WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Neutraceutical 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 a 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, glabranine, 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 hemorrarrhagic fever is first reported in phillippiness in 1953 and in 1981 in south America.([1]) Dengu is an acute viral infection with potential fatal complication. Dengue virus belongs to family Flaviridae 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 belived 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. ([2])

Symptoms: [2,3]

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 hass 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([4]) .The temperatures between 39 and 400C 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 haemorrhagic fever with symptoms such as bleeding from the nose, gums or under the skin. Dengue haemorrhagic 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. Aegyptus is a primarily a daytime feeder ([5,6]). 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, larvicidal and mosquito repellent property. Natural products have become the main source of test material in the development of antiviral drug based on traditional medicals. 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 paniculate:(Kal Megha)

Belongs to Acanthacea, 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 A.peniculata 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 androphaloids are the responsible compounds.([9,10])

2. Carcia papaya:(papaya)

Belongs to Caricaceae.Its leave 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. As per the medical report of patients the number of platelets had increased within the prescribed time (24 hrs) of drinking leaf juice of papaya in all 5 patients of dengue. The increase in number of platelet (leaf extract). Responsible compounds are chymopapain and papain.

3. Hippophage rhomboids:(sea buckthorn)

Belongs to Elaegnaceae. It is deciduous shrub. The fading shows that cell treated with Hippophage 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. Occium 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. Azidarachta indica :(Neem)

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

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 Moroccon. lusitanica extract was found to have a good inhibitory effect on the replication of DENV-2 in C6/36 cells . Previous study demonstrate invitro inhibitory activity of seed extracts. The methanol extract of the seeds completely inhibited (10–1,000 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 Amaranth aceae. 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 virus (ED50 = 47.43).

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 are also increase platelet and water decoction of guava leaves contain quercetin-Inhibit formation of enzyme mRNA in virus.(tracing).

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 VitaminC, beta carotenes ,B complex viruse.
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.[13]

Sl.no	Plant	Common Name	Active constituent/extracts	Part used	Action
LEAVES					
1.	Alternanthera sessilis	Dwarf copperleaf	Petrolium ether	Leaves	Platelet increasing and inhibit DENV2 replications
2.	Andrographis paniculata	Bitterweed	Methanolic exract	Leaves	Anti DENV-1 activity
3.	Carcica papaya	Papaya	Aqueous extract	Leaf extract	Increase platelete count
4.	Hippophae rhamnoides	Seaberry	Ethanolic extracts	Leaves	Decresed TNF alpha & Increased IFN alpha inhibits DENV-2
5.	Occium sanctum	Tulsi	Methanol extract	Leaves	inhibitory effect on DENV-1 based on cytopathic effect
6.	Azidarachta indica	Neem	Azardirachtin	Leaf extract	
7.	Psidium guajava	Guava	Ethanolic extract	Leaves	Inhibited DENV-2 replications
8.	Houttuynia cordata	Hearleaf,Fishwort	Aqueous extract	Stem and laeves	Inhibited DENV-2
SEEDS					
1.	Leucaena leucocephala	White laid tree	Aqueous extract	Seeds	MTT Assay
2.	Mimosa scabrella	Bracatiga	Sulfated galactomanns	Seeds	MTT assay method
3.	Quercus lusitanica:	Gall Ok	Crude methanol exttacts		
WHOLE PLANT					
4.	Alternanthera philoxeroides	Alligator Weed	Petroleum ether	Whole plant	MTT assay method
5.	Cladosiphon okamuranus	Muzuko	Ethanol extract	Whole plant	Fucoidans bind to DENV-2 (Recent insight)
6.	Flagellaria indica	Guard/melon	Ethanol extract	Whole plant	
7.	Piper retrofractum	Long pepper	Ethanol extract	Whole plants(Leaves)	Lethal dose(LC50-79ppm)

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)[14].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.(screen) [15].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-6and IL-10 to attract and activate leucocytes at the site of infection. IFN-γ, IL-8, -12,-10 and -18 and TNF-αplayed an important role against DENV infection. DENV infected monocytes, dendritic cells and macrophages produces cytokines and TNF-αleading 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, terpenoid's, 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 showed activity against DENV. The secondary metabolites of medicinal plants comprise a variety of compounds with a wide range of biological activities. Many plant swith 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.

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