ViraNorm
Capsules

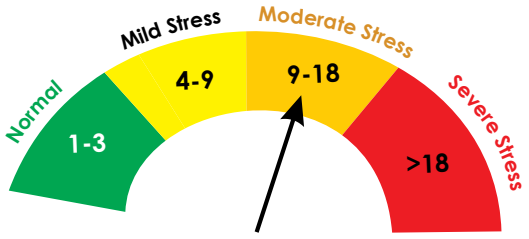
SCINATURE

Powered by Nature
Driven by Hope

Viranorm is the first ayurvedic medicine to systematically prove through a large clinical trial, that it reduces NLR and helps in faster & better recovery from COVID.

Trial data proves that cell level immunity (Cellular Immunity) improves and inflammation at the cell level is reduced with Viranorm.

NLR Stress-o-Meter



Increase in cellular immunity and reduction in cellular inflammation can be measured by using a simple formula called Neutrophils – Lymphocytes Ratio (NLR).

Safe

Clinically Proven

Effective

Viranorm is AYUSH approved immunomodulator and has antiviral properties

Pesticide Free

100% Veg

Rationally Selected

Plant Based Ingredients

All Natural

Scientifically Tested

Gluten Free

Heavy Metal Free

GMP CERTIFIED QUALITY PRODUCT

AYUSH APPROVED PRODUCT
AYUSH

Ingredients

Cissus Quadrangularis / Hadjod | Allium Sativum / Garlic | Zingiber Officinale / Ginger
Withania Somnifera / Ashwagandha | Tinospora Cordifolia / Giloy

Trials registered with CTRI CLINICAL TRIALS REGISTRY INDIA

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Role of Herbal Immunomodulator (Viranorm) as Add-on Treatment in Asymptomatic or Mildly Symptomatic COVID-19 Confirmed Cases

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a highly infectious disease known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Boosting the immune system seems to be a judicious strategy to combat the coronavirus infection. **Objective:** The primary objective of this study was to compare the efficacy and safety of Viranorm + standard of care with standard care alone in the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection. Secondary objective was to compare the immunological response of Viranorm + standard of care with standard care alone in asymptomatic or mildly symptomatic COVID-19 infection. **Results:** Of the 251 randomized subjects, a total of 123 received Viranorm + standard of care and 128 received standard of care alone. After administration of study treatment, on visit 1, follow-up was done on Days 3, 7, 14 and 21. The patients treated with Viranorm + standard of care showed significantly lesser time to resolution of cough than the patients with standard of care alone. At Day 7 and Day 14, the reverse transcription polymerase chain reaction (RT-PCR) results were available for only few patients. Therefore, no firm conclusions can be drawn on the effect of the drug on the incidence of RT-PCR negative subjects. All subjects from both treatment groups reported recovery and no deaths occurred during the study. At Day 14, neutrophil-to-lymphocyte ratio (NLR) values decreased in both treatment groups. The magnitude of decrease in NLR was substantially higher in the group that received Viranorm as an add-on treatment (8% median decrease) compared to the group that received only standard of care (2.6% median decrease). No adverse events or deaths occurred during the entire study duration. **Conclusion:** The add-on treatment with herbal immunomodulator Viranorm for COVID-19 is safe and effective in reducing the duration of cough and is indicative of a significant decrease in systemic inflammation as shown by NLR.

Keywords: COVID-19, SARS-CoV-2, immunomodulatory, NLR, LMR, inflammation

Coronavirus disease 2019 (COVID-19) is a highly infectious disease known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This highly transmissible virus has caused a global pandemic and continues to surge across several countries worldwide.

The death toll due to this viral disease has crossed the 4 million mark globally, and the daily cases continue to spike in different parts of the world.[1] The total COVID-19 case count, as of July 12, 2021, stood at over 187 million.[2]

The novel coronavirus attacks the human body by attaching its spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptors present on the surface of many human cells, including the lungs. This enables the virus to enter the cells.[3] While the virus uses the ACE2 receptor for cell entry, the cellular serine protease TMPRSS2 is required for spike protein priming.[4]

Accumulating evidence points to a considerable increase in inflammatory cytokines in patients with COVID-19. SARS-CoV-2 can induce a cytokine storm in some patients with COVID-19. A cytokine storm is a result of an imbalance between proinflammatory and anti-inflammatory mechanisms and the interaction of numerous cells and cytokines, giving way to immune regulation disorder. It is characterized by increased systemic inflammation.[5]

