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Title:

Management of mild to moderate COVID-19 patients supplemented with "Vedicinals-9" as an adjuvant phyto-nutraceutical to prevent disease progression and improve clinical conditions: a randomized, multi-centered, exploratory study.

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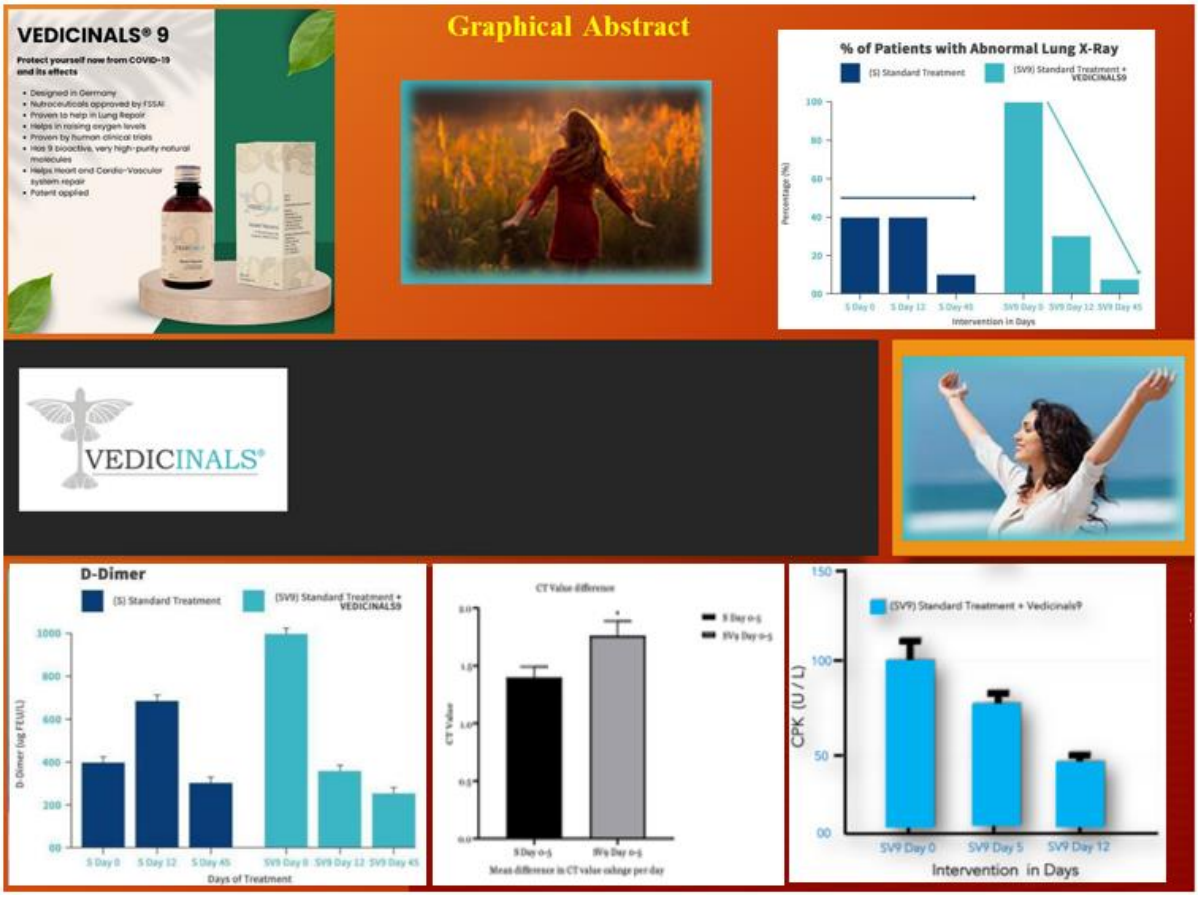

Management of mild to moderate COVID-19 patients with "Vedicinals-9"

Abstract

Background

Currently, with only the known preventive options for COVID-19 including the use of vaccines, there is an urgent need and demand for efficient therapeutic strategies for COVID-19 patients. We aimed this randomized, open-label, parallel efficacy trial to assess the efficacy and safety of Vedicinals-9 (VD9), as an add-on therapy to standard care in mild to moderate COVID-19 patients.

Methods

The study enrolled 124 COVID-19-positive patients 18 to 60 years of age presenting with no symptoms or mild to moderate symptoms. Patients were randomly assigned 1:1 to VD9 in addition to standard care or standard care alone. The treatment was given daily for 14 days and patients were followed-up after 30 days. The dual primary efficacy outcomes assessed were the percentage of patients getting COVID-19 RT-PCR negative along with the time taken to get the same and the change in the altered levels of biomarkers from baseline. The secondary efficacy outcomes included recovery time of fever, delay in progression from asymptomatic to mild to moderate to severe to critical, time to symptom relief, number of days of hospitalization, incidence of respiratory failure, and percent mortality. Safety outcomes included serious adverse events, adverse events, complete blood count, lipid profile, liver and renal function tests, Fasting Blood Sugar, PT, INR, X-Ray, and Urinalysis.

Results

The study revealed that the percentage of COVID-19-positive patients turning negative in 0-4, 5-11, and 12-14 days with 29.03%, 48.39%, and 22.58% respectively in the VD9 adjuvant group that were significant ($p<0.05$) compared to the standard care treatment group with 1.61%, 37.10% and 61.29% respectively. The mean number of COVID-19 patients at risk (staying positive) from day 0 to 14 is significantly low (7.62 ± 0.45, $p<0.01$) in Vedicinals-9 (VD9) adjuvant group compared to the standard treatment group (9.71 ± 0.45).-Assessment of inflammatory biomarkers showed an exponential significant decrease of CRP levels in the VD9 adjuvant group at day 5, day 12, and day 45 ($p<0.001$) compared to baseline and standard treatment alone showed a significant decrease at day 5 ($p<0.01$), day 12 ($p<0.001$) and day 45 ($p<0.001$). IL-6 levels showed a significant reduction at all time-points of day 5, day 12 ($p<0.05$), and day 45 ($p<0.01$) whereas standard treatment showed a significant decrease only at day 45 ($p<0.01$). Both the groups showed statistically significant improvement in excess ferritin levels at day 12 and day 45 ($p<0.001$). VD9 adjuvant group displayed a significant

increase in total COVID-19 antibody levels at all time-points compared to baseline at day 5 ($p<0.05$), day 12 ($p<0.05$), and day 45 ($p<0.01$) while standard treatment showed a significant increase only at day 45 ($p<0.01$). D-dimer levels significantly decreased at day 45 ($p<0.001$) compared to baseline whereas there were no significant changes in the other group. Significant within-group reduction in CPK levels was seen only at day 12 ($p<0.01$) in VD9 adjuvant group. The results of lymphocyte subset count revealed a significant increase in CD4+ and CD8+ T cells at all time-points in both the groups and CD19+ B cells and CD16+ 56+ NK cells did not show any statistically significant changes in any group. The time to recover from the symptoms was shorter though not significant in the VD9 adjuvant group compared to the standard care group including fever, cough, fatigue, myalgia, and hypoxia. The recovery duration of sore throat ($p<0.01$) and prolonged sore throat ($p<0.05$) from treatment initiation was significantly lower compared to the standard treatment alone. 58% of patients in the VD9 adjuvant group were discharged from the hospital in the first 4 to 7 days of testing positive compared to the 37 % in the standard care treatment group. The x-ray findings before the start of the treatment in the VD9 adjuvant group and standard care group revealed abnormal results in 90.32% and 37.10% of cases, respectively. After 12 days of treatment, only 22.95% of cases were left with abnormal findings in the vedicinals-9 adjuvant group compared to the standard group alone which showed no change from baseline. There were no AE or SAE in the study and no safety concerns were observed in any of the patients.

Conclusion

This study establishes that VD9 a phyto nutraceutical containing 9 bioactive phyto constituents acts synergistically by reducing viral load with early negative RT-PCR results, strengthening the natural defenses to COVID-19, attenuating COVID-19 secondary complications by improving the altered levels of biomarkers and improving the recovery duration with early hospital discharge. This indicates a possible positive effect for VD9 as an add-on therapy for the management of COVID-19 in mild to moderate COVID-19 patients.

This clinical study has been registered with the clinical trial registry of India in ctri.nic.in (CTRI/2020/10/028364).

Keywords: COVID-19; SARS-CoV-2; clinical study.

Introduction

The newly described coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a variety of emerging clinical manifestations resulting in disease progression. Apart from causing respiratory tract infections, resulting in pneumonia and acute respiratory distress syndrome (ARDS), SARS-CoV-2 has also shown to disrupt the functions of multiple organ systems such as thromboembolic complications, cardiac injury and arrhythmia, acute coronary syndromes, acute renal injury, gastrointestinal symptoms, liver cell damage, hyperglycemia and ketosis, neurologic deficits, ocular and dermatologic complications that results in even patient death [1,2]. This disease progression may be explained by the five major pathophysiological mechanisms, (a) direct virus-induced cell damage in organs expressing angiotensin-conversing enzyme 2 (ACE2); (b) dysregulation of the renin–angiotensin–aldosterone system (RAAS) resulting from the downregulation of ACE2 due to the binding of ACE2 to receptor binding domain (RBD) of SARS-CoV-2 which prevents the cleavage of angiotensin I and angiotensin II; (c) dysregulation of the immune response caused by the expression of various proinflammatory cytokines and chemokines resulting in the cytokine storm; (d) direct endothelial cell injury and apoptosis by the virus and consequent activation of the coagulation cascade leading to the thrombo-inflammation; and (e) tissue damage and fibrosis [2-4]. It has been observed that the affinity of binding of ACE2 to the receptor binding domain (RBD) of SARS-CoV-2 is much higher which increases the risk of transmission of the virus [5,6]. The long-term health implications for those who have survived the disease are far more alarming. Many symptoms have been reported to persist after several weeks and months of the onset of COVID-19, irrespective of the disease severity. These include fatigue, anosmia, joint pain, shortness of breath, impaired function of lungs, abnormal CT findings including pulmonary fibrosis and thereby decline in the quality of life [7,8].

