Neutaceutical Therapy for the Management of Dengue Fever

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ABSTRACT

Dengue fever is a mosquito borne illness that occurs in tropical and subtropical areas of world. Dengue fever is caused by five dengue virus stenotypes and is an endemic. It is also called as breakbone fever. Population growths, rapid urbanizations play a important role in spreading the disease. Various Phytochemicals such as quercetin, flavonoids, galbranine, sulfated galactomannans can control dengue. Moreover, medicinal plant-based therapeutics can be safer, cost effective and also nontoxic. Due to easy availability, low cost and high affectivity, these natural and herbal remedies are recommended to dengue patients to cure the disease. In this study, a comparative review is done on the effect of various herbal plants against dengue.

KEYWORD: Dengue, Natural Agents, Antioxidants

I. Introduction

The origin of dengue derived from Swahili Phrase ka dinga - which describes disease being caused by evil spirit. Dengue was the second disease after "yellow fever". Dengue hemorrhagic fever is first reported in Philippines in 1953 and in 1981 in South America. Dengue is an acute viral infection with potential fatal complication. Dengue virus belongs to family Flaviviridae and also there are four serotype of virus. It is transmitted mainly by Aedes aegypti and Aedes Albopictus mosquito. The principle vector of dengue Aedes aegypti has been adapted well to environment and breed in stagnant containers.

Epidemiology:

Dengue is believed to infect 50 to 100 million peoples worldwide in a year. The mortality is about 1-5% without treatment and less than 1% with treatment. The incidence of dengue in increased 30 fold between 1960 and 2010. This increase is due to multiple factors like, rapid urbanization, population growth, increase is believed international travel from endemic areas and lastly global warming. In India, First outbreak was reported during 1963 in Kolkata. The next major outbreak of Dengue was reported in Delhi and neighbouring states in 1996.

Symptoms:

High fever (40%)
Severe headache
Pain behind the eyes
Muscle and joint pains
Swollen glands

Individual who are infected for second time are at greater risk of severe dengue.

Pathophysiology of dengue fever:

Dengue infection is caused by bites of the female Aedes aegypti mosquito carrying the Flavivirus. After the mosquito has bitten, the virus incubation period varies between 3 and 14 days and may experience early symptoms such as fever, headache, rash, nausea, and joint and musculoskeletal pain. The temperatures between 39 and 40°C and usually last for 5–7 days. During this period, the virus may get into the peripheral bloodstream and, if left untreated, can damage blood vessels and lymph nodes resulting in dengue hemorrhagic fever with symptoms such as bleeding from the nose, gums or under the skin. Dengue hemorrhagic fever patients also have difficulty in breathing and severe development can lead to dengue shock syndrome.
Aetiology:
Transmission of dengue virus into host is through the vectors and transmitted by female mosquito. Aegypti is a primarily a daytime feeder (10). It lives around human habitation. A mosquito can lay eggs about 3 times in its lifetime and about 100 eggs are produced each time.

TRADITIONAL PLANTS TO TREAT DENGU

Natural drugs possess activity against Aedes aegypti by their antiviral mechanisms, larvicial and mosquito repellent property. Natural products have become the main source of test material in the development of antiviral drug based on traditional medicinals. To date, 31 different species have been found to have potential to treat dengue, some of these have not yet investigated scientifically. Several Ayurvedic herbs have been shown to be effective in treatment of dengue fever. (7,8)

The traditional medical system that uses medicinal plants for treating dengue are popular in Asian countries. They have some advantage over commercial anti dengue, such as safety, cost-effective and non-toxicity. The medicinal plants extracts contain different phytochemicals that are used to treat dengue. These extracts or molecules can act as virucidal and immunomodulators. (Potential medicinal-link). The bioactive constituents reported shows various inhibitory activities against different serotype often. Most of the bioactive compound have Anti-DENV activities are polyphenols and diterpenoids. These compounds have abundantly reported to possess antioxidant and anti-inflammatory activities in many studies.

