Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
South East European Journal of Immunology. 2023 Nov 30; 6(1):109-114.
https://doi.org/10.3889/seejim.2023.6058
eISSN: 1857-9388
Category: *Review article*
Section: *Clinical Immunology*

OPEN ACCESS

Efficacy of Nilavembu Kudineer for Dengue Fever Management – An Overview of Clinical and Preclinical Evidences

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Edited by: Slavica Hristomanova-Mitkovska
Citation: Maideen NMP. Efficacy of Nilavembu Kudineer for Dengue Fever Management – An Overview of Clinical and Preclinical Evidences. South East Eur J Cardiol. 2023 Nov 30; 6(1):109-114. https://doi.org/10.3889/seejim.2023.6058
Keywords: Dengue fever; Dengue hemorrhagic fever; Dengue shock syndrome; Siddha formulations; Herbal formulations; *Nilavembu kudineer*
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Received: 26-Sep-2023
Revised: 19-Oct-2023
Accepted: 17-Nov-2023
Copyright: © 2023 Naina Mohamed Pakkir Maideen
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist
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Abstract

BACKGROUND AND AIM: Dengue viral disease (DVD) is a tropical arboviral disease that is caused by dengue virus (DENV), which is transmitted mainly by the bite of female Aedes aegypti mosquitoes. No specific antiviral drug is approved yet to manage the patients with DENV infection, who are managed using symptomatic therapy and supportive care.

AIM: As a consequence, we intend to review the potential of Nilavembu kudineer in the management of DENV infection.

MATERIALS AND METHODS: To find articles pertinent to the clinical, *in vitro*, and *in silico* studies evaluating the effectiveness of *Nilavembu Kudineer* in the management of DENV infection, the literature was searched in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of science, Embase, Directory of open access journals, and reference lists.

RESULTS: *Nilavembu Kudineer* may be able to alleviate signs and symptoms experienced by patients with DENV infection, according to few clinical, *in vitro*, and *in silico* studies.

CONCLUSION: The effectiveness of *Nilavembu Kudineer* in patients with DENV infection would further be demonstrated by additional randomized controlled clinical trials.

Introduction

Dengue virus (DENV) causes dengue viral disease (DVD), which is the most common arboviral disease around the globe especially in tropical as well as sub-tropical regions including India, Indochina, Indonesia, Bangladesh, the Maldives, Brazil, Colombia, Peru, Paraguay, and many other countries. DENV is a member of Flaviviridae family and flavivirus genus. DVD is caused by four closely related but distinct viruses named DENV-1, DENV-2, DENV-3, and DENV-4, which could be transmitted mainly by the bite of female *Aedes aegypti* mosquitoes and by *Aedes albopictus* to a lesser extent [1].

According to the estimates from the World Health Organization (WHO), about half of the global populace is at risk of contracting DENV infection and approximately 400 million infections are reported each year [2]. The WHO has categorized DVD as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), earlier. However, the WHO later reclassified the DVD as non-severe (dengue without warning signs and dengue with warning signs) and severe DF [3].

The majority of patients with DENV infection have been identified as asymptomatic, according to a meta-analysis of 41 cross-sectional studies comprising of 131,953 patients [4]. However, the symptomatic patients of DVD may fall into three phases based on the signs and symptoms: The febrile phase, the critical phase, and the convalescent (recovery) phase. The patients in febrile phase may experience fever (2–7 days), severe headache, pain behind the eyes, muscle and joint pain, infected oropharynx, rash, minor hemorrhagic manifestations (epistaxis, bleeding gums, hematuria, etc.), leucopenia, and positive tourniquet test. Whereas, those who are in the late stages of the febrile phase may experience warning signs such as severe abdominal pain, persistent vomiting, edema, mucosal bleeding, breathing difficulty, restlessness, postural hypotension, enlarged liver, and increased hematocrit values. While in the critical phase, patients may experience shock, fluid accumulation, pleural effusions, ascites, respiratory distress, thrombocytopenia, severe bleeding (hematemesis, bloody stool, etc.), hemoconcentration, organ impairment, and hypoproteinemia as a result of heightened vascular permeability and severe plasma leakage. Moreover, the patients in convalescent (recovery) phase may begin to reabsorb extravasated intravenous fluids and pleural and abdominal effusions as plasma leakage subsides in this phase [5].

