

## Systematic Review

## Nilavembu Kudineer (Siddha Polyherbal Decoction) for the Management of COVID-19 – Evidence from Clinical and In-silico Studies

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## ABSTRACT

**Background and Aim:** The current pandemic of coronavirus Disease 2019 (COVID-19) is caused by novel coronavirus or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and it is managed mainly by using repurposed antiviral drugs along with symptomatic treatment and supportive care. This review focuses on the use of Nilavembu Kudineer in asymptomatic or mildly symptomatic COVID-19 patients. **Methods:** The literature was searched in databases such as Medline, PubMed Central, PubMed, Google Scholar, Science Direct, bioRxiv, medRxiv, Research Square, EBSCO, Scopus, Web of Science, EMBASE, Directory of Open Access Journals (DOAJ), and reference lists to identify articles relevant to the clinical and in silico studies evaluating the efficacy of Nilavembu Kudineer in the management of COVID-19. **Results:** Many clinical studies revealed that Nilavembu Kudineer might be effective in the management of asymptomatic or mild-symptomatic COVID-19 patients along with standard care. Similarly, many molecular docking studies have been performed to determine the inhibitory potential of phytoconstituents of Nilavembu Kudineer against SARS-CoV-2. **Conclusion:** More randomized, controlled trials would further establish the safety and efficacy of Nilavembu Kudineer in COVID-19 patients.

**Keywords:** SARS CoV-2; COVID-19; Siddha formulations; Herbal formulations; Nilavembu Kudineer

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that first appeared in December 2019 in Wuhan, China [1]. As of 30th 30, 2022, about 599 million people around the globe are infected with SARS-CoV-2, and around 6.5 million deaths have occurred among them, as per the WHO novel coronavirus (COVID-19) situation board.

The clinical characteristics of COVID-19 mainly include pyrexia, dyspnea, and a dry cough [3]. In addition, ageusia (loss of taste) and/or anosmia (loss of smell) were identified as the fourth most commonly reported symptom by COVID-19 patients [4]. The patients with COVID-19 may also

experience respiratory symptoms like dyspnea and gastrointestinal symptoms such as diarrhea, abdominal pain, hyporexia or anorexia, nausea, and vomiting [5]. COVID-19 manifestations that are unusual or atypical include neurological (altered mental status, confusion, dizziness, stroke, cerebral venous thrombosis, etc.) [6, 7], hematological (lymphopenia, thrombocytopenia, and elevated D-dimer levels) [8, 9], ocular (dry eye, conjunctivitis, redness, itching, eye discharge, etc.) [10], cutaneous (urticarial,

Patients with COVID-19 are put into four groups based on how bad their symptoms are: asymptomatic, mild/moderate, severe, and critical [13]. The mild/moderate

symptoms of COVID-19 include fever, cough, hyposmia, hypogeusia, headache, myalgia, nasal congestion, or rhinorrhea [14], whereas the patients with severe COVID-19 may experience lessened oxygen saturation (SpO<sub>2</sub> <94%), higher respiratory frequency (>30 breaths/min), and higher lung infiltrates (>50%) [15], and the critically ill patients with COVID-19 may have respiratory failure, septic shock, and/or multiple organ dysfunction [16].

The patients with COVID-19 could be managed by using repurposed drugs having antiviral potential that inhibit viral entry and/or viral fusion, such as umifenovir, baricitinib, camostat mesilate, and nafamostat mesilate, and that block viral replication, like favipiravir, remdesivir, lopinavir/ritonavir, ribavirin, sofosbuvir, chloroquine, and hydroxychloroquine [17]. In fact, remdesivir is the only antiviral drug approved by the United States Food and Drug Administration (US FDA) for the management of patients with COVID-19 [18]. However, the interim results of the SOLIDARITY trial conducted by the World Health Organization (WHO), which is a large, simple, international, open-label, randomised trial involving hospital-admitted COVID-19 patients, revealed that the administration of four major repurposed drugs, including remdesivir, lopinavir, hydroxychloroquine, and interferon beta-1a, resulted in little or no effect on overall mortality, initiation of ventilation, or duration of hospital stay [19].