Leaves used to treat Dengue fever:
1. Andrographis paniculata (Kal Megha)
   Belongs to Acanthaceae, cultivated widely in southern and south-eastern Asia. In Malaysia it is called ‘Hempedu Bumi’. The methanolic extract showed highest antiviral inhibitory effect on DEN-V by antiviral assay(link). The medicinal plant Apaniculata showed 75% of dengue viral inhibition. Diterpenoids and flavonoids are the main chemical constituents of Andrographis paniculata. Percentages of eggs hatchability for different extracts at various concentration were studied. The hexane extract represented the best result with comparisons to other extracts. Flavanoids andrographoloids are the responsible compounds. (6,8)

2. Carica papaya (papaya)
   Belongs to Caricaceae,Its leaf have been traditionally used for dengue. The aqueous extract of leaves exhibit more activity by increasing platelet count. (link). The observations made during the study were quite interesting. Papaya leaf juice was effective in curing the dengue fever. The increase in number of platelet counts to 100,000/mm³ within a period of approximately 16 h. The medicinal plant A.peniculata showed 75% of dengue viral inhibition.

3. Hippophae rhamnoides (sea buckthorn)
   Belongs to Elaeagnaceae. It is deciduous shrub. The fading shows that cell treated with Hippophae is able to maintain cell viability of Dengue infected cells. (potential). The anti-dengue activity was revealed by significantly reduced plaque number and modulated inflammatory cytokines.

4. Ocimum sanctum (Tulsi)
   Belongs to Labiatae. The methanolic extract against E6 cells invitro shows slightly inhibitory effect on DENV-1 based on cytopathic effect. Tea which is prepared by using Tulsi act as preventive medicament against dengue fever. The methanolic extracts of Sanctum showed a slight inhibitory effect of DENV-1 based on cytopathic effect.

5. Azadirachta indica (neem)
   Belongs to the family Meliaceae. It is fast-growing tree. The in vitro and in vivo inhibitory potential of aqueous extract of Azadirachta indica (neem) leaves on the replication of DENV-2 was evaluated. In vitro inhibitory potential of neem leaves on replication of DENV was evaluated.

6. Psidium guajava (guava)
   Belongs to family Myrtaceae. Psidium guajava leaf extract has been tested in vitro and showed to inhibit the growth of dengue virus. Water boiled with guava leaves was used to avoid bleeding in DHF, and increased platelet counts to 100,000/mm³ within a period of approximately 16 h. Water decoction of guava leaves contain quercetins, mainly act to inhibit the formation of enzyme mRNA in the virus.

7. Houttuynia cordata:
   Belongs to family Saururaceae. It is herbaceous perennial flowering plants growing between 20 and 80 cm, and is native to Japan, Korea, Southern China and Southeast Asia. Ethanol extract from Houttuynia cordata revealed an anti-dengue activity with 35.99 % inhibition against DENV-2 in Vero cells at a concentration of 1.56 lg mL⁻¹. Aqueous extract of H. cordata showed effective inhibitory action against DENV-2 through direct inactivation of viral particles before infection of the cells. Concentration of 100 lg mL⁻¹ also effectively protects the cells from viral entry and inhibits virus activities after adsorption. HPLC analysis of H. cordata extract indicated that hyperoside was the predominant bioactive compound, and was likely to play a role in this inhibition.
8. Momordica charantia: (Bitter melon)

Belongs to family Cucurbitaceae. It is also known as bitter melon or peria (Malaysia), a tropical and subtropical vine found throughout Asia, Africa and the Caribbean. The methanolic extract of M. charantia showed inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects. They exhibit moderate antiviral effect by inhibiting the replication of DENV-1 was conformed through MTT assay.

