Contemporary Clinical Trials Communications 22 (2021) 100755

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

A randomized and comparative study to assess safety and efficacy of supplemental treatment of a herbal formulation - *Aayudh Advance* comprising essential oils in patients with corona virus 2019 (COVID-19)

Jayesh Dutt [a], Bhavdeep Ganatra [b], Nilay Suthar [c], Mohammedebrahim Malek [a], Bhakti Shukla [d], Krupali Shukla [d], Karna Shukla [d], Shreya Pandit [e], Manish Rachchh [f,*], Rina Gokani [f], Mona Bhalani [f]

[a] *Smt. NHL Municipal Medical College & SVPIMSR, Ellisbridge, Ahmedabad, 380006, Gujarat, India*
[b] *Ganatra Ayurveda & Panchkarma Clinic, 125, Advait Complex, Opp Soham Tower, B /s Sandesh Press, Vastrapur, Ahmedabad, 380054, Gujarat, India*
[c] *LG Hospital, Ahmedabad, Gujarat, India*
[d] *M/s Shukla Ashar Impex Pvt. Ltd., Rajkot, 360001, Gujarat, India*
[e] *Pandit Dindayal Gov. Hospital, Rajkot, 360001, Gujarat, India*
[f] *M/s Accuprec Research Labs Pvt Ltd., Ahmedabad, 382213, Gujarat, India*

ARTICLE INFO

Keywords:
Aayudh advance
COVID-19
Standard of care (SOC)
Adverse drug reaction
Covariate adaptive randomization

ABSTRACT

Objective: The purpose of this study was to examine the effect of herbal formulation - Aayudh Advance on viral load as well as recovery duration in mild symptomatic patients diagnosed with Corona Virus Disease 2019 (COVID-19). It also aimed to study the effect of Herbal formulation – Aayudh Advance in terms of clinical improvement of various sign and symptoms in mild symptomatic COVID-19 patients.

Method: Once the patient suffice the requirement of inclusion, exclusion criteria of the study than as per the method of 'Covariate Adaptive Randomization' technique, patient was assigned in either Aayudh Advance arm (Test arm) or Control Arm. Here standard of Care treatment was given to all patients of both the arms. Treatment was given for the period of 14 days or till patient turned COVID-19 negative, which ever was earlier. Clinical signs and symptoms viz. body temperature, SpO 2, Scoring of Cough & Scoring of Shortness of breath were recorded on all 5 Clinical visits along with biochemical testing like RT-PCR (with CT value of E gene and RDRP gene), serum ferritin, CRP and NLR observed on weekly Visit.

Result: Total 74 patients were enrolled in the present study. Out of which 60 patients (30 patients in each group) have completed study as per the protocol, whereas 14 patients have voluntarily withdrawn from the study due to getting early discharge from the hospital. All patients in Aayudh Advance treatment group recovered (100%) after 14 days. This observed recovery was 15.38% more as compared to Standard of Care treatment alone. Further, there was statistically significant reduction ($p < 0.05$) in viral load as indicated by significant increase in CT value of E-gene and RDRP gene. Further, no patients reported any Adverse Reaction as well as no drug to drug interaction was observed with supplemental treatment with Aayudh Advance.

Conclusion: The Aayudh Advance was found safe as well as more effective in terms of reduction of viral load. % recovery was more in Treatment arm as compared to Control arm in mild symptomatic COVID-19 patients.

1. Introduction

Corona viruses are a group of enveloped viruses with non segmented, single-stranded, and positive-sense RNA genomes. Apart from infecting a variety of economically important vertebrates (such as pigs and chickens), six corona viruses have been known to infect human hosts and cause respiratory diseases. Among them, severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS-CoV) are zoonotic and highly pathogenic corona viruses that have resulted in regional and global outbreaks [1].

* Corresponding author.
E-mail addresses: jayeshjdutt@rediffmail.com (J. Dutt), vd.ganatra@gmail.com (B. Ganatra), bhakti@shuklaashar.com (B. Shukla), manish.rachchh@accuprec.com (M. Rachchh).

https://doi.org/10.1016/j.conctc.2021.100755
Received 22 September 2020; Received in revised form 27 January 2021; Accepted 1 March 2021
Available online 11 March 2021

In 2019, the Centers for Disease Control and Prevention (CDC) started monitoring the outbreak of a new corona virus, SARS-CoV-2, which causes the respiratory illness now known as COVID-19. Authorities first identified the virus in Wuhan, China [1].

