Ethnic and Regional Medicine

Bioactive molecules in *Siddha* Polyherbal *Nilavembu Kudineer* alleviating symptoms of Dengue/Chikugunya

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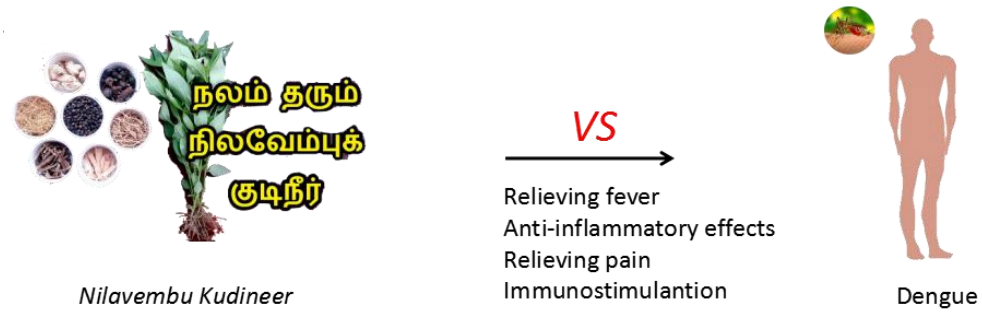
Highlights

The current study aims at exploring the bioactive molecules in *Siddha* Polyherbal *Nilavembu Kudineer* alleviating symptoms of Dengue/ Chikugunya.

Editor's Summary

Nilavembu Kudineer is one of the thirty-two types of internal medicines described in the ancient *Siddha* system of medicine in south India which reduces fever and relieves body aches.



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Abstract

Dengue is the most prevalent arthropod-borne viral diseases in terms of morbidity and mortality in the recent decade with the classic symptoms of high fever, headache as well as muscle and joint pain. *Nilavembu Kudineer* (NK) is one among the 32 types of internal medicines described in the ancient *Siddha* system of medicine in south India which reduces fever and relieves body aches. NK, a polyherbal formulation made up of eight traditional herbs in equal parts, is also recommended for prevention and management of all types of viral infections including Dengue/Chikugunya. Exploration of bioactive compounds in the plants is the primary step for the standardization and bioactivity screening of plants and formulations. So the current study aims at recording the chemical constituents and medicinal activities of each ingredient of NK. The anti-pyretic, anti-inflammatory, analgesic and immunostimulant effects of NK have been attributed to more than one ingredient in NK. The medicinal property of the NK can be also attributed to the combined effect of all phytochemicals present in these eight herbs. The current study encompasses the various chemicals and the activities of individual herbs but a thorough stereoscopic and chromatographic investigation is required to trace out the major phytochemical entities which are retained once the NK is prepared by the traditional methods.

Keywords: Anti-Dengue herbals, Dengue virus, Chikugunya, Fever, Pain, *Flavivirus*

摘要

就发病率和死亡率而言，登革热是近十年来最常见的节肢动物传播的病毒性疾病，以高热、头痛、肌肉和关节疼痛为典型症状。*Nilavembu Kudineer*（NK）是印度南部古代 *SIDDHA* 医学系统中记载的 32 种内科处方之一，它能退烧和缓解身体疼痛。NK 是一种由 8 种传统草药组成的草药配方，被推荐用于预防和治疗各种类型的病毒感染，包括登革热/切昆贡亚热。生物活性成分的研究是药物及其制剂标准化和生物活性筛选的首要步骤。本研究旨在总结 NK 各成分的化学成分和药用活性。NK 的解热、抗炎、镇痛和免疫刺激作用不仅归因于 NK 中的多种化学成分，也归因于这 8 种草药中所有化学成分的联合作用。目前的研究主要围绕单个药物的不同化学成分和活性物质，但需要进行彻底的立体和色谱研究，以追溯一旦采用传统的煎煮方法制备 NK 后保留的主要植物化学物质。

关键词：抗登革热药物；登革热病毒；登革热样疾患；发热；疼痛；黄病毒

Abbreviations: NK, *Nilavembu Kudineer*; DENV, Dengue virus.

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Background

Many of the human diseases are cured by modern medicines which sometimes produces unfavorable reactions and toxic side effects. Plants, being a reservoir of medicinal compounds, help in preventing and curing ailments without serious adverse effects [1]. Compounds derived from living organisms, with their significant pharmacological activity, can compete with modern medicines [2]. Plants produce phytochemical constituents for defense against pathogen owing to their characteristic bioactivities. Therapeutic property of every plant is confined to the bioactive compounds present in it. Hence, the screening of these compounds is necessary for the standardization and validation of herbal drugs formed from it. Alkaloids, flavonoids, phenols, terpenoids, tannins and quinones *etc*. are the important classes of secondary metabolites in plants with significant pharmacological activities. Secondary metabolites derived from plants are reported to possess many important pharmacological characteristics such as anti-oxidant, anti-microbial, anti-allergic, hypoglycemic and anti-cancer properties [3].

