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REVIEW ARTICLE

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 serotype also. DENV is transmitted from person to person by the bite of infected female *Aedes aegypti* and *Aedes albopictus* mosquito. Unfortunately, there are no effective approved anti-dengue agents and vaccine to treat viral infection. Researchers have paid attention toward medicinal plants in search of natural compounds which can be used as anti-dengue. Therefore, our focus is on the extract of medicinal plants which may be more effective, safer, and less toxic than synthetic drugs. In the present review paper, the brief description of 35 medicinal plants which possess anti-dengue activity has been documented along with their active components. This study will be helpful to establish that natural products may have good potential source of new anti-dengue compounds.

Key words: *Aedes aegypti,* dengue fever, derivatives, medicinal plants, mosquito, serotype

INTRODUCTION

Dengue fever (DF) is concern all over the world. Dengue virus (DENV) is single-stranded positive-sense RNA virus, a member of family *Flaviviridae* and genus *Flavivirus*. It is transmitted by the bite of infected female *Aedes aegypti* and *Aedes albopictus* mosquito. Genome of DENV is approximately 11 kb in length.[1-3] Four different serotypes of DENV, viz., DENV-1, DENV-2, DENV-3, and DENV-4, are reported worldwide, but now DENV-5 serotype is also identified.[4] 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).[5-11] Various studies reported that DENV-1 and DENV-3 infections are more serious as compared to DENV-2 and DENV-4.[12-14] Three different types 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.[15,16] 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.[17] 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.[18,19] 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.[20,21]

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.[22] 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.[4,10,11,13,23,24]

HISTORICAL ASPECTS OF DENGUE

First-time two scientists Hotta and Kimura[25,26] 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 suckling mouse at Kolkata in1944 and isolated the virus.[27-29] In India, the first outbreak of dengue documented in Madras (Chennai) in 1780 and Calcutta in

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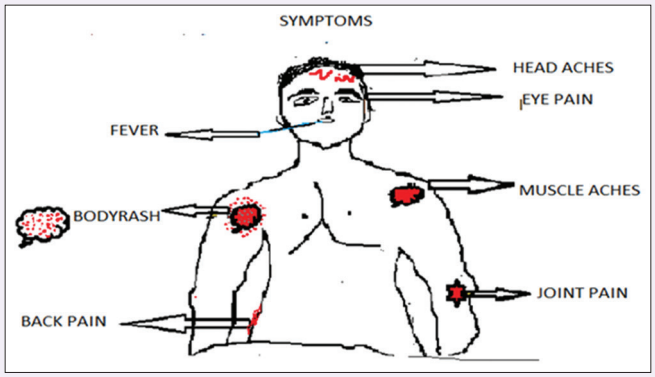


Figure 1: Symptoms of dengue

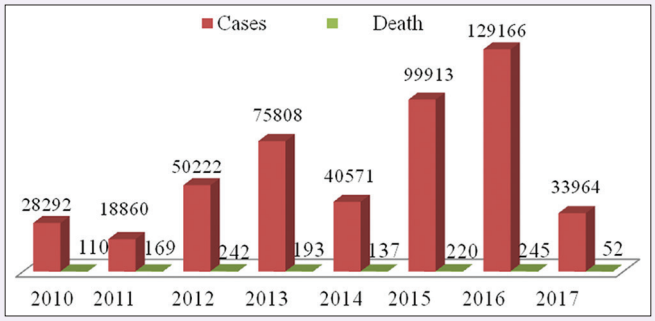


Figure 2: Dengue cases and deaths in the country from 2010 to 2017 (National Vector Borne Disease Control Programme)

1963–1964.[30] The first outbreak of DHF/DF occurred in 1950–1954 in Philippines and Thailand.[27,31] In Delhi, the first outbreak of DHF/DF has been reported in 1996 and DENV-2 serotype was associated with this outbreak.[32,33] National capital of India, New Delhi face many dengue outbreak time to time such as 1967, 1970, 1982, 1988, 1996, 2003, 2007, and 2008, and it occurred annually after this. Now, all the four dengue serotypes are prevailing in and around Delhi.[24,26,34-38]

