 19 |
| Control | 4 | 8 | 12 | 13 |
| Subjects relieved of fatigue | | | | |
| Test | 1 | 8 | 18 | 20 |
| Control | 2 | 5 | 10 | 12 |

**Table 3b**
Changes in mean of inflammatory markers.

| Groups | Mean SD (Standard Deviation) | | | |
|---|---|---|---|---|
| | Madhav Rasayan Plus | | Control | |
| | Screening day | Day 10 | Screening day | Day 10 |
| CRP (mg/L) | 13.42 (16.28) | 3.59* (4.53) | 20.09 (21.36) | 8.83 (13.49) |
| LDH (U/L) | 384 (140.31) | 398.57 (119.52) | 443.64 (163.67) | 479.38 (156.98) |
| Ferritin (ng/ml) | 246.41 (300.43) | 127.84* (99.91) | 115.71 (143.93) | 128.72 (155.76) |

Analysis by student t-test Significant at * $P \leq 0.05$.

**Table 3c**
Changes in mean of Tissue markers in treatment group.

| Parameter | Madhav Rasayan Treatment Group | | | |
|---|---|---|---|---|
| | Screening day | Day 10 | % Reduction | P value |
| Creatinine Phosphokinase (U/L) | 126.35 (125.74) | 72.10 (41.48) | 42.94 | 0.004 |
| NT-Pro BNP (pg/mL) | 107.05 (48.25) | 61.60 (42.62) | 42.46 | 0.05 |
| GFR (mL/min) | 107.24 (21.45) | 112.80 (22.56) | −5.18 | 0.1433 |

Within group analysis by paired t-test, Significant at $P \leq 0.05$.

**Table 4a**
Changes in number of days of supplemental oxygen between groups.

| Groups | Average requirement of supplemental oxygen (in days) |
|---|---|
| Madhav Rasayan Plus | 2.4 |
| Control | 6 |

**Table 4b**
Requirement of ICU admission.

| Groups | Requirement of ICU Admission |
|---|---|
| Madhav Rasayan Plus | 0 (0% patients) |
| Control | 3 (15% patients) |

**Table 4c**
Changes in number of days of hospitalization.

| Days of Hospitalization | No. of subjects | |
|---|---|---|
| | Madhav Rasayan Plus | Control |
| 1–5 days | 10 | 2 |
| 6–10 days | 10 | 18 |

relieved with a decrease in the cognition questionnaire score. There was 84.73 and 43.45% decrease in add-on MR Plus and control group respectively (Table 4d). The add-on MR Plus group significantly ($p < 0.05$) reduced the disturbed cognition score.

### 3.9. Changes in quality of life and mental wellness score

There was significantly increased quality of life in the add-on MR Plus group compared to control. The mental wellness quotient was also improved. There was severe fear regarding health felt by patients on baseline, which got significantly reduced in add-on MR Plus group within 5 days and the patients were free of fear of illness till day 15 (Table 4d).

### 3.10. Requirements of supplemental oxygen

There was a requirement of supplemental oxygen to 25% of patients from the add-on MR Plus group and 20% of patients in the control group at baseline. All of the patients from the add-on MR Plus group required supplemental oxygen for (on average) 2.4 days and were on air later on. On the contrary, patients in the control group required supplemental oxygen for an average of 6 days. There was significant reduction in the number of days of supplemental oxygen (2.5 times reduction) in the treatment group compared to control (Table 4a).

### 3.11. Requirements of ICU admission

There was a requirement of ICU admission to 15% (3 patients) of patients from the control group. In contrast, there was no requirement of ICU admission to the add-on MR Plus group. The reduction in the requirement for ICU in the treatment group can be correlated to improved clinical status, good prognosis and speedy recovery (Table 4b).

### 3.12. Duration of hospitalization

In the add-on MR Plus treatment group, around 50% of patients got discharged from hospital in 5 days and the rest of 50% in less than 8 days. There were only 10% of patients discharged from hospital in 5 days from the control group and the rest got discharged in 9–10 days. There was significant reduction in the number of days of hospitalization in the add-on MR Plus group ($p < 0.05$). The data depicted in Table 4c.

