Dengue has become a worldwide affliction despite incessant efforts to search for a cure for this long-lived disease. Optimistic consequences for dengue vaccine are implausible as the efficiency is tied to previous dengue virus (DENV) exposure and a very high cost is required for large-scale production of vaccine. Medicinal plants are idyllic substitutes to fight DENV infection since they constitute important components of traditional medicine and show antiviral properties, although the mechanism behind the action of bioactive compounds to obstruct viral replication is less explored and yet to be discovered. This review includes the existing traditional knowledge on how DENV infects and multiplies in the host cells, conscripting different medicinal plants that obtained bioactive compounds with anti-dengue properties, and the probable mechanism on how bioactive compounds modulate the host immune system during DENV infection. Moreover, different plant species having such bioactive compounds reported for anti-DENV efficiency should be validated scientifically via different in vitro and in vivo studies.

Keywords: dengue, traditional medicine, plant medicaments, bioactive compound, immunomodulatory response

1 INTRODUCTION

Mosquito-borne diseases cause illness in approximately 700 million people per year globally (Genoud et al., 2018). Dengue is one of the mosquito-borne emerging viral disease endemics prominent in many urban areas of tropical countries. A considerable rise in the dengue infection incidences is noticed all over the world in recent decades. Due to its asymptomatic to mild infectious nature, actual numbers of dengue cases remain unregistered or wrongly diagnosed as other fever infections (Waggoner et al., 2016). According to the World Health Organization report, about 390 million cases of dengue virus (DENV) infections occur annually, of which nearly 96 million find medical treatment and about 20,000 individuals (mostly children and aged individuals) fail to survive the dengue infection (Bhatt et al., 2013; Saxena et al., 2017; World Health Organization 2021a). Remarkably, among 129 countries having a risk of dengue infection, Asia has almost 70% of the total infection load (Brady et al., 2012; Bhatt et al., 2013). Dengue, an arthropod-carried viral infection, is transmitted into humans by female Aedes mosquitoes (Ae. aegypti or, to a lesser extent, by Ae. albopictus and Ae. polynesiensis) (Cao-Lormeau 2009). Common symptoms in dengue infection are mild dengue fever to severe dengue hemorrhagic fever (i.e., DF and DHF), rashes, headache, vomiting, severe headache, low white blood cell count, joint and muscle pain, swollen glands, nausea,
pain behind the eyes, and fever with dengue shock syndrome (DSS) (Murphy and Whitehead 2011; World Health Organization 2021a).

The natural reserve has offered various resources to mankind to combat various infectious diseases. Plants are the most frequently utilized natural sources among the local biodiversity and are linked to folk’s day-to-day needs (Robinson and Zhang 2011). Additionally, plant-based medicaments are in considerable demand because of their safer use and non-toxic nature, and because they are less harmful in comparison to synthetic treatments (Abd Kadir et al., 2013). Multiple uses, such as consumption as food, ethnomedicinal applications, cultural aspects, and sacred faith, are associated with their utilization (Svanberg and Berggren 2019; Fongnzossie et al., 2020).

Traditional knowledge of plants that was commonly practiced among tribal or ethnic populations for their healthcare has now gained considerable attention from the modern populace. Nowadays, people in developing (60%–90%) as well as developed countries (23%–80%) are using ethno-medicines as the primary healthcare regime (Borah and Prasad 2017; Sharma and Pareek 2021). Plant biodiversity used as medicaments is of utmost importance throughout human history, which has led to the accumulation of significant information in the form of scientific research and its validation (Pasa 2011). These conventional plant-based healthcare remedies led the Ayurvedic, Unani, Chinese, and Egyptian medical systems to classify various medicinal herbs (based on color, aroma, shape, flavor, and astronomic and magical attributes) (Larocca et al., 2021). Traditional use and ethnomedicinal knowledge about many plant species in treating various ailments along their chemical validation through scientific research can be promising aspects in the development of contemporary medication to treat arboviral infections like dengue. Also, a plant-based antiviral product assures a more possible choice in combating dengue infection, which may be replacement of inadequate drugs with side effects (Bahuguna et al., 2019).

WHO in the 1970s has effectively executed the spread of traditional knowledge via implementing Traditional Medicine Program, and consequently, following such initiative (taking into consideration the traditional knowledge and scientific research), the associated nations have been redeveloping and improving their public health systems (Larocca et al., 2021). Development of an efficient and safer anti-dengue vaccine is a challenging task, and because of its secondary infection (second time DENV serotype infection), it is linked to the serious clinical manifestations (Toman 2018; Redoni et al., 2020). Based on recent research, various plants and their derivatives have shown anti-dengue properties; among those, flavonoids are the most popular candidates, having the ability to supplement encouraging scope in the existing struggle of drug discovery (Carneiro et al., 2016). Some of the important flavonoids recently reported are discussed with various activities, such as antioxidant, anti-inflammatory, antitumoral, antiviral, and antibacterial effects (Raekiansyah et al., 2018; Deng et al., 2020b; Daneshzadeh et al., 2020; Macedo et al., 2020; Wang et al., 2020). In the present review, a brief idea of the role of these phytoconstituents has been described against dengue infections (Jayadevappa et al., 2020). In addition, the mechanism of action with future possibilities as contemporary medicaments of plant metabolites that endorses traditional knowledge is also included.

2 EPIDEMIOLOGY OF DENGUE

Dengue is a mosquito-borne viral infection, found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas, transmitted by Aedes aegypti and Aedes albopictus, known as the primary and secondary dengue vectors. A range of diseases has been transmitted via Ae. aegypti including yellow fever, chikungunya, zika, and, most importantly, DENV (Silva et al., 2020). DENV was first reported in the 1950s, during dengue epidemics in Thailand and Philippines. Since then, the spread of dengue has extensively widened from South Asian countries to African and South American countries. Over several decades, different countries of continental America conducted a program that aimed to eradicate Ae. aegypti. The program was proposed and commenced via the Pan American Health Organization (PAHO) in 1946 (Pinheiro and Rodrigues 1999). Venezuela, a country on the northern coast of South America, reported dengue fever outbreaks during the 1960s, when almost all South American countries had eradicated Ae. aegypti (Pinheiro and Corber 1997). Furthermore, during the 1970s, DENV-2 and DENV-3 were the main causative serotypes for dengue fever epidemics in Colombia, a country that had attained eradication of the vector during the PAHO program (Pinheiro 1997). In the 1980s, enhanced rate of dengue cases escorted the spreading of Ae. aegypti vector, and during this period, another efficient vector, the Asian mosquito, Ae. albopictus, was introduced in the region (Gubler 1989). In the last 5 decades, the American continent has been massively affected by dengue and an approximately 30-fold rise in disease level was recorded, where almost 390 million cases of dengue with 96 million medical manifestations were reported annually (Bhatt et al., 2013). In 2013, America has declared approximately 2.3 million new severe dengue cases, which was an alarming situation in viral infections (Salles et al., 2018).

Ae. albopictus was mostly found in Asia and further expanded over different countries of European and North American regions, having highly adaptive properties to survive extreme environments and therefore able to survive in cooler regions as well. The probability of an upsurge of arthropod-borne viruses is based on the abundance of vectors involved in transmission as well as the susceptibility of immune-deficient people. Hence, there is a necessity to develop an efficient way to control its population and the spread of the disease. Besides, several other causes such as increased urbanization, ecological changes, migration of people, exchange of goods, and biological contests (e.g., development of resistance for virus) stimulate the spread of disease to new regions (Chaudhry 2019).

3 REPLICATIVE CYCLE AND PATHOGENESIS OF VIRUS

The genomic structure of DENV, approximately 10.7 kb in size, consists of ssRNA with +ve polarity (Chambers et al., 1990).
Besides, the translation of viral genome was completed by three different structural proteins, i.e., Envelop (E), Capsid (C), and Pre-membrane (PrM), and seven non-structural (NS) proteins, NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. These proteins contribute to viral replication (Bartenschlager and Miller 2008; Xie et al., 2017). The infective form of dengue virion possesses a
core of glycoprotein and ssRNA genome enclosed by icosahedral nucleocapsid (Akhtar 2019). Firstly, infected mosquito feed on host and DENV gets transmitted via injecting its saliva into the host. In the meantime, when half-length proboscis is inside the dermis, the vector releases DENV plaque-forming units (nearly 50,000) and causes infection in contiguous skin cells, i.e., Langerhans and keratinocytes (Marcial-Juárez et al., 2017; Schneider et al., 2021). Dendritic cells enter lymphatics after capturing DENV virions or antigens and transport them to local draining lymph nodes. DENV is also suggested to reach draining lymph nodes via the lymphatic flow in a cell-free manner (Yam-Puc et al., 2016). The E protein of DENV assists the binding between DENV and the cell membrane receptor. Receptor-mediated endocytosis is the principal way via which the virus is able to enter the host; a resultant sac-like structure is formed known as an endosome, depending on pH. Virus acutely penetrates and fuse with the membrane of the endosome due to the various irretrievable morphological reorganization as the endocytic vesicles become more acidic, followed by nucleocapsid opening and genetic material (RNA) release into the cytoplasm. RNA succeeds in translating into ribosomes allied to the ER (endoplasmic reticulum) by using the infected cell's machinery; subsequently, the viral polyprotein is cleaved by cellular and viral proteases (Uno and Ross 2018). The newly synthesized RNA is wrapped in the capsid proteins (nucleocapsid), enters the host rER, and ultimately encloses the ER membrane. Further structure proteins (M and E) surround the ER-enveloped nucleocapsid forming immature virus. Subsequent processing in the Golgi apparatus results in the formation of the infectious form of the virus (Aruna 2014). Afterwards, it reaches the lymph node and further disseminates to other body organs. The virus incubation period may vary from 3 to 14 days based on the literature available (Chan and Johansson 2012). A general overview of the DENV infection cycle in humans is shown in Figure 1. After completion of the virus incubation period, the mosquito is capable of spreading the virus in the course of its life. *Ae. aegypti* feeds mostly on human blood and is a daytime feeder, efficiently causing infection in the early morning, and by evening, it infects multiple people during each sucking period (Weissenböck et al., 2010). The infecting efficiency of DENV for different cells including liver, blood vessels (endothelium), immune system, and retinal cells has been reported in the past (Carr et al., 2017; Begum et al., 2019).

### 3.1 Dengue Infection

The occurrence of dengue has intensely spread worldwide in recent decades with a majority of asymptomatic cases (World Health Organization, 2021a). The infection efficiency can vary from subclinical disease to acute flu-like symptoms. Three different categories of symptomatic dengue, namely, dengue fever (DF), dengue hemorrhagic fever (DHF), and undifferentiated fever, were classified by WHO in 1997. Due to the changing epidemiology of infection, it was difficult to fulfill the suggested WHO guidelines (for dengue), and thus, classification was re-evaluated (World Health Organization 2009). In the new classification system, DHF was further categorized up to four levels based on severity of infection, with grades III and IV as DSS. Dengue asymptomatic cases were divided into two different categories: with warning and without warning signs of severe dengue (World Health Organization 2009). Dengue is associated with several complications, which are characterized by headache, appetite loss, high fever, retro-orbital pain, vomiting, abdominal pain, diarrhea, minor bleeding, rash, fatigue, etc. Severe dengue is classified by the presence of severe plasma bleeding, organ impairment, or dengue shock conditions (Khan and Bhutta 2016). It is also designated as “break-bone fever” (Rigau-Pérez 2006; Esler 2009). The severity of infection can be strongly provoked by numerous factors, such as virus serotypes, immunity power, and genomic background of host, among others (Rico-Hes 2010; Dussart et al., 2012). Moreover, four different serotypes of viruses (DENV-1, DENV-2, DENV-3, and DENV-4) of the Flaviviridae family were deliberated as causal forms of dengue (Guzman and Istúriz 2010). Although every serotype has an equal potential to cause infection among the four serotypes of dengue, serotype variances that only affect pathogenesis such as DENV-2 have been associated with severe infection (Halstead 1988; Vaughn et al., 2000).