The recently developed and available vaccines are of utmost importance as preventive care for COVID-19, however, there is no specific treatment for COVID-19 patients to block SARS-CoV-2 infection or kill the virus. This led to the use of a combination of therapies to be administered at different stages of infection to benefit COVID-19 patients. The current treatment strategies for COVID-19 include the use of repurposed drugs, such as remdesivir, hydroxychloroquine, corticosteroids, and anticoagulants along with supportive care including oxygen supply, immunotherapy, convalescent plasma therapy, and organ support [9]. Although remdesivir has been shown to improve recovery time in COVID-19 patients [10], other studies suggest that any benefit is not clinically significant [11,12]. Hydroxychloroquine has shown very limited potential in the treatment of COVID-19. The drug was associated with a higher mortality of 27% compared to 25% in the control, as well as longer hospitalization [13] whereas in the other study, patients receiving higher dosages had a mortality rate of 39% compared to 15% receiving low dosages along with no indication of viral clearance [14]. Studies have also shown hydroxychloroquine to have caused adverse effects related to the cardiovascular and gastrointestinal systems [55,56]. Convalescent plasma therapy can help stop SARS-CoV2 shedding and extend survival in patients with severe COVID-19 [15]. However, there is limited effect on the clinical outcomes of patients [16,17]. The other broad-spectrum anti-virals Lopinavir–ritonavir failed to show any clinical improvement in COVID-19 patients [18,19]. The antibiotics like azithromycin and doxycycline are commonly used for the treatment of COVID-19. Although, both antibiotics are primarily used for bacterial infections but have demonstrated activity against viral infections as well [20]. Corticosteroids such as methylprednisolone and dexamethasone have shown promising results in COVID-19 patients but the use of corticosteroid therapy is associated with a wide range of side-effects [21].

Many pharmaceutical companies have introduced vaccines with an objective to develop immunity to COVID-19 and prevent the disease. [22, 23, 24 25, 26, 27, 28], Some of the SARS-

CoV-2 variants are associated with rapid propagation, enhanced transmissibility, serious clinical conditions, and reduced efficacy of therapeutic medications and vaccines against the variant [29]. With this continuous flow of information and knowledge about the rapidly evolving and mutating SARS-CoV-2, the efficacy of the current options of treatment and vaccine against the new strains of the virus remains unclear [30]. Other limitations to vaccines include insufficient immune response, limited knowledge of side effects, failure of long-lasting immunity, and fear and hesitation towards vaccination [4].

Plant-derived products and their secondary metabolites along with a notable number of traditional medicines, bioactive phytochemicals, traditional Chinese medicines, nutraceuticals, Ayurvedic preparations, and other plant-based products are being explored as possible therapeutics against COVID-19 [31]. Plants have made tremendous contributions in the past to treat or manage many kinds of serious ailments including infectious diseases which give us evidence that medicinal plants have varying potential to exert anti-COVID-19 efficacy through several mechanisms of action [32-35]. Plants contain a variety of secondary metabolites like alkaloids, flavonoids, tannins, polyphenols, lignins, coumarins, terpenoids, etc some of which has reported to exhibit inhibitory actions against viruses and alleviate viral infections by interrupting the viral protein and enzymatic activities by binding with them, preventing the viral entry and replication in the host cells [36]. Moreover, many findings of plant-based products have provided evidence of strengthening the immune response thus providing promising potential against several viruses [37,38].

The multi-faceted nature of the pathophysiology of COVID-19, with its various stages of disease development and progression, limitations of the current treatment and vaccines, and promising evidence of plant-based components, provides a basis for the need for an effective treatment specific to COVID-19 that should also take care of rapid mutations of the virus along with enhancing the immune system. This led us to the development of a broad spectrum, highly

effective, and synergistic nutraceutical composition, Vedicinals-9 (VD9) containing nine standardized phyto components which suggest working effectively and selectively, even on the moving targets like constantly mutating SARS-COV-2. The nine phyto components present in VD9 are (1) Baicalin; (2) Quercetin; (3) Luteolein; (4) Rutin; (5) Hesperidin; (6) Curcumin; (7) Epigallocatechin gallate (EGCG); (8) Piperine; and (9) Glycyrrhizin (Fig. 1).

The search for active biomolecules started with analyzing all documented replication and virus-cell fusion mechanisms. The genetic sequences obtained from the novel coronavirus were compared with previous SARS viruses, conserved regions were identified, and based on previous studies, the kind molecules were narrowed down that was proven to show efficacy in protease inhibition. 3CL protease inhibition was one key drug target pathway. COVID-19 being a multi-systemic condition, the next step was to define a filtering matrix of more than 70 desired drug target pathways. Using a customized program, a selection process was initiated for the most promising candidates out of over 4000 known and documented phytochemicals. The main reasons for targeting phyto chemicals were their well-documented safety profiles and the possibility to create a therapeutic effect that is in compliance with Food for special medical purposes (FSMP) regulation. The dual approach of meta-analysis and computational analysis lead to the final selection of synergistic and well-documented molecules with a high safety profile and the documented potential of covering the desired mechanisms in 4 main areas: 1. Virus protease inhibitors; 2. Host cell receptor blockage, cleavage enzyme down regulation, intracellular replication inhibition; 3. Management of COVID-19 conditions as described; 4. Prevention of development of Long-Covid conditions and retro-viral, as well as bacterial co-infections. The importance of findings from four degrees of evaluation methods was prioritized and subsequently weighed from documented human clinical trials, documented in-vivo animal studies, in-vitro experiments, and computational in-silico analysis with clinical trials marked as highest and in-silico marked as least rating score. If drug target pathways were confirmed

by more than one method the evidence was even rated higher than single outcomes. Findings of synergistic effects between compounds were taken into account.

The promising results of the in-silico analysis and in-vitro/in-vivo studies were encouraging and contributed to our hypothesis that VD9-a multiple molecular-based therapeutic nutraceutical suspension can effectively halt the virus replication through a variety of targets involving structural proteins of SARS-CoV-2 and interacting with host receptors and enzymes. Furthermore, nine selected molecules suggest working synergistically to strengthen the natural defenses and address the host response to clinical manifestations and prevent post-COVID-19 complications.

Hence, to test the hypotheses in evaluating the effectiveness as well as the safety profile of VD9 in human subjects, the current study was designed and orchestrated to assess the therapeutic potential and effect of VD9 at 5000 mg in 50 ml suspension per day, dosed thrice daily in adjunct to standard treatment compared to standard treatment alone for the clinical management of COVID-19 infected patients. The primary objective of the study was to determine the efficacy of VD9 on disease progression by evaluating the time and proportion of patients in getting RT-PCR COVID-19 negative results and altered biomarkers to assess the post-COVID-19 complications.

Materials and Methods

Vedicinals-9 formulation

Vedicinals-9 used in the study was manufactured in a GMP-certified facility and supplied by Vedicinals India Pvt. Ltd. from batch numbers S-SCL-20001, S-SCL-20002, and S-SCL-20003. VD9 is a phyto nutraceutical that contains nine standardized bio-active phyto compounds with specification of compounds not less than 90% - (1) Baicalin; (2) Quercetin;

(3) Luteolein; (4) Rutin; (5) Hesperidin; (6) Curcumin; (7) EGCG; (8) Piperine; and (9) Glycyrrhizin. VD9 is licensed for use by the Food Safety and Standards Authority of India.

Study Design

This randomized, open-label, parallel efficacy, active control, multi-center exploratory trial evaluated 5-day and 12-day courses of the investigational add-on adjuvant nutraceutical "Vedicinals-9" plus standard of care, versus standard of care alone with a 45-day follow-up observational protocol in mild to moderate COVID-19 patients (Fig. 2).

The study was conducted following the ICH-GCP, declaration of Helsinki. The patients were recruited at Aakash Healthcare Super Speciality Hospital, New Delhi, India, and Chirayu Medical College and Hospital, Bhopal, Madhya Pradesh, India. Ethical approval was granted by the Institutional Ethics Committee of Aakash Healthcare Super Speciality Hospital in Delhi and the Vision Independent Ethics Committee at Bhopal before the initiation of any study-related activities involving human subjects. The trial was registered with CTRI (CTRI/2020/10/028364). All necessary patient/participant consent was obtained before all study procedures.

Study Population

The study population consisted of adult and elderly patients 18 years of age or older, with confirmed SARS-COV2 Virus (Covid-19), RT-PCR tested positive report and presenting with no symptoms or mild to moderate symptoms. All patients who met the screening criteria and gave their informed consent to participate were included consecutively. Inclusion criteria: patients of either sex aged 18 to 60 years of age; patients who have tested positive to be infected

with SARS-CoV-2 and presenting with no symptoms or mild to moderate symptoms; patients who gave written informed consent to participate in the study.

Exclusion criteria included: Patients with symptoms classified as severe or critical; patients with uncontrolled, unstable co-morbidities as evaluated by the investigators; patients with pre-existing respiratory conditions, severe primary respiratory disease, or pneumonia; Immuno-compromised patients or those on immunosuppressant; Patients on or requiring parenteral nutrition/care; Pregnant/lactating women; COVID-19 positive patients participating in the interventional arm of other COVID-19 clinical trial; patients with serious complications of diseases such as cancer, heart disease, infraction, stroke, arterial fibrillation, cardiac arrhythmia, disabilities, neurodegenerative disease; patients with alcohol and/or substance dependence; patients with known allergic reactions to any other herbal supplements.

Study Interventions

The patients were randomly assigned into the following two groups; the Standard care group (n=62) and the adjuvant treatment (VD9) group add on to standard treatment (n=62). Patients consumed either standard treatment alone as per the current medication practices (*CLINICAL MANAGEMENT PROTOCOL: COVID-19, Government of India, Ministry of Health and Family Welfare, Directorate General of Health Services, EMR Division, Version 4, 27.06.20*) or in combination with Vedicinals-9 for 14 consecutive days at a dose of 5000 mg in 50ml per day TID daily. The patients in adjuvant treatment received a loading dose of VD9 on day 1 of 25 ml each at 1 hour before breakfast, lunch, and dinner. On subsequent days, the patients received the maintenance dose of 20 ml, 15 ml, and 15 ml at 1 hour before breakfast, lunch, and dinner respectively.

Vedicinals-9 used in the study was manufactured in a GMP-certified facility (Tirupati Lifesciences Pvt. Ltd.) and supplied by Vedicinals India Pvt. Ltd. from batch number S-SCL-

20001, S-SCL-20002, and S-SCL-20003. VD9 is a phyto nutraceutical that contains nine standardized bio-active phyto compounds with specification of compounds not less than 90% - (1) Baicalin; (2) Quercetin; (3) Luteolein; (4) Rutin; (5) Hesperidin; (6) Curcumin; (7) EGCG; (8) Piperine; and (9) Glycyrrhizin. VD9 has been licensed for use by the Food Safety and Standards Authority of India.

Study Procedures

The baseline demographic and patient characteristics were recorded including age, sex, physiological parameters at presentation, and comorbidities were also recorded. Vital signs including temperature, blood pressure, SpO2, pulse, and respiratory rate along with a physical systemic examination were conducted throughout the study. The patients were treated with either standard medication alone or in combination with VD9 at a dose of 5000 mg in 50ml per day TID daily orally for 14 days. After day 14 of the study intervention period and the last dose of VD9, patients were followed-up for an additional observational period of 30 days.

