

Review Article



Current Perspectives of Medicinal Plants Having Anti Dengue Potential

Prakash Deep*, Vivek Srivastava, Shikhar Verma

Amity Institute of Pharmacy, Amity University Uttar Pradesh, Lucknow, Uttar Pradesh, India 226028.

*Corresponding author's E-mail: pdeep@lko.amity.edu

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ABSTRACT

Dengue fever is endemic in tropical and subtropical areas. This is estimated by the World Health Organization (WHO) to cause about 50-100 million infections per year worldwide. Dengue fever causes mortality and morbidity around the world. During the last decades, researchers have turned their attention to nature, trying to identify plants that can be used as dengue antivirals. Various plant based preparations have been used in different parts of India for confronting dengue and simultaneously also being scientifically validated by researchers. However, numbers of such scientific validation studies on phytomedicines are very less in India. The demand for plant-based medicines is growing as they are generally considered to be safer, non-toxic and less harmful than synthetic drugs. Nature represents a vast reservoir of substances that can be explored with the aim of discovering new leads that can be either used directly as pharmaceuticals or can serve as lead structures that can be optimized towards the development of new antiviral agents against dengue. This article reviews potential anti-dengue activities from plants distributed around the world. Further ethnobotanical surveys and laboratory investigations are needed to establish the potential of identified species in contributing to dengue control. In this review we describe an assortment of medicinal plants that have been reported as possessing dengue antiviral activity.

Keywords: Dengue fever, Anti-dengue, Medicinal plants, Phytochemical.

INTRODUCTION

Dengue is a mosquito-borne viral disease that has rapidly spread in recent years.

It is a severe flu-like illness and, sometimes causing a potentially lethal complication called severe dengue. Dengue should be suspected when a high fever (40°C/104°F) is accompanied by 2 of the following symptoms: severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash. Symptoms usually last for 2–7 days, after an incubation period of 4–10 days after the bite from an infected mosquito.

Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding or organ impairment. Warning signs occur 3–7 days after the first symptoms in conjunction with a decrease in temperature (below 38°C/100°F) and include: severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness and blood in vomit. The next 24–48 hours of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death.

Despite the daunting and recurring numbers of annual cases of Dengue fever, most of the cases improve within days, only 1–2% of cases progress to the more severe conditions called dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DHF is characterized by decreasing platelet counts that usually start after the third day. In the DHF group, plasma leakage and severe bleeding may occur resulting in organ failure and death.

No specific treatment is available other than supportive care and pain relief. Death occurs mainly from this group.

Global burden of dengue

Dengue has a long history dates back to 265-420 AD associated with the Chinese medical encyclopedia of the Jin Dynasty.^{22, 13} The incidence of dengue has increased 30-fold over the last 50 years. Up to 50-100 million infections are now estimated to occur annually in over 100 endemic countries, putting almost half of the world's population at risk. Severe dengue (previously known as dengue haemorrhagic fever) was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand.

Vector

The *Aedes aegypti* mosquito is the primary vector of dengue.¹ *Aedes albopictus*, a secondary dengue vector in Asia, has spread to North America and more than 25 countries in the European Region, largely due to the international trade in used tyres (a breeding habitat) and other goods (e.g. lucky bamboo). *Aedes albopictus* is highly adaptive and, therefore, can survive in cooler temperate regions of Europe. After virus incubation for 4–10 days, an infected mosquito is capable of transmitting the virus for the rest of its life. The *Aedes aegypti* mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes *Aedes aegypti* is a day-time feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Aedes aegypti* bites multiple people during each feeding period. Dengue is widespread



throughout the tropics, with local variations in risk influenced by rainfall, temperature and unplanned rapid urbanization.

Aedes mosquitoes are small and black with white markings on the body and legs. Female mosquitoes need blood from biting humans or animals to produce live eggs. It takes 2–3 days for egg development. The principal vector of dengue (*Aedes aegypti*) has adapted well to the urban environment^{2, 3} and always breeds in stagnant containers. Eggs need moist conditions, and mature in 24–72 h.⁴ Mosquito bites are the only route of DENV spread.