Recovery from infection provides enduring immunity against that serotype, although immunity for other serotypes known as cross-immunity is temporary and partial. Consequent contaminations (secondary infection) by different serotypes increase the threat of emerging severe dengue. Dengue has discrete epidemiological forms, allied with the four serotypes of the virus (Halstead 2002; Rico-Hes 2010; Dussart et al., 2012; Kim and Hwang 2020). Different studies based on the data analysis of infection status among the Indian population have been reported (Table 1). Despite this, numerous cases have been found in different regions of India, which is still unexplored in terms of proper data illustrations.

### 4 MODE OF TRANSMISSION

*Aedes* spp. mosquitoes (*Ae. aegypti* and *Ae. albopictus*) are the main source of dengue transmission. Recently, infection dispersed in almost all parts of tropical and subtropical regions and adapted to urban environments, mainly *Ae. aegypti* (Lambrechts et al., 2010). Among two different species, *Ae. aegypti* has been reported to have superior efficiency as a transmission vector; meanwhile, in urban environments, DENV is capable to endure its life cycle between humans and transmitter organisms (Lambrechts et al., 2010; Weissenböck et al., 2010). Human blood is the primary feeding source of *Ae. aegypti*, while *Ae. albopictus* (sylvatic strain) feeds on avian species as well as a variety of mammals (European Centre for Disease Prevention and Control 2018). Sylvatic strains are not that risky compared to “standard” dengue infection (Diallo et al., 2003; Vasilakis et al., 2008). In the initial stage of transmission, uninfected mosquitoes attack (susceptible to dengue) while feeding on host blood. In this process, viral particles are transferred into the mosquito midgut and start replicating and thus infecting the body cavity (hemocoel). From the hemocoel, the virus eventually makes its way to the salivary glands. Next, after completing the incubation
period (approximately 2 weeks), the infected mosquito can disseminate the virus via salivary glands (Coudeville et al., 2009; Guzman et al., 2016).

### 5 IMPACT OF DENGUE INFECTION GLOBALLY AND IN INDIA

Dengue has emerged as one of the most important mosquito-borne, flaviviruses diseases, deceptively intensifying as a global health issue (Zeng et al., 2021). Dengue has been designated as the topmost worldwide health risk by WHO (Kumar et al., 2017; Biswal et al., 2019). A comparison of prior approximations of entire global dengue contagions has been illustrated. Average incidences in India with maximum infected states (Karnataka, Punjab, Tamil Nadu, and Maharashtra) are shown (Alagarasu et al., 2021) (Figure 2). Moreover, dengue infection frequency of different Asian countries and their percentage contribution have been determined where India was found to comprise 9% of total dengue incidences, higher than Pakistan, Singapore, China, Thailand, Nepal, and Cambodia, while Vietnam and Philippines are the leading countries and recorded the highest number of dengue cases in 2021 (till May) (Figure 3A) (European Centre for Disease Prevention and Control 2018; World Health Organization 2021b). Also, dengue infection status recorded in the past 7 years in India can be seen where the average infection was recorded to be the maximum in 2017 (Figure 3B) (NVBDCP, 2021).

### 6 PLANT MEDICAMENTS USED BASED ON TRADITIONAL KNOWLEDGE

Plants have been the main remedial source to cure a variety of ailments since ancient times. Ancestral folks empirically isolate medicinal plants for medical home remedies and pass this knowledge from generation to generation till the present day. Ethnobotany has confirmed the necessity for conserving such information in societies that utilize plants in the treatment of different types of diseases (Gu et al., 2014; Mussin and Giusiano 2020). However, it is critical to note that these practices of exploiting plant medicaments, without scientific understanding, have led to

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**TABLE 1** | Dengue seroprevalence by age, reported in some studies from India.

| Age (years) | Seroprevalence (%) | Age (years) | Seroprevalence (%) | Age (years) | Seroprevalence (%) | Age (years) | Seroprevalence (%) |
|------------|--------------------|------------|--------------------|------------|--------------------|------------|--------------------|
| 0–9        | 47.60%             | 5          | 40.70%             | 9-May      | 77%                | 8-May      | 33.00%             |
| 19-Oct     | 24.00%             | 6          | 50.90%             | 14-Oct     | 90.30%             | 17-Sep     | 34.70%             |
| 20–29      | 26.80%             | 7          | 58.60%             | 15–19      | 91.70%             | 18–45      | 32.30%             |
| 30–39      | 25.00%             | 8          | 67.40%             | 20–29      | 96.30%             | —          | —                  |
| ≥40        | 23.30%             | 9          | 70.80%             | 30–40      | 96.80%             | —          | —                  |
| —          | 73.40%             | 10         | 70.80%             | —          | —                  | —          | —                  |
| Total      | 25.4 (95% CI = 22.3–28.7) | 59.6 (95% CI = 57.7–61.5) | 93 (95% CI = 91.1–94.6) | 42.8 (CI = 40.9–44.7) |

**FIGURE 2** | (A) Dengue cases in different regions of India 2021. (B) State-wise distribution of dengue cases (y-axis) in four states of India from 2015 to 2021 (x-axis) (Source: National Vector Borne disease Control Programme).
placing various plants in the IUCN Red List consisting of threatened species (Trujillo-Correa et al., 2019). The dengue treatment period is suggested to be 10–15 days, which may vary according to the infection level of severity, the regimen carried out during treatment, the conditions, and the response of the organism (Yogarajalakshmi et al., 2020). Different plant-based formulations are reported to be used in various affected parts of India against dengue and have also been approved through scientific research, although limited studies in this reference have been recorded in India (Deep et al., 2018). There are many plant species such as *Carcinoma longa* L., *Lonicera japonica* Thunb., *Acros calamus* L., *Carica papaya* L., *Euphorbia hirta* L., *Tinospora sinensis* (Lour.) Merr., and *Sambucus canadensis* L. used globally as ethnomedicine against dengue fever (Icshyani et al., 2017; Lee et al., 2017; Deep et al., 2018; Yao et al., 2018; Larocca et al., 2021) (Table 2). In another report, plants from a diverse group of plant families (31 in total with 54 species) are reported to exhibit anti-dengue activity based on traditional knowledge, where major representatives reported were Lamiaceae (10.5%), Asteraceae (9.9%), Aristolochiaceae, and Loganiaceae (each 7.2%) families (Saleh and Kamisah 2021). Plants revealed by the local population to exhibit anti-dengue activity included *Baccharis trimera* (Less.) DC., *Aristolochia surinamensis* Willd., *Monordica charantia* L., *Dysphania ambrosioides* (L.) Mosyakin and Clemants, * Ocimum gratissimum* L., *Strychnos pseudoquina* (Rich.) Vahl, and *Gastrodia elata* Blume have also been approved to have an antiviral response against DENV-2 replication and DENV multiplication cycle, respectively (Rahman et al., 2006; McDowell et al., 2010; Ahmad et al., 2011). Also, the polyphenol-rich extract of *Aphloia theiformis* (Vahl) Benn. has recently been reported against ZIKV and DENV infections, which prohibits viral entry (Clain et al., 2018).

7 PLANT EXTRACT AS MOSQUITO REPELLENT AND LARVICIDE

*Ae. aegypti* and *Ae. albopictus*, epidemiologically related arboviruses in the community health context, including Zika, dengue, and chikungunya viruses. Different types of synthetic insecticides are easily accessible in the market, associated with numerous side effects such as the development of resistance to...
### TABLE 2 | List of plants studied for anti-dengue response based on ethnopharmacological use.

| Sr. No | Plant/Common name/Family | Geographical location | Part Used | Studied Model, DENV Serotype | Optimum dosage | Mode of action | Used cell line/animal/human model | Citation |
|--------|--------------------------|-----------------------|-----------|-------------------------------|----------------|--------------|-----------------------------------|----------|
| 1      | *Acacia catechu*. (L.f.) Willd./Khair/ Fabaceae | Maharashtra, Madhya Pradesh, Gujarat, Tamil Nadu, Uttar Pradesh, Karnataka, Andhra Pradesh, and Rajasthan | Dried powder of fruits | DENV 1–4 | IC\(_{50}\) values 1.54 μg/ml and 0.18 μg/ml | Extract contains peptides, subdued DENV infection in the initial phase of infection via decrease foci formation and level of intracellular envelope proteins were also decreased in all serotypes of DENV. Most effective peptide (designated Pep-RTYM) interacted with DENV particles and inhibited cellular entry | Vero cells (kidney epithelial cells isolated from African green monkeys) and Huh7 cells (hepatocellular carcinoma cell line) | Panya et al. (2019); Panya et al. (2020) |
| 2      | *Acorus calamus* L./sweet flag, sway or calamus/ Acoraceae | Europe, China, northern Asia Minor, Indonesia, southern Siberia, in southern Russia, Japan, Sri Lanka, Australia, Burma, as well as southern Canada and Northern United States | Roots | DENV2 | Tatanan A, EC\(_{50}\) = 3.9 μM | Potentially affect DENV2, treatment constrained the initial steps of RNA synthesis as well as post translation modifications | Mosquito larva C6/36 cells were for DENV2 replication and Mouse kidney fibroblast cells (BHK-21) | Yao et al. (2019) |
| 3      | *Andrographis paniculata* (Burm.f.) Nees/Green chiretta/ Acanthaceae | Widely cultivated in Southern and South eastern Asia, Malaysia | Methanolic extract | DENV 2,4 | Andrographolide, the maximum non-toxic dose 15.62 μg/ml | — | C6/36 cell line for DENV replication | Kaushik et al. (2021) |
| 4      | *Basilicum polystachyon* L. Monecch/Musk Basil/Lamiaceae | Asia, Asterids, Africa, Borneo, Indochina Australia, India, China, Indian Ocean | Whole plant | DENV serotype not mentioned | IC\(_{50}\) = 1.4 ± 2/1 μM | — | Vero cells (African green monkey kidney) | Tan et al. (2019) |
| 5      | *Cissampelos pareira* L. Velvet leaf/ Menispermaceae | Western and Eastern Cape Provinces Sandy slopes and scrub of the Northern, northwards into Nambia | Aerial parts | DENV-1–4 | IC\(_{50}\) values 100, 125, 78, and 100 μg/ml, respectively | It obsessed the efficiency to downregulate the synthesis of TNF-α, a type of cytokine allied with acute dengue disease | Mosquito cell line C6/36 and monkey kidney cell lines LLCMK2 | Sood et al. (2015) |
| 6      | *Curcuma longa* L./Turmeric/ Zingiberaceae | Originate from South or Southeast Asia, most probably from Vietnam, western India, or China | Not mentioned | DENV-2 | IC\(_{50}\) = 17.91 μg/ml CC\(_{50}\) = 85.4 μg/ml | — | Huh7/Tt-1 cells | Icheyani et al. (2017) |
| 7      | *Cymbopogon citratus* (DC.) Stapf/ Lemongrass/ Gramineae | Indigenous to Sri Lanka and South India, recently cultivated in the tropical areas of Asia and America | Not mentioned | DENV-2 | CC\(_{50}\) = 183.74 and EC\(_{50}\) = 29.37 μg/ml | After treatment viral replication inhibition increased | Antiviral activity in Huh7/Tt-1 cell lines infected by DENV | Rosmatlena et al. (2019) |
| 8      | *Doratoxylon apetalum* (Poir.) Radlk./ Sapindaceae | Native to Mascarene Islands | Aerial parts | DENV1–4 | IC\(_{50}\) = 96.35, 16.75, 25.90, and 23.30 μg/ml for DENV1–4 individually | Extract-mediated DENV inhibition is allied to an erosion of infectivity | Human lung epithelial A549 cells, Vero cells, and human-derived Huh-7 hepatoma cells | Haddad et al. (2019) |

