Clinical, Virological and Immunological Outcomes of Madhav Rasayan Tablet in COVID-19: Randomized Controlled Clinical Trial

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ABSTRACT

Introduction: The world is facing health emergency of Covid-19. Ayurveda preparations are known for their immunomodulatory as well as antiviral efficacies. Integrated approach and holistic management of Covid 19 patients is need of hour.

Aim: This research was conducted to clinically validate safety and efficacy of Madhav Rasayan tablet, an Ayurvedic formulation in the management of Covid 19.

Materials and Methods: In present RCT, moderate COVID 19 patients (n=60) were randomized in two parallel groups (n=30/group). The interventional group (Treatment) received Madhav Rasayan tablet 250 mg twice a day for 30 days along with standard care (SOC) as per ICMR, while the control group received SOC alone. The primary outcome of the study was to evaluate improvement of clinical symptoms, reduction in levels of inflammatory markers, negative RT-PCR for Covid 19 on day 5 and day 10 of intervention. The secondary outcomes were to reduce supplemental oxygen, hospital stay and ICU admission. Total Covid antibodies and Covid IgG antibodies were assessed on day 10 and day 30 of the intervention. Improvements in certain subjective aspects were assessed through questionnaires.

Results: Madhav Rasayan significantly improved symptoms of COVID 19 like cough, breathlessness, fatigue and reduced inflammatory markers like CRP. The significant population (40%) turned RT-PCR negative on 5th day along with improved quality of life. The antibody status in intervention group was shown to be better. There was reduced hospital stay, need of supplemental oxygen and in intervention group than control.

Conclusion: Madhav Rasayan can be good option for integrating with standard care protocols. There was significant viral load reduction and more negative RT-PCR reports. There was better prognosis, speedy clinical recovery and reduction in inflammatory markers. It is a promising immunomodulator to offer long term protection by helping production of neutralizing antibodies. This study will pave the path for integrating Ayurveda interventions in management of Covid 19.

Key Words: Ayurveda, COVID 19, Madhav Rasayan, Immunomodulatory, Antiviral, Integrative medicine

BACKGROUND AND INFORMATION

The novel SARS-CoV-2 virus has spread around the globe at a rate that has never been seen before in the history of epidemic diseases. The virus produced the sickness COVID-19, which wreaked havoc on the lives of everyone on the planet. The corona virus is affecting 220 countries and territories.¹

Coronavirus Disease 2019 (COVID-19) is putting governments and respective healthcare systems under extraordinary

stress. The extreme facility of transmission of the disease with the incredibly wide range of clinical scenarios (ranging from asymptomatic carriers to critically ill patients) warrants extraordinary research efforts directed to prevention, cure and management of complications of Covid 19.

COVID-19 infection has a wide variety of symptoms, from asymptomatic to life-threatening. Patients with mild disease can present with symptoms of fever, cough, and fatigue² and some patients deteriorate quickly after a short period of

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ISSN: 2231-2196 (Print) ISSN: 0975-5241 (Online)

Received: 30.06.2021

Revised: 05.10.2021

Accepted: 10.12.2021

Published: 01.03.2022

mild symptoms. Sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, and septic shock are commonly observed in critically ill patients.³ Laboratory identification tools like RT-PCR and rapid antigen tests are used to confirm Covid 19 infection. Medical imaging of lung tissue together with some inflammatory markers like serum levels of CRP, LDH and ferritin can be interpreted for assessment of the severity of disease. Together these parameters are indicators of clinical recovery along with the symptom alleviation.⁴

Since the first instances of coronavirus were reported in China and the first sequencing of SARS-CoV-2 was published in December 2019, the virus has undergone several changes. The SARS-CoV-2 pandemic has been occurring in several phases since the emergence. Differences in illness severity could be caused by causes other than the virus or by the virus's evolution. SARS-CoV-2 genes encoding proteins that interact with the host immune system have developed evolutionary significant mutations and deletions. After the first epidemic, the rate of mutations in proteins involved in the immune system's interaction has continued to rise. The pandemic's evolution until the summer of 2020 could be explained by cross-reactivity on the one hand and viral changes on the other. During the summer, mutations in the spike protein, particularly N439K in RBD, appeared: according to Chen et al.,⁵ the most common spike mutations (including D614G, N439K, and S477N) improve its transmissibility. A strain with D614G and RBD mutations is more infectious and resistant to various neutralising antibodies, which has clear implications for COVID-19 patient recovery.⁶

