Efficacy of a polyherbal formulation in the treatment of SARS CoV-2 disease: An open labelled feasibility study

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Research Article

Keywords: Ayurveda, COVID-19, symptomatic management, polyherbal, RT-PCR, NOQ-19

Posted Date: September 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-923003/v1

Abstract

Background: The ongoing pandemic caused by human coronavirus SARS CoV-2 has led to millions of death across the globe. Not only the virus is highly infectious, it is also mutates very easily. Currently there are no approved drugs for the therapeutic cure of COVID-19. The world is in search for an alternative that has antiviral properties directed against virus.

Objective: The present study investigates an Ayurvedic polyherbal formulation of 13 herbs, named NOQ19, targeted against various viral proteins of COVID-19.

Methodology: The study is a single arm, single centric, open label study of 161 RT-PCR positive COVID-19 patients. The enrolled participants were given the ayurvedic intervention, 2 tablets, thrice daily, to be consumed along with the standard care. Follow up COVID-19 RT- PCR was done on Day 5, Day 10 and Day 14 or until the patient turned negative. The time required for turning RT-PCR negative or become asymptomatic was noted.

Results: Subjective analysis demonstrated that 98% of patients turned asymptomatic within 5 days of NOQ19 intake. Also 74% of the subjects turned RT-PCR Negative on Day 5 after taking NOQ19 along with the standard care provided. Also, none of the participant reported any adverse effect or side effect to the medication.

Conclusion: NOQ19 Ayurvedic polyherbal formulation is an effective as well as safe alternative and adjunct treatment for the symptomatic management of COVID-19.

1.0 Introduction:

The human coronavirus was first noted in the year 1960, as common cold[1] caused by the alpha or beta group of the virus.[2] The morphology of the virus is single stranded enveloped RNA virus carrying crown like spikes giving its name.[2] The outbreak of SARS CoV-2, emerged in 2019, was declared a public health emergency on January 30th, 2020 and later as a pandemic on 11th March, 2020 when 3,18000 cases were reported with 13000 deaths.[3] In most cases the severity of the infection varies from mild to moderate. Post entry, the virus binds to Angiotensin Converting Enzyme-2 (ACE-2) receptor, by glycosylated spike protein (S). These ACE-2 receptors are highly expressed in human alveolar type 2 pneumocytes and epithelium of upper esophagus, therefore degrading the alveolar cells and type 2 pneumocytes.[4–6] Although the clinical representation of COVID-19 in most of the patients are either asymptomatic, or symptoms like fever, cough, fatigue, sore throat etc. ,the pathogenesis can create a critical condition for the patient. The severe damage and reduction in type 2 pneumocytes leads to increase in surface tension and dyspnea.[4–6] The damaged cells and viral products are responsible for triggering several inflammatory markers, cytokines, as well as releasing and accumulating excessive cytokines (cytokine storm) at the site of infection. This cytokine excess are responsible for tissue necrosis due to inflammatory responses.[5–6] Furthermore the pro-coagulant factors caused thrombosis leads to

severe organ damage, ischemia and multi-organ dysfunction.[4–6] The above parthenogenesis of virus has led it to be fatal, more so in the case of second wave[7].

Many health systems are intensely looking for solutions to bring an end to the pandemic. Despite continuous efforts from the pharmacological industry, all the current available treatment regimen only target the management of the symptoms and do not possess any specific antiviral properties against Coronavirus.[8] The prominent global milestone in the fight against COVID-19 was the development of vaccination to produce herd immunity.[8] Ayurveda, a 5000 year old practice from India aims to decrease the intensity of the disease, strengthen the immunity and treat disease naturally.[9] Ayurveda means “the science of life”, and the materia medica of Ayurveda focuses on herbs as a potent remedy to prevent and cure illness.[10] Many plant based medicines have flavanoids, alkaloids, phenols and tannins that exhibit antiviral and antimicrobial properties.[11]

