Literature Review on Siddha Herbal Formulations (*Kudineer*) Available for The Management of Dengue

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ABSTRACT

Dengue is a major threat to public health in many countries. There is no vaccine to prevent the infection. In spite of management of the disease with conventional method of treatment, mortality due to dengue is increasing year by year. In India, state of Tamil nadu during 2012 dengue crisis, initiated a new model by including traditional Siddha medicines along with conventional therapy for management of dengue in government hospitals. The result of the initiation was a great success, as the Siddha medicines showed remarkable clinical improvement. As there is no effective dengue specific antiviral drug is available and the widely used NSAIDs show anti platelet activity, there is a need for Siddha formulations to be explored scientifically. This review focuses on Siddha *kudineer* formulations for dengue. *Kudineer* formulations include only dried and grinded herbals. The method of preparation of *kudineer* is simple and the phyto constituents do not undergo any major change while processing and preparation, unlike other traditional formulations. Ingredients of the formulation and their pharmacological action are discussed in the review. The review may act as a keyhole for the dengue drug development.

Key words: Dengue, Siddha medicine, Herbal medicine, *Kudineer*, *Pitha suram*, Anti inflammatory, Anti viral, Anti pyretic.

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INTRODUCTION

Today dengue ranks as most important mosquito borne viral disease in the world. WHO estimates that 50-100 million dengue infections occur each year and almost half of the world's population lives in the countries, where dengue is endemic. Close to 75% of global population exposed to dengue are in Asia-Pacific region.[1]

There are no antiviral medicines available for dengue. Current conventional management focuses on fluid replacement and management of other metabolic consequences of viral infection.

A major problem in fight against virus is rapid adaptation and development of drug resistance as well as emergence of new hybrid viruses. In past few years natural remedies came more and more in centre of interest. Recent studies showing antiviral potential of plant extracts against viral strains resistant to conventional antiviral agents have challenged modern drug discovery practices and deem a very careful look towards exploring natural antiviral components of medicinal plants and exploring traditional medical formulations used in treatment of viral diseases.

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Siddha medicine

Siddha medicine is the traditional medical system widely practised in South India. History of *Siddha medicine* dates back to many centuries. It was enriched with ethnic medical knowledge of Tamil people, native of rich biodiversity zone of Western Ghats. Their trade and cultural contacts with China, Europe and Middle East countries as a hub point in the spice route enabled them to exchange their knowledge of ethno pharmacognosy with other traditional medical systems in the world. The heritage of medical knowledge was further developed by Siddhars, a group of saints with goal of immortal human body and soul. Siddha medical formulations are based on three *kutram* and *panchabootham* philosophy.

Dengue

Dengue fever is an acute febrile illness caused by virus belonging to Flaviviridae family. Four well defined dengue viruses identified are DENV-1, DENV-2, DENV-3 and DENV-4. Each of them has a distinct genetic structure. Dengue virus is transmitted to humans through bites of infective Ades mosquitos- *Ades aegyptii, Ades albopictus*. Dengue fever is characterised by biphasic fever, myalgia, arthralgia and rashes. Dengue haemorrhagic fever is characterised by abnormality in haemostasis and by marked leakage of plasma from the capillaries. The later may lead to Dengue shock syndrome.[2]

MATERIALS AND METHODS

The review process is adopted to collect various *Siddha Kudineer* formulations for the indication *Pitha suram* mentioned in published *Siddha* texts. *Pitha suram* is the equivalent term in *Siddha* for Dengue (Table 1). The data is summarised and list of herbs used in the formulations are identified. The pharmacological activity of each herb, identified by standard scientific procedures and documented in open access scientific journals is sorted out by searching in internet with their botanical name as keyword.

Inclusion and exclusion criteria

Only the *Kudineer* formulations are included. Other formulations such as *Ilagam*, *Mathirai*, *Nei* etc are not included in the review. *Kudineer* formulations with mineral or metal salts, pure metals and animal products as ingredients are excluded from the review.

