Role of Botanical Drugs in Controlling Dengue Virus Disease

Ravindra B. Malabadi[1*], Raju K. Chalannavar[2*], Supriya S[2], Nityasree BR[2], Sowmyashree K[2], Neelambika T. Meti[3]

[1]*Miller Blvd NW, Edmonton, Alberta, Canada*

[2]*Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India*

[3]*Plant Biotechnology Laboratory, Rajiv Gandhi Institute of IT and Biotechnology, Bharati Vidyapeeth University, Pune-Satara Road, Katraj, Pune-411046, Maharashtra State, India*

Corresponding author: Ravindra B. Malabadi, Raju K. Chalannavar

***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 threatning viral infection transmitted from one person to another by the bites of infected female arthopod vector *Aedes aegypti* mosquitoe (Malabadi *et al*. 2011, 2010, 2017a, 2017b; Chaturvedi and Nagar, 2008; Murray *et al*. 2013). Female *Aedes aegypti* mosquitoe is also a major responsible vector for other viral infectious diseases like chikungunya, Zika virus, and Ebola virus diseses 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 distint 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 conutries except India (Malabadi *et al*. 2017a, 2017b; Villar *et al.* 2015; Thomas, 2015; Gottschamel *et al*. 2016; Vannice *et al.* 2015, 2016). Dengavaxia (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 effectve medicine against dengue virus disease based on *in vitro* experimental results, ethnobotanical studies, clinical data in few plants conducted in different laboratories throughout world including India. On the basis of this prelimanary 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 subtropical 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 (CPLE) 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; Singhai *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 ***Myrtacea****e* 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 Ravi and Divyashree, 2014) and guaijaverin 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). The seed contains glycosides, carotenoids, phenolic compounds having antimicrobial 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).

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 antidiarrheal, 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.*

2010). *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 bunched 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).

Euphorbia hirta is the most widely used plant in the folkloric treatment of dengue in the Philippines (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). *Euphorbia hirta*, locally known as ''tawa–tawa'', is used in folk medicine to cure dengue fever by people in rural areas in the Philippines (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; About Health, 2011; Kadir *et al*. 2013). Practitioners of traditional medicines in the Philippines believed that decoction of tawa–tawa (*Euphorbia hirta*) leaves can reverse viral infection and prevented the dengue fever from moving into critical stages, although there are no scientific studies proving its effectiveness (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; About Health, 2011; The Cure Library, 2007; Kadir *et al*. 2013). Sometimes, tawa–tawa (*Euphorbia hirta*) in the Philippines is prepared together with papaya leaves since papaya leaf extract has a function as an antibiotic to cure fever (Guzman *et al.* 2016; Philippine Medicinal Plants, 2011;The Cure Library, 2007; Kadir *et al*. 2013). While papaya leaf extract kills the bacterial infection that caused the fever, tawa–tawa (*Euphorbia hirta*) extract prevented the bleeding (Philippine Medicinal Plants, 2011;The Cure Library, 2007; About Health, 2011;Kadir *et al*. 2013; 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; 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 leucopoenia 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; 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, pimples, 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, flavanoids, 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, antispasmodic, antifertility, antifungal, 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) Azidarachta indica (Neem)

Azidarachta 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 *Azidarachta 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 $C_{6/36}$ (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 $TCID_{50}$ 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 suckling 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 *Azhadirachta indica*, *Quercus lusitanica* and *Wedelia calendulaceae* 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 *Azhadirachta 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 calendulaceae* did not showed 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 and4 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; Sainty *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; Sainty *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; Sainty *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; Sainty *et al*. 1998; Masoodi and Khan. 2012). Leaves are simple, elliptic, and have smooth margins (Buckingham, 1996; Sainty *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; Sainty *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; Sainty *et al*. 1998; Masoodi and Khan. 2012). *Alternanthera philoxeroides* has also reduced water-bird 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).