Siddha is one of the ancient systems medicines, originating in ancient *Tamilakam* in south India and Sri Lanka with several polyherbal therapies which were formulated basing on *Siddha* principles. *Siddha* system of medicine uses the ancient beliefs and healing methodologies listed by the *Siddhars* (*Siddha* physicians) using plants, metals, minerals and various animal products. Diagnosis in this system includes assessing the equilibrium and derangement of the three humors of the body - *Vaadham*, *Pittham* and *Kapam*, the imbalance of which is believed to be the cause of various disease [4].

Dengue is the most prevalent arthropod-borne viral diseases in terms of morbidity and mortality in the recent decade which has re-emerged and remains endemic in more than 110 countries. Two fifths of the world populations (estimating around 100 million) Dengue fever infections, 2.1 million cases of Dengue hemorrhagic fever and 200 thousand deaths worldwide are caused by Dengue every year. Despite extremely high rates of Dengue for decades, Southeast Asia region still recorded an increase of 67% from 1985 - 1989 to 2002 - 2006 [5]. Dengue appears in two forms, the classic and severe Dengue. Classic Dengue fever shows symptoms ranging from mild to high fever with retro-orbital pain, severe headaches, maculo-papular rashes, muscle and joint pain. The severe form, Dengue hemorrhagic fever and Dengue shock syndrome may present with abdominal bleeding, hemorrhage and circulatory failure, which is fatal without prompt and proper management [6]. There are four serologic types of Dengue virus (DENV), DENV-1, -2, -3 and -4. Chikugunya is also an arthropod-borne viral diseases with the classic symptoms of fever, joint pain, rash, *etc*, which is similar to that of Dengue. With the rapid expansion of Dengue and Chikugunya disease in most tropical and subtropical areas of the world, it is crucial to develop effective prevention and control measures, including antiviral drugs and vaccines against them [7].

Siddha medicines are prescribed either as single drug remedy or polyherbal/herb-mineral formulations. *Nilavembu kudineer* (NK) has been prescribed as a curative and preventive medicine against Dengue [8]. NK is a polyherbal formulation prepared by *Andrographis paniculata* (Brum.f.) Nees (whole plant), *Chrysopogon zizanioides* (L.) Roberty (root), *Santalum album* L. (heart wood), *Trichosanthes cucumerina* L. (whole plant), *Cyperus rotundus* L. (rhizome), *Zingiber officinale Roscoe* (rhizome), *Piper nigrum* L. (fruit) and *Mollugo cerviana* (L.) Ser. (whole plant) in equal parts. *Kudineer* (decoction) is the common name given to the *Siddha* formulation in which the whole plant (s) or particular part of plant (s) is ground into coarse powder, called as *Kudineer Choornam* (coarse powder for preparation of decoction). It is then made into *Kudineer* by adding water and heated, so that the mixture of *Kudineer Choornam* and water reduces to 1/4th or 1/8th of its volume as mentioned in the literature. The dosage to be taken is 30 mL before food, three to four times a day. Lifetime of prepared *Kudineer* is 1 *Samam* (3 hours) [9]. The ingredients contain various bioactive compounds like andrographolide, β-vetivenene, α-zingiberene, α-copaene, cyperene, 2-monolinolenin, limonene, β-pinene, β-caryophyllene and α-santalol. The ingredients of the *Kudineer* possess anti-inflammatory, anti-microbial, analgesic, anti-oxidant, anti-viral, cytotoxic, hepatoprotective and anti-diabetic activities [10]. The anti-inflammatory, anti-viral, and analgesic effects of the various phytochemicals present in NK will help in suppressing and curing the clinical symptoms associated with Dengue. Since the studies about this *Kudineer* are very scanty, this review aims the documentation of the bioactive compounds and their characteristic pharmacological activities of NK ingredients to throw some light in support of action NK on Dengue.

Andrographis paniculata Burm.f. Nees

Andrographis paniculata Burm.f. Nees, known as *Nilavembu* in *Siddha*, belongs to family Acanthaceae is used traditionally as a remedy against common cold, fever and inflammation, *etc*. The *Indian Pharmacopoeia* describes it as a major constituent of at least 26 ayurvedic formulations. In traditional Chinese medicine, it has a significant “cold property” which is used to relieve the body heat, and to drive out toxins from the body [11]. The medical use of *Andrographis paniculata* against sore throat has been well known in Thailand [12]. In India, it is used to reduce griping, irregular bowel habits, and loss of appetite of children. Due to its “blood purifying” quality, it is suggested to make use in the treatment of leprosy, gonorrhea, scabies, boils and skin eruptions [13]. The key bioactive component of *Andrographis paniculata*, is the major diterpenoidal constituent, and rographolide. The compound has been reported to have different pharmacological activities like anti-inflammatory [14], anti-cancer [15], anti-microbial [16] and hepatoprotective

activities [17] (Table 1). Along with andrographolide the neoandrograpide also imparts the characteristic medicinal activities to the plant and acts as immunostimulant agents that are reported to have both antigen specific and non-specific immune responses [18]. Some studies proved the side effects of andrographolide in creating infertility [19] had led to the questioning of complete safety of NK.

Andrographis paniculata is an annual herbaceous to arborescent plant with woody branched stem bearing simple, opposite, lanceolate leaves, pink-purple colored, two-lipped zygomorphic flowers and cylindrical to flattened capsules [20]. Beside NK, this plant is the ingredient of other Siddha formulation, *Nilavembu camulam* [21].

