Antiviral and Therapeutic Uses of Medicinal Plants and Their Derivatives against Dengue Viruses

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ABSTRACT
Dengue fever (DF) is occurring worldwide, and it has emerged as a global health threat due to high mortality and morbidity, specifically in tropical and subtropical regions. The World Health Organization has deep concerned to this disease being a large section of population affected. Around 2.5 billion peoples are at risk of dengue virus (DENV). Over 100 countries including Europe and the United states are affected due to DENV. DF is the most widespread viral disease. There are four different serotypes (DENV-1 to DENV-4) of DENV but now discovered DENV-5, and DENV-6, are reported worldwide, but now DENV-5 is also identified. The genome of DENV contains one open reading frame that encodes three structural components, i.e., capsid, premembrane, and glycoprotein envelope and seven different nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Various studies reported that DENV-1 and DENV-3 infections are more serious as compared to DENV-2 and DENV-4, are reported worldwide, but now DENV-5 serotype is also identified. The genome of DENV contains one open reading frame that encodes three structural components, i.e., capsid, premembrane, and glycoprotein envelope and seven different nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). These different serotypes of DENV disease are DF, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). 95%, cases reported as normal DF whereas 5% of the cases were noted for severe DHF and DSS, DF starts in the wet and rainy weather. The water gathered at coolers, ponds, playground, and open places to provide favorable condition for A. aegypti mosquito breeding. Sometimes, DF is also called “break-bone” fever due to its high body pain and muscle ache. Dengue is an antibody-dependent enhancement (ADE), another big problem. When one dengue serotype infected a person, it gives serious effect during the secondary infection of DENVs with other heterologous strains and may cause DHF/DSS. Currently, there are no effective approved vaccines available against the DENV due to its ADE. Worldwide, about 100 million cases are found of DF and 500,000 cases of DHF and approximately 18,000 deaths reported every year in according to the World Health Organization (WHO) data.

SYMPTOMS OF DENGUE
DF starts with a high-grade fever. The body temperature records between 39°C and 40°C. Symptoms are usually appearing 4–6 days after infection and last for up to 10 days. The symptoms of dengue in patients are severe joint and muscle pain, eye pain, body rash, frontal headache, nausea, vomiting, muscle aches and feel weakness, cough, sore throat, nasal stuffiness, and retro-orbital pain [Figure 1]. Clinically, the secondary symptom is very severe in patients characterized by thrombocytopenia, bleeding inpatients due to DHF, and blood plasma leakage in DSS; sometimes, the patient becomes unconscious in that situation. Every serotype of dengue causes different ranges of infection from mild to life-threatening. Majority of dengue cases are self-limiting, but few cases are dangerous in the form of DHF and DSS.

HISTORICAL ASPECTS OF DENGUE
First-time two scientists Hotta and Kimura were isolated DENV in the Japan during the period of the Second World War. They inject serum sample from dengue-suspected US soldiers into the sucking mouse at Kolkata in 1944 and isolated the virus. In India, the first outbreak of dengue documented in Madras (Chennai) in 1780 and Calcutta in 1828.
PLANT SPECIES USED TO TREAT DENGUE

Andrographis paniculata

It is commonly known as “kalmegh.” It is a member of the family Acanthaceae. This plant is found in India and Sri Lanka and widely growing in Southeast Asia. The maximum nontoxic dose (MNTD) of methanol extract was 0.050 mg/ml and about 75% of inhibition activity against the virus in Vero E6 cell lines. It inhibits the DENV-1 serotype. Andrographis paniculata mainly includes secondary metabolites such as diterpenoids, diterpene, flavonoids, flavonoid glycosides, and lactones. Andrographolide[52] is the chief secondary compound derived from A. paniculata which has antiviral activity.[53] However, the MNTD value reported using HepG2 cells was 0.020 mg/ml for A. paniculata. These values were much lower than those reported in Vero E6 cells. It indicates that A. paniculata extracts are more cytotoxic toward HepG2 cells as compared to Vero E6 cells.[53]

