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Tracing plants potential effective against dengue virus: A review

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Abstract: *Dengue fever is one of the most prevalent viral disease caused by dengue virus- a family of flavivirus transmitted through yellow-fever mosquito. It is found in tropical and sub-tropical regions that causes mortality and morbidity round the world. In recent years, transmission has increased predominantly in urban and semi-urban areas which are of major concern to governments and therefore the World Health Organization (WHO). The event of a dengue vaccine is complicated by the antibody-dependent enhancement effect. As there are not any synthetic drugs available, thus, the event of a plant-based antiviral preparation promises a more potential alternative in combating dengue disease. Hence the look for new anti-dengue agents from medicinal plants has assumed more urgency than within the past. Medicinal plants are used widely to treat a spread of vector ailments like malaria. The demand for plant-based medicines is growing as they're generally considered to be safer, non-toxic and fewer harmful than synthetic drugs. This text reviews potential anti-dengue activities from plants distributed round the world.*

Key words: *Dengue fever, Flavivirus, Anti-dengue, Medicinal plants, Aedes aegypti mosquito.*

1. INTRODUCTION:

Dengue is fast emerging pandemic-prone viral disease caused by the arthropode-borne flavi virus named dengue virus (denv), transmitted by the *aedes aegypti* mosquito [1]. Dengue fever virus (denv) is an rna virus of the family flaviviridae and genus flavi virus. Four antigenically related but distinct virus serotypes (denv-1, 2, 3 and 4) have been identified as belonging to the genus flavi virus in the flaviviridae family [2]– [3] which are called serotypes. Dengue fever causes mortality and morbidity around the world, specifically in the tropics and subtropics regions, which has been of major concern to governments and the world health organization (who). Dengue disease regardless of its serotypes is transmitted from person to person by *Aaedes aegypti* and *Aedes albopictus* mosquitoes in the domestic environment. When antibody from the first infection is neutralized, secondary infections by other serotypes can cause more serious infection [4], denv-2 is known to be more lethal than other serotypes [5] and some studies have revealed that primary infection with denv-1 or denv-3 always results in more dangerous disease than infection with denv-2 or denv-4 [6]. The full life cycle of **dengue** virus involves the role of vector and victim i.e., a mosquito and humans respectively.

1.1. Pathophysiology of dengue fever:

Dengue infection is caused by bites of the feminine yellow-fever mosquito carrying Flavivirus. After a person is bitten, the virus incubation period varies between 3 and 14 days [7] after which the person may experience early symptoms such as fever, headache, rash, nausea, joint and musculoskeletal pain [7]-[8]. This classic dengue fever records temperatures between 39-40^{0}C and usually lasts 5–7 days [6]. During this era, the virus may get into the peripheral bloodstream and, if left untreated, can damage blood vessels and lymph nodes leading to DHF with symptoms like bleeding from the nose, gums or under the skin. Dengue hemorrhagic fever (DHF) patients even have difficulty in breathing and severe development can cause Dengue shock syndrome (DSS). DSS may result in death if proper treatment isn't provided. 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 [9]-[10] and always breeds in stagnant containers. Eggs need moist conditions, and mature in 24–72 h. Mosquito bites are the sole route of DENV spread. The transmission of DENV is often from human to human through domestic mosquitoes [6]. An outbreak starts after a mosquito sucks the blood of a patient with Dengue fever/ DHF. 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 [6].

1.2. Plants traditionally used to treat dengue:

According to a World Health Organization (WHO) fact sheet dated December 2008, 80 % of the population in some Asian and African countries depends on traditional medicine as their primary health care due to economic and geographical constraints. Natural products have become the main source of test material in the development of antiviral drugs based on traditional medical practices [11]. Traditional medicines are based on knowledge, experience and practices based on indigenous cultural beliefs and knowledge, and are used to maintain health, prevent, treat and diagnose physical or mental illness. Traditional medicinal plants have been reported to have antiviral activity [12]-[13] and some have been used to treat viral infections in animals and humans.

1.3. Overview of Studies on plant species used against dengue:

Medicinal plants are traditionally used for various sorts of ailments including infectious diseases. The use of herbal-based medicine and medicinal plants to treat many diseases is growing worldwide as they need few or no adverse effects. Many traditionally used herbs contain phytochemicals that would be beneficial for health. These plant-derive compounds and extracts are utilized in many forms for the treatment of varied ailments and as dietary supplements. Traditionally used herbal preparations commonly employed by different tribes and communities across the planet , are the immediate source of data for further discovery of probably beneficial phytochemicals. There is an increasing need for substances with antiviral activity since the treatment of viral infections with the available antiviral drugs often results in the matter of viral resistance and development of a dengue vaccine is complicated by the antibody-dependent enhancement effect. So demand for plant-based medicines is growing as they're generally considered to be safer, cheaper, non-toxic and fewer harmful than synthetic drugs. It is a widely believed that naturally-derived phytochemicals would have lesser side-effects as they're often derived from edible herbs. A number of natural compounds reported in traditional medicinal plants to possess anti-dengue properties were studied [12] Potential of plant bioactive compounds to combat Dengue.

The active compounds showed a wide range of activity against DENV. The isolated products belong to varied chemical classes like sulfated polysaccharides, flavonoids, quercetin and natural chalcone compounds. The secondary metabolites of medicinal plants comprise a spread of compounds with a good range of biological activities. There are reports on medicinal plants extracts and essential oils possessing potential to new antiviral properties. Many plant extracts in different solvents have been reported to exhibit activity against a vector of dengue fever, A. aegypti Medicinal plants that have been investigated for anti-dengue activity.