Chrysopogon zizanioides (L.) Roberty is a perennial grass of Poaceae family known for its fragrance oils and medicinal properties. *Vetiver* oil is composed of more than 170 compounds that are mainly sesquiterpenes and their derivatives (Table 2). Because of the complex nature of the essential oil, it has not been studied intensively [39]. The drug is fibrous, wiry, long, cylindrical roots up to 2 mm in diameter, multi-branched, often attached with stout root stock, smooth or longitudinally grooved, color, light brown, odor strong aromatic, taste and slightly bitter [40]. *Veti ver/Vilamiccam ver* is used in many Siddha formulations, some of which includes *Amirtataik kulikai, Incic chooranam, Maka Vacanta kucumakram, Pitta Curak kudineer, Maka elati kulikai, Nayuruvi nei, Parangi chakkai chooranam* [21, 41].

Chrysopogon zizanoids (L.) Roberty

Table 1 Phytochemical constituents in *Andrographis paniculata* Burm.f. Nees

Constituents	Class	Bioactivity	Reference
Andrographolide	Diterpene	Anti-inflammatory, anti-cancer, anti-microbial	Levita, *et al.*, 2010 [14] Shen, *et al.*, 2009 [15]
Bis-andrographolide	Terpene	Anti-HIV	Reddy, *et al.*, 2005 [22]
14-deoxy-11,12-didehyro andrographolide	Terpene	Anti-fungal	Sule, *et al.*, 2012 [23]
14-deoxyandrographolide	Terpene	Anti-fungal	Sule, *et al.*, 2012 [23]
Neoxyandrographiside	Terpene	Anti-fungal	Sule, *et al.*, 2012 [23]
Ninandrographolide	Terpene	Immunostimulant	Puri, *et al.*, 1993 [18]
Oxygenated flavones	Flavonoids	Anti-bacterial	Xie, *et al.*, 2015 [24]
Oroxylin A	Flavone	Anti-cancer	Li, *et al.*, 2009 [25]
Wogonin	Flavone	Anti-inflammatory, anti-cancer, anti-oxidant	Lin, *et al.*, 1996 [26] Li-weber, *et al.*, 2009 [27]
Carvacrol	Phenol	Anti-microbial	Didry, *et al.*, 1994 [29]
Eugenol	Ether-alcohol	Anti-septic activity	Ali, *et al.*, 2005 [30]
Myristic acid	Fatty acid	Anti-bacterial activity	Agoramoorthy, *et al.* 2007 [31]
Chlorogenic acid	Phenolic acid	Anti-nociceptive effect	Bagdas, *et al.*, 2014 [32]
Hentriacontane	Alkanes	Anti-plasmodial and larvicidal	Sowmiya, *et al.*, 2017 [33]
Tritriacontane	Hydrocarbon	Anti-oxidant	Takaba, *et al.*, 1997 [34]
Caffeic acid	Polyphenol	Clastogenic, anti-oxidant, antiviral, anti-cancer and anti-thrombosis	Hanham, *et al.*, 1983 [35] Jiang, *et al.*, 2005 [36]
Dicaffeoylquinic acid	Carboxylic acid	Anti-oxidant	Danio, *et al.* 2009 [37]
B-sitosterol-D-glucoside	Phytosterol	Anti-inflammatory	Deepak, *et al.*, 2000 [38]

Other compounds whose activities not elucidated are andropholide, isoandrographolides, deoxyandrographiside, andrographiside, 14-deoxy-11-oxoandrographolide, 14-deoxy-15-isopropylidene-11 and 12-didehydroandrographolide.

Cyperus rotundus L.

Cyperus rotundus L. belong to family Cyperaceae is a perennial sedge plant with flowering stem and linear leaves which form a sheath around stem. Rhizome of *Cyperus rotundus* L known as *Koraik kizhangu*, is used for the treatment of stomach, bowel disorders, and inflammatory diseases. Drug is a rhizome clothed with flexuous hair, outer surface dark brown, and white inside [47]. The drug is used as anti-inflammatory [48] and anti-malarial [49] (Table 3).

In Ayurveda the dried rhizome is used in dyspepsia/loss of appetite, indigestion, polydipsia/excessive thirst, irritable bowel syndrome, dyspnoea, cough, dysuria, vomiting, lacteal disorders, puerperal disorders, diarrhoea, rheumatoid arthritis and worm infestation [50]. In *Siddha Cyperus rotundus* is used in many preparations and some are *Athimathura mathirai, Adathodai chooranam, Civatai chooranam, Cukku tailam, Kapada Ilakam, Sanjeevi theenir. Chandraprakasa mathirai, Kapacurak kudineer, Thathupushti kulikai, Parangi chakkai chooranam, Milagu thailam* [21, 41].

