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Original Article

Complementary/Alternative Medicine Section

Evaluation of Efficacy and Safety of Clevira as an Add on Drug in Mild to Moderate COVID-19 Positive Patients: A Randomised Control Trial

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) has caused a devastating pandemic. Despite the worldwide efforts to find a therapeutic strategy and prophylaxis, we have not attained a complete success. Hence, there exists an urgent need for development of alternative solutions from Ayurveda system of medicine for COVID-19.

Aim: To evaluate clevira, a polyherbal ayurvedic formulation, for its efficacy and safety in treatment of mild to moderate COVID-19 patients as an add on drug.

Materials and Methods: This randomised control trial was carried out from May 2020 to July 2020, in 100 patients (50 in test group and 50 in control group) confirmed with COVID-19 infection (mild to moderate cases) by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) at a tertiary care Government Medical College and Hospital in Chennai, India. The test group received tablet clevira orally twice daily after food, in the morning and night for 14 days, as an add on, in addition to standard care of treatment as received by the control group. The primary outcome was assessment of clinical recovery, proportion of patients with swabs negative for COVID-19 in RT-PCR and reduction of viral cycle threshold ratio. The results of the both group were analysed and compared using Chi-square test and Student's t-test.

Results: Total 100 patients were enrolled for the study, mean age of test group was 36.64 and control group was 31.08. Significant improvement (p-value=0.0338) was seen in patients on day 5, who got treated with clevira as add on drug. An 43 (86%) of patients turned out to be COVID-19 RT-PCR test negative on day 5 while in the control group 33 (66%) of patients turned out to be negative. There was a statistically significant difference (p-value=0.0196) between the test and control groups on comparing the mean difference in CT value results between day 1 and day 5. Clevira when given in addition to the standard of care, showed a significant improvement in signs and symptoms of COVID-19 infection.

Conclusion: Clevira, with its polyherbal ingredients showed a significant antiviral action against coronavirus when given in addition to the standard of care medications suggested by Indian Council of Medical Research (ICMR), over a period of 14 days in treatment of mild to moderate COVID-19 patients.

Keywords: *Andrographis paniculata*, Antiviral, Coronavirus disease-2019, *Piper nigrum*, *Tinospora cordifolia*

INTRODUCTION

Coronavirus, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has caused a pandemic of COVID-19. Coronavirus cause mild to severe type of respiratory tract infections. Mild illness include some cases of the common cold, while severe illness can cause SARS virus (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Symptoms) virus, which has led to a death toll of more than 4 million globally [1,2]. Though vaccination has been initiated for Coronavirus Disease-2019 (COVID-19), the effectiveness of the same in controlling the upcoming mutant strains of SARS-CoV-2 is still a debate [3]. Hence, we are in need of a specific and effective antiviral therapy for SARS-CoV-2. Globally, there exists an urgent need for development of an alternative solutions for COVID-19.

In a country like India, there is a rich source of herbs having antiviral and antipyretic activity and Ayurvedic interventions can also be more relevant in management of such pandemics [4]. In recent days the usage of many herbal formulations for various illnesses has increased worldwide and particularly for COVID-19 by the traditional Chinese medicines [5]. Ministry of Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa and Homoeopathy (AYUSH), Government of India has also issued guidelines for boosting immunity with Ayurvedic interventions [6].

Clevira is one among them which is a polyherbal formulation consisting of many ingredients. Clevira is a proprietary Ayurvedic Medicine of apex laboratories Pvt. Ltd., which has been approved by the Government of India and AYUSH for its use in mild to moderate COVID-19 patients as an add on drug to the standard of care treatment [7]. The individual herbal ingredients used are known to have variety of medicinal properties against fever of viral origin and proven to have effective antipyretic, analgesic, antiviral and immuno regulatory properties. Composition of one clevira tablet includes extracts namely: Erandakarkati (*Carica papaya*) Leaf- 100 mg, Mahanimba (*Melia azedarach*) Leaf- 100 mg, Kalmegh (*Andrographis paniculata*) Herb- 100 mg, Usira (*Vettivera zizanoides*) Root- 35 mg, Patola (*Tricosanthus dioica*) whole plant- 35 mg, Musta (*Cyperus rotundus*) Rhizome- 35 mg, Sunthi (*Zingiber officinale*) Rhizome- 35 mg, Maricha (*Piper nigrum*) Fruit- 35 mg, Grismachatraka (*Mollugo cerviana*) Whole plant- 35 mg, Guduchi (*Tinospora cordifolia*) Stem- 10 mg [8].