The following sections describe some species of medicinal plants from various families that have been investigated for anti-dengue activity. In addition, we describe species used as traditional treatment for dengue together with their botanical distribution and isolated compound as follows:

- ***Alternanthera philoxeroides***
  Common name- Alligator Weed
  Family- Amaranthaceae
  Botanical distribution- It is a perennial aquatic plant. It is considered as invasive species and native of South America.
  Medicinal property- This invasive aquatic noxious weed showed antinociceptive and antihyperglycemic activitiy. It was investigated for the antiviral activity of four extracts i.e. petroleum ether, ethyl acetate, ethyl ether and coumane of *A. philoxeroides* [14]. An extract of the plant is used medicinally in India to treat 'female diseases.

- ***Andrographis paniculata***
  Common name- Kalmegh
  Family-Acanthaceae [15]-[16]
  Botanical distribution-It is an erect herb, extremely bitter in taste that has been effectively used as traditional medicine in treating symptoms of upper respiratory tract infections from centuries.
  Medicinal property-In vitro studies of antiviral activity of methanolic extract of *A. paniculata* on dengue (towards DENV-1 serotype) fever had been reported [17] .The methanolic extract of *A. paniculata* was able to maintain most of the normal cell morphologies without causing much CPE to the DENV-1 infected cells. The monolayer sheet of cells still remained normal with low amount of cells death or lysis as well as low percentage of CPE [18].

- ***Anacolosa pervilleana***
  Common name- Gabon nut, African nut
  Family-Olacaceae
  Botanical distribution- Plant is found mainly in tropical regions especially in Madagascar region.

Medicinal property-The acetylenic compounds were isolated from an ethyl acetate extract of *Anacolosa pervilleana*, a Madagascan plant. By using purified DENV RdRp polymerase in enzyme assay, it was found that acetylenic compounds give rise to IC50 values around 3 μmol/L in the DENV RdRp assay. The results show that compounds possess some selectivity toward DENV RdRp. All compounds showed an anti metabolic effect in Vero cells (CC50s between 20 and 30 μmol/L) [19].

- ***Azidarachta indica***
  Common name- Neem
  Family- Meliaceae
  Botanical distribution-It is a fast-growing tree that is native to India, Indonesia, Pakistan, Malaysia and Pakistan and grows throughout tropical and semi-tropical regions with a final height in the range of 15–20 m. Neem [20] is one of the best and fast growing tree is being used for treating several ailments such as jaundice, ulcers, parasitic diseases, malaria and other variety of infections. Several investigations were carried out on leaves, seeds, bark and flowers of neem plants and it was used to cure variety of bacterial and viral infections.
  Medicinal property- In vitro inhibitory potential of aqueous extract of *A. indica* leaves on the replication of DENV-2 was evaluated. Cytotoxicity studies were carried out to determine the Maximum non-toxic dose (MNTD) in a virus inhibition assay. The aqueous extract of neem leaves completely inhibited 100–10,000 tissue culture infective doses TC (Inhibitory concentration) ID50 of virus as indicated by the absence of cytopathic effects at its maximum non-toxic concentration of 1.897 mg /mL.

- ***Boesenbergia rotunda***
  Common name- Chinese ginger; Finger root
  Family- Zingiberaceae
  Botanical distribution- It is widely found in Asian countries such as Malaysia, Thailand, Indonesia, India, and China where it is commonly used as food ingredient. It is a medicinal and culinary herb found throughout China and Southeast Asia. *Boesenbergia rotunda* (L.) is a common spice belonging to the ginger family (Zingiberaceae).
  Medicinal property-The activity of some compounds extracted from *B. rotunda* for the inhibition of dengue virus protease has been tested on DENV-2. The cyclohexenyl chalcone derivatives of *B. rotunda*, 4-hydroxypanduratin A (1) and panduratin A (2) 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 show the potential of 4-hydroxypanduratin A to inhibit DENV-2 NS3 protease in vitro.

- ***Boerhaavia diffusia***
  Common name- Punarnava (Telgu name)
  Family- Nyctaginaceae
  Botanical distribution- It is distributed all over the world like Africa, Asia, North America, South America, and South Pacific.
  Medicinal property-- *B. diffusia* has found to shown various important biological activities like antibacterial, anti-oxidant, antidiabetic, anti-diuretic and anti-inflammatory etc. The root is mainly used to treat gonorrhea, internal inflammation of all kinds, dyspepsia, oedema, jaundice, menstrual disorders, anaemia, liver, gallbladder and kidney disorders, enlargement of spleen, and abdominal pain. Bharati and Sinha [22] have studied the anti-dengue effect of stems of *Tinospora cardifolia* (Wild) Miers (10 gm) and the plant of *Boerhaavia diffusa* Linn (10 gm). Anti-dengue effect was evaluated by giving the Ayurvedic mixture consisting *Tinospora cardifolia* and *Boerhaavia diffusa* to dengue patients 2- 3 times a day [21].

- ***Carica papaya***
  Common name-Papaya
  Family- Caricaceae
  Botanical distribution- It is an erect, evergreen, unbranched, fast-growing and unbranched tree or shrub indigenous to Central America and cultivated in Mexico and most tropical countries for its edible fruits.
  Medicinal property- Papaya is the rich source of nutrients, minerals, vitamins, such as Vitamin A, B, C, and E and is available throughout the year. It also contains two important biologically active digestive enzymes chymopapain and papain. The fruit is an excellent source of beta carotene that prevents the damage caused by free radicals. *C. papaya* is successfully used in treating and improving the gastric disorders like hyperacidity and dyspepsia.