Table 2 Phytochemical constituents in *Chrysopogon zizanoides* (L.) Roberty

Constituents	Class	Bioactivity	References
Vetivone	Sesquiterpene	Anti-bacterial	Dos Santose, *et al.*, 2014 [42]
α-cadinene	Sesquiterpene	Anti-microbial	De Falco, *et al.*, 2013 [43]
α-calacorene	Sesquiterpene	Nil reported	-
Epikhusinol	Sesquiterpene alcohol	Anti-fungal	Kaushal, *et al.*, 2001 [44]
Khusol	Sesquiterpene alcohol	Nil reported	-
Khusenic acid (zizanoic acid)	Sesquiterpene	Anti-bacterial	Dwivedi, *et al.*, 2013 [45]
Zizanol	Sesquiterpene alcohol	Repellent	Khallil, *et al.*, 2011 [46]

Table 3 Phytochemical constituents in *Cyperus rotundus* L.

Constituents	Class	Bioactivity	References
Cyperene	Sesquiterpene	Apoptotic, anti-oxidant and anti-bacterial	Ahn, *et al.*, 2015 [51] Essien , *et al.*, 2018 [52]
β-selinene	Hydrocarbon	Anti-microbial and anti-oxidant	Chandra, *et al.*, 2017 [53]
Cyperenone	Sesquiterpene	Antiulcer	Berger, 2007 [54]
α-cyperone	Sesquiterpene	Selective cytotoxic, anti-inflammatory and nueroprotective	Al-snafi, 2016 [55]
4α-5α,oxidoeudesm-11-en-3α-ol	Sesquiterpenic oxido alcohol	Anti-hepatitis B virus	Hikino, *et al.*, 1976 [56]
Copadiene	Sesquiterpene	Anti-malarial	Khoi, 1999 [57]
Epoxyguaiene	Essential oil	Anti-oxidant, Anti-malarial and Anti-diabetic	Khoi, 1999 [58]
Rotundone	Sesquiterpene	Anti-mutagenic	Kilani, *et al.*, 2005 [59]
Cyperenol	Sesquiterpene	Hypotensive and anti-microbial	Sahu, *et al.*, 2010 [59]
Eugenol	Ether-alcohol	Antiseptic	Didry, *et al.*, 1994 [29]
Cyperol	Sesquiterpene	Insecticidal	Pubchem [60]
Isocyperol	Sesquiterpene	Anti-inflammatory	Seo, *et al.*, 2016 [61]
α-and β-rotunol	Sesquiterpene	Fungitoxic	Hiking, *et al.*, 1971 [62]
Kobusone	Sesquiterpene	Anti-inflammatory and analgesic	Ross, 2003 [63]
Isokobusone	Sesquiterpene	Anti-inflammatory	Kittayaruksakul, *et al.*, 2013 [64]

Table 4 Phytochemical constituents in *Mollugo cerviana* (L.) Ser.

Constituents	Class	Bioactivity	References
Orientin	Flavonoid	Anti-cancer, anti-oxidant and neuroprotection	An, *et al.*, 2015 [68], Xiao, *et al.*, 201 [69], Law, *et al.*, 2014 [70]
Vitexin	Flavonoid	Anti-viral and anti-cancer activity	Pubchem [71], An, *et al.*, 2015 [68]
Orientin-2'O-glucoside	Glucoside	Sedative activity	Gazola, *et al.*, 2018 [72]
Vitexin-2'O-glucoside	Glucoside	Enzyme inhibition	Tao, *et al.*, 2015 [73]

Mollugo cerviana (L.) Ser.

Mollugo cerviana (L.) Ser. is commonly known as *Parpadakam* in Tamil from the family Molluginaceae. It is an erect slender annual herb with slender cylindrical stem bearing leaves in whorls; flowers numerous and having fruits as rounded capsules, used in *Siddha*, Ayurveda and folk medicine. The whole plant possesses medicinal properties. The drug is diuretic, anthelmintic, digestive and relieves constipation. It is bitter, cooling and constrictor [65] and used as laxative, stomachic, antiseptic, febrifuge and diaphoretic. It is found to be effective against burning sensation, burning eyes, gastric diseases and fever [20]. The whole plant is used in NK formulation. The pharmacological activities like anti-bacterial [66] and anti-inflammatory [67] actions of *Mollugo cerviana* have been reported in various studies (Table 4). The plant is also used to prepare *Thonthasurak kutinir*, a siddha formulation used to cure inflammation, fever and cough [41].

Piper nigrum L.

Piper nigrum L. is a perennial climbing vine of family Piperaceae having flowering woody stem with alternating leaves tapering towards the tip. Dried fruits of *Piper nigrum* are commonly used in gastrointestinal disorders. These little seeds with enormous health benefits have been an admirable natural remedy for treating various illnesses ranging from obesity to cancer. Fruit is an indehiscent one-seeded globose berry, ovoid to oblong, coarsely, deeply reticulately wrinkled grayish-black in colour, odour, aromatic, taste very pungent [74]. The drug is used as appetizer and is active against helminthiasis, colic [75, 76]. *Piper nigrum* is used in majority of *Siddha* formulations and some of them are *Amukkara chooranam*, *Aruvatha mathirai, Iraca ganti meluku, Elatic chooranam, Noccit tailaam, Swasakutori chooranam, Milaku tailam, Vilvati tailam, etc* [21, 41]. Piperine, isolated from *Piper nigrum* has anti-inflammatory, anti-nociceptive, and anti-arthritic property [76] (Table 5).

Santalum album L.

