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Anti-dengue medicinal plants: A mini review

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Abstract
Medicinal plants have been identified and used traditionally throughout the world from the beginning of the human civilization. Several plants with various properties of healing have been mentioned earlier in the oldest Indian mythology Rig-Veda and Athar-veda, thus the history of use of medicinal plants in India dates back to 3500-1800 B.C. These medicinal plants contain active principles which are highly potent against parasites. Parasite causes a quantum of health hazard and economic losses to both human and animals. Therefore, medicinal plants are still a concern of research for their anthelmintic activity and other beneficial effects, because of increasing contraindications in the application of synthetic medicines. The use of crude medicinal plants assures health promising effect to mankind and animals due to anthelmintic efficacy without any side effects. The present review gives an introduction to some medicinal plants, to involve in the control of dengue fever.

Keywords: Dengue fever, medicinal plants, anti dengue, viral disease

Introduction
Dengue Fever (Patel, 2004) [5] is the most emerging viral disease in humans caused by arthropode-borne flavivirus named dengue virus (DENV). It is estimated that there are about 50 to 100 million cases of dengue fever and dengue hemorrhagic fever (Chaturvedi, 2008) [3] each year. This virus spread through the *Aedes aegypti* mosquito and it is transmitted in humans through the bite of an infected *Aedes aegypti* mosquito. Mosquitoes become infected when they bite infected humans, and can later transmit the infection to other people. Dengue Fever (DF) is serious viral disease characterized by biphasic fever, headache, joint and muscle pain. The Primary symptom of the disease is dengue fever which is cured with in 5-7 days by self immune response. Secondary symptom is severe dengue hemorrhagic fever characterized by low level of platelets and blood plasma leakage and sometimes it is also called as Dengue Shock Syndrome (Ravi Kumar Pigili and Chinnalalaiah Runja, 2014) [31].

Epidemology of Dengue
Dengue is the rapidly spreading viral diseases in the world wide. In the recent survey reveals that there are 50 million dengue cases was reported and approximately 2 billion people lives in dengue endemic countries (Gubler, 1900 - 2003) [6]. The prevalence of Dengue has increased dramatically in recent years and its now endemic over 100 countries like, Africa, America, Malaysia, Thailand, India, South East Asia and Western Pacific. The first Dengue Hemorrhagic fever was reported in Thailand and Philippines in 1950s where the first two Dengue Virus serotypes were identified, followed by third and fourth serotypes in 1954 (Thomas, 2003) [40].

Dengue Virus
Dengue virus is a single stranded RNA virus belongs to flaviviride family and it was first isolated from Japan in 1942 by Hotta (Harris, 2006) [7]. The prevalence of dengue has grown dramatically in recent decades and is now spreads more than 100 countries. It is found in tropical and subtropical regions around the world predominantly urban and sub-urban areas (Lindenbach, 2003). There are four different serotypes DENV 1, 2, 3 and 4 were identified belonging to genus flavivirus. The genomic RNA is approximately 11 kb in length. Dengue Virus is composed of three structural protein genes. First protein gene is Enveloped (E) protein found on viral surface, second protein is membrane (M) protein which is very important for formation of viral particles. Third protein gene is non structural (NS) proteins which has seven subtypes. These NS proteins are believed to be involved in replication of viral RNA (Kuhn, 2002; Modis, 2003; Ma 2004) [14, 20, 19].

Overview of plant species used as anti-dengue

Medicinal plants have been traditionally used for different kinds of ailments including infectious diseases. There is an increasing need for substances with antiviral activity since the treatment of viral infections with the available antiviral drugs often leads to the problem of viral resistance and development of a dengue vaccine is complicated by the antibody-dependent enhancement effect. So demand for plant-based medicines is growing as they are generally considered to be safer, cheaper, non-toxic and less harmful than synthetic drugs. A number of natural compounds reported in traditional medicinal plants to have anti-dengue properties were studied and were also screened for anti-dengue compounds structure (Shasank Sekhar Swain and Debasmita Dudey, 2013) [35].

Andrographis paniculata

Andrographis paniculata belonging to family Acanthaceae, is an erect herb which is extremely bitter in taste. Tang *et al*., (2012) [17] has reported in vitro studies of antiviral activity of methanolic extract of *A. paniculata* on dengue fever. A. paniculata was found to have high potential to be an anti-dengue agent, particularly towards DENV-1 serotype.