Laboratory assessments included a COVID-19 RT-PCR test that was performed after the initial positive test in all patients on or before 5±2 days and 12±2 days based on clinical remission of symptoms as assessed by the investigator. Other evaluations included biomarkers performed at baseline, day 5, day 12, and day 45 such as Inflammatory biomarkers: C-reactive protein (CRP), Interleukin-6 (IL-6), and Ferritin; Immunological biomarkers: Total COVID-19 Antibody (IgG and IgM); Prognostic marker: D-dimer; cardiac injury marker: Troponin-I and Creatine Phosphokinase (CPK); Lymphocyte subset counts: CD4+ T Cell, CD8+ T Cell, CD19+ B Cell, and CD16+/CD56+ NK Cell. Additional safety parameters evaluated at baseline, day 12, and day 45 were hematological: Complete Blood Count (CBC), Prothrombin Time (PT), and International Normalized Ratio (INR); biochemical: Liver Function Tests (LFT), Renal Function Tests (RFT), Lipid profile and Fasting Blood Sugar (FBS) and

urinalysis. Radiological examination (chest X-ray) was also performed at baseline, days 12 and 45.

Study Outcomes

The trial had dual primary efficacy outcomes, the one being the percentage of patients getting COVID-19 RT-PCR negative and the time taken to get the same. Time in terms of the number of days from treatment initiation was divided into three categories – 0-4 days, 5-11 days, and 12-14 days. The other primary outcome was the change from baseline (CFB) to day 5, 12, and 45 in biomarkers like CRP, Total Antibody, IL-6 and change from baseline (CFB) to day 12 and 45 in Ferritin, D-dimer, Troponin 1, CD4+ T cell, CD8+ T cell, CD19+ B cell, CD16+ CD56+ NK cell. CFB in biomarkers is defined as the improvement in altered biomarkers post-COVID-19 infection.

The secondary outcomes included: Time to allay a fever; arrest or delay in progression in asymptomatic to mild or moderate to severe to critical; time to symptom relief. The composite time points were the number of days required for recovery or improvement from the day of admission, the day of first testing positive, and the day of first noticed symptoms. The recovery time was categorized into less than 7 days and more than 7 days. The symptoms observed in the study were fever, cough, fatigue, myalgia, sore throat, hypoxia, and nasal congestion. Additional secondary outcomes included the number of days of hospitalization; incidence of respiratory failure and requirement of rescue medication; and percent mortality.

The safety outcomes consisted of vital signs (blood pressure, SpO2, pulse, and respiratory rate) and physical examinations that were recorded throughout the study. Other safety assessments included radiological (X-Ray) examination, hematological and biochemical

parameters like CBC, LFT, RFT, lipid profile, FBS, and urinalysis evaluated at baseline, day 12, and day 45. PT and INR were evaluated at baseline, day 5, day 12, and day 45. Treatment-related serious adverse events and adverse events along with their severity and relationship to the study drug were observed throughout the study duration.

Sample Size and Randomization

Based on assuming recovery (turning negative) of COVID-19 in 40% of patients in the Standard treatment group as compared to 20% in the VD9 adjuvant group with 95% Confidence Level ($\alpha = 0.05$), 80% power and expecting a dropout rate of 10%, the number of patients to be enrolled in the study was calculated as approximately 62 in each group. Therefore, the total sample size was 124 COVID-19-positive patients.

The patients were randomly assigned to the standard treatment or the VD9 adjunct to the standard treatment group in a 1:1 ratio according to a random allocation table using a random number generator in a statistics program. Depending on their allocated group, the patients received either of the treatment. This was an open-label study so all the patients and study personnel were known of the treatment allocated.

Data analysis and statistical tests

The analyses included all patients who signed an Informed Consent Form (ICF) and who were randomized to treatment. Safety analyses were performed on patients who were exposed to at least one dose of any study therapy and analyzed according to the treatment received. The primary and secondary efficacy analysis included all randomized patients with efficacy measurement at baseline who had at least one on-treatment assessment (FAS-Full Analysis Set). Efficacy analysis was also conducted as Per the protocol analysis set (PPS) in which a subset of all patients in the FAS were included and all data which met any of the critical

deviation criteria identified in the SAP were excluded. In addition, individual patient visits and data points that did not satisfy protocol criteria were excluded from the PPS. The statistical analysis investigated the effect of treatment measured by changes in the parameters at each time-point in comparison to baseline values in the within-group analysis.

Data was collected in pre-designed Case Report Forms (CRFs) and entered in an electronic format. Qualitative variables are described in Number (%) while quantitative variables are described in mean (SEM) or Median (IQR). For comparisons within groups of continuous variables, student's t-test for paired data or ANOVA was used, as appropriate, according to the characteristics of the study variables. The between-group comparisons of quantitative variables were made using student's t-test or ANOVA and of qualitative variables using chi-square or Fisher's exact test. The planned safety analyses consisted of descriptive summaries of the data as relevant to the scale of data, e.g., frequency and percent for adverse events, and mean changes from baseline as appropriate. The statistical significance level of 0.05 was used for all statistical tests. All calculations were performed using the SAS statistical software package, version 5.

Results

The recruitment and follow-up were done from December 11th, 2020 to April 14th, 2021. 136 patients were screened of which 124 were enrolled and randomly assigned to both treatment groups with 62 patients in each. 1 patient from VD9 adjuvant group withdrew the consent on day 12 of the study. 2 patients from each of the VD9 adjuvant group and standard care group were lost to follow-up on day 45 of the study (Fig. 3).

Patient disposition and characteristics

Baseline characteristics in terms of demographics were well-balanced between the groups. The mean age was 40.71 (SE 1.55) years (IQR 40.50; 18-60), and 35 patients (56.45%) were male in a standard care group and VD9 adjuvant group mean age was 38.82 (SE 1.35) years (IQR 39; 18-60), and 33 patients (53.22%) were male (Table 1).

Primary Efficacy Outcome

The primary efficacy outcome compared between the treatment groups for the proportion of patients showing RT-PCR negative results for COVID-19 in 0-4 days occurred in 18 (29.03%, $p<0.05$) of 62 patients in the VD9 adjuvant group which is much higher compared to the 1 (1.61%) of 62 patients in standard treatment group. The incidence of COVID-19 negative results between 5-11 days in 30 (48.39%, $p<0.05$) patients were also prominent in the VD9 adjuvant group compared to 23 patients (37.10%) in the standard care treatment group. The remaining proportions of patients in both groups turned negative in 12-14 days with 14 patients (22.58%) in VD9 adjuvant group and 38 patients (61.29%, $p<0.05$) in the standard treatment group (Table 2, Fig. 4).

The mean number of days COVID-19 patients were at risk of staying COVID-19 positive on RT-PCR test was significantly low with 7.62±0.45days ($p<0.01$) in VD9 adjuvant group compared to 9.71±0.45 days in standard treatment group. Eventually, the mean difference in increasing Ct value (reduction in viral load) of COVID-19-positive patients from day 0 to day 5 in the VD9 adjuvant group was 1.762±0.125 ($p<0.05$) which was significantly more compared to 1.399±0.092 in the standard treatment group (Table 2, Fig. 4).

Biomarkers

Assessment of inflammatory biomarkers showed that mean CRP levels in VD9 adjuvant group significantly decreased from a baseline value of 10.29±1.44 mg/L to 6.93±0.47 mg/L ($p<0.001$) at day 5, 5.04±0.32 mg/L ($p<0.001$) at day 12 and 3.33±0.18 mg/L ($p<0.001$) at day 45 as compared to the decrease in standard treatment alone from the baseline value of 12.04±0.87 to 9.23±0.49 mg/L ($p<0.01$), 5.15±0.32 mg/L ($p<0.001$) and 3.54±0.18 mg/L ($p<0.001$) at day 5, day 12 and day 45, respectively. Mean IL-6 levels decreased significantly in VD9 adjuvant group from 12.79±5.35 pg/ml at baseline to 4.01±0.36 pg/ml ($p<0.05$), 3.62±0.39 pg/ml ($p<0.05$) and 2.70±0.24 pg/ml ($p<0.01$) at day 5, 12 and 45, respectively while significant decrease in standard treatment group was only observed at day 45 with baseline value of 12.48±4.53 pg/ml to 2.98±0.68 pg/ml at day 45 ($p<0.01$) (Table 3, Fig. 5).

The significant improvement (increase) in mean total COVID-19 antibody levels occurred in VD9 adjuvant group as early as from day 5 of the treatment initiation, 2.61±0.42 g/L at baseline to 5.02±0.47 g/L ($p<0.05$), 5.97±0.46 g/L ($p<0.05$) and 13.64±1.44 g/L ($p<0.01$) at day 5, day 12 and day 45, respectively in contrast to the standard treatment group that was able to show significant increase only at day 45 from baseline value of 1.92±0.37 g/L to 11.23±1.15 g/L ($p<0.01$). The mean CPK levels showed significant improvement in decreasing the levels from a baseline value of 109.1±21.65 U/L to a day 12 value of 76.57±5.34 U/L ($p<0.01$) which then was found to increase at day 45 non-significantly, whereas standard treatment group showed non-significant decrease in levels till day 12 followed by the significant increase in levels from 78.45±5.35 U/L at baseline to 131.5±5.3 U/L ($p<0.05$) at day 45 (Table 3, Fig. 5).

Evaluation of D-dimer revealed that VD9 adjuvant treatment significantly reduced the D-dimer levels from a baseline value of 416±43.45 µg FEU/L to day 45 value of 261.5±14.15 µg FEU/L ($p<0.001$) whereas the changes in D-dimer levels at day 12 and day 45 were not found to be significant within the standard treatment group. In the patients having excess iron

at baseline, statistically significant improvement in the mean ferritin levels was observed in both the groups at day 12 and day 45 ($p<0.001$) (Table 4, Fig. 5).

The results from the analysis of lymphocyte subset counts revealed a significant increase in CD4+ and CD8+ T levels in both the groups at day 12 and day 45. The VD9 adjuvant group showed an increase in CD8+ cells from 797±65.43 at baseline to 1094±105.2 ($p<0.05$) at day 12 and 1113±103.5 cells/µL ($p<0.05$) at day 45. The increase in the standard treatment group was observed from the baseline value of 1002±68.70 cells/µL to 1329±105.5 ($p<0.05$) and 1370±117.5 cells/µL ($p<0.05$) at day 12 and day 45, respectively. The rest of the lymphocyte subset counts like CD19+ B cells and CD16+ 56+ NK cells did not show statistically significant changes before and after treatment in any group (Table 4). There were no reported changes in Troponin-I from baseline in both groups.

Secondary Efficacy Outcome

Prolonged Fever was present in the VD9 adjuvant group for 3.60±0.66 days and 4.12±0.67 days in the standard treatment group (ns) from treatment initiation while saddleback fever was observed for 11.54±0.21 days in VD9 adjuvant group compared to 11.83±0.30 days in the standard group. The duration of respective cough and prolonged cough was 4.53±0.18 days and 11.33±0.14 days in the VD9 adjuvant group and 5.25±0.47 days and 11.57±0.29 days in the standard treatment group. The duration of allaying sore throat in the VD9 adjuvant group was 7.23±0.87 ($p<0.01$) days which was significantly lesser compared to 10.40±0.58 days in the standard treatment group, while the duration of prolonged sore throat at a mean of 08.33±4.17 days ($p<0.05$) compared to 44.67±0.66 days in the standard treatment group (Table 5).

