Rate of Recovery and Symptomatic Efficacy of a Polyherbal AYUSH Formulation in the Treatment of SARS CoV-2 disease: A Single-arm trial

Divya Kanchibhotla (director.ssiar@artofliving.org)
Sri Sri Institute for Advanced Research https://orcid.org/0000-0002-0760-630X

Prateek Harsora
Sri Sri Institute for Advanced Research https://orcid.org/0000-0003-4288-7626

Saumya Subramanian
Sri Sri Institute for Advanced Research https://orcid.org/0000-0001-9215-3933

Dr. Ravi reddy
Sriveda Sattva Pvt. Ltd https://orcid.org/0000-0002-8582-9656

Dr. Hari Venkatesh
Sriveda Sattva Pvt. Ltd https://orcid.org/0000-0003-1176-3831

Research Article

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Abstract

Background

The COVID-19 pandemic, caused by the human coronavirus SARS CoV-2, has led to millions of deaths across the globe. Not only is the SARS CoV-2 virus highly infectious, it also mutates very easily. This creates additional challenges for development of robust therapeutic solutions. Along with modern system of healthcare, there is a definite need for exploring natural plant based antiviral compounds directed against the SARS CoV-2 virus.

Objective

The present observational study investigates the efficacy of an Ayurvedic polyherbal formulation of 19 ingredients, NOQ19, in the management of COVID-19.

Methodology:

A single arm, single centric, open label study design was adopted for this feasibility study. 161 RT-PCR positive COVID-19 patients were enrolled. The enrolled participants were provided the Ayurvedic intervention, 2 tablets of NOQ19, thrice daily along with the standard of care treatment. Follow up COVID-19 RT-PCR tests were conducted on Day 5, Day 10 and Day 14, or until the patient turned negative. The time required for testing negative on the RT-PCR test or becoming asymptomatic was noted.

Results

A subjective analysis demonstrated that 74% of patients turned RT-PCR negative within 5 days of taking NOQ19. Additionally, 98% of the subjects turned RT-PCR Negative on Day 10 after taking NOQ19 in addition to the standard of care treatment of Vitamin C, Zinc and antipyretic (as necessary). None of the participants reported any adverse or side effects to the medication.

Conclusion

NOQ19 Ayurvedic polyherbal formulation can be an effective and safe option for the symptomatic management of COVID-19.

1.0 Introduction

The human coronavirus was first noted in the year 1960, as the virus responsible for common cold\(^1\), caused by the alpha or beta group of the virus.\(^2\) The distinctive shape of the virus, a single stranded
enveloped RNA carrying crown like spikes, gives it its name.\textsuperscript{2} The outbreak of SARS CoV-2, which emerged in 2019, was declared a public health emergency on January 30\textsuperscript{th}, 2020, and a pandemic on 11th March, 2020.\textsuperscript{3} In most cases, the severity of the infection varies from mild to moderate. After entering the body, the virus binds to Angiotensin Converting Enzyme-2 (ACE-2) receptors, via glycosylated spike protein (S). The ACE-2 receptors are highly expressed in human alveolar type 2 pneumocytes and the epithelial lining of upper esophagus. Once attached, the virus easily degrades the alveolar cells and type 2 pneumocytes.\textsuperscript{4-6} Although the clinical presentation of COVID-19 in most patients is asymptomatic, or with mild upper respiratory tract symptoms such as fever, cough, fatigue, sore throat etc., the disease can lead to pneumonia, severe respiratory distress, long term complications and death. The severe damage and subsequent reduction of type 2 pneumocytes leads to increased surface tension in the lungs, which clinically presents as dyspnea.\textsuperscript{4-6} The damaged cells and viral products trigger the release several inflammatory markers known as cytokines, as well as the release and accumulation of excessive cytokines at the site of infection (cytokine storm). The cytokine excesses lead to tissue necrosis secondary to inflammation .\textsuperscript{5-6} Furthermore, thrombosis caused by the pro-coagulant factors leads to severe organ damage, ischemia and multi-organ dysfunction.\textsuperscript{4-6} This parthenogenesis can proceed very quickly in certain individuals and has led to high numbers of fatalities, more so in the second wave\textsuperscript{7}.