It has shown in-vitro antiviral activity against Herpes Simplex Virus 1 and 2 [report attached as Annexure 1]. The antiviral activity of clevira Tablets-Granules and Syrup was carried out against Herpes Simplex Virus-1 (HSV-1) and HSV-2 viruses. The 100 TCID50 (Median Tissue Culture Infectious Dose) virus concentration was used for HSV-1 and HSV-2 viruses. The results includes that the granules showed good percentage of cell protection (71.55%) and

selectivity index (CC50/IC50) {Half maximal cytotoxic concentration/ Half maximal inhibitory concentration} of 11.66 when compare to syrup (55.6%) and selectivity index of 4.81 against HSV-1 virus. The granules of clevira also showed the activity against HSV-2 virus with percentage cell protection of 78.05% and selectivity index of 16.81 when compared with syrup (45.05%) and selectivity index of 3.39. The results clearly indicates that the granules of clevira showed the activity against both the viruses and more specifically with HSV-2 virus when compared to syrup. Clinical studies have shown its antiviral activity against dengue fever of viral origin (Ramesh Kannan S et al., 2019) [9]. Docking studies also support the potential use of clevira against SARS-CoV-2. A total of 52 phytoconstituents present in medicinal plants incorporated in the clevira formulation were screened for their inhibitory potential through molecular docking studies against four targets namely the viral spike protein (S1), Ribonucleic Acid (RNA) dependent RNA polymerase (RdRp), SARS-CoV-2 main protease (3CLpro) and papain like protease (PLpro) that play a pivotal role in the SARS-CoV-2 infectivity and replication cycle [report attached as Annexure 2].

The docking study results obtained showed several of the phytoconstituents present in clevira herbal formulation showed good computational binding affinity against the four targets and some of the phytoconstituents were observed to show computational binding affinity to more than one of the four targets investigated. The phytoconstituents orientin, chlorogenic acid, wogonin, and vitexin showed excellent computational affinity to SARS-CoV-2 papain-like protease whereas the phytoconstituents rutin, ninandrographolide, quercetin, and chlorogenic acid exhibited good computational affinity to SARS-CoV-2 main protease. Four phytoconstituents namely ninandrographolide, rutin, quercetin, tinosporide were predicted to have good binding affinity to SARS-CoV-2 RNA dependent RNA polymerase and four phytoconstituents namely caffeic acid, ninandrographolide, piperine and oroxylin A are predicted to efficiently bind to receptor binding domain of SARS-CoV-2 spike protein (S1) [10-13]. Hence, the present trial was planned with an aim to evaluate the efficacy and safety of clevira against SARS-CoV-2 as an add on drug.

MATERIALS AND METHODS

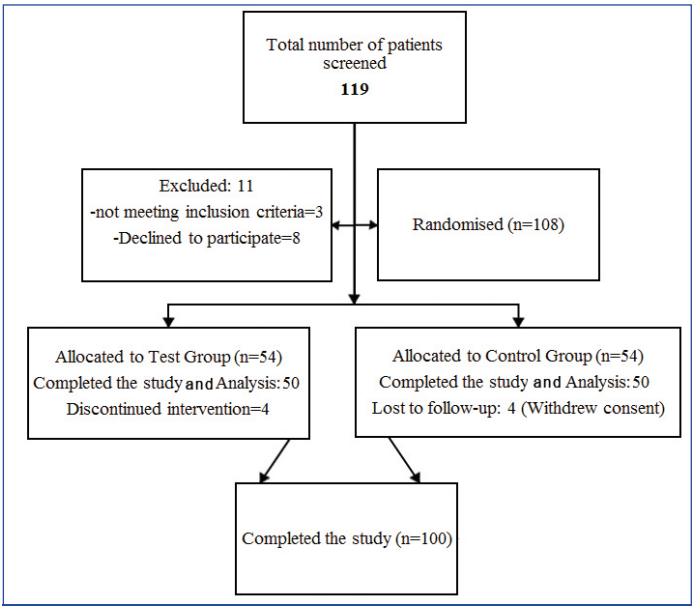
The present randomised, open label, parallel group interventional controlled trial was carried out in Government Medical College and Hospital, Chennai, Tamil Nadu, India during the period of May 2020 to July 2020. The study was approved by the Institutional Ethics committee of Government Medical College, Omandurar Government Estate, Chennai on 22/05/2020 (IEC:05/2020) and the DCGI was notified about the study initiation and the trial was registered in CTRI (CTRI No. CTRI/2020/05/025483).

Sample size calculation: Sample size of 100 was calculated, based on the hypothesis that the proportion of patients showing improvement in control group will be around 20% and proportion of patients showing improvement in treatment group will be around 50%. Hypothesis was postulated, as there were no similar previous studies conducted with ayurvedic medicine, at the time of study initiation. Considering α of 0.05 and β of 0.2, comparing two proportions using sample size calculator software version 1.0, the minimum sample size required per group was 39. Considering 20% dropouts, sample size was rounded off to 50 per group and hence the total sample size obtained was 100.