Considering the nature of the virus, clinical scenario and the mutations and waves of the infections coming in, we should think of holistic management of Covid 19, with an intervention essentially from natural origin that can improve clinical outcomes, can be used along with conventional medication safely and can help in managing any long term complications as well by fundamentally supporting host immunity. Ayurveda (Indian Medicine) fraternity has responded covid crisis at basics as well as clinical levels.^{7,8} The current research was conducted to clinically validate safety and efficacy of Madhav Rasayan tablet, an Ayurvedic formulation in the management of Covid 19. The outcomes are depicted and interpreted in the manuscript.

MATERIALS AND METHODS

Study design

The study was a randomized control trial comprised of Covid 19 patients admitted to Dedicated Covid Hospital, Lokmanya Medical Research Centre, Lokmanya Hospital, Chinchwad, Pune, India. The study was approved by the Institutional Ethics Committee Lokmanya medical Research

Centre and was registered with Clinical Trial Registry of India (CTRI/2021/04/032541). The CONSORT flow of the entire study is depicted in Fig. I

Figure I: CONSORT flow diagram.

Inclusion criteria

Subjects in age range from 18 to 60 years old (both males and females), which had a confirmed Covid 19 positive RT-PCR report and admitted to a study site with moderate to severe symptomatic presentation with no signs of ARDS were recruited in the study. Those subjects who were willing to provide consent and follow up for the duration of the study were included in the study.

Exclusion criteria

Patients with autoimmune illness or syphilis infection were deemed ineligible for the trial. Those subjects not fit for trial as per the discretion of the investigator were excluded. Subjects who belonged to a vulnerable group were not allowed to participate. Pregnant or lactating women were excluded for the study. Subjects requiring ICU admission and mechanical ventilation at the screening were not considered in the trial. Subjects with signs of ARDS, any other comorbidity which is the critical stage at screening which in investigator discretion finds subject not suitable for the trial participation were excluded from study.

Groups

We screened 85 participants of which 60 participants completed the study. They were randomized using a computer-generated randomization sheet, either in the standard treatment arm (Control Group) where the patients were provided

with conventional care as recommended in clinical management protocol for COVID 19 advocated by Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare, Government of India or to the treatment arm where the patients were treated with Madhav Rasayan Plus tablets along with the standard protocol (Treatment Group). See Fig. 1 for the flow of events of this trial.

Sample size

Sample size calculation is derived taking considerations of primary and secondary outcomes by a qualified statistician. The software used for calculation of sample size is SPSS version 10.0

Intervention and dosage

Madhav Rasayan tablets possess key ingredients like *Piper Longum*, *Glycyrrhiza Glabra*, *Eclipta Alba*, *Achyranthes Aspera*, *Embelia Ribes* and *Aloe barbadensis*. The dosage of the intervention was 250 mg tablet twice a day with lukewarm water for 30 days. Subjects were asked not to consume bakery products, fermented food etc. for the study duration as a part of dietary modification.

Outcome measures

The primary outcome of the study was to evaluate improvement of clinical symptoms including cough, breathlessness, gastric disturbance, anosmia, fatigue and myalgia, reduction in elevated levels of inflammatory markers such as C-reactive protein (CRP), low density lipoprotein (LDH) and Ferritin and subject population with negative RT-PCR for Covid 19 on time points like baseline, day 5 and day 10 of intervention.

The secondary outcomes of trial were to evaluate reduced requirements of supplemental oxygen, hospital stay and requirement of ICU admission. Total Covid antibodies and Covid IgG antibodies were assessed on day 10 and day 30 of the intervention. Improvements in certain subjective aspects were assessed through questionnaires; like quality of life, sino-nasal complaints by modified SNOT questionnaire, disturbed sleep questionnaire, cognition questionnaire, modified fatigue severity scale and 5 ED questionnaire. Adverse events were analyzed from baseline to end of the study.

