

Medicinal plants used in dengue treatment: An overview

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Received: 26 November 2013 Accepted: 12 December 2013 Online: 10 January 2014

ABSTRACT

Dengue fever or dengue hemorrhagic fever is the most prevalent viral disease caused by dengue virus a family of flavivirus transmitted through *aedes aegypti* mosquito. Approximately 2.5 billion people world wide affected by this virus. Dengue is single stranded RNA virus, has four serotypes i.e. type 1, 2, 3 and 4. There are no approved antiviral agents or vaccine is available for the treatment of this virus which causes increasing the mortality rate all over the world. As there are no synthetic drugs available, now it is need to focus on medicinal plants which are considered to be effective, safer and non-toxic. There are several medicinal plant extracts were found to have anti dengue activity, but they are not approved for dengue viral treatment. The present article reviews on the medicinal plants available for their anti-dengue activity and also provided the phytochemical constituents present in those medicinal plants.

Keywords: Dengue, Medicinal Plants, RNA Virus

INTRODUCTION

Dengue Fever [1-3] 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 [4] 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.

Epidemiology 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. 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 [5,6].

Dengue Virus

Dengue virus [7] is a single stranded RNA virus belongs to flaviviride family and it was first isolated from Japan in 1942 by Hotta. 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. There are four different serotypes DENV 1, 2, 3 and 4 were identified belonging to genus flavivirus [8,9]. The genomic RNA is approximately 11 kb in length. Dengue Virus is composed of three structural protein genes [10-12]. 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.

Overview of Dengue Virus Replication

There is no detailed functional interaction of dengue viral replication [13,14] although a general understanding is emerging as how dengue proteins regulate the virus replication cycle. After Virus entry into the cell by receptor mediated endocytosis and uncoating of nucleocapsid, RNA molecule is translated as single poly proteins. The poly protein is then undergoes co and post translation by cellular and viral protease enzyme into individual proteins required for viral replication.

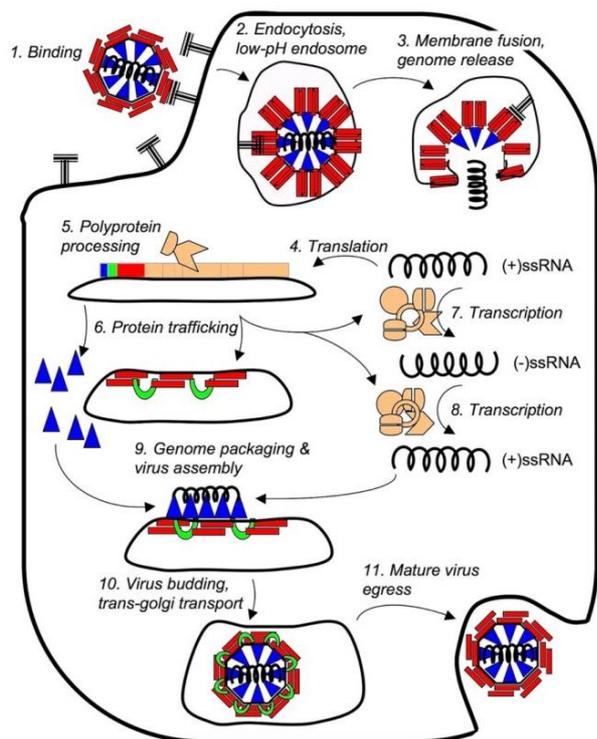


Figure 1. Schematic diagram of Viral Replication

Medicinal Plants Used In Dengue Treatment

Herbal medicines play a major role in treatment of many diseases in humans and animals. Nowadays these medicinal plants [17-21] have emerged as a unique approach to safe, effective and inexpensive new remedies for variety of diseases as they do not have adverse effects. Many natural drugs isolated from plants were showed good antiviral activity against *Aedes aegypti* mosquito. Several investigations were carried out on different plant extracts and few of them showed anti viral activity on dengue virus. In the present paper, we provided useful information about the plants which shows antiviral activity against dengue virus.

Andrographis paniculata

Andrographis paniculata [22, 23] belonging to family Acanthaceae, is an erect herb which is extremely bitter in taste. This plant has been effectively used as traditional medicine for centuries. Chemically, *A. paniculata* has major constituents, like lactones,

Treatment and Management of Dengue

There is no specific antiviral therapy is available for treatment of dengue. Treatment of Dengue Disease consisting primarily of intensive support therapy. Maintaining blood circulation and platelets level is the most important in the management of the disease. Symptomatic treatment of dengue is done using oral fluid administration and antipyretic treatment with paracetamol as recommended. Platelets transfusions are usually given to the dengue patients who develop hemorrhagic manifestation or have low platelets count.