(Continued on following page)
| Sr. No | Plant/Common name/Family | Geographical location | Part Used | Studied Model, DENV Serotype | Optimum dosage | Mode of action | Used cell line/animal/human model | Citation |
|--------|--------------------------|-----------------------|-----------|----------------------------|----------------|---------------|----------------------------------|----------|
| 9      | Ficus septica Burm.f./Haul tree/Moraceae | Japan, Indonesia, Malaysia, Philippines, Solomon Islands, Papua New Guinea, and Taiwan | Stem fruit, heartwood, and leaves | DENV-1 and DENV-2 | IC_{50} = 3.05–>100 μg/ml | — | DENV-1 766733A and DENV-2 PL046 (GenBank accession no. AU988413.1) | Huang et al. (2017) |
| 10     | Oldenlandia uniflora L./Geta Kola/Rubiaceae | Mostly found in Sri Lanka | Leaves, stems, and roots | DENV-2 NS2B-NS3pro | IC_{50} ≤ 100 μg/ml | — | Dengue NS2B-NS3pro | Rothan et al. (2014) |
| 11     | Kaempferia parviflora Wall. ex Baker/krachief Dam/ Zingiberaceae | — | Leaves and stems | DENV-2 | — | — | Umesh Kanna and Krishnakumar (2019) |
| 12     | Nephelium lappaceum L./Rambutan/Sapindaceae | Southeast Asian native to the Malaysian–Indonesian region | Rind | DENV-2 | IC_{50} = 1.75 μM | Restricts early phases of cell and virus interaction via inhibiting the attachment of virus with the binding of E-DIII protein | African Green Monkey kidney cells (Vero) | Abdul Ahmad et al. (2017) |
| 13     | Ocimum tenuiflorum L./Tulsi, basil/Lamiaceae | Indigenous to Iran and India and currently cultivated in France, Egypt, Italy, Hungary, Morocco, and United States. | Whole aerial body | DENV-1 | Maximum non-toxic dose: 23.44 μg/ml | O. sanctum unveiled antiviral efficacy for DENV-1 via inhibiting CPE formation and multiplication of virus | HepG2 cells | Ling et al. (2014) |
| 14     | Paveatelyna canescens DC./Papari/Rubiaceae | E. Asia—India, Sri Lanka, and Philippines | Leaves | DENV-2 | Least LC_{50} and LC_{90} values (5.968 and 7.493 μg/ml) | — | Monolayer culture of C6/C36 mosquito cell line | Pratheeba et al. (2019) |
| 15     | Psidium guajava L./Common guava/Myrtaceae | Native to the Caribbean, Central America, and South America | Bark | DENV-2 | Catechin, CC_{50} = 1,000.0; μg/ml EC_{50} = 7.8 | — | Epithelial VERO cells and C6/36HT cells (from Aedes albopictus mosquito larvae) | Trujillo-Correa et al. (2019) |
| 16     | Schisandra chinensis (Turcz.) Baill./Magnolia-vine, Chinese magnolia-vine/ Schisandraceae | Indigenous to forests of Northern China and the Russian Far East and Korea | — | DENV-1, 2, 3, and 4 | Schisandrin A, EC_{50} = 28.1 ± 0.42 μM | Isolated bioactive compound, restricted RNA replication and translation as well as ominously raised DENV-reduced IFN-α gene expression | DENV-infected Huh-7 cells | Yu et al. (2017) |
| 17     | Tarenna asiatica (L.) Kuntze ex K. Schurm./Bingi Papadi/Rubiaceae | Southern part of India, Sri Lanka, and Malaysia | Leaves | DENV serotype not mentioned | Tetracontane, LC_{50} and LC_{90} values (1.288 and 1.992 μg/ml) | — | Monolayer culture of C6/C36 mosquito cell line | Pratheeba et al. (2019) |
| 18     | Zostera marina L./Eagrass or eelgrass/ Zosteraceae | Northern Hemisphere as well as Australia, New Zealand, Southeast Asia, and southern Africa | Designed and provided by CernoFina, LLC (Portland, ME) | DENV-1–4 | ZA, IC_{50} = 2.3 mM | — | Monkey kidney cell line LLCMK-2 | Rees et al. (2008) |

(Continued on following page)
| Sr. No | Plant/Common name/Family | Geographical location | Part Used | Studied Model, DENV Serotype | Optimum dosage | Mode of action | Used cell line/animal/human model | Citation |
|--------|--------------------------|-----------------------|-----------|------------------------------|----------------|---------------|----------------------------------|----------|
| 19     | Allium sativum L./Garlic/Liliaceae | United States and Canada | Purchased organosulfur garlic compounds | DENV-2 | — | Addition of *Allium sativum* compounds abridged the level of different pro-inflammatory cytokines including IL-8, TNF-α, IL-10 as well as iNOS (nitric oxide synthase) | Cell lines Huh-7 and U937 | Hall et al. (2017) |
| 20     | Garcinia × mangostana L./Purple mangosteen/Clusiaceae | Native to island nations of Southeast Asia and Thailand | Pericarp | DENV-1–4 | α-Mangostin, 20 μM | Remarkably reduced transcription of IL-6, TNF-α (cytokine), IP-10, RANTES, and MIP-1β (chemokine) | Human hepatocellular carcinoma (HePG2), (Huh-7) and African green monkey kidney (Vero) cells | Tarasuk et al. (2017) |
| 21     | Schisandra chinensis (Turcz.) Baill./Magnolia-vine, Chinese magnolia-vine, schisandra/Schisandraceae | — | Purchased compounds | DENV-1–4 | Schisandrin A | Inductive efficacy of antiviral IFN-I exerts gene expression | DENV-infected Huh-7 cells | Yu et al. (2017) |
| 22     | Lonicera japonica Thunb./Japanese honeysuckle/ Caprifoliaceae | Native to eastern Asia | Flower buds | DENV-2 | — | Subdue DENV2 multiplication via luciferase-reporter activity and diminishes NS1 RNA prevention level and treatment occur via instigation of the distinctive miRNA let-7a | Human hepatoma, baby hamster kidney (BHK-21) and Aedes albopictus cells C6/36 | Lee et al. (2017) |
| 23     | Carica papaya L./Pawpaw/Caricaceae | Native to the tropics of the Americas but now is widely cultivated in other tropical regions | Leaves | NM | — | Level of NS1 and envelope protein decreased in the THP-1 cells, erythrocyte damage also declines | DENV-infected THP-1 cells | Sharma et al. (2019) |
| 24     | Schwartzia brasiliensis (Choisy) Bedd. ex G. -Cañas/Nonantea/Marcgraviaeae | Vine native to Brazil | Leaves | DENV-2 | — | Downregulated IL-6, TNF-α, IL-10, and IFN-α secretion, cellular antigenic viral load, and secreted NS1 protein reduction | Buffy coat cells and peripheral blood mononuclear leukocytes | Fialho et al. (2017) |

Section 3: Clinical studies based on animal model

| Sr. No | Plant/Common name/Family | Geographical location | Part Used | Studied Model, DENV Serotype | Optimum dosage | Mode of action | Used cell line/animal/human model | Citation |
|--------|--------------------------|-----------------------|-----------|------------------------------|----------------|---------------|----------------------------------|----------|
| 25     | Carica papaya L./pawpaw/Caricaceae | Native to the tropics of the Americas but now is widely cultivated in other tropical regions | Leaves | — | — | Upsurge in cytokines of plasma in DENV infected AG129 mice with the dosage of freeze-dried 500 and 1,000 mg/kg | AG129 mice infected with DENV-2 | Norahmad et al. (2019) |
| 26     | Cissampelos pareira L./Abuta, ice vine/ Menispermaceae | Tamilnadu, Himachal Pradesh, Bihar, west Bengal, Nagpur, Punjab, and Rajasthan | Aerial parts | DENV-1–4 | Doses as high as 2 g/kg body weight for up to 1 week | — | AG129 mouse model | Sood et al. (2015) |

(Continued on following page)
| Sr. No | Plant/Common name/Family | Geographical location | Part Used | Studied Model, DENV Serotype | Optimum dosage | Mode of action | Used cell line/animal/human model | Citation |
|--------|--------------------------|-----------------------|-----------|-----------------------------|----------------|---------------|-----------------------------------|----------|
| 27     | Lonicera japonica Thunb./Japanese honeysuckle/ Caprifoliaceae | Native to eastern Asia | Flower buds | DENV-2 | Honeysuckle (40 μl) | Up to 30% virus reduction was observed via suppression of DENV2 replication as well as viral titer | C57/B6 and ICR suckling mouse models | Lee et al. (2017) |
| 28     | Euphorbia hirta L./Asthma Weed, Cats hair/ Euphorbiaceae | Warmer regions of India and Australia | Plant parts not specifically mentioned—herbal water | DENV serotype not mentioned | — | Leukocyte count ominously improved from 4,000 to 11,000 mm³ in both female and male patients | — | Mir et al. (2012) |
| 29     | Lonicera japonica Thunb./Japanese honeysuckle/ Caprifoliaceae | Native to eastern Asia | Flower buds | DENV-2 | — | Upregulated miRNAs—let-7a showed highest expression level | — | Lee et al. (2017) |
| 30     | Boerhavia diffusa L./Tanvine/ Nyctaginaceae | India, Australia, Sudan, Pakistan, Sri Lanka, South Africa, Brazil, and the southern United States | Stem | DENV serotype not mentioned | Stems of Boerhavia diffusa L. (10 g) | Lowers body temperature and increases platelet counts more than 85,000. Again, after 24 h, they have normal platelet count and no symptoms of dengue | — | Bharati and Sinha (2012) |
| 31     | Nephelium lappaceum L./ Rambutan/ Sapindaceae | Southeast Asian native to the Malaysian–Indonesian region | Rind | DENV-2 | — | Geraniin binds with DENV E, specifically at DI region | — | Abdul Ahmad et al. (2017) |
| 32     | Glycyrrhiza glabra L./ Licorice/ Fabaceae | England, Iran, Spain, Iraq, Sicily, and Russia | Not specifically mentioned – | — | — | Polyphenolic compounds, chalcones, flavonoids and some phenolics were strong docking ligands for target of dengue virus protein | — | Powers and Setzer (2016) |
| 33     | Psidium guajava L./Common guava/ Myrtaceae | Native to the Caribbean, Central America, and South America | Bark | DENV-2 | Catechin, \(C_{50} = 1,000.0\); \(\mu g/ml\) \(EC_{50} = 7.8\) | Interactions of isolated compounds with the viral envelope protein in silico by docking, only naringin and hesperidin had better scores than the theoretical threshold of \(-7.0\) kcal/mol \((-8.0\) kcal/mol and \(-8.2\) kcal/mol, respectively) | — | Trujillo-Correa et al. (2019) |
these insecticides, having toxic effects on other organs, and ecological health problems (Rodrigues et al., 2020). However, biological control as an alternative for these vectors could be very helpful due to its eco-friendly and cost-effective nature. Govindarajan et al. (2015) reported that methanol extracts of Delonix elata (L.) Gamble leaves and seed (highest concentrations used: 5.0 mg/cm²) offered protection for over 180 and 150 min, respectively, against Ae. aegypti. Herbal oil formulation of different plant species including Eucalyptus globulus Labill., A. indica, Mentha x piperita L., Ocimum basilicum L., and rhizome of Zingiber officinalis Roscoe has also been reported as repellents and bite protectors against Ae. aegypti and Ae. albopictus (Nasir et al., 2015). Terpinen-4-ol, 1,8-cineole, and β-pinene (0.4 mg/cm²) isolated from Artemisia vulgaris L. showed up to 91% inhibition of Ae. aegypti (Hwang et al., 1985). Salvia elegans Vahl possess acetate (11.4%), β-caryophyllene (6.4%), and caryophyllene oxide (13.5%), which exhibited good larvicidal activity against Ae. aegypti (Ali et al., 2015). Essential oils (EOs) extracted from the Hazomalania voyronii (Jum.) Capuron dried bark, stem, and wood are being used to attain protection against the mosquito vector Ae. aegypti (Benelli et al., 2020). As per WHO protocol, extracts were prepared using leaves of Lantana camara L., Hyptis suaveolens (L.) Poir., Nerium oleander L., and Tecoma stans (L.) Juss. ex Kunth, revealing effective larvicidal efficiency in contrast to larvae of Ae. aegypti (Hari and Mathew 2018). The chloroform bark extract of Terminalia arjuna (Roxb. ex DC.) Wight and Arn. showed maximum mortality on Ae. aegypti larvae. The LC₅₀ and LC₉₀ values of T. arjuna on Ae. aegypti larvae were 4.61 and 24.17 μg/ml, respectively (Tamilvelthan and Jayaprakash 2019).

