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Medicinal plants used in treatment and management of dengue: An overview

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Abstract
Dengue virus (DENV) causes a clinical infection called dengue hemorrhagic fever (DHF). Millions of people are impacted by this condition. However, there is currently no specific medication available to stop it. Despite having recently received approval for use in preventing illness, a vaccination against some dengue virus (DENV) serotypes was proven to be ineffective. Some preventative methods utilizing plant extracts demonstrated some encouraging ovicidal action against *Aedes aegypti*. Some antiviral medications are being tested in clinical settings to treat dengue fever, but the results have not yet been reported or validated. Numerous researches have revealed that the possibility of using compounds with plant origins could be excellent agents for the creation of secure and effective treatments for certain illnesses. This review provides scientifically validated knowledge on plants used in the treatment and management of dengue fever along with phytoconstituents responsible for the activity and type of solvent used to extract it.

Keywords: dengue, flavivirus, plant extracts, platelet count, treatment, management

Introduction

The mosquitoes *Aedes aegypti* and *Aedes albopictus* are the arthropods that transmit the flavivirus that causes dengue fever. Dengue virus (DENV) exists in different four serotype (DENV-1 to DENV-4) [1].

The large number of instances is unclear because many are asymptomatic or moderate and self-treated. Many cases are not appropriately diagnosed [2]. The prevalence of dengue fever has significantly increased recently. As of April 30, 2022, 8278 instances and one fatality had been documented, according to the media, which cited health authorities. Since March 21, 2022, there have been 7878 more cases and one death [3].

The management of the vector is still necessary for dengue prevention [4]. Dengue and severe dengue are not specifically treated. Death rates from severe dengue are reduced to about 1% when disease progression is identified early and patients have access to quality medical care [5]. Medical plants have long been practiced a wide range of vector-borne illnesses, including chicken guniya and malaria [6]. There is a greater need now than ever for novel anti-dengue medicines derived from medicinal plants. Plant-based medications are in greater demand since they are usually regarded as being safer, non-toxic, and less hazardous than synthetic drugs.

Research in recent years has focused on the scientific validation of ethanobotanical data as well as its effectiveness in treating dengue fever. Several of the preventive techniques included the use of plant extracts, which may have had ovicidal effects on *Aedes aegypti.*

Plant extracts or molecules can act as virocides and immunomodulators. Various mechanisms like elevation of the platelet count, larvicidal activity, virocidal activity against the dengue virus DENV-1, etc., by which plant extracts exhibit their therapeutic effect have been described. The current review article focuses on information about plants with anti-dengue effects and phytoconstituents with the same potential [7].

Table 1

Common name	Scientific name	Part Used	Extract	Chemical Composition	Result	References
Indian Abutilon, Monkey Bush	*Abutilon indicum* Family: Malvaceae	Whole plant, Leaves	Petroleum ether	Beta-sitosterol	Beta-sitosterol isolated, identified and evaluated against *Aedes aegypti L*. It shows potential new mosquito larvicidal compound with LC50 value of 11.49, 3.58 and 26.67	8