Pithasuram and Dengue comparison

Dengue is endemic in Southeast Asia and India.[3] Distribution of countries at risk of dengue transmission lies in between 10° C January isotherm and 10°C July isotherm.[4] As the homeland of *Siddha*, Tamilnadu lies in centre of this zone; it was prone to dengue since centuries. So the traditional medical system is well aware of the disease. It categorise dengue as *Pithasuram*, one of 64 *Suram* or Fever. Symptoms of *Pitha suram* mentioned in *Siddha* literatures, *Agasthiyar Sura Nool 300*, *Suravakadam* and *Siddha maruthuvam (Pothu)* can be correlated with symptoms of dengue.[4]

Kudineer

Kudineer is the common name given to the Siddha formulation in which the whole plant (s) or particular part of plant (s) is grinded into coarse powder, called as '*kudineer choornam*'. '*Kudineer choornam'* 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. Dose of the *kudineer* is generally 30ml before food, three to four times a day. Lifetime of prepared *kudineer* is 1 *Samam* (3 hours).

Siddha kudineers for Pithasuram

Seenthil kudineer: (reference: *Gunapadam (Mooligai) - Murugesa mudaliar)*

The ingredients include equal quantity of *Seenthil* (*Tinospora cordifolia*), *Parpadagam* (*Mollugo creviana), Santhanam (Santalum album), Vilamichu ver (Plectranthus amboinicus), Chukku (Zingiber officnale), Iruveli (Coleus vettiveroides), Sitramutti (Pavonia zeylanica),* and *Koraikizhangu (Cyperus rotundus).*

Sitramutti kudineer: (reference: Gunapadam (Mooligai) - Murugesa mudaliar)

The ingredients include 15 grams (equal quantity) of *Sitramutti (Pavonia zeylanica)* and *Chukku (Zingiber officinale).*

Sitramutti kudineer: (Reference: *Suravakadam)*

The ingredients include equal quantity of *Vilwam* (Aegle marmelos), *Sitramutti* (Pavonia zeylanica), *Jathipathiri* (Myristicia fragrans), *Suraithandu* (Lagenaria siceraria), *Kothumalli* (Coriandrum sativum), and *Pachaipayiru* (Vigna radiata).

Chukku kudineer: (reference:*Siddha maruthuvam (Pothu) – Murugesa mudaliar)*

Table 1: Comparison of Symptoms of *Pithasuram* and Dengue

	Symptoms of *Pithasuram*.[5]	Symptoms of Dengue.[4]
1	*Udal sikappu niram adaithal* (Red spots on body)	Petechial heamorrage
2	*Siruneer sikappu niram adaithal*	Hematuria
3	*Malam sikappu niram adaithal*	Melaena
4	*Manakalakkam, Mayakkam, Padukkaiyil thankamai*	Restlessness, Symptoms of altered sensorium.
5	*Okaalam(*Vomiting sensation*)*	Nausea
6	*Neervetkai (*Thirst*)*	Thirst due to dehydration
7	*Vayiru kalithal (*Dysentery*)*	Dysentry
8	*Idaividamal athika suram kaaithal (*High grade fever*)*	Hyperpyrexia

'Kuruthi azhal noi' is '*Thunai noi'* (Complication) *of Pithasuram* as mentioned in *'Siddha maruthuvam (Pothu)'*. '*Kuruthi azhal noi*' may be correlated with plasma leakage in Dengue hemorrhagic fever.

Table 2: Pharmacological action of the ingredients of Siddha kudineer formulations used for treatment of Dengue (Pitha *suram*)