C. papaya leaf has been used traditionally in the treatment of Dengue fever. The aqueous extract of leaves of this plant had been investigated and found to exhibit potential activity against Dengue Fever by increasing the platelet (PLT) count, white blood cells (WBC) and neutrophils (NEUT) in blood samples of a 45-year-old patient bitten by carrier mosquitoes [23]. After 5 days of oral administration of 25 ml aqueous extract of *C. papaya* leaves to the patient twice daily, the PLT count increased from 55 to 103/µL to 168 to 103/µL, WBC from 3.7 to 103/ µL to 7.7103/µL and NEUT from 46.0 to 78.3 %. Increased platelets could lead to reduced bleeding, thus avoiding progression to the severe illness of dengue haemmorhagic fever.

- ***Castanospermum australe***
  Common name- Black Bean
  Family- Fabaceae
  Botanical distribution - Native to east coast of Australia.
  Medicinal property-In vitro assay of castanospermine, a natural alkaloid derived from the tree *C. australae* had been investigated for anti viral activity [24]. Castanospermine has showed good inhibitory anti-dengue activity over a broad range of doses from 10 to 250 mg/kg/day. This investigation reveals that castanospermine acts as an ER α-glucosidase I inhibitor and reduces infection of a subset of enveloped RNA and DNA viruses in vitro. Studies of its mechanism of action suggest that castanospermine may disrupt folding of some viral proteins by preventing the removal of the terminal glucose residue on N-linked glycans in dengue virus.

- ***Caesalpinia pulcherrima***
  Common Name: Peacock flower
  Family: Fabaceae
  Botanical distribution: This tree is widely distributed in tropics and subtropics in America and West Indies. It is also found in India.
  Medicinal properties: Crude benzene and ethyl acetate extracts of the leaves of *Caesalpinia pulcherrima* are used as repellent for *Aedes aegypti*. The results were collected by studying the repellent activity at three different concentrations 1.0, 2.5, and 5.0 mg/cm. These concentrations were applied on the skin of forearm of a man and exposed against female *Aedes aegypti*. This plant gives protection against this mosquito without any allergic effect [25].

- ***Chondrus crispus***
  Common name- Carrageen Moss, a species of red algae
  Family-Gigartinaceae
  Botanical distribution- It is abundant in rocky shores and tide pools of Ireland and coast of Europe.
  Medicinal property- *C. crispus*, consisting of a polysaccharide carrageen as an active constituent. Carrageenans are effective in treatment against viral infections of common cold. It had been reported that carrageen and other sulfate polysaccharides were effectively inhibits the dengue virus 2 infection where they were inhibiting virus entry [26].

- ***Cissampelos pareira***
  Common name- Velvet leaf
  Family- Menispermaceae [27]
  Botanical distribution- This plant is widely distributed worldwide.
  Medicinal property-It has been used in the treatment of ulcers, diarrhea, muscle inflammation and rheumatism. Earlier investigations on roots of *C. pareira* revealed that it contain alkaloids hyatin hyatinin, haytidine and bebeerines. A chalcone and flavones dimer was isolated from the aerial parts of the plant named as cissampeloflavone. Anti-dengue activity of extract of aerial parts of *C. pareira* was patented.

- ***Cladogynos orientalis***
  Common name-Lesser Sunda Islands
  Family- Euphorbiaceae
  Botanical distribution- It is a white-stellate-hairy shrub about 2 m high found in Southeast Asia, Malaysia and Thailand.
  Medicinal property-*Cladogynos orientalis* is a thai medicinal plant whose in vitro activity was evaluated against dengue virus 2. Dichloromethane ethanol extract of *C. orientalis* was tested for anti-dengue activities against 10 DENV-2 in Vero cells by the MTT method. Results showed that the ethanol extract of *C. orientalis* at a

concentration of 12.5 µg mL-1 exhibited inhibitory activity on DENV-2 with 34.85 %. In addition, *C. orientalis* at a concentration of 100 µg mL-1 exhibited an inactivated viral particle activity of 2.9 %.

- ***Cladosiphon okamuranus***
  Common name- Mozuko
  Family- Chordariaceae
  Botanical distribution- It is brown seaweed found naturally in Okinawa, Japan.
  Medicinal property-A sulfated polysaccharide named fucoidan from *Cladosiphon okamuranus* was found to potentially inhibit DENV-2 infection [28]. The virus infection was tested in BHK-21 cells in a focus-forming assay. Fucoidan reduced infectivity by 20 % at 10 lg mL-1 as compared with untreated cells. However, a carboxy-reduced fucoidan in which glucuronic acid was converted to glucose attenuated the inhibitory activity on DENV-2 infection.

- ***Cryptonemia crenulata***
  Common name-Reef aquarium rose petal algae
  Family- Halymeniaceae
  Botanical distribution- It is a marine species found throughout the Atlantic Islands, North America, Caribbean Islands, Western Atlantic, South America, Africa, Indian Ocean Islands, Southeast Asia and Pacific Islands.
  Medicinal property-The sulphated polysaccharides from *C. crenulata*, i.e., galactan, were selective inhibitors of DENV-2 multiplication in Vero cells with IC50 values of 1.0 lg mL^{-1}, where the IC50 values for the reference polysaccharides heparin and DS8000 were 1.9 and 0.9 lg mL-1, respectively [29]. However, the compound has lower antiviral effect against DENV-3 and DENV-4, and was totally inactive against DENV-1. The inhibitory effect of C2S-3 against DENV-2 was slightly higher when treatment was by adsorption (EC50 = 2.5 ± 0.1 µg mL^{-1}) with respect to treatment only during internalization (EC50 = 5.5 ± 0.7 µg mL^{-1})[1]. Thus, the inhibitory effect was increased when C2S-3 was included at both stages of adsorption and internalization.