Many health systems are avidly looking for solutions to bring an end to the pandemic. Despite continuous efforts from the pharmacological industry, the currently available treatment regimens focus mainly on symptomatic management and do not possess specific antiviral properties against Coronavirus.\textsuperscript{8} The most significant global milestone in the fight against COVID-19 was the development of a vaccine to produce herd immunity.\textsuperscript{8}

Ayurveda, a 5000 year old practice from India, aims to decrease the intensity of the disease, strengthen immunity and treat disease naturally.\textsuperscript{9} Ayurveda means “the science of life”, and the materia medica of Ayurveda focuses on herbs as potent remedies to prevent and cure illness.\textsuperscript{10} Many plant based medicines have flavanoids, alkaloids, phenols and tannins that exhibit antiviral and antimicrobial properties.\textsuperscript{11}

Molecular docking studies have shown that a wide range of medicinal plants exhibit therapeutic properties against SARS CoV-2.\textsuperscript{12} Kabasura Kudineer, a polyherbal formulation from Siddha system of medicine is noted to have a good binding capacity against spike 2 protein of COVID-19 and is recommended as an immunomodulator for prevention of COVID-19 by the ministry of AYUSH, Government of India.\textsuperscript{13} NOQ19 is a polyherbal Ayurvedic formulation containing 19 ingredients. A molecular docking study found that the active phytochemicals present in Ashwagandha (\textit{Withania somnifera}), Guduci (\textit{Tinospora cordifolia}) and Tulasi (\textit{Ocimum sanctum}), all three present in NOQ19, target and inhibit the main protease Mpro or or 3Clpro of SARS CoV-2 virus.\textsuperscript{14} Another clinical trial on the efficacy of Ashwagandha (\textit{Withania somnifera}) along with COVID-19 vaccine showed an enhancement in the immunogenicity of vaccine against COVID-19.\textsuperscript{15} Vasaka (\textit{Adhatoda vasica}), a component of NOQ19, has a wide variety of therapeutic effects and has potential to be used in the management of COVID-19
symptoms. It has anti-inflammatory, antiviral, antitussive and antioxidants properties.\textsuperscript{16} Bhumiamla (\textit{Phyllanthus fraternus}), another component of NOQ19 was previously used in the treatment of viral infections such as hepatitis and flu.\textsuperscript{17} Bhunimba (\textit{Andrographis paniculata}), also present in NOQ19, is known for its antithrombotic properties and prevents blood clotting, which is a severe clinical presentation in COVID-19 patients.\textsuperscript{18} Haridra (\textit{Curcuma longa}), a well-known therapeutic compound, can inhibit the cytokine release and therefore aid the clinical improvement in flu and other infectious diseases.\textsuperscript{19} Molecular docking has revealed that the active components of Yashtimadhu (\textit{Glycyrrhiza glabra}) possess potential binding properties against the spike glycoprotein and non-structural protein-15 of SARS CoV-2 virus.\textsuperscript{20} Both Haridra and Yastimadhu are components of NOQ19.

The authors hypothesize that NOQ19 may possess good clinical efficacy against SARS-CoV-2. The study investigates the efficacy of NOQ19 as a therapeutic option for COVID-19 through a single arm clinical trial.

- Objective:
  The objective of the study is to evaluate the time to become SARS CoV-2 RT-PCR negative in COVID-19 patients who consume NOQ19 along with the standard treatment and as well as to evaluate the turnaround time for COVID-19 patients to become asymptomatic.

\textbf{2.0 Material And Methods}

\textbf{Study Design:}

A single arm, single center, clinical trial study design was opted to test the efficacy of NOQ19 against COVID-19 viral infection. The study was conducted at Sri Sri Institute for Advanced Research from April 2021 to June 2021. The study was approved by the Institutional ethics committee (IEC) of Sri Sri Institute for Advanced Research bearing registration number SSIAR/IEC/2021/010. All the patients enrolled in the study were provided NOQ19 along with standard of care treatment and followed up for RT-PCR on Day 5, 7, 10 and 14. Symptomatic evaluation was taken verbally everyday by the data collector to monitor the symptoms and adverse effects of the drug.