Virus

There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Which belong to the genus *Flavivirus*, family *Flaviviridae*.^{5, 6, 7} To identify a potential antiviral treatment for DENV, it is necessary to understand the life cycle of the virus. The dengue virion is a small particle with a lipoprotein envelope and an icosahedral nucleocapsid containing a positive single-stranded RNA genome.^{8, 9, 10} Virus infection of the cell begins with binding to the host cell surface. It enters the cell by receptor-mediated endocytosis¹¹, with the cell membrane forming a sac-like structure known as an endosome. In the endosome, the virus penetrates deep into the cell until the endosome membrane acquires a negative charge, which allows it to fuse with the endosomal membrane to open a port for release of genetic material. At this point, the virus in the cell fluid starts to reproduce. Changes in the acidity of the secretory pathway during this viral journey travel play an important role in its maturation DEN-2 is known to be more lethal than other serotypes.⁸ Distinct genotypes have been identified within each serotype, highlighting the extensive genetic variability of the dengue serotypes. Among them, “Asian” genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections. Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.

The human

After being transmitted to a new human host by infected mosquitoes, the virus replicates in the lymph nodes and spreads through the lymph and blood to other tissues.⁸ Infected symptomatic or asymptomatic humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected with the dengue virus can transmit the infection (for 4–5 days; maximum 12) via *Aedes* mosquitoes after their first symptoms appear.

Pathophysiology of dengue fever

After a person is bitten, the virus incubation period varies between 3 and 14 days^{6, 12}, after which the person may experience early symptoms such as fever, headache, rash, nausea and joint and musculoskeletal pain.^{6, 13} This classic Dengue Fever records temperatures between 39 and 40 °C and usually lasts 5–7 days.⁸ 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 (DHF) with symptoms such as bleeding from the nose, gums or under the skin.¹² DHF patients also have difficulty in breathing and severe development can lead to Dengue Shock Syndrome (DSS). DSS can result in death if proper treatment is not provided.

Thrombocytopenia (low platelet count) in DHF is caused by two, virus-induced mechanisms: decreased production and increased peripheral destruction. Bone marrow suppression is attributed to circulating interleukins from a stringent host immune response.⁴⁵ Increased peripheral destruction is attributed to the viral effect on the vascular endothelium which induces a spontaneous aggregation of platelets, ending in peripheral platelet lysis.⁴⁶

Immunization

In late 2015 and early 2016, the first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was registered in several countries for use in individuals 9-45 years of age living in endemic areas.

Possible mechanisms and pathways in the treatment of dengue

There are currently no specific treatments for dengue fever.¹⁴ Only standard treatment for management of fever is given, i.e., nursing care, fluid balance, electrolytes and blood clotting parameters.¹² Patients with dengue fever will be treated symptomatically, for example, sponging, Paracetamol to bring down fever and reduce joint pains,¹⁵ bed rest and oral rehydration therapy, and if signs of dehydration or bleeding occur the patients are usually hospitalized.⁸ Aspirin should be avoided because it may cause bleeding.¹⁵ Platelet count and hematocrit should be measured daily from the suspected day of illness until 1–2 days after *defervescence*.¹⁵ Current prevention of dengue by potential dengue vaccine and vector control is highly cost effective.^{14, 16} In addition, mosquito control programs are the most important preventive method.⁸ However, these are difficult to implement and maintain.¹⁷ Development of a vaccine for dengue is difficult since there are four closely related, but antigenically distinct, serotypes of the virus that can cause disease.^{8, 18} Infection by one serotype does not ensure protection of the patient from infection by the other three serotypes.¹¹ Therefore, if vaccine were produced for only one or two serotypes, the other serotypes would increase the risk of more serious illness.¹⁹ Ribavirin has shown significant in vivo activity against RNA viruses; however, it exhibited only very weak



activity against *Flaviviruses*.²¹ A possible strategy in the treatment of dengue is to use chimeric tetravalent vaccines that show high neutralizing antibody against all dengue serotypes.^{15, 11} Studies on the development of tetravalent vaccines are ongoing in Thailand and these should be available in the near future.⁸ In addition, recombinant vaccines against capsid, pre membrane and envelope genes of DEN-1, -2 and -3 inserted into a copy of a DNA infectious clone of DEN-2 are being developed and are currently undergoing clinical trials.²¹ There are some medicinal plants which have shown good pharmacological response over dengue:

Euphorbia hirta (family Euphorbiaceae)