The pharmacological properties of tulsi (*Ocimum sanctum*) are antimicrobial (including antibacterial, antiviral, antifungal, antiprotozoal, antimalarial, anthelmintic), mosquito repellent, anti-diarrheal, anti-oxidant, anti-cataract, anti-inflammatory, chemopreventive, radioprotective, hepato-protective, neuro-protective, cardio-protective, anti-diabetic, anti-hypercholesterolemia, anti-hypertensive, anti-carcinogenic, analgesic, anti-pyretic, anti-allergic, immunomodulatory, central nervous system depressant, memory enhancement, anti-asthmatic, anti-tussive, diaphoretic, anti-thyroid, anti-fertility, anti-ulcer, anti-emetic, anti-spasmodic, anti-arthritic, adaptogenic, anti-stress, anti-cataract, anti-leukodermal and anti-coagulant activities (Cohen, 2014; Mahajan *et al.* 2013; Mohan *et al*. 2011; Pattanayak *et al*. 2010; Mondal *et al*. 2009, 2011).

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

Andrographis paniculata belongs to family ***Acanthaceae*** is a native to India and Srilanka (Joselin and Jeeva, 2014; Saxena *et al*. 1998; Hossain *et al*. 2014) *Andrographis paniculata* is an erect, branched, annual herbaceous plant erecting to a height of 30-110 cm in moist shady places (Saxena *et al*. 1998; Hossain *et al*. 2014; Joselin and Jeeva, 2014; Kadir *et al*. 2013; Okhuarobo *et al*. 2014; Frederico *et al*. 2017). *Andrographis paniculata* has been used in ancient *Ayurvedic* medicine for the treatment of various ailments (Saxena *et al*. 1998; Hossain *et al*. 2014; Joselin and Jeeva, 2014; Kadir *et al*. 2013; Okhuarobo *et al*. 2014; Frederico *et al*. 2017; Singh and Rawat, 2017).

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

as an alternative herbal treatment for **dengue** (Tang *et al.* 2012; Kadir *et al*. 2013; Frederico *et al*. 2017; Singh and Rawat, 2017).

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 post-natal care, complicated diseases such as jaundice, gonorrhea 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).

The pharmacological properties of *Andrographis paniculata* are antimicrobial, antifungal, antiviral, antibacterial, antioxidant, anti-inflammatory, anti-diarrhoeal, anti-cancer activity, anti-malarial, emollient, controls upper respiratory infections (any infection in the nose, throat, sinuses, and ears), cardiovascular activity, hepatoprotective and choleretic activity, immunomodulatory activity, anti-HIV activity, anti-filarial, anti-protozoal, anti-plasmoidal activity, nematicidal/larvicidal/ adulticial activity, astringent, diuretic, emmenagogue, gastric and liver tonic, carminative, anti-helminthic, and anti-pyretic (Saxena *et al*. 1998; Joselin and Jeeva, 2014; Hossain *et al*. 2014; Okhuarobo *et al*. 2014). Because of blood purifying activity, *Andrographis paniculata* has been recommended for use in cases of leprosy, gonorrhea, scabies, boils, skin eruptions, chronic and seasonal fevers (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 *Cocculeae* (Shah *et al.* 2017; Jain *et al.* 2015; Amresh *et al.* 2008; Vardhanabhuti 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; Vardhanabhuti 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; Vardhanabhuti and Ikeda, 2006; Porto *et al*. 2008). In India, the climbing herb *Cissampelos pariera*, is widely distributed in different parts of Karnataka, Bababuden 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; Vardhanabhuti 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; Vardhanabhuti 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; Vardhanabhuti 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* Linn 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; Vardhanabhuti 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; Vardhanabhuti 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).

The pharmacological activities of *Cissampelos pariera* are anti-dengue, anti-platelet, vasodilator and anti-protozoal, anti-inflammatory, anti-diuretic, anti microbial, anti-malarial, anti-parasitic, anti-ulcer, anti-cancer, anti-oxidant, cardiovascular activity, anti-urolithic, muscle-relaxant, hepatoprotective, anti-diabetic, anti-diarrhoeal, anti-fertility, memory-enhancing activity, anti-venom, neuroprotective, immunomodulatory activity, analgesic and antipyretic (Shah *et al.* 2017; Jain *et al.* 2015; Amresh *et al.* 2008; Vardhanabhuti and Ikeda, 2006; Porto *et al*. 2008).