Drug Targets

The goal of virtual screening is to discover new molecules that can bind to the targets and modulates the functions of biomolecules. Several investigations were carried out to discover the potential targets to treat viral infections. Proteins and viral entry are typical targets for developing new molecules. Viral entry inhibitors [15,16] and protein inhibitors are the major drugs to treat the viral diseases. Recent discoveries revealed that there is several protein and non protein potential targets were discovered to develop anti-dengue agents. Numerous studies have investigated approaches to inhibit the viral particle entry. Membrane (M), and Envelope (E) proteins are the key structural proteins which plays an important role in virus entry in to the cell. These are the one of the main targets to design and develop potential virus entry inhibitors. Non structural (NS) Proteins plays a major role in the viral replication. NS Protein complex include NS3, NS2B, NS3 helicase/ nucleoside triphosphatase, RNA 5' triphosphatase and NS5 methyltransferase/ RNA dependent RNA polymerase enzymes. All these NS proteins serve as potential targets for developing dengue virus since they are required for viral replication.

diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides. It also effectively used in treating symptoms of upper respiratory tract infections. Tang et al., (2012) [24] has reported in vitro studies of antiviral activity of methanolic extract of *A. paniculata* on dengue fever. In this preliminary screening study for anti-dengue agent, methanolic extract of *A. paniculata* was found to have high potential to be an anti-dengue agent, particularly towards DENV-1 serotype.

Alternanthera philoxeroides

Alternanthera philoxeroides [25] (Commonly called Alligator Weed) as is perennial aquatic plant belonging to Amaranthaceae family. Jiang et al (2005) [26] investigated the antiviral activity of four extracts (petroleum ether, ethyl acetate, ethyl ether and coumane) of *A. philoxeroides*. Their results indicated that all extracts possess anti-dengue activity but highest inhibition of dengue virus was observed with petroleum ether extract.

Azadirachta indica

Neem [27] is one of the best and fast growing tree is being used for treating several ailments such as jaundice, ulcers, parasitic diseases, malaria and other variety of infections. *Azadirachta indica* is the biological names of neem belong to Meliaceae family. It is native of India, Indonesia, Pakistan, Malaysia. Several investigations were carried out on leaves, seeds, bark and flowers of neem plants and it was used to cure variety of bacterial and viral infections. Parida et al., (2002) [28] has studied 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 TCID₅₀ of virus as indicated by the absence of cytopathic effects.

Boesenbergia rotunda

Boesenbergia rotunda [29] commonly known as fingerroot belonging to Zingiberaceae family. It is widely found in Asian countries such as Malaysia, Thailand, Indonesia, India, and China where it is commonly used as food ingredient.

TS Kiat et al., (2006) [30] 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 A showed good inhibitory activity at K_i values of 21 μM and 25 μM as compared to pinocembrin, pinostrobin, cardamomin, and alpinetin.

Boerhaavia diffusa

Punarnava is the telugu name of *Boerhaavia diffusa* [31] belonging to the family of Nyctaginaceae. It is distributed all over the world like Africa, Asia, North America, South America, and South Pacific. *Boerhaavia diffusa* has found to show various important biological activities like antibacterial, anti-oxidant, anti-diabetic, anti-diuretic and anti-inflammatory etc. The root is mainly used to treat gonorrhoea, internal inflammation of all kinds, dyspepsia, oedema, jaundice, menstrual disorders, anaemia, liver, gallbladder and kidney disorders, enlargement of spleen, and abdominal pain.

Priyank Bharati and Rajashree Sinha [32] 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.

Carica papaya

Carica papaya [33] is also called as papaya, an evergreen unbranched fast growing plant cultivated in most tropical countries. Papaya is the rich source of nutrients, minerals, vitamins, such as Vit A, B, C, and E

and is available throughout the year. It also contains two important biologically active digestive enzymes chymopapain and papain. The fruit is an excellent source of beta carotene that prevents the damage caused by free radicals. *C. papaya* is successfully used in treating and improving the GIT disorders like hyperacidity and dyspepsia.

Extensive investigations were carried out on *C. Papaya* leaf and it was found that leaf extract was showed potent inhibitory activity against dengue fever. Ahmad N et al. (2011) [34] 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 australe

