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Dengue and natural remedies for its prevention and control: A review

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Abstract
Dengue virus is the most common mosquito borne viral infection and is caused by four different serotypes of dengue virus, named DENV-1, DENV-2, DENV-3 and DENV-4, which belongs to Flaviviridae family and *Flavivirus* genus. It is transmitted by the *Aedes* mosquito from one infected person to another healthy person. A frontal headache, retro-orbital pain, body aches, rashes, nausea, vomiting, weakness and a high body temperature are the main symptoms of dengue infection. Dengue haemorrhagic fever and dengue shock syndrome can result in death in severe cases if proper treatment is not given. Several medical technologies, such as monoclonal antibodies, tetravalent subunits, inactivated and live attenuated vaccines have been adopted globally, but developing and under developed countries cannot afford them due to high costs. Various developing countries use herbal and natural remedies to prevent and control dengue. In this review, we are discussing about various plant species that have antiviral, ovicidal, larvicidal and mosquito repellent properties as well as compound that can be used to treat dengue fever.
Following species of plants *Momordica charantia*, *Alternanthera philoxeroides*, *Andrographis paniculata*, *Cladosiphon okamuranus*, *Carica papaya*, *Momordica charantia*, *Andropogon citratum*, *Curcuma longa*, *Piper longum*, *Piper ribesoides*, *Piper sarmentosum*, *Eupatorium perfoliatum*, *Kaempferia parviflora*, *Solanum villosum*, *Azadirachta indica*, *Pongamia glabra*, *Eupatorium odoratum*, *Catharanthus roseus*, *Nyctanthes arbor-tristis*, *Acalypha alnifolia*, *Delonix elata*, *Ocimum sanctum*, *Tinospora rumphii*, *Citrus grandis*, *Jatropha curcas*, *Ageratum houstonianum*, *Albizia lebbeck*, *Aristolochia bracteata*, *Houttuynia cordata*, *Hippophae rhamnoides*, *Kaempferia parvifora*, *Leucaena leucocephala*, *Mimosa scabrella*, *Piper sarmentosum*, *Psidium guajava*, *Rhizophora apiculata*, *Boesenbergia rotunda* and *Quercus lusitanica* are widely used for treatment and control of dengue. Plant products and herbal remedies provided alternative of medicine for cure and recovery of various diseases including dengue fever.

Keywords: Dengue, *Aedes*, natural remedies, plant, vaccine, symptoms

Introduction
Dengue fever is most common mosquito-borne viral infection and has rapidly become a major global health problem [1]. Dengue fever is a viral disease that has highly influenced human health and caused adverse impacts on tropical and subtropical regions [2]. At present, four different types of dengue serotypes have been identified that are DENV-1, DENV-2, DENV-3 and DENV-4 and which belongs to the Flaviviridae family and *Flavivirus* genus [2, 3, 4]. It is spreaded by *Aedes* mosquitoes, primarily who breeds in urban habitats [2, 3, 4, 5]. According to WHO, dengue is widespread in over 100 nations including the Asia, Americas, Africa, Pacific and Caribbean regions. Dengue cases have sharply risen in worldwide and currently reached pandemic levels [6]. Approximately 2.5 billion peoples are supposed to be at risk of dengue infection and an estimated 50 million cases are reported annually [6]. Dengue disease is not only a burden on health care but also has a negative influence on the economy due to illness, premature death and rising healthcare expenses [7]. At present dengue fever occurs in both epidemic and scattered forms [2, 8]. Most dengue infections cause nonspecific symptoms such as body aches, nausea, vomiting, weakness, rash, retro-orbital pain and frontal headache [9, 10]. Several medical technologies have been used to combat DENV, including monoclonal