Fatigue lasted for 4.44±0.24 days in VD9 adjuvant group and 5.00±0.57 days in the standard treatment group whereas prolonged fatigue was present for 26.44±5.95 days in VD9

adjuvant group compared to 42.13±3.87 in the standard treatment group. The VD9 adjuvant group had a mean duration of allaying myalgia of 7.26±0.73 days compared to 10.29±1.06 days in the standard treatment group, while prolonged myalgia at a mean of 44.75±0.47 days in VD9 adjuvant group compared to 45.25±0.27 days in the standard treatment group (Table 5).

The recovery duration of mild-moderate hypoxia (SpO2>90-94) in VD9 adjuvant group was 2.57±1.06 days compared to 6.58±2.57 days in the standard treatment group, while recovery from severe hypoxia (SpO2<90) in VD9 adjuvant group occurred in 6.00±1.29 days compared to 6.44±2.42 days in the standard treatment group (Table 5).

The study demonstrated that patients in the VD9 treatment group were 21% more likely to have a clinical improvement in the first 4 to 7 days compared with those in the standard of care group as the VD9 adjuvant group had more than 58 % of patients discharged from hospital in the first 4 to 7 days of testing positive compared to the 37 % in the standard treatment group (Table 6).

Overall the VD9 was well tolerated and there was no incidence of respiratory failure and rescue medication and no mortality was observed in the entire trial duration (Treatment and Follow-up period).

Safety Results

The study demonstrated that before the start of the treatment at day 0, 37.10% of cases had abnormal x-ray findings in the standard treatment group and 90.32% in VD9 adjuvant group. After 12 days of treatment, only 22.95% of cases had abnormal findings in VD9 adjuvant group resulting in 77.05% of cases demonstrating normal findings compared to the standard group alone which showed no change from baseline. By day 45, only 3.39% of cases displayed abnormal results in VD9 adjuvant group compared to 5% of patients in standard care alone with the rest of the patients exhibiting normal results (Table 7).

No AE or SAE was recorded during the study. The vital parameters of all the participants were within normal limits in both groups throughout the study. Some significant differences were observed in the safety parameters such as platelets, hematocrit, neutrophil, eosinophil, monocytes, basophil, ESR, ALT, AST, creatinine, FBS levels in both VD9 adjuvant group and standard treatment group. The VD9 adjuvant group reported significant changes in RBC and INR, and the standard treatment group showed the changes in ALP and bilirubin significantly. However, the changes were not biologically significant. No significant changes were found in any parameters of lipid profile in both treatment groups compared to baseline (Table 7).

Discussion

This randomized, open-label, exploratory trial of asymptomatic and mild to moderate COVID-19 patients demonstrated that VD9 adjuvant treatment was able to show a substantial clinical benefit in a much higher proportion of patients by a confirmed negative result on an RT-PCR test as early as within 4 days and 11 days of treatment. These results were supported by an increase in the threshold cycle (Ct value) thereby reduction in viral load in VD9 adjuvant group which standard treatment alone failed to do so. The proportion of patients who remained RT-PCR positive for COVID-19 was also lower in the VD9 adjuvant group than in the standard treatment group. These results suggest VD9 to possess anti-viral properties that can be explained by the selected nine compounds present in VD9 to have 3-CL Protease inhibitory activity thereby stopping SARS-COV-2 proliferation. The 3C-like protease (3CLpro) is a cysteine protease possessing a highly conserved sequence in SARS-CoV-2. It is known to hydrolyze viral polyproteins pp1a and pp1ab to produce functional proteins which is a key function in virus replication. Humans do not have a homologous 3CLpro, which makes 3CLpro an ideal therapeutic antiviral target for COVID-19. Inhibiting 3CLpro can block the replication

of SARS-CoV-2 [39]. Luteolin, quercetin, and EGCG are reported to possess anti-viral activity by inhibiting the proteolytic activity of SARS-CoV 3CLpro [40]. Phenolic compound hesperidin dose-dependently inhibited cleavage activity of the 3CLpro, with an IC50 of 8.3 μM in a cell-based assay and molecular docking identified quercetin-3-β-galactoside as an inhibitor of the protease [41]. Baicalin and baicalein exhibited potent antiviral activities in a cell-based system and were identified as the first non-covalent, non-peptidomimetic inhibitors of SARS-CoV-2 3CLpro [42]. Piperine and curcumin showed the best docking scores and that they are capable of promoting structural changes in the viral protease by inducing the folding of the enzyme 3CLpro [43]. EGCG exhibited stronger molecular interactions within pockets at active sites than remdesvir and chloroquine, especially in the case of 6vw1, which is a potential target of SARS-CoV-2 [44]. Glycyrrhizin was shown to inhibit SARS-coronavirus (SARS-CoV) replication in vitro [45] and exhibited anti-viral activities [46]. The results of molecular docking analysis in a study by Cherrak et al indicated that rutin is a potential candidate to inhibit the function of 3CL pro of Coronavirus [47]. Furthermore, our molecular docking analysis published elsewhere confirmed that all nine compounds have a very good binding affinity towards at least 5 different amino acid moieties of 3-CL Protease. We have specifically focused more on 3-CL Protease since it is a highly conserved structure among all coronaviruses [48] and in case of mutation in the virus, there are fair chances that 3-CL Protease will be conserved again.

The nine bioactive molecules used in the developed therapeutic VD9 belong to the class of flavonoids, polyphenols, saponins, and alkaloids. Six of the molecules are flavonoids that include Baicalin, Quercetin, Luteolin, Rutin, Hesperidin, and EGCG; curcumin is a natural polyphenol, Piperine belongs to the class of alkaloids and Glycyrrhizin is a triterpenoid saponin. More than 60% of the VD9 formulation consists of flavonoids that present a great diversity of biological activities observed in-vitro and in-vivo, such as antioxidant, anti-

inflammatory, antitumoral, antiviral, antibacterial, cardioprotective, immune-modulatory, antidepressant, anticonvulsant, antiproliferative, antihypertensive, antiulcerogenic, antidiabetic and hepatoprotective activity [49-51], which makes them the most interesting natural substances available to enrich the current pharmaceutical and therapy applications. Furthermore, the in silico analysis indicated that flavonoids also exhibit potential inhibitory activity against SARS-CoV-2 by binding to specific viral targets required in virus entry and/ or replication along with exhibiting a high safety profile, suitable bioavailability, and no significant adverse effects [52].

To further understand the mechanism and pharmacological action of VD9, we applied an integrated multidisciplinary approach involving in silico technology that included a network of pharmacological data and molecular docking analysis that provided insight into the Drug-Target-Pathway interactions. 71 pathways were identified to be influenced by bioactive compounds of VD9. Based on their functionality and course of action in COVID-19, these 71 pathways were divided into four categories (a) structural proteins of SARS-CoV-2; (b) host receptors/cells/enzymes; (c) management of COVID-19; and (d) prevention of long COVID and treatment of co-infections.

The meta-analysis suggests each of the nine molecules has potential activity against multiple pathways with quercetin and EGCG each showing activity in 58 pathways, baicalin possessing activity against 51 pathways, 50 pathways influenced by curcumin, 47 pathways by luteolin, glycyrrhizin possessing activities in 41 pathways, hesperidin in 38 pathways, rutin and piperine each with potential action in 34 pathways. Accordingly, the hypothesis tested in our trial was that all these molecules might act synergistically against SARS-CoV-2 infection by reducing the viral load and improving the clinical manifestations.

The structural proteins of SARS-CoV-2 are one of the potential therapeutic targets. The four major structural proteins of the virus are spike protein, membrane glycoprotein, envelope

protein, and nucleocapsid protein which are responsible for viral entry into host cells, maturation and pathogenesis of coronaviruses, viral replication, and amplification, thus all playing multiple vital roles during the whole viral life cycle in hosts [3]. Multiple nonstructural proteins (NSPs) like RNA-dependant RNA polymerase (RdRp), helicase, and nsp16 are produced as a result of cleavage activity by proteases. Inhibitors of these enzymes could potentially block SARS-CoV-2 replication and proliferation [1]. Many studies have evaluated the RdRp inhibitor remdesivir intending to improve the clinical outcome in COVID-19 patients. Some studies have demonstrated the clinical benefit of remdesivir in severe patients, but it has failed to do so in moderate patients. One of the studies by Spinner *et. al.*, in 596 moderate COVID-19 patients revealed that remdesivir treatment for 10 days could not improve the clinical status significantly, and 5-day treatment course of remdesivir had a statistically significant difference in clinical status compared with standard care the difference was of uncertain clinical importance [53]. On the other hand, VD9 through its natural ingredients can act as a potent agent that targets the viral structural proteins [54-58] and also inhibits the papain-like protease (PL-pro) [59, 60], RdRp [61-63], helicase [64, 65], RBD-ACE-2 6VW1 [66-70]. Biacalin, Quercetin, Rutin, Hesperidin, Curcumin, EGCG, and Glycyrrhizin in VD9 possess properties of inhibiting RBD-ACE-2 6VW1 which is a potential target for any therapeutic drug for SARS-CoV-2 [66-70]. Thus, 9 molecules expressing the inhibition activities in 9 pathways of structural proteins of SARS-CoV-2 make VD9 a potent anti-viral agent for the COVID-19 infection (Fig.1). This is validated by the trial results that revealed COVID-19 patients who received VD9 along with the standard care recovered much faster from the infection in an RT-PCR test accompanied by the increase in the Ct value (reduction in viral load) than the patients who received only standard care.

The initial data has shown the increase in inflammatory biomarkers to be associated with disease development and can be considered as an early predictor for severe COVID-19

[71]. The findings of a prospective study indicated that the elevated levels of IL-6 are a result of Cytokine Storm due to acute lung injury and ARDS which can further lead to tissue damage and multiple organ dysfunction [72]. CRP is a marker of acute-phase response in inflammation, infection, and tissue damage, which could be used as an indicator of inflammation [73]. The retrospective clinical analysis provided evidence that non-survivors had higher levels of IL-6, ferritin, and CRP compared to survivors [74, 75]. Flavanoids like Baicalin, Quercetin, Luteolin, Rutin, Hesperidin and EGCG, natural polyphenol curcumin, alkaloid piperine, and saponin Glycyrrhizin are known to exhibit anti-inflammatory activity by inhibiting the release of IL-6 [76-83] and CRP [84-89]. The findings of the study establish that VD9 improved the inflammatory biomarkers IL-6, CRP, and ferritin contributed by the standardized bioactive present in maximum purity, thus proving VD9 to have a potential for anti-inflammatory activity.