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, diarrhea, dysentery kidney infections, skin disorders, scabies, non-healing ulcers, leprosy, migraine, leucorrhoea and gonorrhea and fever (Shah *et al.* 2017; Jain *et al.* 2015; Amresh *et al*. 2008; Vardhanabhuti 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, stomachin, 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 pareira* 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-hydroxypanduratin A (1) and panduratin A (2) showed good competitive inhibitory activities towards dengue virus serotype-2, NS3 protease with Ki values of 21 lM and 25 lM, respectively (Kiat *et al*. 2006; Kadir *et al*. 2013). The small value of Ki shows the potential of 4-hydroxypanduratin 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 IC_{50} 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

et al. 2013; Teixeira *et al.* 2014). Fucoidans isolated from the marine alga brown seaweed *Cladosiphon okamuranus* are a group of polysaccharides which contain considerable percentages of L-fucose and sulfate ester groups. Fucoidans structure is composed of repeating units of sulphated fucose and glucuronic acid residues with antiviral activity (Hidari *et al*. 2008, 2013; Li *et al*. 2008; Kadir *et al*. 2013; Teixeira *et al.* 2014). The investigation conducted with *Cladosiphon* fucoidan demonstrated that this polysaccharide inhibits dengue virus type 2 (DENV-2) infection (Hidari *et al*. 2008, 2013; Li *et al*. 2008; Kadir *et al*. 2013; Teixeira *et al.* 2014). The biological *in vitro* assays evaluated antiviral activity by focus-formed assay using BHK-21 cells. Fucoidan inhibited dengue virus infection in a concentration-dependent matter (Hidari *et al*. 2008, 2013; Kadir *et al*. 2013; Teixeira *et al.* 2014). When the dengue virus was treated with 10μg/mL of fucoidan, infectivity by dengue virus serotype-2 was reduced by 80% compared with that in untreated cells and the determined IC_{50} corresponded to 4.7 μg/mL (Hidari *et al*. 2008, 2013; Kadir *et al*. 2013; Teixeira *et al.* 2014). Dengue virus serotypes 3 and 4 were moderately susceptible to fucoidan (Hidari *et al*. 2008, 2013; Kadir *et al*. 2013; Teixeira *et al.* 2014). For dengue serotype-1, fucoidan did not present an effect on the infection. Fucoidan derivatives were also examined for their effects on infection of BHK-21 cells by dengue virus serotype-2 (Hidari *et al*. 2008, 2013; Kadir *et al*. 2013; Teixeira *et al.* 2014). The desulfation of fucoidan is required for the antiviral activity of glycosaminoglycans (Hidari *et al*. 2008, 2013; Kadir *et al*. 2013; Teixeira *et al.* 2014).

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} aganist 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). This study demonstrated that a heparin sulfate (HS) imitative compound *lambda* had the ability to interfere with DENV-2 replication when added after virus adsorption, and even under these conditions, the antiviral potential of *lambda*-carrageenan was higher than its ability to affect virus adsorption (Teixeira *et al.* 2014; Jiao *et al*. 2011; Talarico *et al*. 2007; Talarico *et al*. 2004, 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 orientali* 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 cytopathic 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 non-toxic 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, myrecene and terpinol methyl heptenone, flavonoids and phenolic compounds, which consist of luteolin, isoorientin 2'-O-rhamnoside, quercetin, kaempferol and apiginin (Shah *et al*. 2011). *Cymbopogon citratus* possesses various pharmacological activities such as anti-amoebic, anti-bacterial, anti-diarrheal, anti-filarial, anti-fungal, anti-inflammatory, hypotensive, antimalarial, anti-spasmodic, anti-mutagenicity, anti-mycobacterial, antioxidant, hypoglycemic, anticonvulsant, analgesic, antiemetic, anti-tussive, anti-rheumatic, antiseptic, gastrointestinal disorders, fevers, and neuro behaviorial (Shah *et al*. 2011).