antibodies [11], tetravalent subunit vaccine [12], inactivated vaccine [13], DNA based vaccine [14] and live attenuated vaccine [15]. However, no licensed dengue vaccines or medications are currently available in the market. There are no effective preventative medications available and only supportive therapy is possible for dengue patients [1, 8]. Medicinal herbs are crucial as primary health care and are used by humans daily to treat a variety of diseases [16, 17]. Naturally obtained products have been identified as an essential alternative for treating a variety of infections, including dengue [18]. Typically fluid balance, an electrolyte supplement and blood clotting measures are used to treat the clinical symptoms of dengue [19]. In some cases, anti-D immune globulin therapy is used to treat severe thrombocytopenia [20], but because it is expensive, it can be difficult for developing and under developed countries to pay for such a treatment plan. Most residents of tropical and subtropical regions rely on herbal remedies in addition to allopathic treatment to treat dengue infection; in reality, herbal medicines have long served as useful therapeutic agents [21].

The purpose of this review is to go over the different types and structures of dengue, the transmission of dengue, the herbal treatment process and the uses of natural plant products for dengue treatment. Plants having antiviral, larvicidal, ovicidal and mosquito repellent properties are also discussed.

Types of dengue virus and structure

Dengue virus is a member of the *Flavivirus* genus and belongs to the Flaviviridae family. It is a mosquito borne human infection with the greatest rate of dissemination in the tropics. Dengue (DEN) virus has four different types of serotypes, namely DENV-1, DENV-2, DENV-3 and DENV-4 are categorized as causing a variety of symptoms, from flu-like dengue fever (DF) to dengue haemorrhagic fever (DHF), a fulminating condition that can lead to dengue shock syndrome (DSS) and finally death of patients[3,4]. At present, dengue fever, dengue haemorrhagic fever and dengue shock syndrome are considered the most significant arthropod borne viral infections and are responsible for significant morbidity and mortality [22]. Dengue virus is spherical, lipid-encapsulated viruses with a positive-strand RNA genome of around 11 kb encoding for seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5) and three structural proteins namely the envelope, membrane and capsid [23]. According to Kuhn [24], Modis [25] and Ma *et al.*, [26] non-structural proteins are involved in replication in the viral RNA of the dengue virus. The envelope protein (E) is essential for a variety of vital functions, including receptor binding, generation of a protective immunological response, blood cell hemo-agglutination, membrane fusion and virion assembly [27]. Domain I is present in the centre while domain II contains an internal fusion loop and domain II is also involved in membrane fusion and dimerization of E protein [27]. An immunoglobulin-like domain known as Domain III is hypothesized to be important in cell receptor binding. Domain II mostly comprises cross-reactive epitopes for flavivirus groups and subgroups. The seven antiparallel strands of the M-protein which is crucial for the development and maturation of the viral particle are held together by three disulphide bonds [27, 28]. The E-glycoprotein is associated with several important biological properties of dengue virus, including receptor binding, erythrocyte hemo-agglutination and the development of neutralizing antibodies and protective immune responses [29, 30]. According to Vaughn *et al.*, [31] primary infection of dengue disease is more frequently caused by serotypes DENV-1 and DENV-3 in the south-east Asian region as compared to serotypes DENV-2 and DENV-4. Infection with a single DENV serotype produces only specific antibodies to particular serotypes. Secondary infections caused by other serotypes are more severe than primary infections if the primary infection is neutralized [32]. Although DENV-2 caused more serious and fatal infections as compared to others serotypes [33]. But some studied concludes that primary infections with DENV-1 or DENV-3 are more severe as compared to infections with serotypes DENV-2 and DENV-4 [34].