SL. No.	Plants	Part used	Botanical name	Pharmacological action
1.	*Seenthil*	Whole Plant	*Tinospora cordifolia*	Analgesic, Anti inflammatory[6], Immuno modulatory, Anti-oxidant, Anti-bacterial.[7]
2	*Parpadagam*	Whole Plant	*Mollugo cerviana*	Anti inflammatory,[8] Antibacterial,[9] anti oxidant.[10]
3	*Santhanam*	Stem	*Santalum album*	Analgesic, Anti inflammatory, Antioxidant,[11] Anti bacterial,[12] AntiViral,[13] Antifungal,[12] Hepato protective, Anti ulcer[14]
4	*Vilamichu ver*	Root	*Plectranthus amboinicus*	Analgesic, Antiinflammatory,[15] Antimicrobial[16]
5	*Chukku*	Dried rhizome	*Zingiber officinale*	Antiinflammatory, Anti emetic, Anti arthritic, Anti nociceptive, Antioxidant, Antitussive, Immunomodulatory, Anti microbial[17]
6	*Iruveli*	Root	*Coleus vettiveroides*	Antibacterial,[18] Antioxidant[19]
8	*Korai kizhangu*	Rhizome	*Cyperus rotundus*	Antiemetic,[21] Antispatic,[21] Anti inflammatory, Anti pyretic, Analgesic,[22] Anticovulsant,[23] Antidiarroheal[24]
9	*Vilwam*	Leaves	*Aegle marmelos*	Antibacterial, Antifungal, Antioxidant, Antiviral, Antiulcer, Antiinflammatory, Antidiarrhoeal [25]
10	*Jathipathiri*	Kernel of seed	*Myristicia fragrans*	Antibacterial,[26] Analgesic,[27] Anticancer,[28] Antidepressant,[29] Antiinflammatory[30]
11	*Surai thandu*	Stem	*Lagneria siceraria*	Antimicrobial[31]
12	*Kothumalli*	Fruit	*Coriandrum sativum*	Antioxidant[32] Diuretic,[33] Anxiolytic,[34] Hepato protective,[35] Anti ulcer,[36] Antimicrobial,[37] Anti-inflammatory, Analgesic[38]
13	*Pachaipayiru*	Seed	*Vigna radiata*	Antioxidant, Anti-inflammatory,[39] Antimicrobial[40]
14	*Arasampattai*	Bark	*Ficus religiosa*	Antiulcer,[41] Antioxidant,[42] Immuno modulatory,[43] Anti-inflammatory[44]
15	*Sirukanjori*	Leaves	*Tragia plukenetti*	Antipyretic, Analgesic, Antispasmodic, Diuretic, Anti asthmatic[45]
16	*Pangampalai*	Whole plant	*Aristolocia bracteolata*	Antipyretic, Anti-inflammatory,[46] Antimicrobial[47]
17	*Nilavembu*	Whole Plant	*Andrographis paniculata*	Hepatoprotective,[48] Antioxidant,[49] Anti-inflammatory,[50] Anti hyperglycaemic,[51] Antipyretic,[52] Antiviral[53]
18	*Milagu*	Fruit	*Piper nigrum*	Antioxidant,[54] Antiinflammatory,[55] Antidiarroheal,[54] Antihypertensive[54] Analgesic, Antipyretic[56]
19	*Peipudal*	Whole Plant	*Trichosanthes cucumerina*	Antiinflammatory,[57] Hepatoprotective,[57] Gastroprotective,[57] Antibacterial[58]
20	*Vettiver*	Root	*Vettiveria zizanoides*	Anti inflammatory,[59] Antioxidant, Antibacterial,[60] antiepileptic[61]
21	*Nochi*	Leaves	*Vitex negundo*	Analgesic, Anti-inflammatory,[62] Antioxidant,[63] Antipyretic[64]

Continued...

22	*Poondu*	Bulb	*Allium sativum*	Antiviral, Antibacterial, Antihypertensive, Antiatherosclerotic, Antioxidant[65]