Methodology

After approval from institutional EC clinical study was registered on Clinical Trials Registry- India (CTRI) website and study was conducted at Lokmanya Medical Research Centre, Lokmanya Hospital, Chinchwad, Pune. On screening visit, a written informed consent was obtained from subjects for their participation in the study. Subject's demographic details were recorded. Clinical examination of each subject was performed. Subject's medical, surgical and treatment history was recorded. Subject's current medication if any was

noted in the case record from (CRF) along with the vitals like pulse, blood pressure heart rate, body temperature were recorded. The subjects were considered for further evaluation as per the inclusion and exclusion criteria. On screening visit all biochemical, hematological and inflammatory marker tests were performed and reviewed on baseline day (Day 0). Subject fitting in all inclusion criteria and showing absence of all exclusion criteria were randomized to either of the two-treatment arm with computer-generated randomization sheet. Subjects were on standard of care for Covid 19 as per ICMR protocol for both the treatment arms. A screening window of 2-3 days was kept, in case if there is delay in the availability of tests reports or in case few tests need to be repeated. The record of concomitant medication was properly maintained. Treatment compliance was assessed daily. All clinical examination and symptom grading were done on daily basis till the hospitalization period of patients. All subjects were advised to follow their diet routine as per designed by study center dietician during the entire study period avoiding bakery and fermented food. The presence of any adverse events was strictly monitored and reported. On day 10 all the blood parameters were repeated. The treatment was followed on subsequent days till day 30. On day 10 and day 30 Covid specific antibodies like total Covid antibodies and IgG antibodies were checked. Symptomatic and quality of life assessment was performed physically if patients visited hospital after discharge or performed telephonically if subject not willing to visit hospital again and there is absence of any adverse events, similarly for blood and swab collection also, the home collection was arranged for the discharged patients not visiting hospital physically.

Data analysis

Patients without any major protocol violation were included in the per-protocol population (pp), including those patients who had good treatment compliance, who did not take any prohibited medications during the study period with completed CRF were used for analysis. Both descriptive and inferential analyses were used in inferring the data.

Demographic and baseline information

Continuous variables that are Age and other demographical characteristics were summarized by using summary statistics i.e. the number of observations, mean and standard deviation. Categorical values like gender and clinical Examination were summarized using frequencies and percentages.

Analysis of primary efficacy parameters

In this study percentage of patients having relieved of symptoms on Day 5 and 10 were analyzed and compared between groups by using Chi-Square Test. Other Primary efficacy variables like inflammatory markers and organ level markers were evaluated by student t-test paired and unpaired wherever applicable.

Secondary efficacy parameters

Secondary variables like day of hospitalization and days of oxygen supplementation were analyzed by chi-square test. All questionnaire and quality of life scores were analyzed by ANOVA test. Covid antibodies were assessed using student t-test between and within groups.

Safety analysis

Biochemical and hematological parameters were evaluated by ANOVA test. Adverse events (AEs) and serious adverse events (SEs) were summarized, counting both the number of separate events and the number of subjects experiencing events occurring during the study period were provided overall, per system organ class and preferred term by presenting. All p-values were reported based on two-sided significance

test and all the statistical tests were interpreted at 5% level of the significance level.

RESULTS AND OBSERVATIONS

Demographic characteristics

In the present study the mean age of male and female subjects in test and control group were comparable and ranged from 42.21 to 39.79 years. The ratio of male to female in test and control group was 67:33 male to female respectively and was comparable between groups (Table 1). Around 25% subjects of the whole study population were presented with comorbidity i.e., hypertension, diabetes mellitus, chronic lung disease etc. The details are presented in table I.

