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Original Research Article

Effectiveness of ayurvedic formulation, NAOQ19 along with standard care in the treatment of mild-moderate COVID-19 patients: A double blind, randomized, placebo-controlled, multicentric trial

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A R T I C L E I N F O

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A B S T R A C T

Background: Medicines in indigenous systems such as Ayurveda have strong antimicrobial activity but double-blind randomized control trials are infrequent in this system of medicine. The efficacy of a new ayurvedic formulation was evaluated during the pandemic.

Methods: 150 mild-moderate COVID-19 patients were enrolled and randomized in 1:1 to NAOQ19 and placebo group. RT-PCR was done on Day 3, 5 and 7. CBC, CRP, LFT, and KFT were assessed at baseline and exit. Duration of hospital stay was noted and clinical assessment was also performed.

Result: The results demonstrated more people turning RT-PCR negative in the NAOQ19 group compared to the placebo group on day 3 (p-value = 0.033). The mean time duration to turn RT-PCR negative was significantly lower in the NAOQ19 group (4.6 days) compared to placebo group (5.2 days) (p-value = 0.018). There was significant reduction in hospital stay among patients in the NAOQ19 arm who were discharged earlier (5.6 days) compared to placebo group (6.4 days) (p-value = 0.046). Patients in NAOQ19 arm did not show any adverse life-threatening events.

Conclusion: The ayurvedic preparation given along with standard of care therapy reduced the duration of hospital stay and there was earlier conversion to RT-PCR negative.The integrated approach can help to reduce patient workload in the hospitals as well as limit the transmission of the virus in the community.

Study registration: CTRI/2021/05/033790.

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1. Introduction

The COVID-19 pandemic has created an unprecedented wave of illness and loss of life compared to any other outbreak in the past few decades. As of 24th May, a total of 527 million people have been infected with the virus while 6.28 million deaths were reported globally [1]. Healthcare professionals from various countries have been fighting the pandemic relentlessly for the past 2 years. Meanwhile, pharmaceutical industry and scientists across the globe have been investigating pre-existing and novel compounds as potential solutions to end this pandemic. Few of the proposed novel antivirals as a therapeutic cure for mild to moderate COVID-19 infected patients include Paxlovid, Molnupiravir, Sotrovimab, and Bebtelovimab. Although these antiviral drugs passed the initial regulatory approvals, they were not considered the drug of choice during the Omicron wave due to their lethal side effects and high cost [2]. However, a huge rollout of vaccination adopted as a prophylactic measure for COVID-19 with 66.4% of the world's population receiving at least one dose of vaccination, has provided relief [3]. To support the cause, traditional systems of medicine have presented a wide set of natural herbs and medicines for the early cure, prophylactic, and therapeutic management of COVID-19. A review of the literature suggests many single drugs or compound formulations emanating from Ayurveda can boost immunity and provide antiviral activity against SARS-CoV-2 [4–8]. Preclinical studies also provide robust evidence of antiviral potency of various phytochemicals present in nature. In silico studies of well-known immuno-boosters like *Ashwagandha* (*Withania somnifera*), *Guduchi* (*Tinospora cordifolia*) and *Tulsi* (*Ocimum sanctum*) show strong docking properties against SARS-CoV-2 viral proteins [9]. The phytoconstituents of *Ashwagandha*, Withanoside V showed a binding energy of −8.96 kcal/mol with the Mpro protein of the virus [10]. A randomized clinical trial on *Ashwagandha* demonstrated an improvement in markers of vaccine response, such as IgG titer, when Ashwagandha was given along with the vaccine, in comparison to receiving the vaccine alone [11]. Similarly, compound sesline from *Bilwa* (*Aegle marmelos*) and several other compounds from *Guduchi* and *Tulsi* may serve as a potential inhibitor against the Mpro protein of SARS-CoV-2 virus, as shown in *in-silico* studies [9,12,13]. Other *in-silico* studies demonstrate that phytochemicals present in herbs used regularly as a part of Indian diet, like *Bilwa*, *Khus* (*Vetiveria zizanioides*), Drumstick (*Moringa oleifera*), and Pomegranate (*Punica granatum*) exhibit significant binding with RdRp and M^{pro} proteins of SARS-CoV-2 virus [14]. Components of *Yashtimadhu* (*Glycyrrhiza glabra*), another well-known ayurvedic herb, were noticed to have a significant binding affinity with various SARS-CoV-2 proteins (main protease, spike protein, and RdRp protein) and host macromolecular targets such as human (ACE2 and furin) proteins [15]. *Vasaka* (*Adhatoda vasica*), another potent ayurvedic compound, exhibited strong binding energy with M^{pro} of SARS-CoV-2 (−114.9 kcal/mol) [16]. *In vivo* studies among animal models showed that ayurvedic nasal formations limited the viral entry and replication [17]. These are just a few ayurvedic herbs and compounds that have shown antiviral properties against SARS-CoV-2 and can be used in the management of COVID-19. A novel polyherbal Ayurvedic formulation called NAOQ19 containing 19 ingredients from 13 herbs has shown efficacy against the SARS-CoV-2 in *in vitro* and *in vivo* studies. NAOQ19 contains several potent antivirals and immunomodulators including *Ashwagandga*, *Tulsi*, *Guduchi*, *Bilwa*, *Vasaka* and *Yasthimadhu*. Other components such as *Bhumiamla* (*Phyllanthus fraternus*), *Bhunimba* (*Andrographis paniculata*), and *Haridra* (*Curcuma longa*) are also used in the formulation. *Bhunimba*, a well-known ayurvedic herb, is used to treat viral and microbial infections [18]. An in-vitro study of *Bhunimba* and *Chiretta* (Andrographolide) in SARS-CoV-2-infected Calu-3 cell lines (infected human lung epithelial cells) showed that these herbs significantly inhibit the production of infectious virions with an IC50 of 0.036 μg/mL and 0.034 μM, respectively [19]. One of the other mentioned uses of *Bhunimba* (*Andrographis paniculata*) is its antithrombotic effect. There is evidence of thrombotic pathways being implicated in COVID-19 with ample instances of thrombotic events leading to mortality in patients [20]. Due to its antithrombotic activity, *Bhunimba* can play a significant role in the management of patients with COVID-19. The crude extracts of *Bhunimba* also demonstrate an antithrombotic property in-vitro [21]. *Haridra*, another constituent of NAOQ19, has excellent anti-inflammatory properties and thereby can regulate the cytokine release during the COVID-19 infection. Curcumin present in *Haridra*, regulates the Toll-like receptors, inflammatory cytokines, and chemokines, which play a major role in the pathophysiology and progression of the disease. Due to its phenolic nature, it also has an intensive antimicrobial effect [22,23].