8 SOME PHYTOCONSTITUENTS WITH ANTI-DENGUE ACTIVITY AND THEIR ACTION MECHANISM

Numerous plants and plant-based products exhibit enormous biological properties (like an antibiotic, antitumor, and antiviral), which are responsible for treating millions of individuals with serious diseases. Among those flavonoids, polysaccharides, hemicelluloses, and hydrophilic colloids are involved in the antiviral properties of plants (Table 3). Some of these biologically active compounds are based on recent research, and their promising role as contemporary medication in the near future has been discussed briefly.

8.1 Castanospermine

Castanospermine (a natural alkaloid) is a derivative of Castanospernum australae A. Cunn. and C. Fraser (black bean) (Whitby et al., 2005) that can easily be isolated through simple purification methods (Pan et al., 1993). One of the possible mechanisms through which it prevents infection is misfolding of viral proteins via obstructing the removal of glucose residues from N-linked glycans (Whitby et al., 2005). This may further lead to inhibit molecular interaction of viral and host proteins (Zhang et al., 1997; Molinari and Helenius 1999). Castanospermine has shown not only inhibitory effects on all the dengue serotypes by preventing the production of DENV but also evidence to prevent mice death when infected with DENV-2 through the intracranial route (Rathore et al., 2011). Evidence of celgosivir (6-O-butanoyl castanospermine) being an antiviral agent against DENV virus both in vitro and in vivo has also been concluded. Castanospermine exhibits glucosidase inhibitor properties that result in early-stage inhibition of glycoprotein processing. As a result, the formation of unstable complexes produces non-productive viral protein (prM and E) folding pathways and ultimately the antiviral response of Castanospermine (Courcegot et al., 2000). Celgosivir is the butylated prodru drug cleaved in cells to produce castanospermine, a bicyclic iminosugar (Miller et al., 2018). It causes misfolding and accumulation of NS1 (DENV non-structural protein) in the endoplasmic reticulum and also alters host protein response leading to the antiviral activity. Based on the previous research and data availability, castanospermine use in anti-dengue medication can be an important contribution in fighting dengue infection (Rathore et al., 2011).

8.2 Baicalin

Baicalin (a flavonoid) demonstrates considerable antiviral potential against DENV-2 by targeting the replication stages post-viral infection (Zandi et al., 2012). Baicalein is reported to be isolated naturally from the roots of Scutellaria baicaulis Georgi, a medicinal plant of China, and can be further converted into baicalin after intake by animals or humans (Xu et al., 2010). Based on the successful results obtained from Baicalin against dengue infection, other plant species having baicalin as a biomolecule can be explored for their anti-dengue properties. The mechanistic approach behind the anti-dengue properties has been demonstrated by researchers where possible ways of antiviral activity (96–99%) are direct inactivation of free DENV-2 particles, inhibited intracellular viral replication, and binding of DENV-2 cells to the host cell (Moghaddam et al., 2014). In molecular docking analysis, both baicalin and baicalein are reported to inhibit the DENV replication by pursuing key DENV genes and exhibit anti-DENV protease (NS2B/NS3) activity. The results of docking studies show that both baicalein and baicalin may interact with NS3–NS2B, E, and NS5 proteins, which can be responsible for their antiviral impact (Hassandarvish et al., 2016; Rasool et al., 2019). Further investigation using these phytoconstituents is still needed to obtain promising results in the form of contemporary medications and future implementation in clinical use.

8.3 Gallic Acid

Gallic acid (main phenolic plant component) exhibits various pharmacological activities (antioxidant, antiviral, antifungal, etc.) and therapeutic uses against neural disorders, dengue, cancer, asthma, and allergic rhinitis, without any cytotoxic effects (Suganthi and Ravi 2019). In a study, inhibitory response of gallic acid with no cytotoxic effect has been elucidated in in vitro conditions on DENV-2 virus along with another compound, emodin, and some plant extracts, i.e., Antennaria microphylla Rydb., Rubus scaber Weihe, Ziziphus jujuba Mill., and
## TABLE 3 | Effective bioactive compounds from plant sources against dengue infection.

| Sr. no | Phytochemical  | Chemical structure | Class | Plant studied for anti-dengue activity | Plant Part used | Other plants containing this phytoconstituent | Citation |
|--------|----------------|-------------------|-------|-----------------------------------------|-----------------|---------------------------------------------|----------|
| 1      | Castanospermine | Tetrahydroxyindolizidine alkaloid | Castanospermum australe A. Cunn. and C. Fraser (Fabaceae) | — | 1. Swainsona canescens (Lindl.) F. Muell. (Fabaceae) | Häusler et al. (2000); Whitby et al. (2005) |
| 2      | Baicalin        | Glycosyloxyflavone | Scutellaria baicalensis Georgi (Lamiaceae) | Roots | 1. Scutellaria baicalensis Georgi (Lamiaceae) inhibit human T-cell leukemia virus type 1 (HTLV-I) 2. Oroxylum indicum (L.) Kurz (Bignoniaceae) | Baylor et al. (1992); Zhao et al. (2016); Zhou et al. (2016); Rojsanga et al. (2020) |
| 3      | Gallic acid     | Phenolic acid      | Psidium guajava L. (Myrtaceae) | Bark | 1. Camellia sinensis (L.) Kuntze (Theaceae) 2. Ficus auriculata Lour. (Moraceae) | Trujillo-Correa et al. (2019); Zhou et al. (2020); Baite et al. (2021) |
| 4      | Quercetin       | Flavonoid glycosides | Momordica charantia L. (Cucurbitaceae) | — | 1. Allium roseum L. (Amaryllidaceae) 2. Vaccinium vitis-idaea L. (Ericaceae) 3. Nyctanthes arbor-tristis L. (Olaceae) | Han et al. (2005); Eid et al. (2010); Agrawal and Pal (2013); Nile et al. (2017) |
| 5      | Epigallocatechin gallate | Polyphenols | Camellia sinensis (L.) Kuntze (Theaceae) | — | — | Vázquez-Calvo et al. (2017) |
| 6      | Galactomannan   | Polysaccharides    | Leucaena leucocephala (Lam.) de Wit (Fabaceae), Mimosa scabrella Benth. (Fabaceae), Lippia alba (Mill.) N.E.Br. ex Britton and P. Wilson (Verbenaceae) | Seed | 1. Trigonella foenum- graecum L. (Fabaceae) 2. Ceratonia siliqua L. (Fabaceae) 3. Cymopopsis tetragonoloba (L.) Taub. (Fabaceae) 4. Caesalpinia spinosa (Molina) Kuntze (Fabaceae) 5. Senna alexandrina Mill. (Fabaceae) | Latgé et al. (1991); Chaubey and Kapoor (2001); Ono et al. (2005); Mathur and Mathur (2005); Ocazionez et al. (2010); Prajapati et al. (2013) |
| 7      | Glabranine, 7-O-methylglabranine | Flavonoid | Tephrosia species | Leaf, Flower | 1. Linum usitatissimum L. (Linaceae) | Sánchez et al. (2000) |
| 8      | Galactan        | Hemicelluloses     | Cryptonemia crenulata J. Agardh (Halymeniaceae), Gymnogongrus torulosus (J.D. Hooker and Harvey) F. Schmitz (Phyllorhaceae) | Whole Plant | 1. Chenopodium quinoa Wild (Amaranthaceae) | Taracino et al. (2005); Wefers et al. (2014) |

(Continued on following page)
| Sr. no | Phytochemical | Chemical structure | Class | Plant studied for anti-dengue activity | Plant Part used | Other plants containing this phytoconstituent | Citation |
|--------|----------------|---------------------|-------|----------------------------------------|-----------------|-----------------------------------------------|----------|
| 9      | Kappa carrageenan | ![Carrageenan Structure](image) | Hydrophilic colloids | Meristella gelidium (J. Agardh) (Solieriaceae), Gymnogongrus griffithsiae (Turner) C. Martius (Phyllophoraceae) | — | 1. Hypnea musciformis (Wulfen) J.V. Lamouroux (Cystoclionaceae) 2. Eucheuma cottoni Weber-van Bosse (Solieriaceae) | Talarico et al. (2000); Arman and Qader (2012); Nur Fatni Nazurah and Nur Hanani (2017) |
| 10     | 4-Hydroxypanduratin A, panduratin A | — | — | Boesenbergia rotunda (L.) Mansf. (Zingiberaeaceae) | — | 1. Boesenbergia rotunda (L.) Mansf. (Zingiberaeaceae) | Kist et al. (2006); Pham et al. (2020) |
| 11     | Zosteric acid | ![Zosteric Acid Structure](image) | Ravonoid | Zostera marina L. (Zosteraceae) | — | — | Rees et al. (2008) |
| 12     | Morin | ![Morin Structure](image) | Ravonoid | Zingiber officinale Roscoie (Zingiberaeaceae) | — | 1. Tinospora crispa (L.) Hook. f. and Thomson (Menispermaceae) 2. Morus alba (L.) (Moraceae) 3. Acridocarpus orientalis A. Juss. (Malpighiaceae) | Yang and Lee (2012); Hussain et al. (2014); Miadiko et al. (2020); Taguchi et al. (2020); Warsinah et al. (2020) |
| 13     | Hyperoside | ![Hyperoside Structure](image) | Ravonoid | Houttuynia cordata Thunb. (Saururaceae) | Whole plants, aerial stem and leaves | 1. Camptotheca acuminata Decne. (Cornaceae) 2. Hypericum perforatum L. (Hypericaceae) 3. Oenothera javanica (Blume) DC. (Apiceae) 4. Zanthoxylum bungeanum Maxim. (Rutaceae) | Li et al. (2005); Kim et al. (2011); Leardkamolkarn et al. (2012); Ahn and Lee (2017); Zhang et al. (2021) |
| 14     | Fucoidan | ![Fucoidan Structure](image) | Polysaccharides | Cladosiphon okamuranus Tokida (Chordariaceae) | Whole plants | 1. Utricularia aurea Lour. (Lentibulariaceae) 2. Undaria pinnatifida (L.) Asarn. (Ariariaeaceae) 3. Sargassum wightii Greville ex J. Agardh (Sargassaceae) 4. Sargassum polyacystum C. Agardh (Sargassaceae) 5. Ascophyllum nodosum (L.) Le Jolis (Fucaceae) 6. Vietnam Sargassum species | Jiang et al. (2010); Skriptsova et al. (2010); Marudhupandi and Kumar (2013); Minh Ly et al. (2017); Patanisamy et al. (2017); Lim et al. (2019) |
| 15     | Daidzein | ![Daidzein Structure](image) | Bioflavonoid | — | — | 1. Glycin max (L.) Merr. (antioxidant) (Fabaceae) 2. Pluchea lanceolata (DC.) C.B. Clarke (Asteraceae) 3. Pueraria candollei Benth. (Fabaceae) | Pongkitwitoon et al. (2011); Juliana et al. (2020) |
8.4 Quercetin