Table I: Demographic details of study subjects

Parameter Group	Treatment		Control	
	Male (n=20)	Female (n=10)	Male(n=20)	Female (n=10)
Age (years)	40.68±7.63	45.27±9.56	40.38±10.40	38.4±10.49
Total Age (years)	42.21±8.53		39.79±10.39	

Primary outcomes of the study

Changes in percent population with negative RT-PCR test

In the present study, there were 12 subjects (40%) from treatment group and 6 (20%) from control group turned RT-PCR negative for nasopharyngeal swab for Covid 19 on day 5 of the study. The results are depicted in graph I.

Graph I: Changes in percent population with negative RT-PCR test

Changes in symptoms of COVID 19

Clinical symptoms such as cough, breathlessness, fatigue, myalgia, gastric disturbance and anosmia were assessed from baseline to day 10. It was evidently observed from the data obtained that there was faster relief of symptoms in

treatment group compared to control. There were more subjects getting relieved of cough, breathlessness, fatigue and myalgia on day 5 and day 10, comparison was statistically significant. The difference in relief from gastric disturbances and anosmia were not statistically significant between treatment and control group. There were 90% subjects from treatment group relieved of cough compared to 40% on day 10. There were 97% subjects relieved of breathlessness in treatment group compared to 67% in the control group. Subjects relieved of fatigue on day 10 were 73% in treatment and 23% in control group. The data of subjects getting relieved of symptoms on the particular days are depicted in table 2.

Table II: Subjects relieved of the symptoms of COVID 19 between groups

Symptoms	No. of subjects relieved of the symptoms					
	Treatment (N=30)			Control (N=30)		
	Day 0	Day 5	Day 10	Day 0	Day 5	Day 10
Cough	3	12	27*	4	8	12
Breathlessness	5	10	29*	3	9	20
Gastric disturbance	25	27	30	24	27	30
Anosmia	10	10	22	12	14	25
Fatigue and myalgia	0	7	22*	0	4	7

Analyzed by Fischer exact test. * Significant $p < 0.05$

Changes in inflammatory markers

Inflammatory markers like CRP, LDH and ferritin were elevated in both groups at baseline. There was a statistically significant reduction in elevated levels of CRP between treatment and control groups. Serum LDH and ferritin were

not changed significantly between groups. There was 61% reduction of elevated serum CRP levels in treatment group compared to 26.6% in control group. Results are displayed in table III

Table III: Changes in inflammatory markers between groups

Parameters	Baseline		P value	Day 10		P value
	Treatment	Control		Treatment	Control	
CRP (mg/L)	29.72±31.91	27.76±25.81	0.4009	11.57±10.19	20.35±27.31	0.0273
LDH (U/L)	458.81±146.21	428.58±138.17	0.216	472.81±168.77	477.74±187.40	0.4595
Ferritin ng/ml	355.62±260.78	279.42±251.95	0.1366	308.42±255.85	318.60±357.54	0.4497

Analyzed by student t-test. Significant at $p < 0.05$

Secondary outcomes of the study

Changes in Sino-nasal Complaints evaluated by modified SNOT questionnaire

There was 91.82% decrease in SNOT questionnaire score in treatment group vs. 52.68% decrease in control group at the end of the study. The difference was statistically significant on day 0 as well as day 10. Refer table IV.

Table IV: Changes in subjective scales and questionnaire between groups

Changes in Disturbed Sleep Cycle score				% Change
Groups	Day 0	Day 5	Day 10	
Test	16±0.74	10.23±1.24	4.63±2.12	71.06
Control	16.43±0.56	14.5±1.44	9.23±2.11	43.82
P Value	0.690	<0.001	<0.001	
Changes in Disturbed cognition score				% Change
Groups	Day 0	Day 5	Day 10	
Test	8.2±0.71	4.70±0.65	2.37±1.78	71.10
Control	8.33±0.60	6.17±1.11	4.00±0.90	51.98
P Value	0.568	<0.001	<0.001	
Changes in SNOT score				% Change
Groups	Day 0	Day 5	Day 10	
Test	33±1.47	13.00±1.98	2.7±3.09	91.82
Control	32.97±1.29	25.2±2.20	15.60±3.39	52.68
P Value	0.4633	<0.001	<0.001	
Changes in modified severity score				% Change
Groups	Day 0	Day 5	Day 10	
Test	24.4±1.89	12.50±2.53	2.53±4.13	89.63
Control	25.07±0.82	21.13±1.91	9.23±3.80	63.18
P Value	0.419	<0.001	<0.001	
Changes in 5ED (Quality of life) score				% Change
Groups	Day 0	Day 5	Day 10	
Test	13.43±0.56	7.00±1.97	2.70±3.06	79.90
Control	13.53±0.50	9.53±1.16	9.13±0.93	32.52
P Value	0.2375	<0.001	<0.001	