					ppm.	
Sweet-flag, Calamus	*Acorus calamus* Family: Acoraceae	Root	Ethanol	Tatanan A	Among 12 isolated compounds Tatanan A showed best anti-DENV activity with an EC50 of 3.9 µM. The antiviral efficacy of tatanan A was further validated by an RNA replication assay. The Time-addition assay demonstrated that Tatanan A inhibited DENV2 mRNA and protein levels.	9
Neem, Margosa	*Azhadirachta indica* Family: Meliaceae	Leaves	Lyophilized aqueous extract	---	Aqueous extract at 500µg/ml gives better antiviral activity for Dengue 2 and 4.	10
Bitterweed, King of Bitters, Creat, Green Chireta, Indian Echinachea, Hempedu Bumi	*Andrographis paniculata* Family: Acanthaceae	Leaves	Ethanol	Andrographalide	Increased phosphorylation of eIF2 in response to andrographolide is a main determinant of andrographolide's anti-DENV action.	11
	Andrographis paniculata Family: Acanthaceae	--	--	Andrographalide (Marketed pure sample)	Showed significant anti DENV activity in both cell lines with EC50 for DENV 2 is 21.3 µM and 22.73 µM for HepG2 and HeLa respectively.	12
Custard apple, Sugar apple or bullock's-heart	*Annona reticulate* Family: Annonaceae	Barks and bulb	Ethyl acetate		Ethyl acetate extract showed the highest mortality (100%) at 200 ppm against Aedes aegypti. Against the 4th instar larvae of *Aedes aegypti* at a lethal concentration (LC50: 72.5 ppm), all enzyme patterns showed differential expression on exposure to the ethyl acetate extract.	13
Alligator weed, Ponnanakanni	*Alternanthera philoxeroides* Family: Amaranthaceae	Whole plants	Petroleum ether		The antiviral activity of four extracts petroleum ether, ethyl acetate, ethyl ether and coumane was tested. The petroleum ether extract showed the strongest inhibitory effects on dengue virus (ED(50)=47.43).	14
Flossflower, bluemink, blueweed, pussy foot or Mexican paintbrush	*Ageratum houstonianum* Family: Asteraceae	leaves	methanol		The effect of 0.1 % methanol extract on oviposition of *Aedes* species indicated effective deterrence ranging from 79.0 to 100.0 % in indoor and 74.6 to 100.0 % in outdoor ovitraps.	15

Indian siris, Shar Sarad, lebbeck tree	*Albizia lebbeck* Family: Fabaceae	Leaf	Methanolic methanol		The methanol extract showed the highest ovicidal activity. 100% mortality was observed at 250, 200, and 150 ppm for methanolic leaf extract.	16
Arrabidaea chica	*Arrabidaea pulchra* Family: Bignoniaceae	Leaves	Ethanol	Caffeoylcallerya nin, Verbascoside, ursolic acid	Inhibited DENV-2 (EC50 = 46.8 ± 1.6 µg mL^{-1}). AP 2 was the most effective anti-DENV-2 constituent, with a Selectivity Indexes (SI) of 20.0.	17
Neem, Margosa, Margo	*Azadirachta indica* Family: Meliaceae.	Leaves	Aqueous	Azadirachtin	An *in vivo* study on the inhibitory effects on virus of NL 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-1 as indicated by the absence of 511-bp dengue group specific amplicons upon RT-PCR.	18
Finger Root, Chinese Ginger	*Boesenbergia rotunda* Family: Zingiberaceae	Rhizom e	Methanol	4-hydroxypandurat in A, panduratin A pinostrobin, pinoc embrin, Cardamon in	*B. rotunda* showed good competitive inhibitory activities towards DENV-2 NS3 protease with Ki values of 21 µM and 25 µM, respectively. The small value of Ki shows the potential of 4- hydroxypanduratin A to inhibit DENV-2 NS3 protease *in vitro*.	19
Papaya, papaw or pawpaw	*Carica papaya* Family: Caricaceae	Leaf	Aqueous juice		One study reported that crude papaya leaves at 15 mg/ kg of body weight increases of thrombocyte count in mice while in another study they observed that 400 and 800 mg/kg of C. papaya leaf aqueous extract increases the platelet count.	20
Red seaweed	*Cryptonamia crenulata* Family: Halymeniaceae	Whole plants		Galactan (DL galactan hybrid C2S3)	It is a potent and selective inhibitor of the multiplication of diverse strains of DENV-2 in Vero cells with higher effectiveness.	21
Sabah Snake Grass, belalai gajah, ki tajam	*Clinacanthus nutans* Family: Acanthaceae	leaves	Chloroform	Phaeophorbide a	Phaeophorbide a Suppressed DV2 replication in A549 cell. It could also inhibit the DV2 replication in post incubation.	22
Adenogynum, Chloradenia	*Cladogynos orientalis* Family: Euphorbiaceae	Whole plant	Ethanolic extract		At a conc. of 12.5 µg/ml ethanolic extract inhibited activity against DENV2 with 34.85% inhibition. The 50% cytytoxic concentration (CC50) of ethanol extract were 312 µg/ml.	23
Haldi, turmeric, Curcuma	*Curcuma longa* Family: Zingiberacea	Rhizom e	Alcohol (90%), Methanol (Fractions)	Curcuminoid	Antiviral activity (IC50) and toxicity (CC50) *in vitro* was examined on Huh7it-1 cells	24