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Fever and cough are the most common symptoms among adults infected by SARS-CoV-2.[6] The spectrum of COVID-19 ranges from asymptomatic to clinical illness marked by acute respiratory failure requiring mechanical ventilation, septic shock and multiple organ failure. A large number of symptomatic patients present with fever, cough and shortness of breath and sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias and diarrhea are some of the less common presentations.[7]

A strong immune system is probably the best defense against coronavirus infection. Having an immuno-compromised state or a weakened immune system can increase an individual's odds of getting severely ill from COVID-19.[8] Some of the immunocompromised people have a risk of prolonged viral replication and poor clinical outcomes.[9]

Therefore, boosting the immune system offers a critical strategy to combat the coronavirus infection. Natural products have long been used in traditional medicine to treat a range of diseases, including viral infections. Herbal preparations strengthen the body's immune system, which may help in the fight against invading infectious viruses.

Natural preparations may have immense potential in prevention and therapeutic management of COVID-19.

Viranorm is a novel Ayurvedic immunomodulator and has been approved by AYUSH. It has been specifically formulated with Ayurvedic herbs that strengthen immunity, possess antiviral activities and play an important role in modulating the cytokine levels associated with viral infections.

The rationale behind this randomized controlled trial was to assess the effect of Viranorm, an Ayurvedic proprietary medicine, on development of symptoms in asymptomatic patients or duration of symptoms in mild COVID-19 patients and time of virus shedding as an important tool to reduce the risk of further community transmissions. This data was intended to provide information for practice of larger community-based clinical studies on clinical efficacy of Viranorm in the treatment and post- and pre-exposure prophylaxis of COVID-19 and as a tool for reduction of community transmission.

OBJECTIVES

Primary objective: To compare efficacy and safety of Viranorm in addition to standard of care, with standard care alone, in the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection.

Secondary objective: To compare the immunological response of Viranorm and standard of care with standard care alone in asymptomatic or mildly symptomatic COVID-19 infection.

Study Endpoints

Primary endpoints:

- Difference in disease manifestation in asymptomatic patients
- Difference in time to resolution of clinical signs and symptoms of mild COVID-19 treated with Viranorm and standard of care or standard care alone
- Proportion of patients with negative COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test at Day 14 in per protocol population
- Difference between Viranorm-treated patients on an ordinal outcome scale until Day 21 (death, admission to intensive care, hospitalization, duration of hospitalization, continuing disease, recovered).

Secondary endpoint:

- COVID-19 antibodies and clinical immunological markers.

METHODS

Study Design

This was a prospective, interventional, randomized, open label, study designed to compare the efficacy and safety of oral Viranorm and standard of care, with standard care alone, for the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection.

Patients diagnosed with asymptomatic or mildly symptomatic COVID-19 were eligible for inclusion in the study. A total of 250 patients were planned for enrollment in this study at multiple study centers after obtaining voluntary written consent. In all, 251 participants were actually enrolled. Efficacy and safety were analyzed in all the enrolled subjects.

The study treatments were administered as 1 capsule orally every 6 hours for 21 days from visit 1 onwards. After administration of study treatment, on visit 1, follow-up was done on Days 3, 7, 14 and 21. The study observation period ended on 29 days from enrollment. The patient's symptoms were analyzed throughout the study period. The viral load was measured at baseline and at Day 7 and Day 14. A telephonic follow-up was also conducted every day with the patients undergoing home isolation and treatment. The total duration of a patient's participation was approximately

30 days and the total duration of the study was approximately 6 months.

Of the 251 randomized subjects, a total of 123 received Viranorm + standard of care and 128 received standard of care. All subjects (100%) completed the study and there were no study discontinuations. The disposition of study participants is described in Figure 1. The composition of Viranorm is summarized in Table 1. The herbal immunomodulator includes *Cissus quadrangularis*, *Allium sativum*, *Zingiber officinale*, *Tinospora cordifolia*, *Withania somnifera* and *Andrographis paniculata*.

C. quadrangularis possesses antiviral activity and anti-inflammatory potential.[10]

A. sativum has anti-inflammatory, antioxidant and antiviral properties.[11]

Z. officinale stimulates mucosal cells to secrete interferons that boost immunity. It has antiviral and anti-inflammatory effects.[12]

T. cordifolia exhibits antiviral and anti-inflammatory properties.[13]

W. somnifera has antiviral effects and immune boosting potential.[14]

A. paniculata has potential anti-inflammatory and antiviral action.[15]

Inclusion Criteria

- Subjects ≥18 years and ≤70 years at the time of signing the informed consent.
- Able to understand and voluntarily sign an informed consent document prior to any study related assessments/procedures.