- ***Cymbopogon citrates***
  Common name- Lemon grass
  Family- Poaceae
  Botanical distribution- It is a tropical plant from Southeast Asia. Luteolin, apigenin, homoorintine flavanoides and its derivatives such as 2-O rhamnosil-limborientino were isolated from *C. citrates* [30]- [31].
  Medicinal property-An antiviral activity was determined based on cytopathic effects shown by the degree of inhibition of DENV-1 infected Vero E6 cells [18]. The methanolic extract of *C. citratus* showed a slight inhibition effect on DENV-1. *C. citratus* was found to be quite a cytotoxic plant as it showed maximum cytotoxicity at 0.075 mg mL^{-1}.

- ***Euphorbia hirta***
  Common name-Tawa–tawa; Gatas-gatas
  Family- Euphorbiaceae
  Botanical distribution- 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.
  Medicinal property- This plant is widely used as a decoction or infusion to treat various ailments including intestinal parasites, diarrhoea, peptic ulcers, amoebic dysentery, asthma, hay fever, kidney stones, menstrual problems and venereal diseases [32]. Phytochemical alaysis of *Euphorbia hirta* revealed the presence of polyphenols, reducing sugar, alkaloids, flavonoids, sterols, tannins and triterpenoids in the whole plant. Apostol *et al*. has studied the platelet increasing activity of decoction of *Euphorbia hirta* plant in ethanolic inducing thrombocytopenic rat models [33]. Continued administration of the plant decoction resulted in the maintenance of this antithrombo cytopenic effect. *E. hirta* contains more reducing polyphenols, active ingredient suspected to be responsible in the increasing platelet count. The water decoction of leaves from *Euphorbia hirta*, locally known as gatas–gatas, is used in the Philippines as a folk medicine to treat Dengue Fever. Internal haemorrhaging will stop and dengue fever will be cured after 24 h. The tea obtained from boiled leaves of *E. hirta* is used to cure DF. In the Philippines, *Euphorbia hirta* is used in folk medicine to cure dengue fever by people in rural areas. Practitioners of traditional medicines believe that decoction of tawa–tawa leaves can reverse viral infection and prevent the fever from moving into critical stages, although there are no scientific studies proving its effectiveness. Sometimes, tawa–tawa is prepared together with papaya leaves since papaya leaf extract has a

function as an antibiotic to cure fever. While papaya leaf extract kills the bacterial infection that caused the fever, tawa–tawa extract prevents bleeding.

- ***Flagellaria indica***
  Common name-False Rattan
  Family- Flagellariaceae
  Botanical distribution- *F. indica* is robust perennial climber that grows in many of the tropical and subtropical regions of the Old World, India, Southeast Asia, Polynesia and Australia.
  Medicinal property- It was investigated for its anti-dengue properties in Vero cells. The antiviral assay results show that 45.52 % inhibition of DENV-2 was observed in vitro in the presence of 12.5 μg mL^{-1} of ethanol extract of the plant. By conducting 3-(4, 5-Dimethylthiazol-2-yl)-2, 5- diphenyltetrazolium bromide (MTT) assays, the cytotoxicity of *F. indica* was determined. The CC50 of ethanol extract of *F. indica* were 312 gmL^{-1}. Thus, this study indicates that *F. indica* has a significant potential effect on DENV.

- ***Gastrodia elata***
  Common name- Gastrodia
  Family- Orchidaceae
  Botanical Distribution- *G. elata* has been known as famous and important chinese medicinal herb.
  Medicinal Property-This traditional Chinese herb has been used to treat various diseases like stroke, rheumatism, insomnia, Alzheimer's disease, depression, convulsions, neuronal diseases, fungal infections etc. Chemical analytical studies revealed that this plant contains nine kinds of phenolic compounds, and sixteen kinds of amino acids which are beneficial to health. Some D-glucans from *G. elata* were isolated [34] and sulfated derivatives were prepared and they were investigated anti-dengue activity against dengue 2 virus. These sulfated D-glucan derivatives were strongly interfering with the dengue 2 virus infections with an EC (50) value of 0.68+/-0.17 μg/mL, mainly interfered with virus adsorption, in a very early stage of the virus cycle.

- ***Gymnogongrus griffithsiae***
  Common name-Dry Limu
  Family- Phyllophoraceae
  Botanical distribution- *G. griffithsiae* is red seaweed found in Ireland, Europe, Atlantic Islands, North America, South America, Caribbean Islands, Africa, Southwest and Southeast Asia and Australia and New Zealand.
  Medicinal property- The inhibitory properties against DENV-2 of the sulphated polysaccharide from *Gymnogongrus griffithsiae*, kappa carrageenan was evaluated in Vero cells. The compound effectively inhibits DENV-2 multiplication at the IC50 value of 0.9 μg /mL, which is the same as the IC50 value for the commercial polysaccharides DS8000. However, the compound has lower antiviral effect against DENV-3 and DENV-4, and was totally inactive against DENV-1.

- ***Gymnogongrus torulosus***
  Common name-Red sea weed
  Family- Phyllophoraceae
  Botanical distribution- *G. torulosus* is red seaweed found in Australia and New Zealand.
  Medicinal property-It was investigated for its in vitro antiviral properties against DENV-2 in Vero cells. Galactan extracted from this plant was active against DENV-2, with IC50 values in the range of 0.19–1.7 μg mL^{-1}.