Cantanakkattai, the heart wood of *santalum album* L, is used as the ingredient drug in many formulations. Sandalwood oil has been widely used in folk medicine for treatment of common colds, bronchitis, skin disorders, heart ailments, general weakness and fever, *etc*. The heartwood occurs as solid heavy pieces of log or as chips varying in length and width and density. On transversely cut surface it is diffuse porous with medullary ray appearing as fine reddish line [101]. *Santalum album* L. is used to treat utricaria, diarrhoea and dysentery [102]. *Santalum album* is used in the preparation of formulations such as *Arakku tailam, Cintil nei, Cukku tailam, Ilaku Cantanatit tailam, Naciroka Nacat tailam, Vallarai nei* [21], *Kirichannangaluku ennei, Kumari thailam* and *Mahavilvathi ilakam* [41] (Table 6).

Trichosanthes cucumerina L.

Trichosanthes cucumerina L., known as *Peipudal* in *Siddha*, is an annual climber widely used as a medicinal plant in different traditional medicine systems due to its various medicinal values. The fruit is usually consumed as a vegetable due to its good nutritional value [106]. The plant is rich in flavonoids, carotenoids and phenolic compounds which contributes to the antidiabetic, hepatoprotective, cytotoxic, anti -inflammatory, larvicidal effects of the plant. The fruit and roots of this plant contains bryonolic acid, bryononic acid, dihydrocucurbitacin B, chondrillasteryl glucoside and cucurbitacin B [107]. All these active constituents show antiviral characteristics and anti-malarial activity (Table 7). *Trichosanthes cucumerina* is a climber with palmately lobed leaves with unisexual flowers and ovoid-fusiform fruits [108]. Whole plant is used in the preparation of *Cintil nei*, *Thonthakara kudineer* and *Manjal noiku kudineer* [21, 41].

Zingiber officinale Roscoe

Known as *Chukku* in *Siddha*, *Zingiber officinale* Roscoe is a perennial herb of family Zingiberaceae with thick rhizome which containing several bioactive constituents, possessing health promoting properties. The characteristic odor and flavor of ginger root come from a volatile oil composed of shogaol and gingerols which make up about 1-3% of the weight of fresh ginger [118]. The main pharmacological actions of compounds isolated include immuno-modulatory, anti-tumorigenic, anti-inflammatory, anti-apoptotic, anti-hyperglycemic, anti-lipidemic and

anti-emetic activities [119] (Table 8). The major phytochemicals reported from essential oil of the rhizome are 6-shogaol, 6-gingerol and α-zingiberene. *Zingiber officinale* Roscoe is considered as a safe herbal medicine with only few and insignificant side effects. Dried drug consists of sympodially branched laterally compressed pieces of horizontal growing rhizome measuring 5 to 12 cm in length, 3 to 5 cm in height and 1 to 2 cm in thickness; the surface is marked with circular closely placed leaf scars, and small circular root scars at places, pale buff to brownish in colour with aromatic odour and pungent taste [74]. *Zingiber officinale* Roscoe has anti-inflammatory, hepatoprotective and antioxidant property in paracetamol induced animal model [120]. The drug is used in colic, haemorrhoids, diseases of throat and inflammation [74]. Dried *Zingiber officinale* Roscoe is a major ingredient in most of the *Siddha* preparations and some of them include *Agathi ennei, Kapada ilakam, Pooranathi ilakam, Milaku tailam, Cukku tailam, Nellikai ilakam, Kapa curak kudineer, Talicati curanam, Vilvati ilakam, etc* [21, 41].

Table 5 Phytochemical constituents in *Piper nigrum* L.

Constituents	Class	Bioactivity	References
Piperine	Alkaloid	Anti-inflammation, anti-nociceptive, anti-arthritic, anti-cancer and immunomodulatory	Bang, *et al.*, 2009 [77] Rodgers, *et al.*, 2009 [78]
Piperonal	Aldehyde	Antiobesity	Meriga, *et al.*, 2017 [79]
Piperoleine B	Organic compound	Hepatoprotective	Pubchem [80]
Pipercide	Alkaloid	Hepatoprotective	Pubchem [81]
Sabinene	Monoterpene	Anti-oxidant and repellent	Jeramillo, *et al.*, 2012 [82]
D-limonene	Monoterpene	Chemoprevention	Sun, 2007 [83]
β-caryophyllene	Sesquiterpenoid	Anti-inflammatory, analgesic, antipyretic, and platelet-inhibitory actions	Pubchem [84]
α-pinene	Terpene	Anti-inflammatory	Kim, *et al.*, 2015 [85]
β-ocimene	Monoterpene	Insecticidal	Pubchem [86]
δ-cadinol	Alcohol	Antioxidant	Zeng, *et al.*, 2011 [87]
Guaiacol	Phenolic compound	Expectorant and antiseptic	Pubchem [88]
N-trans-feruloylpiperidine	Phenolic compound	Antioxidant	Abdulazeez, *et al.*, 2016 [89]
1,8 cineole	Phenol	Repellent	Tripathy *et al.*, 2001 [90]
p-cymene	Monoterpene	Antioxidant and vasorelaxant	Silva *et al.*, 2015 [91]
N-trans-feruloyl tyramine	Phenol	Anti-inflammatory	Pubchem [92]
Guineensine	Alkene	Anti-plasmodial	Pubchem [93]
Feruperine	Alkaloid	Antioxidant	Nakatani, *et al.*,1986 [94]
Trachyone	Pyrollidine Alkamide	Antibacterial	Reddy, *et al.*,2004 [95]
Isopiperolein B	Pyrollidine Alkamide	Antibacterial	Reddy, *et al.*,2004 [95]
Pergumidiene	Pyrollidine Alkamide	Antibacterial	Reddy, *et al.*,2004 [95]
Pellitorine	Pyrollidine Alkamide	Antibacterial	Reddy, *et al.*,2004 [95]
Pipnoohine	Amide	Insecticidal	Siddiqui, *et al.*,2004 [96]
Pipyahyine	Amide	Insecticidal	Siddiqui, *et al.*,2004 [96]
N-isobutyl-2E,4E-octadec adienamide	Amide	Hepatoprotective	Pubchem [97]
N-isobutyl-2E,4E,8Z-eico satrienamide	Amide	Antibacterial	Reddy, *et al.*, 2004 [95]
Piperchabamide D	Amide	Insecticidal	Hwang, *et al.*, 2017 [98]
Retrofractamide A	Amide	Adipogenetic	Mourad, *et al.*, 2013 [99]
Dehydroretrofractamide	Amide	Enzyme inhibition	Rho, *et al.*, 2004 [100]