Castanospermum belongs to the Fabaceae family and has only one species -*Castanospermum australe*, commonly referred to as the Black Bean. Whitby et al., (2005) [35] has investigated anti viral activity of castanospermine, is a natural alkaloid derived from the tree *C. australae* by in Vitro assay. Castanospermine has showed good inhibitory anti-dengue activity over a broad range of doses from 10 to 250 mg/kg/day. This investigation reveals that castanospermine acts as an ER α-glucosidase I inhibitor and reduces infection of a subset of enveloped RNA and DNA viruses in vitro. 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. It is abundant in rocky shores and tide pools of Ireland and coast of Europe. *Chondrus crispus*, consisting polysaccharide carrageen as active constituent. Carrageenans are effective in treatment against viral infections of common cold. Talarico et al (2007) [36] 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 [37] is also known as velvet leaf, belongs to family of Menispermaceae. This plant is widely distributed worldwide and has been used in the treatment of ulcers, diarrhea, muscle inflammation and rheumatism. Earlier investigations on roots of *Cissampelos pareira* revealed that it contain alkaloids hyatin hyatinin, haytidine and bebeerines. A chalcone and flavones dimer was isolated from the aerial parts of the plant named as cissampeloflavone. Bhatnagar and Co-workers (2012) [38] patented anti-dengue activity of 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 comprising *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.

Gastrodia elata

Gastrodia elata has been known as famous and important Chinese medicinal herb belonging to family Orchidaceae. This traditional Chinese herb has been used to treat various diseases like stroke, rheumatism, insomnia, Alzheimer's disease, depression, convulsions, neuronal diseases, fungal infections etc. Chemical analytical studies revealed that this plant contains nine kinds of phenolic compounds, and sixteen kinds of amino acids which are beneficial to health. Qui H (2007) and Tong (2010) et al., [39] 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.

Euphorbia hirta

Euphorbia hirta is popular herb also known as tawatawa (gatas-gatas) belongs to family of Euphorbiaceae. It is a common medicinal plant grown in India, Australia and Philippines. This plant is widely used as a decoction or infusion to treat various ailments including intestinal parasites, diarrhoea, peptic ulcers, amoebic dysentery, asthma, hay fever, kidney stones, menstrual problems and venereal diseases [40]. Phytochemical analysis of *Euphorbia hirta* revealed the presence of polyphenols, reducing sugar, alkaloids, flavonoids, sterols, tannins and triterpenoids in the whole plant. Apostol et al., [41] 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 ethanol-induced thrombocytopenia after 7 days of administration. Continued administration of the plant decoction resulted in the maintenance of this anti-thrombocytopenic effect. *E. hirta* contains more reducing polyphenols, active ingredient suspected to be responsible in the increasing platelet count.

Houttuynia cordata

Houttuynia cordata is a Chinese herb belonging to family of Saururaceae native to many Asian countries. This is one of the most potential plants in Saururaceae family has been used to treat several diseases like Anti-hypertensive, anti-cancer, anti-mutagenic, anti-inflammatory, and many others. Several active chemical constituents were isolated from this plant and out of which six major constituents such as alkaloids, flavonoids, fatty acids, sterols, phenols, and essential oils were proved to be important components of this plant. Recently, this plant extract was screened for its anti-viral activity against dengue virus. Vijitara et al., (2012) [42] 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 an effective dose of 0.8 µg/mL.

Hippophae rhamnoides

Hippophae rhamnoides is a spiny deciduous shrub belongs to Elaeagnaceae which has medicinal and nutritional values. The leaves and fruits of this plant are rich in vitamin A, B, C, E, K, flavonoids, lycopene, carotenoids and phytosterols [43]. Medicinally it was found to possess anti-oxidant, immunomodulating activity, anti-cancer, anti-inflammatory, anti-bacterial, anti-viral and wound healing activities. The anti-dengue activity [44] of *Hippophae rhamnoides* was investigated by Mounika Jain et al., (2008). 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 and IFN-γ respectively.

Kaempferia parviflora

Kaempferia parviflora is also known as krachai Dam, a Thai traditional herb belonging to Zingiberaceae. Leaves and stem of this plant are used traditionally to treat many viral infections. Main chemical constituents of *Kaempferia parviflora* are borneol and flavonoids. Previous investigations reported that it has various activities like anti-ulcer, anti-allergic, anti-fungal, anti-mycobacterial etc. Recently, it has demonstrated very good activity against Dengue type 2 virus. Phurimask et al., (2005) [45] 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* inactivate the Dengue type 2 virus particles.

Lippia citriodora

Lippia citriodora is a perennial shrub also called as Lemon verbena belonging to family of Verbenaceae. It is a great topiary plant with nice fragrance and very rich in aromatic oil. Its lemon-like aroma of the plant leaves is used to prepare herbal tea. It has been used for long time treatment of asthma, fever, cold and its several biological activities like, anti-bacterial, anti-malarial, cytotoxic, anti-spasmodic etc. *Lippia* species very important essential oils such as limonene, β-caryophyllene, p-cymene, camphor, linalool, p-pinene and thymol. The main chemical constituents present in this plant are Salvigenin, eupatorin, eupafol, hispidulin, 6-hydroxyluteolin, cismaritin and chrysoeriol apygenin. The in vitro anti-dengue effect of essential oils of *Lippia citriodora* and *Lippia alba* [46] was evaluated by Ocazionez et al., (2010). The dengue virus treated with essential oil for 2 h at 37 °C 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 IC50 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.