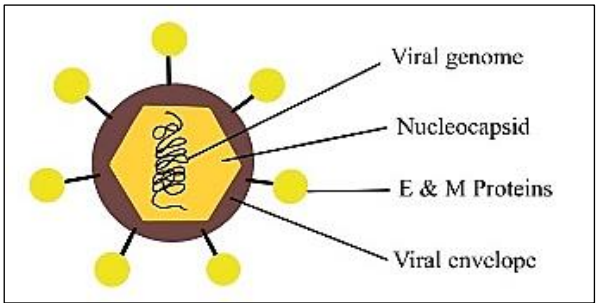

Fig 1: Structure of Dengue virus

Sign and symptoms of dengue

The body of an *Aedes* mosquito is small and black, with white markings present on the body and legs. A female *Aedes* mosquito sucks blood from biting animal or human being to produce eggs. *Aedes aegypti* is potentially breed in stagnant water-filled containers of urban habitat [5, 35]. For further development and maturation of eggs moist environmental conditions are necessary.

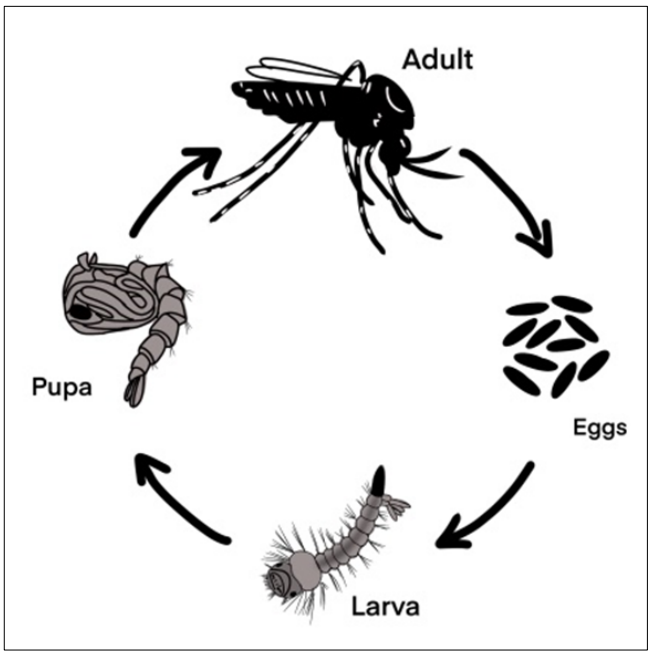

Fig 2: Life cycle of *Aedes* mosquitoes

DENV is frequently spread from person to person by *Aedes* mosquitoes [33]. An outbreak begins when a mosquito feeds on the blood of a dengue fever or dengue haemorrhagic fever patient and then feeds on uninfected persons. The dengue

virus replicates in the lymph nodes and spreads in other tissues through the lymph and blood, after being spread by infected mosquitoes to a new human host [33]. The dengue virus is a small particle having an icosahedral nucleo-capsid with a lipoprotein envelope and containing a single standard positive RNA genome [33, 36]. When a virus binds to the host cell surface, infection occurs in the host cell. The receptor-mediated endocytosis process adopted by dengue virus for entering the host cell creates a sack-like structure also called an endosome [37].