14) Cryptonemia crenulata (Red seaweed)

Cryptonemia crenulata is a marine red seaweed plant belongs to family ***Halymeniaceae.*** *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-3 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 rattan, 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 *in vitro* antiviral assay using ethanol (12.5l 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 *Flagellaria indica* was determined by adopting MTT assays and the CC_{50} of ethanol extract of *Flagellaria indica* were 312 µg mL^{-1}(Klawikkan *et al*. 2011; Kadir *et al*. 2013). Therefore, this study confirmed that *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 ***Phyllophoraceae*** 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 IC_{50} value of 0.9 µg mL^{-1}, which is the same as the IC_{50} 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 titter 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; Kabir *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; Kabir *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; Kabir *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; Kabir *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; Kabir *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; Kabir *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 anti-microbial, 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 serotyp-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 (Subabool) 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 Central America and the West Indies from the Bahamas and Cuba to Trinidad and Tobago (Kadir *et al.* 2013; Meenadevi *et al.* 2013). *Leucaeana leucocephala* (Subabul) is a small tree commonly cultivated in garden as a ornamental, avenue and forage crop in India (Meenadevi *et al.* 2013). *Leucaena leucocephala* (Subabul) commonly known as *White Lead tree* has been naturalized in many tropical and sub-tropical locations (Meenadevi *et al.* 2013). *Leucaena leucocephala* (Subabul) has been promoted for its forage production and naturally spreads like a weed (Meenadevi *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, provide shade, controls soil erosion (Meenadevi *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 (Meenadevi *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 *Solieriaceae* 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 IC_{50} 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 (CC_{50}) 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 37^0C 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 (IC_{50}) (Ocazionez *et al.* 2010). *Lippia alba* oil resulted in a less cytotoxicity than *Lippia citriodora* oil (CC_{50}: 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 IC_{50} 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 widly distributed in North Eastern region of India, Bhutan, Nepal, China, Vietnam, Thailand, Indonesia, Japan, Mynamaar 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).

Leaf juice of *Houttuynia cordata* is consumed for the treatment of cholera, dysentery, curing of blood deficiency, purification of blood, and used as antidote and astringent (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-helmentic, 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

of the cells (Klawikkan *et al*. 2011; Leardkamolkarn *et al*. 2012; Goel *et al*. 2004; Kadir *et al*. 2013). A concentration of 100 µg mL^{-1} also effectively protected the cells from viral entry and inhibited virus activities after adsorption (Goel *et al*. 2004). HPLC analysis of *Houttuynia cordata* extract indicated that hyperoside was the predominant bioactive compound, and was likely to play a role in this inhibition (Klawikkan *et al*. 2011; Leardkamolkarn *et al*. 2012; Goel *et al*. 2004; Kadir *et al*. 2013).

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 pocess medicinal properties, such as astringent, anti-inflammatory, antiviral, antidiabetic, 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 10-1,000 $TCID_{50}$ 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). Therfore, *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, immunonomodulant and anti-oxidant 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

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 downright 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 alkaloidal fraction pentacyclic oxindole of *Uncaria tomentosa*. The pentacyclic oxindole alkaloid-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 spcies 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 aganist 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 anacolosine (**1**), together with three known acetylenic acids, the octadeca-9,11,13-triynoic acid (**2**), (13*E*)-octadec-13-en-9,11-diynoic acid (**3**), (13*E*)-octadec-13-en-11-ynoic acid (**4**), two terpenoids, lupenone (**5**) and *β*-amyrone (**6**), and one 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 (EC_{50} 77 and 86 µM, respectively) and the acetylenic acids produced IC_{50} 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, upto 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, 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 *Flacourtiaceae*. *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 IC_{50} values were 9.3 ± 2.8 µmol/L for tested compunds 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 cherrieri