Corona viruses will infect most people at some time during their lifetime. Corona viruses can mutate effectively, which makes them so contagious. To prevent transmission, people should stay at home and have to take complete rest while symptoms are active [1].

Suspected cases can be screened for the virus with nucleic acid amplification tests (NAAT), such as RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) with confirmation by nucleic acid sequencing, if required [2].

In humans, the COVID-19 infection shows the signs and symptoms depending up on the severity of the disease. The patients with uncomplicated (mild) illness usually show symptoms of upper respiratory tract viral infection, including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise and patient may have GIT symptoms like diarrhea and vomiting. In complicated illness patients may have various stages of Pneumonia (moderate and severe) and critical (Acute Respiratory Distress Syndrome and sepsis) [3].

Globally as of 14 July 2020, there were 1,29,29,306 confirmed cases of COVID-19 reported, including 5,69,738 deaths reported to WHO. In India, from Jan 30 to 14 July 2020, there have been 9,06,752 confirmed cases of COVID-19 with 23,727 deaths.

Number of medicines have been suggested as potential investigational therapies. Many of these are now being studied under various phases of clinical trials or will soon be studied in clinical trials. In many countries, doctors are giving Hydroxychloroquine, remdesivir, favipiravir or dexamethasone as a front line therapy to COVID-19 patients [4].

The most common adverse events observed with hydroxychloroquine and chloroquine are gastrointestinal upset along with nausea, vomiting, and diarrhea. Other adverse effects from acute use of hydroxychloroquine and chloroquine for instance, the most common adverse events observed with hydroxychloroquine and chloroquine are gastrointestinal distress such as nausea, vomiting, and diarrhea. Other adverse effects from acute use of hydroxychloroquine and chloroquine include hypoglycemia in diabetic patients, neurotoxicity in the form of tinnitus, headaches, and mood changes, and hemolytic anemia in patients with G6PD deficiency. Severe COVID-19 patients also commonly suffer other adverse effects of hydroxychloroquine such as vascular complications (e.g. endothelium damage) and vasculitis-like manifestations [2,5–8].

Remdesivir is a broad spectrum anti-viral drug that has shown to inhibit SARS-CoV2, *in vitro* and *in vivo*. Remdesivir has shown a mixed results in patients of COVID-19 with an acceptable side effects. Phase-1, blinded-studies conducted with remdesivir in healthy individuals displayed adverse events in 5% of the classes. The adverse events included phlebitis, constipation, headache, ecchymosis, nausea and pain in the extremities [2,9].

In a study by Grein et al. common adverse events noted during compassionate use of remdesivir in patients with COVID-19 included rash, diarrhea, hypotension, abnormal liver function and renal impairment. Additionally, serious adverse events such as - acute kidney injury, septic shock, multi-organ failure were noted in 23% of the cases, while 60% of the cases had at least one adverse event and 8% of the cases discontinued due to various side effects of remdesivir [2,10].

Q. Cai et al. (2020) studied the effects of Favipiravir (FPV) versus Lopinavir (LPV)/ritonavir (RTV) for the treatment of COVID-19 in an open label non-randomized control study. The adverse events observed in the FPV arm of the study included diarrhea, liver injury, a poor diet compared to the control arm [Lopinavir (LPV)/ritonavir (RTV)] [2,11].

The use of glucocorticoids like Dexamethasone may delay the clearance of viral nucleic acids in patients and should be avoided during viral replication. The reduction of viral load can be detected by the presence of the viral RNA in feces. Ling Y et al. (2020) observed that the clearance of viral RNA from patients' stools was delayed in the patients who ingested Dexamethasone versus the control. This delay in excretion of the viral RNA strongly contraindicates the administration of glucocorticoids in the treatment of COVID-19 patients, especially for those who experience mild symptomps of the disease [2,12,13].

Therefore, given the seriousness of the disease and the limitation of the available medications. There is a strong requirement to develop and identify a medicine that is highly effective against the disease and very safe in COVID-19 mild symptomatic patients.

India is the country where the world's oldest living health care system originated and therefore it is being carefully watched by the world community that how India handles the crisis using its own resources [14].