Analyzed by student t-test. Significant at $p < 0.05$

Changes in disturb sleep cycle score

There was reduced disturbed sleep cycle score (Table 4) in both treatment groups but the treatment group demonstrated around 71.06% decrease and control group with 43.82% respectively. The between-group analysis revealed treatment group significantly ($p < 0.05$) reduced the disturbed sleep cycle score.

Changes in cognition score

There were cognition-related symptoms portrayed by patients on screening day in both groups. The symptoms eventually relieved with decrease in the cognition questionnaire score. There was 71.10 and 51.98% decrease in treatment and control group respectively (Table 4). The treatment group significantly ($p < 0.05$) reduced the disturbed cognition score.

Changes in modified fatigue severity score

Moderate to severe fatigue was common complaint in patients of both groups on baseline. There was 89.63% reduction in fatigue severity score in treatment group compared to 63.18% in control group. The difference in the fatigue severity score was significantly reduced ($p < 0.05$) (Table 4) in treatment group on day 5 and day 10.

Changes in Quality of life and mental wellness score

There was significantly increased quality of life in treatment group compared to control on baseline and day 10 as well as end of study (Table 4). The mental wellness quotient was also improved. There was severe fear regarding health felt by patients on baseline got significantly reduced in treatment group within 5 days and the patients were free of fear of illness till day 10.

Duration of hospitalization

Around 45% of subjects got discharged from hospital in 4-5 days and cumulatively around 90% subjects got discharged

in less than 8 days (Average days of hospitalization for treatment group was around 6.59 ± 1.75 days). The mean average of the days of hospitalization for control group subjects was 9.15 ± 1.90 days) (Fig. II).

Figure II: Clinical recovery and outcome assessment.

Requirements of supplemental oxygen

There was requirement of supplemental oxygen to around 60% subjects in both groups on baseline. All of the subjects from treatment group required supplemental oxygen for average 2.53 days and were maintaining saturation above SpO_2 97% on air later on, on the contrary subjects in control group required supplemental oxygen for average 6 days. There was significant reduction in number of days of supplemental oxygen (2.3 times reduction) in treatment group compared to control (Fig. I).

Requirements of ICU admission

There was requirement of ICU admission to 20% (6 subjects) of subjects from the control group on the contrary there was no requirement of ICU admission in treatment group (Fig. I).

Changes in Covid specific antibodies between groups

There was increase in total Covid antibodies in treatment group from day 10 to day 30 (26% increase) but the change is

not statistically significant when compared to control group. In case of Covid specific IgG antibody levels, treatment group showed 60% increase in levels compared to 21% in control group (Graph II, III).

Graph II: Changes in total Covid antibodies between groups.

Graph III: Changes in Covid specific IgG antibodies between groups.

Safety outcomes

Biochemical parameters like liver, renal function test 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 table V.