- ***Hippophae rhamnoides***
  Common name-Sea buckthorn
  Family- Elaeagnaceae
  Botanical distribution- *H. rhamnoides* is a deciduous shrub occurring throughout Europe including Britain, from Norway south and east to Spain and in Asia to Japan and the Himalayas.
  Medicinal property-The anti-dengue activity of extracts of *H. rhamnoides* leaves was investigated against dengue virus type-2 (DENV-2) in infected blood-derived human macrophages. The findings showed that cells treated with *H. rhamnoides* leaf extracts was able to maintain cell viability of dengue-infected cells on par with Ribavirin, a commercial anti-viral drug along with a decrease and increase in TNF-a and IFN-c, respectively [35]. Moreover, *H. rhamnoides* leaf extract proved its anti-dengue activity as indicated by a decrease in plaque numbers after the treatment of infected cells.
- ***Houttuynia cordata***

Common name- Chameleon plant
Family- Saururaceae
Botanical distribution- *H. cordata* is a Chinese herbaceous perennial flowering plants growing between 20 and 80 cm, and is native to Japan, Korea, Southern China and Southeast Asia.
Medicinal property- It has been used to treat several diseases like anti-hypertensive, anti-cancer, anti-mutagenic, anti inflammatory, and many others. Recently, this plant extract was screened for it anti-viral activity against dengue virus. Inhibitory activity of aqueous extract of *Houttuynia cordata* on dengue virus had been studied. This study revealed that the extract of this plant strongly inhibiting the viral RNA replication at a effective dose of 0.8µg/mL. HPLC analysis of *H. cordata* extract indicated that hyperoside [36] was the predominant bioactive compound, and was likely to play a role in this inhibition.

- ***Kaempferia parviflora***
Common name- Krachai Dam
Family- Zingiberaceae
Botanical distribution- *K. parviflora* is a thai traditional herb. Leaves and stem of this plant are used traditionally to treat many viral infections. Main chemical constituents of *K. parviflora* are borneol and flavanoids.
Medicinal property-Investigations reported that it has various activities like anti-ulcer, anti-allergic, antifungal, antimycobacterial etc. Recently, it has demonstrated very good activity against DENV-2. Virucidal activity of leaves and stem extracts of *K. parviflora* against DENV-2 had been studied. It suggested that some of the bioactive compounds in *K. parviflora* inactivate the DENV-2 particles.

- ***Leucaena leucocephala***
Common name- White lead tree
Family- Fabaceae
Botanical distribution- *L. leucocephala* is a species of Mimosoid tree indigenous throughout Southern Mexico and Northern Central America and the West Indies from the Bahamas and Cuba to Trinidad and Tobago.
Medicinal property-Galactomannans extracted from seeds of *L. leucocephala* have demonstrated activity against yellow fever virus (YFV) and DENV-1 in vitro and in vivo. Galactomannans are polysaccharides consisting of a mannose backbone with galactose side groups, more specifically their structure consists of a main chain of (1 - 4)-linked b-D-mannopyranosyl units substituted by a-D-galactopyranosyl units. *L. leucocephala* show protection against death in 96.5 % of YFV-infected mice. In vitro experiments with DENV-1 in C6/36 cell culture assays showed that the concentration producing a 100-fold decrease in virus titer of DENV-1 was 37 mg L^{-1}.

- ***Lippia alba* and *Lippia citriodora***
Common name- Lemon verbena (*Lippia citriodora*)
Family- Verbenaceae
Botanical distribution- They are flowering plants native to Southern Texas, Mexico, the Caribbean, Central and South America. *Lippa citriodora* is a perennial shrub, great topiary plant with nice fragrance and very rich in aromatic oil. Its lemon like aroma of the plant leaves is used to prepare herbal tea. It has been used for long time treatment of asthma, fever, cold and it several biological activities like, anti-bacterial, anti malarial, cytotoxic, anti-spasmodic etc.
Medicinal property- The in vitro anti-dengue effect of essentials oils of *Lippia citriodora and Lippa alba* [37] was evaluated by Ocazionez *et al*., (2010)[38]**.** The dengue virus treated with essential oil for 2 h at 37 masculine Cells before cell adsorption and experiments were conducted to evaluate inhibition of untreated-virus replication in the presence of oil. Virus plaque reduction for all four dengue serotypes was observed by treatment of the virus before adsorption on cell. The IC50 values for *L. alba* oil were between 0.4-32.6 µg/mL and between 1.9-33.7 µg/mL for *L. citriodora* oil [39].
Essential oils from *L. alba* and *L. citriodora* showed a considerable inhibitory effect on dengue virus serotype replication in Vero cells [38]. A 50 % reduction in virus plaque number values was found with *L. alba* oil at between 0.4–32.6 lg mL-1 whereas for *L. citriodora* oil, the IC50 values were between 1.9 and 33.7 µg mL-1. *L. alba* essential oil was more effective against DENV-2 than other serotypes, while for *L. citriodora* essential oil, the virucidal action against DENV-1, 2 and 3 were similar but lower than against DENV-4. Essential oil of *L. alba* was observed to produce a 100 % reduction of YFV yield at 100 µg mL^{-1}.

- ***Meristiella gelidium***
Common name- Chinese ginger

Family- Solieriaceae
Botanical distribution- *M. gelidium* is a marine species found in Atlantic Islands, North America, Caribbean Islands and South America.
Medicinal property- *Meristiella gelidium* were more effective inhibitors of DENV-2 compared to those derived from *G. griffithsiae*. The antiviral property evaluation was performed *in vitro* using Vero cells and virus plaque reduction assay.
The antiviral activity of kappa carragenan in *Meristiella gelidium* was evaluated against DENV-2. The IC50 of carragenans isolated from *M. gelidium* was in the range of 0.14–1.6 μg mL-1. The results show that the extract and the fraction derived from *M. gelidium* were more effective inhibitors of DENV-2 when compared with reference polysaccharides (heparin and DS 8000).