Alternanthera philoxeroides

Alternanthera philoxeroides (Commonly called Alligator Weed) as is perennial aquatic plant belonging to Amaranthaceae family. Jiang *et al* (2005) [10] investigated the antiviral activity of four extracts (petroleum ether, ethyl acetate, ethyl ether and coumane of *A. philoxeroides.* Their results indicated that all extracts posses anti-dengue activity but highest inhibition of dengue virus was observed with petroleum ether extract.

Azidarachta indica

Azadirachta indica is the biological names of neem belong to Meliaceae family. Parida *et al*., (2002) [25] has studies the in vitro antiviral inhibitory effect of aqueous leaf extract of *Azadirachta indica* on the replication of replication of dengue virus 2 and the invitro assay results showed inhibition of virus replication. The aqueous extract of neem leaves at its maximum non-toxic concentration of 1.897 mg/ml completely inhibited 100-10,000 TCID (50) of virus as indicated by the absence of cytopathic effects.

Boesenbergia rotunda

Boesenbergia rotunda commonly known as fingerroot belonging to Zingiberaceae family. TS Kiat *et al*., (2006) [13, 2] has demonstrated that the flavonoids and cyclohexenyl of *Boesenbergia rotunda* showed significant inhibitory activity against dengue 2 virus NS3 proteins. Based on results obtained cyclohexenyl derivatives such as 4-hydroxypanduratin A and Panduratin Awhoed good inhibitory activity at Ki values of 21 μM and 25 μM as compared to pinocembrin, pinostrobin, cardamonin, and alpinetin.

Boerhaavia diffusia

Boerhaavia diffusia belonging to the family of Nyctaginaceae. Priyank Bharati and Rajashree Sinha have studied the anti-dengue effect of stems of *Tinospora cardifolia* (Wild) Miers (10 gm) and the plant of *Boerhaavia diffusa* Linn (10 gm). Anti-dengue effect was evaluated by giving the Ayurvedic mixture consisting *Tinospora cardifolia* and *Boerhaavia diffusa* to dengue patients 2- 3 times a day.

Boesenbergia rotunda

Boesenbergia rotunda belongs to family Zingiberaceae. It is a medicinal and culinary herb known as Chinese ginger. The activity of some compounds extracted from B. rotunda for the inhibition of dengue virus protease has been tested on DENV-2 (Kiat, 2006) [13, 2].

Cryptonemia crenulata

Cryptonemia crenulata belongs to family Halymeniaceae. It is a marine species found throughout the Indian Ocean Islands, Southeast Asia and Pacific Islands. The sulfated polysaccharides from *Cryptonemia crenulata*, i.e., galactan were selective inhibitors of DENV-2 multiplication (Talarico, 2005) [38].

Cladosiphon okamuranus

Cladosiphon okamuranus belongs to family Chordariaceae. It is brown seaweed found naturally in Okinawa. A sulfated polysaccharide named fucoidan is obtained from *Cladosiphon okamuranus* was found to potentially inhibit DENV-2 infection. The active compound is Fucoidan against dengue (Srivastava, 2005) [36].

Carica papaya

Carica papaya is also called as papaya. Ahmad N *et al*. (2011) [21] in have demonstrated that aqueous leaf extracts of C. papaya exhibited potential activity against dengue fever by increasing the platelets count, WBC and neutrophils.

Castanospermum austral

Castanospermum belongs to the Fabaceae family Whitby *et al*., (2005) [12] has investigated anti viral activity of castanospermine, is a natural alkaloid derived from the tree *C. australae* by in Vitro assay. Studies of its mechanism of action suggest that castanospermine may disrupt folding of some viral proteins by preventing the removal of the terminal glucose residue on N-linked glycans in dengue virus.

Chondrus crispus

Chondrus crispus commonly called as carrageen moss is a species of red algae. Talarico *et al* (2007) [39] has reported that carrageen and other sulfate polysaccharides were effectively inhibited the dengue virus 2 infection where they were inhibiting virus entry.

Cissampelos pareira

Cissampelos pareira is also known as velvet leaf, belongs to family of Menispermaceae. Bhatnagar and Co-workers (2012) patented anti-dengue activityof extract of aerial parts of *Cissampelos pareira*. Their investigations related to anti-dengue activity of *Cissampelos pareira* extracts and a pharmaceutical compounds were also provided comprisning *Cissampelos pareira* extracts. Methanolic extractx of *Cissampelos pareira* showed anti-viral activity against all types of dengue virus in conventional assay with PRNT50 values in the range of 1.2-11.1 μg/mL.