Other compounds whose activities not elucidated are 1-piperylpyrrolidine, *N*-5-(4-hydroxy-3-methoxyphenyl)-2E,4E-pentadienoylpiperidine, *N*-isobutyleicosa-*trans*-2-*trans*-4-dienamide, *E,E,E*)-11-(1,3-benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4,10-undecatrienamide, *(E,E,E*)-13-(1,3-benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4,12-tridecatrienamide, *(E,E)*-*N*-(2-methylpropyl)-2,4-decadienamide, *N*-isobutyl-2*E*, 4*E*-decadienamide, δ-guaiene.

Table 6 Phytochemical constituents in *Santalum album* L.

Constituents	Class	Bioactivity	References
α, β-santalol	Sesquiterpene	Chemoprevention and antifungal activity	Kim, *et al.*, 2017 [103]
α, β-santalals	Sesquiterpene		Kim, *et al.*, 2006 [104]
α, β-santaldiol	Sesquiterpene		Kim, *et al.*, 2006 [104]
10(Z)-sandalnol	Sesquiterpene	Anti-cancer activity	Kim, *et al.*, 2006 [104]
α-santalenoic acid	Sesquiterpene	Anti-cancer activity	Kim, *et al.*, 2006 [104]
Vanillic acid 4-O-Neohesperidoside	Sesquiterpene	Anti-cancer activity	Kim, *et al.*, 2006 [104]
2α,12-dihydroxy10(Z)-Campherene	Sesquiterpene	Antifungal and cytotoxic activity	Kim, *et al.*, 2017 [103]
2β,12-dihydroxy10(Z)-Campherene	Sesquiterpene	Antifungal	Kim, *et al.*, 2017 [103]
2,12,13-trihydroxy-10-Campherene	Sesquiterpene	Antifungal and cytotoxic activity	Kim, *et al.*, 2017 [103]
(Z)-lanceol	Sesquiterpene	Anti-microbial activity	Ochi, *et al.*, 2005 [105]
(Z)-7-hydroxynuciferol	Sesquiterpene	Anti-microbial activity	Ochi, *et al.*, 2005 [105]
Eugenol-4-O-rhamnosyl glucoside	Glycoside	Anti-cancer activity	Kim, *et al.*, 2006 [105]
Methoxyeugenol-4-O-rhamnosyl glucoside	Glycoside	Anti-cancer activity	Kim, *et al.*, 2006 [104]
2*R*-(*Z*)-campherene-2,13-diol	Sesquiterpenes	Anti-bacterial activity	Ochi, *et al.*, 2005 [105]
(*Z*)-2β-hydroxy-14-hydro-β-santalol	Sesquiterpenes	Anti-bacterial activity	Ochi, *et al.*, 2005 [105]
(*Z*)-2α-hydroxy-albumol	Sesquiterpenes	Anti-bacterial activity	Ochi, *et al.*, 2005 [105]
(*Z*)-1β-hydroxy-2-hydrolanceol	Sesquiterpenes	Anti-bacterial activity	Ochi, *et al.*, 2005 [105]

Table 7 Phytochemical constituents in *Trichosanthes cucumerina* L.