**Seeds used to treat Dengue:**

1. *Leucaena leucocephala:* (white lead tree)

Belongs to family Fabaceae. Galactomannans extracted from seeds of *Leucaena leucocephala* have demonstrated activity against yellow fever virus (YFV) and DENV-1 in vitro and in vivo. Galactomannans are polysaccharides consisting of backbone with galactose side group. In vitro experiments with DENV-1 in C6/36 cell culture assays showed that the concentration producing a 100 -fold decrease in virus titer of DENV-1 was 37 mg L⁻¹.

2. *Mimosa scabrella:* (Bractitiga)

Belongs to family Fabaceae. It is a fast growing, 15–20 m high and up to 50 cm diameter tree native to the cool, subtropical plateaus of South-eastern Brazil. Galactomannans extracted from seeds of *Mimosa scabrella* have demonstrated activity against YFV and DENV-1 in vitro and in vivo. *M. scabrella* showed protection against death in 87.7 % of YFV-infected mice. These plant contains some bioactive compounds such as carbohydrate, flavonoids, alkaloids and phenols.

3. *Quercus lusitanica:* (Gall oak)

Belongs to family Fagaceae. It is a species of oak native to Morocco. *lusitanica* extract was found to have a good inhibitory effect on the replication of DENV-2 in C6/36 cells. Previous study demonstrate inhibitory activity of seed extracts. The methanol extract of the seeds completely inhibited (10–100 fold) the TCID50 of virus at its maximum non-toxic concentration of 0.25 mg mL⁻¹ as indicated by the absence of cytopathic effects. Proteomics techniques were used to demonstrate that the effect of *Q. lusitanica* was to downregulate NS1 protein expression in infected C6/36 cells after treatment with the methanol extract.

**Whole plants used to treat dengue:**

1. *Alternanthera philoxeroides:* (Alligator weed)

*Alternanthera philoxeroides* belongs to family Amaranthaceae. A. philoxeroides is also called “Alligator Weed”, and is an immersed aquatic plant. It originated from South America but is currently invading Australia. The effect of A. philoxeroides extracts against dengue virus was investigated in vitro. An MTT assay was carried out to determine the cytotoxicity of A. philoxeroides on C6/36 cell lines. Coumarin extract of A. philoxeroides showed lowest toxicity on cells (TD50 = 535.91), whereas a petroleum ether extract of A. philoxeroides had the strongest inhibitory effect on dengue activity of *Piper retrofractum*.

2. *Cladosiphon okamuranus:* (Mozuko)

*Cladosiphon okamuranus* belongs to family Chordariaceae. It is a brown seaweed found naturally in Okinawa, Japan. A sulfated polysaccharide named fucoidan from *Cladosiphon okamuranus* was found to potentially inhibit DENV-2 infection. The virus infection was tested in BHK-21 cells in a focus-forming assay. Fucoidan reduced infectivity by 20 % at 10 lg mL⁻¹ as compared with untreated cells. However, a carboxy-reduced fucoidan in which glucuronic acid was converted to glucose attenuated the inhibitory activity on DENV2 infection.

3. *Flagellaria indica:* (Whipe vine)

*Flagellaria indica* belongs to family Flagellariaceae. It is robust perennial climber that grows in many of the tropical and subtropical regions of the Old World, India, Southeast Asia, Polynesia and Australia. *Flagellaria indica* was investigated for its anti-dengue properties in Vero cells. The antiviral assay results show that 45.52 % inhibition of DENV-2 was observed in vitro in the presence of 12.5 lg mL⁻¹ of ethanol extract of the plant. By conducting MTT assays, the cytotoxicity of *F. indica* was determined. The CC50 of ethanol extract of *F. indica* were 312 lg mL⁻¹. Thus, this study indicates that *F. indica* has a significant potential effect on DENV.