Molecular docking studies have shown a wide range of medicinal plants exhibiting therapeutic properties against SARS CoV-2.[12] Kabasura Kudineer, a polyherbal formulation from Siddha text is noted to have good binding site against spike 2 protein of COVID-19 and is recommended as an immuno modulator for prevention of the COVID-19 by the ministry of AYUSH, government of India.[13] NOQ19 is a polyherbal Ayurvedic formulation containing 13 herbs – Ashwagandha (*Withania somnifera*) powder and extract, Bilwa (*Aegle marmelos*), Yashtimadhu (*Glycyrrhiza glabra*) powder and extract, Rasna (*Pluchea lanceolata*), Vasaka (*Adhatoda vasica*) powder and extract, Pippali (*Piper longum*), Haridra (*Curcuma longa*), Patha (*Cissampelos pareira*), Bhumiamla (*Phyllanthus fraternus*) powder and extract, Bhunimba (*Andrographis paniculata*) powder and extract, Saptaparna (*Alstonia scholaris*), Tulasi (*Ocimum sanctum*) and Guduci (*Tinospora cordifolia*) powder and extract. A molecular docking study found that the active phytochemicals present in Ashwagandha (*Withania somnifera*), Guduci (*Tinospora cordifolia*) and Tulasi (*Ocimum sanctum*) target and inhibit the main protease Mpro or or 3Clpro of SARS CoV-2.[14] Another clinical trial on efficacy of Ashwagandha with COVID-19 vaccine showed enhancement in immunogenicity of vaccine against COVID-19.[15] Vasaka (*Adhatoda vasica*) has a wide variety of therapeutic effects and is potentiality used in the management of COVID-19 symptoms. It has anti-inflammatory, antiviral, antitussive and antioxidants properties.[16] Bhumiamla (*Phyllanthus fraternus*), another component of NOQ19 was previously used in treatment of viral infections like hepatitis and flu.[17] Bhunimba (*Andrographis paniculata*), is known for its antithrombotic properties and prevents blood clotting, which is a severe clinical presentation in COVID-19 patients.[18] Haridra (*Curcuma longa*), a very well known therapeutic compound can inhibit the cytokine release and therefore correlates with clinical improvement in flu and other infectious diseases.[19] Molecular docking has revealed that the active components of Yashtimadhu (*Glycyrrhiza glabra*) have potential binding properties against spike glycoprotein and other non-structural protein-15 of SARS CoV-2.[20]

The present study determines the clinical efficacy of NOQ19, a polyherbal formulation, as a therapeutic option for COVID-19 through an single arm clinical trial.

Objective :

- To evaluate the time to become SARS CoV-2 RT-PCR negative in COVID–19 patients who consume NOQ19 along with standard care of treatment
- To evaluate the turnaround time for patients to be asymptomatic

2.0 Material And Methods

The present study was a single arm, single centre, clinical trial to test the efficacy of NOQ19 against COVID-19 viral infection. The participants who tested positive by means of RT-PCR test were enrolled in the study. RT-PCR is considered gold standard test for detection of COVID-19. The participants were evaluated for their symptoms at the time of enrollment in the study and a follow up for 14 days was conducted to investigate their symptoms, side effects and RT- PCR tests.

Inclusion Criteria

- Age 18 to 55 years, both genders
- Asymptomatic or mild confirmed cases of COVID-19 infection as per RT-PCR
- Subjects willing to participate in the study, after providing an informed consent
- Subjects willing to take Ayurvedic treatment

Exclusion criteria

- Patients not willing to give consent or participate in the clinical trial or adhering to follow the Ayurvedic medicine regime
- Women who were pregnant or lactating mothers
- Severe COVID-19 cases with SpO_2 less than 95% on room air, in ICU or on ventilation

The present study was a pilot study to understand the turn around time for RT-PCR negative results and safety of NOQ19. Therefore the sample size was restricted to 160 participants. Since this was a pilot study, a minimum of 50 participants are enrolled as per thumb rule.[21] Considering loss to follow up or dropouts, 161 patients were recruited in the study.