- ***Mimosa scabrella***
Common name-Bracatinga
Family- Fabaceae
Botanical distribution: *M. scabrella* is a fast growing, multipurpose tree 15–20 m high and up to 50 cm diameter tree native to the cool, subtropical plateaus of south eastern Brazil.
Medicinal property- All parts of this tree have medicinal values and invite attention of researchers for its pharmacological activities such as anti-diabetic, anti-hepatotoxin, and wound healing. Along with these activities recently it also found to inhibit dengue type 2 viruses. This plant contains some important bioactive compounds such as carbohydrates, flavanoids, alkaloids and phenols. Two galactomannans were isolated from the seeds of *Mimosa scabrella* and seeds of *Leucaena leucocephala*. These two active compounds were tested for *in vitro* anti-viral property against yellow fever virus and dengue virus.
In vitro experiments in C6/36 cell culture assay showed the inhibitory activity against dengue virus at concentration of 347 and 37 mgl-1 Galactomannans extracted from seeds of *M. scabrella* have demonstrated activity against YFV and DENV-1 in vitro and in vivo. *M. scabrella* showed protection against death in 87.7 % of YFV-infected mice. In vitro experiments with DENV-1 in C6/36 cell culture assays showed that a concentration of 347 mg L-1 produced a 100-fold decrease in virus titer of DENV.

- ***Momordica charantia***
Common name- Bitter melon or Peria (Malaysia)
Family- Cucurbitaceae
Botanical distribution: *M. charantia* is a tropical and subtropical vine found throughout Asia, Africa and the Caribbean. *M. charantia* possessed a total flavonoid content of 21.7%, of which some of them could be luteolin, kampherol and quercetin[40].
Medicinal property- *M. charantia* also exhibited moderate antiviral effects inhibiting replication of DENV-1 was confirmed through MTT assay, whereby the viability of cells treated with *M. charantia* extracts were not significantly affected upon infection with DENV-1[18]. Methanolic extract of *M. charantia* was investigated against Vero E6 cells in vitro. *M. charantia* recorded a maximal dose that was not toxic to cells of 0.20 mg mL^{-1}. The methanolic extract of *M. charantia* showed inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects [41].

- ***Murraya koenigii***
Common name- Kari patah or, Karipat
Family- Rutaceae
Botanical distribution: *Murraya koenigii* is a tropical and subtropical shrub found throughout Asia.
Medicinal property: In an experiment, the pupal stage and adult mosquitoes were fed normally and were allowed to grow in hexane, diethyl ether, dichloromethane and ethyl acetate crude extracts of the whole plant. The result of the experiment showed larval and pupal deformations and there was also inhibition of adult emergence. Hence it causes abnormalities in adult formation. So, it can be used as larvicidal [42]. Larvicidal activity against *Aedes aegypti* larvae have been showed by the acetone and petroleum ether extracts of *Murraya koenigii* leaves at a concentration range 250-900ppm.

- ***Ocimum sanctum***
Common name- Tulsi
Family- Lamiaceae

Botanical distribution- *O. sanctum* is an aromatic herb and shrub native to the tropical regions of Asia and the Americas. Medicinally importance flavonoids identified in *O. sanctum* were orientin, vicenin and luteolin [43]-[44]. Orientin and vicenin are reported to have radical scavenging activity [45]. While lutoelin is known to be anti-inflammatory agent and have therapeutic action against multiple sclerosis [46]-[47].

Medicinal Property- Tea, which is traditionally prepared by using *O. sanctum* boiled leaves, acts as a preventive medicament against Dengue fever [48]. The MNTD of methanolic extract of *O. sanctum* against Vero E6 cells in vitro was investigated. However, no significant difference in MNTD for *O. sanctum* was recorded. The methanolic extract of *O. sanctum* showed a slight inhibitory effect on DENV-1 based on cytopathic effects.

- ***Phyllanthus urinaria***

Common name- Chamber bitter, Gripe weed
Family- Phyllanthaceae
Botanical distribution- *P. urinaria* is a plant that originated in tropical Asia and widely distributed in South India, South America and China.
Medicinal property- It is used for treatment of several diseases like hepatitis, jaundice, urinary tract infections, syphillis, asthma, bronchitis, anaemia and joint pains etc. It was also found to have anti-cancer activity.7'-hydroxy-3',4',5',9',9'- pentamethoxy-3,4-methylene dioxy lignin isolated from the ethylacetate extract of *P. urinaria* was shown to exhibit anticancer activity [49] by inducing apoptosis. Recently this plant also shown to have anti dengue activity. Lee *et al.,* (2013) has studied the anti-dengue effect of aqueous and methanolic extract of four species of *Phyllanthus* such as *P. amarus, P. niruri, P. urinaria, P. wastonii* [50] -[51]. These species showed strongest inhibitory activity against DENV2 with more than 90% of virus reduction in simultaneous treatment at maximal non toxic dose of 250.0 µg/mL and 15.63 µg/mL.

- ***Piper retrofractum***

Common name-Long Pepper
Family- Piperaceae
Botanical distribution- *P. retrofractum* is a flowering vine native to Southeast Asia and cultivated in Indonesia and Thailand mostly for its fruit.
Medicinal property- In vitro anti-dengue activity of *P. retrofractum* in Vero cells was investigated [2]. The inhibitory activity against DENV-2 infected cells was determined on dichloromethane ethanol extract by the MTT method. The ethanol extract of *P. retrofractum* exhibited an inactivated viral particle activity or 84.93 % at a concentration of 100 µg mL-1. Previous study has shown that an aqueous extract of long pepper, *P. retrofractum*, gives the highest level of activity against mosquito larvae [52].