Indian Ayurvedic Medicine system across the country has been put on alert to serve the nation. AYUSH healthcare facilities are also being read yield to be converted into quarantine facilities in times of need. Therefore given the preexisting infrastructure and resources of the AYUSH healthcare system, the nation would greatly benefit from an Ayurveda based intervention plan to treat COVID-19 [14,15].

The present study tests a patented and proprietory Ayurvedic liquid formulation called 'Aayudh Advance' in mild symptomatic COVID-19 patients. Aayudh Advance is a liquid formulation comprising 21 different types of essential oils along with an artificial sweetner as listed in Table 1. These ingredients are reported in the scriptures of the Ayurveda to be effective and safe to be used for the human consumption. Aayudh Advance comprises of specific combinations of phenols, saturated and unsaturated medium chained fatty acids and alcohols that are derived from natural sources and converted in to colloids, without the use of heavy metals, for increased efficacy without comprising patient safety. The oral toxicity study of the herbal formulation - Aayudh Advance was also performed as per OECD 423 guideline and it was categorized under Category 5 or unclassified and the observed LD50 value was >5000 mg/kg in experimental rat.

Further, Aayudh Advance has been approved by state FDCA (Ayurved), Gujarat and licenced (GA/1800) for the manufacturing and marketing purposes. Further, in-vitro anti-viral activity of Aayudh Advance was tested against H1N1 influenza virus as per EN 14473:2013 guideline and was found effective in reducing viral load by 4.275 log which was equivalent to 67.06% inhibition of the viral load.

Table 1
Composition of aayudh advance.

Sr. No.	Name of Ingredients
1	Extract of Coconut
2	Extract of Corn
3	Extract of Sugarcane
4	Oregano oil
5	Clove oil
6	Lemongrass oil
7	Cinnamon oil
8	Coconut oil
9	Neem oil
10	Blackseed oil
11	Spearmint oil
12	Peppermint oil
13	Franckincense oil
14	Lemon oil
15	Eucalyptus oil
16	Coriander oil
17	Lavender oil
18	Rosemary oil
19	Thyme oil
20	Tea tree oil
21	Sweet orange oil
22	EDTA
23	Sweetener as Sucralose
24	Water

The essential oils used in herbal formulation - Aayudh Advance work synergistically to yield immune-modulatory effects. These hinder various bacteria, viruses and fungi from exploiting the immune system and absorb free radicals that are produced that tend to cause havoc to the body. Furthermore, the propreitary formulation - helps to generate a faster systemic reaction against pathogens. In addition, the herbal formulation has various properties that help protect organs and reduce any unnecessary hypertrophy of the organs that may have resulted from pre-existing diseases such as diabetes, heart diseases, liver diseases, renal diseases, allergies, etc. Aayudh Advance combines the Ayurvedic knowledge of creating synergies between various extracts (i.e. essential oils) with the modern sciences of creating colloids [16–36].

The objective of this study was to examine the efficacy and safety of the herbal formulation – aayudh Advance in patients exhibiting mild to moderate symptoms of COVID-19. The effectivity would be evaluated on the reduction of the viral load and improvement of the recovery rate upon the administration of the formulation. The safety of the formulation would be determined based on the observed side effects. Adverse reactions and the requirement of adjunctive medication.

2. Methods

2.1. Clinical trial site

The present clinical trial was conducted at Smt. NHL Municipal Medical College & SVPIMSR, Ahmedabad, Gujarat, India. The protocol of the present study ARL/CSP/2020/002–01 was approved by Institutional Ethics Committee of Smt. NHL Municipal Medical College, Ahmedabad (NHLIEC), Gujarat, India and the protocol was registered with Clinical Trial Registry of India (CTRI) with Registration No.: CTRI/2020/05/025161 [Registered on: 13/05/2020].

2.2. Patients' recruitment

Patients were recruited amongst those complying with inclusion – exclusion criteria. Patients were given the patient information sheet in vernacular language comprising of the, experimental nature of study, alternative treatments, study procedures that were to be followed probable risks due to test drug Aayudh Advance the information was also verbally explained by the principal Investigator and or Co-Principal Investigator. Patients who gave their written consent were enrolled in the study. In addition, patient's demographic data, medical history and ongoing treatment related information were gathered and compiled during the patient recruitment process.

2.3. Inclusion criteria

Subject willing to sign informed consent. Subject age group of 18 years and above of both gender. All patients with COVID-19 RT-PCR positive (within 7 days)/any COVID-19 test kit, admitted to the hospital/healthcare center. Patients having mild to moderate symptoms of COVID-19 disease and tested positive for COVID-19 test.

