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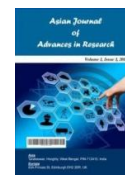
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## THERAPEUTIC EFFICACY OF KABASURA KUDINEER (SIDDHA FORMULATION), IN COVID-19 – A REVIEW OF CLINICAL AND MOLECULAR DOCKING STUDIES

NAINA MOHAMED PAKKIR MAIDEEN<sup>1\*</sup>

<sup>1</sup>Dubai Health Authority, PB No: 4545, Dubai, UAE.

### AUTHOR'S CONTRIBUTION

The sole author designed, analysed, interpreted and prepared the manuscript.

**Received: 02 June 2021**

**Accepted: 07 August 2021**

**Published: 14 August 2021**

**Review Article**

### ABSTRACT

Coronavirus disease 2019 (COVID-19), which is brought about by novel coronavirus or Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could be managed mainly by using repurposed antiviral drugs. This review focuses on the utilization of Kabasura Kudineer in asymptomatic or mild symptomatic COVID-19 patients. The databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of science, EMBASE, Directory of open access journals (DOAJ), and reference lists have been looked to distinguish articles pertinent to the clinical and in-silico studies assessing the efficacy of Kabasura Kudineer in the management of COVID-19. A few clinical investigations have exhibited the adequacy of Kabasura Kudineer in the management of asymptomatic or mild-symptomatic COVID-19 patients alongside standard care. Additionally, numerous molecular docking studies have been performed to determine the inhibitory capability of phytoconstituents of Kabasura Kudineer against SARS-CoV-2. More randomized controlled clinical trials would further establish the safety and efficacy of Kabasura Kudineer in COVID-19 patients.

**Keywords:** SARS CoV-2; COVID-19; siddha formulations; herbal formulations; Kabasura Kudineer.

### 1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by novel coronavirus or Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged first in Wuhan, China in December 2019. As of 12<sup>th</sup> June 2021, about 175 million of people around the globe are infected by SARS-CoV-2 and 3.8 million deaths occurred among them, according to the World Health Organization (WHO) novel Coronavirus (COVID-19) Situation Board [1].

The prominent symptoms of COVID-19 include high-grade fever, dry cough, and fatigue. A household study from the Centers for Disease Control and Prevention (CDC) determined that ageusia (loss of taste) and/or anosmia (loss of smell) as the fourth most detailed manifestation by COVID-19 patients [2]. In addition, patients with COVID-19 may likewise encounter symptoms including neurological manifestations such as headache, dizziness, impaired consciousness, stroke, ataxia, etc [3] and Gastrointestinal manifestations such as diarrhea, anorexia, nausea, vomiting, abdominal pain [4], and body ache, which are less common [5].

\*Corresponding author: Email: nmmaideen@dha.gov.ae;

Severe COVID-19 could be anticipated in patients with specific variables including advanced age, comorbidities (hypertension, obesity, diabetes mellitus, cardiovascular disease, chronic kidney disease, and chronic respiratory disease), immune response, radiographic findings (ground-glass opacities), and laboratory markers (elevated levels of D-dimer, C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), lactate dehydrogenase (LDH), and high sensitivity cardiac troponin I) [6].

Major structural proteins of SARS-CoV-2 include spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein [7]. The Receptor Binding Domain (RBD) of spike (S) protein ties to the cell surface protein angiotensin-converting enzyme 2 (ACE2) to infect the human cells. The priming of spike (S) protein is mediated by the cellular transmembrane serine protease 2 (TMPRSS2) enzyme, followed by the entry of SARS-CoV-2 into the host cell and fusion of viral and cellular membranes [8]. The shape of the viral envelope is defined by M protein whereas the N protein binds to the RNA genome and is involved in viral assembly followed by, transportation of virions to the cell surface where they are released by exocytosis [9].

The management of patients with SARS-CoV-2 infection should be possible by using drugs having antiviral potentials, which restrain viral entry and/or viral fusion such as umifenovir, Baricitinib, camostat mesylate, Nafamostat mesylate, and that block viral replication like favipiravir, Remdesivir, Lopinavir /ritonavir, Ribavirin, Sofosbuvir, chloroquine, and Hydroxychloroquine [10]. Moreover, the patients with COVID-19 could likewise be overseen by adjuvant therapies including corticosteroids, interferons, monoclonal antibodies, interleukin-1 (IL-1) inhibitors, TNF- $\alpha$  inhibitors, colchicine, etoposide, ruxolitinib, anticoagulants, convalescent plasma, immunoglobulins, mesenchymal stem cells, natural killer (NK) cells, and inhaled nitric oxide (iNO) [11]. However, the interim results of the SOLIDARITY trial conducted by the World Health Organization (WHO), which is a large, simple, international, open-label, randomized trial hospital-admitted COVID-19 patients, uncovered 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, commencement of ventilation and duration of hospital stay [12].