### 3.13. Safety outcomes

Biochemical parameters like liver, renal function tests and hematological parameters like complete blood count were assessed on baseline and day 10. There were no significant changes in the parameters between groups. The data depicted in Tables 5 and 6.

### 3.14. Adverse events

There were no adverse events except toothache and menstrual pain in 7 cases of the control group and 3 cases of treatment groups respectively. The complaints got resolved without rescue medication and there was no need to stop the medication in all three groups. There were no adverse events related to possible engagement of test intervention.

**Table 4d**
Changes in quality of life questionnaires.

| Changes in disturb sleep cycle score | | | | |
|---|---|---|---|---|
| Groups | Baseline | Day 7 | Day 15 | % Change |
| Madhav Rasayan Plus | 14.65 (1.17) | 9.75 (0.95) | 2.85 (1.55) | 80.55 |
| Control | 15.05 (1.18) | 14.75 (1.32) | 9.85 (1.03) | 34.56 |
| P value | 0.2931 | <0.05 | <0.05 | |
| Changes in disturbed cognition score | | | | |
| Madhav Rasayan Plus | 7.2 (0.76) | 4.95 (1.04) | 1.1 (0.96) | 84.73 |
| Control | 7.25 (0.95) | 7.15 (0.92) | 4.1 (0.84) | 43.45 |
| P value | 0.8572 | <0.05 | <0.05 | |
| Changes in SNOT (Sino Nasal Outcome Test) score | | | | |
| Madhav Rasayan Plus | 27.15 (2.51) | 15.6 (1.65) | 8.9 (2.02) | 67.22 |
| Control | 27.45 (1.30) | 21.5 (1.93) | 11.6 (1.45) | 57.75 |
| P value | 0.6417 | <0.05 | <0.05 | |
| Changes in 5ED (Quality of life) score | | | | |
| Madhav Rasayan Plus | 13.05 (1.18) | 8 (1.15) | 5.7 (0.72) | 56.33 |
| Control | 12.75 (0.90) | 12.25 (1.10) | 10.35 (1.58) | 18.67 |
| P value | 0.3764 | <0.05 | <0.05 | |

Between group analysis by one-way ANOVA, Significant at $P \leq 0.05$.

**Table 5**
Safety profile.

| Parameters | Screening day | | | Day 10 | | |
|---|---|---|---|---|---|---|
| | Madhav Rasayan Plus | Control | P Value | Madhav Rasayan Plus | Control | P Value |
| Alkaline Transaminase(U/l) | 58.08 (83.52) | 34.78 (30.13) | 0.2464 | 34.24 (17.10) | 28.95 (10.91) | 0.2750 |
| Aspatate Amino transferase (U/l) | 56.00 (64.71) | 41.49 (23.87) | 0.3617 | 31.06 (9.05) | 29.87 (6.28) | 0.6494 |
| Bilirubin Total (mg/dl) | 4.86 (19.85) | 0.52 (0.24) | 0.3471 | 0.61 (0.14) | 0.62 (0.21) | 0.8514 |
| Bilirubin Direct (mg/dl) | 0.16 (0.05) | 0.16 (0.06) | 0.7411 | 0.19 (0.05) | 0.18 (0.05) | 0.5844 |
| Bilirubin Indirect (mg/dl) | 0.36 (0.12) | 0.36 (0.18) | 0.9869 | 0.42 (0.09) | 0.45 (0.17) | 0.6592 |
| Gamma Glutamyl Trasferase (U/l) | 46.51 (32.37) | 51.62 (55.70) | 0.7216 | 40.85 (21.94) | 40.44 (26.88) | 0.9621 |
| BUN (mg/dl) | 11.53 (5.17) | 13.19 (4.28) | 0.2731 | 15.98 (5.47) | 14.31 (5.89) | 0.3954 |
| Serum Creatinine (mg/dl) | 1.33 (2.40) | 0.72 (0.16) | 0.2744 | 0.81 (0.30) | 0.71 (0.14) | 0.2028 |
| Serum Uric Acid (mg/dl) | 4.09 (1.96) | 3.53 (1.28) | 0.2946 | 4.92 (1.99) | 4.68 (1.39) | 0.6793 |

Data analyzed by student t test significant at $p < 0.05$.