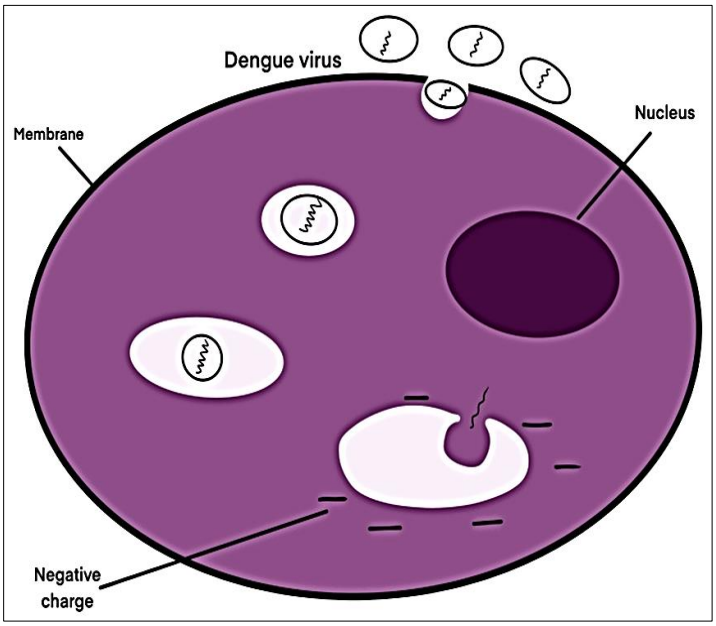

Fig 3: Dengue virus transmission cycle in cell

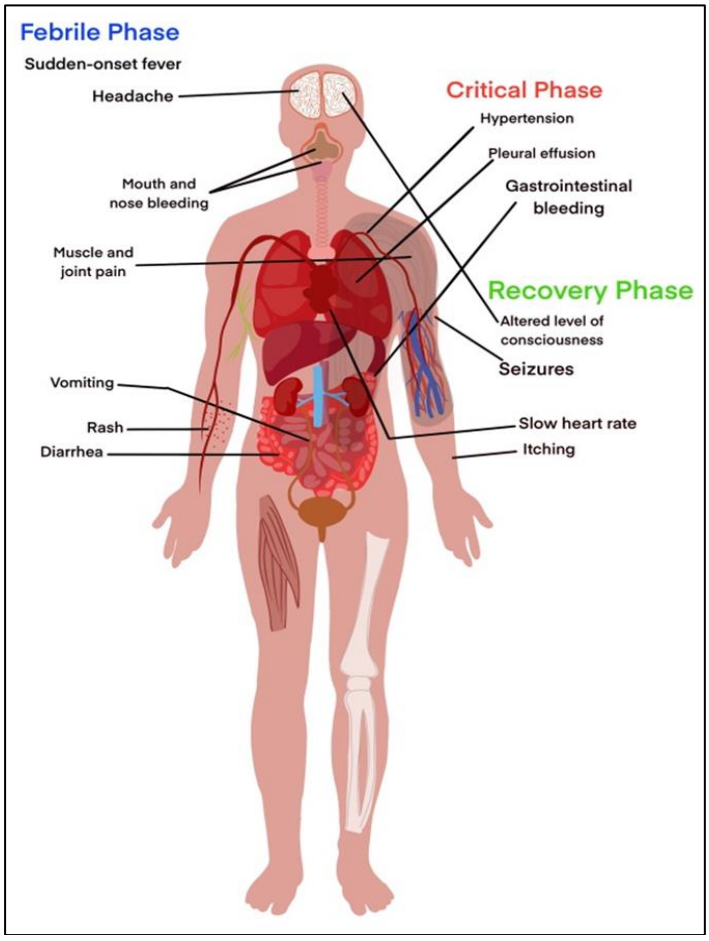

Fig 4: Showing symptoms of dengue fever in human body

The virus enters the cell with the help of an endosome and the membrane becomes negatively charged at that point it is combined with the membrane to provide a place for releasing genetic material in the cell. The virus in the cell now begins to