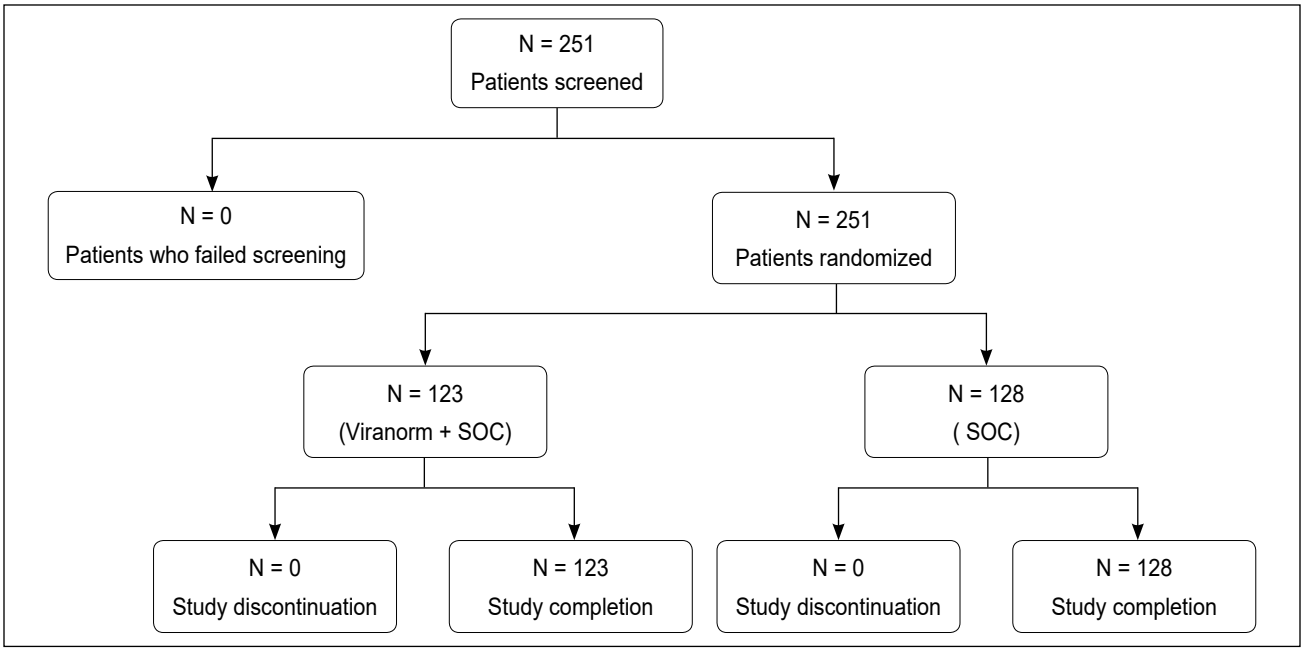

Figure 1. Disposition of study participants.

SOC = Standard of care.

Table 1. Composition of Study Drug

Ingredient	Common name
Cissus quadrangularis	Asthisamharaka, Hadjod, Pirandai
Allium sativum Linn	Garlic, Lahasu, Lasuna
Zingiber officinale	Ginder, Adrak
Tinospora cordifolia	Guduchi, Giloy, Gulvel
Withania somnifera	Asvagandha, Asgandha, Ashvagandha
Andrographis paniculata	Chirota, Neemba

- Able to adhere to the study visit schedule and other protocol requirements.
- Asymptomatic or mildly symptomatic, PCR positive for COVID-19 infection (with or without comorbid conditions) with outpatient/inpatient management as decided by the treating physician.
- With early warning score for COVID-19–infected patients <5.
- Females of childbearing potential were required to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 21 days before starting study drug, while participating in the study (including dose interruptions), and for at least 21 days after study treatment discontinuation and agreed to perform regular pregnancy testing during this timeframe.
- Members of the same household could participate in the study as long as they met study inclusion and exclusion criteria.

Exclusion Criteria

- Requirement for oxygen administration.
- Shortness of breath in resting position.
- Creatinine >2.0 mg/dL.
- Concomitant bacterial respiratory infection documented by respiratory culture (Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who were positive for SARS-CoV-2, were allowed in the study).
- Women during pregnancy and lactation.
- Participation in other clinical trials or observation period of competing trials.
- Use of adrenocorticosteroids (except topical or inhaled preparations or oral preparations ≤10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers).
- Serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months and/or moderate or severe hepatic insufficiency).
- Physician decision that involvement in the study is not in the patient's best interest.
- History of alcohol or drug abuse in the previous 2 years.