It is a common weed in garden beds, garden paths and wastelands and is found throughout Java, Sunda, Sumatra, Peninsular Malaysia, the Philippines and Vietnam. The water decoction of leaves from *Euphorbia hirta*, locally known as tawas-tawas, is used in the Philippines as a folk medicine to treat dengue fever.²⁵ Internal haemorrhaging will stop and dengue fever will be cured after 24 h. However, the mechanism of action is still unknown and the antiviral properties and its ability to increase blood platelets are currently investigated. The tea obtained from boiled leaves of *E. hirta* is used to cure dengue fever.²⁶

Carica papaya (family Caricaceae)

It is an erect, fast-growing and unbranched tree or shrub indigenous to Central America and cultivated in Mexico and most tropical countries for its edible fruits. *C. papaya* leaf has been used traditionally in the treatment of dengue.²⁷ The leaf has been investigated for its potential against dengue fever. The aqueous extract of leaves of this plant exhibited potential activity against dengue fever by increasing the platelet count, white blood cells and neutrophils in blood samples of a 45-year-old patient bitten by carrier mosquitoes.¹⁵ After 5 days of oral administration of 25 mL aqueous extract of *C. papaya* leaves to the patient twice daily, the platelet count increased from 55 9 103/IL to 168 9 103/IL, WBC from 3.7 9 103/ IL to 7.7103/IL and neutrophils from 46.0 to 78.3 %. Increased platelets could lead to reduced bleeding, thus avoiding progression to the severe illness of DHF.

Tinospora cordifolia (family Menispermaceae)

Its common name is Giloy. It is a creeper herb which maintains the metabolism rate of the human body. It strengthens the immune system and protects against infections. It is a sure shot remedy against fevers of all etiologies. A decoction made from its leaves and stems helps regains strength and vigor. Adding a few leaves of Tulsi (Basil) will enhance its efficacy.

Trigonella foenum (family Fabaceae)

Methi or fenugreek leaves help in controlling pain during Dengue fever. It also helps stabilize blood pressure, which is crucial in Dengue induced fever. Soak fresh leaves in water and consume. It also helps in reducing fever.

Cladosiphon okamuranus (family Chordariaceae)

It is brown seaweed found naturally in Okinawa. A sulfated polysaccharide named fucoidan from *Cladosiphon okamuranus* was found to potentially inhibit DENV-2 infection.²⁸ The active compound is Fucoidan against dengue.

Leucaena leucocephala (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 and *L. leucocephala* show protection against death in 96.5 % of YFV-infected mice.⁹

Tephrosia madrensis (family Fabaceae)

Glabranine is the main active compound for dengue fever treatment.²⁹ The flavonoids isolated from *T. madrensis*, glabranine and 7-O-methyl-glabranine exert strong inhibitory effects on dengue virus replication.

Cryptonemia crenulata (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.¹

Gymnogongrus torulosus (family Phylloporaceae)

It is red seaweed found in Australia and New Zealand. *Gymnogongrus torulosus* was investigated for its in vitro antiviral properties against DENV-2.³⁰

Houttuynia cordata (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-2.³¹

Meristiella gelidium (family Solieriaceae)

It is a marine species found in Atlantic Islands. The antiviral activity of kappa carragenan in *Meristiella gelidium* was evaluated against DENV-2.³²

Boesenbergia rotunda (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-2.³³

Zostera marina (family Zosteraceae)

It is an aquatic plant known as eelgrass and is native to North America and Eurasia. A compound from the temperate marine eelgrass, *Zostera marina* has been identified as possessing antidengue virus activity.¹⁹



Myrtopsis corymbosa (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.³⁴ 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.

Andropogon citratus (family Poaceae)

Its common name is citronella grass. Active constituents of this plant are essential oil and citronella oil. This oil is put in candles and lanterns that can be burned to repel mosquitoes. Its mosquito repellent qualities have been verified by research, including effectiveness in repelling *Aedes aegypti*.³⁵ The nano-emulsions of this plant oil have more integrity and was investigated both in-vivo and in-vitro, have shown prolong activity of mosquito repellent.³⁶

Andrographis paniculata (family Acanthaceae)

Malaysia, it is called (Hempedu Bumi), which has a bitter taste. The maximum nontoxic dose (MNTD) of methanolic extract of *A. paniculata* against Vero E6 cells in vitro was investigated.³⁷ The methanolic extract of *A. paniculata* showed the highest antiviral inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects.