**Table 6**
Hematological parameters.

| Parameters | Screening day | | | Day 10 | | |
|---|---|---|---|---|---|---|
| | Madhav Rasayan Plus | Control | P Value | Madhav Rasayan Plus | Control | P Value |
| Total Leukocyte Count (/cumm) | 6.07 (3.39) | 5.74 (1.82) | 0.6988 | 9.82 (2.95) | 10.91 (4.69) | 0.4403 |
| Neutrophils (%) | 71.58 (15.95) | 72.20 (13.33) | 0.8944 | 29.20 (10.05) | 73.78 (10.48) | 0.1981 |
| Lymphocytes (%) | 23.87 (13.56) | 24.54 (12.00) | 0.8683 | 25.94 (9.59) | 21.14 (8.99) | 0.1368 |
| Monocytes (%) | 2.76 (1.71) | 2.11 (1.20) | 0.1765 | 3.34 (1.24) | 3.04 (1.24) | 0.4702 |
| Eosinophil (%) | 1.35 (2.34) | 0.71 (0.71) | 0.2501 | 0.91 (0.78) | 1.12 (1.53) | 0.6225 |
| Basophils (%) | 0.31 (0.18) | 0.29 (0.16) | 0.6548 | 0.34 (0.20) | 0.41 (0.30) | 0.4922 |
| Total RBC Count (million/cumm) | 4.78 (0.50) | 4.61 (0.51) | 0.3023 | 4.88 (0.52) | 5.03 (0.56) | 0.4252 |
| Hemoglobin (g/dL) | 13.59 (1.50) | 12.66 (1.89) | 0.0904 | 13.51 (1.67) | 13.69 (1.98) | 0.7795 |
| Platelets (/cumm) | 220.38 (53.94) | 231.55 (64.28) | 0.5494 | 291.20 (108.03) | 353.79 (99.49) | 0.0115 |

## 4. Discussion

This preliminary RCT evaluated the effect of Madhav Rasayan Plus tablets in COVID-19 as an adjuvant. It has revealed add-on Madhav Rasayan Plus significantly improved symptoms of COVID-19 like cough, breathlessness, fatigue and gastric disturbance along with reduced inflammatory markers like CRP, Ferritin as well as restored tissue level markers like creatinine phosphokinase and NT- Pro BNP in COVID-19 patients. There was improved quality of life assessed through different questionnaires. There was reduced hospital stay and supplemental oxygen in Madhav Rasayan plus treated group than control. Overall, incorporating Madhav Rasayan Plus (as adjuvant) in the treatment protocol of COVID-19, there was early clinical recovery with protection to vital organs.

The ingredients of Madhav Rasayan Plus are excellent modulators of immunity. Use of 'cocktails' of immunodrugs to restore immun-homeostasis was proposed by prominent interdisciplinary scientists as the same can simultaneously address several components of our immune defenses and can produce sufficient therapeutic effects [8,16]. The same is being reciprocated in the present study as the use of Madhav Rasayan Plus has provided immunomodulatory activity to produce improved therapeutic benefit and faster clinical recovery of COVID-19 patients. The formulation is prepared with appropriate repurposing of ayurvedic ingredients after understanding of clinical picture and pathological understanding of COVID-19 in Ayurveda perspective. Molecular docking study has reported Tinospora Cordifolia (Giloy) may significantly hinder main protease (Mpro or 3Clpro) of SARS-CoV-2 [17]. Adhatoda Vasica is repurposed here as it attenuates inflammatory and hypoxic responses in preclinical mouse models [18]. Recent report suggest the dual ability of Glycyrrhizin to concomitantly halt SARS Cov-2 virus replication and dampen proinflammatory mediators in Covid-19 [19]. Ashwagandha the ingredient of formulation was in fact first herb envisioned for repurposing it for COVID-19 [5]. The same (Ashwagandha) was later found to be useful for remarkable downregulation of TMPRSS2 mRNA in treated cells predicting dual action of Wi-N to block SARS-CoV-2 entry into the host cells [20].