					by focus assay and a MTT assay, respectively, the acquired value of IC50 was 17,91 µg/mL whereas the value of CC50 was 85,4 µg/mL.	
Amaltas, Golden Shower Tree, Indian laburnum, or pudding-pipe tree.	*Cassia fistula* Family: Fabaceae (Leguminosae)	Leaf	Methanol, benzene and acetone		The extract exhibited dose dependent activity and produced significant mortality. The 24 h LC50 concentration of the extract against Aedes aegypti were observed at 10.69, 18.27 and 23.95 mg/l respectively. Mean percent hatchability of the ovicidal activity was observed 120.00 h after treatment. The percent hatchability was inversely proportional to the concentration of extract and directly proportional to the eggs.	25
Nam Nam, Katak Puru, Puki Anjing.	*Cynometra cauliflora* Family: Fabaceae	Leaves	Methanol		Cytotoxicity screening against Vero cells using MTT assay showed that the CC50 values for the extract was 36 mg/ml and the 50% Effective Concentration, EC50, was 2.19 mg/ml. The selectivity index (SI = CC50 / EC50) for the extract was 16.	26
Amphilophium elongatum	*Distictella elongate* Family: Bignoniaceae	Leaves, stems and fruits Leaves	Ethanol	Pectolinarin and Acacetin-7-O-rutinoside (Fruit)	Fruit ethanolic extract has presented anti-DENV-2 activity (EC5011.1±1.6 µg ml^{-1}); SI > 45).	27
Tawa-Tawa, Asthma Weed, snake weed, spurge	*Euphorbia hirta* Family: Euphorbiaceae	Leaves	Ethyl acetate extract	Taraxerone, Lupeol.	Potent antiviral activity against DENV 1 and 2 by plaque reduction neutralization test. The EtOAc fraction significantly reduced (85 %) the plaque forming capacity of dengue virus serotype 1 from ~1400 to ~200 PFU & serotype 2 (~90 % reduction).	28
Tongkat Ali, Pasak bumi, or Longjack	*Eurycoma longifolia* Family: Simaroubaceae	Root	Water		***In vitro***-Inhibited DENV-1, DENV-2, DENV-3 and DENV-4 (IC50 = 33.84, 33.55, 58.35 and 119 g/mL, respectively) ***In vivo***-30% lower viral load and 12% higher platelet count compared to the control group. The selectivity index (SI) values determined as the ratio of cytotoxic concentration (CC50) to inhibitory concentration (IC50) was the lowest for DENV-2 at 28.9.	29