Constituents	Class	Bioactivity	References
Bryonolic acid	Triterpenoid	Neurotoxic activity, anti-inflammatory activity	Que, *et al.*, 2016 [109] Gatbonton-Schwager, *et al.*, 2012 [110]
Cucurbitacin B	Triterpenoid	Inhibition of carcinoma cells	Piao, *et al.*, 2018 [111]
Cucurbitacin E	Triterpenoid	Anti-cancer and immunomodulatory actions	Attard, *et al.*, 2015 [112]
Isocucurbitacin B	Triterpenoid	Cytotoxic	Bean, *et al.*, 1985 [113]
β-sitosterol	Phytosterol	Anti-cancer and anti-atherogenic	Mahaddalkar, *et al.*, 2015 [114], Zhao, *et al.*, 1990 [115]
Stigmasterol	Phytosterol	Anti-cancer and anti-trypanosomal	Aminu , *et al.*, 2017 [116]
23, 24-dihydrocucurbitacin D	Triterpenoid	Anti-inflammatory activity	Park, *et al.*, 2004 [117]

Table 8 Phytochemical constituents in *Zingiber officinale* Roscoe

Constituents	Class	Bioactivity	References
6-Shogaol	Phenol	Anti-inflammatory, anti-cancer and anti-oxidant	Li, *et al.*, 2012 [121], Zhu, *et al.*, 2013 [122], Bak, *et al.*, 2012 [123]
6-Gingerol	Phenol	Anti-cancer, anti-inflammatory and anti-oxidant activity	Weng, *et al.*, 2014 [124]
Zingiberol	Sesquiterpene alcohol	Anti-cancer activity	Ezebuo, *et al.*, 2016 [125]
β-phellandrene	Monoterpene	Anti-bacterial activity	Utegenova, *et al.*, 2018 [126]
α-zingiberene	Sesquiterpene	Anti-cancer activity	Aras, *et al.*, 2014 [127]
Ar-curcumine	Sesquiterpene	Anti-oxidant and anti-microbial activity	El-Baroty, *et al.*, 2010 [128]
β-bisabolene	Sesquiterpene	Cytotoxicity against breast cancer cells	Yeo, *et al.*, 2015 [129]
Gingerenones A, B & C	Diarylheptenones	Anti-fangal activity	Endo, *et al.*, 1990 [130]
Isogingerenone B	Diarylheptenones	Anti-fangal activity	Endo, *et al.*, 1990 [130]
Hexahydrocurcumin	Diarylheptenones	Anti-inflammatory and antioxidant	Li, *et al.*, 2012 [121]
Gingerdiols	Phenols	Anti-microbial activity	Pubchem [131]
6-gingesulphonic acid	Methoxy phenols	Anti-ulcer property	Yoshikawa, *et al.*, 1994 [132]
Gingerglycolipids A, B & C	Glycerol	Anti-ulcer property	Yoshikawa, *et al.*, 1994 [133]
Paradols	Ketone	Anti-oxidative and anti-cancer	Pubchem [134]
Farnesol	Alcohol	Apoptotic activity	Rioja, *et al.*, 2000 [134]
Geraniol glycosides	Terpene glycoside		
α-santalol	Sesquiterpene	Chemoprevention and antifungal activity	Kim, *et al.*, 2017 [103]
β-eudesmol	Sesquiterpene	Anti-inflammatory activity	Kim, *et al.*, 2018 [135]
Nerolidol	Sesquiterpene	Anti-inflammatory activity	Pubchem [136]
Elemol	Sesquiterpene	Insecticidal activity	Pubchem [137]
1,8 cineole	Phenol	Repellent	Tripathy, *et al.*, 2001 [90]
α-pinene	Monoterpene	Anti-inflammatory and anti-microbial activity	Pubchem [78], Silva, *et al.*, 2012 [138]
β-pinene	Monoterpene	Anti-microbial activity	Silva, *et al.*, 2012 [138]
Camphene	Monoterpene	Anti-microbial activity	Pubchem [139]
Sabinene	Monoterpene	Anti-oxidant and repellent	Jeramillo, *et al.*, 2012 [82]
Limonene	Cyclohexene	Anti-crcinogenic	Elson, *et al.*, 1988 [140]
Myrcene	Monoterpene	Analgesic activity	Lorenzetti, *et al.*, 1991 [141]

Other compounds whose activities not elucidated are (+)-angelicoidenol-2-O-β-D-glucopyranodise, gingerdiacetates, neral, geranial aliphatic alkanes, alcohols, aldehydes, ketones, sulfides.

Discussion

This review is an attempt to analyze the phytochemicals present in the ingredient drugs of NK so as to see what chemicals reported so far from the ingredients has actions beneficial for treating Dengue and Chikungunya. Essentially a Dengue/Chikungunya medicine must possess properties like analgesic, antipyretic, anti-inflammatory, and antiviral actions to alleviate the reported symptoms such as high fever, headaches, pain behind the eyes, joint and muscle pain, fatigue, nausea, vomiting, skin rash, mild bleeding from nose/gums, bruises, damage to lymph/blood vessels, liver enlargement, and circulatory system failure [142, 143].

Every polyherbal combination in *Siddha* is based on philosophy of *Tridosham* (three humours) and *Panchamahabhutas* (five basic elements) in consideration with the disease conditions. NK was formulated basing on ancient *Siddha*. But, not any specific bioactives necessarily are responsible for the therapeutic function of each drugs in modern perspective. As the drug is producing beneficial effects in cases of fevers, specifically Dengue and Chikungunya fevers, there is a need to see any connection between the symptoms and bioactivity of the molecules present in each ingredient. As all these eight ingredients are mixed and decoction made by boiling such individualistic action may not be so derogatory in deciding the action of NK. The synergistic action of all these bioactive compounds together may be imparting NK its characteristic medicinal property.