Distinguished Ayurveda stalwarts have enlightened the interrelation of Rasavaha, Pranavaha, Udakavaha, Raktavaha and annavaha srotas in context with respiratory pathologies [21]. Contemporary scholars have interpreted left lung as 'Phupphusa' and right lung as 'Kloma' (kloma is an organ involved in water metabolism and water electrolyte balance) and thus have provided broader canvas and leads for drug design for respiratory ailments [22].

Ayurveda herbs do not only target immune mechanism but the interconnected pathways of neuroendocrine system, the immune system and peripheral or target organs. The similar activity set was demonstrated by Madhav Rasayan Plus in this study. Add on treatment of Madhav Rasayan Plus has not only improved clinical status of patients but also significantly reduced supplemental Oxygen requirement, pro inflammatory markers and marker related to vital organ like creatinine phosphokinase and NT-Pro BNP. This perhaps confirms potential of Madhav Rasayan Plus in protecting Pulmonary as well as extra pulmonary organs like heart, muscle and neuro-endocrinological system in COVID-19 [23].

The outcomes of this preliminary study are encouraging as there is significant reduction in inflammatory biochemical markers as well as reduction in the requirement of supplemental oxygen and hospital stay. However, an important limitation of this work remains the sample size. As it was preliminary study the sample size was forty with twenty in each group. Study with more sample size is needed for better confirmation of efficacy.

## 5. Conclusion

It can be concluded from this preliminary work that Madhav Rasayan Plus as add on treatment to COVID-19 patients provides an added advantage over the conventional standard of care like early clinical recovery, significant better recovery of Ferritin and CRP

levels, significant reduction in requirement of supplemental oxygen and ICU. This trial is important as it was conducted on moderate COVID-19 patients including oxygen dependent patients and not mere mild ones. However the sample size of the study could be the limiting component and RCT with a large cohort is warranted.

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## Declaration of competing interest

Dr. Sameer Jamadagni, Dr. Prasad Pandkar and Dr. Girish Shirke and Dr. Shailesh Malekar are consultants at Shri Vishwavati Chikitsalaya and Research center, and were involved in basic and literary research work about formulation. Dr Tushar Saundankar also associated with Shri Vishwavati Chikitsalaya and Research center.