\textbf{Participants}

COVID-19 patients who tested positive on RT-PCR were enrolled in the study. RT-PCR is considered the gold standard for detection of COVID-19.\textsuperscript{21} A total of 161 home isolated COVID-19 patients were enrolled in the study based on the inclusion and exclusion criteria (below). The participants were evaluated for their symptoms daily from the time of enrollment, until the 14 day follow up. Side effects were noted. RT-PCR test was conducted at day 5, 7, 10 and 14 or until the patient turned negative.
Inclusion Criteria

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

Exclusion criteria

- Patients unwilling to give consent or participate in the clinical trial or adhere to the Ayurvedic medicine regime
- Pregnant women or lactating mothers
- Severe COVID-19 cases with SpO$_2$ less than 95% on room air, in Intensive care or on ventilation

Intervention

NOQ19 preparation is a combination of 19 ingredients from 13 Ayurvedic herbs: Ashwagandha (Withania somnifera), Bilwa (Aegle marmelos), Yashtimadhu (Glycyrrhiza glabra), Rasna (Pluchea lanceolata), Vasaka (Adhatoda vasica), Pippali (Piper longum), Haridra (Curcuma longa), Patha (Cissampelos pareira), Bhumiamla (Phyllanthus fraternus), Bhunimba (Andrographis paniculata), Saptaparna (Alstonia scholaris), Tulasi (Ocimum sanctum) and Guduci (Tinospora cordifolia). Some of the herbs were used only as a powder while Ashwagandha (Withania somnifera), Yashtimadhu (Glycyrrhiza glabra), Vasaka (Adhatoda vasica), Bhumiamla (Phyllanthus fraternus), Bhunimba (Andrographis paniculata), and Guduci (Tinospora cordifolia) were used as both powder and extract.

The subjects who qualified as per the inclusion criteria were enrolled in the study and were provided the intervention drug NOQ19 along with the standard of care treatment. The medicine was manufactured and procured from Sriveda Sattva Private Limited, a Good Manufacturing Practice (GMP) certified company, to ensure good quality. The drug was licensed by the ministry of AYUSH with the license number AUS-782. The medicine was taken as 2 tablets, thrice a day after food. The standard of care treatment included only antipyretics such as paracetamol and supplements such as zinc and vitamins. The NOQ 19 tablets were packed in a bottle of 90 tablets and given to each subject at the time of enrollment. Dosage compliance and symptom monitoring was conducted over the phone.

Outcomes

Primary Outcome: RT-PCR tests were obtained to measure the time required by participants to acquire a negative test. 2 nasopharyngeal swabs were collected from the patients reporting to the nearby PHC or
clinic with symptoms. RT-PCR analysis was done to determine the viral load. The test was repeated using
the nasal and throat swabs as per the ICMR guidelines on Day 5, Day 10 and Day 14. The participants
were followed up for 14 days or until their RT-PCR test turned negative, whichever occurred earlier.

Secondary Outcomes: The turnaround time to become asymptomatic. Regular symptom assessment was
conducted to monitor the efficacy and safety of the drug. Adverse events or side effects were monitored.

Sample Size

The present study was a pilot study to evaluate the time to turn RT-PCR negative and to assess the safety
of NOQ19. Therefore, the sample size was restricted to 160 participants. Since this was a pilot study, a
minimum of 50 participants were enrolled as per thumb rule. Accounting for loss to follow up or
dropouts, a total of 161 patients were recruited for the study.

Statistical Analysis:

All the symptomatic parameters were assessed using descriptive statistical methods using Microsoft
excel 2019 (16.0.12026.20334) 32-bit. The parameters were calculated in terms of Mean or proportion.
All the data were kept highly confidential.

3.0 Results

A total of 161 participants were enrolled in the study. 4 subjects dropped out from the study due to
dosage noncompliance. A total of 118 male subjects and 43 female subjects were enrolled. The
participants had comparable demographic data with respect to age and comorbidities. The average age
of the study group was 43 years. 5 subjects underwent RT-PCR on day 7 instead of day 5 due to
unavailability of kits. 4 patients dropped out on day 5. 2 patients did not state appropriate reason for drop
out. while 2 others dropped out because the severity of disease. Rest of the patients showed complete
compliance with the intervention. All the patients were followed up at respective time points, unless they
turned RT-PCR negative. A total of 42 patients were evaluated after day 5 since the other 115 were RT-PCR
negative on day 5 (Fig 1).