Azadirachta indica

It is commonly known as neem. It is a member of family Meliaceae. It is found in India and Pakistan and grows all over the temperate regions. The aqueous extract prepared from neem leaves powder showed the anti-dengue activity against DENV-2 serotype in vitro and in vivo. The aqueous extract prepared from leaves of A. indica with MNTD of 1.897 mg mL⁻¹ demonstrated 100% inhibition of DENV-2. The inhibitory
experiment on dengue has been done on intracerebral injection in 1-day-old suckling mice.[34]

**Andropogon citratus**

It is commonly known as citronella grass. It is a member of family Poaceae. Citronella oil has isolated from these plants, and the oil is put on candle, lanterns drop by drop, and burned the candle for repelling *Aedes* mosquitoes. The nanoemulsion (oil in water) of this plant also used to repel the *A. aegypti* mosquitoes.[35] This film increased the vaporization of the oil and helps prolong mosquito repellent.[36]

**Boesenbergia rotunda**

It is commonly known as Chinese ginger. It is a member of the family Zingiberaceae. The compounds 4-hydroxypanduratin A (1) and panduratin A (2) were isolated from these plants. These chemicals exhibited anti-dengue activity against DENV-2 NS3 protease enzyme in vitro study.

**Cymbopogon citratus**

It is commonly known as lemon grass. It is a member of the family Poaceae. It is a tropical plant found in Southeast Asia. The methanol extract effectively inhibits the DENV-1 serotype very slightly at a concentration of 0.001 mg mL⁻¹ with TCID₅₀ at 0.075 mg mL⁻¹ in Vero E6 cells. *Cymbopogon citratus* has many elements such as luteolin, apigenin, and homoorintine flavonoids.[14]

**Carica papaya**

It is commonly known as paw (papaya). It is a member of the family Caricaceae. It is cultivated in Central America and grows in Mexico. The aqueous leaves extract of *Carica papaya* showed inhibitory activity against DF. The leaves juice of *C. papaya* increased the blood platelets, white blood cells, or neutrophils and repairs the liver to help DF patients.[45,46,48] *C. papaya* has two active compounds chymopapain and papain.[39] Some secondary compounds screened out into *C. papaya* plant were alkaloids, phenolics, flavonoids, and amino acids.[40–43]

**Cladosiphon okamuranus**

It is commonly known as bladderwrack, originated in Okinawa, Japan. It is a member of the family Chordariaceae. A sulfated polysaccharide fucoidan[37] isolated from this plant showed the activity against DENV-2 serotype. It is able to reduce 20% infection at concentration of 10 μg mL⁻¹.

**Castanospermum australe**

It is commonly known as black bean or Moreton Bay and is a member of the family Fabaceae. Castanospermine[48] alkaloid isolated from *Castanospermum australe*, showed good inhibitory activity against DENV by preventing the attachment of terminal glucose residue on N-linked glycans.

**Chondrus crispus**

It is also known as carrageen moss, red algae belong to family Gigartinaeae. It is found in rocky shores and coast of Europe. The active polysaccharides lambda carrageenans[39] were isolated from these plants. It has been reported that carrageen and another sulfated polysaccharides inhibit the DENV-2 virus entry.

**Euphorbia hirta**

It is commonly known as dudhi. It is a member of the family Euphorbiaceae. It is found in India, Philippines, and Australia.[49] Now, *Euphorbia hirta* is utilized against mosquito repellents, and 272.36 ppm of petroleum ether extract prepared from hirta is effective against mosquitoes.[50] Many flavonoids are found into the plant extract such as euphorbianin, leucocyanidin, camphol, quercitrin, and quercitol.[71,72] The tea prepared from boiled leaves showed the anti-viral activity and has capacity to increase blood platelets of dengue patients.