Patients with COVID-19 may also benefit from treatments like corticosteroids, interferons, monoclonal antibodies, IL-1 inhibitors, TNF-inhibitors, colchicine, etoposide, ruxolitinib, anticoagulants, convalescent plasma, immunoglobulins, mesenchymal stem cells, natural killer (NK) cells, and inhaled nitric oxide (iNO) [20]. In fact, the "RECOVERY trial" showed that the COVID-19 patients who needed mechanical ventilation or oxygen and were given dexamethasone (6 mg/day for up to 10 days) had a lower chance of dying [21].

Nowadays, the use of traditional medicine is very common among the global population, especially in underdeveloped or developing countries. The general public residing in rural and remote areas seeks traditional medicine for their primary healthcare [22]. Many patients with COVID-19 from different parts of the world are using various traditional medicines, including Siddha, Ayurveda, traditional Chinese medicine, traditional African medicine, traditional Persian medicine, etc., along with repurposed antiviral drugs and standard care. Moreover, several clinical and in silico studies have evaluated the potential of black seeds (*Nigella sativa*), a traditional medicine, against the SARS-CoV-2 infection [23–25].

In this review, we focus on the therapeutic potential of "Nilavembu Kudineer" against SARS-CoV-2 infection as we review the potential of another Siddha polyherbal decoction, "Kabasura Kudineer," in the management of patients with COVID-19 [26]. Nilavembu Kudineer is a poly-herbal Siddha formulation, and it contains Nilavembu (*Andrographis paniculata*) as its prime herb along with 8 other herbs, including Vettiver (*Chrysopogon zizanioides*), Sandanam (*Santalum album*), Sukku (*Zingiber officinale*), Milagu (*Piper nigrum*), Korai Kilangu (*Cyperus rotundus*), Parpadagam (*Mollugo cerviana*), and Peipudal (*Trichosanthes cucumerina*), in equal proportions [27].

Nilavembu Kudineer was found to contain various phytochemicals, including flavonoids, alkaloids, glycosides, phenols, tannins, terpenoids, and carbohydrates [28]. Moreover, the phytochemical analysis of Nilavembu Kudineer revealed the presence of several bioactive phytoconstituents, including Andrographolide, Vetivone, Vetiverol, Naphtalenol, Bisabolol,  $\alpha$ -Santalol,  $\beta$ -Santalol, Cucurbitacin B, Sugenol, Rotundone, Cyperenon, Zingerone, Gingerdiol, Zingibrene, Gingerols, Piperine, Piperamide, Piperamine, Pipericide, Piperolin, Piperidine, and many others [29].

Generally, the herbs found in Nilavembu Kudineer and their bioactive phytoconstituents possess antiviral, antioxidant, anti-inflammatory, immune-modulatory, antimicrobial, and hepatoprotective properties, which are all relevant to the causative organism and signs and symptoms of COVID-19 [30]. Above all, the consumption of 60 ml of Nilavembu Kudineer after food is recommended by the ministry of AYUSH (the Government of India) for the symptomatic management of patients with COVID-19 [31, 32].

## METHODS

The literature was searched in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, bioRxiv, medRxiv, Research Square, EBSCO, Scopus, Web of Science, EMBASE, the Directory of Open Access Journals (DOAJ), and reference lists have been searched to identify articles relevant to the clinical and in-silico studies evaluating the efficacy of Nilavembu Kudineer in the management of COVID-19 using terms like SARS CoV-2, COVID-19, Siddha formulations, herbal formulations, and Nilavembu Kudineer. The publications supporting the use of Nilavembu Kudineer for the management of COVID-19 were included in this review, while the duplicates were excluded.

**RESULTS & DISCUSSION**

Some clinical studies have determined the therapeutic efficacy of Nilavembu Kudineer in the management of asymptomatic or mildly symptomatic COVID-19 patients (Table 1). In addition, a few molecular docking studies have been performed to determine the inhibitory potential of phytoconstituents of Nilavembu Kudineer against SARS-CoV-2 (Table 2).

*Clinical studies supporting the use of Nilavembu Kudineer for COVID-19*

A double-blind, three-arm, single-center, placebo-controlled, exploratory and comparative randomised controlled trial of 125 mild to moderate COVID-19 patients found that taking 60 ml of Nilavembu Kudineer twice daily along with standard allopathic therapy for a maximum of 10 days resulted in a significant decrease in viral load as well as a significant reduction in the duration of hospital stay and the time required to alleviate COVID-19 symptoms [33].