Table V: Changes in hemogram and biochemical parameters between groups

Parameters	Baseline		Day 10	
	Treatment	Control	Treatment	Control
Complete blood count				
Total Leukocyte (/cumm)	6.63 ± 2.48	5.96 ± 2.60	8.76 ± 2.77	9.42 ± 3.75
Neutrophils (%)	74.16 ± 11.70	74.36 ± 11.29	73.15 ± 9.83	73.93 ± 9.07
Lymphocytes (%)	20.35 ± 9.43	20.88 ± 9.92	20.87 ± 8.93	20.54 ± 8.04

Table V: (Continued)

Parameters	Baseline		Day 10	
	Treatment	Control	Treatment	Control
Monocytes (%)	3.61±3.18	2.93±1.47	3.26±2.33	2.95±0.97
Eosinophil (%)	1.44±2.32	1.32±1.07	1.18±0.93	1.59±2.02
Basophils (%)	0.18±0.06	0.21±0.06	0.25±0.16	0.29±0.20
Total RBC Count (million/cumm)	4.80±0.66	4.72±0.44	4.70±0.60	4.68±0.52
Hemoglobin (G/dl)	13.71±2.18	13.31±2.20	13.53±1.81	13.15±1.85
Hematocrit (%)	45.12±4.48	43.67±4.69	42.63±3.34	43.04±4.20
Platelets (/cumm)	194.90±83.83	196.54±61.18	301.35±133.29	307.29±114.20
Platelet Distribution (fL)	12.00±1.54	11.92±1.77	13.49±3.34	12.87±2.71
Mean Platelet Volume (fL)	10.43±0.77	10.47±0.72	10.86±1.24	10.84±1.01
Liver profile				
Bilirubin Total (mg/dl)	0.64±0.17	0.58±0.27	0.59±0.39	0.54±0.21
Bilirubin Direct (mg/dl)	0.22±0.07	0.18±0.08	0.16±0.07	0.14±0.08
Bilirubin Indirect (mg/dl)	0.43±0.12	0.41±0.19	0.43±0.33	0.38±0.13
Aspartate Aminotransferase (SGOT) (IU/L)	77.00±175.92	36.03±16.76	40.19±16.08	31.98±11.95
Alkaline Transaminase (SGPT) (IU/L)	69.7±181.56	28.18±15.24	44.75±29.73	31.83±16.43
Alkaline Phosphatase (U/L)	82.23±26.96	75.19±19.01	88.16±20.59	78.94±26.52
Gamma Glutamyl Transferase (U/L)	50.09±35.88	41.54±31.32	63.70±41.27	41.78±31.78
Total Proteins (gm/dl)	7.09±0.54	6.92±0.58	9.23±9.69	6.70±0.97
Serum Albumin (gm/dl)	4.29±0.44	4.29±0.48	3.88±0.53	3.83±0.62
Serum Albumin/Globulin Ratio	1.60±0.31	1.68±0.35	2.32±4.67	1.59±1.01
Renal profile				
Serum Calcium (mg/dl)	8.32±1.66	8.67±0.49	8.49±0.89	8.74±0.74
Serum Uric Acid (mg/dl)	4.85±2.99	4.64±1.90	4.04±1.04	4.49±1.69
Blood Urea Nitrogen (mg/dl)	14.76±4.56	16.56±6.80	14.34±4.97	14.58±6.00
Serum Creatinine (mg/dl)	1.41±3.26	0.84±0.27	0.91±0.95	0.74±0.19
BUN / Creatinine Ratio	20.04±6.26	19.81±5.68	20.87±5.23	18.46±6.38

Analyzed by student t test. Non-significant (p>0.05)

Adverse events

There were no adverse events related to study medication throughout the study period. There were no adverse events related to possible engagement of test intervention.

DISCUSSION

This randomized, controlled trial evaluated the effect of Madhav Rasayan tablets in COVID-19 has revealed that when used along with standard of care treatment, Madhav Rasayan significantly improved symptoms of COVID 19 like cough, breathlessness and fatigue, reduced inflammatory markers like CRP. There was greater number of population (40%) turned RT-PCR negative for Covid 19 in five days of treatment. Decline in antibodies is again a major

concern and there is scope for supplements that can boost antibodies.⁹ There was improved quality of life assessed through different questionnaires. There was reduced hospital stay and supplemental oxygen in Madhav Rasayan treated group than control. Overall incorporating Madhav Rasayan in treatment protocol of COVID 19 there was faster clinical recovery with improved prognosis.