Several other AYUSH formulations have been explored in treating mild-moderate COVID-19 patients. AYUSH-64, a well-known ayurvedic formulation of 4 ingredients has been extensively researched for its efficacy against COVID-19. AYUSH-64 was studied in asymptomatic to mild COVID-19 patients along with standard of care therapy. The results demonstrated an earlier clinical recovery of the intervention group participants with 60% recovery compared to control group participants [24]. Another study compared the efficacy of two different ayurvedic formulations to standard of care in the treatment of COVID-19. Intervention arm 1 received *Vyaghryadi Kashaya* with *Pippali* and *Samshamani vati* while intervention arm 2 received *Shunthi* and *Rasona* paste as the treatment. Results showed a higher percentage of population turning RT-PCR negative in both the intervention arms compared to the control arm [25]. Another ayurvedic regime consisting of nasal drops and ayurvedic tablets was also tested for its efficacy against COVID-19 patients. The treatment group witnessed 71% RT-PCR recovery by day 3 and 100% recovery by day 7 compared to the placebo group [26].

A previous *in vitro* study conducted on NAOQ19 demonstrated its antiviral efficacy among Vero E6 SARS-CoV-2 infected cell lines. The treatment of virus-infected cells with 0.9 mg/ml concentration of NAOQ19 resulted in 100% viral elimination [27]. The NAOQ19 was further tested in the Syrian golden hamster animal model. A 78.2% viral load reduction in hamsters' lungs was observed with NAOQ19. No toxicity was reported in the animal model [28]. With the preclinical efficacy established, the drug was further tested in an open-label feasibility study. The study showed a 74% rate of recovery among the COVID-19 patients after 5 days of NAOQ19 consumption [29]. To evaluate further effectiveness and therapeutic role of NAOQ19, this multicentric study was conducted with the hypothesis that NAOQ19 will contribute towards early recovery of patients with mild-moderate SARS-CoV-2 infection.

2. Methods

2.1. Trial design

A multicentric, double-blind randomized control design was adopted for this study. The study was approved by Institutional Ethics Committee with registration number as follow: AIIMS/IEC/2021/3626; AIIMS/IEC/21/306 and SMVMCH-ECO-AL/153/2021. The study was registered at the Clinical Trial Registry, India bearing registration number CTRI/2021/05/033790. The protocol of the study was standardized and finalized at all the sites and was in compliance with Helsinki ethical standards and Good Clinical Practice. The study included patients from the second and third wave of the pandemic in India. The study period included 31st May 2021 to 30th January 2022. Each patient was monitored for 7 days or until they turned RT-PCR negative.

