Role of Botanical Drugs in Controlling Dengue Virus Disease

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Abstract:- Dengue is a mosquito-born viral infection which is one of the serious threats to human population and economic burden in tropical and sub-tropical region particularly in Asia. The viral infection causes flu-like symptoms and can develop into a potentially fatal form of the disease – dengue haemorrhagic fever (DHF) which eventually leads to dengue shock syndrome (DS). The severity of dengue fever is further amplified by the lack of treatment. Till today there is no treatment or medicine for controlling the dengue fever and except Dengavaxia which is not enough for the protection from infection of all the four serotypes of dengue. India has a rich diversity of herbal medicine which is used in traditional ethnomedicine. Indian rural population still depends upon herbal medicine for the treatment of various viral fevers including dengue virus disease because of its cost effectiveness and easily availability. Therefore, Indian traditional/folk medicine system known as Ayurveda plays an important role in controlling many viral infections including dengue disease. Hence new antiviral medicines of botanical origin could be easily accepted, being non-toxic and inexpensive. This review paper updated and discussed most of the published research work on the use of herbal medicine for the treatment of dengue fever which could be the primary knowledge on the anti dengue plants. These anti dengue plants could be further analyzed and studied for the future development of botanical drugs for controlling dengue viral disease.

Key words: Anti dengue plants, Ayurveda, dengue viral disease, herbal medicine, India

I. INTRODUCTION

Epidemic dengue is one of the life threatening viral infection transmitted from one person to another by the bites of infected female arthropod vector Aedes aegypti mosquito (Malabadi et al. 2011, 2010, 2017a, 2017b; Chaturvedi and Nagar, 2008; Murray et al. 2013). Female Aedes aegypti mosquito is also a major responsible vector for other viral infectious diseases like chikungunya, Zika virus, and Ebola virus diseases too (Malabadi et al. 2016a). Dengue virus disease is endemic in more than 100 countries including India leading to the death of 390 million people with children in dengue endemic region (Malabadi et al. 2017a, 2017b; Malabadi et al. 2010, 2011; Bhatt et al. 2013; Gubler, 2012; Ganguly et al. 2013a, 2013b, 2013c, 2013d; Ganguly et al. 2014, 2015; Halstead, 2007). Dengue virus disease is characterized by four closely but distinct serotypes DENV-1, DENV-2, DENV-3 and DENV-4 (Halstead, 2007; Malabadi et al. 2011, 2017a, 2017b; Malabadi et al. 2010, 2011; Gubler, 2012; Ganguly et al. 2013a, 2013b, 2013c, 2013d; Ganguly et al. 2014, 2015; Halstead, 2007; Khetarpal and Khanna, 2016). The serotype characterization of dengue has made a very difficult task for the development of a dengue vaccine (Malabadi et al. 2011, 2017a, 2017b; Malabadi et al. 2010, 2011; Gubler, 2012; Ganguly et al. 2013a, 2013b, 2013c, 2013d; Ganguly et al. 2014, 2015; Halstead, 2007; Swaminathan et al. 2013; Swaminathan et al. 2016; Swaminathan and Khanna, 2009). Till today there is no antiviral drug or vaccine for the treatment of dengue except only one tetravalent formulated French vaccine (Dengvaxia) (CYD-TDV) (Sanofi Pasteur’s, France) available since 2015 in few endemic countries except India (Malabadi et al. 2017a, 2017b; Villar et al. 2015; Thomas, 2015; Gottscham et al. 2016; Vannice et al. 2015, 2016). Dengvaxia (CYD-TDV) (Sanofi Pasteur’s, France) has not yet approved in India due to the lack of enough clinical data in the Indian population. Other major problems of Sanofi Pasteur branded Dengvaxia (CYD-TDV) are 1) serotype interferences, 2) imbalance viral replication of the four monovalent serotypes along with epitopes-linked immunodominance had been observed when the vaccine was administrated as tetravalent formulation (Villar et al. 2015; Thomas, 2015; Guy et al. 2009; Malabadi et al. 2017a, 2017b; Tripathi et al. 2015; Whitehead, 2016; Martin and Hermida, 2016; Vannice et al. 2015, 2016; Pang and Loh, 2017). Dengvaxia (CYD-TDV) confirmed unbalanced protection against the different dengue serotypes and increased risk for haemorrhagic disease particularly among children (Vannice et al. 2015, 2016; Tripathi et al. 2015; Pang and Loh, 2017). Therefore, next generation dengue vaccines such as , new viral vectors, viral vectored subunit, VLP’s, peptide chimeras, and DNA vaccines would be better option and might play an important role in the production of suitable dengue vaccines (Malabadi et al. 2016b; Malabadi et al. 2017a, 2017b; Vannice et al. 2015, 2016; Tripathi et al. 2015; Pang and Loh, 2017).

In India, dengue virus was first isolated in the year 1944 in Kolkata from the serum samples of infected US soldiers (Sabin and Schlesinger, 1945; Singh and Rawat, 2017). In 1996, the first major epidemics of Dengue Haemorrhagic Fever (DHF) and/or Dengue Shock Syndrome (DSS) occurred near Delhi and Lucknow in Uttar Pradesh and
thereafter the dengue virus started spreading across India (Dar et al. 1999; Agarwal et al. 1999; Shah et al. 2004; Singh and Rawat, 2017). Reported dengue infected cases and mortality due to dengue in Indian states were thoroughly evaluated for last 20 years using licensed version of www.indiastat.com (Singh and Rawat, 2017). Epidemic dengue viral disease causes an acute febrile illness known as dengue fever (DF) followed by dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) (WHO, 2009; Malabadi et al. 2017a; Vannice et al. 2015, 2016; Pang and Loh, 2017). Dengue induced thrombocytopenia is life threatening and a major health disorder resulted in the lower platelet count in patients with dengue fever (DF) (WHO, 2009; Malabadi et al. 2017a, 2017b). The common dengue virus diseases symptoms are sudden onset of high fever accompanied by abdominal pain, nausea, cold, headache, pain in the neck, eyes, myalgia and arthralgia, flushing of the face, anorexia (WHO, 2009). Rash is frequently seen on the trunk, on the insides of the arms and thighs (WHO, 2009; Malabadi et al. 2017a). Laboratory abnormalities may include leukopenia and thrombocytopenia (WHO, 2009; Malabadi et al. 2017a, 2017b). Warning signs of severe dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2 cm, or an increase in haematocrit concurrent with a rapid decrease in platelet count (WHO, 2009). Criteria for severe dengue include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment (WHO, 2009; Malabadi et al. 2017a). There are numerous dengue vaccine candidates in pipeline throughout world including India but none of them not yet promoted vaccination (Malabadi et al. 2017a).

Medicinal plants plays an important role in primary health care and therefore, becomes an integral part of human life to combat many diseases (Malabadi, 2008; Malabadi and Vijayakumar, 2008; Malabadi et al. 2009, 2010; Malabadi et al. 2012a, 2012b, 2012c, 2012d; Malabadi et al. 2016a, 2016b, 2016c, 2016d; Malabadi et al. 2017a, 2017b; Singh and Rawat, 2017; Nityasree et al. 2017; Supriya et al. 2017; Sowmyashree et al. 2017). Herbal medicines of antiviral activity are of great interest and have been widely explored. Plant based antiviral compounds can block or inhibit dengue virus replication cycle by interfering with virus attachment to cells, interfering with viral enzymes or suspending dengue viral genome replication.

In India, traditional use of herbal medicines known as Ayurveda is being passed from one generation to generation due to many reasons such as availability, acceptability, compatibility, and affordability (Malabadi et al. 2016a, 2016b, 2016c, 2016d; Singh and Rawat, 2017). Ayurveda is the most ancient science of life having a holistic health approach. Ayurvedic system of medicines is one of the worlds oldest use of herbal medicines which was originated and practised in India more than 3,500 years ago and remained one of the best solution for many human health ailments. Therefore, Ayurvedic science is dynamic and progressive. Traditional healers with rich knowledge of medicinal plants have been exploited for the purpose of treatment of many patients in the rural parts of India. It is one of the age-old tradition of using plant-based-medicines for preventive and curative healthcare in India (Singh and Rawat, 2017). In India dengue fever is currently being managed by clinicians through various adjuvant and alternative therapeutic options (Singh and Rawat, 2017).

This review paper highlights the list of potential anti-dengue plants and their preliminary studies on the role of botanical drugs as an effective medicine against dengue virus disease based on in vitro experimental results, ethnomedical studies, clinical data in few plants conducted in different laboratories throughout world including India. On the basis of this preliminary literature study reported, there is a ray of hope for the potential development of a new herbal medicine drugs against dengue could be developed.

1) Carica papaya (Papaya)

Papaya (Carica papaya L.,) belongs to family Caricaceae is one of the economically important fruit crop with medicinal values in tropical and sub-tropical countries (Malabadi et al. 2011; Aravind et al. 2013; Sarala and Paknikar, 2014; Vij and Prashar, 2015). There are many reports of clinical, experimental and pilot studies which confirmed the use of crude leaf preparations of Carica papaya for the treatment of dengue infections (Kasture et al. 2016; Dhungat and Gore, 2016; Pangtey et al. 2016; Patil et al. 2013; Gowda et al. 2015; Sarala and Paknikar, 2014; Ranasinghe et al. 2012; Swati et al. 2013; Siddique et al. 2014; Dhara et al. 2016; Jayanthi, 2016; Asadullah et al. 2017; Senthilvel et al. 2013; Sathasivam et al. 2009; Subenthiran et al. 2013). An increase in the platelet count within 24 h of treatment by the oral administration of papaya leaf extract in patients suffered from dengue fever has been reported (Kumar, 2010; Ahmad et al. 2011; Sarala and Paknikar, 2014; Ranasinghe et al. 2012; Siddique et al. 2014; Subenthiran et al. 2013; Ansari, 2016). A study reported by Yunita et al. (2012) in Indonesia, confirmed that the use of Carica papaya leaf extracts capsules (CPC) increased platelets count in dengue infected patients (Yunita et al. 2012; Sarala and Paknikar, 2014). Another study found that Carica papaya leaf aqueous extract at a concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model (Patil et al. 2013; Sarala and Paknikar, 2014). Subenthiran et al. (2013) investigated the platelet increasing property of Carica papaya leaves juice (CPLJ) in patients with dengue fever (DF) (Subenthiran et al. 2013; Ansari, 2016). Furthermore, fresh C. papaya leaf extract significantly increased the platelet and RBC counts in the test group as compared to controls (Dharmarathna et al. 2013; Wiwanitkit, 2013). A pilot study confirmed the platelet increasing property of Carica papaya leaf extract (CPLJ) in patients with dengue fever (DF) (Gowda et al. 2015). Carica papaya leaf extract could be used in dengue fever with thrombocytopenia patients (Kala, 2012;
Gadhwal et al. 2016; Agarwal et al. 2016). Charan et al. (2016) reported that Carica papaya leaf extract could be considered as one of the potential herbal medicine to increase platelet count in patients suffering from dengue fever (DF) (Charan et al. 2016; Wiwanitkit, 2013; Vij and Prashar, 2015; Ching et al. 2016; Chinnappan et al. 2016; Solanki et al. 2017). Kasture et al. (2016) reported the administration of Carica papaya leaf extract significantly increased the platelet count in cases of thrombocytopenia associated with dengue, preventing the patient from dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) conditions (Kasture et al. 2016; Dhungat and Gore, 2016; Benazir and Abhinayani, 2015; Singhal et al. 2016; Singh and Rawat, 2017).

Hence Carica papaya leaf extract (Caripill) could be used as an additional or as a complementary botanical drug in acute febrile illness patients with thrombocytopenia since optimum dose of papaya leaf accelerates the increase in the platelet count (Dhara et al. 2016; Manohar, 2013; Asadullah et al. 2017; Solanki et al. 2017). Carica papaya leaf extract (Caripill) is the tablet released by a Bengalure based pharmaceutical company Micro Labs Bengalure, Karnataka, India for treating patients suffering from dengue fever (The Times of India, 2015; News Gram, 2015). Therefore, papaya leaf extract could be considered as a oral first aid treatment for dengue and papaya got scientific endorsement.

2) Psidium guajava (Guava)

Guava (Psidium guajava) belongs to family Myrtaceae is a small tree native to Mexico, Central America, and northern South America (Malabadi and Nataraja, 2002; Ravi and Divyashree, 2014; Rastogi and Mehrotra, 2002a, 2002b). India is known worldwide for its Ayurvedic treatment (Ravi and Divyashree, 2014). The oldest remedies known to mankind are botanical medicines (Cohen, 2014; Solanki et al. 2017). The Indian indigenous system of medicine, namely, Ayurvedic, Siddha, and Unani, has been in existence for several centuries (Kumar et al. 2010; Rastogi and Mehrotra, 2002a, 2002b). Ayurveda has a holistic approach to health and disease that focuses on preserving and promoting good health and preventing disease through healthy lifestyle practices (Cohen, 2014). Therefore, plants occupy a very important place as the raw material for some important drugs and plants provide the starting material for the synthesis of conventional drugs (Solanki et al. 2017; Kumar et al. 2010; Rastogi and Mehrotra, 2002a, 2002b; Ravi and Divyashree, 2014).

In rural parts of India, the leaf extract of Psidium guajava has been used in controlling dengue fever (DF) particularly increasing platelet count. However, there is no enough clinical and experimental data and scientific evidence for the approval of the leaf extract of Psidium guajava in controlling dengue fever. One of the unpublished research has found that Psidium guajava leaves are a good way to increase platelets, thus helping to avoid bleeding (Healthy Lifestyle, 2010; Kadir et al. 2013; Pink Roses, 2011; Solanki et al. 2017). A water decoction of guava (Psidium guajava) leaves contains quercetin, which acts to inhibit the formation of enzyme mRNA in the virus (Healthy Lifestyle, 2010; About Health, 2011; Kadir et al. 2013; Solanki et al. 2017).