**Flagellaria indica**

It is commonly known as false rattan. It is a member of family Flagellariaceae. It is found in India, Southeast Asia, and Australia. The ethanol extract of *Flagellaria indica* (12.5 μg mL⁻¹) showed the anti-dengue activity with the inhibition of 45.52% in DENV-2 serotype. The cytotoxicity concentration (CC₅₀) of ethanol extract of *F. indica* was 312 μg mL⁻¹ being revealed by 3-(4, 5-dimethyl thiazole-2-yl)-2, 5-diphenyl tetrazolium (MTT) assay.[4]

**Gymnogongrus griffithsiae**

It is a member of family Phyllophoraceae, found all over the Europe, Atlantic Island, Africa, North America, Caribbean Islands, Southern Asia, Australia, and New Zealand. A kappa carrageenan[50] secondary compound extracted from this plant reported for anti-dengue activity against DENV-2 serotype with the IC₅₀ value of 0.9 μg mL⁻¹ in Vero cell lines. It also showed anti-dengue activity against DENV-3 and DENV-4, but antiviral effect was less in comparison to DENV-2, and it is completely inactive against DENV-1.

**Gymnogongrus torulosus**

It is red seaweed originated in New Zealand and Australia which belongs to family Phyllophoraceae. The secondary compound galactan[23] isolated from *Gymnogongrus torulosus* showed the inhibition against DENV-2 serotype with IC₅₀ values of 0.19–1.7 μg mL⁻¹ in Vero cells.

**Gastrodia elata**

It is commonly known as Rhizoma Gastrodiae, Ming Tian Ma. It is a member of family Orchidaceae. It is found in China, India, Nepal, Bhutan, and Japan. D-glucans and sulfated derivatives have been isolated from this
plant. They exhibit anti-dengue activity against DENV-2 serotype with half maximum effective concentration value of 0.68 µg mL⁻¹. These compounds interfere at early stages of DENV cycle with virus adsorption.

**Houttuynia cordata Thunb**

It is commonly known as heart leaved or fish leaf. It is a member of family *Saururaceae*. It is native on Japan, Korea, and Southeast Asia. The aqueous extracts of the plant showed the anti-dengue activity against DENV-2 serotype. The isolated active compound was hyperoside. The ethanol extract also showed the anti-DENV-2 activity with 35.99% inhibition activity of the virus at a concentration 1.56 µg mL⁻¹ found in Vero cell lines. The secondary metabolites reported from this plant were alkaloids, flavonoids, many fatty acids, phenols, sterol, and essential oils.

**Hippophae rhamnoides**

It is commonly known as sea buckthorn which belongs to family *Elaeagnaceae*. It is found in all over Europe, Britain, Himalayas, from many parts of Norway, east and south to Spain, as well as Asia to Japan. An anti-dengue activity has been reported against DENV-2 of Hippophae rhamnoides leaves extract.[4]

**Kaempferia parviflora**

It is commonly called krachai dam. It is a member of the family *Zingiberaceae*. The chemical compounds such as borneol and flavonoids[5] are present in this plant. The leaves and stem extracts of this plant showed the anti-viral activity against DENV-2 serotype.

**Leucaena leucocephala**

It is commonly known as white lead trees. It is a member of the family *Fabaceae*. It is found all over South Mexico, many parts of America and West Indies from the Bahamas and Cuba to Tobago. A secondary metabolite galactomannans[6] isolated from this plant showed the anti-dengue activity against DENV-1 serotype and yellow fever virus (YFV) in C6/36 cell lines in vitro and in vivo. It inhibits the 100-fold decrease in DENV-1 virus titer at concentration of 37 mg L⁻¹.[7]

**Lippia alba**

It is commonly known as bushy mat grass, bushy lippia. It is a member of the family *Verbenaceae*. It is found in Central and South America, Mexico, and Southern Texas. *Lippia alba* and *Lippia citridora* are flowering plants and the oil is extracted from these plants. The oil of *L. alba* and *L. citridora* showed the inhibitory activity against DENV. *L. alba* oil showed 50% inhibition against DENV-2 serotype at a concentration in between 0.4 and 32.6 µg mL⁻¹ and *L. citridora* oil showed the virucidal activity against DENV-1, 2, and 3 serotype and IC₅₀ values were in between 1.9 and 33.7 µg mL⁻¹.[8]

**Mimosa scabrella**

It is commonly known as bracatingais. It is a member of the family *Fabaceae*. The secondary compound galactomannans[9] were isolated from Mimosa scabrella seed. It inhibited the YFV and DENV-1 both in vitro and in vivo.