2.2. Participants

A total of 150 mild-moderate patients across the sites were enrolled in the study. The participants enrolled were from the in-patient ward (IPD) or the out-patient clinic (OPD) in strict adherence to study enrollment criteria. The patients who presented with COVID-19 symptoms and had a positive RT-PCR test were briefed about the study by the

Table 1
Ingredients of NAOQ19[27].

S.No	Name of the herb	Scientific Name	Part Used	Nature of herb	Quantity (mg)
1	*Ashwagandha*	*Withania Somnifera*	Root	Fine Powder	30
2	*Bilwa*	*Aegle marmelos*	Leaf	Fine Powder	30
3	*Yashtimadhu*	*Glycyrrhiza glabra*	Root	Fine Powder	20
4	*Rasna*	*Pluchea lanceolata*	Leaf	Fine Powder	30
5	*Vasaka*	*Adhatoda vasica*	Leaf	Fine Powder	25
6	*Pippali*	*Piper longum*	Fruit	Fine Powder	30
7	*Bhumiamla*	*Phyllantus fraternus*	Plant	Fine Powder	35
8	*Bhunimba*	*Andrographis paniculata*	Whole plant	Fine Powder	30
9	*Saptaparna*	*Alstonia scholaris*	Stem bark	Fine Powder	30
10	*Haridra*	*Curcuma longa*	Rhizome	Fine Powder	25
11	*Patha*	*Cissampelous pareira*	Root	Fine Powder	25
12	*Tulsi*	*Ocimum sanctum*	Whole plant	Fine Powder	20
13	*Guduchi*	*Tinospora cordifolia*	Stem	Fine Powder	20
14	*Ashwagandha*	*Withania Somnifera*	Root	Extract	30
15	*Yashtimadhu*	*Glycyrrhiza glabra*	Root	Extract	15
16	*Vasaka*	*Adhatoda vasica*	Leaf	Extract	25
17	*Bhumiamla*	*Phyllantus fraternus*	Plant	Extract	30
18	*Bhunimba*	*Andrographis paniculata*	Whole plant	Extract	35
19	*Guduchi*	*Tinospora cordifolia*	Stem	Extract	15

research personnel in the presence of the doctor on duty, at all three locations. Based on their medical history, patients who met the eligibility criteria, mentioned below, were invited to participate in the study and informed consent was obtained.

2.3. Inclusion criteria

a. Symptomatic COVID-19 infection with or without comorbidities.
b. Patients with mild to moderate symptoms as classified by ICMR guidelines.
c. Patients between the age of 18–75 years
d. Indian Nationals
e. Either gender (Male or Female)
f. Willingness to participate in the study with a written consent

2.4. Exclusion criteria

b. Pregnant women or lactating mothers
c. Patient not willing to participate in the study
a. Patients with severe disease as per ICMR guidelines

2.4.1. Intervention

All the patients were provided a bottle of intervention drug or placebo based on the computer generated sequence of randomization. The allocation was sequentially numbered and sealed in opaque envelopes which were later allocated to the patients as they enrolled in the study. Each bottle contained 90 tablets both placebo and NAOQ19 looking alike. The patients were advised to take 2 tablets, thrice a day for the study period, after food. Both the placebo and NAOQ19 bottles were packaged identically to avoid bias. Compliance was monitored by the data collector individually over the phone for OPD patients and in person for IPD patients.

2.4.2. NAOQ19 preparation

NAOQ19 is a 19 ingredient polyherbal formulation, containing 13 potent antiviral and anti-inflammatory compounds such as *Ashwagandha* powder and extract, *Yashtimadhu* powder and extract, *Vasaka* powder and extract, *Bilwa*, *Rasna* (*Pluchea lanceolata*), *Pippali (Piper longum)*, *Haridr*, *Patha* (*Cissampelos pareira*), *Bhumiamla* (*Phyllanthus fraternus*) powder and extract, *Saptaparna* (*Alstonia scholaris*), *Tulsi*, *Bhunimba* powder and extract, and *Guduchi*powder and extract. Table 1 demonstrates the detailed ingredients and dosage of each ingredient in the formulation. The drug was produced by Sriveda Sattva Pvt Ltd, Bangalore (Sri Sri Tattva), a GMP-certified company. It was licensed by the Ministry of AYUSH, Govt. of India (License number- AUS782). The crude forms of all the herbal extracts were subjected to quality control. The certificate of analysis with the required quality check, identification, and authentication along with HPLC tests of individual herbs and finished products wherever applicable are provided in the supplementary files. The voucher specimen of the individual herbs used in the tablet had been stored in Sriveda Sattva Pvt. Ltd. quality control lab with voucher specimen no. SST/VS-NF2/2021 for future reference. Thereafter, the ingredients were blended with excipients followed by granulation, drying and compression. After QC analysis, the tablets were packed using the standard procedure.