OCCURRENCE OF DENGUE FEVER IN INDIA

There is no continuous surveillance of dengue or any other viruses in India. Laboratory facility is also limited; therefore, clinical symptoms and rapid detection kits are the main criteria of diagnosis. The Ministry of Health and Family Welfare, Government of India, New Delhi, under its National Vector Borne Disease Control Programme collected the data from all over India as shown in Figure 2.[39]

DENGUE TRANSMISSION

The female *Aedes* mosquitoes (*A. aegypti* and *Aedes albopectus*) are the main vectors that transmit the virus that causes DENV fever (DF) among the humans.[1,40,41] The life cycle of dengue involves two host humans and mosquito. Mosquito acts as a carrier. The virus is transmitted to human by biting of infected mosquito. Once transmitted, the human become the main carriers and multiplier of virus, serving as a source of the virus for uninfected mosquitoes. DENVs may damage infected person's blood vessels and lymph nodes. The severe clinical symptoms of dengue are bleeding from gums, nose, and skin. Sometimes, the patient died if proper action is not provided due to DF, DHF, and DSS.[42,43]

DENGUE TREATMENT AND MANAGEMENT

There is no specific treatment for dengue; only symptomatic and supportive cares are advised by doctors. Appropriate dose of paracetamol is recommended for relieving the DF, and ibuprofen, aspirin, and naproxen (Aleve) should be avoided. Fluids replacement are very effective when patients suffering with dehydration. Fluid balance, electrolytes, nursing care, and blood clotting parameters should be taken care of a dengue patient. Patients should be hospitalized as per expand of symptoms.[42,44,45]

Nowadays, it has been noted that some natural home remedies such as *Papaya* leaves juice, Giloy, kiwi, and other natural sources have been taken by patients on the recommendation of Ayurvedic practitioner to increase the blood platelet counts.[46] At present, no vaccines and no effective treatment against dengue are available. Therefore, our focus is on the extract of medicinal plants which may be more effective, safer, and less toxic than synthetic drugs. It is the time to scientifically isolate or developed natural anti-dengue remedy from the various medicinal plants.

PLANT SPECIES USED TO TREAT DENGUE

Historically, medicinal plants are always important part of traditional remedy and treatment sources for various diseases in India as well as worldwide. The medicinal plants are famous to their bioactive compounds, which are the rich source of pharmaceuticals, some of which contains good antiviral activity.[47,48] The WHO and Ayurveda suggested that the use of medicinal plant extracts and their derivatives is helpful to fight against dengue disease.[49] The WHO considers that ayurvedic medicines which are isolated from medicinal plants are generally more secure, nontoxic, comparatively less harmful, and cheaper than synthetic drugs[14] Now, the researchers have turned their attention toward nature and tried to identify the compounds that can be used as antiviral agents against dengue. Many medicinal plants and their secondary metabolites already used widely to treat a variety of diseases such as malaria and dengue in many parts of the world. It is notable that the studies have shown that extract from different parts of medicinal plants provides better antiviral results as compared to their synthetic analogues.

STUDIES ON MEDICINAL PLANTS USED AS ANTI-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.[14] *Andrographis paniculata* mainly includes secondary metabolites such as diterpenoids, diterpene, flavonoids, flavonoid glycosides, and lactones.[50] Andrographolide[51] is the chief secondary compound derived from *A. paniculata* which has antiviral activity.[52] However, the MNTD value reported using HepG2 cells was 0.020 mg/ml for *A. paniculata*. These values that 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.[54]

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.[55] This film increased the vaporization of the oil and helps prolong mosquito repellent.[56]

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)[57] 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 lemongrass. 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 $TCID_{50}$ at 0.075 mg mL^{-1} in Vero E6 cells. *Cymbopogon citratus* has many elements such as luteolin, apigenin, and homoorintine flavonoides.[14]