4. *Piper retrofractum:* (Long pepper)

*Piper retrofractum* belongs to family Piperaceae. It is a flowering vine native to Southeast Asia and cultivated in Indonesia and Thailand mostly for its fruit. In vitro anti-dengue activity of *Piper retrofractum* in Vero cells was investigated. The inhibitory activity against DENV-2 infected cells was determined on dichloromethane ethanol extract by the MTT method. The ethanol extract of *P. retrofractum* exhibited an inactivated viral particle activity or 84.93 % at a concentration of 100 lg mL⁻¹. Previous study has shown that an aqueous extract of long pepper, *P. retrofractum*, gives the highest level of activity against mosquito larvae.

5. *Psidium guajava:* (Guava)
Psidium guajava belongs to family Myrtaceae. It is an evergreen shrub or small tree indigenous to Mexico, the Caribbean and Central and South America. Psidium guajava leaf extract has been tested in vitro and showed to inhibit the growth of dengue virus. P. guajava ripe fruit or juice has healing properties in cases of DF by improving the declining levels of platelets. They also increase platelet and water decoction of guava leaves contain quercetin-Inhibit formation of enzyme mRNA in virus.

**FRUITS IMPORTANT FOR DENGUE**

1. Papaya leaf juice and pulp are taken during viral infections. Papaya contains biologically active compounds like papain, carcain. The nutritional composition of papaya leaves contains Vitamin C, beta caroten, B complex virus.

2. Kiwi fruit: The combined use of kiwi fruit and leaves of papaya demonstrated a significant therapeutic effects on the febrile condition of dengue, they lessen muscle pain and skin rashes during dengue. While taking kiwi fruits and also fruits containing high vitamin C thus stimulate lymphocyte production and strengthens body’s immune systems.

<table>
<thead>
<tr>
<th>Sl.no</th>
<th>Plant</th>
<th>Common Name</th>
<th>Active constituent/extracts</th>
<th>Part used</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAVES</td>
<td></td>
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<tr>
<td>1.</td>
<td>Alternanthera sessilis</td>
<td>Dwarf copperleaf</td>
<td>Petroleum ether</td>
<td>Leaves</td>
<td>Platelet increasing and inhibit DENV2 replications</td>
</tr>
<tr>
<td>2.</td>
<td>Andrographis paniculata</td>
<td>Bitterweed</td>
<td>Methanolic extract</td>
<td>Leaves</td>
<td>Anti DENV-1 activity</td>
</tr>
<tr>
<td>3.</td>
<td>Carica papaya</td>
<td>Papaya</td>
<td>Aqueous extract</td>
<td>Leaf extract</td>
<td>Increase platelet count</td>
</tr>
<tr>
<td>4.</td>
<td>Hippophae rhamnoides</td>
<td>Seaberry</td>
<td>Ethanol extracts</td>
<td>Leaves</td>
<td>Decreased TNF alpha &amp; Increased IFN alpha inhibits DENV-2</td>
</tr>
<tr>
<td>5.</td>
<td>Ocicium sanctum</td>
<td>Tului</td>
<td>Methanol extract</td>
<td>Leaves</td>
<td>Inhibitory effect on DENV-1 based on cytopathic effect</td>
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<tr>
<td>6.</td>
<td>Azadarachta indica</td>
<td>Neem</td>
<td>Azadirachatin</td>
<td>Leaf extract</td>
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<tr>
<td>7.</td>
<td>Psidium guajava</td>
<td>Guava</td>
<td>Ethanol extract</td>
<td>Leaves</td>
<td>Inhibited DENV-2 replications</td>
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<tr>
<td>8.</td>
<td>Houttuynia cordata</td>
<td>Hearleaf/Fishwort</td>
<td>Aqueous extract</td>
<td>Stem and leaves</td>
<td>Inhibited DENV-2</td>
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<tr>
<td>SEEDS</td>
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<tr>
<td>1.</td>
<td>Leucaena leucocephala</td>
<td>White laid tree</td>
<td>Aqueous extract</td>
<td>Seeds</td>
<td>MTT Assay</td>
</tr>
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<td>2.</td>
<td>Mimosa scabrella</td>
<td>Bracatiga</td>
<td>Sulfated galactomanns</td>
<td>Seeds</td>
<td>MTT assay method</td>
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<td>3.</td>
<td>Quercus lusitanica</td>
<td>Gall Ok</td>
<td>Crude methanol extracts</td>
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<tr>
<td>WHOLE PLANT</td>
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<tr>
<td>4.</td>
<td>Alternanthera philoxeroides</td>
<td>Alligator Weed</td>
<td>Petroleum ether</td>
<td>Whole plant</td>
<td>MTT assay method</td>
</tr>
<tr>
<td>5.</td>
<td>Cladosiphon okamuranus</td>
<td>Muzuko</td>
<td>Ethanol extract</td>
<td>Whole plant</td>
<td>Fucoidans bind to DENV-2 (Recent insight)</td>
</tr>
<tr>
<td>6.</td>
<td>Flagellaria indica</td>
<td>Guard/melon</td>
<td>Ethanol extract</td>
<td>Whole plant</td>
<td></td>
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<tr>
<td>7.</td>
<td>Piper retrofractum</td>
<td>Long pepper</td>
<td>Ethanol extract</td>
<td>Whole plants(Leaves)</td>
<td>Lethal dose(LC50-79ppm)</td>
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</tbody>
</table>