Inclusion criteria: The study included both male and female patients between the age of 18-60 years, newly diagnosed with mild to moderate COVID-19 associated disease as defined by the World Health Organisation (WHO) with confirmed SARS-CoV-2 infection as determined by RT-PCR, with an illness of 1-2 days of duration and febrile/afebrile [14]. Febrile-defined as temperature ≥36.6°C armpit, ≥37.2°C oral, or ≥37.8°C rectal documented within 24 hours of consent.

Exclusion criteria: The study excluded patients who participated in any other clinical trial of an experimental treatment for COVID-19, concurrent treatment with other agents with direct antiviral activity against SARS-COV-2 like remdesivir and oseltamivir which was prohibited 24 hours prior to study medication initiation. The study also excluded pregnant women or women who were breastfeeding and immunocompromised; patients taking medication upon screening and with stage 4 severe chronic kidney disease or requiring dialysis {estimated glomerular filtration rate (eGFR) <30 mL/min) or with elevated liver enzymes-Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) >5 times of Upper Limit of Normal (ULN)}.

Screening was done for 119 patients and out of which, 108 patients confirmed with COVID-19 infection (mild to moderate cases) by RT-PCR and satisfying the inclusion and exclusion criteria were included in the study after getting proper written informed consent and randomised using computer software generated random number table [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.

Procedure

The test group (n=54) was administered with tablet clevira orally twice daily after food, in the morning and night for 14 days, as an add on, in addition to standard care of treatment suggested by ICMR and the control group (n=54) received standard treatment of care as per ICMR guidelines.

Mild cases: The mild disease included symptomatic patients (fever, cough, fatigue, anorexia, shortness of breath, myalgia, sore throat, nasal congestion, headache, nausea, vomiting, diarrhoea, loss of smell and loss of taste) meeting the case definition of COVID-19 without evidence of viral pneumonia.

Moderate cases: Moderate disease included symptomatic patients with clinical signs of pneumonia (fever, cough, dyspnoea and fast breath) but no signs of severe pneumonia [14].

Standard of care treatment given to all patient (as per hospital regulation) as per the ICMR guidelines are as follows [14]; tab. hydroxychloroquine 400 mg twice daily on day 1, followed by 200 mg twice daily from day 2 to day 5. Tablet azithromycin 500 mg stat followed by 250 mg twice daily from day 2 to day 5. Tablet ivermectin 12 mg stat single dose, tablet vitamin C 500 mg, tablet multivitamin and zinc once daily for 14 days. Tablet cetrizine 10 mg at night and tab. paracetamol 500 mg was administered on need basis [14]. This was the standard of care treatment given during the study period, as recommended by the Government of India, Ministry of Health and Family Welfare. All the RT-PCR and blood samples were analysed in a neutral independent NABL accredited laboratory (VRR Diagnostic services) in Chennai, India.

Primary outcome measure: The primary outcome measure was to assess the efficacy of clevira from day one of enrollement/treatment initiation, soon after the confirmation of COVID-19 illness, which is defined as time taken for clinical recovery i.e., normalisation of pyrexia and body pain, respiratory rate less than 24/minute, SpO_2 rate greater than 94%, relief from cough and maintenance of above features for more than 72 hours and finally proportion of patients with swabs negative for COVID-19 in RT-PCR at day 5, 10 and 15 (time frame: upto 30 days calculated from day one of enrollement in the study soon after the confirmation of COVID-19 illness) and reduction of viral CT (Cycle Threshold) ratio from that of the baseline RT-PCR CT value.

Secondary outcome measures: The secondary outcome measures were improvement in laboratory parameters and clinical status of subjects at day 5, 10 and 15 on a 6 point ordinal scale namely:

1) Discharged having reached clinical recovery criteria;
2) Hospital admission, but not requiring supplemental oxygen;
3) Hospital admission, requiring supplemental oxygen;
4) Hospitalised, on non invasive ventilation or high flow oxygen devices;
5) Hospitalised, on invasive mechanical ventilation or Extra Corporeal Membrane Oxygenation (ECMO);
6) Death, assessed during a time frame upto 15 days.

The proportion of patients in each category of six point scale at day 5, 10 and 15 after randomisation was also recorded with details of all cause of death/mortality, duration of hospitalisation and adverse events if any.

STATISTICAL ANALYSIS

The results of the control and treatment arm were analysed and compared using Chi-square test and Student's t-test using Statistical Package for the Social Sciences (SPSS) software version 21.0.

RESULTS

The demographic details are mentioned in [Table/Fig-2,3]. The male:female ratio (30:20 in test and 35:15 in control group) was comparable, but there was a significant difference between the groups with respect to mean age. The details of disease severity of COVID-19 patients enrolled in the study in listed out in [Table/Fig-4].