Azadirachta indica (family Meliaceae)

It is native to India and Pakistan and grows throughout tropical and subtropical regions. The in vitro and in vivo inhibitory potential of aqueous extract of *Azadirachta indica* (neem) leaves on the replication of DENV-2 was evaluated.³⁸ Cytotoxicity studies were carried out to determine the maximum nontoxic dose in a virus inhibition assay. The aqueous extract of neem leaves completely inhibited 100–10,000 tissue culture infective dose (TCID) 50 of virus as indicated by the absence of cytopathic effects at its maximum non-toxic concentration of 1.897 mg/ml. An in vivo study on the inhibitory effects on virus of neem leaves aqueous extract in day-old suckling mice was carried out by intracerebral inoculation. It was shown that the aqueous extract inhibited the virus at nontoxic doses in the range of (120–30 mg/ml), as indicated by the absence of 511-bp dengue group specific amplicons upon RT-PCR.

Curcuma longa (family Zingiberaceae)

Its rhizome is used as herbal remedy. It is also used in foods and in cosmetics. Ethyl acetate extract of *Curcuma longa* rhizomes gives three curcuminoids which show activity in inhibiting topoisomerase I and topoisomerase II, which play important role in DNA replication. Out of these three curcuminoides, curcumin III is the most effective. Turmerone obtained from volatile oil of *Curcuma longa* give 100% mosquitocidal activity against *Aedes aegypti*.³⁹

Mimosa scabrella (family Fabaceae)

It is a fastgrowing, 15–20 m high and up to 50 cm diameter tree native to the cool, subtropical plateaus of Southeastern Brazil. Galactomannans (7) extracted from seeds of *Mimosa scabrella* have demonstrated activity against DENV-1 in vitro and in vivo.⁹ In vitro experiments with DENV-1 in C6/36 cell culture assays showed that a concentration of 347 mg/ltr produced a 100-fold decrease in virus titer of DENV-1.

Momordica charantia (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 maximum non toxic dose of the methanolic extract of *Momordica charantia* against Vero E6 cells was investigated in vitro.³⁷ *M. charantia* recorded a maximal dose that was not toxic to cells of 0.20 mg/ml. The methanolic extract of *M. charantia* showed inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects.

Murraya koenigii (family Rutaceae)

The hexane, diethyl ether, dichloromethane and ethyl acetate crude extracts of the whole plant was prepared and adult mosquitoes were allowed to grow over there. During the experiment adults were fed normally. As a result of the experiment there was the inhibition of adult emergence by losing their consciousness. Hence, adults cannot bite and don't show any activity because of the knock-down ability of this plant. Thus, it can be used as Mosquitocidal.⁴⁰

Piper longum (family Piperaceae)

Also known as papal or pippli, it belongs to three species i.e. *Piper longum* L. *P. ribesoides* Wall and *P. sarmentosum* Roxb of this family, as ethanolic extract have been used in research. Efficacy of these species is in following order: *P. longum* > *P. sarmentosum* Roxb > *P. ribesoides* Wall. This study conclude that Pepper plant possess activity against *Aedes aegypti*.⁴¹

Psidium guajava (family Myrtaceae)

It is an evergreen shrub or small tree indigenous to Mexico, the Caribbean and Central and South America. It is cultivated widely in tropical and subtropical regions around the world. *Psidium guajava* leaf extract has been tested in vitro and showed to inhibit the growth of dengue virus.⁴² 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.⁴³ *Psidium guajava* ripe fruit or juice has healing properties in cases of dengue fever by improving the declining levels of platelets.²⁷

Quercus lusitanica (family Fagaceae)

Also known as mazu phal is a small tree or a shrub. It contains gallic acid and ellagic acid. The whole plant is used as drug. *Quercus lusitanica*, also known as *Quercus*



infectoria, Test was performed on methanol crude and fractionated extracts of *Quercus lusitanica*. The cytotoxicity of these plant extracts was evaluated by determining the maximum non-toxic dose (MNTD) on C6/36 cells. Antiviral activity was estimated by the reduction of the cytopathic effect of DENV-2 in C6/36 cells and by the reduction of virus titre. The crude methanol extracts of *Q. lusitanica* at the concentration of 180µg/ml was found to completely inhibit the dengue virus infection. The extract of the plant inhibits the replication of virus.⁴⁴

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