Statistical Methods

In general, continuous variables were summarized by using summary statistics (number of observations, mean and standard deviation, median, minimum and maximum). Categorical values were presented using frequencies and percentages. Safety analysis set, modified intention-to-treat analysis set (mITT), per-protocol analysis set (PP) were used for analysis purpose.

Time of onset of change in the patient's clinical condition was estimated by using Kaplan-Meier method. The 95% confidence intervals of the median time for each treatment were presented along with 95% confidence intervals. Log rank test was used to compare the two treatments in terms of time of onset of change in the patient's clinical condition.

Proportion of patients with negative COVID-19 PCR test at Day 14 was presented for each treatment with 95% confidence intervals. Treatment difference for proportion of patients with negative COVID-19 PCR test at Day 14 was also be presented with 95% confidence intervals.

The ordinal outcome scale values were summarized descriptively for both the treatments arms. Proportion of all-cause mortality was presented for each treatment with 95% confidence intervals. Treatment difference for proportion for all-cause mortality was presented with 95% confidence intervals.

The study was conducted according to the protocol and in compliance with the regulatory requirements in India (The New Drugs and Clinical Trials Rules, 2019, Ministry of Health and Family Welfare, Government of India; and ethical guidelines for biomedical research on human participants, Indian Council of Medical Research [ICMR] 2017), and applicable international guidelines (ICH-GCP and the Declaration of Helsinki 2013).

RESULTS

Demographic Characteristics

The overall mean age of the subjects was 46.58 years (age range, 18-70 years). The mean age was 48.35 years in Arm A (Viranorm + SOC) and 44.88 years in Arm B (SOC). A total of 84 subjects enrolled in the study were <40 years of age, total of 102 subjects were between the age of 40 and 60 years and total of 65 subjects were >60 years.

The proportion of male subjects (57.8%) was slightly higher than female subjects (42.2%), with a comparable

distribution observed across both the study arms. Majority of subjects (87.6%) had no diabetes or hypertension (87.3%) when enrolled in the study.

Overall, the majority of subjects did not receive any concomitant medication, a small portion of study participants (<4%) received at least 1 concomitant medication during the study, and the frequency was comparable across treatment groups.

Efficacy

Time to resolution of clinical signs and symptoms

The mean time for resolution of cough, fever and shortness of breath was about 14 days in both treatment groups. The patients treated with Viranorm + SOC had a lesser time to resolution of cough than the patients with standard of care alone. The p value on log rank test to compare the overall time to cough resolution showed statistical significance ($p < 0.0001$). No significant difference between the treatment groups was observed in time to resolution of other symptoms of fever and shortness of breath ($p = 0.3229$ and 0.1703, respectively).

The time for resolution of clinical signs and symptoms is presented in Table 2.

Incidence of negative RT-PCR test

All the subjects were RT-PCR positive at the time of enrollment. On Day 7 (3rd visit), 2.4% in Arm A and 3.9% in Arm B had positive RT-PCR. At 4th visit, 0.8% in both the arms had RT-PCR positive results. The RT-PCR results were not available for most of the patients. No definite conclusions can be drawn on the effect of Viranorm add-on treatment on the incidence of RT-PCR negative subjects.

Ordinal outcome scale until Day 21

All the subjects enrolled in the study were hospitalized during the study duration; none of them was admitted to intensive care unit (ICU). At the end of the study period on Day 21, all the subjects recovered and no deaths occurred during the study duration.

Evaluation of biomarkers

The neutrophil-to-lymphocyte ratio (NLR) was evaluated at screening and at Day 14. At baseline, the mean NLR across treatment arms was 5.36 and 6.00 in Viranorm + SOC and SOC groups, respectively. At Day 14, there was decrease in NLR values in both treatment groups. The magnitude of decrease in NLR was substantially higher in the group that received Viranorm as an add-on treatment (8% median decrease) compared to the group that received only standard of care (2.6% median decrease). The change in NLR assessed by excluding outliers showed a significant decrease in the group with Viranorm add-on treatment compared to the group that received standard of care (Table 3; $p = 0.0488$). Similar trend in NLR decrease was observed when the assessment was carried out stratified by age (<40 years of age, 40-60 years >60 years) and diabetes status.

The platelet-to-lymphocyte ratio (PLR) was evaluated at screening and at Day 14. At baseline, the mean PLR was 165.83 and 211.83 in Viranorm + SOC and SOC groups, respectively. At Day 14, there was decrease in PLR values in both treatment groups, though the difference between the groups was not statistically significant. There were no significant differences in the PLR change between Viranorm add-on group and SOC group across the age groups.