Demographic data	Test group	Control group	p-value
Male	30	35	0.087
Female	20	15	
Mean age±SD (years)	36.64±8.9	31.08±7.7	0.001

[Table/Fig-2]: Gender distribution data of COVID positive patients.

Age group (years)	Test group (n)	Control group (n)
18-25	7	14
26-35	12	21
36-45	21	14
46-55	10	1
Total	50	50

[Table/Fig-3]: Age wise frequency distribution of patients.

Disease severity of COVID-19 patients	Test group (n)	Control group (n)
Mild	40	48
Moderate	10	2
Total	50	50

[Table/Fig-4]: Disease severity of COVID-19 patients.

The primary outcome of the status of COVID-19 RT-PCR test results on day 5 and day 10, presented in [Table/Fig-5,6]. There was a statistically significant improvement (p-value=0.0338) in the number of patients who turned out to be negative on day 5 and who got treated with clevira as add on drug. Out of 100 patients enrolled, 86% (43) of patients turned out to be COVID-19 RT-PCR test negative on day 5 while in the control group 66% (33) of patients turned out to be negative for COVID-19 RT-PCR test. There was no difference between the groups on day 10 as patients of both test and control group turned out to be negative for COVID-19 RT-PCR test.

Patient data on day 5	Test	Control	Total
No. of subjects enrolled	50	50	100
No. of COVID-19 RT-PCR test-Negative	43	33	76
No. of COVID-19 RT-PCR test-Positive	7	17	24
Cure % on day 5	86%	66%	
p-value	0.0338		

[Table/Fig-5]: Status of COVID-19 RT-PCR test results on day 5.
p-value <0.05 was considered statistically significant

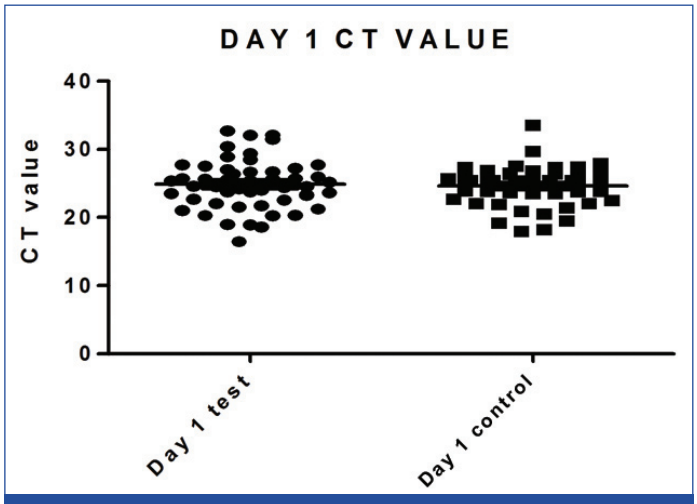
Patient data on day 10	Test	Control	Total
No. of subjects enrolled	50	50	100
No. of COVID-19 RT-PCR test-Negative	50	50	100
No. of COVID-19 RT-PCR test-Positive	0	0	0

[Table/Fig-6]: Status of COVID-19 RT-PCR test on day 10.

[Table/Fig-7] depicts the comparison of CT value of test and control group on day 1. There was no statistically significant difference (p-value=0.788) between the test and control groups on comparing day 1 CT values [Table/Fig-8]. Thus, both the groups have a comparable data on baseline.

Day 1	Mean±SD CT value of test	p-value
Test	24.87±3.6	0.788
Control	24.76±2.8	

[Table/Fig-7]: Comparison of mean CT value of test and control group on day 1.
p-value <0.05 was considered statistically significant

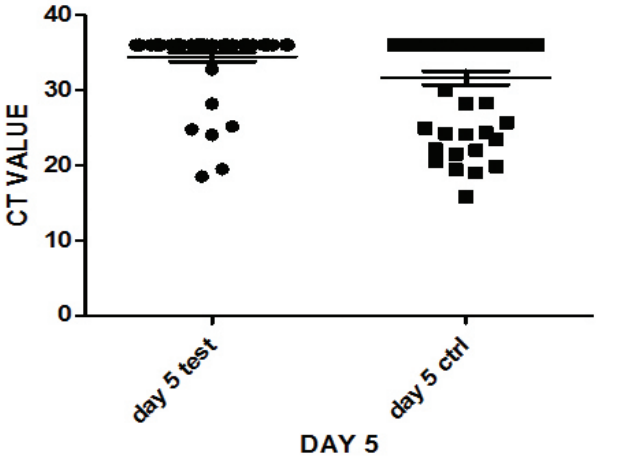


[Table/Fig-8]: DOT plots of CT values on day 1.

[Table/Fig-9] depicts the comparison of CT value of test and control group on day 5. There was a statistically significant difference (p-value=0.018) between the groups on comparing with day 5 CT value results [Table/Fig-10]. Hence, there was a significant improvement in the CT value in Test group when compared to control group on day 5.