Pak Kan Thong, Chameleon Plant	*Houttuynia cordata* **Family:** Saururaceae	Whole plant	Aqueous	Hyperoside	The results showed that pre- and post-incubation of H. cordata extract (10–100 µg/mL) with HepG2 cells significantly reduced intracellular DEN-2 RNA production correlating with the decrease in dengue protein expression. In the direct blocking mode, the extract bound with DEN-2 and strongly inhibited the intracellular viral RNA replication with an effective dose (EC50) of 0.8 µg/mL.	30
Sea buckthorn	*Hippophae rhamnoides* Family: Elaeagnaceae	Leaf	Ethanol		Ethanolic extract decreased the TNF-a and increased the IFN-g production in Dengue-infected cells. SBTLAE proved its antidengue activity by indicating decreased plaque numbers after the treatment of infected cells.	31
Ramontchi, Governor's plum, Madagascar plum and Indian plum	*Flacourtia ramontchi* Family: Salicaceae	Stem barks	Ethyl acetate	phenolic glycosides, named flacourtosides A−F	In the DENV RNA polymerase assay, significant inhibition was observed with betulinic acid 3β-caffeate (IC50 = 0.85 ± 0.1 µM) and to a lesser extent for the flacourtosides A and E (1 and 5, respectively), and scolochinenoside D (IC50 values ∼10 µM).	32
Faramea	*Faramea bahinensis* Family: Rubiaceae	Leaves	Methanol	Flavanone glycoside: 5-hydroxy-4′-methoxy-flavanone-7-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside, the known 5,4′-dihydroxy-flavanone-7-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside and a diateroisomeric epimer pair of the known 5,3′,5′-trihydroxy-flavanone-7-*O*-β-D-glucopyranoside.	The treatment of DENV-2 infected HepG2 cells with the new flavanone was able to control viral replication promoting a reduction of the number of infected cells (12%), together with a decrease of infectious particles in the culture supernatant (97%) and of the number of RNA copies of DENV-2 in HepG2 cells (67%).	33
Malabar nut, Adhatoda, Vasa, Vasaka	*Justicia adhatoda* Family: Acanthaceae	Leaf	hexane, ethyl acetate and methanol		Methanolic extract of *J. adhatoda* (LC_{50}=75.30) showed highest mortality against the test larvae.	34
White Lead tree, Petai Belalang	*Leucaena leucocephala* Family: Fabaceae	Seed	Ethanol	Galactomanan	*In vitro* experiments with DEN-1 in C6/36 cell culture assays showed that concentrations that produced	35

					a 100-fold decrease in virus titer of DEN-1 were 347 and 37 mgl(-1).	
White lippia, Bushy lippia	*Lippia alba* Family: Verbanaceae *Lippia citriodora* Family: Verbanaceae	Aerial parts	Essential oil	Linalool (Isolated)	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. Inhibition was observed by treatment of virus before adsorption on cell IC50	36
Bitter-melon, bitter gourd or karela.	*Mormordica Charantia* Family: Curcubitatceae	Root & Entire fruit	Methanol		Showed 50 % inhibition of Vero cells that infected with DENV I based on cytopathic effect. In cytotoxicity study maximum non-toxic dose was 0.20 mg/mL.	37
Myristica magnifica, Myristica nutmeg	*Myristica fatua Myristica fragrans* Family: Myristicaceae	Leaves	Methanol		*Myristica fatua* Shown antiviral effects against DENV 2 with highest percentage inhibition -122.7 %.	38
Tulsi, Holy basil	*Ocimum sanctum* Family: Lamiaceae	Whole aerial parts	Methanol		Exhibit antiviral properties toward DENV 1 through inhibition of cytopathic formation and viral replication. The maximum non-toxic dose (MNTD) was 23.44 µg/mL. Upon treating the DENV-1 infected cells with O. sanctum, the percentage of cell viability recorded was 64.29% and 68.67%, respectively at MNTD and ½MNTD.	39
Cat's Whiskers, Java Tea, Kidneys Tea Plant, Misai Kuchin.	*Orthosiphon stamineus* Family: Lamiaceae	Leaves	Aqueous		Inhibited DENV-2 replication (88% at a dose of 0.31 mg/mL). The EC50 value of the extracts tested against the DENV-2 was ~ 0.36 mg/ml	40
Guava, yellow guava, lemon guava, or apple guava	*Psidium gujava* Family: Myrtaceae	Bark	Ethanol	Isolated compounds, Gallic acid, quercetin, catechin, naringin	All four compounds selectively inhibited DENV 2 replication with EC50 values bark (7.8 µg/mL), Gallic acid (28.8 µg/mL), quercetin(19.2 µg/mL), catechin (33.7 µg/mL), naringin (47.9 µg/mL)	41
Javanese long pepper, long pepper	Piper retrofractum Family: Piperaceae	whole plant	Dichloromethane, Ethanol		It exhibited an inactivated viral particle activity with 84.93% at a concentration of 100 µg/ml.	42
Indian gooseberry, gale of the wind	Phyllanthus sp Family: Phyllanthaceae (*Phyllanthus amarus, P.niruri, P.urinaria, P.watsonii*) Family:	All Aerial part	Aqueous and methanol	Gallic acid, Geraniin (present in high amount), syringin, and corilagen	Inhibited DENV-2 replication (91.48% at a dose of 250 _g/mL) MNTD for aqueous and methanolic extracts were 250 µg/ml and 15.63 µg/ml, respectively. Phyllanthus showed the strongest antiviral activity	43