2.4. Exclusion criteria

Patients younger than 18 years. Women who were pregnant or who intend to become pregnant for the next three months after taking the drug. Patients allergic to type medications or any of the ingredient of the formulation. Patients with a neurological history (seizures, epilepsy, etc.). Patients with a previous history of psychiatric illnesses (depression, anxiety, suicide attempt).

Patients with cardiac pathologies or relevant chronic diseases that in the judgment of the clinician recommend the non-inclusion of the patient in the study. Patients who were on artificial ventilation or oxygen supply. Very severe patients of COVID-19. Patients with severe hypertension, diabetes or any other chronic disease shall be excluded.

2.5. Study procedures

After receiving the written consent from the patient, the patient was assigned to either Treatment arm (Aayudh Advance + Standard of Care) or Control arm (Standard of Care alone) using covariate adaptive randomization technique. The Standard of Care treatment recommended by Ministry of Health, Government of India and includes multivitamin supplements with zinc, Vitamin C, Paracetamol, Levocetrizine, Pantoprazole, Ondensetron, Azithromycin, Cefpodoxine etc and prescribed by the Investigator as required for enrolled subjects.

After enrollment of the patients in the study, clinical parameters like body temperature, SpO_2 level, severity of cough and shortness of breath have been observed by Co-Principal Investigator and recorded in Case Report Form (CRF). Other biochemical parameters like CT value of E gene and RDRP gene, CRP, serum ferritin, and NLR ratio were also tested on Day 1 (Visit 1) for both the arms of the study. Visit 2 was scheduled on Day 3. During Visit 2, the temperature, shortness of breath, cough severity, any adjunctive medication requirements and any supplementation related side effects were measured, observed and recorded. Visit 3 was scheduled on Day 7. Visit 3 included monitoring of all the parameters as mentioned in the Visit 2 as well as additional biochemical parameters like CT value of E gene and RDRP gene, CRP, serum ferritin, and NLR. Visit 4 was scheduled on Day 10 and parameters observed like Visit 2. Visit 5 was scheduled on Day 14 and parameters observed were like Visit 3. The study ended when patient became COVID-19 negative followed by the discharge from the hospital. This way, no further follow-up visits. Would be required post discharge.

2.6. Early withdrawal criteria

Patients may withdraw from the study at any given time, and for any of the following reasons:

If any adverse reaction or side effect observed during the study, then the patient may withdraw from the study as per investigator's decision. If the severity of the symptoms of COVID-19 increases in the study patients then the patient may withdraw from the study as per investigator's decision. The patient can withdraw, herself/himself from the study due to early discharge from the hospital as per their right or withdrawal as mentioned in protocol and informed consent form.

2.7. Patient enrollment summary

A total of 110 patients were screened out of which 74 subjects were found to be eligible for the study. The informed consent was given by all 74 subjects. The study was completed by 60 patients, wherein there were 30 patients were allotted in each arm of the study. Total 14 patients voluntarily withdrew from the study because they became asymptomatic within a week of enrollment and were discharged from the hospital without undergoing COVID-19 test.

2.8. Clinical observations

2.8.1. Oxygen saturation level (SpO_2)

The oxygen saturation level (SpO_2) was observed using pulse oximeter in terms of % saturation.

2.8.2. Fever

The body temperature was recorded in °F using an infrared thermometer.

2.8.3. Cough

The symptom of cough was categorized based upon severity from 0 to 3 scale. 0 = no cough, 1 = mild, 2 = moderate, 3 = severe.

2.8.4. Shortness of breath

The symptom of shortness of breath was categorized based upon a severity from 0 to 3 scale. 0 = no shortness of breath, 1 = Shortness of breath with moderate intensity exercise, 2 = Shortness of breath while walking on flat surface, 3 = short of breath while getting dressed or performing daily activities.

2.8.5. Recovery ratio

In given period of time, a comparison of the number of enrolled patients, between treatment and control study arms, who turned COVID-19 negative.

2.8.6. Recovery period

The total number of days required for enrolled patients to become COVID 19 negative. The number of days is counted from the day of enrollment to the day of discharge.

2.8.7. CT value

The Cycle Threshold value (CT value) was determined for E gene and RDRP gene during RT-PCR testing for COVID 19 on Visit 1, Visit 3 and Visit 5 only took place if the patient was not COVID 19 negative by Day 14.