replicate. During the viral journey, variations in the acidity of the secretory pathway influence potential dengue treatment mechanisms [38]. The clinical manifestations of dengue can range from mild to severe [39]. The signs and symptoms of dengue range from a mild flu-like syndrome also called as dengue fever (DF) to the more severe conditions of the illness known as dengue haemorrhagic fever (DHF), which eventually results in dengue shock syndrome (DSS) and death of person and is characterized by coagulopathy, plasma leakage and enhancement of vascular permeability [39]. The increasing number of dengue fever (DF) patients acquiring dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are typically a signs of dengue associated mortalities [40]. The lack of appropriate treatment exacerbates the severity of dengue [21]. The bite of female *Aedes aegypti* mosquitos carries the flavivirus to transmit dengue fever. After being bitten by a female *Aedes* mosquito, the virus incubation period ranges from 3 to 14 days [33]. The person may have earlier symptoms including headache, fever, nausea, rashes, joint and musculoskeletal pain. The period of dengue fever typically varies between five to seven days and body temperatures range between 39°C to 40°C [19, 30]. During this time the virus can enter the peripheral bloodstream and cause damage in blood vessels and lymph nodes, resulting in dengue haemorrhagic fever (DHF) conditions with symptoms like bleeding from nose, gums or under the skin if left untreated [19]. Patients with DHF also experience breathing or respiratory problems and if the condition progresses severely, it can lead to dengue shock syndrome (DSS). These conditions result in the death of a dengue patient if proper treatment is not provided [30, 41]. Dengue haemorrhagic fever, the most severe of all three types affects about 5% of all dengue patients [42]. It often lasts for 2–7 days before giving way to significant joint and muscle pain [43]. After the initial symptoms of dengue virus it causes hepatitis, organ failure, maculopathy, neurological and cardiac dysfunction, rhabdomyolysis and other consequences [44]. Dengue fever clinical manifestations are divided into three stages: the febrile period, the critical period and the recovery period. During the critical period it causes thrombocytopenia with a platelet count of less than 100,000 per mm^3 of normal value and induces hemo-concentration with a 20% increase in hematocrit test [45].

It primarily affects Southeast Asian children and is characterized by plasma leakage, rises vascular permeability, thrombocytopenia and haemorrhagic manifestations. Dengue haemorrhagic and dengue shock syndrome are fatal and finally leads to death of patient [8]. There are two different types of infections caused by the dengue virus: primary and secondary [46]. A primary infection causes dengue fever (DF), which leads to an acute febrile illness that is cleared within a week by an immune response. While secondary infections are more severe and causes dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) conditions [46].

Transmission of dengue virus

Dengue epidemics are endemic and wider spread in more than 100 countries around the world including America, Western Pacific, Africa, Eastern Mediterranean and the Southeast Asian region [19, 47]. International traveling, rapid expansion of urban areas and increasing human populations creates favourable conditions for spread of dengue vector *Aedes aegypti* and these conditions leads to rapid expansion of dengue virus in new areas [10, 35, 37].

Human is primary vertebrates host of dengue virus. All four serotypes of dengue viruses are transmitted by *Aedes* mosquitoes of the sub genus *Stegomyia* especially *Aedes aegypti*, *Aedes albopictus* and *Aedes polynesiensis* as the primary mosquito vectors [15]. The epithelial cells of mid gut become infected after ingestion of a virus containing blood meal. The virus then penetrates the hemocoel and infects the salivary gland after escaping from the midgut epithelium. Finally, when probing, a virus is secreted in the saliva resulting in infection. A virus may penetrate the fully developed egg at the time of oviposition, because the genital tract is also infected [48]. Female *Aedes aegypti* must bite an infected individual during the viraemic phase of the disease which typically lasts 4 to 5 days but can last as long as 12 days [49]. *Aedes aegypti* can be infected with two different serotypes without compromising their yield [50]. Interrupted eating and repetitive probing of one or more hosts are characteristics of the mosquito's feeding behaviour [51]. Despite having a relatively low susceptibility to oral dengue virus infection, *Aedes aegypti* is still the most significant vector because it is highly adapted to urban habitats [52]. Because mosquito transmission is necessary for dengue virus persistence, high viral titres must grow in hosts. According to Vector Borne Viral Infection [53], the interaction between the vector and the virus may have a crucial role in the selection and spread of pathogenic dengue strains in urban areas.