DENV infection targets several host cells including immune cells such as dendritic cells,

monocytes, macrophages, and B cells. Various host factors including the development of DENV-specific cross-reactive CD8 T cells that exhibit higher interferon-γ, and tumor necrosis factor-α (TNF-α) cytokine responses, the antibody-dependent enhancement (ADE) of infection that contributes to severe DVD, anti-nonstructural protein 1 (NS1) antibodies that stimulate the release of pro-inflammatory mediators such as interleukin-6 (IL-6), interleukin-8 (IL-8), and other cytokines and chemokines, and different viral factors such as NS1 of DENV, and genome of DENV are involved in the pathogenesis of DENV infection. The viremia of DENV is enhanced by ADE through facilitated viral uptake and infection of fragment-γ receptor–bearing cells, during secondary dengue infection. In addition, DENV-specific cross-reactive CD8 T cells activate the macrophages and monocytes resulting into the release of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α,) and chemokines C-X-C motif chemokine ligand 10 (CXCL10), C-X-C motif chemokine ligand 11 (CXCL11) and other inflammatory mediators, which leads to enhanced vascular permeability and DHF [6].

Severe dengue affects infants and patients with secondary dengue infection the most, but elderly people and people with comorbid conditions such as diabetes, renal diseases, asthma, and heart diseases are also at risk [7], [8]. Reduced platelets, an increased hematocrit, lethargy, severe abdominal pain, persistent vomiting, hepatomegaly, ascites, pleural effusion, rapid breathing, bleeding gums or nose, and blood in vomit or stool are warning signs of severe dengue [9].

Taking precautions against mosquito bites, controlling mosquito populations both indoor and outdoor, educating the public about DENV infection spread by mosquitoes, and conducting active mosquito and DENV surveillance are some of the preventive measures against DENV infection [10].

Patients diagnosed with DENV infection are currently managed using symptomatic therapy and supportive care. This approach is adopted due to the absence of specific antiviral medications that have been approved for the treatment of this infection to date. Recently, we have reviewed and performed Petra/Osiris/Molinspiration analysis to identify therapeutic potentials of black seeds (*Nigella sativa*) against DENV [11]. Moreover, the guidelines from AYUSH Ministry, Government of India, recommend 30 mL of *Nilavembu kudineer* 2 times daily for 7 days, for the clinical management of DF [12]. We therefore plan to review the potential of *Nilavembu kudineer* in the management of DENV infection. However, to prevent mortality, the severe dengue patients need to receive immediate medical care to maintain patients' body fluid volume.

Materials and Methods

The literature was searched in 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 to identify articles relevant to the clinical, *in vivo*, *in vitro*, and *in silico* studies evaluating the efficacy of *Nilavembu Kudineer* in the management of dengue viral infection using terms such as dengue, DF, DHF, DSS, Siddha formulations, herbal formulations, and *Nilavembu Kudineer*. English language publications supporting the use of *Nilavembu Kudineer* for the management of DF were included in this review, but duplicate publications were excluded from the study.

Results

Nilavembu Kudineer is a poly-herbal Siddha formulation and it contains Nilavembu (*Andrographis paniculata*) as its prime herb along with 8 more herbs including Vettiver (*Chrysopogon zizanoids*), Vilamichuver (*Plectranthus amboinicus*), Sandanam (*Santalum album*), Sukku (*Zingiber officinale*), Milagu (*Piper nigrum*), Koraikilangu (*Cyperus rotundus*), Parpadagam (*Mollugo cerviana*), and Peipudal (*Trichosanthes cucumerina*), in equal proportions [13]. *Nilavembu Kudineer* is found to contain various phytochemicals including flavonoids, alkaloids, glycosides, phenols, tannins, terpenoids, and carbohydrates [14], [15]. Moreover, the phytochemical analysis of *Nilavembu Kudineer* revealed the presence of several bioactive phytoconstituents including andrographolide, vetivone, vetiverol, naphtalenol, bisabolol, α-santalol, β- santalol, cucurbitacin B, sugenol, rotundone, cyperenon, zingerone, gingerdiol, zingibrene, Gingerols, Piperine, Piperamide, Piperamine, Pipercide, Piperolin, Piperidine, and many others [16], [17], [18].

The therapeutic effectiveness of *Nilavembu Kudineer* in the management of patients with DENV infection has been determined by some clinical studies (Table 1).

A pilot study of 20 patients with DENV infection, who were treated with *Nilavembu Kudineer* and Adathodai manappagu for 7 days found satisfactory symptomatic relief as well as a significant improvement in laboratory results, including a drastic increase in platelet count, and a mean decrease in packed cell volume on each day without any notable adverse effects [19]. In addition, a prospective case–-control study of 176 cases and 352 controls reported that the

Table 1: Clinical studies supporting the use of *Nilavembu Kudineer* for dengue virus infection