2.8.8. Serum ferritin

Serum ferritin was tested during Visit 1, Visit 3 and Visit 5, using Chemiluminescence Enzyme Immunoassay (CLIA) method and represented in terms of ng/ml (Normal range: 22–322 ng/ml).

2.8.9. C-reactive protein

C-Reactive Protein (CRP) was tested during Visit 1, Visit 3 and Visit 5, using Immuno Turbidimetry method and represented in terms of mg/L (Normal range: 0–5 mg/L).

2.8.10. NLR

Neutrophil to Lymphocyte Ratio (NLR) was tested during Visit 1, Visit 3 and Visit 5, using Flow cytometric method and represented in terms of ratio (Normal range: 0.78–3.53).

2.8.11. Supplementation side effects

The presence of any adverse secondary effects from the supplementation of Aayudh Advance, was recorded in respective CRF of the patient.

2.8.12. Adjunctive medications

Number of patients who were prescribed adjunctive medications for any supplementation side effects (if observed) were recorded in respective CRF of the patient.

2.9. Statistical analysis

All data were represented as Mean ± SEM. p-value less than (<) 0.05 was considered statistically significant. Depending upon data type, either one way ANOVA followed by Tukey's post hoc test or Un paired *t*-test with Welch correction test was used to analyze the data.

3. Results & discussion

3.1. Demographic details

There was no statistically significant difference (i.e. $p > 0.05$) observed in demographic parameters like gender, age, height, etc. This insignificance dictates that there was no biological variation in both the treatment groups (Table 2).

3.2. Effect on SpO_2 level

There was no statistically significant difference (i.e. $p > 0.05$) observed in SpO_2 level within the groups as well as between the groups when tested using One way ANOVA followed by Tukey's post hoc test (Table 3).

3.3. Effect on body temperature

There was no statistically significant difference (i.e. $p > 0.05$) observed in body temperature within the groups as well as between the groups when tested using One way ANOVA followed by Tukey's post hoc test (Table 3).

Table 2
Summary of demographics data of enrolled patients.

Sr. No.	Parameters	AAYUDH ADVANCE	SOC
1	Age (Years)	33.87 ± 1.94	36.67 ± 1.81
2	Height (cm)	164.7 ± 2.31	165.5 ± 1.77
3	Weight (kg)	69.72 ± 2.89[a]	62.63 ± 1.78
4	BMI (kg/m2)	25.61 ± 0.84[a]	22.93 ± 0.65

All values are in Mean ± SEM, n = 30 in each group.
[a] $p < 0.05$ when compared with SOC Group using Unpaired *t*-test with Welch's correction, two tailed, n = 30 in each group.

Table 3
Summary of clinical data of enrolled patients.

Sr. No.	Parameter	AAYUDH ADVANCE		SOC	
		Day 1 (n)	Day 7 (n)	Day 1 (n)	Day 7 (n)
1	% SPO2 level	98.23 ± 0.13 (30)	97.76 ± 0.18 (25)	97.73 ± 0.14 (30)	98.00 ± 0.15 (22)
2	Body Temp (^{0}F)	98.04 ± 0.11 (30)	98.11 ± 0.13 (25)	98.41 ± 0.21 (30)	98.00 ± 0.14 (22)
3	Change in Score of Cough	1.03 ± 0.033 (30)	0.60 ± 0.12*** (25)	1.00 ± 0.00 (30)	0.60 ± 0.11*** (22)
4	Score of Shortness of breath	0.10 ± 0.06 (30)	0.09 ± 0.06 (23)	0.07 ± 0.05 (30)	0.04 ± 0.04 (27)
5	Recovery Ratio[a]	1.00 ± 0.00 (30)	−1 ± 0.00*** (30)	1.00 ± 0.00 (30)	−0.73 ± 0.13*** (26)
6	No. of Days for Hospital Stay[a]	8.53 ± 0.65 (30)		7.9 ± 0.60 (30)	

All values are in Mean ± SEM, n = No. of patients in each group.
*$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$ when compared between two treatment arm as well as within the arm (Day 1 Vs Day 7) using one way ANOVA followed by Tukey's post hoc test.
[a] In this case, observation up to 14 days were considered.

3.4. Effect on cough severity

Statistically significant difference (i.e. $p < 0.0001$) was observed in Cough severity within the groups when tested using one way ANOVA followed by Tukey's post hoc test (Table 3).