Day 5	Mean±SD CT value of test	p-value
Test	34.4±4.3	p=0.018
Control	31.8±6.2	

[Table/Fig-9]: Comparison of mean CT Value of test and control group on day 5.
p-value <0.05 was considered statistically significant



[Table/Fig-10]: DOT Plots of CT values on day 5.

Comparison of mean CT value between test and control groups on day 1 and day 5 is mentioned in [Table/Fig-11]. Data was analysed using two tailed independent t-test. There was a statistically significant difference (p-value=0.0196) between the test and control groups on comparing the mean difference in CT value results between day 1 and day 5. Hence, there was a significant improvement in the CT value in test drug (clevira) treated group when compared to control group on day 5. Thus, the COVID-19 concentration has been brought down to significant levels in the test drug (clevira) treated group.

Group	Mean difference of CT value (Day 1-Day 5)	p-value
Test group	9.62±4.64	0.0196
Control group	7.05±6.99	

[Table/Fig-11]: Comparison of mean CT value between test and control groups on day 1 and day 5.
p-value <0.05 was considered statistically significant

[Table/Fig-12] shows the clinical (signs and symptoms) recovery status of the patients on day 15 post enrollment. There was a statistically significant difference (p-value=0.0001) between the test and control groups on comparing the mean day of relief of signs and symptoms. Thus, the test group shows better improvement of signs and symptoms of COVID-19 infection by 4.1 days when compared to control group where it was 6.28 days.

Parameters	Test group (n)	Control group (n)
Cough	23	38
Shortness of breath and SpO_2 >94%	15	3
Fever	7	13
Headache	4	1
Myalgia	12	29
Loose stool	1	5
Loss of smell	33	23
Loss of taste	40	24
Signs and symptoms relieved (Mean days)	4.1±1.7	6.28±2.5
p-value	p=0.0001*	

[Table/Fig-12]: Clinical (Signs and Symptoms) recovery status on day 15-compared between the test and control group.
*Data was analysed using two tailed independent t-test; p-value <0.05 was considered statistically significant

[Table/Fig-13] shows the clinical improvement status using 6 point ordinal scale. There was no statistically significant difference (p-value=0.93) between the test and control groups on comparing the mean duration of hospital stay and 6 point ordinal scale data. However, there was improvement in the mean ordinal scale from 2.5 on day 1 to 1.6 on day 5 with an improvement of 0.9 in the test group. While there was improvement in the mean ordinal scale from 2.06 on day 1 to 1.85 on day 5 with an improvement of 0.21 in the control group.

Parameters	Test (Mean)	Control (Mean)	p-value
Hospital stay (in Days)	6.48	7.14	0.93
Ordinal scale on Day 1	2.5	2.06	
Ordinal scale on Day 3	2.2	2.06	
Ordinal scale on Day 5	1.6	1.85	
Ordinal scale on Day 7	1.4	1.5	
Ordinal scale on Day 10	1.1	1.2	

[Table/Fig-13]: Clinical improvement status using 6 point ordinal scale.
Data was analysed using two tailed independent t-test; p-value <0.05 was considered as significant

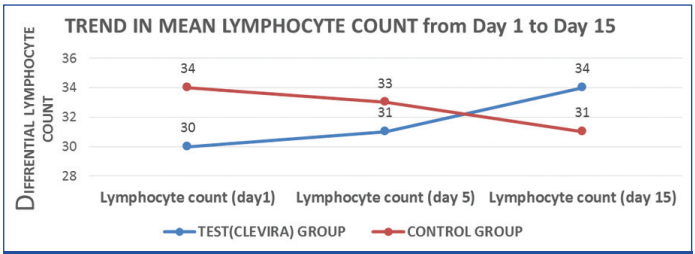
[Table/Fig-14] shows the haematological and biochemical laboratory data analysis on day 1, day 5 and day 15/post study. There was a statistically significant difference (p-value <0.01) on comparing the mean values of total White Blood Cells (WBC) count, platelet count,