Covid 19 patients who develop acute respiratory distress syndrome have a high mortality rate in general. It is thought that a hyper-inflammatory state is induced by the infection which leads to multi-organ dysfunction syndrome.¹⁰ In addition to the medical issues, the long duration of quarantining has psychological effects that are not always recognized. Integrative medicine can play an important role in supporting the immune system and also help patients, families and the public cope

with the physiological and psychological aspects of a pandemic.¹¹

In the present research, participants from Madhav Rasayan treated group, did not show need of admission to intensive care unit. This fact is supported by the less requirement of the supplemental oxygen to the patients in Madhav Rasayan treated group along with 28% reduction in hospital stay. These are the valid implications of integrative approach of incorporating Madhav Rasayan in standard of treatment which can put off encumbrance on healthcare systems and ease out economic proposition for patients. On the yardstick of advantages of integrating an Ayurveda based intervention in Covid management protocol; Madhav Rasayan has proved itself worth scheduling. Another important concern around integrating traditional medicine is safety and patient compliance. In the present study, we have assessed hematological and biochemical parameters like liver and renal profile, which suggested no significant change post-treatment indicating safety of the intervention. From patient compliance standpoint, all patients were compliant to Madhav Rasayan consumption for 30 days; the main reason being improved quality of life for the patients which became the motivation for patients to get out of the post-Covid recovery. Incorporation of Madhav Rasayan in Covid 19 management has taken care of the emotional, psychological paradigm of the patients and shown good improvement in scores related physical and psychological wellbeing.

In COVID-19 dyspnea being predominant symptom, it becomes very crucial to manage and maintain SpO₂ levels more than 94-95% for better clinical outcomes.¹² Though statistically not-significant treatment with Madhav Rasayan demonstrated increased SpO₂ levels during the study period compared to baseline, reflected in significantly reduced breathlessness further lowering risk profile of disease.

Patients in Madhav Rasayan treated group showed faster recovery in symptoms like cough, breathlessness and fatigue; which can be very well connected to improved prognosis of disease. There is a strong relationship between symptom regressions and recovery in COVID 19. Our results depict that subjects treated with Madhav Rasayan were relieved of cough, breathlessness, fatigue and gastric disturbances more effectively and within five days of treatment, this further mitigates the risk of severity of COVID-19.

The impressive outcome of the study is reduction in viral load and thus more population of patients turning RT-PCR negative in just five days, its significant activity when compared to only standard of treatment where 50% less subjects turned RT-PCR negative in same time span.

In this study, both groups were comparable in terms of clinical characteristics, disease severity and comorbidity status which removed the prejudice at baseline. Subjects were

showing moderate to severe symptoms with 60% subjects were on supplemental oxygen at baseline. The presenting symptoms were breathlessness, fever, diarrhea, fatigue and anosmia. In Madhav Rasayan treated group the patients on average required supplemental oxygen for just above 2 days; compared to 5-6 days in only standard of care treated group.

Many types of research support the fact that immuno-inflammatory responses play a critical role in the progression of COVID-19.^{13,14} Triggered inflammatory responses are the result of rapid viral replication of SARS-CoV-2. Viral replication and cellular destruction can stimulate release of cytokines and chemokine through macrophages and monocytes¹⁵ activating acquired immune responses. This cascade leads to cytokine storms in Covid 19.¹⁶ Inflammatory markers such as serum lactate dehydrogenase, serum ferritin, C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be positively correlated to the high risks of severity and fatality in COVID-19.¹⁷ Elevated inflammatory markers bear the risk of lung involvement (higher HRCT score) possibly forecasting fatality in COVID-19. One of the main objective of all clinicians treating Covid 19 is always to lower the aggravated response of the cytokines and to lower down their levels to mitigate the risk.

In the present study, treatment with Madhav Rasayan has demonstrated excellent anti-inflammatory activity by reducing serum levels of CRP significantly i.e. around 60% reduction in elevated levels in 10 days. Madhav Rasayan can we think of an intervention with balanced immunomodulatory and anti-inflammatory activity.