Table 2: Cont'd

SL. No.	Plants	Part used	Botanical name	Pharmacological action
23	*Vetrilai*	Leaves	*Piper betle*	Analgesic, Antioxidant, Anti-inflammatory,[66] Hepatoprotective,[67] Immunomodulatory[68]
24	*Pathiri*	Root bark	*Stereospermum colais*	Analgesic,[69] Antidiabetic, Antioxidant[70]
25	*Athimathuram*	Root	*Glycyrrhiza glabra*	Anti inflammatory, Antioxidant, Antiviral, Hepatoprotective, Antimicrobial, Antiviral, Antiprotozoal, Antidepressent, Immunomodulatory[71]
26	*Kostam*	Rhizome	*Costus speciosus*	Antipyretic, Antiinflammatory,[72] Antibacterial,[73] Antioxidant[74], Diuretic[75]
27	*Nannari*	Root	*Hemidesmus indicus*	Anti-inflammatory,[76] Antioxidant,[77] Antimicrobial,[78] Diuretic,[79] Hepatoprotective[80]
28	*Nilavarai*	Leaves	*Cassia senna*	Antimicrobial, Anticancer[81]
29	*Seeragam*	Fruit	*Cuminum cyminum*	Antibacterial, Antioxidant, Anticancer, Immunomodulatory, Anti-inflammatory, Analgesic, Antiepileptic, Hypotensive, Hepatoprotective, Gastroprotective[82]
30	*Thumbai ver*	Root	*Leucas aspera*	Antiinflammatory,[83] Antibacterial[84]
31	*Pericham kai*	Fruit	*Phoenix dactylifera*	Immunomodulatory,[85] Antioxidant[86]
32	*Thippili*	Fruit	*Piper longum*	Antiinflammatory,[87] Antioxidant,[87] Antimicrobial,[87] Antistress[87] Hepatoprotective,[87] Antidiabetic,[87] Antitumor, Immuno modulatory[88]
33	*Nellimulli*	Fruit	*Embelia officinalis*	Antioxidant, Antiinflammatory, Antidiabetic, Antidepressant, Hypolipidemic, Antibactrial, Hepatoprotective[89]

Table 3: List of activities with the herbals used in the treatment of Dengue

Ingredients with Dengue specific antiviral activity	*Nilavembu(Andrographis paniculata)*
Ingredients with Immunomodulatory activity	*Seenthil (Tinospora cordifolia),Arasampattai(Ficus religiosa),Vetrilai (Piper betle), Athimathuram (Glycyrrhiza glabra), Seeragam (Cuminum cyminum), Pericham kai (Phoenix dactylifera), Thippili (Piper longum)*
Ingredients with Anti-inflammatory activity	*Seenthil (Tinospora cordifolia), Parpadagam (Mollugo cerviana), Santhanam (Santalum album), Vilamichu ver (Plectranthus amboinicus), Chukku (Zingiber officinale), Sitramutti (Pavonia zeylanica), Korai kizhangu (Cyperus rotundus), Vilwam (Aegle marmelos), Jathipathiri (Myristicia fragrans), Kothumalli (Coriandrum sativum), Pachaipayiru (Vigna radiate), Arasampattai(Ficus religiosa), Pangampalai (Aristolocia bracteolata), Nilavembu (Andrographis paniculata), Milagu (Piper nigrum), Peipudal (Trichosanthes cucumerina), Nochi (Vitex negundo), Vetrilai (Piper betle), Athimathuram (Glycyrrhiza glabra), Kostam (Costus speciosus), Nannari (Hemidesmus indicus), Seeragam (Cuminum cyminum), Thumbai ver (Leucas aspera), Thippili (Piper longum), Nellimulli (Embelia officinalis), Vettiver (Vettiveria zizanoides)*
Ingredients with Antipyretic activity	*Korai kizhangu (Cyperus rotundus), Sirukanjori (Tragia plukenetti), Pangampalai (Aristolocia bracteolata), Nilavembu (Andrographis paniculata), Milagu (Piper nigrum), Nochi (Vitex negundo), Kostam (Costus speciosus)*

The ingredients include equal quantity of Chukku (Zingiber officinale), Iruveli (Coleus vettiveroides), Arasampattai (Ficus religiosa), Koraikizhangu (Cyperus rotundus), Sirukanjori (Tragia plukenetti), and Pangampalai (Aristolochia bracteolate).