Parameters	Group	Day 1	Day 5	Day 15/Post study	p-value
Red blood count (million/mm)	Test	4.79±0.54	4.81±0.44	4.80±0.48	0.83
	Control	4.98±0.50	5.01±0.53	4.95±0.49	0.77
Haemoglobin (%)	Test	13.02±2.02	13.08±1.85	13.20±1.90	0.87
	Control	14.23±1.89	14.22±1.90	14.01±2.01	0.97
Packed cell volume (%)	Test	41.00±5.07	41.28±4.71	41.18±4.55	0.77
	Control	44.40±5.29	44.31±5.24	43.44±5.58	0.93
White blood cell count (10^9/L)	Test	7518.00± 2243.99	8720.00± 3605.63	8182.04± 2677.60	**0.04**
	Control	7130.80± 2185.67	6972.40± 1853.88	7925.27± 2958.46	0.69
Lymphocytes (10^9/L)	Test	30.23±11.17	31.44±10.61	34.07±7.40	**0.04**
	Control	34.43±9.69	33.03±8.33	31.99±7.01	0.15
Neutrophil (10^9/L)	Test	62.63±11.84	61.61±11.49	57.70±8.08	**0.01**
	Control	58.04±10.61	58.74±9.41	61.05±8.25	0.11
Eosinophil (10^9/L)	Test	2.88±2.56	2.59±1.86	3.75±3.36	0.51
	Control	3.07±3.17	3.38±3.09	2.68±1.81	0.62
Monocyte (10^9/L)	Test	3.71±1.28	3.74±0.99	3.86±1.17	0.89
	Control	3.91±1.47	4.27±1.33	3.77±0.89	0.18
Basophil (10^9/L)	Test	0.53±0.24	0.59±0.33	0.63±0.25	0.30
	Control	0.54±0.27	0.57±0.19	0.66±0.18	0.52
Platelet count (10^9/L)	Test	2.96±0.86	3.33±0.9	3.00±0.97	**0.03**
	Control	2.46±0.55	2.62±0.56	2.88±0.59	0.15
Erythrocyte sedimentation rate (mm/hr)	Test	23.98±21.7	18.94±16.41	20.59±20.04	0.19
	Control	15.14±15.5	14.46±16.39	14.01±12.84	0.81
Urea (mmol/L)	Test	19.72±8.00	21.70±8.89	18.79±4.64	0.24
	Control	21.60±7.23	19.66±5.14	20.41±4.72	0.11
Creatinine (mg/dL)	Test	0.89±0.21	0.87±0.14	0.84±0.18	0.57
	Control	0.96±0.16	0.84±0.15	0.89±0.16	**0.03**
Total bilirubin (µmol/L)	Test	0.54±0.37	0.50±0.30	0.52±0.26	0.55
	Control	0.73±0.37	0.67±0.34	0.72±0.38	0.67
Aspartate aminotransferase (U/L)	Test	33.6±18.45	29.28±17.85	21.63±7.10	**0.0001**
	Control	35.54±20.74	28.78±13.44	22.44±7.30	**0.0005**
Alanine aminotransferase (U/L)	Test	56.68±30.2	57.44±60.4	42.63±21.80	**0.008**
	Control	55.62±32.87	44.98±26.16	38.92±20.77	**0.003**
Alkaline phosphatase (U/L)	Test	77.86±28.18	77.84±28.22	86.26±32.05	0.16
	Control	86.50±29.59	82.64±37.12	85.25±22.87	0.80
Gamma-glutamyl transferase (U/L)	Test	69.78±68.79	73.14±71.59	58.04±58.08	0.36
	Control	48.16±22.28	48.32±27.85	40.00±19.19	0.056

[Table/Fig-14]: Haematology and biochemistry laboratory data analysis on day 1, day 5 and day 15/post study.
p-value <0.05 was considered as statistically significant

lymphocytes, neutrophils, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) of day 1, day 5 and day 15 of test group (clevira). And there was significant difference (p-value <0.01) on comparing the mean values of ALT, AST and creatinine levels on comparing day 1 and day 15 of control group.

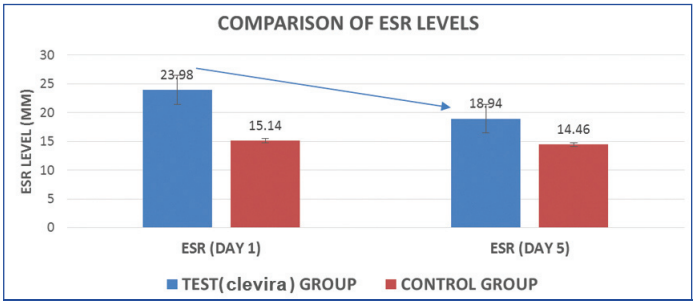
There was a significant increase in the White Blood Cell (WBC) count on day 5 and 15 in clevira treated test group and there was also a significant increase (p-value <0.01) in the lymphocyte count [Table/Fig-15] on comparing day 1 and day 15 of test group, which acts as an indicator of immunoregulatory property of clevira.



[Table/Fig-15]: Trend in Lymphocyte count.

There was also a significant increase in the platelet count on day 5 and day 15 in clevira treated test group, which confirms the proved fact that clevira can be used in patients with thrombocytopenia.

There was also a moderate decrease in the Erythrocyte Sedimentation Rate (ESR) levels from day 1 to day 5 in clevira treated group when compared to control group, which proves the anti-inflammatory property of clevira, which will be beneficial in treating COVID-19 positive patients [Table/Fig-16].