Study design	Number of patients	Treatment	Outcome
Pilot study	20	Nilavembu Kudineer and Adathodai manappagu for 7 days	Satisfactory symptomatic relief as well as a significant improvement in laboratory results, including a drastic increase in platelet count, and a mean decrease in PCV on each day without any notable adverse effects [19]
Prospective case–control study	176 cases and 352 controls	Nilavembu Kudineer, *Adhatoda vasica* leaves with water, and 30 mL of Carica papaya leaves juice, twice daily for 15–20 days	Enhanced platelet counts and prevention of deterioration in patients with DENV infection [20]
Pilot study	20	Nilavembu Kudineer and Papaya juice	Decreased oxidative markers, improved biochemical and hematological parameters, and speedy recovery [21]
Prospective descriptive study	37	30 mL of *Nilavembu kudineer* twice daily	Satisfactory improvement in symptoms, and a significant increase in platelet count [22]
Randomized double-blind, placebo-controlled clinical trial	14	30 mL of *Nilavembu kudineer* with 5 mL of honey, twice daily, before food, for 5 days	Significant reduction of body temperature and a significant improvement in platelet counts [23]

PCV: Packed cell volume, DENV: Dengue virus.

consumption of *Nilavembu Kudineer* along with 10 g of ground paste of *Adhatoda vasica* leaves with water, and 30 mL of *Carica papaya* leaves juice, twice daily for 15–20 days ensued in enhanced platelet counts and prevention of deterioration in patients with DENV infection [20]. Moreover, decreased oxidative markers, improved biochemical and hematological parameters, and speedy recovery were observed in a pilot study of 20 patients with DENV infection, who were administered with *Nilavembu Kudineer* and Papaya juice [21].

Satisfactory improvement in symptoms and a significant increase in platelet count were observed in a prospective descriptive study of serologically confirmed 37 cases of DF, due to the administration of 30 mL of *Nilavembu kudineer* twice daily [22]. In a similar manner, significant reduction of body temperature, and a significant improvement in platelet counts were observed in a randomized double-blind, placebo-controlled clinical trial of 14 patients diagnosed with DF, who consumed 30 mL of *Nilavembu kudineer* with 5 mL of honey, twice daily, before food, for 5 days [23].

The DENV inhibitory potential of phytoconstituents of *Nilavembu Kudineer* against DENV was demonstrated by a limited number of *in-vitro* experiments (Table 2).

Table 2: *In vitro* experiments supporting the use of *Nilavembu Kudineer* for dengue virus infection

Type of cell lines	Treatment	Outcome
Vero E6 cells infected with DENV-1	Methanolic extract of *Andrographis paniculata* of *Nilavembu kudineer*	Inhibition of DENV-1 activity [24]
DENV 1-4 infected Vero cells	Ethanolic extract of *Andrographis paniculata* of *Nilavembu Kudineer*	Inhibition of viral load [25]
Human hepatoma cell line HepG2 and human cervical cancer cell line HeLa	Andrographolide of *Andrographis paniculata* of *Nilavembu Kudineer*	Significant anti-dengue activity against DENV-2 [26]
Human hepatoma cell line HepG2	Andrographolide of *Andrographis paniculata* of *Nilavembu Kudineer*	Significant anti-dengue activity against DENV-4 [26]
DENV-2 propagated cell line C6/36	Andrographolide of *Andrographis paniculata* of *Nilavembu Kudineer*	Diminished replication of DENV [27]
C6/36 cell lines	Andrographolide of *Andrographis paniculata* of *Nilavembu Kudineer*	97.23% anti-dengue activity against DENV-2 [28]

DENV: Dengue virus.

The methanolic extract of *A. paniculata* of *Nilavembu kudineer* determined to inhibit DENV-1 activity in Vero E6 cells infected with DENV-1 [24]. In a similar vein, an *in vitro* study of DENV 1-4 infected Vero cells determined that the ethanolic extract of *A. paniculata* of *Nilavembu kudineer* inhibited the viral load [25].

Andrographolide is a major bioactive phytoconstituent of *A. paniculata* of *Nilavembu Kudineer*. In human hepatoma cell line HepG2 and human cervical cancer cell line HeLa, andrographolide was found to exhibit significant anti-dengue activity against DENV-2 and against DENV-4 in HepG2 cell lines [26]. In DENV-2 propagated cell line C6/36, which was derived from *Aedes albopictus* mosquitoes, andrographolide diminished the DENV replication [27]. In addition, an *in vitro* study reported that the andrographolide of *A. paniculata* exhibited 97.23% anti-dengue activity against DENV-2 in C6/36 cell lines [28].

Moreover, some *in silico* analyses (Table 3) have also been carried out to assess the DENV inhibitory potential of phytoconstituents of *Nilavembu Kudineer* against DENV. Higher binding energy was observed for andrographolide and 14-deoxy-11- oxoandrographolide of *A. paniculata* against dengue viral NS5 protein, in an *in silico* study performed by Nithya *et al*. [29]. In addition, an *in silico* study of *Nilavembu Kudineer* demonstrated that the phytoconstituents such as monolinolein and palmitic acid had binding energies more than 90 Kcal/mol toward the binding site of NS-5 methyltransferase, which is responsible for capping the nascent genomic RNA of DENV [30]. Moreover, the bioactive phytoconstituents of *A. paniculata* such as andrographolide, and magnoflorine were determined to possess effective docking against DENV-2 NS2B-NS3 [31].