Quercetin (flavonoid) exhibits various pharmacological responses against viruses, tumors, inflammation, etc. In accordance with previous studies available, quercetin is one of the main components of different plant extracts (E. hirta and P. guajava) exerting consistent antiviral effect against dengue infection (DENV-2) (Zandi et al., 2011; Saptawati et al., 2017; Suganthi and Ravi 2019). A possible mechanism is similar to the previously discussed metabolites that inhibit viral replication by targeting RNA polymerase enzyme. Quercetin is reported to exhibit antiviral properties via impeding viral attachment and viral replication against DENV serotypes (1–4) (Zandi et al., 2011; Sharma et al., 2018). In addition, quercetin is one of the main components present in P. guajava leaf extract demonstrating the inhibitory effect on DENV infection with no involvement in the inhibition of viral surface proteins and receptors. These findings also suggest the presence of other bioactive compounds in P. guajava leaf formulations that may exhibit anti-dengue behavior (Dewi et al., 2020). *Houttuynia cordata* Thunb. leaves ethyl acetate fraction (including quercetin, quercitrin, and rutin) has also been reported, which reveals the efficient anti-DENV-2 activity of bioactive components quercetin (IC$_{50}$ of 176.76 µg/ml) and quercitrin (IC$_{50}$ of 467.27 µg/ml). The synergistic effect of both components is also depicted in the past presenting antiviral properties with an IC$_{50}$ of 176.76 µg/ml (Chiow et al., 2016). These results conclude that plant formulations and their metabolites signify a promising preventative substance in P. guajava. L. leaf extract, which might prevent DENV attachment by inhibition of DENV surface protein along with the receptor inhibition (Dewi et al., 2020).

8.5 Epigallocatechin Gallate

Epigallocatechin gallate (flavonoid) and delphinidin (structurally related polyphenol) from plants and their products (wine, green tea, curcumin, and delphinidin) have proved their antiviral qualities regardless of the DENV serotypes. These compounds are suggested to exhibit virucidal effects or inhibit viral production by acting upon the viral life cycle at its attachment and entry points (Vázquez-Calvo et al., 2017; Raekiansyah et al., 2018; Clain et al., 2019). In another study, epigallocatechin gallate, a biologically active component of green tea, curcumin, and delphinidin, is reported to have the least cytotoxic effects. It is believed to prevent viral infection at early stages by direct interaction with the virion (when the virus is preincubated with epigallocatechin gallate), which leads to an approximate drop of 90% in DENV antigen present in intracellular fluid. Similarly, epigallocatechin, another bioactive compound, also has a strong repressive impact on viral growth (Raekiansyah et al., 2018). The inhibition mechanism as suggested by Raekiansyah et al. is to develop a virucidal effect through direct binding with molecules present on the DENV surface (Raekiansyah et al., 2018).

8.6 Other Bioactive Compounds

Apoifuranoside (flavane glycosides), obtained from *Faramea bahiensis* Mull. Arg., is efficiently involved in the treatment of dengue via controlling viral replication as well as reducing the number of infected cells (12%) and RNA copies of DENV-2 (67%) in HepG2 cells (Nascimento et al., 2017). Flacourtoside A, a phenolic glycoside exhibited in *Flacourtia indica* (Burn.f.) Merr., effectively inhibited DENV replication with the 9.3 µM IC$_{50}$ values (Bourjot et al., 2012). Trigocherrin A and Trigocherriolide B and C (diterpenoids) found in *Trigonostemon cherrieri* Veillon are also able to impede DENV replication with 12.7 µM and 3.1 and 16.0 µM IC$_{50}$ values, respectively (Allard et al., 2012). *Arrabidaea pulchra* (Cham.) L.G. Lohmann synthesizes another important bioactive compound, verbascoside (phenyl glycoside), which is reported to display good anti-DENV-2 (IC$_{50}$ = 3.4 µg/ml) properties (Brandão et al., 2013). Also, pectolinarin, a type of flavone found in *Amphilophium elongatum* (Vahl) L.G. Lohmann exhibited anti-DENV-2 effects with an EC$_{50}$ value of 86.4 µg/ml (Simões et al., 2011).

Note that the action mechanism and the minimal cytotoxicity levels of natural compounds can contribute to the development of anti-dengue medication, which will be safer as well as more effective in use, although limited research has been done in this aspect and there are limited publications. Thus, further investigations are necessary to develop a fruitful antiviral drug (to cure DENV).

9 IMMUNOMODULATORY RESPONSE OF PLANT EXTRACTS

With the onset of dengue infection, the host can experience a complex interplay of host immune factors and viral particles, which may include amplified immune cell infection due to the presence of non-deactivating antibodies and stimulation of cross-reactive autoimmunity responses (i.e., activation of T cells and autoantibodies, cytokine deregulation, complement, and coagulation systems) (Jasso-Miranda et al., 2019). Being an acute febrile infection (thrombocytopenia, arthralgia, and hemorrhagic symptoms), it may lead to the host deterioration due to the hemorrhagic attack, plasma leak, intense shock, organ collapse, and ultimately, death (Pan American Health Organization (PAHO) 2016; Jasso-Miranda et al., 2019). Dengue infection is hypothesized to be more fatal due to the
antibody-dependent enhancement of infection, which is associated with the transformation of the disease. Two DENV infections in a specific sequence, the interval of two infections, and how much the human host is causative in terms of age, health, ethnicity, and genetic background (Guzman et al., 2013). Generation of cross-reactive antibodies, post-first-time dengue infection in association with the second infecting virus, results in the formation of more harmful immune compounds like non-deactivating antibodies (critical players of the pathogenic response in severe dengue conditions) (Kuczera et al., 2018). This consequently increases the infected cell count and thus increased viral output in the form of high cytokine production, which further causes vascular permeability, intense shock, and, ultimately, death (Puerta-Guardo et al., 2013). Various other immune factors like interferons (IFN-α and -γ), interleukin (IL-6, -8, and -10), and tumor necrosis factors (TNF-α), and elevated expression of cytokine signaling suppressors are linked to severe dengue infections (Bozza et al., 2008; Chen et al., 2014; Flores-Mendoza et al., 2017). Another study revealed a potential immunomodulatory response (against DENV virus) by Schuxtapenia brasiliensis (Choisy) Bedell ex Gir.-Cañas Choisy extract, which helps in antigen load reduction (NS1 protein, a viral load indicator) in the cells. Crude S. brasiliensis extract was most efficient against dengue activity while the dichloromethane fraction resulted in strong immunoregulatory activities. Downregulation of various immune factors like TNF-α, IFN-α, IL-6, and IL-10 was evidenced as the key reason behind the antiviral effects (Fialho et al., 2017). Significant immunoregulation and antiviral response with Uncaria tomentosa (Willd ex Schult.) DC. fractions have also been demonstrated, in which DENV-infected monocytes (human) were tested. The anti-DENV activity was associated with decreased cytokine levels such as TNF-α and modulation of IL-10 (Reis et al., 2008). Successful molecular assessment and manipulations of various immune responses and associated factors can be useful research to develop anti-dengue drugs. Traditionally, C. papaya leaf extract has been proven for its immunomodulatory activities (Pandey et al., 2016; Anjum et al., 2017; Razak et al., 2021). In dengue patients (suffering from thrombocytopenia), oral administration of papaya leaf extract has resulted in increased platelet count activity (40–48 h) (Subenthiran et al., 2013). In other similar findings with the use of C. papaya leaf extract, beneficial impacts are reported where a significant increase in WBC and platelet count is evidenced with negligible side effects (Hettige 2008; Gowda et al., 2015). Rhodiolia imbricata Edgew. (a flowering plant) is also demonstrated to induce pharmacological modifications in response to the DENV infection. It induces NK cells and cytokines like interferon b (IFN), IL-8, IL-1β, IL-6, and TNF-α and upregulates phosphorylated NF-kb, eIF-2α, and PKR in DENV-infected cells (Diwaker et al., 2014). In addition, the immunomodulatory potential against DENV is stated by its ability to regulate cytokine production, phagocytic activity, and white blood cell proliferation (Razak et al., 2021).

10 COMPLEMENTARY AND ALTERNATIVE DENGUE THERAPEUTICS

Dengue vaccines have been classified into five main categories, i.e., live attenuated vaccines (CYD-TDV, TV003/TV005), DENAVaxin activated virus vaccine (PV), recombinant subunit vaccine (V180), DNA vaccine (D1ME100, TVDV), and viral vectored vaccine (TLAV Prime/PV boost and reverse order) (Deng et al., 2020a). Dengvaxia (CYD-TDV) by Sanofi Pasteur (the first dengue vaccine) was registered in several endemic countries for individuals of the age group 9–45 years (Deep et al., 2018; Deng et al., 2020a). It consists of DENV (1–4) serotype structural genes (encoding PrM and E proteins) introduced in the attenuated yellow fever vaccine strain genome. According to the reports, it exerts 56%–61% virucidal efficacy against dengue in Asia and Latin America (Capeding et al., 2014; Biswal et al., 2019). This anti-dengue vaccine is only recommended for patients having evidence of past DENV infection due to infection severity in seronegative candidates via stimulating non-neutralizing antibody generation (Sridhar et al., 2018). This drawback is considerable in the development of other alternatives of anti-dengue drug discovery. Another tetravalent dengue medicine, TAK-003 (Takeda), consisting of live attenuated DENV-2 genetic backbone for all DENV serotypes, has been designed by experts at the Division of Vector-Borne Diseases, Centers for Disease Control and Prevention (CDC) (Huang et al., 2013). Overall vaccine efficiency is documented to be 80.9%, and the seronegative populations showed 74.9% vaccine efficacy for the new dengue vaccine (TAK-003) (Biswal et al., 2019). The vaccination priming with drugs used in combination has been reported to provide more effective immunogenic protection in animals. In addition, analysis of the immune response and the mechanism of viral elements can be a revolutionary success in vaccine development (Liu et al., 2016). Anti-dengue drugs, such as chloroquine, colchicine, halapiravir, prednisolone, and lovastatin, have been stated to undergo medical examinations against DENV infection (Kaptein and Neys 2016; Low et al., 2017), although no effective dengue treatment has been developed from any of these composites. Therefore, the search for more effective antiviral compounds (plant-derived or second-use medicines) is still a vital prerequisite in overcoming dengue’s lethal effects (Trujillo-Correa et al., 2019). Besides, the specific anti-dengue vaccine is not yet developed, as few to none of the potential anti-dengue candidates have been tested clinically (Razak et al., 2021).