Nilavembu kudineer: (reference: Siddha research pharmacopeia- G.D.Naidu, Siddha vaidya thirattu)

This kudineer is mentioned as '*Thunai marunthu'* (vehicle) for the compound drug – 'Dengue influenza cure powder' mentioned in Siddha research pharmacopeia- G.D.Naidu. The ingredients include equal quantity of Nilavembu (Andrographis paniculata), Vilamichu ver (Plectranthus amboinicus), Chukku (Zingiber officinale), Milagu (Piper nigrum), Koraikizhangu (Cyperus rotundus), Peipudal (Tricosanthes cucumerina), Vettiver (Vettiveria zizanoides), Santhanam (Santalum album), and Parpadagam (Mollugo

cerviana).

Nochi kudineer: (reference: Siddha research pharmacopeia- G.D Naidu, Siddha vaidya thirattu)

This *kudineer* is mentioned as '*Thunai marunthu*' (vehicle) for the compound drug – 'Dengue influenza cure powder' in Siddha research pharmacopeia- G.D Naidu. The ingredients include equal quantity of *Vilamichuver (Plectranthus amboinicus), Sirukanjori ver (Tragia plukenetti), Vilwaver (Aegle marmelos), Pathiriver (Stereospermum colais), Athimathuram (Glycyrrhiza glabra), Kostam (Costus speciosus), Nannari (Hemidesmus indicus), Nilavarai (Cassia senna), Seeragam (Cuminum cyminum), Kothamalli (Coriandrum sativum), Thumbai ver (Leucas aspera), Pericham kai (Phoenix dactylifera), Thippili (Piper longum), Nellimulli (Embelia officinale),* and *Chukku (Zingiber officinale).*

DISCUSSION

Pathophysiology of dengue may be explained under three headings, viremia, host immune response and inflammatory mediators. In dengue, viremia peaks at the onset of infection or shortly after infection and may remain detectable for 2-12 days depending upon the strain of virus and immune status of the person infected. Particularly the person with second infection with heterologus virus type have a risk of developing Dengue hemorrhagic fever or Dengue shock syndrome through a process known as 'Antibody Dependent Enhancement'(ADE). Severity of the disease associated with dengue infection depends on the number of cell infected with virus and number of cells infected with virus is related to ADE infection of peripheral leukocytes in secondary infection.

In sequence, viremia is followed by host immune factors playing its role. Dengue virus specific CD4+ CD8- and CD4- CD8+ lymphocytes are detectable in humans after natural dengue infections. Infection with a single serotype induces both serotype specific and serotype cross reactive CD4+ memory T cells. CD8+ T lymphocytes have virus specific cytotoxic activity.

Host immune factors induce the production of inflammatory mediators. CD4+ lymphocytes produce inflammatory mediators such as Gamma interferon, and Interlukins, IL-2, IL-4, IL-5, IL-6, IL-10 and Lymphotoxin. Virus infected macrophages and monocytes produce inflammatory mediators, Tumor necrosis factor (TNF), Interlukins-IL-1, IL-1B, IL-6 and Platelet aggregation factor (PAF). The inflammatory mediators causes increased vascular permeability, plasma leakage, shock and malfunction of coagulation system which may lead to severe haemorrhage [90]

Pathophysiology of dengue infection clearly indicates that target areas in the drug development of dengue is controlling viremia, immuno modulation and anti-inflammation.

There is no any dengue specific antiviral drug. Anti-inflammatory drugs such as NSAIDs inhibit platelet cyclooxygenase and block the formation of Thromboxane A2. Thromboxane A2 is essential for platelet aggregation. So NSAIDs should not be used in treatment of dengue as it may aggravate bleeding tendency. There is a great need for effective anti-inflammatory drug which will not interfere in clotting mechanism.

Herbal ingredients of *Siddha Kudineer* formulations have antiviral, anti-inflammatory and immune modulator activity. It is evident from Table.2 and is summarised below,

The ingredients used in Siddha *kudineer* formulations were already evaluated for their antipyretic, anti-inflammatory, antiviral and immunomodulatory activity (Table 3). Their pharmacological properties must be confirmed; active principles traced and clinical studies may be conducted using these polyherbal formulations. As there is a lack of effective antiviral and anti-inflammatory drugs for the treatment of dengue, *Siddha* formulations may be explored to fill up the vacuum.

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