Table 2. Time to Resolution of Clinical Signs and Symptoms (mITT Population)

Characteristics	Viranorm + SOC (n = 123)	SOC (n = 128)
Cough		
N	103	109
Mean	14.08	14.26
SD	1.41	1.33
Median	14.00	14.00
Fever		
N	76	77
Mean	14.12	14.00
SD	1.63	0.16
Median	14.00	14.00
Shortness of breath		
N	63	57
Mean	14.27	14.47
SD	1.99	1.81
Median	14.00	14.00

Table 3. Percentage Change in NLR without Outliers

Parameter	Statistics	Viranorm + SOC	SOC
Change from baseline to Day 14	N	99	120
	Mean	-12.66	-3.12
	SD	62.59	68.87
	Median	-23.53	-5.46
P value		0.0488	

The lymphocyte-to-monocyte ratio (LMR) was evaluated at screening and at Day 14. There was no statistically significant difference in LMR values in the two study groups at follow-up.

C-reactive protein (CRP) was evaluated at screening, Day 7 and Day 14. At baseline, the mean CRP across treatment groups was comparable with mean values of 37.37 mg/dL and 36.49 mg/dL in Viranorm + SOC and Viranorm groups. At Day 7 and Day 14, there were decreases in CRP in both groups. Between the treatment groups, the differences were not statistically significant ($p = 0.0677$ and 0.1121, at Day 7 and 14, respectively). Similar trends were observed when CRP was assessed stratified by age, diabetes status and hypertension status.

COVID-19 antibodies (IgM and IgG)

The proportion of patients developing the antibodies was similar across the treatment groups.

Laboratory evaluation

Blood testing was performed for all the subjects enrolled in the study during screening and at visit 4. There was increase in mean absolute lymphocyte count at the follow-up visit for both the arms, as compared to screening test.

Safety Evaluation

There were no adverse events reported across the treatment groups in the study. There were no deaths during the study. No serious adverse events occurred during the study. Additionally, there were no discontinuations due to adverse events.

Treatment with the herbal immunomodulator as an add-on treatment to standard of care in asymptomatic or mildly symptomatic COVID-19 patients was safe and well-tolerated.

DISCUSSION AND CONCLUSION

The purpose of this study was to evaluate the role of herbal immunomodulator Viranorm as add-on treatment in asymptomatic or mildly symptomatic COVID-19 confirmed cases.

Patients treated with Viranorm + standard of care showed significantly lesser time to resolution of cough, compared to patients treated with standard of care alone ($p < 0.0001$ based on log rank test). Cough is one of the most commonly reported symptoms in COVID-19. A systematic review and meta-analysis including 148 studies from 9 countries, involving 24,410 adults with confirmed COVID-19, noted that cough was among the most prevalent symptoms in the patients. It was noted in 57% of the cases.[6] A study conducted by researchers at the Leipzig University Hospital also noted cough as the second most frequently reported symptom (67%) in COVID-19 outpatients.[16] Add-on treatment with Viranorm resulted in quicker resolution of cough in COVID-19 patients, thereby decreasing the discomfort in these patients.

Increasing amount of evidence supports the role of inflammation in the progression of viral pneumonia, including in COVID-19. Severe inflammatory responses add to the weakening of adaptive immune response, thus leading to immune response imbalance. Biomarkers known to represent inflammation and immune status have been shown to predict the prognosis of COVID-19 patients. Peripheral white blood cell (WBC) count, NLR, PLR and LMR have potential role in predicting the prognosis of patients with viral pneumonia. Yang and colleagues noted in their study that NLR could be an independent biomarker for indicating poor clinical outcomes in COVID-19 patients. Elevated NLR has been tied to illness severity.[17]

In this study, after 14 days of treatment, patients receiving Viranorm as an add-on treatment had higher reduction in NLR compared to the group that received standard of care alone. Similar results were shown when assessed across age groups, including the vulnerable age group of >60 years. Viranorm add-on treatment also showed greater decreases in NLR in patients with diabetes.

Although statistical significance of Viranorm add-on treatment associated with NLR and LMR could not be shown with the ITT population, the ad-hoc analysis conducted excluding the outliers showed a statistically significant decrease in NLR in Viranorm add-on treatment group ($p = 0.0488$). Further large-scale studies designed to detect and quantify the changes in NLR and LMR with Viranorm add-on treatment are required.

No adverse events or deaths occurred during the entire study duration. And the add-on treatment with Viranorm in asymptomatic or mildly symptomatic COVID-19 patients was safe and well-tolerated.

Overall, the add-on treatment with the herbal immunomodulator Viranorm for COVID-19 was safe and effective in reducing the duration of cough and is indicative of a significant decrease in systemic inflammation as shown by NLR.

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