The phytochemical constituents of guava (Psidium guajava) are vitamins, tannins, phenolic compounds, flavonoids, essential oils, sesquiterpene alcohols and triterpenoid acids (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002; Rastogi and Mehrotra, 2002a, 2002b). Leaves contain phenolic compounds, isoflavonoids, gallic acid, catechin, epicatechin, rutin, naringenin, kaempferol having hepatoprotective, antioxidant, anti-inflammatory, antispasmodic, anticancer, antimicrobial, anti-hyperglycemic, analgesic actions (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002). The leaf contains two important flavonoids quercetin known for its spasmolytic, antioxidant, antimicrobial, anti-inflammatory actions (Ravi and Divyashree, 2014) and guaijererin known for its antibacterial action (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002). Pulp contains ascorbic acid, carotenoids (lycopenes, β-carotene) possessing antioxidant, anti-hyperglycemic, antineoplastic (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002).

Guava (Psidium guajava) has been used in the treatment of diarrhea, dysentery, menstrual disorders, vertigo, anorexia, digestive problems, gastric insufficiency, inflamed mucous membrane, laryngitis, skin problems, ulcers, vaginal discharge, cold, cough, cerebral ailments, nephritis, jaundice, diabetes, malaria and rheumatism (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002). The pharmacological properties of guava (Psidium guajava) are antiarrheal, antimicrobial, antiparasitic, antitussive, hepatoprotective, antioxidant, antigenotoxic, antimutagenic, antiallergic, anticancer and anti-hyperglycemic effects (Ravi and Divyashree, 2014; Dakappa et al. 2013; Joseph and Priya, 2011; Sanda et al. 2011; Rishika and Sharma, 2012; Mittal et al. 2010; Arima and Danno, 2002).

3) Euphorbia hirta (Tawa-Tawa): Asthma-plant

Euphorbia hirta (sometimes called Asthma-plant) (Kannad name: Achchedida) belongs to family Euphorbiaceae, is a pan tropical weed, a native of India is a medicinal annual herb often characterized by the presence of white milky latex which is more or less toxic (Kumar et al.
Euphorbia hirta is found in open grassland, roadside, distributed throughout the hotter parts of India and Australia, often found in waste places along the roadsides (Kumar et al. 2010; Sood et al. 2005; Rastogi and Mehrotra, 2002a, 2002b).

Tawa-Tawa (Euphorbia hirta Linn) or Asthma weed is a bushy, slender-stemmed plant that grows up to a height of two inches and has several tiny flowers bunch together with opposite rhombus leaves, which have a toothed margin (Guzman et al. 2016; Tungol-Paredes et al. 2014; Paredes et al. 2014; Apostol et al. 2012; Arollado et al. 2013; Mir et al. 2012; http://rubygoldaid.com/product-specials/tawa-tawa-capsule). This plant had been used in traditional medicine to treat respiratory tract problems, laryngeal spasm, ulcerated cornea and conjunctivitis (http://rubygoldaid.com/product-specials/tawa-tawa-capsule). It is believed that Euphorbia hirta could augment blood platelet count in the body which is normally low among all dengue fever patients, hence, many native people in the Philippines boil the leaves of Euphorbia hirta and drink it as a tea (http://rubygoldaid.com/product-specials/tawa-tawa-capsule).

Dengue-Aid-Tawa-Tawa (Euphorbia hirta Linn) (Ruby Gold herbal enterprises, the Philippines) is a potent herbal supplement in capsules which is taken from pure extracts from the Euphorbia hirta Linn herbs which is commonly known as “Tawa-Tawa” by the local residents in the Philippines (http://rubygoldaid.com/product-specials/tawa-tawa-capsule). Dengue-Aid Tawa-Tawa (Euphorbia hirta Linn) used all the parts, roots, stems and leaves of the Euphorbia hirta Linn herbs. Euphorbia hirta Linn had been associated mainly in helping dengue fever victims recovery quickly from the dengue viral infection in the Philippines (http://rubygoldaid.com/product-specials/tawa-tawa-capsule, Business Diary.com, the Philippines, 2017).


Apostol et al. (2012) and Arollado et al. (2013) demonstrated the lyophilized leaf decoction of Euphorbia hirta augmented platelet count in thrombocytopenic rats (Apostol et al. 2012; Arollado et al. 2013). The study reported by Guzman et al. (2016) documented the anecdotal and traditional self-care uses of Euphorbia hirta in the treatment of dengue in 3 indigenous communities in Pangasinan in Philippines according to demography, relative importance, and fidelity levels (FL) from April to June of 2015 (Guzman et al. 2016). Therefore, the study conducted by Guzman et al. (2016) highlighted the ethnobotanical uses of Euphorbia hirta in controlling dengue (Guzman et al. 2016). During this study, respondents, dominated by the age group 60-80 and mostly females with at least primary and secondary education, provided the information on the use of Euphorbia hirta (Guzman et al. 2016). High fidelity levels (FL) values and corrected major use agreements (cMUA) of at least 35% were obtained for cardinal symptoms of dengue-related to bleeding episodes while low corrected major use agreements (cMUAs) (i.e. 2-4%) were obtained for symptoms during the recovery phase (Guzman et al. 2016). High fidelity levels (FL) values were obtained for symptoms observed during the febrile phase (Guzman et al. 2016). The most widely used dosage forms were decoctions of the leaves and barks of Euphorbia hirta (Guzman et al. 2016). Mir et al. (2012) described “tawa-tawa” water was effective in increasing platelet count and improved the health conditions of dengue patients (Mir et al. 2012). The platelet count and TLC were increased non significantly after treatment of herbal water of Euphorbia hirta (Mir et al. 2012). Haematocrit value decreased non significantly after using the herbal water of Euphorbia hirta (Mir et al. 2012). Over 70% of patients showed moderate increase in their platelet count (Mir et al. 2012). However leucopenia improved significantly after the use of aqueous extract of Euphorbia hirta (Mir et al. 2012). In another study, Paredes et al. (2014) reported that the beneficial effect of Euphorbia hirta in dengue patients depends upon the degree of changes in platelet levels.

Despite these developments, there is no scientific evidence that revealed the effectiveness of Euphorbia hirta in humans infected with the dengue virus. Since little information is known about the purported therapeutic claim of Euphorbia hirta against dengue and other illnesses. Since Euphorbia hirta was found to be effective against most symptoms of dengue in the initial, febrile and recovery stages (Guzman et al. 2016; Tungol-Paredes et al. 2014; Paredes et al. 2014; Apostol et al. 2012; Arollado et al. 2013; Mir et al. 2012; Philippine Medicinal Plants, 2011; The Cure Library, 2007; Kadir et al. 2013).
2007; About Health, 2011; Kadir et al. 2013). These findings further warranted the development of the plant into dosaged forms that could be utilized in clinical trials aimed at ensuring the efficacy and safety of *Euphorbia hirta* in the supportive therapy of dengue (Guzman et al. 2016; Kadir et al. 2013).

*Euphorbia hirta* is often traditionally used for female disorders, respiratory ailments (cough, coryza, bronchitis, and asthma), worm infestations in children, dysentery, jaundice, pimpls, gonorrhea, digestive problems, and tumors (Kumar et al. 2010; Galvez et al. 1993; Lanhers et al. 1991; Johnson et al. 1999; Liu et al. 2007; Rastogi and Mehrotra, 2002a, 2002b; Ogbulie et al. 2007; Suresh et al. 2008). *Euphorbia hirta* reported to contain alkanes, triterpenes, phytosterols, tannins, polyphenols, flavonoids, amino acids, and alkaloids (Kumar et al. 2010; Galvez et al. 1993; Lanhers et al. 1991; Johnson et al. 1999; Liu et al. 2007; Rastogi and Mehrotra, 2002a, 2002b; Ogbulie et al. 2007; Suresh et al. 2008). *Euphorbia hirta* possesses antibacterial, anthelmintic, antiasthmatic, sedative, antipsammodic, antiptifungal, and antimalarial properties (Kumar et al. 2010; Galvez et al. 1993; Lanhers et al. 1991; Johnson et al. 1999; Liu et al. 2007; Rastogi and Mehrotra, 2002a, 2002b; Ogbulie et al. 2007; Suresh et al. 2008).

4) *Azadirachta indica* (Neem)

*Azadirachta indica* belongs to family *Meliaceae*. It is fast-growing tree with a final height in the range of 15–20 m. It is native to India and grows throughout tropical and semi-tropical regions. *In vitro* and *in vivo* inhibitory potential of crude aqueous extract of *Azadirachta indica* (neem) leaves and pure neem compound (Azadirachtin) on the replication of dengue virus type-2 has been reported (Parida et al. 2002). *In vitro* antiviral activity of aqueous neem leaves extract assessed in C636 cloned cells of larvae of *Aedes albopictus* cells employing virus inhibition assay showed inhibition in dose dependent manner (Parida et al. 2002). The aqueous extract of neem leaves at its maximum non-toxic concentration of 1.897 mg/ml completely inhibited 100–10,000 TCID50 of virus as indicated by the absence of cytopathic effects (Parida et al. 2002). The *in vivo* protection studies with neem leaves extract at its maximum non-toxic concentrations of 120–30 mg/ml resulted in inhibition of the virus replication as confirmed by the absence of dengue related clinical symptoms in sucking mice and absence of virus specific 511 bp amplicon in RT-PCR (Parida et al. 2002). The pure neem i.e. Azadirachtin did not revealed any inhibition on dengue virus type-2 replication in both *in vitro* and *in vivo* systems (Parida et al. 2002).

In another study reported by Shanthi and Rajarajan, (2014), an *in vitro* antiviral activity of aqueous, aqueous-ethanolic and ethanolic extracts of *Azadirachta indica*, *Quercus lusitanica* and *Wedelia calandulacea* on dengue 2&4 serotypes in vero cell line and compared with known antiviral drug Ribavirin has been reported (Shanthi and Rajarajan, 2014). The antiviral activity of lyophilized aqueous extract of *Azadirachta indica* showed better activity for dengue 2&4 at a maximum nontoxic dose concentration of 500μg/ml and the ethanolic extracts were partially inhibited at the concentration of 500μg/ml to dengue 2 but not in dengue 4 (Shanthi and Rajarajan, 2014). Whereas the aqueous-ethanolic extract of neem, three extracts of *Quercus lusitanica* and *widely calandulaceae* did not show any inhibition on dengue 2 & 4 (Shanthi and Rajarajan, 2014; Singh and Rawat, 2017). The antiviral activity of Ribavirin exhibited 7.5μg/ml for dengue 2&4 serotypes (Shanthi and Rajarajan, 2014). These data suggested that the lyophilized aqueous extracts of *Azhadirachta indica* possessed the ability of inhibiting the activity of dengue 2 and 4 by *in vitro* assays (Shanthi and Rajarajan, 2014; Singh and Rawat, 2017). Hence the leaves of *Azhadirachta indica* could potentially be sourced in developing the anti-dengue drugs (Shanthi and Rajarajan, 2014). Isolation, purification and characterization of the active compounds from *Azhadirachta indica* in order to discover the potential anti-dengue compounds should be carried out (Shanthi and Rajarajan, 2014). Furthermore, investigations into the mode of action of anti-dengue activities of the active compounds could be done to provide more insight into the inhibition of dengue and dengue virus replication and to explore its potential use as a therapeutic weapon to combat dengue (Shanthi and Rajarajan, 2014). Therefore, the use of leaves of *Azhadirachta indica* received scientific endorsement as a herbal medicine for dengue. In addition to this, there is also a cocktail of papaya leaf juice, leaves of *Azhadirachta indica* (Neem) often mixed with hill neem were also used as the best cure for increasing the platelet count during dengue fever (DF) in some rural parts of Tamilnadu, Karnataka and Kerala states in India (The Times of India-chennai, 2012).

5) *Alternanthera philoxeroides* (Alligator Weed)

*Alternanthera philoxeroides* belongs to family *Amaranthaceae* is a noxious invasive aquatic weed widespread throughout the world (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). It is originated from South America but currently invaded Wular lake, Kashmir, India, other parts of India, and Australia (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). This weed plant tends to differ in appearance, the plant can often be identified by its fleshy stems and white flowers (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). These horizontal stems, which formed dense mats on the surface of lakes and ponds, could grow up to 10 meters in length (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). These weeds have simple, elliptic, and have smooth margins (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). The plant flowers from December to April and usually grows around 13 mm in diameter and tend to be papery and ball-shaped (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). It has reduced water flow and quality by preventing light penetration and oxygenation of the water (Buckingham, 1996; Sainy et al. 1998; Masoodi and Khan. 2012). *Alternanthera philoxeroides* has also reduced waterbird activity and caused the death of fish and native plants. Alligator weed mats created a favorable habitat for breeding
mosquitoes (Buckingham, 1996; Sainty et al. 1998; Masoodi and Khan. 2012). The in vitro effect of Alternanthera philoxeroides extracts against dengue virus was investigated (Jiang et al. 2005; Kadir et al. 2013). An MTT assay was carried out to determine the cytotoxicity of Alternanthera philoxeroides on C6/36 cell lines (Jiang et al. 2005; Kadir et al. 2013). This study confirmed that coumarin extract of Alternanthera philoxeroides showed the lowest toxicity on cells (TD50=535.91), whereas a petroleum ether extract of Alternanthera philoxeroides had the strongest inhibitory effect on dengue virus (ED50 = 47.43) (Jiang et al. 2005; Kadir et al. 2013). Therefore, Alternanthera philoxeroides Griseb possesses an in vitro antiviral effects on dengue virus (Jiang et al. 2005; Kadir et al. 2013).