Additionally, VD9 was able to decrease CPK in patients who received VD9 along with standard care, which is a marker for cardiac injury that was found in hospitalized patients suggesting that patients with severe symptoms often have complications involving acute myocardial injury [90]. The mechanism of action of VD9 includes the protection of the cardiovascular system by baicalin, quercetin, luteolin, curcumin, and EGCG exerting prophylactic and therapeutic effects in cardiovascular disorders by providing beneficial effects in preventing cardiac dysfunction due to cardiac I/R injury as well as other cardiac pathologies thus playing the role of cardioprotection [91-95]. The animal studies investigated the effects of rutin and piperine suggested that rutin inhibits coronary heart disease in a porcine model [96] and piperine protected against cardiac fibrosis in mice [97] through extracellular signal-regulated kinase (ERK) 1/2 and Akt signaling pathways. The results of another animal study demonstrated the cardioprotective effect of Glycyrrhizic acid (GA) on myocardial ischemia (MI) injury in rats induced by isoproterenol (ISO) [98]. Many studies have evaluated the

cardioprotective role of hesperidin and have displayed its beneficial effects on high blood pressure mediated by the vascular nitric oxide (NO) synthase pathway increasing NO production and by an improvement in the endothelial function [99]. This can be supported by the results of the in-vivo study conducted on VD9 published elsewhere that concluded VD9 displayed cardio-protective activities by significantly reducing CK-MB and GPT in isoproterenol-induced myocardial infarction in rats after treatment of VD9.

D-dimer appears to be increased in COVID-19 patients with potential mechanisms for the increase including pulmonary and systemic endothelial injury with diffuse thrombosis of smaller vessels or larger veins, inflammation-associated deposits of intra-alveolar fibrin, and coagulopathy [100]. Antithrombotic activities are possessed by quercetin [101], rutin [102], luteolin [103], curcumin [104], hesperidin [105], EGCG [106], glycyrrhizin [107, 108]. Thrombin-induced cell injury was investigated in human umbilical vein endothelial cells (HUVECs) which showed that baicalin significantly reduced thrombin-induced apoptosis of HUVECs. These results indicated that baicalin has protective effects on thrombin-induced cell injury in HUVECs possibly through inhibition of PAR-1 expression and its downstream NF-κB activation, which was mediated by ERK1/2 activation, raising the possibility of the use of baicalin as a drug for the prevention and treatment of atherosclerosis [109]. A randomized clinical trial tested the effect of curcumin with piperine in COVID-19 patients. The use of orally administered curcumin with piperine as adjuvant therapy in COVID-19 treatment showed faster symptomatic recovery, reduced morbidity and mortality, less requirement of supplementary oxygen, and better clinical outcomes leading to early hospital discharge in patients compared to patients of the control group and thus suggested to be a safe and natural therapeutic option to prevent Post-Covid thromboembolic events [104]. These data provide evidence that VD9 could be a potent natural thrombolytic agent that caused the decline of the D-dimer levels in the COVID-19 patients observed in the study.

The preliminary immune response against viral infection is by the production of IgM antibodies whereas, long-term immunity and immunological response are produced by the high-affinity IgG antibody [110]. The current study presented evidence that VD9 was able to significantly raise the total antibody (IgG+IgM) levels way early after initiation of treatment at day 5 which continued to rise exponentially till the end of the study period whereas the standard treatment alone showed the effect only at day 45. A similar study conducted in 72 mild to moderate COVID-19 patients assessed the effect of a polyherbal formulation on antibody levels that revealed a reduction of IgG and IgM antibodies and no significant changes in COVID antibodies on day 30 [111]. All 9 phytoconstituents of VD9 exerted their action through immunomodulatory effects such as increased proliferation of immune cells, modulation of cytokines, and increased antibody titers thus strengthening the host immune system [112-121].

Furthermore, the increased levels of CD4+ and CD8+ T cells indicate that VD9 could effectively elicit immune responses and eliminate virus-infected cells. CD8+ T cells are reported to be an independent predictor for COVID-19 severity as well as for treatment efficacy because a decrease in CD8+ T cells was associated with severe virus infection and poor treatment efficacy [122]. Several studies are showing that selected compounds have good T cell stabilization activity which will help in strengthening the immune system of COVID-19 patients [123-131].

VD9 showed significant symptomatic effectiveness in patients with sore throat and although statistically non-significant, the lesser recovery duration was seen in the resolution of fever, cough, fatigue, myalgia, and hypoxia. A possible explanation for this might be the small number of symptomatic patients. Overall, a numerical but non-significant reduction in time for the resolution of the symptoms indicates a possible positive effect for VD9 as an add-on therapy for COVID-19 which led to more patients getting discharged from the hospital in the first 4 to

7 days in VD9 adjuvant group compared to the standard treatment group (58% vs 37%). VD9 was well tolerated in the trial with no AE or SAE observed.

The trial had certain limitations. We evaluated the effect of VD9 on limited biomarkers to assess the disease progression and severity. Although the combined results from the docking analysis and meta-analysis on compounds demonstrated the action potential of VD9 on several drug target pathways, however, this needs to be validated by testing several other inflammatory, immunological, and coagulation markers such as IFN, IL-1, IL-4, IL-5, IL-6, IL-13, TNF-α. Furthermore, the study population was inclusive of asymptomatic patients in addition to symptomatic patients with mild to moderate symptoms. As a result, the analysis of fewer patients with symptoms contributed to inconclusive results for the validation of VD9 in the recovery duration of most of the symptoms. Hence, this should be further investigated in future studies with inclusion criteria confining to symptomatic patients and in bigger study populations as this study has the limitation of a small number of subjects. Moreover, with the current study bounded to only asymptomatic, mild, or moderate patients, future studies are required for the evaluation of VD9 in severe patients.

Conclusion

This retrospective study demonstrates a potential promising role of phyto nutraceutical - VD9 as an adjuvant therapy primarily targeting the virus and evaluating the VD9 efficacy on RT-PCR results for infection and viral load along with assessing the effectiveness on the clinical symptoms. VD9 signified the prevention of disease progression by reduction of viral load and early negative RT-PCR results for SARS-CoV-2 infection, strengthening the natural defenses to COVID-19 by increasing the T cells and COVID antibody levels, and attenuating COVID-19 secondary complications by improving the altered levels of biomarkers like IL-6, CRP,

CPK, and D-dimer. The recovery time in the symptoms for the VD9 treated patients was shorter in comparison to the standard treatment alone and the data provided some promising evidence that VD9 might shorten the symptomatic course of COVID-19 in patients with mild and moderate symptoms. All the nine molecules acted synergistically and anti-viral, anti-inflammatory, and immuno-modulatory effects detected with adjuvant treatment of VD9 indicates that it is beneficial and safe to administer VD9 along with standard of care in COVID-19-positive patients with mild to moderate or no symptoms. However, a similar randomized trial would be purposeful to evaluate the effect of the VD9 formulation in severe patients.

Abbreviations

ACE2- Angiotensin-Converting Enzyme 2

AD/T-Admission/Treatment

AE- Adverse Event

ALP- Alkaline Phosphatase

ALT- Alanine Transaminase

ANOVA- Analysis of variance

ARDS- Acute Respiratory Distress Syndrome

ARDS- Acute Respiratory Distress Syndrome

AST- Aspartate Aminotransferase

CBC- Complete Blood Count

CFB- Change from Baseline

CK-MB- Creatine Kinase-MB

COVID- 19- coronavirus disease of 2019

CPK- Creatine Phosphokinase

CRFs- Case Report Forms

CRP- C-Reactive Protein Test

CT- Cycle threshold

CTRI- Clinical Trials Registry of India

DNA- Deoxyribonucleic acid

EGCG- Epigallocatechin Gallate

ESR- Erythrocyte Sedimentation Rate and Sedimentation Rate

FAS- Full Analysis Set

FBS- Fasting Blood Sugar

FTP-First testing positive

GMP- Good manufacturing practice

GPT- Glutamic-Pyruvic Transaminase

ICF- Informed Consent Form

ICH-GCP- International Conference on Harmonization-Good Clinical Practice

IFN- Interferon

IgG- Immunoglobulin G

IgM- Immunoglobulin M

IL- 6- Interleukin-6

IL-1- Interleukin-1

IL-13- Interleukin-13

IL-4- Interleukin 4

IL-5- Interleukin 5

IL-6- Interleukin-6

INR- International Normalized Ratio

LFT- Liver Function Test

NSP- Nonstructural Proteins

ON- Onset

PDI- Protein Disulfideismomerase

PPS- Per Protocol Analysis

PT- Prothrombin Time

RAAS- Renin–Angiotensin–Aldosterone System

RBD- Receptor Binding Domain

RFT- Renal Function Test

RNA- Ribonucleic acid

RT- PCR- Reverse Transcription Polymerase Chain Reaction

S-Standard

SAE- Serious Adverse Event

SAP- Systems, Applications & Products in Data Processing

SARS-CoV-2- Severe Acute Respiratory Syndrome Coronavirus 2

SPO2- Saturation of Peripheral Oxygen

SV9-Standard+Vedicinals-9

TNF-α- Tumor Necrosis Factor Alpha

VD9-Vedicinals-9

X-Ray- X-radiation

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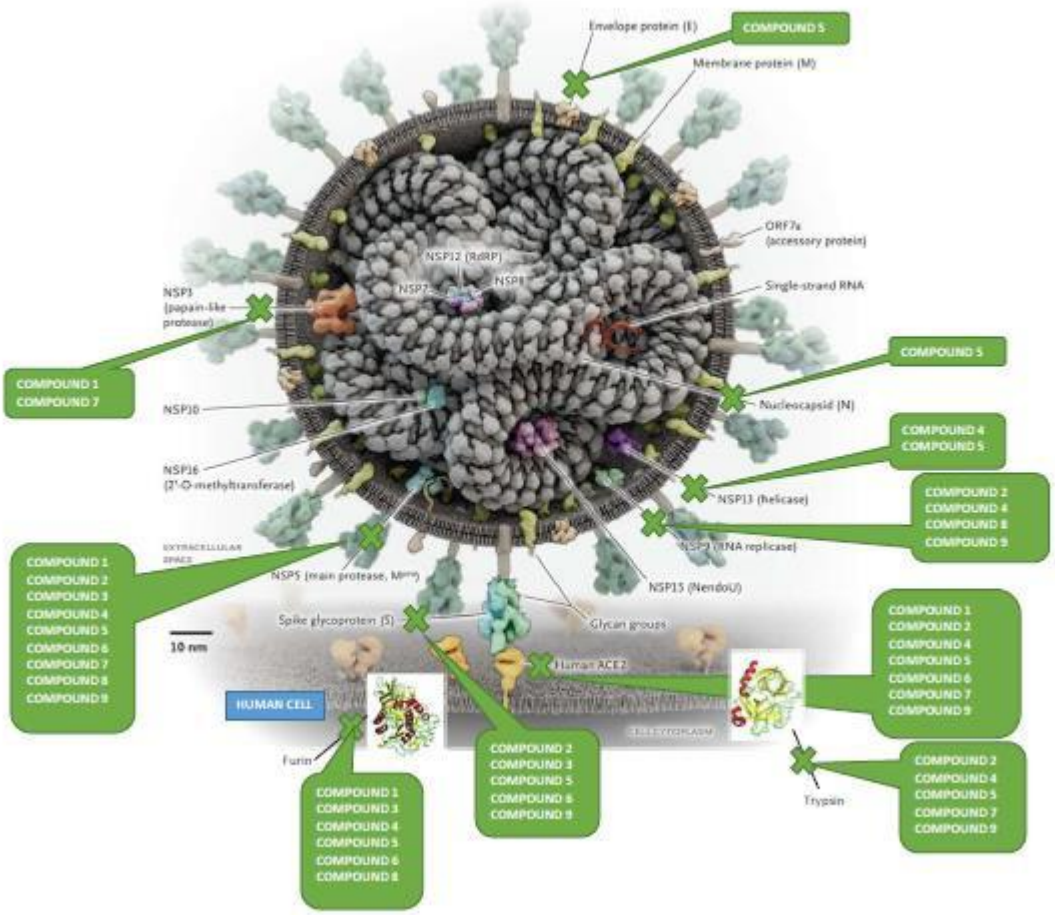