**Momordica charantia**

It is commonly known as bitter gourd (karela). It is a member of family *Cucurbitaceae*. This plant is found in tropical and subtropical regions, which is extremely bitter to taste. The MNTD occurs in methanolic extract was 0.20 mg/ml in Vero cell lines. It showed anti-dengue activity against DENV-1 around 50% inhibition.[10] It contained flavonoids such as luteolin, kaempferol, and quercetin.[11]

**Merisitella gelidium**

It is a member of the family *Solieriaceae*. This plant is found in Atlantic Islands. The secondary compound kappa carrageenan[12] was isolated from this plant. It demonstrated strong antiviral activity against DENV-2 serotype with a range of IC₅₀ of 0.14-1.6 µg mL⁻¹.

**Myrtopsis corymbosa**

It is a member of family *Rutaceae*. The compound isolated from this plants bark extract was myrsellin, ramosin, and myrsellin.[13] It showed strong 87% inhibitory activity against DENV polymerase. Some alkaloids were isolated from the leaves of Myrtopsis corymbosa, i.e., skimmianine, γ-fagarin, and haplopin, but these alkaloids were little effective against DENV-NS5.

**Ocimum sanctum**

It is commonly known as holy basil (tulsi). It is a member of family *Labiateae*. It is found in Asia and the Americas. The extract of Ocimum sanctum contained many flavonoids such as orientin, vicenin, and luteolin. The tea prepared from the leaves of O. sanctum is also used for dengue cure.[14] The MNTD of O. sanctum extract was 0.10 mg mL⁻¹ with cytotoxic values of 1.5 mg mL⁻¹. It inhibits the DENV-1 serotype in cell lines.[15] However, the MNTD value obtained from HepG2 cells was 0.023 mg mL⁻¹ which is much lower than those reported in Vero E6 cells. This shows that the extracts are more cytotoxic toward HepG2 cells as compared to Vero cell.[16]

**Phyllanthus urinaria**

It is commonly known as Bhumiamla. It is a member of the family *Phyllanthaceae*. It is found in South India, South America, and China. The methanol and aqueous extracts of Phyllanthus amarus, Phyllanthus niruri, Phyllanthus urinaria, and Phyllanthus watsonii showed the strong anti-dengue activity against DENV-2. The nontoxic dose of methanol extract was reported 15.63 µg/mL and for aqueous extract 250.0 µg mL⁻¹. Phyllanthus urinaria exhibited 90% inhibition against DENV-2 serotype. Many compounds have been isolated from this plant such as gallic acid, geraniin, syringing, and corilagin[17] via high-performance liquid chromatography and liquid chromatography mass spectrometry/mass spectrometry analysis.

**Piper retrofractum**

It is commonly known as dei-phei in Cambodia. It is a member of *Piperaceae*. It is found in Southeast Asia and cultured in Indonesia and Thailand. The virucidal activity against DENV-2 was investigated from ethanol and dichloromethane extracts of *Piper retrofractum*. The ethanol extract of *P. retrofractum* showed antiviral activity. It inhibited 84.93% virus at concentration of 100 µg mL⁻¹ in Vero cells by the MTT method.[18] The earlier study revealed that *P. retrofractum* aqueous extract also showed the highest activity against mosquito larvae.[19]

**Psidium guajava**

It is commonly called guava. It is a member of the family *Myrtaceae*. It is found in Mexico and Central and South America. *P. guajava* contains a number of active ingredients such as terpenoids, flavonoids, and tannins. The leaf extract of this plant has been tested, and it showed the in vitro anti-dengue activity.[20] The guava leaves boiled in water to use to treat bleeding problem due to DHF. The boiled leaves extract increased the platelets to 100,000/mm³ within a time of around 16 h.[21] The mature fruit or juice of guava has also been given to the DF patients to increase the level of platelets.
Table 1: List of medicinal plants and their bioactive compounds reported for anti-dengue activity