- ***Piper sarmentosum***

Common name- Lolot Pepper
Family- Piperaceae
Botanical distribution- *P. sarmentosum* is economically important because of their medicinal and culinary uses.
Medicinal property- Leaves of this plant are traditionally used as condiment and also used for its carminative property. The whole plant having medicinal properties and is used to treat inflammation, skin diseases, rheumatism, diarrhoea and root is used for the treatment of cough and asthma. *P. sarmentosum* contains many chemical constituents such as ascaricin, α-ascarone, β- sitosterols and also contains Vitamin C, Vitamin E, Carotenes, Xanthophylls etc. The ethanol extract of *P. sarmentosum* possesses larvicidal effect against early 4th instar larvae of *Aedes aegypti* mosquitoes. Udom *et al*., (2005) has studied the larvicidal activity of three species of pepper plants on *Aedes aegypti* [53].

- ***Psidium guajava***

Common name-Guava
Family- Myrtaceae
Botanical distribution: *P. guajava* 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.
Medicinal property- *P. guajava* leaf extract has been tested in vitro and showed to inhibit the growth of dengue virus. Water boiled with guava leaves was used to avoid bleeding in DHF, and increased platelet counts to 100.000/mm^3 within a period of approximately 16 h. *P. guajava* ripe fruit or juice has healing properties in cases of DF by improving the declining levels of platelets. In addition, unpublished research has found that *Psidium*

leaves are a good way to increase platelets, thus helping to avoid bleeding. A water decoction of guava leaves contains quercetin, which acts to inhibit the formation of enzyme mRNA in the virus.

- ***Quercus lusitanica*** **(**also known as ***Quercus infectora*****)**
  Common name- Gall Oak
  Family- Fagaceae
  Botanical distribution- *Q. lusitanica* is a species of oak native to Morocco, Portugal Greece, Asia, Iran Spain, and India.
  Medicinal property- In India gall extract is used to treat minor sore throat and chronic diarrhea. The gall extracts of *Q. infectoria* are extensively used in traditional medication as karkatasringi for the preparation of Balachaturbhadra, Shringyadi churna, Karkatadi churna, Kantkaryavaleha. *Quercus lusitanica* have been investigated for several medicinal properties such as astringent, anti-diabetic, anti-inflammatory, anti-bacterial and gastro protective activities.

  This plant was also analysed for anti-viral activity against dengue virus. Previous study demonstrates in vitro inhibitory activity of *Quercus lusitanica* seed extract. The result showed the down regulation of NS1 protein expression of infected cells after treating with seed extract. Same plant extract was evaluated again for anti dengue activity which showed seed extract of *Quercus lusitanica* inhibited Dengue type 2 virus in the concentration 0.032 to 0.25 mg/ml.

  Its extract was found to have a good inhibitory effect on the replication of DENV-2 in C6/36 cells. The methanol extract of the seeds completely inhibited (10–1,000 fold) the TCID50 of virus at its maximum non-toxic concentration of 0.25 mg mL-1 as indicated by the absence of cytopathic effects. A low dose of *Q. Lusitanica* (0.032 mg mL^{-1}) showed 100 % inhibition with 10 TCID50 of virus. Proteomics techniques were used to demonstrate that the effect of *Q. lusitanica* was to down regulate NS1 protein expression in infected C6/36 cells after treatment with the extract.

- ***Rhizophora apiculata***
  Common name- Tall-Stilt Mangroove
  Family- Rhizophoraceae
  Botanical distribution- *R. apiculata* is a mangrove tree up to 20 m tall that grows in Australia (Queensland and Northern Territory), Guam, India, Indonesia, Malaysia, Micronesia, New Caledonia, Papua New Guinea, the Philippines, Singapore, the 15 Solomon Islands, Sri Lanka, Taiwan, Maldives, Thailand and Vietnam.
  Medicinal property- Renugadevi *et al*., (2012) had studied the larvicidal activity of petroleum ether extracts of *Rhizophora apicuata* against *A.aegypti* mosquito [54]. Petroleum ether extract of *R. apiculata* is most effective with LC50 of 25.7µg/L. The extract further shows synergistic larvicidal activity with pyrethrum.

  Anti-dengue properties of the ethanolic extract of *R. apiculata* in DENV-2 in Vero cells have been reported[2]. *R. apiculata* exhibited inhibitory activity and an inactivated viral particle activity of 56.14 % and 41.5 % at concentrations of 12.5 and 100 µg mL^{-1}, respectively.

- ***Scutellaria baicalensis***
  Common name-Baikal skullcap
  Family- Lamiaceae
  Botanical Distribution- *S. baicalensis* is one of the traditional Chinese medicinal herbs that have been shown to possess many health benefits.
  Medicinal Property- *S. baicalensis* is one of the most widely used medicinal plants, and is officially listed in the Chinese Pharmacopoeia. Extracts of its roots have been widely used in the treatment of inflammation, cancer, infectious diseases, hypercholesterolemia and hypertension [55]. The roots of this plant contain a plethora of bio actives, for instance different types of flavonoids such as baicalein and wogonin [56]. Recently, several flavonoids including quercetin, fisetin [57]-[58] and baicalein[59] possessed significant antiviral activities against DENV has been reported in this plant. In vitro antiviral activities of aqueous extract of the roots of *S. baicalensis* were evaluated against all the four dengue virus (DENV) serotypes. The IC50 values for the *S. baicalensis* extract on Vero cells following DENV adsorption ranged from 86.59 to 95.19 µg/mL for different DENV serotypes. Weak prophylactic effects with IC50 values that ranged from 269.9 to 369.8 µg/mL were noticed when the cells were pre-treated 2 hours prior to virus inoculation. The concentration of baicalein in the *S. baicalensis* extract was ~1% (1.03 µg/gm dried extract). Study demonstrates the in vitro anti-dengue virus replication property of *S. baicalensis* against all the four DENV serotypes investigated. The extract reduced DENV infectivity and replication in Vero

cells. The extract was rich in baicalein, and could be considered for potential development of anti-DENV therapeutics.