11 CONCLUSION

An update about various plants with pharmacological and ethnobotanical uses against dengue treatment was presented. Besides the global status of the dengue epidemic, existing vaccination measures have been conferred in the current review. Solely, the folkloric knowledge and uses of natural resources have been promising due to the exhaustive investigation carried out on the ethnopharmacologically important plant species. Many plant species and their
respective extracts and pure compounds have been shown to exhibit potential as anti-DENV medicaments. The plant bioactive metabolites exhibit antiviral response directly or through the stimulation of immunomodulatory response cascades against DENV at different infection stages, i.e., viral adsorption, intracellular replication, and proliferation. Plant metabolites also help to reduce the antigen load and manipulate various immune factors in the host. Plant-mediated immunomodulation leads to the regulated cytokine production, enhanced platelet count, and phagocytic pathway activation. However, there are several plants still used for their anti-dengue properties via traditional methods and are yet to be investigated for scientific approval. Whether the antiviral properties are a result of a single phytoconstituent or the interaction of multiple phytoconstituents present in the plant extract(s) is critical to justify. Thus, extensive research is required to assess the immunologic potentials along with the phytochemical richness of plants and further clinical probes to develop an effective medicine. Another significant aspect of medicinal plants is their insecticidal properties, which make them an eco-friendly and sustainable substitute for Aedes mosquito control. Since vaccine development is a time-consuming process, finding an alternate treatment is crucial to overcome the lethal impacts of the DENV virus. Plant natural compounds are valuable sources to accomplish the speedy discovery of anti-DENV drugs because of their safer use and positive immunomodulatory responses. Nevertheless, the most crucial task is to reveal the molecular machinery of viral components and their capability to mutate rapidly during replication. Moreover, there are some vaccines available to treat dengue infection, but with some limitations. In this scenario, research is being carried out on some medicinal plant species, i.e., Nyctanthes arbor-tristis L., Firmiana simplex (L.) W. Wight, T. sinensis, and Moringa oleifera Lam., to investigate their metabolic profiles supporting their anti-dengue properties (antilarval or anti-DENV, in the authors’ laboratory). Besides, N. arbor-tristis, M. oleifera, and T. sinensis are also reported for their larvicidal activities. Furthermore, the GC-MS profiling of F. simplex also reveals the presence of natural compounds having insecticidal properties against dengue vectors.

Besides, a lot of scientific research is dedicated towards anti-DENV drug development and further research is needed to identify phytochemicals for their antiviral efficacy, mode of action, and successful clinical implementation.

**REFERENCES**

Abd Kadir, S. L., Yaakov, H., and Mohamed Zulkilli, R. (2013). Potential Anti-dengue Medicinal Plants: A Review. *J. Nat. Med.* 67, 677–689. doi:10.1007/s11418-013-0767-y

Abdul Ahmad, S. A., Palanisamy, U. D., Tejo, B. A., Chew, M. F., Tham, H. W., and Syed Hassan, S. (2017). Geranium Extracted from the Rind of Nephelem Lappaceum Binds to Dengu Virus Type-2 Envelope Protein and Inhibits Early Stage of Virus Replication. *Virol. J.* 14, 229. doi:10.1186/s12985-017-0895-1

Agrawal, J., and Pal, A. (2013). Nyctanthes Arbor-Tristis Linn—a Critical Ethnopharmacological Review. *J. Ethnopharmacol.* 146, 645–658. doi:10.1016/j.jep.2013.01.024

Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B. H., Mohammad, I., and Fazal, L. (2011). Dengue Fever Treatment with Carica Papaya Leaves Extracts. *Asian Pac. J. Trop. Biomed.* 1, 330–333. doi:10.1016/S2221-1691(11)60055-5

Ahn, H., and Lee, G. S. (2017). Isorhamnetin and Hyperoside Derived from Water Dropwort Inhibits Inflammasome Activation. *Phytomedicine* 24, 77–86. doi:10.1016/j.phymed.2016.11.019

Akhbar, I. N. (2020). “Viral Genetics and Structure,” in Dengue Virus Disease: From Origin to Outbreak (Academic Press), 85–113. doi:10.1016/B978-0-12-818270-3.00006-0

Alagarasu, K., Patil, I. A., Kakade, M. B., More, A. M., Yogesh, B., Newase, P., et al. (2021). Serotype and Genotype Diversity of Dengue Viruses Circulating in India: a Multi-centre Retrospective Study Involving the Virus Research Diagnostic Laboratory Network in 2018. *Int. J. Infect. Dis.* 111, 242–252. doi:10.1016/j.ijid.2021.08.045

Ali, A., Tabanca, N., Demirci, B., Blythe, E. K., Ali, Z., Basir, K. H., et al. (2015). Chemical Composition and Biological Activity of Four Salvia Essential Oils and

**AUTHOR CONTRIBUTIONS**

MMS: Conceptualization, Validation, Supervision. MD: Writing—original draft preparation, Formal analysis, Validation, Writing—review and editing. LS: Writing—original draft preparation, Formal analysis, Validation, Writing—review and editing. AD: Data collection, Formal analysis. PD: Chemical structure.

**ACKNOWLEDGMENTS**

The authors are grateful to Manipal University Jaipur, Rajasthan, India, for supporting the present work. The entire team is thankful to Manipal University Jaipur for vital support and amenities.

**Individual Compounds against Two Species of Mosquitoes.** *J. Agric. Food Chem.* 63, 447–456. doi:10.1021/acs.jafc.5b04976

Allard, P. M., Leysen, P., Martin, M. T., Bourjon, M., Dumontet, V., Eydoux, C., et al. (2012). Antiviral Chlorinated Daphnane Diterpenoid Orthoesters from the Bark and wood of Trigonostemon Cherrieri. *Phytochemistry* 84, 160–168. doi:10.1016/j.phytochem.2012.07.023

Anjum, V., Arora, P., Ansari, S. H., Najmi, A. K., and Ahmad, S. (2017). Antithrombocytopenic and Immunomodulatory Potential of Metabolically Characterized Aqueous Extract of Carica Papaya Leaves. *Pharm. Biol.* 55, 2043–2056. doi:10.1080/13880209.2017.1346690

Arman, M., and Qader, S. A. U. (2012). Structural Analysis of Kappa-Carrageenan Isolated from Hypnea Musciformis (Red Algae) and Evaluation as an Elicitor of Plant Defense Mechanism. *Carbohydr. Polym.* 88, 1264–1271. doi:10.1016/j.carbpol.2012.02.003

Aruna, R. (2014). Review on Dengue Viral Replication, Assembly and Entry into the Host Cells. *Int. J. Microb. Appl. Sci.* 8, 1.

Arunabha, M. (2019). Trigonella Foenum-Gracum: A Review on its Traditional Uses, Phytochemistry and Pharmacology. *Int. J. Adv. Sci. Res.* 5 (5), e5217. doi:10.7439/ijasr

Bahuguna, V., Matura, R., and Sharma, N. (2019). Potential Use of Medicinal Plants for Dengue: a Systematic Mini Review of Scientific Evidence. *J. Appl. Life Sci.* 2, 10–16.

Baite, T. N., Mandal, B., and Purkait, M. K. (2021). Ultrasound Assisted Extraction of Gallic Acid from Ficus Auriculata Leaves Using green Solvent. *Food Bioproducts Process.* 128, 1–11. doi:10.1016/j.fbp.2021.04.008

Bartenschlager, R., and Miller, S. (2008). Molecular Aspects of Dengue Virus Replication. *Future Microbiol.* 3, 155–165. doi:10.2217/17460913.3.2.155