The subjects who qualified for the inclusion and exclusion criteria were enrolled in the study and were given the intervention drug NOQ19 along with standard care of treatment. The medicine was manufactured and procured from Sriveda Sattva Private Limited, a Good Manufacturing Practice (GMP) certified company in order to ensure the good quality. The drug was licensed by ministry of AYUSH with license number AUS-782. The medicine dosage was administered as 2 tables, thrice a day after food. The standard care of treatment included antipyretic like paracetamol and supplements such as zinc and vitamins.

Outcomes measured

The method of assessment included RT-PCR test using the nasal and throat swabs as per the ICMR guidelines. RT-PCR test was conducted on Day 5, Day 10 and Day 14. The maximum follow up time was 14 days or RT-PCR negative time point, whichever occurred earlier. Another outcome was to measure the turnaround time to become asymptomatic. Efficacy and safety of the drug was also based on symptom assessments. Adverse events or side effects were monitored, if any. The tablets were packed in a bottle and given to each subject at the time of enrollment. Dosage compliance and symptom monitoring was conducted over the phone.

Statistical Analysis:

All the symptomatic parameters were assessed in terms of proportion/Mean.

Ethical clearance

The study was approved by the Institutional ethics committee (IEC) of Sri Sri Institute for Advanced Research bearing registration number SSIAR/IEC/2021/010 and registered at Clinical Trials Registry - India CTRI/2021/08/036025.

3.0 Results

A total of 161 participants were enrolled in the study. Out of 161 subjects, 6 subjects dropped out from the study as they were not compliant with the doses. A total of 118 male subjects and 43 female subjects were enrolled. All the participants had similar demographic details with respect to age and comorbidities. The average age of the enrolled subjects was 43 years. 5 subjects had undergone RT-PCR on Day 7 instead of day 5 due to unavailability of kits.

All the patients showed similar clinical presentation at the onset of symptoms. It was noted that 87 participants presented fever, 30 participants presented headache, 43 participants presented weakness/ malaise/ tiredness, 53 participants and 40 participants had complaints of throat pain and common cold respectively, and 31 participants had cough on the day of enrollment. 11 patients were asymptomatic.

Table 1 demonstrated a significant reduction in symptoms among participants on day 1 of the study. Only 3 participants had fever, while most of them presented with tiredness and cough. The symptoms reduced to a significant extent after 3 days of the intake of medicines and 125 people turned asymptomatic on day 3 itself. By Day 5 most of the participants had turned asymptomatic.

Table 1
SYMPTOMATIC ASSESSMENT OF PATIENTS

Symptom	Number of patients in which the symptom was present				
	Day 0	Day 1	Day 3	Day 5	Day 7
Fever	87	3	3	1	NP*
Cold	40	11	NP	1	NP
Cough	31	88	15	3	1
Tiredness	43	113	21	4	2
Sore throat/ Throat pain	53	5	NP	NP	NP
Headache	30	1	NP	NP	NP
Loss of Smell/ Taste	6	4	1	NP	NP
Others	4	3	4	NP	2
None	11	11	125	152	155
*NP: Not present in the subject					

Table 2 represents RT-PCR test results. The test demonstrated that 115 (74%) subjects turned RT-PCR Negative on Day 5 after taking NOQ19 along with the standard care provided, 23 (14%) subjects turned RT-PCR Negative on Day 7 after taking NOQ19 along with the standard care. 16 (10%) subjects turned RT-PCR Negative on Day 10 after taking NOQ19 along with the standard care. 1 subject turned RT-PCR Negative on Day 14 after taking NOQ19 along with the standard care. None of the patients in the study reported any side effects. No adverse events were reported.