In vitro assay using Vero cells an FFURA to assess antiviral activity against DENV-2 was conducted. This flavonoid inhibited DENV-2 serotype replication in Vero cells displaying an IC50 of 6.46 μg/mL and a selectivity index of 17.8 when it was added after adsorption to the cells. The IC50 against DENV-2 is 5.39 μg/mL and the selectivity index increased to 21.3 when Vero cells were treated before virus infection and continuously up to 4 days post-infection. Substance displayed direct virucidal (IC50 of 1.55 μg/mL) as well as anti-adsorption (IC50 of 7.14 μg/mL) effects against DENV-2. The results suggest that a possible mechanism for the extracellular and intracellular activities of baicalein against DENV-2 could be attributed to its ability to bind and/or to inactivate important structural and/or non-structural protein(s) of DENV-2.

- ***Tephrosia crassifolia, Tephrosia madrensis* and *Tephrosia viridiflora***
  Common name- Sarpunkha
  Family- Fabaceae
  Botanical Distribution-Genus *Tephrosia* is an herb, under shrub or shrub, distributed mainly in tropical and subtropical regions of the world.
  Medicinal Property- Three species from this family (*Tephrosia crassifolia*, *Tephrosia madrensis* and *Tephrosia viridiflora*) were investigated. 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.

- ***Uncaria tomentosa***
  Common name- Cat's Claw
  Family- Rubiaceae
  Botanical Distribution- *U. tomentosa* is a large, woody vine growing in the tropical jungles of Central and South America, native to the Amazon and Central American rainforests [60]. It is used widely as traditional medicine by native people of the Peruvian rainforest.
  Medicinal Property- Root and bark extracts of *U. tomentosa* plant exhibited immune stimulating activity, anticancerous, antileukemic, anti-viral properties have been demonstrated.

  Anti-Viral activity of hydro-alcoholic extract of *Uncaria tomentosa* plant was evaluated on human monocytes infected with Dengue type 2 virus. The results of this study demonstrated an *in vitro* inhibitory activity by extracts reducing Dengue –Ag+ cell rates in treated monocytes [60].

- ***Zostera marina***
  Common name- Eelgrass
  Family-Zosteraceae
  Botanical Distribution- *Z. marina* is an aquatic plant that is native to North America and Eurasia.

2. Medicinal Property- A compound from the temperate marine *Z. marina* has been identified as possessing anti dengue virus activity in a focus forming unit assay in LLCMK2 cells [61]. The anti-adhesive compound p-sulfoxycinnamic acid, zosteric acid, ZA10, derived from *Z. marina* showed a modest IC50 of approximately 2.3 mm against DENV-2. The other compound with related chemistries, CF 238, showed the most activity, with IC50 values of 24, 46, 14 and 47 μM against DENV-1, DENV-2, DENV-3 and DENV-4, respectively.

This review has covered 40 plant species belonging to different families and their potential active compounds that would be utilized in the treatment of dengue. The available research highlights the knowledge available regarding various medicinal plants parts and their extracts for the treatment of dengue. This review highlights about all the prominent pharmacological activity of plant compounds against dengue. Moreover, such discoveries review may cause the event of highly efficient and safe anti-dengue treatments and great impact on future viral research in conjunction with interesting for isolation of furthermore natural compounds for medical treatment.The development of latest anti-dengue products from bioactive compounds is vital so on hunt down simpler and fewer toxic anti-dengue drugs. Therefore, any extensive study on the potential of plants with isolated active compounds that have shown anti-dengue activities should undergo additional *in vitro* and *in vivo* animal testing followed by toxicity and clinical tests. This route may reveal a promising compound to be optimized and thus be suitable for application within the assembly of latest anti-dengue compounds. If pursued from drugs derived from medicinal plants around the continents, this work

may prove valuable to the health of individuals and to nations. However, to identify potential anti-dengue plants or compounds, knowledge of the mechanisms of virus infection need to be understood so on facilitate the design for and development of the foremost appropriate drugs. Further research is required to figure out the target the foremost appropriate stages to prevent the spread of virus infection that specialize in each introduce the life cycle of the virus, new compounds could prevent (1) infection of host cells, (2) the viral maturation process, (3) synthesis of viral RNA, or (4) the spread of viral particles.

3. CONCLUSION:

During the last decades, the exploitation of the natural product pool has afforded a selection of compounds possessing activity against dengue virus serotypes. In several cases, very interesting activities are associated with the described compounds. It is often stated, though, that only a little fraction of the vast reservoir of compounds available from nature has been explored with the aim to hunt out antivirus effective against dengue. From nature, it's possible that effective dengue antiviral compounds with low toxicity to citizenry will certainly be found. Moreover, the structures of the natural compounds can function prototypes which can be optimized by synthetic campaigns so on hunt down even more active substances against dengue virus. Dengue fever regardless of its serotypes has been the foremost prevalent arthropod-borne viral diseases among the earth population. The event of a dengue vaccine is complicated by the antibody-dependent enhancement effect. Thus, the event of a plant-based antiviral preparation promises a more potential alternative in combating dengue disease.

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