6) Ocimum sanctum (Tulsi)

Tulsi (Ocimum sanctum) belongs to basil family Lamiaceae (tribe ocimeae) is an aromatic shrub originated in India (Bast et al. 2014; Cohen, 2014). In Ayurveda, tulsi is known as “The Incomparable One,” “Mother Medicine of Nature” and “The Queen of Herbs” (Singh et al. 2010; Cohen, 2014). Tulsi (Ocimum sanctum) is one of the best examples of Ayurveda’s holistic lifestyle approach to health (Cohen, 2014). Therefore, ancient Ayurvedic wisdom, suggested that tulsi (Ocimum sanctum) is a tonic for the body, mind and spirit that offers solutions to many modern day health disorders (Cohen, 2014). Tulsi (Ocimum sanctum) has been recommended as a treatment for a range of health disorders including anxiety, cough, asthma, diarrhea, fever, dysentery, arthritis, eye diseases, otalgia, indigestion, hiccups, vomiting, gastric, cardiac and genitourinary disorders, back pain, skin diseases, ringworm, insect, snake and scorpion bites and malaria (Cohen, 2014; Mohan et al. 2011; Pattanayak et al. 2010; Mondal et al. 2009).


Tulsi (Ocimum sanctum) being antiviral in nature frequently consumed as a herbal tea or chai acts as a preventive botanical medicine against dengue fever (DF) (Tang et al. 2012; Mondal et al. 2011; Gbolade and Lockwood, 2008; Kadir et al. 2013). The maximum non-toxic dose (MNTD) of methanolic extract of Ocimum sanctum against Vero E6 cells in vitro was investigated (Tang et al. 2012; Kadir et al. 2013; Solanki et al. 2017). However, no significant difference in maximum non-toxic dose (MNTD) for Ocimum sanctum was recorded (Tang et al. 2012; Kadir et al. 2013). The methanolic extract of Ocimum sanctum showed a slight inhibitory effect on dengue-1 based on cytopathic effects (Tang et al. 2012; Kadir et al. 2013; Solanki et al. 2017; Singh and Rawat, 2017). In addition to this, the toxicity of tulsi (Ocimum sanctum) L. essential oil to Aedes aegypti larvae has been reported by Gbolade and Lockwood, (2008).

A study was designed to evaluate the immunomodulatory effects of ethanolic extract of Tulsi (Ocimum sanctum) leaves through a double-blinded randomized controlled cross-over trial on healthy volunteers (Mondal et al. 2011). During this study, three hundred milligrams capsules of ethanolic extracts of leaves of Tulsi (Ocimum sanctum) or placebo were administered to 24 healthy volunteers on empty stomach and the results of 22 subjects who completed the study were analyzed (Mondal et al. 2011). This study confirmed the significant increase in the levels of IFN-γ (interferon-γ) (p = 0.039), IL-4 (interleukin-4) (p = 0.001) and percentages of T-helper cells (p = 0.001) and NK-cells (p = 0.017) were observed after 4 weeks in the Tulsi (Ocimum sanctum) extract intervention group in contrast to the placebo group (Mondal et al. 2011). Therefore, this study strongly ascertained the immunomodulatory role of Tulsi (Ocimum sanctum) leaves extract on healthy volunteers (Mondal et al. 2011).

7) Andrographis paniculata


In one of the study, Tang et al. (2012) confirmed the antiviral effects of standardised methanolic extracts of Andrographis paniculata against dengue virus serotype-1(Tang et al. 2012; Kadir et al. 2013; Frederico et al. 2017; Singh and Rawat, 2017). Antiviral assay based on cytopathic effects (CPE) denoted by degree of inhibition upon treating DENV1-infected Vero E6 cells with the maximum nontoxic dose (MNTD) of Andrographis paniculata has the most antiviral inhibitory effects (Tang et al. 2012; Kadir et al. 2013; Frederico et al. 2017). The methanolic extracts of Andrographis paniculata possess the highest ability of inhibiting the activity of dengue virus serotype-1 by in vitro antiviral assay based on cytopathic effects (Tang et al. 2012; Kadir et al. 2013; Frederico et al. 2017). Therefore, this study confirmed that Andrographis paniculata could be considered...

Andrographis paniculata has been used by traditional healers for stomach-aches, inflammation, pyrexia, and intermittent fevers (Hossain et al. 2014; Joselin and Jeeva, 2014; Kadir et al. 2013; Okhuarobo et al. 2014). The whole plant has been used for several applications such as antidote for snake-bite and poisonous stings of some insects, and to treat dyspepsia, influenza, dysentery, malaria and respiratory infections (Joselin and Jeeva, 2014; Hossain et al. 2014; Kadir et al. 2013; Okhuarobo et al. 2014). The leaf extract is a traditional remedy for the treatment of infectious disease, fever causing diseases, colic pain, loss of appetite, irregular stools and diarrhoea (Hossain et al. 2014; Joselin and Jeeva, 2014; Kadir et al. 2013; Okhuarobo et al. 2014; Frederico et al. 2017). In Indian Ayurvedic medicinal system, Andrographis paniculata has been used for a variety of ailments like dysmenorrhoea, leucorrhoea, pre-natal and postnatal care, complicated diseases such as jaundice, gonorrhoea and general ailments like wounds, cuts, boils and skin diseases (Saxena et al. 1998; Hossain et al. 2014; Joselin and Jeeva, 2014; Okhuarobo et al. 2014).


8) Cissampelos pariera Linn (Kannada name-Padavali)

Cissampelos pariera Linn is a sub erect dioecious flowering herb belongs to family Menispermaceae of tribe Cocculaeae (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). Cissampelos pareira was first described from Latin America as Abuta but distributed throughout tropics (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). Cissampelos pareira is mainly native to India and distributed in Asia, east Africa and America (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). In India, the climbing herb Cissampelos pariera, is widely distributed in different parts of Karnataka, Bababudan hills of Mysore, Western Ghats forests, Himachal Pradesh, Tamilnadu, Maharashtra-Nagpur, Bihar, west Bengal, Punjab and Rajasthan states (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). In Indian traditional Ayurveda, Cissampelos pariera is commonly called as Laghupatha (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008; Solanki et al. 2017).

Cissampelos pariera was used for the treatment of broad range of ailments in folk medicine across many countries, centuries, and continents (Shah et al. 2017). Cissampelos pariera has been used for the treatment of urinary problems, fever and skin infections. In the rainforests of South America, Cissampelos pariera commonly known as the “Midwife’s herb” (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). The roots of Cissampelos pariera has been used to treat many women’s ailments i.e. menstrual cramps, to stop uterine haemorrhages after childbirth, prevents threatened miscarriage, ease childbirth and postpartum, because of its intense relaxant effect on smooth muscle. The roots of Cissampelos pariera has also been used as a promising neuromuscular blocking agent and a substitute for tubocurarine (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). The tubers of Cissampelos pariera were also used in pseudo-pregnancy in Malawi (Shah et al. 2017). Cissampelos pariera was traditionally used in the preparation of curares, the famous South American arrow poison used in hunting to cause death by asphyxiation (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). Cissampelos pariera is also rich source of many bioactive alkaloids including aporphines and bisbenzylisoquinolines (Shah et al. 2017).


According to Ayurvedic Pharmacopeia of India, Cissampelos pariera has been prescribed for the treatment of health disorders such as cough, abdominal pain, heart, leprosy, epilepsy, delirium, madness, stimulant, convulsions, sensation, asthma, bronchitis, cystitis, dysuria and lactation disorders, kidney stones, arthritis, diabetes, dysentery kidney infections, skin disorders, scabies, non-healing ulcers, leprosy, migraine, leucorrhoea and gonorrhoea and fever (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhu and Ikeda, 2006; Porto et al. 2008). Leaves are used in skin ailments, burns, eye trouble, wounds, fever, sedative, analgesic and as a tonic, narcotic and in controlling fever due
to cold (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhuti and Ikeda, 2006; Porto et al. 2008). Cissampelos pariera is also used for augmentation of milk production in dairy cows, food systems for various purposes i.e. thickeners, texture modifiers, gelling agents, and stabilizers in Asia (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhuti and Ikeda, 2006; Porto et al. 2008). The Cissampelos pariera roots are bitter, pungent, carminative, astringent, anthminthic, stomachic, digestive, diuretic, expectorant and anti-inflammatory activity root decoction used in controlling malaria and pneumonia (Shah et al. 2017; Jain et al. 2015; Amresh et al. 2008; Vardhanabhuti and Ikeda, 2006; Porto et al. 2008).

Pigili and Runja, (2014) reported anti-dengue activity of extract of aerial parts of Cissampelos pariera (Shah et al. 2017). The alcoholic extract of Cissampelos pariera Linn (Cipa extract) was a potent inhibitor of all four dengue serotypes in cell based assays (Sood et al. 2015). On other words an alcoholic extract prepared from Cissampelos pariera Linn inhibited the replication of dengue viruses in living cells in culture and protected mice against dengue infection (Sood et al. 2015). This was assessed in terms of viral NS1 antigen secretion using ELISA, as well as viral replication, based on plaque assays (Sood et al. 2015). Virus yield reduction assays showed that Cissampelos pariera (Cipa extract) decreased viral titers by an order of magnitude (Sood et al. 2015). The Cissampelos pariera (cipa) extract conferred statistically significant protection against dengue virus infection using the AG129 mouse model (Sood et al. 2015). A preliminary evaluation of the clinical relevance of Cissampelos pariera (Cipa extract) showed that it had no adverse effects on platelet counts and RBC viability (Sood et al. 2015). In addition to inherent antipyretic activity in Wistar rats, it possessed the ability to down-regulate the production of TNF-α, a cytokine implicated in severe dengue disease (Sood et al. 2015). Cissampelos pariera (Cipa extract) showed no evidence of toxicity in Wistar rats, when administered at doses as high as 2g/Kg body weight for up to 1 week (Sood et al. 2015). In addition, Cissampelos pariera extract also manifested dose-dependent protective efficacy in an in vivo model, and appeared to be compatible with future clinical uses (Sood et al. 2015). This study confirmed that Cissampelos pariera as a source for the development of an inexpensive herbal formulation for dengue therapy but warranted further more clinical and experimental work (Sood et al. 2015). This might be of practical relevance to a dengue-endemic resource-poor country such as India (Sood et al. 2015).

9) Boesenbergia rotunda (Chinese ginger or Finger-root)

Boesenbergia rotunda is a medicinal ginger herb belongs to family Zingiberaceae that grows in Southeast Asia, India, Malaysia, Sri Lanka, and China (Eng-Chong et al. 2012; Kadir et al. 2013). The finger like rhizome of Boesenbergia rotunda has been used as a medicinal condiment-food additive due to its aromatic flavour, which promotes appetite with many local synonyms names, such as Chinese keys or Chinese ginger, and Finger-root in English (Eng-Chong et al. 2012; Kadir et al. 2013). Boesenbergia rotunda is one of the a common edible ingredient in many Asian countries such as India, Srilanka, Nepal, Bhutan, Thailand, Malaysia, Indonesia, Singapore and China (Eng-Chong et al. 2012). Boesenbergia rotunda has been used for the treatment of illnesses such as rheumatism, diuretic, muscle pain, aphrodisiac, febrifuge, gout, gastrointestinal disorders, flatulence, carminative, stomach ache, dyspepsia, peptic ulcer, tonic for women after childbirth as well as a beauty aid for teenage girls and to prevent leukorrhea, inflammatory diseases, such as dental caries, dermatitis, dry cough and cold, tooth and gum diseases, swelling, wounds, diarrhoea, and dysentery, leaves has been shown to alleviate food allergies and poisoning (Eng-Chong et al. 2012).

The pharmacological activities of Boesenbergia rotunda are antiviral, anti-microbial, anti-parasitic, anti-fungal, oral infections, anti-scabies agent, anti-oxidant, anti-ulcer, obesity treatment, anti-mutagenic, anti-tumor, anti-cancer, anti-fungal, anti-protozoal, anti-inflammatory, Inhibition of Platelet-Activating Factor (PAF), and wound healing (Eng-Chong et al. 2012). The activity of some compounds extracted from Boesenbergia rotunda for the inhibition of dengue virus protease has been tested on dengue virus serotype-2 (Kiat et al. 2006; Kadir et al. 2013). The cyclohexenyl chalcone derivatives of Boesenbergia rotunda, 4-hydroxyxypanduratin A (1) and panduratin A (2) showed good competitive inhibitory activities towards dengue virus serotype-2, NS3 protease with Ki values of 21 IM and 25 IM, respectively (Kiat et al. 2006; Kadir et al. 2013). The small value of Ki shows the potential of 4-hydroxyxypanduratin A to inhibit DENV-2 NS3 protease in vitro (Kiat et al. 2006; Kadir et al. 2013).

10) Gymnogongrus torulosus (Red seaweed)

Gymnogongrus torulosus is a red seaweed belongs to family Phyllophoraceae. A series of DL-galactan hybrids isolated from the red seaweed plant Gymnogongrus torulosus was assessed in vitro against dengue virus serotype-2 by virus reduction assay in Vero cells (Pujol et al. 2002; Kadir et al. 2013; Teixeira et al. 2014). Galactan (4) extracted from this plant was active against dengue virus serotype-2 with IC50 values in the range of 0.19–1.7 μg mL (Pujol et al. 2002; Kadir et al. 2013). In addition to their inhibitory activity, the galactan (4) compounds did not present cytotoxic effects on stationary or on actively dividing cells, and they presented anticoagulant properties (Pujol et al. 2002; Kadir et al. 2013; Teixeira et al. 2014). It was suggested that the mechanism of action of these compounds corresponds to interference in the binding of the surface glycoprotein with the cell receptor (Pujol et al. 2002; Kadir et al. 2013; Teixeira et al. 2014).