2.4.3. Comparator group

The comparator group in this trial were given a placebo tablet. The placebo tablet was made of starch (100%). The placebo tablets were also tested for quality control and packed in bottles identical to NAOQ19.

2.4.4. Standard of care treatment

The standard of care treatment was administered as per the guidelines provided by the Ministry of Health and Family welfare, Government of India, during the second wave and third wave of COVID-19 respectively [30,31].

2.4.5. Outcomes

2.4.5.1. Primary outcome. To evaluate the effect of NAOQ19 in COVID-19 patients in time to become SARS-CoV-2 RT-PCR negative, efficacy of the intervention in reducing the symptoms associated with COVID-19 and duration of hospital stay for Inpatients (IPD).

2.4.5.2. Secondary outcome. To evaluate the efficacy of NAOQ19 on blood parameters like CBC, RBS, anti-inflammatory marker C- reactive protein (CRP) and to measure the safety of the drug as measured by Liver function test (LFT) and Kidney function test (KFT).

2.4.5.3. Follow-up and assessment. The RT-PCR tests were conducted on day 0, day 3, day 5, and day 7. Blood biomarkers were tested on day 0 and day 7. Other clinical markers such as CBC, CRP, LFT, and KFT were assessed at baseline and exit. Patients were monitored for a maximum of 7 days, or until RT-PCR negative result, whichever was earlier. Inpatients were also monitored for the duration of their stay in the hospital. Information about any adverse events reported by the patients following the intervention was also collected.

1. Sample calculation

The study by Dutt J et al. [32] observed a 100% of the COVID-19 patients recovered in treatment group while 84.62% of patients recovered in standard of care treatment alone following a herbal intervention. Taking these values as reference, the minimum required sample size with 95% power of study and 5% level of significance was found to be 72 patients in each study group. To reduce the margin of error, the total sample size taken was 150 (75 patients per group).

150 male or female volunteers who were mild-moderate in illness and were symptomatic for COVID-19 were enrolled in the study. The data was analyzed using ITT (intention to treat) approach for all the patients who were randomized to the respective intervention.

2. Randomization and blinding

The study participants were allocated into different study arms with the help of a computer-generated randomization code. The computer-generated randomization was conducted at AIIMS Jodhpur. Each center nominated a randomizer who was not part of the trial and was mailed the allocation details. Sealed opaque envelopes were prepared for each study and control group.The randomization was done by selection of these sealed envelopes. The allocation was sequentially numbered and was later allocated to the patients by the randomizer, as they enrolled in the study. The participants, outcome assessor, data collector, and the laboratory technician were blinded to the allocated study group.

3. Statistical analysis

The presentation of the categorical variables was done in the form of numbers and percentages. On the other hand, the quantitative data with normal distribution were presented as mean ± SD and the data with non-normal distribution as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov–Smirnov test. The analysis was performed using the ITT approach where all patients randomized were included in the analysis. The cases in which the data was not normal, non-parametric tests were used. The following statistical tests were applied to get the results.

1. Quantitative variables that were not normally distributed were compared using the Mann–Whitney U test (two groups) and the Wilcoxon signed-rank test (follow-up comparisons). Paired t-test was used for comparison of normally distributed data across follow up.