**Table 1. Clinical studies supporting the use of Nilavembu Kudineer for COVID-19**

Study design	Type of Patients	Outcome
Double blind, three arm, single centre, placebo controlled, exploratory and comparative randomized controlled trial [33]	Mild to moderate COVID-19 patients	Significant reduction of duration of hospital stays and time taken to alleviate the COVID-19 symptoms
Case report of a 39-year-old female COVID-19 patient [34]	Mild COVID-19 patient	Symptomatic improvement and negative RT-PCR results after 14 days of therapy
Case report of a 30-year-old female COVID-19 patient [35]	Mild COVID-19 patient	Negative RT-PCR results after 8 days of treatment

Moreover, another case report of a 30-year-old female COVID-19 patient with confirmed Real Time Polymerase Chain Reaction (RT-PCR) results and having mild COVID-19 symptoms revealed that the administration of Nilavembu Kudineer and Vasantha Kusumakaram tablets for 2 weeks along with medicated steam inhalation of Nochi leaves (*Vitex negundo*) for 10 days ensued in negative RT-PCR results after 8 days of treatment [35].

In addition, a case report of a 39-year-old female COVID-19 patient with confirmed Real Time Polymerase Chain Reaction (RT-PCR) results and showing all the peculiar COVID-19 clinical features determined that the management of the patient with 60 ml of Nilavembu Kudineer two times daily in conjunction with biomedicine for 14 days resulted in symptomatic improvement and negative RT-PCR results after 14 days of therapy [34].

**Table 2. In-silico studies explored Nilavembu Kudineer efficacy against SARS-CoV-2**

Potential Phyto-constituents of Nilavembu Kudineer	Molecular Target	Outcome
Andrographolide, Vetiverol, Piperine, Piperidine, 6-Gingerol, and $\alpha$ -Bisabolol [37]	RdRP of SARS-CoV-2	Potent binding with RdRP to prevent SARS-CoV-2 viral replication
Piperine, and Cucurbitacin B [38]	Protein structures of SARS-CoV-2	Potent binding with protein structures to prevent SARS-CoV-2 viral replication
Benzene 123 triol [39]	ACE2	Effective binding with ACE2 to prevent SARS-CoV-2 viral entry
Stigmasterol and Stigmasta-5, 22-dien-3-ol [40]	Multiple target proteins	Potential binding affinity with multiple proteins of SARS-CoV-2

In addition, many clinical studies are registered in the Clinical Trials Registry-India (CTRI) for the evaluation of the safety and efficacy of AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa, and Homeopathy) medicines against COVID-19, including 4 recovery studies and 1 preventive study that evaluate Nilavembu Kudineer [36].

*In-silico studies explored the efficacy of Nilavembu Kudineer against SARS-CoV-2*

A molecular docking study revealed that the bioactive phytoconstituents of Nilavembu Kudineer such as Andrographolide, Vetiverol, Piperine, Piperidine, 6-Gingerol, and -Bisabolol had potential binding affinity with the target amino acid residue of RNA dependent RNA

polymerase (RdRP) of SARS-CoV-2 [37]. The bioactive phytoconstituents of Nilavembu Kudineer, including Piperine, and Cucurbitacin B, have been identified to bind with the protein structures of SARS-CoV-2 [38].

Furthermore, another molecular docking study found that benzene-1,2,3-triol from an aqueous extract of Nilavembu Kudineer effectively bound with ACE2 [39]. In addition, the phytoconstituents like stigmaterol and stigmasta-5, 22-dien-3-ol of *Andrographis paniculata*, which is one of the component herbs of Nilavembu Kudineer, have shown potential binding affinity with multiple target proteins of SARS-CoV-2, including the main protease, spike protein, membrane protein, envelope protein, receptor binding domain, non-structural protein 9, and non-structural protein 3 [40].

## CONCLUSION

Based on the available clinical evidence, asymptomatic or mildly symptomatic COVID-19 patients may use Nilavembu Kudineer in conjunction with standard allopathic treatment to achieve faster recovery, shorter hospital stays, and faster negative RT-PCR results. Moreover, many in-silico molecular docking studies determined that several bioactive phytoconstituents of Nilavembu Kudineer have exhibited higher binding affinity towards ACE2, spike glycoprotein, and the molecular target proteins of SARS-CoV-2. More randomized, controlled clinical trials would further establish the safety and efficacy of Nilavembu Kudineer in patients with COVID-19.

*Abbreviations:* WHO - World Health Organization, COVID 19 - Coronavirus disease 2019, SARS-CoV-2 - Severe acute respiratory syndrome coronavirus-2

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