3.5. Effect on shortness of breath

There was no statistically significant difference (i.e. $p > 0.05$) observed in Shortness of breath within the groups as well as between the groups when tested using one way ANOVA followed by Tukey's post hoc test (Table 3).

3.6. Effect on recovery ratio

Statistically significant difference was observed in the recovery ratio within the groups (i.e. $p < 0.0001$) as well as between the groups ($p < 0.01$) when tested using one way ANOVA followed by Tukey's post hoc test (Table 3). The percentage (%) Recovery ratio was 100% in Aayudh advance treatment group after 14 days whereas it was only 84.61% for standard of care treatment (SOC) alone. The percent improvement in Aayudh Advance treatment was 15.38% higher than SOC group.

3.7. Effect on E gene and RDRP gene

Statistically significant difference (i.e. $p < 0.05$) was observed in E gene and RDRP gene within the groups in Aayudh advance groups when tested using one way ANOVA followed by Tukey's post hoc test (Table 4), whereas there was no statistically significant difference ($p > 0.05$) observed between the Aayudh Advance and SOC groups.

3.8. Effect on serum ferritin

There was a 38.88% reduction in serum ferritin value in Aayudh Advance treatment group whereas only a 18.96% reduction in case of SOC. Although the Treatment arm showed greater reduction in serum ferritin level than the Control arm, no statistically significant difference (i.e. $p > 0.05$) was observed in serum ferritin within the groups as well as between the groups when tested using one-way ANOVA followed by Tukey's post hoc test (Table 4).

3.9. Effect on CRP level

There was a 17% reduction in CRP level in Aayudh Advance treatment group whereas a 47.4% reduction in SOC treatment group. No statistically significant difference (i.e. $p > 0.05$) was observed in CRP Level within the groups as well as between the groups when tested using one-way ANOVA followed by Tukey's post hoc test (Table 4).

3.10. Effect on NLR

There was no statistically significant difference (i.e. $p > 0.05$) observed in NLR within the groups as well as between the groups when tested using one way ANOVA followed by Tukey's post hoc test (Table 4).

3.11. Supplementation side effects

No any Supplementation related side effects observed.

3.12. Presence of adverse reactions

No Adverse reactions were not observed in any patient during the study period.

3.13. Requirement of adjunctive medication

There was no requirement of any adjunctive medication to be provided to patient as supplementation related side effects was not observed.

4. Discussion & conclusion

From the observation and results obtained in the present study, we can conclude that the supplement treatment of Aayudh Advance (along with SOC) was safe and effective in mild symptomatic COVID 19 patients.

Patients recovered faster in the Aayudh Advance treatment group as compared to the standard of care treatment alone. The observed recovery was 15.38% more in case of supplement treatment of Aayudh Advance (along with SOC) as compared to Standard of Care treatment alone at the end of 14 days of the study. The reduction in viral load (inferred from the increase in CT value of E gene and RDRP gene) in case of Aayudh Advance treatment found statistically significant ($p < 0.05$) as compared to Standard of Care treatment alone. The above-mentioned points indicate the efficacy of Aayudh Advance in treating patients with mild symptomatic COVID-19 patients.

Aayudh Advance comprising of 21 different essential oils and extracts, it possess various active chemicals which plays its role for its effectiveness against SARS-Co2 virus. The probable targets for chemicals inhibiting SARS-CoV2 virus includes interference with attachment of SARS-CoV2 virus with host cell, inhibit fusion/endocytosis, inhibit proteolysis, inhibit transcription, inhibit translation and inhibit exocytosis [37]. Hence, Aayudh Advance may be acting on single target or multiple targets for inhibiting SARS-CoV2 viral load. Studies are ongoing to understand the molecular mechanism of Aayudh Advance for its effectiveness against SARS-Co2 virus.

Further, in case of Aayudh Advance treatment group, the patient health did not deteriorate in any form or develop any Aayudh Advance related complications. No patients reported any Adverse Reaction to the Supplemental treatment with Aayudh Advance. No drug to drug in-

Table 4
Summary of biochemical parameters.