Euphorbia hirta

Euphorbia hirta is belongs to family of Euphorbiaceae. Apostol *et al*., has studied the platelet increasing activity of decoction of Euphorbia hirta plant in ethanolic inducing thrombocytopenic rat models. Administration of 100mg/kg of the lyophilized decoction of *E. hirta* increased platelet count in ethanolinduced thrombocytopenia after 7 days of administration. Continued administration of the plant

decoction resulted in the maintenance of this antithrombocytopenic effect. *E. hirta* contains more reducing polyphenols, active ingredient suspected to be responsible in the increasing platelet count.

Gymnogongrus torulosus

Gymnogongrus torulosus belongs to family Phyllophoraceae. It is red seaweed found in Australia and New Zealand. *Gymnogongrus torulosus* was investigated for its in vitro antiviral properties against DENV-2 (Pujol, 2002) [28].

Gastrodia elata

Gastrodia elata has been known as famous and important chinese medicinal herb belonging to family Orchidaceae. Qui H (2007) [29] and Tong (2010) [29] *et al*., has isolated some D-glucans from *Gastrodia elata* and sulfated derivatives were prepared and they were investigated anti-dengue activity against dengue 2 virus. These sulfated D-glucan derivatives were strongly interfering with the dengue 2 virus infections with an EC (50) value of 0.68+/-0.17 microg/mL, mainly interfered with virus adsorption, in a very early stage of the virus cycle.

Houttuynia cordata

Houttuynia cordata belongs to family Saururaceae. It is herbaceous perennial flowering plants growing between 20 and 80 cm, and is native to Japan and Southeast Asia. The hyperoside was the predominant bioactive compound,and was likely to play a role in this inhibition action against DENV-2 (Leardkamolkarn, 2012) [8, 16].

Houttuynia cordata

Houttuynia cordata is a Chinese herb belonging to family of saururaceae Vijjitara *et al*., (2012) has studied inhibitory activity of aqueous extract of *Houttuynia cordata* on dengue virus. This study revealed that the extract of this plant strongly inhibiting the viral RNA replication at a effective dose of 0.8μg/mL.

Hippophae rhamnoides

Hippophaerhamnoides is see buckthorn is spiny deciduous shrub belongs to Elaeagnaceae The anti-dengue activity of *Hippophae rhamnoides* was investigated by Mounika Jain *et al*., (2008) [9]. The leaf extract of this plant was evaluated for anti-dengue activity in Dengue type 2 virus infected blood-derived human macrophages as the primary targets. This study showed that this extract was able to maintain cell viability of dengue infected cells and increases in TNF-α an d IFN-γ respectively.

Kaempferia parviflora

Kaempferia parviflora is also known as krachai Dam, a thai traditional herb belonging to Zingiberaceae. Phurimask *et al*., (2005) has studied virucidal activity of leaves and stem extracts of *Kaempferia parviflora* against dengue virus type 2. It was suggested that some of the bioactive compounds in *Kaempferia parviflora* inactivates the Dengue type 2 virus particles.

Lippia citriodora

Lippa citriodora is a perennial shrub also called as Lemon verbena belonging to family of Verbenaceae. The dengue virus treated with essential oil for 2 h at 37 masculineC before cell adsorption and experiments were conducted to evaluate inhibition of untreated-virus replication in the presence of oil. Virus plaque reduction for all four dengue serotypes was observed by treatment of the virus before adsorption on cell. The IC_{50} values for *L. alba* oil were between 0.4-32.6 microg/mL and between 1.9-33.7 microg/mL for L. citriodora oil (Ocazionez *et al*., 2010) [22]

Leucaena leucocephala

Leucaena leucocephala belongs to family Fabaceae. Galactomannans extracted from seeds of *L. leucocephala* have demonstrated activity against DENV-1 in vitro and in vivo level. (Ono, 2003) [23-24].

Mimosa scabrella

Mimosa scabrella belongs to family Fabaceae and Galactomannans extracted from seeds of *Mimosa scabrella* have demonstrated activity against DENV-1 in vitro and in vivo (Ono, 2003) [23-24].

Meristiella gelidium

Meristiella gelidium belongs to family Solieriaceae. It is a marine species found in Atlantic Islands. The antiviral activity of kappa carragenan in *Meristiella gelidium* was evaluated against DENV-2 (Tischer, 2006) [41].