About 80 % of the global population relies on traditional medicine to treat infectious diseases, as per the estimation of the World Health Organization (WHO) [13]. Moreover, WHO encourages the

researchers to assess the safety and efficacy of various traditional medicines against SARS-CoV-2 infection. Various traditional medicines including Siddha, Ayurveda, Traditional Chinese medicine, Traditional African medicine, Traditional Persian medicine, and so forth alongside repurposed antiviral drugs and standard care, are in use to manage the patients with COVID-19 in different parts of the world. Moreover, the prophylactic and therapeutic efficacy of black seeds (*Nigella sativa*), a traditional medicine, have been evaluated in different clinical and in-silico studies [14, 15].

Similarly, this review focuses on the remedial capability of a Siddha poly-herbal formulation named “Kabasura Kudineer” against SARS-CoV-2 infection. Kabasura Kudineer is coined from different Tamil terms such as *kabam* (Phlegm), *suram* (Fever), and *Kudineer* (Concoction). As the name implies, Kabasura Kudineer is indicated in the management of phlegmatic fever and fever with symptoms of respiratory infections. Kabasura Kudineer contains 15 herbs including Ginger (*Zingiber officinale*), Long pepper (*Piper longum*), Clove (*Syzygium aromaticum*), Green chiretta (*Andrographis paniculata*), Spanish chamomile (*Anacyclus pyrethrum*), Chebulic myrobalan (*Terminalia chebula*), Malabar nut (*Justicia Vasica*), Nutsedge (*Cyperus rotundus*), Tea weed (*Sida acuta*), Blue fountain bush (*Clerodendrum serratum*), Giloy (*Tinospora cordifolia*), Stingling nettle (*Tragia involucrata*), Koshtam (*Costus speciosus*), Thick-leaf lavender (*Anisochilus carnosus*) and African eggplant (*Solanum anguivi*). This load of 15 spices are blended in equivalent amounts and powdered coarsely to set up the decoction by blending 35 g of powder in with 3 liters of water, bubbled, and diminished to its quarter volume [16].

The phytochemical examination of Kabasura Kudineer determined that it contains various chemical compounds including flavonoids, alkaloids, cardiac glycosides, glycosides, carbohydrates, terpenoids, tannins, and phenols [17, 18]. Besides, the bioactive phytoconstituents of Kabasura Kudineer include Gingerols, shogaols, Piperine, eugenol, quercetin, rutin, Pyrethrine,  $\beta$ -sitosterol, chebulagic acid, Vasicine, vasicinone, Carvacrol, Andrographolide, and many others [19]. Kabasura Kudineer has been identified with various pharmacological activities such as Antiviral, Anti-inflammatory, Antioxidant, Anti-asthmatic, and Antipyretic, which are related to the signs and symptoms of COVID-19, in several studies [20]. The ministry of AYUSH (Government of India) recommends the consumption of 60 ml of Kabasura Kudineer after food, for the symptomatic management of patients with COVID-19 [21].

## 2. METHODS

The databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of Science, EMBASE, Directory of open access journals (DOAJ), and reference lists have been searched to identify articles relevant to the clinical and in-silico studies assessing the viability of Kabasura Kudineer in the management of COVID-19 using terms like SARS CoV-2, COVID-19, Siddha formulations, herbal formulations, and Kabasura Kudineer. The publications supporting the use of Kabasura Kudineer for the management of COVID-19 done in English included in this review while the copies were barred.

## 3. RESULTS AND DISCUSSION

A few clinical examinations have shown the viability of Kabasura Kudineer in the management of asymptomatic or mild-symptomatic COVID-19 patients (Table 1). Similarly, many molecular docking studies have been performed to determine the inhibitory capability of phytoconstituents of Kabasura Kudineer against SARS-CoV-2 (Table 2).

### 3.1 Clinical Studies Supporting the use of Kabasura Kudineer for COVID-19

An open-label, two-arm, randomized controlled interventional clinical study of 200 COVID-19 patients demonstrated that twice-daily administration of 60 ml of Kabasura Kudineer, 1 tablet of 130 mg of Vasantha kusumakaram mathirai, 2 g of Thippili rasayana, and 15 ml of Adathodai manapagu along with allopathic standard treatment of care, ensued in significantly accelerated recovery, significant reduction of the percentage of COVID pattern lung involvement, and significant decline in Neutrophil/Lymphocyte Ratio (NLR) compared to standard group [22]. In addition, a significant decline in viral load, and significant reduction of the duration of hospital stay and time taken to alleviate the COVID-19 symptoms were observed in a double-blind, three-arm, single-center, placebo-controlled, exploratory, and comparative randomized controlled trial of 120 mild to moderate COVID-19 patients by the administration of 60 ml of Kabasura Kudineer two times daily along with standard allopathic therapy, for a maximum of 10 days [23].