Carica papaya

It is commonly known as paw 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.[45,46,58] *C. papaya* has two active compounds chymopapain and papain.[59] Some secondary compounds screened out into *C. papaya* plant were alkaloids, phenolics, flavonoids, and amino acids.[60-63]

Cladogynos orientalis

It is commonly known as cleaner-clingfish. It is a member of the family *Euphorbiaceae*. This plant is cultivated or naturally found in many parts of Southern and Eastern Asia. The dichloromethane and ethanol extracts of *C. orientalis* displayed anti-dengue activity against DENV-2 serotype in Vero cells. Ethanol plant extract at concentration of 12.5 μg mL^{-1} displayed 34.85% inhibition of DENV-2 serotype.[5,43]

Curcuma longa

It is commonly known as turmeric (haldi). It is a member of *Zingiberaceae* family. The secondary active compound curcumin isolated from this plants which constitutes an average 3.14% of turmeric powdered which slightly bitter and its smell mustardy.[64] Another secondary metabolite turmerone[65] isolated from the oil of *Curcuma longa* showed the 100% activity against *A. aegypti* at 10 mg mL^{-1}.

Cryptonemia crenulata

It is commonly known as Red ribbon macroalgae. It is a member of the family *Halymeniaceae*. It is found all over the Atlantic Islands, North America, Western Atlantic, Africa, Indian Ocean Islands, Southern and Eastern parts of Asia. A sulfated polysaccharide galactan[66] compound extracted from this plant showed anti-dengue activity against DENV-2 strain in Vero cell with half maximum inhibitory concentration (IC_{50}) value of 1.0 μg mL^{-1}.

Cladosiphon okamuranus

It is commonly known as bladderwrack, originated in Okinawa, Japan. It is a member of the family *Chordariaceae*. A sulfated polysaccharide fucoidan[67] 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,[68] 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 *Gigartinaceae*. It is found in rocky shores and coast of Europe. The active polysaccharides lambda carrageenans[9] 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.[69] Now, *Euphorbia hirta* is utilized against mosquito repellents, and 272.36 ppm of petroleum ether extract prepared from hirta is effective against mosquitoes.[70] Many flavonoids are found into the plant extract such as euphorbianin, leucocyanidol, 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 (CC_{50}) 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.[5]

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[66] secondary compound extracted from this plant reported for anti-dengue activity against DENV-2 serotype with the IC_{50} 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[73] isolated from *Gymnogongrus torulosus* showed the inhibition against DENV-2 serotype with IC_{50} 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}.[74] 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.[52] 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 reported against DENV-2 of *Hippophae rhamnoides* leaves extracts.[16]

Kaempferia parviflora

It is commonly called krachai dam. It is a member of the family *Zingiberaceae*. The chemical compounds such as borneol and flavonoids[75] 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[23] isolated of 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}.[76]

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 citriodora* are flowering plants and the oil is extracted from these plants. The oil of *L. alba* and *L. citriodora* 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. citriodora* oil showed the virucidal activity against DENV-1, 2, and 3 serotype and IC_{50} values were in between 1.9 and 33.7 μg mL^{-1}.[77]

Mimosa scabrella

It is commonly known as bracatingais. It is a member of the family *Fabaceae*. The secondary compound galactomannans[23] 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.[14] It contained flavonoids such as luteolin, kaempferol, and quercetin.[78]

Meristiella gelidium

It is a member of the family *Solieriaceae*. This plant is found in Atlantic Islands. The secondary compound kappa carrageenan[79] was isolated from this plant. It demonstrated strong antiviral activity against DENV-2 serotype with a range of IC_{50} 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 myrsellinol, ramosin, and myrsellin.[80] 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 *Labiatae*. 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.[81] 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-1serotype in cell lines.[14] 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.[53]

Phyllanthus urinaria

It is commonly known as Bhumi amla. 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[82] via high-performance liquid chromatography and liquid chromatography mass spectrometry/mass spectrometry analysis.