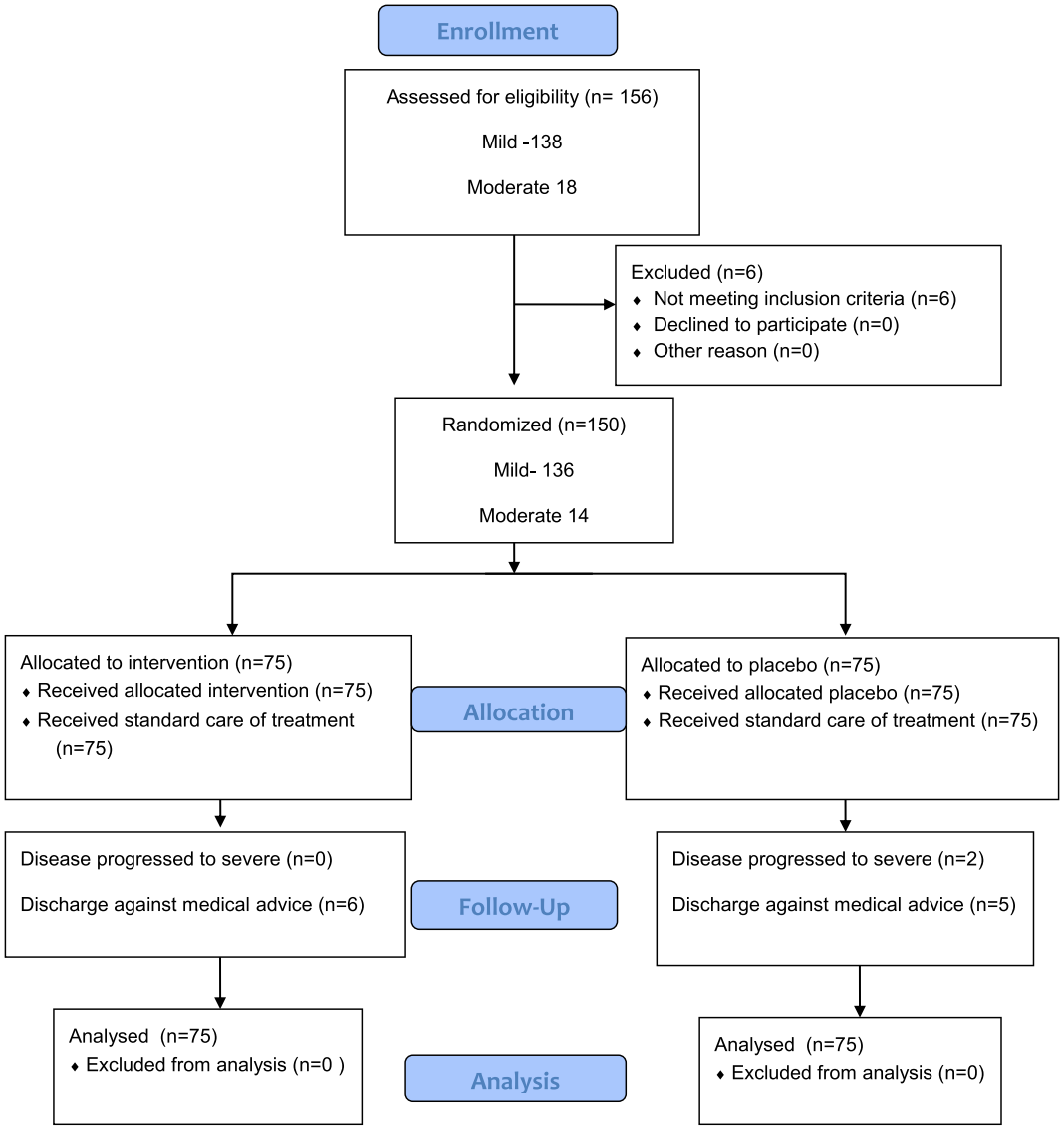

Fig. 1. Consort Flow diagram of the trial.

Independent t test was used for comparison of normally distributed data between two groups.
2. The comparison of the variables which were qualitative in nature was done using Chi–square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.
3. Kaplan Meier survival analysis curve was used for duration taken to become RT-PCR negative and log-rank test was used for comparison.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was completed using theStatistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0.

For statistical significance, p-value of less than 0.05 was considered statistically significant.

3. Results

(Fig. 1) represents the CONSORT Flow diagram of the study.

The present study evaluates the therapeutic efficacy of NAQO19 in treating COVID-19 measured by the rate of conversion of RT-PCR positive to negative, reduction in hospital stay, and management of symptoms associated with COVID-19. Along with the assessment of signs and symptoms, the study also measured changes in anti-inflammatory markers (CRP), blood investigations (CBC), LFT, and KFT to measure the safety of the drug. A detailed table depicting all the ingredients of the test formulation along with the specific dose of each ingredient along with their scientific name has been included (Table 1). Table 2demonstrates the demographic details of the population. The distribution of gender was comparable between NAOQ19 and placebo. (Female: - 50.67% vs 38.67% respectively, Male: - 49.33% vs 61.33% respectively) (p-value = 0.139). The distribution of severity was comparable between NAOQ19 and placebo. (Mild:89.33% vs 92% respectively, Moderate:10.67% vs 8% respectively) (p-value = 0.575). The median (25th-75th percentile) of age (years) in NAOQ19 was 40 (27.5–53.5) and placebo was 41 (27–52) with no significant difference between them. (p-value = 0.742) (Table 2).

Table 3 depict the comparison between two arms regarding the percentage population that turned RT-PCR negative at various time points. The proportion of patients with RT-PCR negative at day 3 was significantly higher in the NAOQ19 arm as compared to placebo (Negative: - 53.33% vs 36% respectively, p-value = 0.033). The distribution of RT-PCR at day 5 was comparable between NAOQ19 and placebo. (Negative: - 68% vs 56% respectively. The proportion of patients with RT-PCR negative at day 7 was significantly higher in NAOQ19 as compared to placebo (Negative: - 89.33% vs 74.67% respectively, p-value = 0.019). The analysis showed a lower mean time to turn RTPCR negative in the intervention arm which was 4.6 days as compared to 5.2 days in the placebo arm. This difference was significant, $\chi 2 = 5.557$, p = .018 by Log Rank (Mantel–Cox) test (Table 4, Fig. 2).