	Phyllanthaceae				against DENV2 during the simultaneous mode of treatment with more than 83 - 95% reduction of virus inhibition.	
Bakau Minyak, True mangroves	*Rhizophora apiculata* Family: Rhizophoraceae	Whole plant	Ethanol		Inhibited DENV-2 replication by 56.14 % at concentrations of 12.5.	44
Elderberry, European black elderberry, elder.	*Sambucus nigra* Family: Adoxaceae	Flowers and leaves	Methanol		Exhibit anti DENV 2 activity at 400 µg/ml. At this concentration, cell viability was between 60% and 80%.	45
Hog plum, Yellow mombin	*Spondias mombin* & *Spondias tuberosa* Family: Anacardiaceae	Leaves	Methanol:water (Hydroalcohol)	Rutin, quercetin and ellagic acid.	*In vitro* Inhibited DENV-2 replication (3.31% at a dose of 500 g/L) Inhibited DENV-2 replication (99% at a dose of 500 17.98 g/mL)	46
Chinese skullcap, huangqin, baikal, and scutellaria	*Scutellaria baicalensis* Family: Lamiaceae	Root	Water	Baicalein	The IC50 values for the S. baicalensis extract on Vero cells following DENV adsorption ranged from 86.59 to 95.19 µg/mL for the different DENV serotypes. The IC50 values decreased to 56.02 to 77.41 µg/mL when cells were treated with the extract.	47
Clove, Keriang Batu, Kelat Paya	*Syzygium grandulae Syzygium campanulatum* Family: Myrtaceae	Flower bud		Isolated compounds- Cyclododecane, nhexadecanoic acid and carrophyllene	The findings revealed that cyclododecane and n-hexadecanoic acid found in the leaf extracts of S. grande and caryophyllene in extracts of S. campanulatum were likely the lead-compound that imparted the observed inhibitory effect on the DENV2 NS2B-NS3 protease.	48
	Tephrosia madrensis Tephrosia crassifolia Tephrosia viridiflora Family:	Leaves and flowers		Glabranine, 7-O-methylglabranine	The flavonoids isolated from *T. madrensis*, glabranine and 7-*O*-methyl-glabranine exert strong inhibitory effects on dengue virus replication in LLC-MK2 cells. Methyl-hildgardtol A isolated from *T. crassifolia* exhibited a moderate to low inhibitory effect, while hildgargtol A from *T. crassifolia* and elongatine from. *T. viridiflora* had no effect on viral growth.	49
Cat's claw,	*Uncaria tomentosa* Family: Rubiaceae	Stem barks	Water-alcohol	Alkaloid (oxindole alkaloids)	Reducing DENV-Ag+ cell rates	50
Marine eelgrass	*Zostera marina* Family: Zosteraceae	Whole plant	Water	Zosteric acid	The anti-adhesive compound zosteric acid (ZA), derived from *Z. marina* showed a	51

					modest IC50 of approximately 2.3 mM against DENV-2.	

Conclusion

In various regions of India, several plants and their formulations have been traditionally utilised to treat dengue. The present review gives a detailed idea of the scientifically proven action of herbal extract. As per the stage of dengue, these herbal formulations can be used for treatment or management of the disease. Finding better, more potent and less harmful anti-dengue medications requires the formulation and development of novel anti-dengue medicines from bioactive chemicals. Therefore, the compilation of potent isolated active phytoconstituents with anti-dengue action and their toxicity in preclinical and clinical studies should be done. The mechanisms like ovicidal, larvicide against dengue vectors, antiviral activity, inhibitor of the multiplication of diverse strains of DENV-2, cytotoxic effect, and increase in the platelet count of different plant extracts prove that herbal formulations provide either potent or adjuvant therapy.

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