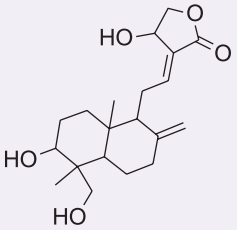
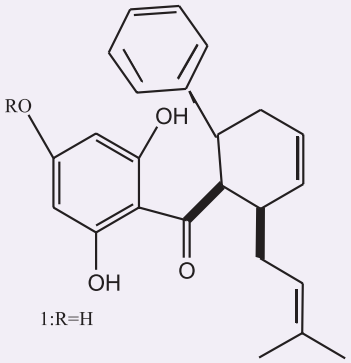
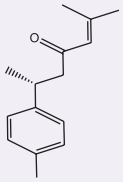
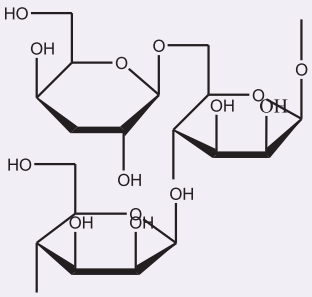
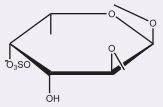
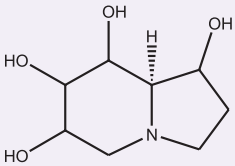
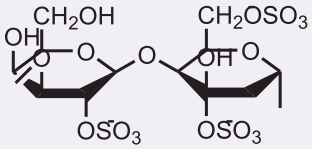
Piper retrofractum

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.[5] The earlier study revealed that *P. retrofractum* aqueous extract also showed the highest activity against mosquito larvae.[83]

Psidium guajava

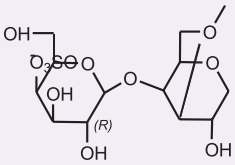
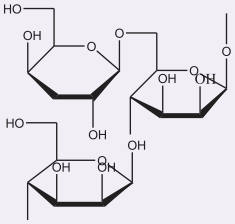
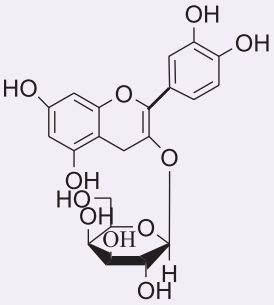
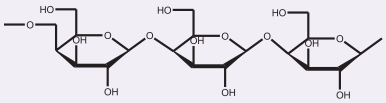
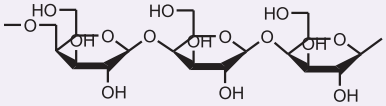
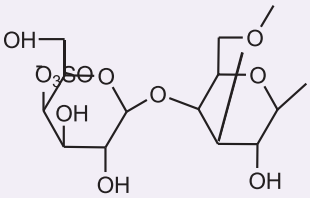
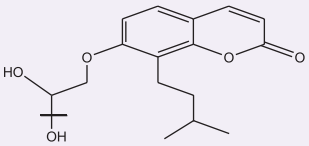
It is commonly called guava. It is a member of the family *Myrtaceae*.[84] It is found in Mexico and Central and South America. *P. guajava* contains a number of active ingredients such as terpenoids, flavonoids, and tannins. The leaf extract of this plant has been tested, and it showed the *in vitro* anti-dengue activity.[85] 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/mm^3 within a time of around 16 h.[86] 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

Plants name	Family	Antiviral compounds	Compounds structure	Dengue type	References
Andrographis paniculata	*Acanthaceae*	Andrographolide		DENV-1	[50,51]
Azadirachta indica	*Meliaceae*	-	-	DENV-2	[54]
Andropogon citratus	*Poaceae*	-	-	-	[55,56]
Boesenbergia rotunda	*Zingiberaceae*	4hydroxypanduratin A, panduratin A		DENV-2	[57]
Carica papaya	*Caricaceae*	-	-		[59]
Cladogynos orientalis	*Euphorbiaceae*	-	-	DENV-2	[5,43]
Curcuma longa	*Zingiberaceae*	Turmerone		DV	[64,65]
Cryptonemia crenulata	*Halymeniaceae*	Galactan		DENV-2	[66]
Cladosiphon okamuranus	*Chordariales*	Fucoidan		DENV-2	[67]
Castanospermum austral	*Fabaceae*	Castanospermine		DV	[68]
Chondrus crispus	*Gigartinaceae*	Lambda carrageenans		DENV-2	[9]
Cymbopogon citratus	*Poaceae*	-	-	DENV-1	[14]
Euphorbia hirta	*Euphorbiaceae*	-	-	DV	[71,72]
Flagellaria indica	*Flagellaria*	-	-	DENV-2	[5]