<table>
<thead>
<tr>
<th>Plants name</th>
<th>Family</th>
<th>Antiviral compounds</th>
<th>Compounds structure</th>
<th>Dengue type</th>
<th>References</th>
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<td>Andrographis paniculata</td>
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<td>[55,56]</td>
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<th>Compounds structure</th>
<th>Dengue type</th>
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Quercus lusitanica

It is commonly known mazuphal. It is a member of Fagaceae family. The Quercus lusitanica contained gallic acid and ellagic acid which are the chemical compounds. Methanolic seed extract of Q. lusitanica inactivates the virus with (10–1000 = fold) the TCID<sub>50</sub> and MNTD of 0.25 mg mL<sup>−1</sup> without any cytopathic effects. Q. lusitanica exhibited 100% inhibition against DENV-2 virus (10 TCID<sub>50</sub>) with a dose of 0.032 mg mL<sup>−1</sup> in C6/36 cell- lines.\(^6\)

Rhizophora apiculata

It is commonly known as true mangroves. It is a member of the family Rhizophoraceae. It is found in Australia Guam, India, Malaysia, Singapore, and Sri Lanka. The ethanolic extract showed the anti-dengue activity against DENV-2 in Vero cell lines.\(^5\) Rhizophora apiculata showed 41.5% inhibition against the DENV activity at concentration of 100 µg mL<sup>−1</sup>.

Tephrosia madresis

It is commonly known as legume, pea, or bean. It is member of family Fabaceae. Some flavonoids such as glabranine\(^1\) and 7-O-methylglabranine were isolated from this plant. The extracted compounds from this plant strongly inhibit the replication of DENV in Rhesus monkey kidney epithelial cells (LLC-MK2). cells.

Uncaria tomentosa

It is member of Rutaceae family. It originates in the jungle of South and Central America. It also called as cat’s claw because of its claw-like thorns. The hydro-alcoholic extract of this plant showed anti-viral activity on human monocyte which decreases the activity of dengue antigen at concentration of 1–10 µg mL<sup>−1</sup>. Many alkaloids derived from root and bark play a major role against DENV-2 on human monocytes.\(^3\)

Zostera marina

It is commonly known as sea-wrack and eelgrass. It is a member of family Zosteraceae. It is found in North pacific, North Atlantic, North America, and Canada. A secondary metabolite known as P-sulfooxy cinnamic acid\(^4\) has been isolated from this plant. This plant compound showed the anti-dengue activity against DENV-2 serotype in LLC-MK2 cell lines.\(^1\) Zostera marina showed inhibitory effect against DENV with IC<sub>50</sub> values of 24 µM against DENV-1, 46 µM against DENV-2, 14 and 47 µM against DENV-3 and DENV-4 serotype, respectively.

ANTI-DENGUE BIOACTIVE COMPOUNDS STRUCTURE

The extracts prepared from the plants have tested to identify inhibition activity against DENV are listed in Table 1 with the help of Chemdraw software (CambridgeSoft Corporation, USA). There are a number of chemical compounds isolated from different medicinal plants parts. They possessed anti-dengue activity hence can be used for the treatment of dengue after validation. There is need to identified species specific anti-dengue-active components which can contribute to control the dengue.

CONCLUSION

Dengue is a very serious disease occurring worldwide. Therefore, regular surveillance is needed. There are no antiviral agents available. Some plants have reported to its anti-dengue activity, but there is no wide research carried out on these plants. Hence, we required to develop new anti-dengue product through medicinal plants. This review has covered only 35 medicinal plants and 16 bioactive compounds isolated from the plants that could be used in DENV treatment. There is need to isolate and identify some compounds from the medicinal plants which are beneficial for DENV treatments. The natural compounds are considered to be safe, nontoxic than synthetic agents.

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Conflicts of interest

There are no conflicts of interest.

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