Table 3
Comparison of RT-PCR between NAOQ19 and placebo.

RTPCR	NAOQ19 (n = 75)	Placebo (n = 75)	P value
Day 1			
Positive	75	75	–
Day 3			
Negative	40	27	0.033[a]
Day 5			
Negative	51	42	0.13
Day 7			
Negative	67	56	0.019[a]

[a] <0.05-significant **<0.001- very significant.

Table 4
Time to event (Kaplan Meier) analysis for RTPCR negative.

Intervention	Mean no. of days		Significance
	Estimate	Std. Error	
NAOQ19	4.6	0.207	0.018[a]
Placebo	5.2	0.209	

**<0.001-very significant.
[a] <0.05-significant.

3.1. Duration of stay

The mean number of days of hospital stay was calculated (duration of stay). Among the admitted patients, patients in NAOQ19 arm were discharged earlier (mean number of days- 5.6) in the NAOQ19 arm compared to the placebo arm (mean number of days- 6.42) (p-value = 0.046) (Table 5).

Table 6 demonstrates the clinical symptom recovery among the patients in both arms, across different time points. The number of patients experiencing symptom resolution were not statistically significant among the two groups, except in headache. The proportion of patients with headache at day 5 was significantly higher in placebo as compared to NAOQ19. (p-value = 0.013).

Table 7 demonstrates changes in immune marker CRP levels between the two arms. No significant difference was seen in C-reactive protein at day 1 (p-value = 0.524) or day 7/exit (p-value = 0.96) between NAOQ19 and placebo group.

4. Discussion

Ayurveda, an ancient Indian system of medicine contains a vast repository of plants and herbs with therapeutic properties. In the fight against COVID-19, herbal extracts with robust scientific evidence of therapeutic efficacy against SARS-CoV-2 can support rapid recovery and reduce mortality due to COVID-19. Our study investigated the effectiveness of NAOQ19, an Ayurvedic polyherbal formulation, in clinical improvement and rate of recovery from the SARS-CoV-2 infection. This multi-centric trial demonstrated an early recovery and reduced

Table 2
Comparison of demographic characteristics between NAOQ19 and Placebo group.

Demographic characteristics	NAOQ19 (n = 75)	Placebo (n = 75)	Total	P value
Gender				
Female	38	29	67	0.14
Male	37	46	83	
Severity				
Mild	67	69	136	0.58
Moderate	8	6	14	
Age (years)	40 (27.5–53.5)	41 (27–52)	40.5 (27–52)	0.74
Pandemic Wave				
Second Wave	39	37	76	0.87
Third Wave	36	38	74	

*<0.05-significant **<0.001- very significant.