11) Cladosiphon okamuranus (Marine alga)

Cladosiphon okamuranus is a brown seaweed plant found naturally in Okinawa, Japan belongs to family Chordariaceae (Hidari et al. 2008, 2013; Li et al. 2008; Kadir
A sulfated polysaccharide named fucoidan from *Cladosiphon okamuranus* was found to potentially inhibit dengue virus serotype-2 infection (Hidari et al. 2008, 2013; Kadir et al. 2013; Teixeira et al. 2014). The virus infection was tested in BHK-21 cells in a focus-forming assay. Fucoidan reduced infectivity by 20% at 10 μg mL\(^{-1}\) against untreated cells (Hidari et al. 2008, 2013; Kadir et al. 2013; Teixeira et al. 2014). However, a carboxy-reduced fucoidan in which glucuronic acid was converted to glucose attenuated the inhibitory activity on dengue virus serotype-2 infection (Hidari et al. 2008, 2013; Kadir et al. 2013; Teixeira et al. 2014). Therefore, it was concluded that the glucuronic acid residue as well as the sulphate groups are fundamental for the inhibitory activity of fucoidan against dengue virus serotype-2 (Hidari et al. 2008, 2013; Kadir et al. 2013; Teixeira et al. 2014). It was also reported that glucuronic acid and sulfated fucose residues of the *Cladosiphon* fucoidan appear to critically affect the interaction of dengue virus serotype-2 with cellular receptors, but the precise molecular mechanism of the inhibitory effects of this compound has not been elucidated (Hidari et al. 2008, 2013; Li et al. 2008; Kadir et al. 2013; Teixeira et al. 2014).

Several polysaccharides known as galactans have been isolated from red seaweeds (Teixeira et al. 2014; Estevez et al. 2001; Talarico et al. 2004; Paint, 1983; Kraan, 2012). The galactans can be classified as carrageenans—these correspond to sulfated polysaccharides with 4-linked α-galactose residues of the D-series or their 3, 6-anhydro derivatives (Teixeira et al. 2014; Jiao et al. 2011; Estevez et al. 2001; Talarico et al. 2004; Paint, 1983; Kraan, 2012; Talarico et al. 2007; Talarico et al. 2005). Commercially available iota, kappa and lambda carrageenans were evaluated against DENV 1–4 serotypes (Teixeira et al. 2014; Jiao et al. 2011; Talarico et al. 2007; Talarico et al. 2005). The polysaccharides were more effective on DENV-2 and DENV-3 serotypes (Teixeira et al. 2014; Jiao et al. 2011; Talarico et al. 2007; Talarico et al. 2005). It was also determined that the carrageenans lambda and iota are potent inhibitors of DENV-2 and DENV-3 multiplication in Vero and HepG2 cells with EC\(_{50}\) (effective concentration 50%) ranging from 0.14 to 4.1 μg/mL (Teixeira et al. 2014; Jiao et al. 2011; Estevez et al. 2001; Talarico et al. 2004; Paint, 1983; Kraan, 2012) The results showed that the lack of dependence of the antiviral potency of carrageenans on the infecting virus inoculum was even more evident when the assays were performed simultaneously at a wide range of multiplicities (Teixeira et al. 2014; Jiao et al. 2011; Talarico et al. 2007; Talarico et al. 2005). The mechanism of the inhibitory multiplication effect of the iota carrageenan was not described (Teixeira et al. 2014; Jiao et al. 2011; Talarico et al. 2007; Talarico et al. 2004, 2005).

12) **Cladogynos orientalis** *(Thai medicinal plant)*

*Cladogynos orientalis* is a Thai medicinal plant with white-stellate-hairy shrub about 2 m high belongs to family **Euphorbiaceae** which has been used in traditional medicine as anti-flatulent, anti-stomachache, and tonic agent (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). *Cladogynos orientalis* commonly known in Thai as Chettaphangki (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). It is found in Southeast Asia, Thailand, Vietnam, Cambodia, Malaysia, Indonesia, Philippines, and China (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). The extract from the whole plant of *Cladogynos orientalis* promoted anti dengue virus effect using MTT assay (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). The leaf extract also promoted effective inhibition of human hepatocarcinoma (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). The in vitro activity of *Cladogynos orientalis* against dengue virus was evaluated (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). The dichloromethane ethanol extract of *Cladogynos orientalis* was tested for anti-dengue activities against DENV-2 in Vero cells by the MTT method (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). The experimental results showed that the ethanol extract of *Cladogynos orientalis* at a concentration of 12.5 μg mL\(^{-1}\) exhibited 34.85
% inhibitory activity on DENV-2 (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015). In addition, Cladogynos orientalis at a concentration of 100 μg mL\(^{-1}\) exhibited an inactivated viral particle activity of 2.9 % (Klawikkan et al. 2011; Kadir et al. 2013; Sithisarn et al. 2015).

13) Cymbopogon citratus (Lemon grass)

Cymbopogon citratus is native to South India, and Sri Lanka belongs to family Poaceae (Shah et al. 2011). It is a grass species known as lemon grass or oil grass and is a tropical plant from Southeast Asia and found abundant in India, Sri Lanka, Malaysia, Thailand, Nepal, Philippines and Indonesia used as a fragrance and flavoring agent in folk medicine (Shah et al. 2011; Tang et al. 2012; Kadir et al. 2013). The dried leaves can also be brewed into a tea, either alone or as a flavoring in other teas, imparting a flavor reminiscent of lemon juice (Shah et al. 2011). Cymbopogon citratus have been used in traditional medicine and are often found in herbal supplements and teas (Shah et al. 2011).

The antiviral activity of Cymbopogon citratus was determined based on cytotoxic effects shown by the degree of inhibition of DENV-1 infected Vero E6 cells (Tang et al. 2012; Kadir et al. 2013). The methanolic extract of Cymbopogon citratus showed a slight inhibition effect on dengue virus serotype-1(Tang et al. 2012; Kadir et al. 2013). This result was further confirmed with an inhibition assay by the MTT method (Tang et al. 2012; Kadir et al. 2013). However, Cymbopogon citratus showed no significant inhibition (Tang et al. 2012; Kadir et al. 2013). Moreover, Cymbopogon citratus showed the lowest of maximum nontoxic dose (MNTD) at concentration of 0.001 mg mL\(^{-1}\) (Tang et al. 2012; Kadir et al. 2013). Cymbopogon citratus was found to be quite a cytotoxic plant as it showed maximum cytotoxicity at 0.075 mg mL\(^{-1}\) (Tang et al. 2012; Kadir et al. 2013).

The essential oil of the plant is used in aromatherapy (Shah et al. 2011). The compounds identified in Cymbopogon citratus are mainly terpenes, alcohols, ketones, aldehyde and esters (Shah et al. 2011). The phytoconstituents of Cymbopogon citratus are essential oils that contain citral α, citral β, nerol geraniol, citronellal, terpinolene, geranyl acetate, myrcene and terpinol methyl heptenone, flavonoids and phenolic compounds, which consist of luteolin, isoorientin 2'-O-rhamnoside, queretin, kaempferol and apiginin (Shah et al. 2011). Cymbopogon citratus possesses various pharmacological activities such as anti-amoeboic, antibacterial, anti-diarrheal, anti-filarial, anti-fungal, anti-inflammatory, hypotensive, antimalarial, anti-spasmodic, anti-mutagenicity, anti-mycobacterial, antioxidant, hypoglycemic, anticonvulsant, analgesic, anti-emic, anti-tussive, anti-rheumatic, anti-septic, gastrointestinal disorders, fevers, and neuro behavioral (Shah et al. 2011).

14) Cryptonemia crenulata (Red seaweed)

Cryptonemia crenulata is a marine red seaweed plant belongs to family Haliymentaceae. Cryptonemia crenulata found throughout the Indian Ocean Islands, Atlantic Islands, North America, Caribbean Islands, Western Atlantic, South America, Africa, Southeast Asia and Pacific Islands (Kadir et al. 2013).

The sulfated polysaccharides from Cryptonemia crenulata, i.e., galactan (4), were selective inhibitors of dengue virus serotype-2 multiplication in Vero cells with IC\(_{50}\) values of 1.0 μg mL\(^{-1}\) where the IC\(_{50}\) values for the reference polysaccharides heparin and DS8000 were 1.9 and 0.9 μg mL\(^{-1}\) respectively (Talarico et al. 2005, 2007; Kadir et al. 2013; Teixeira et al. 2014; Talarico and Damonte, 2007). However, the compound has lower antiviral effect against dengue virus serotype-3 and dengue virus serotype-4, and was totally inactive against dengue virus serotype-1 (Talarico et al. 2005, 2007; Kadir et al. 2013; Teixeira et al. 2014). The inhibitory effect of C2S against dengue virus serotype-2 was slightly higher when treatment was by adsorption (EC\(_{50}\) = 2.5 ± 0.1 μg mL\(^{-1}\)) with respect to treatment only during internalization (EC\(_{50}\) = 5.5 ± 0.7 μg mL\(^{-1}\)) (Talarico et al. 2005, 2007; Kadir et al. 2013; Teixeira et al. 2014). Thus, the inhibitory effect was increased when C2S-3 was included at both stages of adsorption and internalization (Talarico et al. 2005, 2007; Kadir et al. 2013; Teixeira et al. 2014).

15) Flagellaria indica (whip vine)

Flagellaria indica is a climbing medicinal plant belongs to family Flagellariaceae. It is a robust perennial climber that grows in many of the tropical and subtropical regions of the Old World, India, Bangladesh, Southeast Asia, Polynesia and Australia (Kadir et al. 2013). Because of its wide distribution, many local common names were used, such as whip vine, hell tail, supplejack, false rattle, and bush can (Kadir et al. 2013). Flagellaria indica was investigated for its anti-dengue properties in Vero cells (Klawikkan et al. 2011; Kadir et al. 2013). The \textit{in vitro} antiviral assay using ethanol (12.51 μg mL\(^{-1}\)) extract of the plant confirmed 45.52 % inhibition of dengue virus serotype-2 (Klawikkan et al. 2011; Kadir et al. 2013). The cytotoxicity of \textit{Flagellaria indica} was determined by adopting MTT assays and the CC\(_{50}\) of ethanol extract of \textit{Flagellaria indica} were 312 μg mL\(^{-1}\) (Klawikkan et al. 2011; Kadir et al. 2013). Therefore, this study confirmed that \textit{Flagellaria indica} has a significant inhibitory effect on dengue virus (Klawikkan et al. 2011; Kadir et al. 2013).

16) Gymnogongrus griffithsiae (Red seaweed)

Gymnogongrus griffithsiae is a red seaweed belongs to family Phyllorophoraceae found in Ireland, Europe, Atlantic Islands, North America, South America, Caribbean Islands, Africa, Southwest and Southeast Asia and Australia and New Zealand (Kadir et al. 2013). The sulfated polysaccharide kappa carrageenan (5) isolated from Gymnogongrus griffithsiae showed inhibitory activity in Vero cells against dengue virus serotype-2 (Talarico and Damonte, 2007; Talarico et al. 2005; Kadir et al. 2013; Teixeira et al. 2014).
The compound effectively inhibits dengue virus serotype-2 multiplication at the IC₅₀ value of 0.9 µg mL⁻¹, which is the same as the IC₅₀ value for the commercial polysaccharides DS8000 (Talarico and Damonte, 2007; Talarico et al. 2005; Kadir et al. 2013; Teixeira et al. 2014). However, the sulfated polysaccharide kappa carrageenan (5) compound has the lower antiviral effect against dengue virus serotype-3 and dengue virus serotype-4, and was totally inactive against dengue virus serotype-1 (Talarico and Damonte, 2007; Talarico et al. 2005; Kadir et al. 2013; Teixeira et al. 2014).

17) *Mimosa scabrella*

*Mimosa scabrella* is a fast growing tree species, native of Brazil belongs to family Fabaceae (Kadir et al. 2013). Galactomannans extracted from seeds of *Mimosa scabrella* have demonstrated in vitro and in vivo inhibitory activity against Yellow Fever Virus (YFV) and dengue virus serotype-1 (Ono et al. 2003; Kadir et al. 2013). *Mimosa scabrella* showed 87.7 % protection against death of Yellow Fever Virus (YFV)-infected mice (Ono et al. 2003; Kadir et al. 2013). In vitro experiments with dengue virus serotype-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 dengue virus serotype-1 (Ono et al. 2003; Kadir et al. 2013).

18) *Momordica charantia* (Kannada- Hagalakai)

*Momordica charantia* (Hagalakai) commonly known as bitter melon in India belongs to family Cucurbitaceae (Joseph and Jini, 2013; Tang et al. 2012; Kadir et al. 2013). *Momordica charantia* is a flowering medicinal vine distributed in tropical and subtropical Asia, India, Malaysia, Thailand, Bhutan, Nepal, Africa and the Caribbean (Joseph and Jini, 2013; Tang et al. 2012; Kadir et al. 2013). *Momordica charantia* fruit has distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd (Joseph and Jini, 2013; Tang et al. 2012; Kadir et al. 2013). The bitter melon fruits were used for controlling type1 diabetes (Joseph and Jini, 2013). The methanolic extract of *Momordica charantia* showed inhibitory effect on dengue virus serotype-1 (DENV-1) by antiviral assay based on cytopathic effects (Tang et al. 2012; Kadir et al. 2013). During this study, the maximum non-toxic dose (MNTD) of the methanolic extract of *Momordica charantia* against in vitro Vero E6 cells was investigated (Tang et al. 2012; Kadir et al. 2013). *Momordica charantia* recorded a maximal dose that was not toxic to cells of 0.20 mg mL⁻¹ (Tang et al. 2012; Kadir et al. 2013).