Mimosa scabrella

Mimosa scabrella is a multipurpose tree belonging to family of Fabaceae. Wollinger *et al*., (2003) [23-24] was isolated two galactomannans from the seeds of *Mimosa scabrella* and seeds of *Leucaena leucocephala*. These two active compounds were tested for invitro anti-viral property against yellow fever virus and dengue virus. Invitro experiments in C6/36 cell culture assay showed the inhibitory activity against dengue virus at concentration of 347 and 37 mgl-1

Myrtopsis corymbosa

Myrtopsis corymbosa belongs to family Rutaceae. Compound ramosin, myrsellinol and myrsellin are the main active compound of M. corymbosa from its bark. The bark extract is the strongest and even inhibits 87% of DENV polymerase. Alkaloids content of leaves were also investigated compounds identified as skimmianine, γ-fagarin and haplopin but isolated alkaloids were only slightly active against the DENV-NS5 (Kumar, 2012) [15].

Phyllanthus urinaria

Phyllanthus urinaria is commonly called chmberbitter, gripeweed belongs to the family of Phyllanthaceae. Sau Har Lee *et al*., (2013) [34] has studied the anti-dengue effect of aqueous and methanolic extract of four species of Phyllanthus such as P.*amarus, P.niruri, P.urinaria*, *P.wastonii*. These species showed strongest inhibitory activity against DENV2 with more than 90% of virus reduction in simultaneous treatment at maximal non toxic dose of 250.0 μg/mL and 15.63 μg/mL

Piper sarmentosum

Piper sarmentosum belongs to the family Piperaceae. Udom *et al*., (2005) [42] has studied the larvicidal activity of three species of pepper plants on *aedes aegypti*.

Quercus lusitanica

Quercus lusitanica is also known as *Quercus infectora* belongs to the family of Fagaceae. Sylvia *et al*. (2006) was demonstrated in vitro inhibitory activity of *Quercus lusitanica* seed extract. The result showed the down regulation of NS1

protein expression of infected cells aftr treating with seed extract. In 2008 again the same plant extract was evaluated for antidengue activity by Sylvia *et al*. This study showed seed extract of *Quercus lusitanica* inhibited Dengue type 2 virus in the concentration 0.032 to 0.25 mg/ml

Rhizophora apiculata

Rhizophora species are wide spread throughout most tropical coastal areas of western pacific region and east Africa. It consists of three species Rh*izophora mucronata, Rhizophora stylosa* and *Rhizophora apiculata*. *R. apiculata* found in India, Australia, indonasia, Malaysia etc. T. Ramanathan *et al*. has studied larvicidal activity of petroleum ether extracts of *Rhizophora apicuata* against *A. aegypti* mosquito. Petroleum ether extract of *R. apiculata* is most effective with LC_{50} of 25.7µg/L. The extract further shows synergistic larvicidal activity with pyrethrum.

Tephrosia madrensis

Tephrosia madrensis also belongs to family Fabaceae and Glabranine is the main active compound for dengue fever treatment. The flavonoids isolated from *T. madrensis*, glabranine and 7-O-methyl-glabranine exert strong inhibitory effects on dengue virus replication (Sanchez, 2000) [33].

Zostera marina

Zostera marina belongs to family Zosteraceae. It is an aquatic plant known as eelgrass and is native to North America and Eurasia. A compound from the temperate marine eelgrasss *Zostera marina* has been identified as possessing antidengue virus activity (Rees, 2008) [32].

Conclusion

The development of new anti-dengue products from bioactive compounds is necessary in order to find more effective and less toxic anti-dengue drugs. Therefore, any extensive study on the potential of plants with isolated active compounds that have shown anti-dengue 16 activity should go through additional in vitro and in vivo animal testing followed by toxicity and clinical tests. This route may reveal a promising compound to be optimized and thus be suitable for application in the production of new anti-dengue compounds. If pursued from drugs derived from medicinal plants around the continents, this work may prove valuable to the health of individuals and to nations. Moreover, such discoveries may lead to the development of highly efficient and safe anti-dengue treatments. However, to identify potential anti-dengue plants or compounds, knowledge of the mechanisms of virus infection need to be understood in order to facilitate the search for and development of the most appropriate drugs. Further research is needed to determine how to target the most appropriate stages to prevent the spread of virus infection. Focusing on each phase in the life cycle of the virus, new compounds could prevent (1) infection of host cells, (2) the viral maturation process, (3) synthesis of viral RNA, or (4) the spread of viral particles.

Conclusion

This paper has covered some medicinal plants species and their potential active compounds that could be used in the treatment of dengue and about all the prominent pharmacological activity of plant compounds against dengue. Moreover, such discoveries review may lead to the development of highly efficient and safe anti-dengue treatments and great impact on future viral research along with interesting for isolation of more and more natural compounds for medical treatment.

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