Figure 1: Vedicinals-9 Interaction Scheme: Mechanisms/pathways and action points of Vedicinals-9 compounds/molecules on SARS-CoV-2

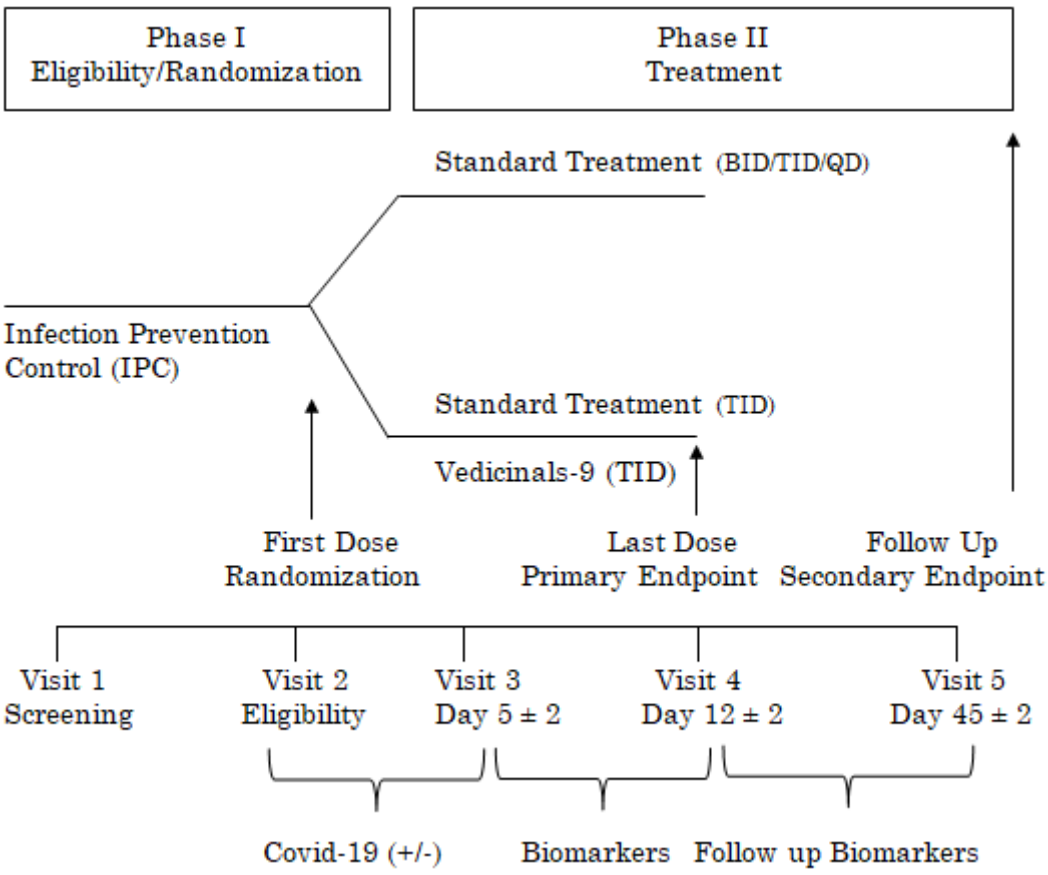

Figure 2: Study Design

BID: twice a day, TID: Thrice a day, QD: once a day.

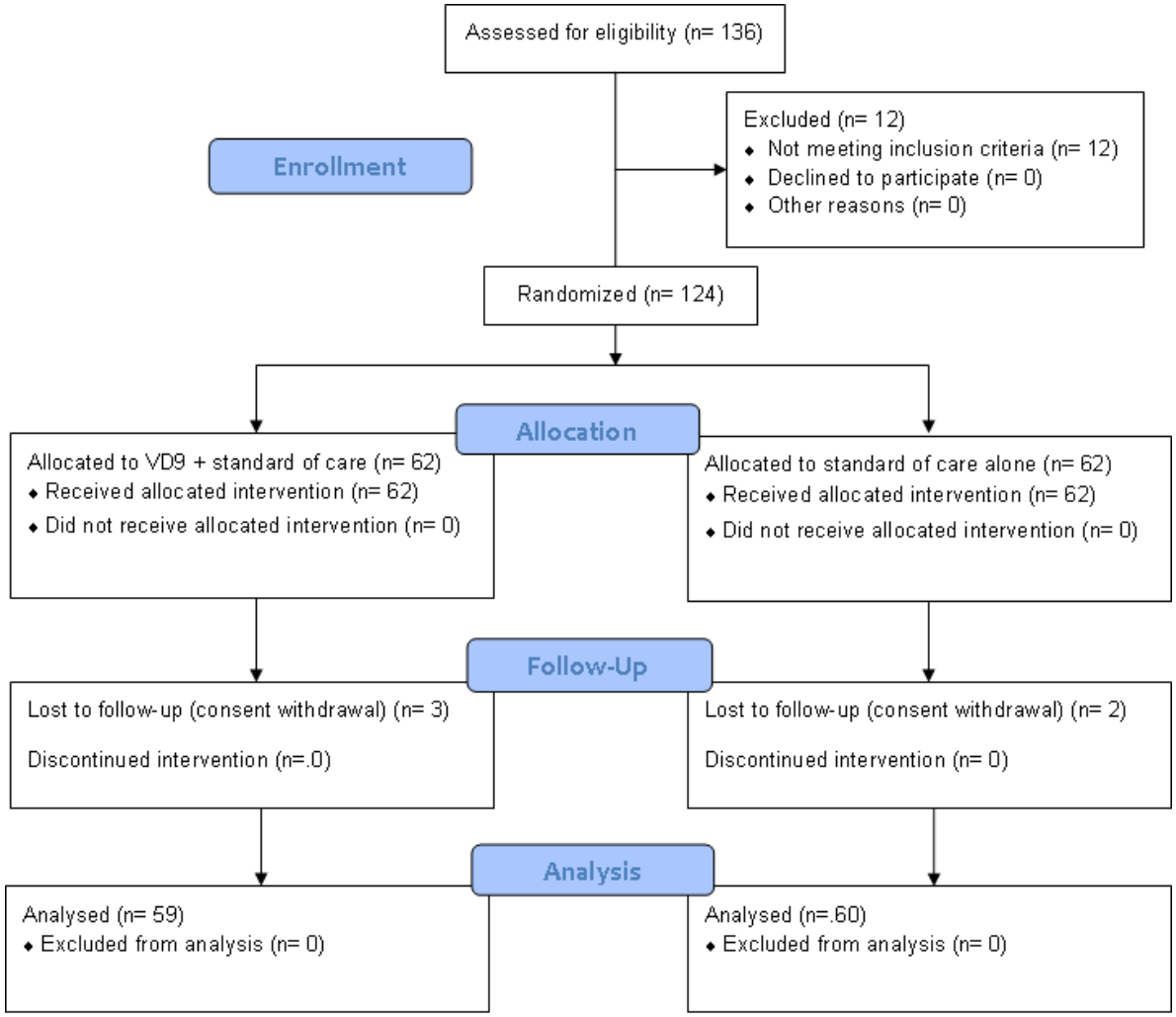

Figure 3: Study Flowchart

Table 1: Baseline characteristics: Demographics, Vitals and Physical Systemic Examination

	Standard + Vedicinals-9 (N=62)	**Standard (N=62)**	**p-value (SV9 vs S)**
Age[a] **(years)** Mean ± SEM Median (Min-Max)	 38.82 ± 1.35 39.00 (18-60)	 40.71 ± 1.55 40.50 (18-60)	ns
Gender[b] [n (%)] Male Female	 33 (53.22%) 29 (46.78%)	 35 (56.45%) 27 (43.55%)	ns
Nationality[b] [n (%)] Indian Other	 62 (100%) 0 (0.0%)	 62 (100%) 0 (0.0%)	ns
Marital status[b] [n (%)] Married Unmarried	 52 (83.87%) 10 (16.13%)	 52 (83.87%) 10 (16.13%)	ns
Height[a] [(cms) (Mean ± SEM)]	166.0 ± 0.88	166.5 ± 1.26	ns
Weight[a] [(kg) (Mean ± SEM)]	73.25 ± 1.47	74.93 ± 1.89	ns
Vitals sign			
Temperature[a] [(F) (Mean ± SEM)]	99.48 ± 0.19	99.49 ± 0.22	ns
Pulse Rate[a] [(beats/min) (Mean ± SEM)]	82.61 ± 0.89	83.52 ± 0.86	ns

Respiratory Rate[a] [(breaths/min) (Mean ± SEM)]	19.05 ± 1.89	19.44 ± 0.26	ns
SpO2[a] [(%)(Mean ± SEM)]	95.39 ± 0.39	94.62 ± 0.45	ns
Systolic[c] [(mmHg) (Mean ± SEM)]	126.0 ± 0.96	125.3 ± 0.90	ns
Diastolic[c] [(mmHg) (Mean ± SEM)]	80.65 ± 0.87	81.92 ± 0.92	ns
Physical Systemic Examination			
General Appearance[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 60 (96.78%) 2 (3.22%)	ns
Skin[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Eyes, Ears, Nose & Throat[b] [n (%)] Normal Abnormal	 57 (91.93%) 5 (8.07%)	 59 (95.16%) 3 (4.84%)	ns
Head, Neck & Thyroid[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 60 (96.78%) 2 (3.22%)	ns
Cardiovascular[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Respiratory[b] [n (%)] Normal Abnormal	 6 (9.68%) 56 (90.32%)	 40 (64.51%) 22 (35.49%)	<0.0001
Abdomen[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Extremities[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Genitalia[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Anorectal[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Lymph Nodes[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Muscular-Skeletal[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns
Neurological[b] [n (%)] Normal Abnormal	 62 (100%) 0 (0)	 62 (100%) 0 (0)	ns

Data are stated as Mean ± SEM or Median or n (%).
[a]Comparison between the groups by Unpaired t-test; [b]Comparison by Fisher's exact test; [c]Comparison by two-way ANOVA

Table 2: Primary outcome: COVID-19 patients turning negative and time taken in days

Outcome in Days	Standard + Vedicinals-9	Standard	*p*- value (SV9 vs S)
Patients turning negative in 0-4 days[a]	29.03	1.613	<0.05
Patients turning negative in 5-11 days [a]	48.39	37.10	<0.05

Patients turning negative in 12-14 days[a]	22.58	61.29	<0.05
COVID-19 patients staying positive in days[b]	7.62±0.45	9.71±0.45	<0.01
Mean difference in CT Value from baseline to day 5[c]	1.762±0.125	1.399±0.092	<0.05

Data are stated as % of patients or mean ± SEM,

[a]Percentage of patients tested RT-PCR negative between 0-4, 5-11 and 12-14 days after treatment in both the groups compared by Chi-Square test for proportions.