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## References

[1] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). JAMA 2020;324:782–93. https://doi.org/10.1001/jama.2020.12839.
[2] Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology 2020;35:288–301. https://doi.org/10.1152/physiol.00019.2020.
[3] Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648–55. https://doi.org/10.1161/CIRCULATIONAHA.120.046941.
[4] Kotecha R. The journey with COVID-19: initiatives by Ministry of AYUSH. J Ayurveda Integr Med 2021;12:1–3. https://doi.org/10.1016/j.jaim.2021.03.009.
[5] Bhushan Patwardhan, Preeti Chavan-Gautam, Manish Gautam, girish Tillu, Chopra Arvind, Sunil Gairola, et al. Ayurveda rasayana in prophylaxis of Covid 19. Curr Sci 2020;118:1158–60.
[6] Pandkar PD, Sachdeva Vinay. Pathophysiology of Covid-19 and host centric approaches in Ayurveda. J Ayurveda Integr Med 2020;13(1):100380. https://doi.org/10.1016/j.jaim.2020.11.010.
[7] Puthiyedath R, Kataria S, Payyappallimana U, Mangalath P, Nampoothiri V, Sharma P, et al. Ayurvedic clinical profile of COVID-19 – a preliminary report. J Ayurveda Integr Med 2020;13(1). https://doi.org/10.1016/j.jaim.2020.05.011.
[8] Patwardhan B, Gautam M. Botanical immunodrugs: scope and opportunities. Drug Discov Today 2005;10:495–502. https://doi.org/10.1016/S1359-6446(04)03357-4.
[9] Verma MD, Singh RH, Upadpa KN. Physiological, endocrine and metabolic studies on the effect of rasayana therapy in aged persons. J Res Indian Med 1973;8:1–10.
[10] Rajkumar RP. Ayurveda and COVID-19: where psychoneuroimmunology and the meaning response meet. Brain Behav Immun 2020;87:8–9. https://doi.org/10.1016/j.bbi.2020.04.056.
[11] Sepahvand E, Jalali R, Khaledi Paveh B, Rezaei M. Development and validation of sleep disturbance questionnaire in patients with acute coronary syndrome. Int Sch Res Notices 2014;1–8. https://doi.org/10.1155/2014/978580.
[12] Lechien JR, Cabaraux P, Chiesa-Estomba CM, Khalife M, Hans S, Calvo-Henriquez C, et al. Objective olfactory evaluation of self-reported loss of smell in a case series of 86 <scp>COVID</scp> -19 patients. Head Neck 2020;42:1583–90. https://doi.org/10.1002/hed.26279.
[13] Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, et al. The landscape of cognitive function in recovered COVID-19 patients. J Psychiatr Res 2020;129:98–102. https://doi.org/10.1016/j.jpsychires.2020.06.022.
[14] Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep 2008;31:1601–7. https://doi.org/10.1093/sleep/31.11.1601.
[15] Schrag A. The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;69:67–73. https://doi.org/10.1136/jnnp.69.1.67.
[16] Sutmuller RPM, Offringa R, Melief CJM. Revival of the regulatory T cell: new targets for drug development. Drug Discov Today 2004;9:310–6. https://doi.org/10.1016/S1359-6446(03)03021-6.
[17] Shree P, Mishra P, Selvaraj C, Singh SK, Chaube R, Garg N, et al. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants - withania somnifera (Ashwagandha), Tinospora cordifolia (Giloy) and Ocimum sanctum (Tulsi) - a molecular docking study. J Biomol Struct Dyn 2020:1–14. https://doi.org/10.1080/07391102.2020.1810778.
[18] Gheware A, Dholakia D, Kannan S, Panda L, Rani R, Pattnaik BR, et al. Adhatoda Vasica attenuates inflammatory and hypoxic responses in preclinical mouse models: potential for repurposing in COVID-19-like conditions. Respir Res 2021;22:99. https://doi.org/10.1186/s12931-021-01698-9.
[19] Gowda P, Patrick S, Joshi SD, Kumawat RK, Sen E. Glycyrrhizin prevents SARS-CoV-2 S1 and Orf3a induced high mobility group box 1 (HMGB1) release and inhibits viral replication. Cytokine 2021;142:155496. https://doi.org/10.1016/j.cyto.2021.155496.
[20] Kumar V, Dhanjal JK, Bhargava P, Kaul A, Wang J, Zhang H, et al. Withanone and Withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. J Biomol Struct Dyn 2020:1–13. https://doi.org/10.1080/07391102.2020.1775704.
[21] Nanal VM. The organ kloma: a fresh appraisal. Ancient Sci Life 1989;9:61–5. https://doi.org/22557676.
[22] Patwardhan K. Concepts of human physiology in Ayurveda. In: Roy PK, editor. Sowarigpa and Ayurveda, central institute of higher Tibetan studies; 2008. p. 53–73. Sarnath, Varanasi.
[23] Rege NN, Thatte UM, Dahanukar SA. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytother Res 1999;13:275–91. https://doi.org/10.1002/(SICI)1099-1573(199906)13:4<275::AID-PTR510>3.0.CO;2-S.