19) *Hippophae rhamnoides* (Sea buckthorn, SBT)

Sea buckthorn (*Hippophae rhamnoides*) is a deciduous spiny tree widely distributed over Asia, Himalayas and Europe belongs to family Elaeagnaceae (Suryakumar and Gupta, 2011; Zeb, 2004; Cho et al. 2014; Jain et al. 2008; Agarwal et al. 2016; Zeb, 2004). It is a hard thorny plant, tolerant against drought and cold, and is useful for land reclamation and farmstead protection having complex root system with nitrogen-fixing nodules (Suryakumar and Gupta, 2011; Cho et al. 2014; Agarwal et al. 2016; Zeb, 2004). Sea buckthorn is a promising medicinal plant with potential beneficial applications in human health (Suryakumar and Gupta, 2011; Cho et al. 2014; Agarwal et al. 2016; Zeb, 2004). It is currently domesticated in several parts of the world due to its nutritional and medicinal properties. Sea buckthorn berries were rich in carbohydrates, proteins, organic acids, and abundant ascorbic acid (Suryakumar and Gupta, 2011; Cho et al. 2014; Zeb, 2004). Because of many health-promoting properties of Sea buckthorn, *Hippophae rhamnoides* (Sea buckthorn) have been well recognized since ancient times (Suryakumar and Gupta, 2011; Cho et al. 2014; Agarwal et al. 2016; Zeb, 2004). Seeds were also rich in linoleic and linolenic acids, including palmitoleic, vaccenic, and oleic acids (Suryakumar and Gupta, 2011; Cho et al. 2014). Sea buckthorn leaf extracts prevented chromium-induced oxidative damage in an in vivo model (Suryakumar and Gupta, 2011; Cho et al. 2014; Jain et al. 2008; Zeb, 2004). Sea buckthorn leaves have been shown to have antimicrobial, anti-viral, antioxidant, and anti-inflammatory properties both in vivo and in vitro (Suryakumar and Gupta, 2011; Cho et al. 2014; Zeb, 2004). Pharmacological activities of sea buckthorn include prevention of gastric ulcers, treatment of asthma, skin diseases, lung disorders and hepatic fibrosis, reduction of blood glucose and cholesterol levels, relief of inflammation and heartburn, and anti-mutagenic, and anti-tumor activities, antioxidant, immunomodulatory, anti-atherogenic, anti-stress, hepatoprotective, radioprotective and tissue repair, anti-inflammatory, anti-atherogenic, cardioprotective and wound healing from its different parts (leaves, fruits and seeds) (Suryakumar and Gupta, 2011; Cho et al. 2014; Zeb, 2004).

In one of the study, anti-dengue activity of *Hippophae rhamnoides* (Sea buckthorn, SBT) leaf extract was evaluated in dengue virus type-2 infected blood-derived human macrophages since macrophages are the primary target of dengue virus infection (Jain et al. 2008; Suryakumar and Gupta, 2011; Kadir et al. 2013). Infected cells were treated with *Hippophae rhamnoides* (Sea buckthorn, SBT) leaf extract and compared with commercially available anti-viral drug, Ribavirin (Jain et al. 2008; Suryakumar and Gupta, 2011; Kadir et al. 2013). The extract was able to maintain the cell viability of dengue-infected cells at par with Ribavirin along with the decrease and increase in TNF-α and IFN-γ respectively (Jain et al. 2008; Suryakumar and Gupta, 2011; Kadir et al. 2013). Anti-dengue activity of *Hippophae rhamnoides* (Sea buckthorn, SBT) extract was further determined by the traditional plaque assay (Jain et al. 2008; Suryakumar and Gupta, 2011; Kadir et al. 2013). These observations confirmed that the *Hippophae rhamnoides* (Sea buckthorn, SBT) leaf extract has a significant anti-dengue activity, and has the potential for the treatment of dengue (Jain et al. 2008; Suryakumar and Gupta, 2011; Kadir et al. 2013). Another recent study by Agarwal et al. (2016) investigated the effect of *Hippophae rhamnoides* (Sea buckthorn, SBT) alcoholic leaf extract and other well-known medicinal plants.
in dengue infected U-937 cells (Human Monocytic cell line) since monocytes were the host cells for dengue virus (Agarwal et al. 2016). This study confirmed the maximum cell viability and minimum cytotoxicity with *Hippophae rhamnoides* (Sea buckthorn, SBT) leaf in U937 cells (Agarwal et al. 2016). The anti-dengue activity of Sea buckthorn (SBT) was revealed by reduced plaque numbers and modulated pro-inflammatory cytokines (Agarwal et al. 2016). This study also confirmed significant high anti-dengue activity of *Hippophae rhamnoides* (Sea buckthorn, SBT). Therefore, *Hippophae rhamnoides* (Sea buckthorn, SBT) is considered as a potential candidate for the treatment and management of dengue infection (Agarwal et al. 2016).

20) *Piper retrofractum* (Long pepper)

*Piper retrofractum* (Long pepper) belongs to family *Piperaceae*. It is a flowering vine native to Southeast Asia and cultivated in Indonesia, Thailand, Malaysia, Philippines, and Vietnam mostly for its fruit which is usually dried and used as a spice and seasoning (Kadir et al. 2013; Klawikkan et al. 2011; Chansang et al. 2005). *In vitro* anti-dengue activity of *Piper retrofractum* in Vero cells was investigated (Klawikkan et al. 2011; Kadir et al. 2013). The inhibitory activity against dengue virus serotype-2 infected cells was determined on dichloromethane ethanol extract by the MTT method (Klawikkan et al. 2011; Kadir et al. 2013). The ethanol extract of *Piper retrofractum* exhibited an inactivated viral particle activity or 84.93 % at a concentration of 100 µg mL⁻¹ (Klawikkan et al. 2011; Kadir et al. 2013). An aqueous extract of long pepper, *Piper retrofractum*, notified the highest level of activity against mosquito larvae (Chansang et al. 2005; Kadir et al. 2013).

21) *Leucaena leucocephala* (Subabul)

*Leucaena leucocephala* (Subabul) belongs to family *Fabaceae* (Meenadevi et al. 2013; Kadir et al. 2013). It is a species of Mimosoid tree indigenous throughout Southern Mexico and Northern America and the West Indies from the Bahamas and Cuba to Trinidad and Tobago (Kadir et al. 2013; Meenadevi et al. 2013). *Leucaena leucocephala* (Subabul) is a small tree commonly cultivated in garden as an ornamental, avenue and forage crop in India (Meneadevi et al. 2013). *Leucaena leucocephala* (Subabul) commonly known as *White Lead tree* has been naturalized in many tropical and sub-tropical locations (Meneadevi et al. 2013). *Leucaena leucocephala* (Subabul) has been promoted for its forage production and naturally spreads like a weed (Meneadevi et al. 2013). It grows up to 20 m height and leaves are looking like that of tamarind having white flowers tinged with yellow, and having long flattened pods. *Leucaena leucocephala* (Subabul) tree has multifarious uses like firewood, timber, greens, fodder, green manure, shade, controls soil erosion (Meneadevi et al. 2013). The kernel of seeds of *Leucaena leucocephala* (Subabul) contains more than 20% oil and it can be used as a bio energy crop (Meneadevi et al. 2013). The seeds may also be used as concentrates for dairy animals, as manure, as a protein source, as an oil seed and as a potential source of commercial gum (Meenadevi et al. 2013). Galactomannans extracted from seeds of *Leucaena leucocephala* (Subabul) have demonstrated activity against yellow fever virus (YFV) and dengue virus serotype-1 in *vitro* and in vivo (Ono et al. 2003; Kadir et al. 2013; Tang et al. 2012).

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 (Srivastava and Kapoor, 2005; Kadir et al. 2013). *Leucaena leucocephala* (Subabul) showed protection against death in 96.5 % of Yellow fever virus (YFV)-infected mice (Srivastava and Kapoor, 2005; Kadir et al. 2013). *In vitro* experiments with dengue virus serotype-1 in C6/36 cell culture assays showed that the concentration producing a 100-fold decrease in virus titer of dengue virus serotype-1 was 37 mg L⁻¹ (Kadir et al. 2013).

22) *Meristiella gelidium* (seaweed)

*Meristiella gelidium* is a marine seaweed species belongs to family *Soliieriaeae* found in Atlantic Islands, North America, Caribbean Islands and South America (Tischer et al. 2006; Kadir et al. 2013; Swain and Dudey, 2013). The antiviral activity of kappa carragenan in *Meristiella gelidium* was evaluated against dengue virus serotype-2 (Tischer et al. 2006; Kadir et al. 2013; Swain and Dudey, 2013). The IC₅₀ of carragenans isolated from *Meristiella gelidium* was in the range of 0.14—1.6 µg mL⁻¹ (Tischer et al. 2006; Kadir et al. 2013; Swain and Dudey, 2013). The experimental results confirmed that the carragenans extract and the fraction derived from *Meristiella gelidium* were more effective inhibitors of dengue virus serotype-2 when compared with reference polysaccharides (heparin and DS 8000) (Tischer et al. 2006; Kadir et al. 2013; Swain and Dudey, 2013).

23) *Lippia alba* and *Lippia citriodora* (Essential oil plants)

*Lippia alba* and *Lippia citriodora* are flowering herbaceous plants belong to family *Verbenaceae* (Meneses et al. 2009; Ocazionez et al. 2010; Kadir et al. 2013). *Lippia alba* and *Lippia citriodora* are native to Southern Texas, Mexico, the Caribbean, Central and South America and found in India and Australia too (Meneses et al. 2009; Ocazionez et al. 2010; Kadir et al. 2013). Lemon verbena, *Lippia citriodora* Kunth is generally recognized for its lemon-like aroma used in herbal tea preparations, as it is known for its antispasmodic, antipyretic, sedative, digestive properties, analgesic, anti-inflammatory, antioxidant effects, antimicrobial and is traditionally used to treat oral problems and *Candida* (Meneses et al. 2009; Ocazionez et al. 2010; Kadir et al. 2013). The leaves were used in giving flavour to drinks, desserts, fruit salads, jellies and for spicing up food. A decoction made from the leaves and flowers is given as febrifuge, sedative and anti-flatulent (Meneses et al. 2009; Ocazionez et al. 2010; Kadir et al. 2013).
Essential oils from Lippia alba and Lippia citriodora showed a considerable inhibitory effect on dengue virus serotype in vitro replication in Vero cells (Meneses et al. 2009; Ocazionez et al. 2010; Kadir et al. 2013). The cytotoxicity (CC50) was evaluated by the MTT assay and the mode of dengue viral inhibitory effect was investigated with a plaque reduction assay (Ocazionez et al. 2010). The dengue virus was treated with the essential oil from Lippia alba and Lippia citriodora for 2 h at 37°C before cell adsorption and experiments evaluated inhibition of untreated-virus replication in the presence of oil (Ocazionez et al. 2010). Dengue antiviral activity was defined as the concentration of essential oil that caused 50% reduction of the virus plaque number (IC50) (Ocazionez et al. 2010). Lippia alba oil resulted in a less cytotoxicity than Lippia citriodora oil (CC50: 139.5 vs. 57.6 microg/mL) (Meneses et al. 2009; Ocazionez et al. 2010). Virus plaque reduction for all four dengue serotypes was observed by the treatment of virus before adsorption on cell (Ocazionez et al. 2010). The IC50 values for Lippia alba oil were between 0.4-32.6 μg/mL and between 1.9-33.7 μg/mL for Lippia citriodora oil (Ocazionez et al. 2010). No viral inhibitory effect was observed by the addition of the essential oil after virus adsorption (Meneses et al. 2009; Ocazionez et al. 2010). The inhibitory effect of the essential oil caused direct dengue virus inactivation before adsorption on host cell (Meneses et al. 2009; Ocazionez et al. 2010). In another study, essential oil of Lippia alba was observed to produce a 100 % reduction of yellow fever virus yield at 100 μg mL-1 (Meneses et al. 2009).

24) Houttuynia cordata

Houttuynia cordata is commonly known as Chinese lizard tail belongs to family Saururaceae (Rathi et al. 2013; Hynniewta and Kumar, 2008; Kadir et al. 2013). It is a perennial herbaceous flowering plant with stoloniferous rhizome having two distinct chemotypes growing between 20 and 80 cm (Rathi et al. 2013; Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012;Kadir et al. 2013). Houttuynia cordata is native to Japan, Korea, Southern China and Southeast Asia (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012;Kadir et al. 2013; Rathi et al. 2013). Houttuynia cordata is widely distributed in North Eastern region of India, Bhutan, Nepal, China, Vietnam, Thailand, Indonesia, Japan, Myanmaa and South Korea (Rathi et al. 2013). Houttuynia cordata is available in India, especially in Meghalaya, Arunachal Pradesh, and Brahmaputra valley of Assam and is utilized by various tribes of North Eastern region of India in the form of vegetable as well as traditional medicine (Rathi et al. 2013; Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Kadir et al. 2013). Leaves and rhizomes of Houttuynia cordata were used as vegetables, condiments and spices either cooked or raw (Rathi et al. 2013). The roots, and leaves were consumed as a green salad by the tribal people of North Eastern region of India and the herb is currently used as a folk medicine (Rathi et al. 2013). In the North-Eastern part of India, the whole plant of Houttuynia cordata is consumed as a raw medicinal salad for lowering the blood sugar level (Rathi et al. 2013;Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012). The leaves were recommended for the treatment of measles, dysentery and gonorrhea (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Rathi et al. 2013). Young shoots and leaves were consumed raw or cooked as a pot-herb in Meghalaya, Arunachal Pradesh, Assam, Nagaland, Manipur, Sikkim of India (Rathi et al. 2013; Hynniewta and Kumar, 2008). A decoction of this plant is used internally for the treatment of many ailments including cancer, coughs, dysentery, enteritis and fever (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Rathi et al. 2013). Externally Houttuynia cordata is used for the treatment of snake bites and skin disorders (Rathi et al. 2013). The leaves and stems were harvested during the growing season and are used as fresh decoctions in Meghalaya, Sikkim, Assam, Manipur, Nagaland, and Arunachal Pradesh States in India (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Rathi et al. 2013). The root, young shoots, leaves and sometimes the whole plant is traditionally used to cure various human ailments throughout South-East Asia (Rathi et al. 2013). In North Eastern part of India, Houttuynia cordata is considered for its cooling, resolvent and emmenagogue properties (Rathi et al. 2013).