Conversely, a single-center, two-arm, open-labelled, randomized controlled clinical trial of 30 mild to moderate cases of COVID-19 revealed that there was no distinction in the quality of life scores accomplished by the administration of Kabasura Kudineer tablets, Shakti drops and Turmeric plus

along with standard care for 21 days, contrasted with the patients who received standard care alone [24].

Significantly earlier SARS-CoV-2 viral clearance has been observed in asymptomatic and mild to moderate symptomatic COVID-19 patients admitted in a tertiary care hospital, by the administration of 60 ml of Kabasura Kudineer for 5 days, in a prospective observational study of 100 patients. The greater part of the patients in the intervention group got negative Real-Time Polymerase Chain Reaction (RT-PCR) results on the 6<sup>th</sup> day compared to half of the patients in control group who got negative RT-PCR results on the 10<sup>th</sup> day, which indicate earlier SARS-CoV-2 viral clearance among the patients who received Kabasura Kudineer [25].

Similarly, the length of hospital stay was shortened by the administration of Kabasura Kudineer along with vitamin C and zinc supplements, observed in a retrospective cross-sectional data analysis of 251 asymptomatic and mild symptomatic COVID19 patients admitted in a COVID care hospital [26]. Moreover, a cross-sectional explanatory/descriptive research questionnaire survey of 200 participants from different parts of Tamilnadu, India demonstrated that a significant number of participants consume Kabasura Kudineer which can always be used as a home remedy to boost up the immunity and prevent viral and fungal infection [27].

In addition, many clinical studies are registered in Clinical Trials Registry-India (CTRI) for the evaluation of safety and efficacy of AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa, and Homeopathy) medicines against COVID-19 including 14 recovery studies and 2 preventive studies which evaluate Kabasura Kudineer [28-30].

### 3.2 In-silico Studies Explored the Efficacy of Kabasura Kudineer against SARS-CoV-2

As Kabasura Kudineer is a poly-herbal formulation of 15 herbs, it contains heaps of bioactive phytoconstituents having distinctive pharmacological activities. A molecular docking study determined that the bioactive phytoconstituents of Kabasura Kudineer such as Cordiofoliside B, Andrographolide, Vasicine, Apigenin, and Pyrethrin exhibited potent binding affinity towards the Spike(S) glycoprotein of SARS-CoV-2 to prevent the binding of host receptors [31]. Likewise, the bioactive phytoconstituents of Kabasura Kudineer like Chrysoeriol and Luteolin were found to have high binding affinity and good binding interactions with spike glycoprotein of SARS-CoV-2 to prevent the binding of host receptors, dictated by another molecular docking study [32].

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

<b>S. No</b>	<b>Study design</b>	<b>Type of Patients</b>	<b>No of Participants</b>	<b>Outcome</b>
<b>1</b>	Open label, two arm, randomized controlled interventional clinical study [22]	Asymptomatic, mild-moderate symptomatic patients with COVID-19	200 (All the 100 patients treated with Siddha medicines were discharged by day 5)	Significantly accelerated recovery, significant reduction of percentage of COVID pattern lung involvement, and significant decline in Neutrophil/Lymphocyte Ratio (NLR)
<b>2</b>	Double blind, three arm, single center, placebo controlled, exploratory and comparative randomized controlled trial [23]	Mild to moderate COVID-19 patients	120 (All the 40 patients treated with KSK were discharged by day 6)	Significant decline in viral load, and significant reduction of duration of hospital stay and time taken to alleviate the COVID-19 symptoms
<b>3</b>	Single center, two arm, open labelled, randomized controlled clinical trial [24]	Mild-moderate symptomatic patients with COVID-19	30 (All the 15 patients treated with Siddha medicines were completely resolved of symptoms by day 7)	No difference in the quality of life scores observed in intervention group as well as control group
<b>4</b>	Prospective observational study [25]	Asymptomatic, mild-moderate symptomatic patients with COVID-19	100 (49 patients treated with KSK became RT-PCR negative by day 6)	Significantly earlier SARS-CoV-2 viral clearance
<b>5</b>	Retrospective cross-sectional data analysis [26]	Asymptomatic, mild symptomatic COVID19 patients	251 (Average length of hospital stay in patients treated with KSK was 13.5 days)	Shortened length of hospital stay