[Table/Fig-16]: Comparison of Erythrocyte Sedimentation Rate (ESR) levels.

There was a significant decrease (p-value <0.05) in the AST and ALT levels in both test and control groups on day 15.

All the patients recovered of the above mentioned adverse events without any specific medical intervention. There were no documented Serious Adverse Event (SAE) or death (mortality) of the study participants, during the entire study period [Table/Fig-17]. All the patients enrolled in the study recovered from the COVID-19 illness and are staying healthy, as confirmed by our post study follow-up on day 30.

Adverse events	Test group (n)	Control group (n)
Loss of appetite	3	4
Nausea	2	1
Abdominal pain/gastritis	7	3
Diarrhoea	1	5

[Table/Fig-17]: Adverse events encountered during the first 15 days of the study period (Postintervention).

DISCUSSION

The pandemic of COVID-19 caused by novel coronavirus (SARS-CoV-2) infection is a public health emergency of international concern for the World Health Organisation (WHO) and for Indian Council of Medical Research (ICMR) (India). At present, the efforts of various countries are focused on the rapid diagnosis and isolation of patients, as well as to find a cure for COVID-19 in order to combat the serious impact of the disease. The number of reported COVID-19 virus infections is still increasing globally. In the lack of confirmed effective treatments, due to public health emergencies, it is vital to study the promising effects of various existing approved antivirals drugs for SARS-CoV-2 like Ivermectin, which has been suggested to be an effective and safe chemoprophylactic drug in management of COVID-19 [15].

Traditional Indian medical practices like ayurveda, siddha, unani, and homeopathy are a vast reservoir of knowledge about various medicinal plants. The pharmacological properties of these plants have paved way for developing novel therapeutic options against coronavirus infection. By identifying various phyto compounds, it is possible to effectively characterise medicinal herbs that could help to alleviate COVID-19 infection. Hence, by repurposing the Indian medicinal plants, more innovative treatment options can be penned down for their role in defeating this viral transmission. At the time of worldwide anxiety, it is imperative to find long term solutions to prevent the transmissions of such pandemics.

Clevira is one such proprietary ayurvedic medicine where the individual herbal ingredients used are known to have variety of medicinal properties against fever of viral origin and proven to have effective antipyretic, analgesic, antiviral and immune regulatory properties. It provides faster relief in conditions of viral fever in chikungunya and dengue, which has been proved clinically [9,16,17]. The present study has shown that there was a significant improvement in the patients on day 5, who got treated with clevira as add on drug. Total 43 (86%) of patients turned out to be COVID-19 RT-PCR test negative on day 5 while in the control group 33 (66%) of patients turned out to be negative for COVID-19 RT-PCR test. There was also a significant improvement in the CT value in Test drug treated group when compared to control group on day 5. The present study shows, that the COVID-19 concentration has been brought down to significant levels in the test drug treated group.

This effect is probably due to the presence of antiviral property of *Andrographis paniculata, Carica papaya, Tinospora cordifolia* and *Melia azedarach* which are the active ingredient of clevira. *Andrographis paniculata* a medicinal plant which has been reported to have anti-HIV, antipathogenic bacteria and immunoregulatory activities which also possess blood purifying activity and thus eliminates the toxic metabolites and have anti-inflammatory, antipyretic and analgesic activity [18,19]. Recent studies have shown that *Andrographis paniculata* modulates NOD-Like Receptor Protein 3 (NLRP3), caspase-1, and interleukin-1β molecules which are extensively involved in the pathogenesis of SARS-CoV and likely SARS-CoV-2 as well. Docking studies have also shown that *Andrographis paniculata* is a potential inhibitor of the main protease of SARS-CoV-2 (Mpro) [10,20].

Tinospora cordifolia an active ingredient of clevira, is known to strengthen host immune system by activating macrophages, NF-kappa beta translocation and cytokine production. It has antipyretic, antiviral and hepato-protective activity [21], it has also shown to have antiviral properties against SARS-CoV-2 [11,13,22]. Also, docking studies have shown that Limonoids from *Melia azedarach* (an ingredient of clevira) are also a potential inhibitor of SARS-CoV-2 proteins [12]. Limonoids from *Melia azedarach* fruits has inhibitory activity on Flaviviruses and Mycobacterium tuberculosis [23,24]. *Carica papaya*, another active ingredient of clevira is also known for its antiviral activity against Dengue virus which is also single stranded RNA virus similar to SARS-CoV-2. Its efficacy has been well proved in various clinical studies and it also has platelet augmentation activity [9,16,17].

The study results also illustrate a significant increase in the WBC count on day 5 and day 15 in clevira treated test group with a significant increase in the lymphocyte count on day 15, which suggests the immune regulatory property of clevira. *Andrographis paniculata, Tinospora cordifolia* and *Piper nigrum* (ingredients of

clevira) have proven immunomodulatory activity [18,19,21,25]. This helps in combating COVID-19 infection and hence can be used for SARS-CoV-2 infected patients as an add on drug.