Mimosa scabrella

Mimosa scabrella is a multipurpose tree belonging to family of Fabaceae. It is very fast growing medicinal plant native to southern Brazil. All parts of this tree have medicinal values and invite attention of researchers for its pharmacological activities such as anti-diabetic, anti-hepatotoxin, and wound healing. Along with these activities recently it also found to inhibit dengue type 2 viruses. This plant contains some important bioactive compounds such as carbohydrates, flavanoids, alkaloids and phenols. Wollinger et al., (2003) [47] 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 mg^l⁻¹

Phyllanthus urinaria

Phyllanthus urinaria is commonly called chamberbitter, gripweed belongs to the family of Phyllanthaceae. It is believed that the plant originated in tropical asia and widely distributed in South India, South America and China. It is used for treatment of several diseases like Hepatitis, jaundice, Urinary Tract Infections, Syphilis, Asthma, Bronchitis, Anemia and joint pains etc. It was also found to have anti-cancer activity. 7'-hydroxy-3',4',5,9,9'-pentamethoxy-3,4-methylene dioxy lignan isolated from the ethylacetate extract of *P. urinaria* was shown to exhibit anticancer activity ¹⁷by inducing apoptosis. Recently this plant also shown to have anti-dengue activity. Sau Har Lee et al., (2013) [48] 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 Piperaceae family which is economically important because of their medicinal and culinary uses. It is also called as Lolot Pepper and leaves of this plant are traditionally used as condiment and also used for its carminative property. The whole plant having medicinal properties and is used to treat inflammation, skin diseases, rheumatism, diarrhea and root is used for the treatment of cough and asthma. *Piper sarmentosum* contains many chemical constituents such as ascaricin, α-ascarone, β-sitosterols and also contains Vitamin C, Vitamin E, Carotenes, Xanthophylls etc. The ethanol extract of *Piper sarmentosum* possesses larvicidal effect against early 4th instar larvae of *Aedes aegypti* mosquitoes. Udom et al., (2005) [49] has studied the larvicidal activity of three species of pepper plants on *aedes aegypti*.

Quercus lusitanica

Quercus lusitanica [50] is also known as *Quercus infectora* belongs to the family of Fagaceae. The gall oak (commonly known as *Quercus lusitanica*) is found in Greece, Asia, Iran and India. In india gall extract is used to treat minor soar throat and chronic diarrhea. The gall, extracts of *Q. infectoria*, are extensively used in traditional medication as karkatasringi for the preparation of Balachaturbhadra, Shringyadi churna, Karkatadi churna, Kantkaryavaleha. *Quercus lusitanica* have been investigated for several medicinal properties such as astringent, anti-diabetic, anti-inflammatory, Anti-bacterial and gastro protective activities. Further research on this plant was carried out for anti-viral activity against dengue virus. In previous study Sylvia et al. (2006) [51] 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 anti-dengue 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 *Rhizophora mucronata*, *Rhizophora stylosa* and *Rhizophora apiculata*. *R. apiculata* found in india, Australia, indonasia, Malaysia etc. T. Ramanathan et al [52] 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 LC₅₀ of 25.7µg/L. The extract further shows synergistic larvicidal activity with pyrethrum.

Uncaria tomentosa

Cat's claw is a large, woody vine found in tropical South and Central America, including Peru, Colombia, Ecuador, Guyana, Trinidad and Venezuela. It is belongs to Rutaceae family having different medicinal properties. In addition to its immunostimulating activity, other in vitro anticancerous properties have been documented for these alkaloids and other constituents in cat's claw. Five of the oxindole alkaloids have been clinically documented with in vitro antileukemic properties, and various root and bark extracts have demonstrated. Anti-Viral activity of hydro-alcoholic extract of *Uncaria tomentosa* plant was evaluated on human monocytes infected with Dengue type 2 virus by Valente et al., (2008) [53]. The results of this study demonstrated an invitro inhibitory activity by extracts reducing Dengue -Ag+ cell rates in treated monocytes.

CONCLUSION

Dengue viral infection is becoming one of the major health issue worldwide. Unfortunately there are no approved anti-viral agents to treat dengue infection in humans. However there are several plants were found to possess anti-dengue activity, but the there is no

extensive research carried out on those plants. It is very important that, the future development of anti-dengue drugs should be developed from the medicinal plants which are considered to be safer, effective and non-toxic than synthetic agents. Now it is the time to develop synthetic and natural anti-dengue agents through the various useful animal models. Similarly innovative approaches to prevent the transmission of virus should be focused.

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