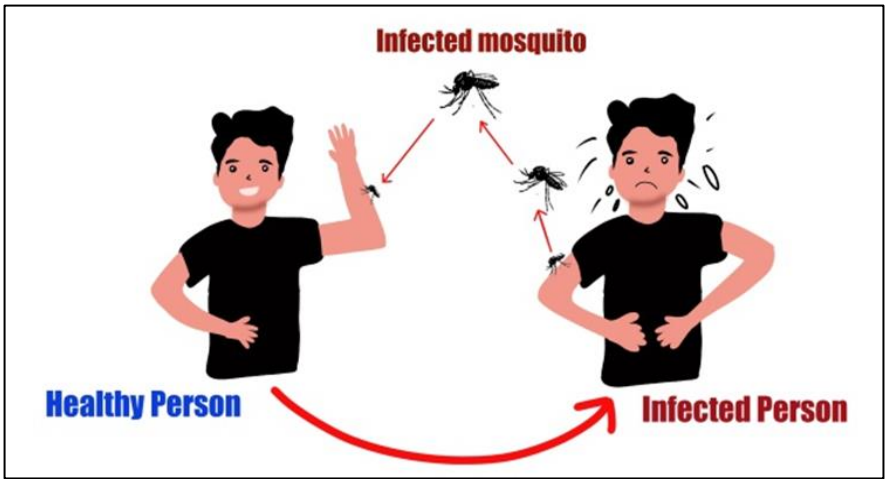

Fig 5: Transmission of dengue from infected person to healthy person

Herbal remedial treatment of dengue fever

Home remedies are the most effective for preventing dengue and have no side effects because they are obtained naturally. They help in treating various diseases including dengue fever and its associated symptoms [21]. According to various studies, traditional medicinal herbs and plants have antiviral and anti-dengue properties and were used to treat viral infections in both humans and animals. According to Kadir *et al.*, [21] about 30 different plant species have the potential to treat dengue fever including *Momordica charantia*, *Alternanthera philoxeroides*, *Andrographis paniculata*, *Cladosiphon okamuranus*, *Carica papaya* and *Momordica charantia* [21]. In Asian countries *Carica papaya* leaf juice is widely used as an herbal remedy against dengue fever [45]. Several studies demonstrated that *Carica papaya* leaf extract which is commonly used as a membrane stabilizing factor increases the platelet activation rate while improving the properties of white blood cells [45, 54].

Carica papaya also had a moderate to low inhibitory effect on dengue serotype II (DENV-2) growth *in vitro* [55]. The juice of *Carica papaya* leaves is widely used to enhance platelet counts in dengue patients [45]. The presence of various phytochemical components namely papain, phenols, flavonoids, alkaloids, ascorbic acid and saponins in *Carcia papaya* leaf juice is utilized for the treatment of dengue [56]. In the Philippines, *Euphorbia hirta* is widely used to treat dengue fever by rural people [21]. It exhibits a broad range of medicinal properties, including anti-bacterial, antimalarial, antiviral, antifungal, anti-inflammatory, anti-tumor and anthelmintic [57]. Apostol *et al.*, [58] evaluated the platelet raising activity of *Euphorbia hirta* in ethanol (intra-peritoneal injection) in thrombocytopenic Sprague-Dawley rats. The results showed that 14-day administration of 100 mg/kg of *Euphorbia hirta* lyophilized decoction enhanced platelet counts in Sprague-Dawley rats [58]. The decoction of *Euphorbia hirta* reduced the bleeding time that was elevated by the intra-peritoneal injection of ethanol lowered by *Euphorbia hirta* decoction [58]. *Euphorbia hirta* treated rats show shorter clotting time as compared to ethanol-induced thrombocytopenic rats [58]. The oral treatment of *Euphorbia hirta* leaves continuously for nine days also enhanced the mean platelet count in Sprague-Dawley rats that were previously treated for 15 days with Anagrelide for the induction of thrombocytopenia [59]. In a clinical trial involving dengue patients (ages 30-55 and 14-25) admitted to the hospital Sir Ganga Ram Hospital Lahore, an oral treatment with *Euphorbia hirta* herbal water raised platelet and total leukocyte counts after 24 hours [60]. A significant platelet count increase was also found in the 30-55 age group following treatment with *Euphorbia hirta*, but no significant enhancement was found in the 14–25 age groups when compared to the 30-55 age groups [60].