The plant is also used in the treatment of eye troubles, skin diseases, hemorrhoids, relieving fever, resolving toxin, reducing swelling, draining pus, promoting urination and in certain diseases of women (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Goel et al. 2004; Rathi et al. 2013). Among the important pharmacological activities reported includes, cardiovascular disorders, anti-helmintic, slow laxative, analgesic, stomach ulcer, detoxification agent, pulmonary tuberculosis, diuretics, constipation, hypertension, anti-mutagenic, anti-cancer, adjuvanticity, anti-obesity, anti-oxidant, hepatoprotective, anti-viral, anti-bacterial, anti-inflammatory, free radical scavenging, anti-microbial, anti-allergic, anti-leukemic, chronic sinusitis, inhibitory effects on anaphylactic reaction, mast cell activation and nasal polyps activities (Kumar et al. 2014; Hynniewta and Kumar, 2008; Leardkamolkarn et al. 2012; Rathi et al. 2013).

Ethanol extract of Houttuynia cordata revealed an anti-dengue activity with 35.99 % inhibition against dengue virus serotype-2 in Vero cells at a concentration of 1.56 μg mL-1 (Klawikkan et al. 2011; Leardkamolkarn et al. 2012; Goel et al. 2004; Kadir et al. 2013). Aqueous extract of Houttuynia cordata showed an effective inhibitory action against dengue virus serotype -2 through direct inactivation of viral particles before infection
25) *Quercus lusitanica*

*Quercus lusitanica* is commonly known as gall oak, Lusitanian oak, or dyer's oak belongs to family Fagaceae. *Quercus lusitanica* is a small tree or shrub growing 4 to 6 feet tall of oak native to Morocco, Portugal and Spain (Muliawan et al. 2006; Kadir et al. 2013). The galls of *Quercus lusitanica* were used since ages as a home remedy for sore throat and chronic diarrhea in both rural and urban areas. The galls of *Quercus lusitanica* have been known to possess medicinal properties, such as astringent, anti-inflammatory, antiviral, antiabetic, larvicidal, antibacterial, antiulcerogenic and gastroprotective activities. *Quercus lusitanica* extract was found to have a good inhibitory effect on the replication of dengue-2 in C6/36 cells (Muliawan et al. 2006; Kadir et al. 2013). Muliawan et al. (2006) reported the *in vitro* inhibitory potential of crude extract of *Quercus lusitanica* (*Quercus lusitanica*) seeds on the replication of dengue virus type 2 (DENV-2) (Muliawan et al. 2006; Kadir et al. 2013). *In vitro* antiviral activity of *Quercus lusitanica* extract, assessed in C6/36 cells (cloned cells of *Aedes albopictus* larvae) employing a virus inhibition assay, showed dose-dependent inhibition (Muliawan et al. 2006; Kadir et al. 2013). The *Quercus lusitanica* extract at its maximum non-toxic concentration of 0.25 mg/ml completely inhibited 10,000 TCID$_{50}$ of virus, as indicated by the absence of cytopathic effect (CPE) (Muliawan et al. 2006; Kadir et al. 2013). The low dose of *Quercus lusitanica* (0.032 mg/ml) showed 100% inhibition with 10 TCID$_{50}$ of virus, but only 50% and 25% inhibition with 100 and 1,000 TCID$_{50}$ respectively (Muliawan et al. 2006; Kadir et al. 2013). Furthermore, the evaluation of *Quercus lusitanica* extract as an antiviral compound and the investigation of effect of *Quercus lusitanica* extract on the NS1 protein expression of infected C6/36 cells was carried out through proteomics technique (Muliawan et al. 2006; Kadir et al. 2013). The experimental results confirmed downregulation of NS1 protein expression of infected C6/36 cells after treatment with this extract (Muliawan et al. 2006; Kadir et al. 2013). Therefore, *Quercus lusitanica* extract has a good inhibitory effect on the replication of dengue virus type 2, both in conventional cell culture and proteomics technique (Muliawan et al. 2006; Kadir et al. 2013)

26) *Rhizophora apiculata*

*Rhizophora apiculata* belongs to family Rhizophoraceae (Klawikkan et al. 2011; Kadir et al. 2013). It is a mangrove tree up to 20 meter tall that grows in India, Bangladesh, Malaysia, Australia (Queensland and Northern Territory), Guam, Indonesia, Micronesia, New Caledonia, Papua New Guinea, the Philippines, Singapore, the Solomon Islands, Sri Lanka, Taiwan, Maldives, Thailand and Vietnam (Klawikkan et al. 2011; Kadir et al. 2013). Anti-dengue properties of the ethanolic extracts of *Rhizophora apiculata* in dengue virus serotype-2 (DENV-2) in Vero cells have been reported (Klawikkan et al. 2011; Kadir et al. 2013). *Rhizophora apiculata* exhibited inhibitory activity and an inactivated viral particle activity of 56.14 % and 41.5 % at a concentrations of 12.5 and 100 lg mL$^{-1}$ respectively (Klawikkan et al. 2011; Kadir et al. 2013).

27) *Zostera marina* (Eelgrass)

*Zostera marina* belongs to family Zosteraceae. It is a marine flowering plant known as eelgrass and is native to North America and Eurasia (Rees et al. 2008; Kadir et al. 2013). The marine flowering plant *Zostera marina* is a rhizomatous herb which produces a long stem with hairlike green leaves that measures up to 1.2 cm wide and might reach over 1.0 m long (Rees et al. 2008; Kadir et al. 2013). The anti-adhesive compound p-sulfoxy-cinnamic acid, zosteric acid (ZA), is derived from the temperate marine eelgrass, *Zostera marina*. Zosteric acid (ZA) and five combinatorial chemistries based on zosteric acid (ZA) were evaluated for their anti-viral properties against dengue virus in a focus forming unit reduction assay (Rees et al. 2008; Kadir et al. 2013). None of the compounds showed evidence of toxicity to the monkey kidney cell line LLCMK-2 over the tested concentration ranges (Rees et al. 2008; Kadir et al. 2013). Zosteric acid (ZA) showed a modest IC$_{50}$ of approximately 2.3 mM against DENV-2. Three other compounds showed IC$_{50}$ values of 2.5, 2.4, 0.3 mM, with a fourth not achieving a 50% inhibitory concentration against DENV-2 (Rees et al. 2008; Kadir et al. 2013). The most active compound, CF238, showed IC$_{50}$ values of 24, 46, 14 and 47 µM against DENV-1, DENV-2, DENV-3 and DENV-4, respectively (Rees et al. 2008; Kadir et al. 2013). CF238 showed evidence of inhibition at an entry step in the viral life cycle and enhanced virus:cell binding as evidenced by a quantitative RT-PCR assay system (Rees et al. 2008; Kadir et al. 2013). CF238 may promote inappropriate virus: cell attachments common to all dengue virus strains that interfere with receptor interactions required for viral entry (Rees et al. 2008; Kadir et al. 2013). Therefore, this study confirmed that these and other related chemistries might be useful as reagents for studying dengue virus entry, capturing, detecting dengue, and development of pharmaceuticals (Rees et al. 2008).

28) *Uncaria tomentosa*

*Uncaria tomentosa* belongs to family Rubiaceae has been used as anti-inflammatory, immunomodulants and antioxidant agent. It is a woody vine growing in the tropical jungles of Central and South America (Reis et al. 2008; Vijayan et al. 2004; Kadir et al. 2013). *Uncaria tomentosa* is a large wood vine native to the Amazon and Central American rainforests (Reis et al. 2008; Vijayan et al. 2004; Kadir et al. 2013). It is used widely as traditional medicine by native

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people of the Peruvian rainforest (Reis et al. 2008; Vijayan et al. 2004; Kadir et al. 2013). The biological activity of of Uncaria tomentosa was recognized mainly due to the presence of the pentacyclic oxindole alkaloids. The anti-neoplastic potential of Uncaria tomentosa is another important pharmacological activity of this plant. Indeed, various extracts and compounds derived from Uncaria tomentosa have been found to alter or downregulate inhibited the growth and proliferation of several different tumour lineages including human neuroblastoma and glioma. The antiviral activity of Uncaria tomentosa was revealed by viral antigen (DENV-Ag) detection in monocytes by flow cytometry in C6/36 cells (Reis et al. 2008; Vijayan et al. 2004; Kadir et al. 2013). The most effective activity emerged from the alkaaloid fraction pentacyclic oxindole of Uncaria tomentosa. The pentacyclic oxindole alkaaloid-enriched fraction of Uncaria tomentosa was observed as most effective at decreasing DENV-Ag detection in monocytes at concentrations of 1 µg mL⁻¹ whereas the crude hydroethanolic extract demonstrated inhibitory activity at concentrations of 10 µg mL⁻¹ (Reis et al. 2008; Vijayan et al. 2004; Kadir et al. 2013).

29) Tephrosia crassifolia, Tephrosia madrensis and Tephrosia viridiflora

All the three species of Mexican plant Tephrosia (Tephrosia crassifolia, Tephrosia madrensis and Tephrosia viridiflora) belong to family Fabaceae (Sanchez et al. 2000; Kadir et al. 2013). Genus Tephrosia is an herb, undershrub or shrub, distributed mainly in tropical and subtropical regions of the world (Sanchez et al. 2000; Kadir et al. 2013). In this study different flavonoids extracted and identified from three species of Fabaceae family (Tephrosia crassifolia, Tephrosia madrensis and Tephrosia viridiflora) were investigated for the antiviral effect on dengue virus (Sanchez et al. 2000; Kadir et al. 2013). The flavonoids isolated from Tephrosia madrensis, glabranine (8) and 7-O-methyl-glabranine (9) exhibited strong inhibitory effects on dengue virus replication in LLC-MK2 cells (Sanchez et al. 2000; Kadir et al. 2013). On the other hand Methyl-hildgardtol A isolated from Tephrosia crassifolia showed a moderate to lower inhibitory effect on dengue viral growth while hildgargtol A from Tephrosia crassifolia and elongatine from Tephrosia viridiflora had no effect on dengue viral growth (Sanchez et al. 2000; Kadir et al. 2013). These results showed that glabranine and 7-O-methyl-glabranine isolated from Tephrosia species showed a dose-dependent inhibitory effect in vitro on the dengue virus (Sanchez et al. 2000; Kadir et al. 2013).

30) Anacolosa pervilleana

Anacolosa pervilleana belongs to family Olacaceae is a plant genus of 15 to 22 species grown as shrubs or trees in the tropical and subtropical region (Bourjot et al. 2012a; Teixeira et al. 2014). The acetylenic compounds isolated from an ethyl acetate extracts of Madagascan plant Anacolosa pervilleana were tested against dengue virus activity (Bourjot et al. 2012a; Teixeira et al. 2014). In an effort to identify novel inhibitors of chikungunya (CHIKV) and dengue (DENV) virus replication, a systematic study with 820 ethyl acetate extracts of Madagascan plants was performed in a virus-cell-based assay for CHIKV and a DENV NS5 RNA-dependant RNA polymerase (RdRp) assay (Bourjot et al. 2012a; Teixeira et al. 2014). The extract obtained from the leaves of Anacolosa pervilleana was selected for its significant activity in both assays (Bourjot et al. 2012a; Teixeira et al. 2014). One new (E)-tridec-2-en-4-ynedioic acid named anacolanol (1), together with three known acetylenic acids, the octadeca-9,11,13-trinoic acid (2), (13E)-octadeca-13-en-9,11-dyinoic acid (3), (13E)-octadeca-13-en-11-ynioic acid (4), two terpenoids, lupenone (5) and β-amyrone (6), and a cyanogenic glycoside, (S)-sambunigrin (7) were isolated (Bourjot et al. 2012a; Teixeira et al. 2014). Their structures were elucidated by comprehensive analyses of NMR spectroscopy and mass spectrometry data (Bourjot et al. 2012a; Teixeira et al. 2014). The inhibitory potency of these compounds was evaluated on CHIKV, dengue RNA-dependant RNA polymerase (RdRp) and West-Nile polymerase virus (WNV RdRp) (Bourjot et al. 2012a; Teixeira et al. 2014). Both terpenoids showed a moderate activity against CHIKV (EC₅₀ 77 and 86 µM, respectively) and the acetylenic acids produced IC₅₀ values around 3 µM in the dengue RdRp assay (Bourjot et al. 2012a; Teixeira et al. 2014). These results confirmed that compounds isolated from Anacolosa pervilleana possessed some selectivity towards dengue virus RNA-dependant RNA polymerase (RdRp) assay (Bourjot et al. 2012a; Teixeira et al. 2014). The presence of an additional acidic group in compounds probably prevents its penetration through the cell membrane, which might explain the absence of cytotoxicity (Bourjot et al. 2012a; Teixeira et al. 2014). This study confirmed that two triterpenoids with a moderate anti-CHIKV activity, four polyacetylenic acids possessing dengue RNA-dependant RNA polymerase (RdRp) inhibiting activity, and one cyanogenic glycoside, (S)-sambunigrin, were isolated from the leaves of this species (Bourjot et al. 2012a; Teixeira et al. 2014).