Sr. No.	Parameter	AAYUDH ADVANCE		SOC	
		Day 1 (n)	Day 7 (n)	Day 1 (n)	Day 7 (n)
	Effect on CT value of E gene	24.19 ± 1.123 (26)	31.22 ± 1.45* (09)	26.26 ± 1.35 (19)	31.75 ± 1.38 (04)
	Effect on CT value of RDRP gene	24.88 ± 1.20 (26)	31.22 ± 1.45* (09)	27.55 ± 1.40 (20)	32.25 ± 1.03 (04)
	Effect on Serum Ferritin Level (ng/ml)	158.2 ± 59.69 (28)	103.2 ± 22.76 (25)	146.6 ± 23.49 (23)	118.8 ± 25.27 (14)
	Effect on CRP Level (mg/L)	10.1 ± 3.60 (22)	7.49 ± 3.07 (22)	15.4 ± 6.00 (25)	8.10 ± 5.95 (14)
	Effect on NLR Ratio	3.00 ± 0.40 (28)	2.70 ± 0.45 (21)	2.51 ± 0.52 (20)	2.61 ± 0.53 (16)

All values are in Mean ± SEM, n = No. of patients in each group.
*$p < 0.05$ when compared between the treatment arm as well as within the arm (Day 1 Vs Day 7) using one way ANOVA followed by Tukey's post hoc test.

teraction was observed from the Supplemental treatment with Aayudh Advance. The above-mentioned points indicate safety of Aayudh Advance in treating patients with mild symptoms of COVID-19. Furthermore, we can also infer that the treatment of Aayudh Advance was 100% safe for all age groups (18 +) in both genders as established in the present Clinical trial involving mild symptomatic COVID-19 patients.

Aayudh Advance has proven to be highly effective and very safe in the treatment of COVID-19 patients displaying mild symptoms. The high effectivity and safety of the formulations can prove to be helpful in reducing the spread of the virus and the fatalities caused by it. In addition, since no side effects, adverse effects or drug-to-drug interactions were reported through the course of this study, wide-spread use of Aayudh Advance can be deliberated from the results.

Further studies should also be conducted to explore the potential of Aayudh Advance in comparison with the current medical alternatives in the market in the treatment of moderate to severe cases of COVID-19.

Ethics approval and consent to participate

Ethical principles in the Helsinki Declaration and as specified in the ICH-GCP Guidelines, ethical guidelines of ICMR, New Delhi and Clinical Trial guideline of Ministry of AYUSH, New Delhi were adopted for this study. No serious adverse effects occurred due to the study drug. No subjects were recruited without his/her informed consent for the study. The study protocol (ARL/CSP/2020/002–01) was approved by Institutional Ethics Committee, Smt. NHL, Municipal Medical College, Ahmedabad (NHLIEC) dated 10-May-2020 and the protocol has been registered on Clinical Trial Registry of India (CTRI) with registration no. CTRI/2020/05/025161 [Registered on: 13/05/2020].

Funding

This clinical trial was funded by M/s Shukla Ashar Impex Pvt. Ltd., 205–206 Orbit Plaza, Dr. Yagnik Road, Rajkot – 360001, Gujarat, India.

Authors' contributions

Dr. Jayesh Dutt served as Principal Investigator; Dr. Bhavdeep Ganatra as Co-Principal Investigator (AYUSH), Dr. Nilay Suthar as Co-Investigator, Dr. Ibrahim Malik as a Research fellow, Ms. Bhakti Shukla, Mr. Karna Shukla and Ms. Krupali Shukla as Research Coordinator from the sponsor side, Dr. Shreya Pandit as Research fellow, Dr. Manish Rachchh as Study Director, Dr. Rina Gokani as Deputy study director and Ms. Mona Bhalani as Research associate from CRO side.

Declaration of competing interest

We would like to declare that, there was no conflict of interest by publishing this article.

Acknowledgement

We would like to thank Mr. Deap Shukla of M/s Shukla Ashar Impex Pvt. Ltd, Rajkot for providing all financial assistance for execution of this entire study. We would also like to thank Mr. Kalpesh Joshi and Mr. Ravin Vyas for extending their support by providing timely supply of test items. Further, we would like to express our special thanks to Shri Atulbhai Pandit for managing to get all administrative approvals for the trial. Further, would like to thank Shri Rajubhai Nakum and Mr. Mayur Kandoriya for providing logistic supports. We would also like to express our gratitude of thanks to Dr. Pratik Patel, Dean of Smt. NHL Medical College and Dr. Falguni Majumdar, Member secretary- NHLIEC for providing administrative support for execution of clinical trial at hospital site.

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