However, from this review, it is evident that these ingredients are used traditionally in the treatment of fever, inflammation, arthritis, gastric ulcer, jaundice and general debility condition while NK is also claimed to have antipyretic, anti-inflammatory, antiviral, and immunomodulatory actions [144]. The bioactives ingredients in combination might be providing relief from body pain, inflammation of the joints and enhancing immune mechanism suppressing the virus. The phytochemicals present in the ingredients also have antiviral and anti-microbial characteristics, which make it suitable medicine for the management of viral fevers. The combination of these ingredient drugs can be substantiated in modern terms on account of its immunostimulant action increasing the defense response in the body which will help an infected person to fight against the viral infection [143].

Potency of bioactives of NK ingredients to combat symptoms of Dengue and Chikungunya

Andrographolide from *Andrographis paniculata* has been proved to possess anti-inflammatory and hepatoprotective activity, while ninandrographolide has shown immunostimulant property, B-sitosterol-D-glucoside and wogonin also have anti-inflammatory activities (Table 1). *Chrysopogon zizanioides* has been reported to possess anti-bacterial and anti-fungal activities, while antiviral activity is yet to be established (Table 2). Cyperenone from *Cyperus rotundus* possess antiulcer activity; α-cyperone has anti-inflammatory and neuroprotective activity; kobusone has antinflammatory and analgesic activities; isokobuson and iso-cyperol also possess anti-inflammatory effects (Table 3). *Mollugo cerviana* possesses bioactives with good anti-oxidant potentials which is indirectly beneficial in combating many pathological conditions of body (Table 4). Piperoleine B from *Piper nigrum* has proved anti-inflammatory and hepatoprotective properties while pipercide has hepatoprotective action, while piperin showed immunostimulant and anti-inflammatory actions (Table 5). *Santalum album* has been reported to possess anti-bacterial and anti-fungal activities, while antiviral activity is yet to be established (Table 6). Cucurbitacin E from *Trichosanthes cucumerina* possesses immuno-modulatory actions (Table 7). 6-Gingerol, 6-shogaol, hexahydrocurcumin and nerolidol from *Zingiber officinale* have anti-inflammatory property (Table 8). While aforesaid are from isolated compounds. At extract level, some other properties beneficial in Dengue/Chikungunya like anti-fever (antipyretic) action of *Andrographis paniculata* and *Mollugo cerviana,* anti-emetic property of *Cyperus rotundus* and *Zingiber officinalis* and antiviral property of *Trichosanthes cucumerina* have been proved.

Studies in lines with prevention of Dengue using ingredients of NK

In a study carried out by Tang *et al.* [7] for the preliminary screening study for anti-Dengue agent, methanolic extract of *Andrographis paniculata* was able to maintain most of the normal cell morphologies without causing much cytopathic effect to the DENV-1 infected cells. Thus it possesses high potential to be an anti-Dengue agent, particularly towards DENV-1 serotype. Neoandrographolide, one of the principal diterpene lactones, isolated from a medicinal herb *Andrographis paniculata* possesses significant anti-inflammatory effects [145]. The name given to the formulation stands to this ingredient which substantiates the naming.

The aqueous extract of *Zingiber officinale* may play an important role in the regulation of plasma leakage in Dengue virus infection and decrease the chances of severe Dengue complications by inhibiting the activity and expression of MMP-2 and MMP-9 while upregulating the expression of TIMP-1 and TIMP-2. Therefore, it can help in the development of new anti-Dengue agents [146].

Setback for *Nilavembukudinner*

Andrographolide a major phyto chemical present in *Andrographis paniculata* has been proven to affect spermatogenesis in rats by preventing cytokinesis of the dividing spermatogenic cell lines with appearances of sertoli cell damage and a spermatotoxic effect [19]. The study pointed to a male reproductive toxic effect of a therapeutic use of andrographolide and confirmed the possible prospective use of andrographolide as a male contraceptive. The anti-spermatogenic abilities as well as

ovulation preventive effect of the *Andrographis paniculata* reported may be the main reasons which lead to the controversy of safety of NK as drug. Hence the in-depth studies with standard clinical trials are required to clearly understand the effectiveness of this important formulation and to evade out the misconceptions generated so far. *Trichosanthes cucumerina* has been shown to induce liver damage in rats [147]. Very little publication on scientific validations of NK in peer reviewed journals, lack of distinct standard operating procedure for its preparation, deliberative depressing misinformation will be a threat to this valuable traditional medicine.

Conclusion

Bio-actives reported from NK ingredients have shown efficacy for all major symptom of Dengue/Chikungunya. Anti-pyretic, anti-inflammatory, analgesic and immunostimulant effects have been attributed to more than one ingredient in NK. Though these bioactive molecules are present in individual drugs, there might be changes occurring in the structure of these molecules during preparation of *Kudineer* by mixing and heating all these eight plants with water. Hence more studies have to be undertaken for the scientific evaluation of mode of action of combination of these molecules on fevers like Dengue and Chikungunya. Scientific validation and standardization of the drug is also necessary to maintain its high degree of quality in the global herbal market.

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