[b]Comparison of Persistent COVID-19 RT-PCR positivity between the groups: positive COVID-19 RT-PCR test till 14 days analysed by Unpaired t-test with Welch's correction

[c]Comparison of mean change in CT value from baseline to day 5 between the groups analysed by unpaired t-test with Welch's correction: Viral Load by RT-PCR.

Table 3: Primary outcome: Improvement in biomarkers in the two groups from baseline to day 5, day 12 and day 45.

Biomarker	Standard + Vedicinals-9 (SV9)							Standard (S)						
	Time-points				*p-value*			Time-points				*p-value*		
	Baseline	Day 5	Day 12	Day 45	Baseline vs Day 5	Baseline vs Day 12	Baseline vs Day 45	Baseline	Day 5	Day 12	Day 45	Baseline vs Day 5	Baseline vs Day 12	Baseline vs Day 45
IL-6 (pg/mL)	12.79±5.35	4.01±0.36	3.62±0.39	2.70±0.24	<0.05	<0.05	<0.01	12.48±4.53	5.91±1.53	6.18±1.83	2.98±0.68	ns	ns	<0.01
CRP (mg/L)	10.29±1.44	6.93±0.47	5.04±0.32	3.33±0.18	<0.001	<0.001	<0.001	12.04±0.87	9.23±0.49	5.15±0.32	3.54±0.18	<0.01	<0.001	<0.001
Total COVID-19 Antibody (IgG & IgM)	2.61±0.42	5.02±0.47	5.97±0.46	13.64±1.44	<0.05	<0.05	<0.01	1.92±0.37	3.64±0.72	3.63±0.27	11.23±1.15	ns	ns	<0.01
CPK (U/L)	109.1±21.65	96.84±16.84	76.57±5.34	124.1±5.70	ns	<0.01	ns	78.45±5.35	71.63±3.78	68.91±4.73	131.5±5.30	ns	ns	<0.05

Data are stated as Mean±SEM, p-values are by One-way ANOVA followed by Dunnett's multiple comparisons test with comparison between the baseline and day 5, day 12 and day 45 within each group.

Table 4: Primary outcome: Improvement in biomarkers in the two groups from baseline to day 5, day 12 and day 45.

Biomarker	Standard + Vedicinals-9 (SV9)					Standard (S)				
	Time-points			*p*- value		Time-points			*p*- value	
	Baseline	Day 12	Day 45	Baseline vs Day 12	Baseline vs Day 45	Baseline	Day 12	Day 45	Baseline vs Day 12	Baseline vs Day 45
D-dimer (µg FEU/L)	416.7±43.45	351.8±28.48	261.5±14.15	ns	<0.01	410.8±45.67	687.7±187.2	285.4±12.34	ns	ns
Ferritin [ID] (µg/L)	12.71±2.09	47.24±22.12	67.83±16.35	<0.05	<0.01	14.57±2.18	36.02±13.02	62.13±09.45	ns	<0.05
Ferritin [IO] (µg/L)	558.5±52.71	262.6±46.11	152.0±18.14	<0.001	<0.001	541.5±40.89	295.7±11.68	142.8±15.04	<0.001	<0.001
Ferritin [NI] (µg/L)	91.29±12.67	94.50±13.77	162.7±13.56	ns	<0.001	50.10±06.87	56.57±4.32	192.9±14.40	ns	<0.001
CD4+ T (cells/µL)	957.6±69.24	1201±94.19	1289±115.2	<0.01	<0.01	1190±67.65	1607±107.9	1655±117.5	<0.05	<0.05
CD8+ T (cells/µL)	797±65.43	1094±105.2	1113±103.5	<0.05	<0.05	1002±68.70	1329±105.5	1370±117.5	<0.05	<0.05
CD19+ B cell (cells/µL)	240.6±19.55	270.8±20.88	242.5±21.09	ns	ns	263.5±28.30	241.3±19.06	194.8±15.83	ns	ns
CD16+/56+ NK cells (cells/µL)	205.1±17.73	246.8±21.72	219.7±19.51	ns	ns	230.3±24.08	216.5±22.61	179.6±18.09	ns	ns

Data are stated as Mean±SEM, comparison by One-way ANOVA followed by Dunnett's multiple comparisons test between the baseline and day 12 and day 45 within each group.

Table 5: Secondary outcomes: Comparison of symptoms and disease progression of VD9 adjuvant to standard treatment and Standard treatment alone.

Symptom	Standard + Vedicinals-9 (SV9)			Standard (S)			p-value (SV9 vs S)		
	Days from FTP	Days from AD/T	Days from ON	Days from FTP	Days from AD/T	Days from ON	Days from FTP	Days from AD/T	Days from ON
Prolonged Fever	5.14±0.79	3.60±0.66	5.42±0.69	7.12±1.10	4.12±0.67	6.12±0.66	ns	ns	ns
Saddleback fever	13.38±0.41	11.54±0.21	13.54±0.31	13.17±0.40	11.83±0.30	14.00±0.36	ns	ns	ns
Cough	5.69±0.32	4.53±0.18	4.53±0.18	6.50±0.28	5.25±0.47	5.25±0.47	ns	ns	ns
Prolonged Cough	13.17±0.44	11.33±0.14	11.33±0.14	12.79±0.70	11.57±0.29	11.57±0.29	ns	ns	ns
Fatigue	5.78±0.32	4.44±0.24	4.44±0.24	9.33±1.20	5.00±0.57	5.00±0.57	ns	ns	ns
Prolonged Fatigue	25.40±5.45	26.44±5.95	26.00±5.78	36.50±5.051	42.13±3.87	41.13±3.78	ns	ns	ns
Myalgia	09.00±0.81	7.26±0.73	6.53±0.59	11.14±1.29	10.29±1.06	9.57±1.11	ns	ns	0.03
Prolonged Myalgia	45.25±0.75	44.75±0.47	44.75±0.47	47.67±0.65	45.25±0.27	45.25±0.27	0.02	ns	ns
Sore throat	8.15±0.70	07.23±0.87	7.23±0.87	11.47±0.32	10.40±0.58	10.40±0.58	0.001	0.009	0.009
Prolonged Sore throat	10.33±5.23	08.33±4.17	08.33±4.17	45.00±1.00	44.67±0.66	44.67±0.66	0.03	0.01	0.01
Hypoxia or Dyspnoea	4.75±0.94	2.57±1.06	5.50±1.00	6.94±2.53	6.58±2.57	7.64±2.56	ns	ns	ns
Prolonged Hypoxia or Dyspnoea	6.14±1.26	6.00±1.29	7.00±1.29	6.77±2.39	6.44±2.42	7.50±2.41	ns	ns	ns

Data are stated as Mean±SEM, comparison between the groups by paired t-test.
FTP = First testing positive, AD/T = Admission/Treatment, ON = Onset

Table 6: Secondary outcome: Length of hospitalization of patients in days

Days	Standard + Vedicinals-9 (SV9)	Standard (S)
4 to 7 days	36 (58.06%)	23 (37.09%)
8 to 12 days	18 (29.03%)	27 (43.54%)
>12 days	8 (12.90%)	12 (19.35%)

Data are stated as n (%) for the patients hospitalized.

Table 7: Safety Outcomes: Laboratory indices and Radiological examination in the two groups at baseline, day 12 and day 45

Index	Standard + Vedicinals-9 (SV9)					Standard (S)				
	Time-points			*p*- value		Time-points			*p*- value	
	Baseline	Day 12	Day 45	Baseline vs Day 12	Baseline vs Day 45	Baseline	Day 12	Day 45	Baseline vs Day 12	Baseline vs Day 45
Complete Blood Routine[a]										
Hemoglobin (gm/dL)	13.13±0.23	13.50±0.17	13.76±0.13	ns	0.0055	13.79±0.21	13.27±0.20	14.03±0.14	0.0089	ns
RBC (x 10^{12}/L)	4.59±0.07	4.73±0.05	4.77±0.04	ns	0.0070	4.80±0.08	4.63±0.06	4.83±0.03	ns	ns
WBC (x 10^{9}/L)	7.32±0.39	7.13±0.25	6.82±0.22	ns	ns	7.45±0.46	6.95±0.25	7.19±0.18	ns	ns
Platelets (x 10^9/L)	231.90±13.51	244.80± 10.49	291.5±9.52	ns	<0.0001	246.00±10.75	241.00±10.75	304.9±13.51	ns	0.0002
Hematocrit (%)	40.16±0.64	41.47±0.44	44.75±0.98	0.0218	0.0002	41.59±0.55	40.15±0.52	44.41±0.52	0.0094	0.0002
Neutrophil (%)	62.92±1.61	57.75±1.33	57.93±0.73	0.0059	0.0007	63.20±1.62	58.17±1.27	58.97±0.73	0.0122	0.0113
Eosinophil (%)	2.46±0.19	3.21±0.20	4.03±0.19	0.0020	<0.0001	2.10±0.19	3.10±0.18	4.63±0.20	0.0004	<0.0001
Lymphocyte (%)	31.32±1.52	31.27±0.96	30.65±0.58	ns	ns	30.63±1.60	31.93±1.03	30.93±0.60	ns	ns
Monocyte (%)	3.97±0.32	3.73±0.30	2.86±0.11	ns	<0.0001	4.87±0.37	4.74±0.33	3.30±0.11	ns	<0.0001
Basophil (%)	0.12±0.21	0.30±0.07	0.28±0.28	0.0196	ns	0.24±0.03	0.35±0.07	0.00±0.00	ns	<0.0001
ESR (mm/hr)	19.65±1.36	13.28±0.88	6.51±0.52	<0.0001	<0.0001	16.85±1.31	14.32±1.19	6.24±0.77	ns	<0.0001
Liver Function[a]										
ALT/SGPT (U/L)	48.91±2.29	41.35±2.06	38.48±1.81	0.0009	0.0001	51.74±2.09	40.11±1.27	36.93±1.11	<0.0001	<0.0001
AST/SGOT (U/L)	45.57±1.73	39.84±1.45	39.17±0.96	0.0059	0.0006	49.64±1.85	41.44±1.47	38.66±1.11	0.0002	<0.0001
ALP (U/L)	101.6±4.49	109.3±3.59	97.82±3.21	ns	ns	103.8±5.23	112.2±3.86	100.6±2.93	0.0349	ns
Bilirubin (mg/dL)	0.68±0.07	0.59±0.02	0.65±0.02	ns	ns	0.71±0.03	0.58±0.02	0.70±0.02	0.0003	ns
Renal Function[a]										
BUN (mg/dL)	13.03±0.37	13.19±0.32	13.49±0.39	ns	ns	13.65±0.34	13.94±0.38	14.31±0.37	ns	ns
Creatinine (mg/dL)	0.71±0.02	0.72±0.02	0.89±0.06	ns	0.0125	0.74±0.02	0.65±0.03	0.92±0.02	0.0301	<0.0001
Lipid panel[a]										
Total Cholesterol (mg/dL)	179.9±4.48	182.2±3.24	181.8±3.80	ns	ns	182.2±3.28	189.3±3.40	183.9±3.46	ns	ns