Baylerian, N. W., Fu, T., Yan, Y. D., and Russett, F. W. (1992). Inhibition of Human T Cell Leukemia Virus by the Plant Flavonoid Baicalin (7-glucoconic Acid, 5,6-dihydroxyflavone). *J. Infect. Dis.* 165, 433–437. doi:10.1093/infdis/i65.3.433
Hari, I., and Mathew, N. (2018). Larvicidal Activity of Selected Plant Extracts and Dhiman et al. Ethnopharmacology in Treating Dengue; A Deadly Virus Häusler, H., Kawakami, R. P., Mlaker, E., Severn, W. B., Wrodnigg, T. M., and Govindarajan, M., Rajeswary, M., Hoti, S., Benelli, G., Benelli, G., and Amsath, A. Gu, R., Wang, Y., Long, B., Kennelly, E., Wu, S., Liu, B., et al. (2014). Prospecting Guzman, M. G., Alvarez, M., and Halstead, S. B. (2013). Secondary Infection as a Their Combination against the Mosquito Vectors Aedes aegypti J. Carbohydr. Chem. (2016). In Silico study on Baicalein and Baicalin as Inhibitors of Dengue Virus 018-1515-3 Häusler, H., Kawakami, R. P., Rezai, S., Yusof, R., Abubakar, S., and Zandi, K. (2016). In Silico study on Baicalin and Baicil as Inhibitors of Dengue Virus Replication. RSC Adv. 6, 31235–31247. doi:10.1039/c6ra00817h Hausler, H., Kawakami, R. P., Måler, E., Severn, W. B., Wrodnigg, T. M., and Stütz, A. E. (2000). Sugar Analogues with Basic Nitrogen in the Ring as Anti-infectives. J. Carbohydr. Chem. 19, 435–449. doi:10.1080/07383000008544092 Huang, C. Y., Kinney, R. M., Livergood, J. A., Bolling, B., Arquello, J. J., Luy, B. E., et al. (2013). Genetic and Phenotypic Characterization of Manufacturing Seeds for a Tetravalent Dengue Vaccine (DENVax). Plos Negl. Trop. Dis. 7, e2243. doi:10.1371/journal.pntd.0002243 Huang, N. C., Hung, W. T., Tsai, W. L., Lai, F. Y., Lin, Y. S., Huang, M. S., et al. (2017). Ficus Septica Plant Extracts for Treating Dengue Virus In Vitro. PeerJ 5, e3448. doi:10.7717/peerj.3448 Hussain, J., Ali, L., Khan, A. L., Rehman, N. U., Jabeen, F., Kim, J. S., et al. (2014). Isolation and Bioactivities of the Flavonoids Morin and Morin-3-O-β-D-Glucopyranoside from Acidocarpus Orientalis-A Wild Arabian Medicinal Plant. Molecules 19, 17763–17772. doi:10.3390/molecules191117763 Hwang, Y. S., Wu, K. H., Kumamoto, J., Axelrod, H., and Mulla, M. S. (1985). Isolation and Identification of Mosquito Repellents in Artemisia Vulgaris. J. Chem. Ecol. 11, 1297–1306. doi:10.1007/BF01024117 Ichyani, M., Ridhanya, A., Risanti, M., Desti, H., Ceria, R., Putri, D. H., et al. (2017). Antiviral Effects of Curcuma Longa L. Against Dengue Virus In Vitro and In Vivo. IOP Conf. Ser. Earth Environ. Sci. 101, 012005. doi:10.1088/1755-1315/101/1/012005 Jaso-Miranda, C., Herrera-Camacho, I., Flores-Mendoza, L. K., Dominguez, F., Vallejo-Ruiz, V., Sanchez-Burgos, G. G., et al. (2019). Antiviral and Immunomodulatory Effects of Polypheonols on Macrophages Infected with Dengue Virus Serotypes 2 and 3 Enhanced or Not with Antibodies. Infect. Drug Resist. 12, 1833–1852. doi:10.2147/IDR.S210890 Jayadevappa, M. K., Karkera, P. R., Siddappa, R. Y., Tellkar, S., and Karunakara, P. (2020). Investigation of Plant Flavonoids as Potential Dengue Protease Inhibitors. J. Herbed Pharmcol. 9, 366–373. doi:10.3747/jhp.2020.46 Jiang, Z., Okimura, T., Yokose, T., Yamasaki, Y., Yamaguchi, K., and Oda, T. (2010). Effects of Sulfated Fucan, Ascosphyllan, from the Brown Alga Ascosphyllum Nodosum on Various Cell Lines: A Comparative Study on Ascosphyllan and Fucoxidan. J. Biosci. Bioeng. 110, 113–117. doi:10.1016/j. jbioc.2010.01.007 Juliana, C., Lister, I. N. E., Giesang, E., Nasution, A. N., and Widowati, W. (2020). Antioxidant and Elastase Inhibitor from Black Soybean (Glycine max L.) and its Compound (Daidzein). J. Biomed. Transl. Res. 6, 11–14. doi:10.14710/jbtr.v6i1.5540 Kaptein, S. J., and Neyts, J. (2016). Towards Antiviral Therapies for Treating Dengue Virus Infections. Curr. Opin. Pharmacol. 30, 1–7. doi:10.1016/j.coph.2016.06.002 Kaushik, S., Dar, L., Kaushik, S., and Yadav, J. P. (2021). Identification and Characterization of New Potent Inhibitors of Dengue Virus NS5 Proteinase from Andrographis Paniculata SuperCritical Extracts on Animal Cell Culture and In Silico Approaches. J. Ethnopharmacol. 267, 113541. doi:10.1016/j.jep.2020.113541 Khan, A. M., and Bhutta, Z. A. (2017). “Childhood Infectious Diseases: Overview,” in International Encyclopedia of Public Health (Elsevier), 517–538. doi:10.1016/B978-0-12-806785-0.00056-5 Khanh Pham, N., Tuan Nguyen, H., and Binh Nguyen, Q. (2021). A Review on the Ethnomedicinal Uses, Phytochemistry and Pharmacology of Plant Species Belonging to Kaempferia Genus (Zingiberaceae). Pharm. Sci. Asia 48, 1–24. doi:10.29090/PSA.2021.01.19.070 Kiat, T. S., Pippen, R., Yusof, R., Ibrahim, H., Khalid, N., and Rahman, N. A. (2006). Inhibitory Activity of Cyclohexenyl Chalcone Derivatives and Flavonoids of Fingerroot, Boesenbergia Rotunda (L.), towards Dengue 2 Virus NS5 Protease. Bioorg. Med. Chem. Lett. 16, 3337–3340. doi:10.1016/j.bmcl.2005.12.075 Kim, J., and Hwang, E. S. (2020). Multiplexed Diagnosis of Four Serotypes of Dengue Virus by Real-Time RT-PCR. Biochip J. 14, 421–428. doi:10.1007/s13206-020-4409-7 Kim, S. J., Um, J. Y., Lee, J. Y., and Lee, J. Y. (2011). Anti-inflammatory Activity of Hyperoside through the Suppression of Nuclear Factor-Kb Activation in Mouse Peritoneal Macrophages. Am. J. Chin. Med. 39, 171–181. doi:10.1142/S0120801011008737 Kucera, D., Assolini, I. P., Tomatello-Pellissier, F., Pavaneli, W. R., and Silveira, G. F. (2018). Highlights for Dengue Immunopathogenesis: Antibody-dependent Enhancement, Cytokine Storm, and beyond. J. Interferon Cytokine Res. 38, 69–80. doi:10.1089/jir.2017.0037 Kularatne, S. A. M. (2008). Dengue Fever. Sri Lankan Fam. Physician 1, h4661. doi:10.1136/bmj.h4661
Kumar, A., Rongcharpi, S. R., Dewan Duggal, S., Gur, R., Choudhary, S., and Khare, P. (2017). Clinical, Epidemiological and Microbiological Profile of Dengue Fever at a Tertiary Care Hospital in Delhi, India. J. Infect. Dis. Med. 02, 1. doi:10.14272/1278-1420.1000110

Lambrecht, L., Scott, T. W., and Gubler, D. J. (2010). Consequences of the Expanding Global Distribution of *Aedes albopictus* for Dengue Virus Transmission. Plos Negl. Trop. Dis. 4, e646. doi:10.1371/journal.pntd.0000646

Larocca, D. G., Júnior, N. G. R., Vicente, R., and Silva, I. V. (2021). Ethnobotanical Treatment of Tropical Diseases, Malaria and Dengue, Prescribed by Bioenergetico Practitioners and Profile of the Involved Population in Meridional Amazon. Revista Etnobiologia. 19, 114–128.

Latgé, J. P., Debeaupuis, J. P., Moutaouakil, M., Diasquin, M., Sarfati, J., Prévost, M. C., et al. (1991). Galactomannan and the Circulating Antigens of Aspergillus fumigatus. Springer. 143–155. doi:10.1007/978-3-642-70674-7_11

Leardkamolkarn, V., Sirigulpanit, W., Phurimaks, C., Kunkmate, S., Himakou, L., and Srnipandikulkchai, B. (2012). The Inhibitory Actions of Houttuynia Cordata Aquous Extract on Dengue Virus and Dengue-Infected Cells. J. Food Biochem. 36, 86–92. doi:10.1111/j.1745-4510.2010.00514.x

Lee, Y. R., Yeh, S. F., Ruan, X. M., Zhang, H., Hsu, S. D., Huang, H. D., et al. (2017). Antifungal Activity of Fucoidan from Strains of *Cladosiphon Okamuranus* (Okinawa Mozuku). Food Chem. 272, 222–226. doi:10.1016/j.foodchem.2018.08.034

Ling, A. P. K., Khoo, B. F., Seaf, C. H., Foo, K. Y., Cheah, R. K., Chye, S. M., et al. (2019). Honeysuckle Aquous Extract and Induced Let-7a Suppress Dengue Virus Type 2 Replication and Pathogenesis. J. Ethnopharmacol. 198, 109–121. doi:10.1016/j.jep.2016.12.049

Li, M., Zhang, Z., Zou, Y., Wang, B., Long, M., and Taylor, J. (2005). Antifungal Activity of Campothecin, Trifolin, and Hyperoside Isolated from *Camptotheca acuminate*. J. Agric. Food Chem. 53, 32–37. doi:10.1021/jf0484780

Lim, S. J., Wan Aida, W. M., Schiehser, S., Rosenau, T., and Böhmdorfer, S. (2019). Structural Elucidation of Fucoidan from Cladosiphon Okamuranus (Okinawa Mozuku). Food Chem. 272, 222–226. doi:10.1016/j.foodchem.2018.08.034

Ling, A. P. K., Khoo, B. F., Seaf, C. H., Foo, K. Y., Chye, R. K., Chye, S. M., et al. (2014). “Inhibitory Activity of Methanol Extracts of Andrographis Paniculata and *Ocimum sanctum* against Dengue-1 Virus,” in International Conference on Biological Environmental and Food Engineering (Bali, Indonesia: IEEE). doi:10.15222/icbfe.814913

Liu, Y. X., Li, F. X., Liu, Z. Z., Jia, Z. R., Zhou, Y. H., Zhang, H., et al. (2016). Integrated Analysis of miRNAs and Transcriptomes in *Aedes albopictus* Midgut Reveals the Differential Expression Profiles of Immune-Related Genes during Dengue Virus Serotype-2 Infection. Insect Sci. 23, 377–385. doi:10.1111/1744-7917.12339

Low, J. G., Ooi, E. E., and Vasudevan, S. G. (2017). Current Status of Dengue Therapeutics Research and Development. J. Infect. Dis. 215, 596. doi:10.1093/infd/jixw423

Macedo, T., Ribeiro, V., Oliveira, A. P., Pereira, D. M., Fernandes, F., Gomes, N. G. M., et al. (2020). Anti-inflammatory Properties of Xylopia Aethiopica Leaves: Interference with Pro-inflammatory Cytokines in THP-1-Derived Macrophages and Flavonoid Profiling. J. Ethnopharmacol. 148, 112312. doi:10.1016/j.jep.2019.112312

Mascal-Juárez, E., Yam-Puc, J. C., Cedillo-Barrón, L., García-Cordero, J., Ling, A. P. K., Khoo, B. F., Seah, C. H., Foo, K. Y., Cheah, R. K., Chye, S. M., et al. (2021). Management of Thrombocytopenia in Severe Dengue Patients with Ribofuranosyl-3-Ethynyl-[1,2,4]triazole (ETAR), Exhibits Efficacy against a Broad Range of Flaviviruses In Vitro. Antivir. Res. 87, 78–80. doi:10.1016/j.antiviral.2020.04.007

Mendoza, A., Silva, M., and Castro, E. A. (2020). Etnobotánica medicinal de comunidades Nuu Savi de la Montaña de Guerrero. México. Etnobiología 2, 1.
Palaivasamy, S., Vinosh, M., Marudhupandi, T., Rajasekar, P., and Prabhu, N. M. (2017). Isolation of Flavocuin from Sargassum Polyscyphon Brown Algae: Structural Characterization, In Vitro Antioxidant and Anticancer Activity. Int. J. Biol. Macromol. 102, 401–402. doi:10.1016/j.ijbiomac.2017.03.182

Pan American Health Organization (PAHO) (2016). Dengue. United States: Guidelines for patient care in the region of the Americas.

Pan, Y. T., Ghidoni, J., and Elbein, A. D. (1993). The Effects of Castanospermine on the Activity and Synthesis of Intestinal Sucrase. Arch. Biochem. Biophys. 303, 134–144. doi:10.1006/abbi.1993.1264

Pandey, S., Cabot, P. J., Shaw, P. N., and Hewavitharana, A. K. (2016). Anti-Dengue Effects of the green tea Molecule EGCG against Dengue Virus Infection. Arch. Virol. 163, 1649–1655. doi:10.1007/s00705-018-3769-y

Rahman, N. A., HadinurMuliawan, S., Rashid, N. N., Muhamad, M., and Yusof, R. (2006). Studies on Quercus Isusitana Extracts on DENV-2 Replication. Dengue Bull. 1, 1.