The existence of nine chemicals was found during the further purification of the ethyl acetate fraction of *Euphorbia hitra* [61]. It was thought that these chemicals either alone or in combination could have contributed to anti-dengue activity [61]. *Euphorbia hirta* is also effective in raising platelet counts in dengue patients in the 30 to 55 year-old age groups [60]. Treatment with *Euphorbia hirta* significantly reduced flu-like symptoms and also exhibited anti-inflammatory properties [60, 61].

Oil of *Andropogon citratum* is used to prepare mosquito repellent candles and lanterns. Studies showed that *Andropogon citratum* oil had mosquito repellent properties, particularly for *Aedes aegypti* [30, 62]. Turmerone extracted from *Curcuma longa* volatile oil shows mosquitocidal action against *Aedes aegypti* [30, 63]. *Piper longum* (Papal or Pippli) belongs to the Piperaceae family and its fruit, root and stem parts are used for treatment of dengue. Piperine is a substance found in *Piper longum*. Chaithong *et al.*, [64] studied the effectiveness of ethanolic extracts of *Piper ribesoides*, *Piper sarmentosum* and *Piper longum* against *Aedes aegypti*. *Piper longum* was found to be the most effective against *Aedes aegypti*, followed by *Piper sarmenstosum* and *Piper ribesoides* [64]. The isolated pipernonaline from *Piper longum* fruit demonstrated potent larvicidal effects on the four stages of *Aedes aegypti* larvae [65]. Female of *Stegomyia aegypti* is more susceptible to ethanol-extracted *Piper* species at different doses depending on the plant species [66]. Petroleum ether and acetone extracts of *Murraya koenigii* leaves also exhibit larvicidal activity against *Aedes aegypti* larvae [67]. Turmerone volatile oil is obtained from *Curcuma longa* and its exhibits mosquitocidal activity against *Aedes aegypti* [63]. *Eupatorium perfoliatum* is used to treat dengue fever and is taken orally as a tea [68]. The leaves and stem of *Kaempferia parviflora* are used as herbal remedies to treat viral infection [69].

According to Moon [69], the bioactive compound of *Kaempferia parviflora* directly inhibits DENV-2 virus particles. *Solanum villosum* extract has larvicidal activity against *Stegomyia aegepti* [70]. Shoot bark extracts of *Combretum collinum* show larvicidal activity against *Aedes aegypti* [71]. PON-NEEM a combined herbal formulation of *Azadirachta indica* and *Pongamia glabra* has ovicidal, larvicidal and oviposition deterrent activity against *Aedes albopictus* and *Aedes aegypti* [72]. Leaf extracts of *Eupatorium odoratum*, *Catharanthus roseus* and *Nyctanthes arbor-tristis* exhibit larvicidal activity against *Aedes aegypti* [73]. *Citrus limetta* extract had larvicidal activity against *Aedes aegypti* [74]. Leaf extract of *Acalypha alnifolia* exhibits larvicidal activity against *Aedes stephensi* and *Aedes aegypti* [75]. Seed and leaf extracts of *Delonix elata* show ovicidal and larvicidal activities against *Aedes stephensi* and *Aedes aegypti* [76]. *Ocimum sanctum* also contained phytochemicals that are mosquito repellent and larvicidal, such as farnesyl acetone, alpha-farnesene, caryophyllene and eugenol [77]. The leaf, bark and stem extracts of *Tinospora rumphii*, *Citrus grandis* and *Jatropha curcas* exhibits effective larvicidial activities. Steroids, flavonoids, tannins, saponins, flavonoids, steriod and alkaloids of *Jatropha curcas*, *Citrus grandis* and *Tinospora rumphii* are toxic to the third instar larvae of *Aedes aegypti* [79]. Tennyson *et al.*, [80] studied the ovicidal activity of three extracts, including ethyl acetate, hexane and methanol forms of the *Ageratum houstonianum* plant. They observed that all three extracts exhibit the most potent ovicidal activity at doses ranging from 2.5 to 20 mg/l [80]. Individually, chloroform, ethyl acetate, benzene, hexane and methanol chemicals were used to isolated extract from *Albizia lebbeck* with the help of Soxhlet device [81].