HDL Cholesterol (mg/dL)	45.47±2.57	42.12±0.67	47.17±0.65	ns	ns	40.12±0.79	41.01±0.61	46.18±1.10	ns	<0.0001
LDL Cholesterol (mg/dL)	104.1±4.23	106.6±3.67	99.68±4.04	ns	ns	112.6±3.83	114.6 ±3.51	108.0±4.18	ns	ns
VLDL (mg/dL)	30.28±2.09	28.87±7.70	31.87±0.88	ns	ns	28.66±2.26	29.89±2.74	29.05±1.02	ns	ns
Triglycerides (mg/dL)	147.2± 10.16	143.0±7.25	151.8±4.75	ns	ns	143.5±11.08	147.0±12.96	137.9±4.47	ns	ns
FBS (mg/dL) [a]	108.3±5.16	106.6±4.89	91.16±1.77	ns	0.0008	110.0±6.79	100.1±4.21	94.45±1.41	ns	0.0258
X-Ray[b]										
Normal [n (%)]	6 (9.68%)	47 (77.05%)	57 (96.61%)	NA	NA	39 (62.90%)	39 (62.90%)	57 (95.00%)	NA	NA
Abnormal [n (%)]	56 (90.32%)	14 (22.95%)	2 (3.39%)	NA	NA	23 (37.10%)	23 (37.10%)	3 (5.00%)	NA	NA

Data are stated as Mean ± SEM or n (%)

[a]Comparison of baseline values with day 12 and day 45 within each group by paired t-test.

[b]Proportion of patients with normal and abnormal findings of X-ray in both the groups.

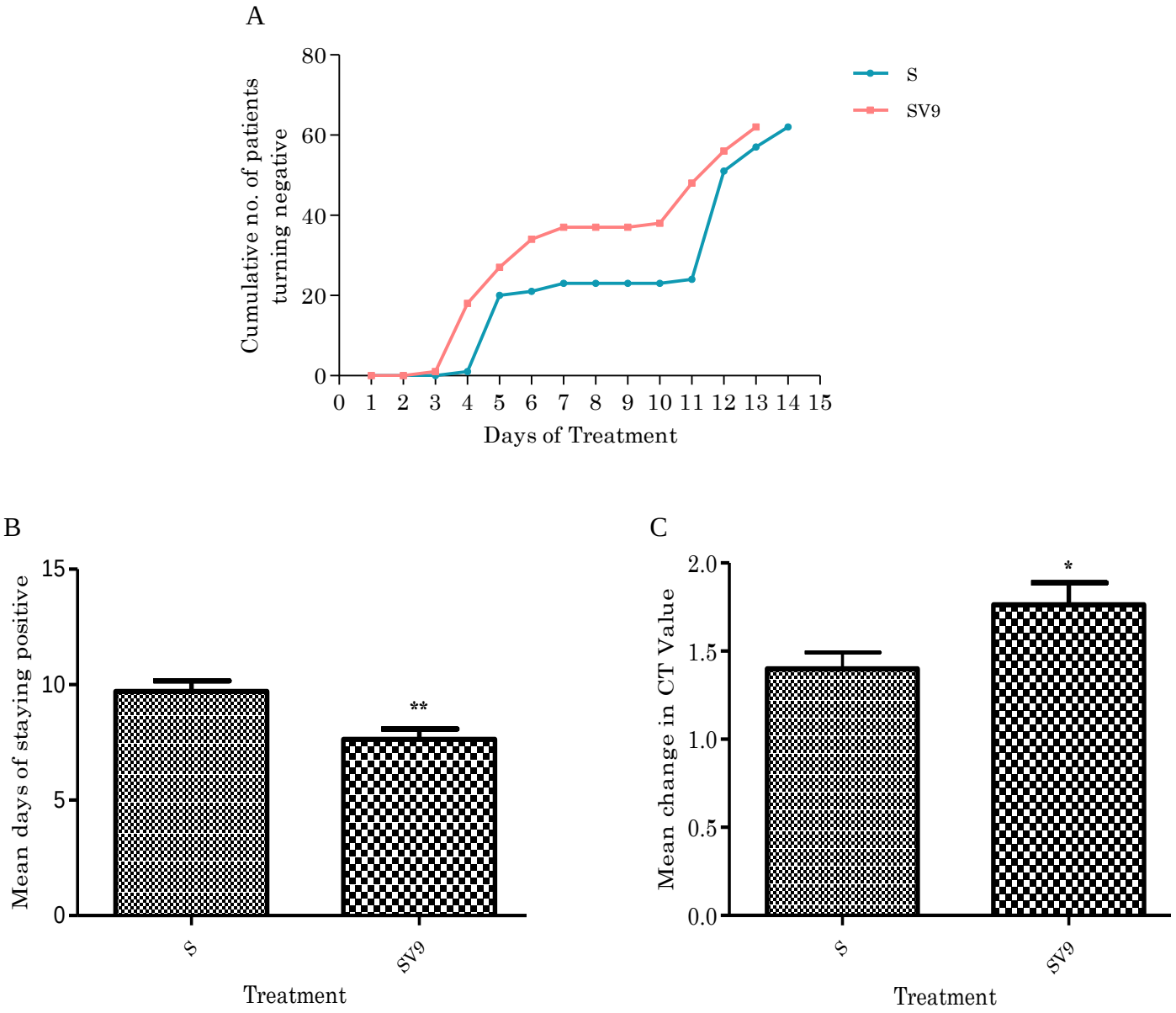

Figure 4: Graphical plot of the primary outcome of treatment (A) Cumulative no. of COVID-19 patients turning negative in days (RT-PCR), (B) Mean days of COVID-19 patients staying positive, (C) Mean change in CT Value from baseline to day 5; Significant between-group analysis: *p<0.05, **p<0.01.

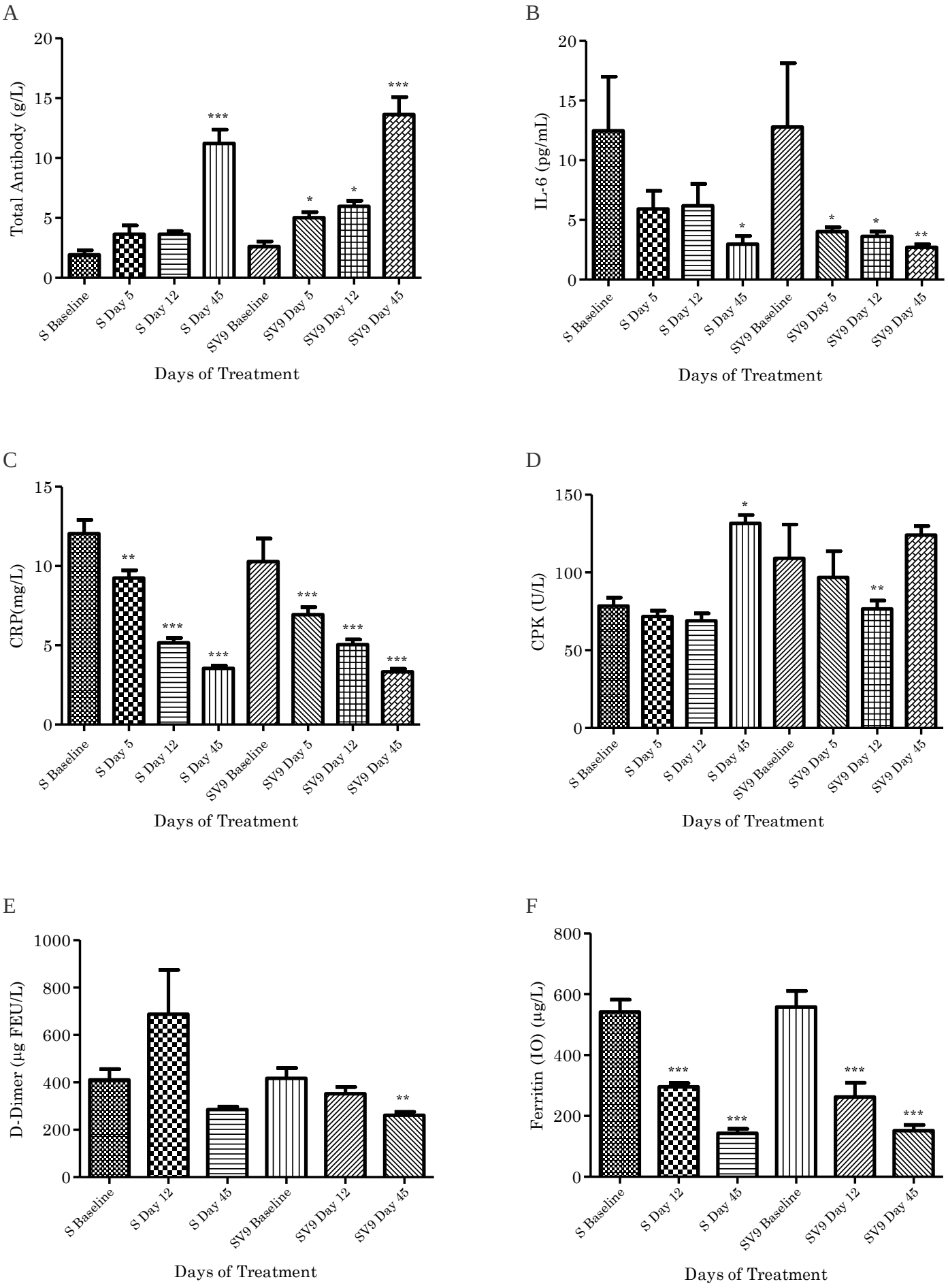

Figure 5. Bar plot of biomarkers: (A) Total antibody levels, (B) IL-6, (C) CRP, (D) CPK, (E) D-dimer and Ferritin (IO). Significant within-group analysis: *p<0.05, **p<0.01, ***p<0.001.