Trigonostemon cherrieri belongs to family *Euphorbiaceae*. The bark and the wood of *Trigonostemon cherrieri*, 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 IC_{50} 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, leucorrhea, 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. Cytotoxity was determined *in vitro* against LLCMK2 and Vero cells by MTT colorimetric assay (Brandão *et al*. 2013; Teixeira *et al.* 2014). The determined EC_{50} and the selectivity indexes for the compounds were as follows: (EC_{50} = 3.2 ± 0.6 µg/mL; selectivity index = 3.1); (EC_{50} = 2.8 ± 0.4 µg/mL; selectivity index = 20.0); (EC_{50} = 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 antivirus 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 EC_{50} 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 phytochemical investigation of the ethanol extracts from *Distictella elongate* (Vahl) Urb (Bignoniaceae), a potentially useful source of antidengue 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 (EC_{50} of 11.1 ± 1.6 μg/mL and selectivity index > 45) than pure petcolinarin (EC_{50} 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, pelvicinflammation, 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 IC_{50} 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 IC_{50} 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 (IC_{50} of 1.55 μg/mL) as well as anti-adsorption (IC_{50} 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 (IC_{50})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 (IC_{50})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 IC_{50} that ranged from 74.33 to 95.83 μg/ mL for all DENV serotypes (Zandi *et al.* 2013). Weak prophylactic effects with Inhibitory concentration (IC_{50}) 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 baicalein, 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} =Inhibirory 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 inhibitary 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 shown various important biological activities like antibacterial, anti-oxidant, antidiabetic, 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 diffusa* 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 diffusa* 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 inhibitary 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+/-0.17 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).

44) Phyllanthus urinaria

Phyllanthus urinaria belongs to family *Phyllanthaceae*, originated in tropical Asia and widely distributed in South India, South America and China (Sau *et al*. 2013; Sarangi and Padhi, 2014). *Phyllanthus urinaria* used for the treatment of several diseases like hepatitis, jaundice, urinary tract infections, syphillis, asthma, bronchitis, anemia, joint pains and anti-cancer activity (Sau *et al*. 2013; Sarangi and Padhi, 2014). *Phyllanthus urinaria* shown to have anti dengue activity (Sau *et al*. 2013). Sau *et al*. (2013) reported the anti-dengue effect of aqueous and methanolic extracts of four species of *Phyllanthus* such as *P.amarus*, *P.niruri*, *P.urinaria* and *P.wastonii* (Sau *et al*. 2013; Sarangi and Padhi, 2014). These *Phyllanthus* species showed strongest inhibitory activity against DENV-2 with more than 90% of virus reduction in simultaneous treatment at maximal non toxic dose of 250.0 µg/mL and 15.63 µg/mL (Sau *et al*. 2013; Sarangi and Padhi, 2014; Solanki *et al.* 2017).

45) Piper sarmentosum

Piper sarmentosum belongs to family *Piperaceae* and leaves were traditionally used as condiment with carminative property (Udom *et al*. 2006; Sarangi and Padhi, 2014). *Piper sarmentosum* is an important medicinal plant used for the treatment of inflammation, skin diseases, rheumatism, diarrhea and root was particularly used for the treatment of cough and asthma (Udom *et al*. 2006; Sarangi and Padhi, 2014). *Piper sarmentosum* contained many bioactive compounds such as ascaricin, α-ascarone, *β*-sitosterols, vitamin C, and vitamin E (Udom *et al*. 2006; Sarangi and Padhi, 2014). The ethanol extracts of *Piper sarmentosum* possessed larvicidal effect against early 4th stage larvae of *Aedes aegypti* mosquitoes (Udom *et al*. 2006; Sarangi and Padhi, 2014). Udom *et al*. (2006) reported the larvicidal activity of three species of pepper plants on *Aedes aegypti* (Udom *et al*. 2006; Sarangi and Padhi, 2014).