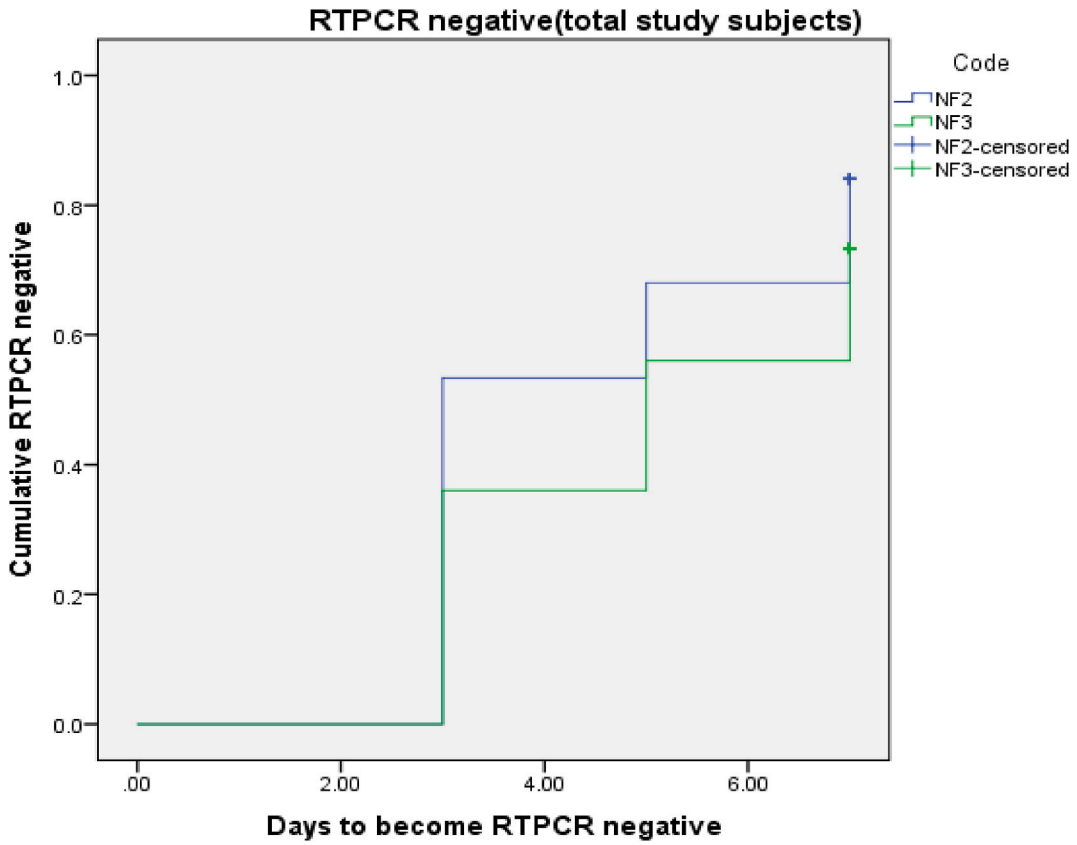

Fig. 2. Time to event (Kaplan Meier) analysis for RTPCR negative.

Table 5
Comparison of duration of hospital stay (days) between NAOQ19 and Placebo.

Duration of hospital stay (days)	NAOQ19	Placebo	P value
Mean (SD)	5.6 (0.17)	6.42 (0.16)	0.046[a]

[a] <0.05-significant **<0.001-very significant.

hospitalization among patients who took NAOQ19 along with standard of care treatment, compared to those who received standard of care alone. The study was conducted during the second and third wave of COVID-19 pandemic in India.

Our results demonstrated a significant reduction in time to recover from COVID-19 among the NAOQ19 group compared to the placebo group. The study showed no adverse events to the intervention drug used in the study demonstrating its tolerability in COVID-19 patients. Early recovery in COVID-19 patients is of utmost importance especially in the hospital setting. During the second wave, shortage of hospital infrastructure to facilitate the pernicious spread of the virus was the prime issue [33]. Resources that help in faster recovery and discharge of the patients were a boon that could provide the required facility to the next set of victims of COVID-19. While the implications of third wave were quite gentle on the Indian population, it resulted in the faster spread of the virus due to the negligence of the infected ones [34]. Early recovery of patients with viral load reduction, during the third wave, offered lower chances of transmission of the virus.

The presence of multiple strong antiviral agents such as *Yashtimadhu*, *Guduchi*, *Ashwagandha*, *Vasaka*, *Haridra*, *Pippali,* and *Bhumi Amla* in NAOQ19 could act as a probable mode of action in early clearance of viral load among COVID-19 patients in the NAOQ19 arm [35]. Besides, phytochemicals from Yashtimadhu and Vasaka demonstrate good binding energies against M^{pro} and RdRp protein targets of the virus. It also Other active pharmacological properties against the virus such as

Table 6
Comparison of symptoms between NAOQ19 and Placebo.

Symptoms	NAOQ19 (n = 75)	Placebo (n = 75)	Total	P value
Fever				
Day 1	48	51	99	0.605
Day 3	6	8	14	0.575
Day 5	1	4	5	0.367
Day 7	2	0	2	0.497
Sputum				
Day 1	10	13	23	0.497
Day 3	5	3	8	0.719
Day 5	1	2	3	1
Day 7	0	0	0	–
Headache				
Day 1	28	19	47	0.113
Day 3	26	22	48	0.484
Day 5	6	17	23	0.013[a]
Day 7	6	11	17	0.198
Sore throat				
Day 1	22	22	44	1
Day 3	5	9	14	0.262
Day 5	2	2	4	1
Day 7	3	3	6	1
Cough				
Day 1	49	56	105	0.212
Day 3	24	34	58	0.094
Day 5	11	15	26	0.388
Day 7	4	4	8	1
Shortness of breathing				
Day 1	17	8	25	0.049[a]
Day 3	8	6	14	0.575
Day 5	1	4	5	0.367
Day 7	0	2	2	0.497

[a] <0.05-significant **<0.001-very significant.

Table 7
Comparison of C-reactive protein between NAOQ19 and Placebo.

C-reactive protein	NAOQ19 (n = 75)	Placebo (n = 75)	Total	P value
Day 1	3.06 (0.855–20.165)	4.04 (1.2–25.595)	4.01 (0.925–23.625)	0.52
Day 7/exit	2.63 (1.235–5.777)	2.89 (0.951–14.556)	2.69 (1.089–8.425)	0.96

*<0.05-significant **<0.001-very significant.

inhibiting viral entry and replication [15–17].

Similar results pertaining to time to recover and duration of stay in hospital were noted among patients consuming Kabasura Kudineer, a siddha formulation, along with standard therapy [36]. Comparing the ingredients between Kabasura Kudineer and NAOQ19, it was noted that several components are similar between the two formulations such as *Piper longum*, *Tinospora cordifolia*, *Cissampelos pareira*, *Andrographis paniculata* and *Adathoda vasica*.