Studies have shown that COVID-19 infection decreases the total and differential WBC count, which starts improving from 8th day onwards [26]. The present study has shown that on intervention with clevira plus standard treatment, the WBC count and lymphocyte count increased on day 5 and day 15. Thus, clevira will be beneficial in improving WBC count and help in early recovery of COVID-19 positive patients.

Studies also showed that there is a decrease in the platelet count in COVID-19 positive patients and is associated with an increased risk of severe disease and mortality [26,27]. The present study results showed a significant increase in the platelet count on day 5 and day 15 in clevira treated test group which will play a vital role in decreasing the severity of the infection and preventing the mortality. This platelet augmentation activity is mainly due to the effect of *Carica papaya* (active ingredient of clevira) which is also known for its antidengue property. It is reported to be having enhancement of arachidonate 12- lipoxygenase and the platelet activating factor receptor gene expression which is responsible for increased platelet production [16,17]. Also, *Vettivera zizanoides* (another ingredient of clevira) has an effective antiviral property. Docking studies have shown that Ethyl 4-(4-methylphenyl)-4-pentenoate from *Vetiveria Zizanioides* inhibits dengue NS2B-NS3 protease and prevents viral assembly [28].

The present study outcome also elicits a moderate decrease in the ESR levels from day 1 to day 5 in test product treated group when compared to control group, which supports the anti-inflammatory property of clevira, which will be beneficial in treating COVID-19 positive patients. The various ingredients of clevira like *Andrographis paniculata, Tricosanthus dioica, Mollugo cerviana, Piper nigrum, Zingeber officinaleis* and *Cyperus rotandus* have potent anti-inflammatory property [29-33] and also antipyretic property which will be beneficial in curing the symptoms of COVID-19 positive patients like fever, headache and myalgia. The various chemical constituents present in *Tricosanthus dioica* are vitamin A, vitamin C, tannins, saponins, alkaloids, mixture of noval peptides, proteins tetra and pentacyclic triterpenes which possess antipyretic and anti-inflammatory property [32]. This effect of the test product is evident from the present study outcome which shows that patients treated with clevira along with standard of care treatment show a significant improvement in signs and symptoms of COVID-19 infection by 4.1 days when compared to control group where it was 6.28 days.

Various studies [34] have shown that there is a frequent incidence of liver injury in COVID-19 patients, and it is often manifested as transient elevation of serum amino transferases (AST and ALT). In the present study, there were 12 subjects who presented with elevated levels of serum amino transferases and it got normalised on treatment with clevira along with standard of care treatment. There was also a significant decrease in the AST and ALT levels on day 15. It may be due to the property of *Piper nigrum*, which protects the liver and neutralizes the endotoxins and detoxifies pathogenic remnants from liver and blood [33]. Also, *Mollugo cerviana* has hepatoprotective efficiency and photo-protective capacity due to the presence of phytochemicals like carbohydrates, saponins, tannins, terpenoids, flavonoids, steroids, phenols, proteins and alkaloids [29]. Presence of *Zingeber officinale* in clevira helps in the recovery of appetite and digestion by stimulating the secretion of gastric enzyme [33].

Limitation(s)

The major limitation of the study was placebo controlled double blinded study was not conducted, as during the first COVID-19 outbreak it was not feasible. Immunological blood markers were not tested, as much insight was not available during the first COVID-19 outbreak. Pre and Post analysis of clinical signs and symptoms improvement within group was not performed. Further phase 4 clinical trial with larger sample size and with added testing parameters like the immunological markers can be conducted in future.

CONCLUSION(S)

The results obtained in this study concluded that clevira, with its poly herbal ingredients shows a significant antiviral action against COVID-19 when given in addition to the medications suggested by WHO/ICMR, over a period of 14 days. On treatment with tab. clevira along with standard of care treatment 86% of patients turned out to be COVID-19 RT-PCR test negative on day 5 and 100% of patients turned out to be COVID-19 RT-PCR test negative on day 10 with a significant reduction in the RT-PCR CT-values. Clinical improvement of signs and symptoms of COVID-19 infection was achieved by 4.1 days. It is also eliciting a probable immune regulatory property and certain platelet augmenting property, with no serious side effects of concern. Clevira has a very good patient compliance with twice daily administration over a period of 14 days. It is also hepato-protective in nature. Thus, clevira can be given as an add on therapy in treating patients with mild to moderate COVID-19 positive patients and help in early recovery. Thus, it may be helpful in reducing the disease transmission and bring down the incidence of COVID-19. Further prospective studies for determining the prophylactic use of clevira are on the docket.

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