Table 2
RT-PCR ANALYSIS

Time Point	Number of Subjects RT-PCR Positive	Number of Subjects turned RT-PCR Negative	Total percentage of subjects who turned RT-PCR negative
Day 5	42	115	74%
Day 7	17	23	88%
Day 10	1	16	98%
Day 14	0	1	100%

4.0 Discussion

This is the first study to determine the efficacy and safety of a novel Ayurvedic formulation NOQ19 against COVID-19. The study evaluates the turn around time of a COVID-19 positive patient to become RT-PCR negative and asymptomatic. NOQ19 contains 13 potent herbs that possess antiviral and immune modulating properties against COVID-19.[22–23] Our results demonstrated that within 3 days of medicine intake 80% of the patient had turned asymptomatic. Also, within a week of consumption of medicine, all the subjects were asymptomatic with little tiredness. The clinical symptoms were at par with the RT-PCR test reports which showed that 74% patients turned negative by Day 5 while 98% patients turned negative by Day 7. In a clinical trial conducted on AYUSH 64, 69.7% patients had a mean time recovery of one week from the start of intervention.[24] Another study on an ancient Siddha drug Kabasura Kudineer and Nilavembu kudineer compared the efficacy of the herbal formulations against standard treatment for COVID-19. The authors noticed that patients who consumed herbal medicines along with standard treatment took only 2.7 days approximately to turn asymptomatic while those with standard care of treatment took 4.2 days.[25] It was noted that few ingredients were common between Kabasura Kudineer and NOQ19.

Our study demonstrated a faster rate of viral load reduction. A probable reason for that could be the presence of Glycyrrhizin component present in the Yashtimadhu (*Glycyrrhiza glabra*) that inhibits the viral replication protein.[26–28] An *in-vitro* study by Gowda et al. demonstrated the inhibition of viral replication in dose dependent manner in Vero E6 cell lines by Glycyrrhizin. Another important contribution of glycyric acid derative from Yashtimadhu is the prevention of high mobility group box 1 (HMGB1) which is responsible for heightened inflammatory responses in COVID-19 patients.[26] Yet another key finding of our study was the reduction of fever and running nose within a day of intervention treatment. According to Ayurvedic literature Guduci (*Tinospora cordifolia*) and Pippali (*Piper longum*) are antipyretic in nature.[29] A clinical trial on the antipyretic effects of the two herbs showed a substantial reduction in the fever. The authors suspect the antipyretic-analgesic property of NOQ19 is due to the presence of flavonoids and phelonic compunds.[29]

However, the authors do recognise that this is an initial pilot study on the novel herbal composition NOQ19, with the aim to investigate its therapeutic action against COVID-19. Further *in vitro*, *in vivo* studies are required to understand the mechanism of action of NOQ19 and anti-viral properties of the drug against COVID-19 or other flu like virus. Further prospective randomised control trials which measure blood parameters along with RT-PCR and symptom progression are ongoing on NOQ19. These studies will shed a light on the efficiency of NOQ19 for the clinical and symptomatic management of COVID-19.

5.0 Conclusion

The world is in search for a safe and effective treatment that has antiviral properties directed against COVID-19 virus. The present study proposes an Ayurvedic formulation of 13 herbs, NOQ19, targeted against various viral proteins of COVID-19. Efficacy of the medicine in clinical management of COVID-19 infected population was observed. 74% of the patients turned RT-PCR negative within 5 days from the

start of NOQ19 treatment. A total of 98% of the patients turned asymptomatic by day 5. NOQ19 did not show any adverse side effects and therefore can be safely administered among COVID-19 patients.

Declarations

Conflict of Interest: The authors have no conflict of interests to declare.

Funding:

This research study was funded by Sri Sri Institute for Advanced Research, Bangalore, Karnataka.

Ethical statement: The study was approved by institutional ethics committee of Sri Sri Institute for Advanced Research bearing registration number SSIAR/IEC/2021010. The informed consent form were obtained from all the participants.

Clinical Trial: CTRI/2021/08/036025

Data availability: The data will be made available upon request.

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