**ROLE OF GARLIC IN DENGUE FEVER**

The development of inflammation during severe form of dengue have been associated due to oxidative stress and leads to inflammatory cytokines productions. The organosulfur compound present in the garlic have ability to inhibit TNF alpha induced inflammations. The recent studies shows that garlic reduces both inflammation and oxidative stress during dengue infections. Garlic active compound diallyl disulphide and diallyl sulfide and also allin reduced inflammation during DENV infection and shows that this reduction is due to effect on oxidative stress and also suggests that garlic can be used for the dengue preventions.

The studies shows that higher doses of garlic compounds, levels of MDA produced from the infected cells were reduced. In addition, lipid peroxidation has also been linked with an increase in pro-inflammatory cytokines in patients with severe dengue disease. Garlic has also been shown to act as an anti-oxidant in liver cells by inducing the antioxidant enzyme glutamate-cysteine ligase, which increases glutathione (GSH) content and the study, found that garlic organosulfur compounds were able to reduce both inflammation and oxidative stress during dengue virus infection of human cells. This could lead to a novel alternative therapeutic for treatment of infection and/or prevention of progression to severe disease.
II. DISCUSSION

During dengue infection, inflammation is the main process involved in the host immune response. Cells infected with the DENV produce nitric acid and protective pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-6 and IL-10 to attract and activate leukocytes at the site of infection. IFN-γ, IL-8, -12, -10 and -18 and TNF-α played an important role against DENV infection. DENV infected monocytes, dendritic cells and macrophages produces cytokines and TNF-α leading to endothelial activation and nuclear factor-κB (NF-κB), which stimulates platelet-activating factor (PAF) productions. Mast cells produces vascular endothelial growth factor (VEGF) which acts on secretory phospholipase A2 (sPLA2) that also contributed to PAF production. DENV may directly infect platelets directly and produces cytokines.

Molecules with anti-dengue activity belongs to all different class of compound including phenolic derivatives, alkaloids, flavonoids, terpenoids, celasterol, polysaccharides. A lot of natural or herbal drugs or medicines improves the immune systems.

III. CONCLUSION

The various active compounds present in the herbal plants have showed activity against DENV. The secondary metabolites of medicinal plants comprise a variety of compounds with a wide range of biological activities. Many plant with different solvent extracts have been reported to exhibit activity against a vector of dengue fever. The development of new bioactive compounds from herbal plants found to be more effective, low cost and also lesser toxic when compared to allopathy drugs. Various invitro and invivo study of various plants have shown anti-dengue activities. The importance of medicinal plants and its derivatives is growing rapidly with the human progress so herbal medicine have been considered as promising future medicine.

REFERENCE

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