All the patients showed similar clinical presentation at the onset of symptoms. 87 participants presented
with fever, 30 participants presented with headache, 43 participants presented with weakness/ malaise/
tiredness, 53 participants complained of throat pain, 40 participants complained of common cold, and
31 participants had cough on the day of enrollment. 11 participants were asymptomatic.
Evaluation of symptom progression (Table 1) demonstrated a significant reduction in the symptoms among participants on day 1 of the study. Only 3 participants had fever, and most of them presented with tiredness and cough. The symptoms reduced even further after 3 days of taking NOQ-19 medication and 125 people turned asymptomatic by day 3. By Day 5, most of the participants had turned asymptomatic.

Table 2 represents the RT-PCR test results. The evaluation of test results demonstrated that 115 (74%) subjects turned RT-PCR Negative on Day 5 after taking NOQ19 along with the standard of care treatment, 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.

4.0 Discussion

This is the first study to determine the efficacy and safety of a novel Ayurvedic formulation NOQ19 in the management of COVID-19. This was an open label feasibility study. The study evaluates the turnaround time of a COVID-19 positive patient to become RT-PCR negative and asymptomatic while taking NOQ19. NOQ19 contains 19 herbal ingredients that possess antiviral and immune modulating properties against COVID-19.\textsuperscript{23-24} A previous in-vitro study on NOQ19 demonstrated a 100% efficacy of the drug against SARS-CoV-2 on Vero E6 infected cell lines.\textsuperscript{25} The study was further extended in an in-vivo setting where the NOQ19 drug demonstrated strong (78.2%) anti-viral efficacy on hamsters with no adverse effects.\textsuperscript{26} Our results demonstrated that by the third day of taking the medicine, 80% of the patients had turned asymptomatic, and by the seventh day, all the subjects reported being asymptomatic, except for minor fatigue. The clinical symptoms matched the RT-PCR test reports which showed that 74% of the patients turned negative by Day 5, and 98% of the patients turned negative by Day 10. In an earlier clinical trial conducted on AYUSH 64, 69.7% patients had a mean time recovery of one week from the start of intervention.\textsuperscript{27} Another study on Siddha medicine, Kabasura Kudineer and Nilavembu kudineer, compared the efficacy of these herbal formulations against the standard treatment for COVID-19. The authors of that study observed that patients who consumed herbal medicines along with standard treatment took only 2.7 days approximately to turn asymptomatic, while those who took standard care of treatment alone took 4.2 days.\textsuperscript{28} It is worthwhile to note that few ingredients are common between Kabasura Kudineer and NOQ19.

Our study demonstrated a faster rate of viral load reduction. A probable reason for this could be the presence of Glycyrrhizin, a component present in Yashtimadhu (\textit{Glycyrrhiza glabra}), that inhibits the viral replication protein.\textsuperscript{29-31} An \textit{in-vitro} study by Gowda et al. demonstrated the inhibition of viral replication in a 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 response in COVID-19 patients.\textsuperscript{29}

Another key finding was the reduction in fever and runny nose within a day of taking the intervention treatment. According to Ayurvedic literature, Guduci (\textit{Tinospora cordifolia}) and Pippali (\textit{Piper longum}) are antipyretic in nature.\textsuperscript{32} A clinical trial on the antipyretic effects of these two herbs showed a substantial reduction in fever. The authors suspect the antipyretic-analgesic property of NOQ19 is due to the presence of flavonoids and phelonic compounds.\textsuperscript{33}

However, the authors do recognize 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 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.

\textbf{5.0 Conclusion}

The world is in search of a safe and effective treatment with antiviral properties directed specifically against the COVID-19 virus. The present study on an Ayurvedic formulation of 19 ingredients, NOQ19, demonstrates its efficacy in clinical management of COVID-19 patients. 74\% and 98\% of the patients turned RT-PCR negative within 5 and 10 days, respectively, from the start of NOQ19 treatment. Also, none of the subjects consuming NOQ19 reported any adverse side effects.

\textbf{Declarations}

\textbf{Conflict of Interest:} The test resources were provided by Sriveda Sattva Pvt. Ltd (Sri Sri tattva). Dr. Ravi Reddy is the chief scientific officer of Sriveda Sattva Pvt Ltd. In addition Dr Hari Venkatesh is the research head and development head at Sriveda Sattva Pvt. Ltd. Besides providing the NOQ19 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.

\textbf{Funding:}

No funding

\textbf{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.

\textbf{Clinical Trial:} CTRI/2021/08/036025

\textbf{Data availability:} The data will be made available upon request.
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Tables
**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: 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%                                                   |

**Figures**
**Figure 1**

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