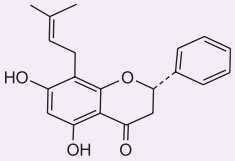
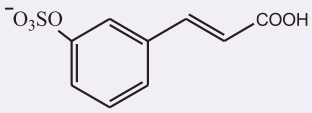
Contd...

Table 1: Contd...

Plants name	Family	Antiviral compounds	Compounds structure	Dengue type	References
Gymnogongrus griffithsiae	*Phyllophoraceae*	Kappa carrageenan		DENV-2	[66]
Gymnogongrus torulosus	*Phyllophoraceae*	Galactan		DENV-2	[73]
Gastrodia elata	*Orchidaceae*	-	-	DENV-2	[74]
Houttuynia cordata	*Saururaceae*	Hyperoside		DENV-2	[52]
Hippophae rhamnoides	*Elaeagnaceae*	-	-	DENV-2	[16]
Kaempferia parviflora	*Zingiberaceae* *Elaeagnaceae*	-	-	DENV-2	[75]
Leucaena leucocephala	*Fabaceae*	Galactomanan		DENV-1	[23]
Lippia alba	*Verbenaceae*	-	-	DENV-2	[77]
Mimosa scabrella	*Fabaceae*	Galactomanan		DENV-1	[23]
Momordica charantia	*Cucurbitaceae*	-	-	DENV-1	[78]
Meristiella gelidium	*Solieriaceae*	Kappa carrageenan		DENV-2	[79]
Myrtopsis corymbosa	*Rutaceae*	Myrsellinol		DENV-NS5	[80]
Ocimum sanctum	*Lamiaceae*	-	-	DENV-1	[14,53,81]
Phyllanthus urinaria	*Phyllanthaceae*	-	-	DENV-2	[82]
Piper retrofractum	*Piperaceae*	-	-	DENV-2	[83]
Psidium guajava	*Myrtaceae*	-	-	DENV-2	[85]
Quercus lusitanica	*Fagaceae*	-	-	DENV-2	[87]
Rhizophora apiculata	*Rhizophoraceae*	-	-	DENV-2	[5]

Contd...

Table 1: Contd...

Plants name	Family	Antiviral compounds	Compounds structure	Dengue type	References
Tephrosia madrensis, *T. viridiflora*, *T. crassifolia*	*Rutaceae*	Glabranine, 7-0-methyl-glabranine		DV replication	[15]
Uncaria tomentosa	*Fabaceae*	-	-	DENV-2	[88]
Zostera marina	*Zosteraceae*	P-sulfoxycinnamic acid, zosteric acid		DENV-2	[89]

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 $TCID_{50}$ and MNTD of 0.25 mg mL^{-1} without any cytopathic effects. *Q. lusitanica* exhibited 100% inhibition against DENV-2 virus (10 $TCID_{50}$) with a dose of 0.032 mg mL^{-1} in C6/36 cell- lines.[87]

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^{-1}.

Tephrosia madrensis

It is commonly known as legume, pea, or bean. It is member of family *Fabaceae*. Some flavonoids such as glabranine[15] 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^{-1}. Many alkaloids derived from root and bark play a major role against DENV-2 on human monocytes.[88]

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-sulfoxycinnamic acid[89] has been isolated from this plant. This plant compound showed the anti-dengue activity against DENV-2 serotype in LLC-MK2 cells lines which contain IC_{50} value of just about 2.3 mm. The another derivatives CF 238 also showed inhibitory effect against with IC_{50} 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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