46) Catunagegam spinosa

Catunaregam spinosa Linn. belongs to family *Rubiaceae* is an important medicinal plant listed in Indian *Ayurvedic* system of medicine (Senthamarai *et al.* 2011; Patil and Khan, 2017). *Catunaregam spinosa* is a medicinal shrub or tree about 9 meter in height found throughout India (Senthamarai *et al.* 2011; Patil and Khan, 2017). The seeds contains essential oil and organic acid. The fresh fruits contained a high amount of carbohydrate, and saponins (Senthamarai *et al.* 2011; Patil and Khan, 2017). The raw fruits have a highly astringent taste due to high tannin content (Senthamarai *et al.* 2011; Patil and Khan, 2017). The fruit pulp dried and powdered is credited with emetic properties (Senthamarai *et al.* 2011; Patil and Khan, 2017). The edible parts such as leaves and flowers of the plant were cosumed as vegetables in Nasik district of Maharashtra, Karnataka, Tamilnadu states of India (Senthamarai *et al.* 2011; Patil and Khan, 2017). The main medicinal uses of *Catunaregam spinosa* are nauseant, expectorant, anthelmintic and abortifacient properties (Senthamarai *et al.* 2011; Patil and Khan, 2017). It also showed hypoglycaemic, pesticidal, insecticidal and anti-cancer activities (Senthamarai *et al.* 2011; Patil and Khan, 2017). The seeds are tonic to induce appetite and their decoction is taken for relief from headache (Senthamarai *et al.* 2011; Patil and Khan, 2017). The phytochemical analysis of *Catunaregam spinosa* reported the presence of alkaloid, flavanoid, glycoside, carbohydrate, phenolic compounds, triterpenoidal saponins, essential oil, veleric acid, tannins and resin (Senthamarai *et al.* 2011; Patil and Khan, 2017). *Catunaregam spinosa* bark reported for the treatment of diarrhoea, dysentery, as abortifacient, anthelmintic and antipyretic (Senthamarai *et al.* 2011; Patil and Khan, 2017). *Catunaregam spinosa* was also considered to be sedative, hypoglycemic, used in case of stomach ache as first aid remedy, roots were used in the treatment of epilepsy, eye ache, urinary infection, fruit was used as fish poison, emetic and the leaves were used in pulmonary infections (Senthamarai *et al.* 2011; Patil and Khan, 2017). *Catunaregam spinosa* is carminative, alexiteric, antipyretic; cures abscess, ulcers, inflammations, wounds, tumours, and skin diseases (Senthamarai *et al.* 2011; Patil and Khan, 2017).

A very recent study by Supriya *et al*. (2017a, 2017b) reported the phytochemical analysis, antioxidant property and larvicidal activity of *Punica granatum* L. and *Catunaregam spinosa* (Thunb.) Tirveng leaf extract on dengue transmitting mosquito *Aedes aegypti* (Supriya *et al*. 2017a, 2017b). Expeimental results confirmed the presence of alkaloids, flavonoids, phytosterols, phenols, proteins, amino acids, and glycosides (Supriya *et al*. 2017). The extracts of *P. granatum* exhibited moderate larval activity (Supriya *et al*. 2017a). On the other hand poor antioxidant property and least larval death were observed in *Catunaregam spinosa* leaf extracts of petroleum ether, ethyl acetate and methanol (Supriya *et al*. 2017). These collective results suggested that leaf extracts showed moderate and least activity on controlling *Aedes aegypti* larvae which is responsible for dengue transmitting disease (Supriya *et al*. 2017a, 2017b). Further work is under progress for the identification of bioactive compounds and their inhibitory effect on dengue vector control measures (Supriya *et al*. 2017a, 2017b).

Sood *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 *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 *et al*. 2015). The roots of ***Coptis teeta*** (Inhibitory concentration, IC_{50} <25µg/ml); The whole plant of ***Desmodium gangeticum*** (Inhibitory concentration, IC_{50} <25µg/ml); whole plant of ***Fumaria indica*** (Inhibitory concentration, IC_{50} <25µg/ml); whole plant of ***Phyllanthus amarus*** (Inhibitory concentration, IC_{50} <25µg/ml); rhizome of ***Picrorhiza kurroa*** (IC50 = ~25µg/ml); bark of ***Premna mucronata*** (Inhibitory

concentration, IC_{50} <25µg/ml); fruit of ***Terminalia chebula*** (Inhibitory concentration, IC_{50} <25µg/ml); stem of ***Tinospora cordifolia*** (Inhibitory concentration, IC_{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* Linn, and *Phyllanthus amarus* were effective in curbing DENV-3 (IC_{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*, *Achyranthus 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 a 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 compunds 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 validiation 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 cosidered 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 compunds 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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