A review of ayurvedic literature presents robust preclinical evidence for efficacy of multiple NAOQ19 ingredients such as *Ashwagandha* and *Guduchi*, along with *Amalaki* in proliferation of B and T cells and activation of non-specific immunity [37]. Especially molecular docking studies on *Tinospora cordifolia*' s chemical constituents demonstrated good binding energies with human ACE 2 receptors and M^{pro} viral spike proteins [38]. In addition, several other components of NAOQ19 have been highlighted for their antiviral properties previously [10,37,39]. *Yashtimadhu* contains glycyrrhizin, a strong antiviral compound. In a previous study, treatment with different concentrations of glycyrrhizin lowered SARS-CoV viral antigen in a cell culture. At a concentration of 4000 mg/ml, glycyrrhizin completely blocked the viral replication [40]. Another clinical trial on patients with COVID-19 showed early recovery and reduced length of hospital stay with an ayurvedic regime consisting of *Dasamoolkaduthrayam Kashaya* and *Guluchyadi Kwatham* [41]. A similar observation was noted in our study. Further investigation of the above two rasayanas showed the presence of *Bilwa*, *Pippali*, *Vasaka,* and *Guduchi* herbs in the *rasayanas* that were also present in NAOQ19. Much before the prescient of the third wave in India, in October 2021, India had crossed 1 billion vaccination doses across the country [42]. This marked an active adaptive immune response to the SARS-CoV-2 during the surge of the third wave. In spite of vaccination against the SARS-CoV-2, the omicron surpassed the adaptive immune response creating a huge spike in the cases from beginning of January to the end of February [43]. Researchers attribute the mild severity of the virus to population immunity [44]. Mutation of the virus is a constant phenomenon but together with innate and adaptive immunity, the virus can be conquered. Recent research estimates the role of innate humoral immunity like pattern recognition molecules (PRMs) like involvement of Toll-like receptors (TLRs) in the therapeutic efficacy of SARS-CoV-2 [45]. Ayurvedic management of disease actively involves in the activation of innate immunity [46]. Given the large percentage of Indians who rely on traditional remedies, administering an ayurvedic formulation like NAOQ19 along with standard of care can increase adoption and provide a sustainable and effective option to overcome COVID-19 infection safely and quickly. This may also be relevant in societies where people are open to therapeutic options from traditional systems of medicine. The authors acknowledge the limitations of the study and present further scope to improve the limitations. The key limitations of the study include lack of significance in the symptom resolution and a lack of significance in the CRP levels between the two study groups. CRP anti-inflammatory markers, are dynamic in nature. One probable explanation of the presented CRP values is due to mild infection in patients. By the end of the study, most patients were cured of the infection, hence restoring CRP levels to normal condition. Further studies with larger sample sizes and relatively longer duration and shorter time point estimates can investigate in-depth efficacy and mechanism of action of NAOQ19 in patients with COVID-19. The findings of this study create an interesting backdrop for exploring the role of NAOQ19 in moderate to severe COVID-19 patients with acute infection.

5. Conclusion

Traditional and complementary formulations can provide a helping hand to the medical sector in the therapeutic management of COVID-19. The proposed polyherbal formulation, NAOQ19, composed of well-known ayurvedic herbs demonstrated a significant early recovery in mild-moderate patients with COVID-19. The results of the present study demonstrated an earlier recovery from COVID-19 in the NAOQ19 arm as compared to placebo arm when used as an adjuvant treeatment. Both mild and moderate patients showed an expedited improvement in NAOQ19 arm compared to the placebo arm. The mean number of days to turn RT-PCR negative was 1.5 days lower in the NAOQ19 arm compared to the placebo arm. The duration of hospital stay also reduced in NAOQ19 arm compared to placebo arm. Such findings with reduced hospital stay and early recovery can develop an integrated approach model of the ancient ayurvedic system and standard care of therapy to provide optimum length of stay, reduce nosocomial infection, and reduce patient overload.

Author contributions

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Declaration of competing interest

Besides providing the NAOQ19 intervention tablets, Sriveda Sattva Pvt. Ltd. was not involved in any aspect of this study. All the other authors have no conflicts of interest to declare.

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Ethical approval

The study was approved by Institutional Ethics Committee with registration number as follows: AIIMS Jodhpur AIIMS/IEC/2021/3626; AIIMS Rishikesh AIIMS/IEC/21/306 and SMVMCH, Puducherry SMVMCH-ECO-AL/153/2021. The study was registered at Clinical Trial Registry, India bearing registration number CTRI/2021/05/033790.

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