31) Glycyrrhiza glabra (Licorice shrub)

The licorice shrub Glycyrrhiza glabra Linn is a member of the pea family Leguminosae and grows in subtropical climates to a height of four or five feet (Kataria et al. 2013). Glycyrrhiza glabra Linn is a tall perennial herb, up to 2 meter height found cultivated in Europe, Persia, Afghanistan and to little extent in some parts of India (Kataria et al. 2013). In India, the plant is cultivated in Punjab and sub Himalyan tract (Kataria et al. 2013). The licorice plant Glycyrrhiza glabra has an extensive root system with a main taproot and numerous runners (Kataria et al. 2013). The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior (Kataria et al. 2013). Glycyrrhiza glabra Linn (Fam. Leguminosae) consists of dried, unpeeled, stolon and root. The plant is meant to hold glycyrrhizin, glycyrrhizic acid, glycyrrhetinic acid, asparagine, sugars, resin and starch as main constituents (Kataria et al. 2013).
Glycyrrhizin is the major component responsible for the sweet-tasting constituent of Glycyrrhiza glabra (liquorice) root, which has been tested against eleven flaviviruses including DENV-1, DENV-2, and DENV-3 (Crance et al. 2003; Teixeira et al. 2014). The dengue antiviral evaluation was performed in vitro with Vero cells by plaque reduction assay (Crance et al. 2003; Teixeira et al. 2014). This antiviral compound glycyrrhizin has already been used in patients in the treatment of other diseases (Crance et al. 2003; Teixeira et al. 2014). It should be further considered for use, either alone or in combination with another antiviral compounds tested in this work (interferon, ribavirin, 6-azauridine) for the treatment of flavivirus infections (Crance et al. 2003; Teixeira et al. 2014).

32) Flacourtia ramontchi

Flacourtia is a genus of flowering plants in the willow family Salicaceae. It was previously placed in the now defunct family Flacourticaceae. Flacourtia genus contains 15 species of shrubs and small trees that are native to the African and Asian tropics and subtropics. Several phenolic glycosides have been isolated as a result of the screening of 850 ethyl acetate extracts of Madagascan plants Flacourtia ramontchi (Bourjot et al. 2012b; Teixeira et al. 2014). Dengue antiviral activity was assessed by conducting an enzyme assays with purified enzyme NS5 polymerase of dengue virus (Bourjot et al. 2012b; Teixeira et al. 2014). In this study, the most active phenolic derivatives were evaluated against DENV NS5 polymerase (Bourjot et al. 2012b; Teixeira et al. 2014). The observed activity was moderate and the determined IC50 values were 9.3 ± 2.8 μmol/L for tested compounds during this study was 9.5 ± 5.0 μmol/L (Bourjot et al. 2012b; Teixeira et al. 2014). The mechanism of action of these compounds needs to be further investigated (Bourjot et al. 2012b; Teixeira et al. 2014).

33) Trigonostemon cherieri

Trigonostemon cherieri belongs to family Euphorbiaceae. The bark and the wood of Trigonostemon cherieri, a rare plant of New Caledonia were investigated for their chemical composition resulting in the isolation and characterization of several oxygenated terpenes (Allard et al. 2012; Teixeira et al. 2014). The oxygenated terpene compounds were evaluated for the ability to interfere with NS5 DENV polymerase by an enzyme assay with purified enzyme (Allard et al. 2012; Teixeira et al. 2014). All of them indeed presented inhibitory effects on enzyme activity with the IC50 of 12.7 ± 0.2, 3.1 ± 0.2 and 16.0 ± 1.3 μmol/L. There is no report on the mechanism of inhibition of the compounds (Allard et al. 2012; Teixeira et al. 2014).

34) Arrabidaea pulchra

Arrabidaea pulchra belongs to family Bignoniaceae. The genus Arrabidaea belongs to the tribe Bignonieae (family Bignoniaceae), a large clade of neotropical lianas occurring in Central America, Amazonia, the Atlantic forests of eastern Brazil, and the open dry forests and savannas of Argentina, Bolivia, Brazil, and Paraguay (Brandão et al. 2013). Some Arrabidaea species are reported as anti-inflammatory, astringent, anti-syphilitic, and are used in different South American countries for the treatment of diarrhea, leucorrhrea, anemia, leukaemia and skin diseases (Brandão et al. 2013). A bioguided investigation was conducted and obtained antiviral chemical constituents from an ethanol extract of leaves from Arrabidaea pulchra resulted in the isolation of triterpene compound along with phenolic derivatives (Brandão et al. 2013; Teixeira et al. 2014). The isolated compounds displayed activity against DENV-2. Cytotoxicity was determined in vitro against LLCMK2 and Vero cells by MTT colorimetric assay (Brandão et al. 2013; Teixeira et al. 2014). The determined EC50 and the selectivity indexes for the compounds were as follows: (EC50 = 3.2 ± 0.6 μg/mL; selectivity index = 3.1); (EC50 = 2.8 ± 0.4 μg/mL; selectivity index = 20.0); (EC50 = 3.4 ± 0.4 μg/mL; selectivity index = 3.8) (Brandão et al. 2013; Teixeira et al. 2014). The same assay was conducted with Human Herpesvirus-1 (HSV-1), Vaccinia Virus Western Reserve (VACV-WR) and Murine Encephalomyocarditis virus (EMCV) (Brandão et al. 2013; Teixeira et al. 2014). The inhibition of HSV-1 and VACV-WR was lower than that of DENV-2, and no inhibition was observed for EMCV (Brandão et al. 2013; Teixeira et al. 2014). Further investigations are needed to understand the mechanisms of the antiviral activity which displayed the lowest toxicity in LLCMK2 cells and was active only against DENV-2 (Brandão et al. 2013; Teixeira et al. 2014; Solanki et al. 2017). Further assays are also needed to investigate virucidal activity and targets in the viral replication cycle (Brandão et al. 2013; Teixeira et al. 2014).

35) Castanospermum australe

Castanospermum australe (Moreton Bay Chestnut or Blackbean), the only species in the genus Castanospermum is a flowering plant belongs family Fabaceae. Castanospermum australe is native to the east coast of Australia in Queensland and New South Wales, and to the Pacific islands of Vanuatu, New Caledonia, and the island of New Britain (Papua New Guinea). Members of this genus accumulate iminosugars in their leaves. The water soluble alkaloid castanospermine is derived from Castanospermum australe (black bean or Moreton Bay chestnut tree) (Whitby et al. 2005; Teixeira et al. 2014). An in vitro and in vivo experiments were conducted to ascertain whether this alkaloid can inhibit all dengue virus serotypes (Whitby et al. 2005; Teixeira et al. 2014). The in vitro experiment investigated antiviral activity used BHK-21 cells in a plaque reduction assay and was verified with western blotting, ELISA and fluorogenic RT-PCR(Whitby et al. 2005; Teixeira et al. 2014). In vivo experiment was also conducted with A/J mice (28 to 31 days old). Alkaloid castanospermine inhibits all dengue virus serotype infections in vitro and dengue virus serotype 2 in vivo. It was found that inhibition occurs at the level of secretion and infectivity of viral particles. Additionally, castanospermine prevented mortality in a mouse model of dengue virus infection, with doses of 10, 50, and 250 mg/kg of body weight per day being...
highly effective at promoting survival (Whitby et al. 2005; Teixeira et al. 2014; Solanki et al. 2017).

36) Coptis chinensis Franch

Coptis chinensis Franch belongs to family Ranunculaceae is an important Chinese medicinal flowering plant for the treatment of bacterial, inflammatory, fungal and other diseases presenting no significant side effects or toxicity to humans at clinical doses (Jia et al. 2010; Teixeira et al. 2014). This vegetal species presented a high concentration of an alkaloid palmatine which was screened in vitro for its antiviral activity against DENV-2 using Vero cells via viral titer reduction assays (Jia et al. 2010; Teixeira et al. 2014; Solanki et al. 2017). Vero cells were infected with DENV-2 and the EC50 was estimated to be 26.4 μmol/L and the selectivity index to be 39 (Jia et al. 2010; Teixeira et al. 2014). Furthermore, Jia et al. (2010) also demonstrated an enzyme assay that alkaloid palmatine could inhibit the NS2B-NS3 protease of West Nile Virus (WNV) (Jia et al. 2010; Teixeira et al. 2014). The mechanism by which alkaloid palmatine inhibited the virus is not yet clear; the authors of this investigation planed to clarify the mechanism of action mainly based on a viral reverse genetics system, virus-encoded proteases, selection and characterization of alkaloid palmatine-resistant viruses (Jia et al. 2010; Teixeira et al. 2014).

37) Distictella elongate

In another phychemical investigation of the ethanol extracts from Distictella elongate (Vahl) Urb (Bignoniaceae), a potentially useful source of antidiengue drugs has been reported from the state of Minas Gerais, Brazil (Simões et al. 2011). This study led to the isolation of petcolinarin from the leaf extract and a mixture of petcolinarin and acacetin-7-O-rutinoside from fruit extract (Simões et al. 2011; Teixeira et al. 2014). In vitro MTT colorimetric assays using Vero and LLCMK2 cells were conducted to assess antiviral activity against DENV-2 (Simões et al. 2011; Teixeira et al. 2014). The mixture of petcolinarin and acacetin-7-O-rutinoside presented better anti-DENV-2 activity (EC50 of 11.1 ± 1.6 μg/mL and selectivity index > 45) than pure petcolinarin (EC50 of 86.4 ± 3.8 μg/mL and selectivity index of 4.6) (Simões et al. 2011; Teixeira et al. 2014). However, mechanism of inhibition of the compounds is unclear, but it was reported that it might correspond to one of the putative mechanisms already described for flavonoids (Simões et al. 2011; Teixeira et al. 2014).

38) Scutellaria baicalensis (Baikal skullcap)

Scutellaria baicalensis (Baikal skullcap) is a flowering medicinal herb belongs to family Lamiaceae (Zandi et al. 2012, 2013; Teixeira et al. 2014). Scutellaria baicalensis (Baikal skullcap) is used for the treatment of respiratory infections, hay fever, and fever, gastrointestinal (GI) infections, liver problems including viral hepatitis and jaundice. Scutellaria baicalensis (Baikal skullcap) is also a remedy for HIV/AIDS, kidney infections, pelvisinflammation, and sores or swelling, scarlet fever, headache, irritability, red eyes, flushed face, seizures, epilepsy, hysteria, nervous tension, and to relieve a bitter taste in the mouth. The roots of Scutellaria baicalensis yielded flavonoid baicalein. Zandi et al. (2012, 2013) conducted an in vitro assay using Vero cells an FFURA to assess antiviral activity against DENV-2 (Zandi et al. 2012; Teixeira et al. 2014). This flavonoid baicalein 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 (Zandi et al. 2012, 2013; Teixeira et al. 2014). The IC50 against DENV-2 is 5.39 μg/mL and the selectivity index increased to 21.3 when Vero cells were treated before dengue virus infection and continuously up to 4 days post-infection (Zandi et al. 2012; Teixeira et al. 2014). Flavonoid baicalein displayed direct virucidal (IC50 of 1.55 μg/mL) as well as anti-adsorption (IC50 of 7.14 μg/mL) activity against DENV-2 (Zandi et al. 2012, 2013; Teixeira et al. 2014). These results suggested that a possible mechanism for the extracellular and intracellular activities of baicalein (33) 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 (Zandi et al. 2012, 2013; Teixeira et al. 2014).

In another parallel study, Zandi et al. (2013) evaluated the in vitro antiviral activity of aqueous extract of the roots of Scutellaria baicalensis (Baikal skullcap) against all the four dengue virus (DENV) serotypes (Zandi et al. 2013). During this study aqueous root extract of Scutellaria baicalensis was prepared by microwave energy steam evaporation method (MEGHE™), and the anti-dengue virus replication activity was evaluated using the foci forming unit reduction assay (FFURA) in Vero cells (Zandi et al. 2013). Quantitative real-time polymerase chain reaction (qRT-PCR) assay was used to determine the actual dengue virus RNA copy number (Zandi et al. 2013). The presence of baicalein, a flavonoid known to inhibit dengue virus replication was determined by mass spectrometry (Zandi et al. 2013).

The inhibitory concentration (IC50) values for the Scutellaria baicalensis extract on Vero cells following DENV adsorption ranged from 86.59 to 95.19 μg/mL for the different DENV serotypes (Zandi et al. 2013). The inhibitory concentration (IC50) values decreased to 56.02 to 77.41 μg/mL when cells were treated with the extract at the time of virus adsorption for the different DENV serotypes (Zandi et al. 2013). The extract showed potent direct virucidal activity against extracellular infectious virus particles with IC50 that ranged from 74.33 to 95.83 μg/mL for all DENV serotypes (Zandi et al. 2013). Weak prophylactic effects with Inhibitory concentration (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 (Zandi et al. 2013). The concentration of baicalein in the Scutellaria baicalensis extract was ~1% (1.03 μg/gm dried extract) (Zandi et al. 2013). Therefore, this study demonstrated the in vitro anti-dengue virus replication property of Scutellaria baicalensis against all the four dengue virus serotypes investigated (Zandi
et al. 2013). The root extract reduced dengue virus infectivity and replication in Vero cells (Zandi et al. 2013). The root extract was rich in baikaline, and could be considered for potential development of anti-DENV therapeutics (Zandi et al. 2013; Solanki et al. 2017).