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

S.No	Potential Phytoconstituents of <i>N. sativa</i>	Molecular Target	Outcome
1	Cordifoliside B, Andrographolide, Vasicine, Apigenin and Pyrethrin [31]	Spike(S) glycoprotein of SARS-CoV-2	Potent binding affinity towards S protein to prevent the binding of host receptors
2	Chrysoeriol and Luteolin [32]	Spike(S) glycoprotein of SARS-CoV-2	Higher binding affinity towards S protein to prevent the binding of host receptors
3	Acetoside, Luteolin 7 -rutinoside, rutin, Chebulagic acid, Syrigaresinol, Acanthoside, Violanthin, Andrographidine C, and myricetin [33]	3 Chymotrysin-like protease (3CL <sup>pro</sup> ) enzyme	Higher binding affinity towards 3CL <sup>pro</sup> to prevent SARS-CoV-2 replication
4	$\beta$ -amyrin, Furanolactone, Sesamine, Berberine, Clerodane 6,7 dione, lupeol, piperine, piperlongumine, $\beta$ -sitosterol, Clerodanediol and Berberine [34]	Main protease enzymes and RdRP of SARS-CoV-2	Higher binding affinity towards main protease enzymes and RdRP of SARS-CoV-2
5	Vasicinone, Vasicine, Luteolin, and Scutellarein [35]	Main protease enzymes of SARS-CoV-2	Very strong binding affinity towards main protease enzyme of SARS-CoV-2
6	Piperidine, Piperine, Andrographolide, $\beta$ -sitosterol, Rutin, Vetiverol, Carvacrol, and 6- Gingerol [36]	RdRP of SARS-CoV-2	Potent binding affinity with RdRP of SARS-CoV-2

Moreover, a molecular docking study of bioactive phytoconstituents of Kabasura Kudineer revealed that the phytochemicals such as Acetoside, Luteolin 7 - rutinoid, rutin, Chebulagic acid, Syringaresinol, Acanthoside, Violanthin, Andrographidine C, and myricetin were exhibited high binding affinity towards 3 Chymotrysin-like protease (3CL<sup>pro</sup>) enzyme, which assumes a significant role in SARS-CoV-2 replication. All these phytochemicals exhibited better binding affinity towards 3CL<sup>pro</sup> compared to synthetic drugs such as Ritonavir, Lopinavir, Oseltamivir, Hydroxychloroquine, Ivermectin, and Azithromycin [33]. In addition, another molecular docking study of bioactive phytoconstituents of Kabasura Kudineer demonstrated that the phytochemicals such as  $\beta$ -amyrin, Furanolactone, Sesamine, Berberine, Clerodane 6,7 dione, lupeol, piperine, piperlongumine and  $\beta$ -sitosterol have a higher binding affinity towards the main protease enzyme of SARS-CoV-2 and the phytochemicals like  $\beta$ -sitosterol, Sesamine, Piperlongumine, Piperine, Lupeol, Furanolactone, beta Amyrin, Clerodanediol, and Berberine has exhibited higher binding affinity towards RNA dependent RNA polymerase (RdRP) [34].

Many bioactive phytoconstituents of Kabasura Kudineer were found to interact with more than 2 protein structures of the SARS-CoV-2 virus, in a molecular docking study performed by Shah et al. However, the phytochemicals such as Vasicinone, Vasicine, Luteolin, and Scutellarein have shown a very strong binding affinity towards main protease enzyme of SARS-CoV-2 [35]. In addition, another molecular docking study performed by Sivaraman et al. demonstrated that the bioactive phytoconstituents of Kabasura Kudineer such as Piperidine, Piperine, Andrographolide,  $\beta$ -sitosterol, Rutin, Vetiverol, Carvacrol, 6- Gingerol, and others have shown potent binding affinity with RdRP of SARS-CoV-2 [36]. Moreover, significant inhibition of replication of SARS-CoV-2 in E6 cells was observed by the administration of Kabasura Kudineer, in an in-vitro study [37].

#### 4. CONCLUSION

Earlier viral clearance, accelerated recovery, and shortened hospital stay were noted in asymptomatic or mild symptomatic COVID-19 patients who received Kabasura Kudineer along with standard care. Moreover, many in-silico molecular docking studies determined that several bioactive phytoconstituents of Kabasura Kudineer have exhibited higher binding affinity towards Spike glycoprotein and enzymes like main proteases and RdRP of SARS-CoV-2. Henceforth, the patients with COVID-19 may use

Kabasura Kudineer alongside repurposed antiviral drugs and standard care, in the earlier stages of illness to forestall the crumbling which might bring about reduced severity of illness, decreased intensity of symptoms, attenuated mortality rate, and diminished side effects of modern medicines. More randomized controlled clinical trials would further establish the safety and efficacy of Kabasura Kudineer in COVID-19 patients.

#### DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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