Table 3: *In silico* analyses explored *Nilavembu Kudineer* efficacy against dengue virus

Phytoconstituents	Molecular target	Outcome
Andrographolide and 14-deoxy-11-oxoandrographolide	NS-5 methyltransferase	Higher binding energy [29]
Monolinolein and palmitic acid	NS-5 methyltransferase	Binding energies >90 Kcal/mol [30]
Andrographolide, and magnoflorine	DENV-2 NS2B-NS3	Effective docking [31]
Oleanolic acid	NS-5 methyltransferase	Potential inhibitory activity [32]
Andrographolide	Envelope protein and NS-5 methyltransferase	Potential inhibitory activity [33]
Andrographolide	RdRp	Potential inhibitory activity [34]

RdRp: RNA dependent RNA polymerase, DENV: Dengue virus.

An *in silico* study of phytoconstituents of *Nilavembu Kudineer* revealed that oleanolic acid has potential inhibitory activity against NS-5 methyltransferase of DENV [32]. In addition, a molecular docking study found that the andrographolide of *A. paniculata* has potential inhibitory activity against envelope protein and NS-5 methyltransferase

of DENV [33]. Moreover, the andrographolide of *A. paniculata* showed a potential inhibitory activity against RNA dependent RNA polymerase of DENV [34].

Discussion

In addition to anti-DENV potentials, *Nilavembu Kudineer* has been found to have many pleiotropic effects such as antipyretic, analgesic, anti-inflammatory, and antioxidant properties, which would help the patients with DF to alleviate their signs and symptoms [35], [36]. The levels of pain and fever significantly decreased in patients who received *Nilavembu Kudineer*, according to a quasi-experimental design clinical study of 60 participants [37]. A prospective case–control study with 176 cases and 352 controls also discovered a significant drop in body temperature after taking *Nilavembu Kudineer* [20]. Moreover, significant reduction of fever, body ache, and joint pain were observed in a prospective interventional cohort study in dengue prevalent area, by the administration of *Nilavembu Kudineer* [38]. In addition, significant reduction of body temperature was observed in a randomized double-blind, placebo-controlled clinical trial involving 14 patients with DF, who consumed 30 mL of *Nilavembu kudineer* with 5 mL of honey, twice daily, before food, for 5 days [23].

There are many preventive measures and control methods including personal protection, vector control methods, and prophylactic vaccination have been suggested by experts to minimize the spread of DENV infection.

Personal protection from mosquito bites could be achieved by wearing clothes that cover whole body, using mosquito nets in the bedroom, fixing window screens, applying mosquito repellents containing N, N-diethyl-meta-toluamide, picaridin, or ethyl butylacetylaminopropionate (IR3535), and using mosquito coils and vaporizers [39].

The vector control methods may include physical control methods (geographical information system mapping of dengue foci, focused and effective surveillance, determination of oviposition sites, community-based vector control programs for elimination of dengue mosquirtoes, education of preventive strategies), biological control methods (paratransgenesis using *Wolbachia* bacteria, genetic modification of vector species, use of sterile insect technique, use of larvivorous fish, and crustacean), and chemical control methods (use of insecticides and plant derivatives, use of insect growth regulators, and use of pheromones (attracticides) as integrated pest management) [10], [40].

Dengue vaccines such as Dengvaxia and Qdenga are approved in some countries for the prophylaxis of DENV infection, at present. Dengvaxia (ChemariVax-Dengue -based bivalent and tetravalent) is a chimeric vaccine made using recombinant DNA technology and it was first approved in Mexico in December 2015, by United States Food and Drug Administration in May 2019, and nearly 20 countries including European union [41]. The WHO Strategic Advisory Group of Experts on Immunization recommends the Dengvaxia vaccine only for the individuals who were previously infected with DENV infection [42], [43]. Qdenga is a recombinant chimeric live attenuated dengue vaccine that is approved for people aged four and above in many countries including United Kingdom, Brazil, Argentina, Indonesia, Thailand, and European Union [44].

Conclusion

The effectiveness of *Nilavembu Kudineer* in the management of patients with DENV infection was only partially established by clinical as well as preclinical studies. Moreover, a small number of studies have supported pleiotropic effects of *Nilavembu Kudineer*, including antipyretic, analgesic, ant--inflammatory, and antioxidant properties, all of which would benefit the patients with DF by easing their signs and symptoms. Based on the scant evidence currently available, patients with DENV infection may use *Nilavembu Kudineer* in addition to standard allopathic therapy to hasten recovery and shorten hospital stays. The safety and efficacy of *Nilavembu Kudineer* in patients with DENV infection would be further proven through additional randomized controlled clinical trials.

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