39) Cryptocarya chartacea Kostern

Allard et al. (2011) reported that the bark extracts of Cryptocarya chartacea Kostern, a species belonging to Lauraceae family yielded non-alkylated flavonoid pinocembrin as well as series of new mono and dialkylated ones named chartaceones (Allard et al. 2011; Teixeira et al. 2014). Screening of bioactive compounds against DENV-2 NS5 polymerase showed that the chartaceones compounds were the most active in inhibiting polymerase activity (IC$_{50}$ =Inhibitory concentration-ranging from 1.8 to 4.2 µmol/L) while the other chartaceones were less effective (Allard et al. 2011; Teixeira et al. 2014). On the contrary, other compound was completely inactive (Allard et al. 2011; Teixeira et al. 2014). These findings suggested that the presence of alkylated chains in the structures of chartaceones played an important role in terms of inhibitory activity on DENV-2 NS5 polymerase (Allard et al. 2011; Teixeira et al. 2014). Other compounds were also screened against bovine diarrhea virus (BVDV) NS5 polymerase and no dengue virus inhibitory activity was observed (Allard et al. 2011; Teixeira et al. 2014). Therefore, it was confirmed that these natural substances presented some selectivity towards DENV2-NS5 polymerase (Allard et al. 2011; Teixeira et al. 2014). Considering that the activity of compounds against DENV-2 NS5 polymerase was similar, this study concluded that bioactive compounds played an equivalent role in terms of biological activity (Allard et al. 2011; Teixeira et al. 2014; Solanki et al. 2017).

40) Boerhaavia diffusia

Boerhaavia diffusia belongs to family Nyctaginaceae which is distributed in Africa, Asia, North America, South America, and South Pacific (Sarangi and Padhi, 2014; Mahesh et al. 2012; Bharati and Sinha, 2012). Boerhaavia diffusia has been found to show various important biological activities like antibacterial, anti-oxidant, anti-diabetic, anti-diuretic and anti-inflammatory (Sarangi and Padhi, 2014; Mahesh et al. 2012; Bharati and Sinha, 2012). The root is mainly used for the treatment of gonorrhea, internal inflammation, dyspepsia, oedema, jaundice, menstrual disorders, anaemia, liver, gallbladder and kidney disorders, enlargement of spleen and abdominal pain (Sarangi and Padhi, 2014; Mahesh et al. 2012; Bharati and Sinha, 2012). Bharati and Sinha, (2012) have reported the anti-dengue activity of stems of Tinospora cardifolia (Wild) Miers (10 gm) and the plant of Boerhaavia diffusia Linn (10 gm) (Sarangi and Padhi, 2014; Mahesh et al. 2012; Bharati and Sinha, 2012). Anti-dengue effect was evaluated by giving the Ayurvedic mixture consisting of Tinospora cardifolia and Boerhaavia diffusia to dengue patients 2-3 times a day (Sarangi and Padhi, 2014; Mahesh et al. 2012; Bharati and Sinha, 2012; Solanki et al. 2017).

41) Chondrus crispus (Red algae)

Chondrus crispus commonly called as carrageen moss is a species of red algae which is abundant in rocky shores and tide pools of Ireland and coastal Europe (Sarangi and Padhi, 2014; Talarico and Damonte, 2007). Chondrus crispus consisting of polysaccharide carrageen as active constituent (Sarangi and Padhi, 2014; Talarico and Damonte, 2007). Carrageenans were effective for the treatment of viral infections of common cold (Sarangi and Padhi, 2014; Talarico and Damonte, 2007). Talarico and Damonte, (2007) has reported that carrageen and other sulfate polysaccharides were strongly inhibited the dengue virus type-2 infections where they were inhibiting virus entry (Sarangi and Padhi, 2014; Talarico and Damonte, 2007; Solanki et al. 2017).

42) Gastrodia elata

Gastrodia elata a Chinese medicinal herb belongs to family Orchidaceae has been used for the treatment of various health disorders like stroke, rheumatism, insomnia, alzheimer’s disease, depression, convulsions, neuronal diseases, fungal, bacterial and viral infections (Sarangi and Padhi, 2014; Qiu et al. 2007). Gastrodia elata contained nine kinds of phenolic compounds, and sixteen kinds of amino acids which are beneficial to health (Sarangi and Padhi, 2014; Qiu et al. 2007). D-glucans isolated from Gastrodia elata and sulfated derivatives were investigated for inhibitory activity against dengue type-2 virus (Sarangi and Padhi, 2014; Qiu et al. 2007). These sulfated D-glucan derivatives were strongly interfering with the dengue type-2 virus infections with an EC$_{50}$ value of 0.68+/-.017 µg/mL mainly interfered with virus adsorption in a very early stage of the virus cycle (Sarangi and Padhi, 2014; Qiu et al. 2007; Solanki et al. 2017).

43) Kaempferia parviflora

Kaempferia parviflora, a Thailand medicinal herb belongs to family Zingiberaceae commonly known as krachai Dam (Phurimsak and Leardkamolkarn, 2005; Sarangi and Padhi, 2014). Leaves and stem of Kaempferia parviflora were used traditionally for the treatment of many viral infections. Main chemical constituents of Kaempferia parviflora are borneol and flavanoids exhibited anti-ulcer, anti-allergic, anti-fungal and antimycobacterial activities (Phurimsak and Leardkamolkarn, 2005; Sarangi and Padhi, 2014). Kaempferia parviflora has demonstrated a strong inhibitory activity against dengue type-2 virus (Phurimsak and Leardkamolkarn, 2005; Sarangi and Padhi, 2014). Phurimsak and Leardkamolkarn, (2005) has studied virucidal activity of leaves and stem extracts of Kaempferia parviflora against dengue virus type-2 (Phurimsak and Leardkamolkarn, 2005; Sarangi and Padhi, 2014). This study reported that some of the bioactive compounds in Kaempferia parviflora inactivated the dengue type-2 virus particles (Phurimsak and Leardkamolkarn, 2005; Sarangi and Padhi, 2014; Solanki et al. 2017).
Catunaregam spinosa L. belongs to family \textit{Rubiaceae} is an important medicinal plant listed in Indian \textit{Ayurvedic} system of medicine (Senthamarai \textit{et al.} 2011; Patil and Khan, 2017). \textit{Catunaregam spinosa} is a medicinal shrub or tree about 9 meter in height found throughout India (Senthamarai \textit{et al.} 2011; Patil and Khan, 2017). The seeds contains essential oil and organic acid. The fresh fruits of \textit{Catunaregam spinosa} contains essential oil and organic acid. The fresh fruits of \textit{Catunaregam spinosa} possesses carried out against dengue virus by Supriya \textit{et al.} (2017a). The work is under progress for the identification of bioactive compounds and their inhibitory effect on dengue vector control measures (Supriya \textit{et al.} 2017a, 2017b).

Sood \textit{et al.} (2015) reported the anti dengue activity of some of the Indian medicinal plants. During this study, only methanolic plant extracts manifested dengue antiviral activity when assayed against dengue serotype-2 or dengue serotype-3 (Sood \textit{et al.} 2015). The hydroalcoholic and aqueous extracts of all the plants selected for the study did not manifest any antiviral activity when tested against these two DENV serotypes (IC50 = 100μg/ml) (Sood \textit{et al.} 2015). The roots of \textit{Copitis tecta} (Inhibitory concentration, IC50 < 25μg/ml); The whole plant of \textit{Desmodium gangeticum} (Inhibitory concentration, IC50 < 25μg/ml); whole plant of \textit{Fumaria indica} (Inhibitory concentration, IC50 < 25μg/ml); whole plant of \textit{Phyllanthus anamur} (Inhibitory concentration, IC50 < 25μg/ml); rhizome of \textit{Picrorhiza kurroa} (IC50 = 25μg/ml); bark of \textit{Premna mucronata} (Inhibitory concentration, IC50 = 25μg/ml).
concentration, IC\textsubscript{50} <25μg/ml); fruit of *Terminalia chebula* (Inhibitory concentration, IC\textsubscript{50} <25μg/ml); stem of *Tinospora cordifolia* (Inhibitory concentration, IC\textsubscript{50} <25μg/ml) (Sood et al. 2015). Among these plants only two plants *Cissampelos pareira* and *Phyllanthus amarus* manifested potent inhibitory activity (Sood et al. 2015). *Cissampelos pareira* and *Phyllanthus amarus* were effective in curbing DENV-3 (IC\textsubscript{50} values <150 μg/ml) (Sood et al. 2015). Extending the type-2 assay to DENV-1, -2 and -4 revealed that both these extracts possessed the ability to inhibit all four DENVs even after their entry into cells (Sood et al. 2015).

*Solanum virginianum* leaf decoction mixed with pepper and ginger has been used by local traditional healers for controlling dengue fever in the rural parts of Orissa and West Bengal states of India (Shibabrata et al. 2012; Sahu et al. 2013; Singh and Rawat, 2017). In the rural parts of Chhattisgarh, Bihar, Madhya Pradesh states and other parts of India, local traditional healers adopted the whole plant extracts of *Alternanthera sessilis*, *Solanum xanthocarpum*, *Achyranthes aspera*, *Abutilon indicum*, *Swertia chirata*, *Brassica juncea*, leaf and bark of *Calotropis procera*, leaf extract of *Datura metel* and *Coriandrum sativum*, powdered seeds of *Peganum harmala* root extract of *Cassia fistula* as a remedy for dengue fever (Smita, 2015; Das et al. 2016; Singh and Rawat, 2017; Lalla et al. 2014). Dengue fever control by the whole plant extracts of *Plectranthus vettiveroides* were also used by the traditional healers in South India (Nisheeda et al. 2016; Singh and Rawat, 2017). Rajalakshmi et al. (2016) reported the use of leaf extract of *Adhatoda vasica* as an effective herbal medicine by the traditional healers for the treatment of dengue fever (Rajalakshmi et al. 2016; Singh and Rawat, 2017).

The active compounds isolated from above listed plant species showed an inhibitory activity against dengue virus (Kadir et al. 2013; Vijayan et al. 2004; Grzybowski et al. 2011; Newman et al. 2003; Garcia et al. 2003; Choochote et al. 2004). The isolated products belong to various chemical classes such as sulfated polysaccharides (Fucoidans are a group of polysaccharides), phenolics, flavonoids, terpenoids, quercetin, polycyclic quinones, alkaloids with related compounds and natural chalcone compounds (Vijayan et al. 2004; Grzybowski et al. 2011; Teixeira et al. 2014; Newman et al. 2003; Garcia et al. 2003; Choochote et al. 2004; Kadir et al. 2013). The bioactive compounds of medicinal plants comprise a variety of compounds with a wide range of biological activities (Vijayan et al. 2004; Grzybowski et al. 2011; Newman et al. 2003; Garcia et al. 2003; Choochote et al. 2004; Kadir et al. 2013). There are reports on medicinal plants extracts and essential oils possessing potential to new antiviral properties (Vijayan et al. 2004; Grzybowski et al. 2011; Newman et al. 2003; Garcia et al. 2003; Choochote et al. 2004; Kadir et al. 2013). Many plant extracts in different solvents have been reported to exhibit activity against a vector of dengue fever, *Aedes Aegypti* (Vijayan et al. 2004; Grzybowski et al. 2011; Newman et al. 2003; Garcia et al. 2003; Choochote et al. 2004; Kadir et al. 2013).

Polyphenols are aromatic-rich plant metabolites that have been identified in a number of food sources and dietary supplements such as cranberry juice, grape seeds, pomegranate and unripe apple peels (Kimmel et al. 2011). Oligomeric procyanidins (OPCs) from Applepoly® have been shown to have antiviral and immunostimulatory effects (Kimmel et al. 2011). Oligomeric procyanidins (OPCs) isolated from non-ripe apple peel were tested for capacity to reduce dengue virus (DENV) titers (Kimmel et al. 2011). Oligomeric procyanidins (OPCs) from Applepoly® exhibited direct antiviral activity (Kimmel et al. 2011). Treatment of DENV infected human PBMCs with oligomeric procyanidins (OPCs) from Applepoly® decreased viral titers and affected the expression of critical innate antiviral immune products (Kimmel et al. 2011). This study demonstrated the direct viral interaction to block dengue viral infection and enhancement of several different aspects of innate antiviral immunity (Kimmel et al. 2011). Therefore, dietary supplements that contained high concentrations of oligomeric procyanidins (OPCs) such as Applepoly®, might enhance antiviral innate immunity to benefit patients facing viral challenge (Kimmel et al. 2011).

II. CONCLUSION

This review paper highlighted 71 plant species of potential anti dengue activity that could be used as a first hand herbal medicine in the treatment of dengue virus disease. On the basis of available literature, it was concluded that different parts of plants and particularly leaf extracts were used for the treatment of dengue. However, limitations of this review paper are the lack of valid scientific evidence in some of the listed plants for claiming anti dengue activity. Another major problem is the lack of clinical studies for the development of drugs against dengue. Most of these studies presented in this review paper works well in a laboratory settings and experimental data is also not enough for the further validation of anti dengue activity. Herbal medicine treatments have been used in different parts of India for combating dengue but there is no scientific validation studies on plants which is a major problem for the development of botanical drugs. The information presented in this review paper is the primary knowledge of herbal medicines and formed a strong baseline for the further research on anti-dengue plants. Therefore, information on the anti dengue activity of the plants presented in this review paper is not sufficient and further detailed study is essential for the confirmation of the botanical drugs. For the development of drugs for dengue, a complete detailed phytochemical study followed by isolation and identification of bioactive compounds should be considered as the first priority. Biological activity of these botanical drugs should also be considered particularly against dengue viral disease. Furthermore bioactive compounds of potential anti dengue plants should also go through the additional *in vitro* and *in vivo* animal testing followed by toxicity level studies and clinical tests. Human clinical studies of promising bioactive compounds should also be considered for the effective new
botanical anti-dengue drugs. Therefore, the collection of literature on anti dengue plants presented in this review paper warranted further investigation through studies such as drug discovery, polypharmacology, and drug delivery using nanotechnology for controlling dengue disease.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

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