The ovicidal effects of each extract were evaluated by measuring egg mortality and hatchability. If there is less egg hatching, then the plant extracts have stronger ovicidal activities [81]. No egg hatching results in 100% egg mortality. The majority of doses were found to be efficient at killing *Aedes* mosquito eggs [81].

According to Krishnappa and Elumalai [82], methanol extracts

of the *Aristolochia bracteata* plant exhibit impressive ovicidal activity. Leaf extracts of *Azadirachta indica* exhibit a strong effect against dengue virus, mainly serotype II [83]. The aqueous extract of *Houttuynia cordata* inhibited the replication of DENV-2 by directly inactivating viral particles prior to cell infection [32]. The leaf extract of *Hippophae rhamnoides* exhibits anti dengue activity against DENV-2 [84]. According Jain *et al.*, [84] leaf extract of *Hippophae rhamnoides* improves the viability of dengue-infected cells and enhanced TNF- α and TNF-γ levels. Leaf and stem extracts of *Kaempferia parvifora* exhibit virucidal activity against DENV-2.

The bioactive compound of *Kaempferia parviflora* suppresses the growth of the viral particle DENV-2 [85]. Galactomannas (7), a compound extract from the seeds of *Leucaena leucocephala* has antiviral activity against DENV-1 and Yellow fever virus (YFV) *in-vivo* and *in-vitro* [9, 38]. Galactomannas (7) compound isolated from seeds of *Mimosa scabrella* exhibits antiviral activity against DENV-1 and Yellow fever virus in *in-vivo* and *in-vitro* conditions [9]. Chemical compounds found in *Piper sarmentosum* include α-ascarone, ascaricin, β-sitosterols, carotenes, xanthophyll, vitamin C and vitamin E. The ethanol extract of *Piper sarmentosum* exhibits larvicidal activity against the 4th instar larvae of *Aedes aegypti* mosquitoes [38, 86].

In-vitro leaf extract of *Psidium guajava* inhibits the growth of the dengue virus [87]. Boiled leaf extract of *Psidium guajava* reduced bleeding during dengue homographic fever conditions and enhanced platelet counts to 100.000/mm^3 within 16 hours time [88]. An ethanolic extract of *Rhizophora apiculata* exhibits anti-dengue properties against the DENV-2 serotypes in Vero cells [89]. Some compounds extracted from *Boesenbergia rotunda* inhibited the DENV-2 dengue virus [90]. According to Muliawan *et al.*, [91] extract of *Quercus lusitanica* exhibits an inhibitory effect on the replication of DENV-2 in C6/36 cells.

Conclusion

Dengue infection is caused by the dengue virus, which belongs to the *Flavivirus* genus and Flaviviridae family and is transmitted in humans through *Aedes* mosquitoes. Dengue exhibits a variety of symptoms from flu-like dengue fever to dengue haemorrhagic fever and dengue shock syndrome. During dengue fever, patients suffer from headache, fever, nausea, rash and joint and musculoskeletal pain. After the initial symptoms of dengue virus, it causes hepatitis, organ failure, maculopathy, neurological and cardiac dysfunction, rhabdomyolysis and other consequences [44].

Extracts from various parts of plants, including leaves, fruits, bark and stems are utilized in the treatment of various diseases including dengue-related problems. The phytochemical composition of plant species exhibits various activities like larvicidal, ovicidal, virucidal and mosquitocidal effects against dengue virus and its vector and some plant compounds also exhibit mosquito repellent properties. The use of natural remedies and plant-based products increased immunity to viral diseases such as dengue.

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