Ayurveda herbs target immune mechanism along with the interconnected pathways of neuroendocrine system, the immune system and peripheral or target organs.¹⁸

In Madhav Rasayan Treated group the Covid specific total antibodies and neutralizing IgG antibodies were produced in greater magnitude suggesting immunomodulatory activity and may offer long term support from reinfection. Though the large cohort study with longer duration needs to be planned to get the data around this hypothesis.

Sino-nasal Complaints evaluated by modified SNOT questionnaire revealed that there were significantly reduced sino-nasal complaints in Madhav Rasayan treated group than control. There are disturbed cognition symptoms that are very evident in COVID 19 involving memory, concentration, and foggiess of thoughts. The treatment of Madhav Rasayan significantly improved cognitive symptoms. As a result of sino-nasal symptoms, fatigue and breathlessness along with the emotive upset in COVID 19, led to impaired sleep pattern with mid night awakenings in patients. It was observed through a disturbed sleep cycle questionnaire that treatment with Madhav Rasayan improved sleep quality of subjects significantly than control group. Overall quality of life was

improved significantly by Madhav Rasayan treatment compared to control.

Glycyrrhiza glabra which is important constituent of Madhav Rasayan is a researched molecule as a target for SARS Cov 2. Glycyrrhizin (GLR) *Glycyrrhiza glabra* has anti-viral and immunity modulating activity against SARS viruses confirmed through docking studies.¹⁹ At the membrane level, GLR induces cholesterol-dependent disorganization of lipid rafts, vital for the entry of coronavirus into cells. At the intracellular and circulating levels, GLR can trap the high mobility group box 1 protein (HMGB1) and thus blocks the upsetting functions of HMGB1 which is a key initiator of neuroinflammation.²⁰ The membrane and cytoplasmic activity of GLR, coupled with long-established medical use as a relatively safe drug, make GLR a good candidate to be used alone and in combination with other drugs in the management of Covid 19.

Most of the pathogenic viruses like HIV, HSV, HCMV, and HPV are known to bind with the heparan sulfate proteoglycan (HSPG) receptor of the host cell. Studies have confirmed that SARS-associated viruses like SARS-CoV, HCoV-NL63, and other coronaviridae also show empathies to bind to the HSPG.^{21,22} Some active phytoconstituents like luteolin, wedelolactone, and apigenin, from the leaf extract of *Eclipta alba* are known to inhibit the receptor and can act have potential antiviral action.²³ *Eclipta alba* is one of the key ingredient of Madhav Rasayan.

There are three approaches in which Madhav Rasayan can prove as good candidate for integrating in Covid 19 standard care protocol. First, significant in reducing viral load thus negative RT-PCR report, second- offering speedy clinical recovery getting burden off on healthcare infrastructure and easing economic drain of patients and third- promising immunity modulator to offer long term protection through helping producing neutralizing antibodies.

No significant post-treatment change in any of the biochemical investigations was observed in both the groups like liver, kidney, and hematological parameters. This denotes safety of using Madhav Rasayan in management of COVID 19. There was no abnormality in pulse rate; blood pressure was observed after treatment of Madhav Rasayan. There were no possibly related adverse events due to Madhav Rasayan. The present research confirms safety and efficacy of the treatment of Madhav Rasayan in COVID 19 patients. However, large scale multi-centric cohort study is warranted. Rasayan in COVID 19 patients. However, large scale multi-centric cohort study is warranted.

CONCLUSION

It can be concluded that there are three approaches in which Madhav Rasayan can prove as good candidate for integrating

in Covid 19 standard care protocol like first, significant in reducing viral load thus negative RT-PCR report, second- offering speedy clinical recovery getting burden off on healthcare infrastructure and easing economic drain of patients and third- promising immunity modulator to offer long term protection through helping producing neutralizing antibodies.

ACKNOWLEDGEMENT

The authors would like to acknowledge the research team and the back-office team involved in the research work.

Conflict of interest:None.

Funding: None

Individual author's contribution:

JS - Conceptualization of whole product

PP- Medical writing and trial design

ST - Product development

SG - assist in manufacturing

MM - assist in manufacturing

VV - principal investigator for trial

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