Rao, V. B., and Yeturu, K. (2020). Possible Anti-viral Effects of Neem (Azadirachta indica) on Dengue Virus. United States: bioRxiv. doi:10.1101/2017.03.182

Basol, N., Ashraf, A., Waseem, M., Hussain, W., and Mahmood, S. (2019). Computational Exploration of Antiviral Activity of Phytochemicals against NS2B/NS3 Proteases from Dengue Virus. Turkish J. Biochem. 44, 261–277. doi:10.1515/tjb-2018-0002

Bathore, A. P., Paradkar, P. N., Watanabe, S., Tan, K. H., Sung, C., Connolly, J. E., et al. (2011). Celgosivir Treatment Misfolds Dengue Virus NS1 Protein. Produces Cellular Pro-survival Genes and Protects against Lethal challenge Mouse Model. Antivir. Res. 92, 453–460. doi:10.1016/j.antiviral.2011.10.002

Redoni, M., Yacob, S., Rivino, L., Giacobbe, D. R., Luzzati, R., and Di Bella, S. (2020). Dengue: Status of Current and Under-development Vaccines. Rev. Med. Virol. 30, e2101. doi:10.1002/rmv.2101

Rees, C. R., Comini, J. M., Fink, R. C., McMichael, M., Fontaine, K. A., Isen, S., et al. (2008). In Vitro inhibition of Dengue Virus Entry by P-Sulfooxy–Cinnamic Acid and Structurally Related Combinatorial Chemistries. Antivir. Res. 80, 135–142. doi:10.1016/j.antiviral.2008.05.007

Reis, R. S., Valente, L. M., Sampaio, A. L., Siani, A. C., Gandini, M., Azeredo, E. L., et al. (2008). Immunomodulating and Antiviral Activities of Uncaria Tomentosa on Human Monocytes Infected with Dengue Virus-2. Int. Immunopharmacol. 8, 468–476. doi:10.1016/j.intimp.2007.11.010

Rico-Hesse, R. (2010). Dengue Virus Virulence and Transmission Determinants. Curr. Top. Microbiol. Immunol. 338, 45–55. doi:10.1007/978-3-642-02215-9_4

Rigau-Pérez, J. G. (2006). Severe Dengue: the Need for New Case Definitions. Lancet Infect. Dis. 3, 1. doi:10.1016/S1473-3099(06)70345-0

Robinson, M. M., and Zhang, X. (2011). Traditional Medicines. Geneva, Switzerland: global situation, issues and challenges.

Rodrigues, A., Morais, S., and Martins, V. E. (2020). Larvicidal Efficacy of Plant Extracts and Isolated Compounds from Annonaceae and Piperaceae against Aedes aegypti and Aedes albopictus. Asian Pac. J. Trop. Med. 13, 384. doi:10.4103/1939-6452.290583

Rodriguez-Barraquer, L, Solomon, S. S., Kuganathan, P., Srikrishnan, A. K., Vasudevan, C. K., Qbal, S. H., et al. (2015). The Hidden Burden of Dengue and Chikungunya in Chennai, India. PLoS Negl. Trop. Dis. 9, e0003906. doi:10.1371/journal.pntd.0003906

Rojsanga, P., Bunusupa, S., and Sithisarn, P. (2020). Flavones Contents in Extracts from Oroxylum Indicum Seeds and Plant Tissue Cultures. Molecules 25, 1. doi:10.3390/molecules25071545

Rosmalena, R., Ely, A., Dwei, B. E., Fitrihyah, F., Desti, H., Angelina, M., et al. (2019). The Antiviral Effect of Indonesian Medicinal Plant Extracts against Dengue Virus In Vitro and In Silico. Pathogens 8, 1. doi:10.3390/pathogens8020085

Rothan, H. A., Zafarqarnain, M., Ammar, Y. A., Tan, E. C., Rahman, N. A., and Yusof, R. (2014). Screening of Antiviral Activities in Medicinal Plants Extracts against Dengue Virus Using DENV2-NS3 Protease Assay. Trop. Biomed. 31, 286–296.

Saleh, M. S. M., and Kamisah, Y. (2021). Potential Medicinal Plants for the Treatment of Dengue Fever and Severe Acute Respiratory Syndrome-Coronavirus. Biomolecules 11, 42. doi:10.3390/biom11010042

Selles, T. S., da Encarnação Sá-Guimarães, T., De Alvarenga, E. S. L., Guimarães-Ribeiro, V., De Menezes, M. D. F., De Castro-Salles, P. F., et al. (2018). History, Epidemiology and Diagnostics of Dengue in the American and Brazilian Contexts: a Review. Parasites Vectors 11, 1. doi:10.1186/s13371-017-2830-8

Sánchez, I., Gómez-Garibay, F., Taboada, J., and Ruiz, B. H. (2000). Antiviral Effect of Flavonoids on the Dengue Virus. Phytol. Res. 1, 1. doi:10.1002/(SICI)1099-1573(200003)14:2<89::AID-TPR569>3.0.CO;2-C

Saptawati, L., Febrinari, S. R., Yudhoni, R. D., Yono, H., Faza, A. G., Luthfiani, S., et al. (2017). In Vitro study of Eight Indonesian Plants Extracts as Anti Dengue Virus. Health Sci. J. Indonesia 8, 1. doi:10.22435/hjsi.v8i1.6601.12-18
Sharma, K., Guleria, S., and Razdan, V. K. (2020). Green Synthesis of Silver

Shah, P. S., Deoshatwar, A., Karad, S., Mhaske, S., Singh, A., Bachal, R. V., et al.

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Saxena, S. K., Haikerwal, A., Shaske, S., Singh, A., Bachal, R. V., et al.

Sarker, M. M. R., Khan, F., and Mohamed, I. N. (2021). Dengue Fever: Therapeutic

Sharma, N., Mishra, K. P., Chanda, S., Bhardwaj, V., Tanwar, H., Ganju, L., et al.

Sharma, N., and Pareek, A. (2021). Ethnobotanical Properties of Plants Used by the

Taguchi, K., Tano, I., Kaneko, N., Matsumoto, T., and Kobayashi, T. (2020). Plant

Suganthi, A., and Ravi, T. K. (2019). Chemical Methodologies Estimation of Anti-

Simões, L. R., Maciel, G. M., Brandão, G. C., Kroon, E. G., Castilho, R. O., and

Sridhar, S., Ludekhe, A., Langevin, E., Zhu, M., Bonaparte, M., Machabert, T., et al.

Sriram, N., and Paknikar, S. (2014). Papaya Extract to Treat Dengue: A Novel

Taralrico, L. B., Pujol, C. A., Zibetti, R. G., Faria, P. C., Noseda, M. D., Duarte, M. E., et al. (2005). The Antiviral Activity of Sulfated Poly saccharides against Dengue Virus Is Dependent on Virus Serotype and Host Cell. Antivir. Res 66, 103–110. doi:10.1016/j.antiviral.2005.02.001

Tamilvethan, A., and Jayaprakash, A. (2019). Larvicidal Activity of Terminalia Anurika Bark Extracts on Dengue Fever Mosquito Aedes Aegypti. Res. Jour. Pharmac. Technol. 12, 87. doi:10.9794/RJPT2019.00017.9

Tan, Y. P., Xue, Y., Savchenko, A. I., Houston, S. D., Modhiran, N., McMillan, C. L. D., et al. (2019). Basimolos A, B, and C, Highly Oxygenated Pimarane Diterpenes from Basidiocaula Polystackhan. J. Nat. Prod. 82, 2828–2834. doi:10.1021/acs.jnatprod.9b00522

Tarasuk, M., Songtrakphon, P., Chimrra, P., Sratongno, P., Na-Bangchang, K., and Yenchitsomanus, P. T. (2017). Alpha-mangostin Inhibits Both Dengue Virus Production and Cytokine/chemokine Expression. Virus Res. 240, 180–189. doi:10.1016/j.virusres.2017.08.011

Toman, J. (2018). Anti-infective Properties of Epigallocatechin-3-Gallate (EGCG), a Component of green tea. J. Sci. Food Agric. 1, 1. doi:10.4155/MBL.94.3

Trujillo-Correa, A. L., Quintero-Gil, D. C., Díaz-Castillo, F., Quiñones, W., Robledo, S. M., and Martínez-Gutiérrez, M. (2019). In Vitro and In Silico Anti-dengue Activity of Compounds Obtained from Psidium Guajava through Bioprospecting. BMC Complement. Altern. Med. 19, 298. doi:10.1186/s12906-019-2695-1

Umesh Kanna, S., and Krishnakumar, N. (2019). Anti-dengue Medicinal Plants: A Mini Review. J. Pharmacogn. Phytochem. 1, 1. doi:10.3389/fphy.2013.00377–0377-y

UNO, N., and Ross, T. M. (2018). Dengue Virus and the Host Innate Immune Response. Emerg. Microbes Infect. 7, 167. doi:10.1038/s41426-018-0168-0

Vasilakis, N., Fokam, E. B., Hanson, C. T., Weinberg, E., Sall, A. A., Whitehead, S. S., et al. (2008). Genetic and Phenotypic Characterization of Sylastic Dengue Virus Type 2 Strains. Virology 377, 296–307. doi:10.1016/j.virology.2008.04.044

Vaughn, D. W., Green, S., Kalayanarooj, S., Inns, B. L., Nimmanitya, S., Sunatayakorn, S., et al. (2000). Dengue Viremia Titer, Antibody Response Pattern, and Virus Serotype Correlate with Disease Severity. J. Infect. Dis. 181, 2–9. doi:10.1086/315215

Vázquez-Calvo, Á., Jiménez de Oya, N., Martin-Acebes, M. A., Garcia-Moruno, E., and Saiz, J.-C. (2017). Antiviral Properties of the Natural Polyphenols Delphinidin and Epigallocatechin Gallate against the Flaviviruses West Nile Virus, Zika Virus, and Dengue Virus. Front. Microbiol. 8, 1. doi:10.3389/fmicb.2017.01314

Waggoner, J. J., Greesh, L., Vargas, M. J., Ballesteros, G., Tellez, Y., Sada, K. J., et al. (2016). Viremia and Clinical Presentation in Nicaraguan Patients Infected with Zika Virus, Chikungunya Virus, and Dengue Virus. Clin. Infect. Dis. 63, 1584–1590. doi:10.1093/cid/ciw589

Wang, M. Y., Ma, Z. L., He, C. L., and Yuan, X. Y. (2020). The Antioxidant Activities of Flavonoids in Jerusalem Artichoke (Helianthus Tuberosus L.) Leaves and Their Quantitative Analysis. Nat. Prod. Res. 1, 1, 5. doi:10.1080/17446761.2019.1839464

Warsinah, W., Baroroh, H. N., and Harwoko, H. (2020). Phytochemical Analysis and Antioxidant Activity of Brotowali (Tinospora Crispa L. Mier) Stem. Molecuk 15, 73. doi:10.20884/j.molecuk.2020.15.2.533

Webers, D., Tyl, C. E., and Bunzel, M. (2014). Novel Arabinin and Galactan Oligosaccharides from Dicorytenoid Plants. Front. Chem. 2, 100. doi:10.3389/fchem.2014.00100

Weissenböck, H., Hubálek, Z., Bakonyi, T., and Nowotny, N. (2010). Zoonotic Transmission of the Dengue Virus. Vet. Microbiol. 140, 271–280. doi:10.1016/j.vetmic.2009.08.025

Whitby, K., Pierson, T. C., Geiss, B., Lane, K., Engle, M., Zhou, Y., et al. (2005). The Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. Am. J. Trop. Med. Hyg. 72, 79–86. doi:10.4269/ajtmh.2005.72.079

Whitby, K., Persson, T. C., Geiss, B., Lane, K., Engle, M., Zhou, Y., et al. (2005). Casers supervised, a Potent Inhibitor of Dengue Virus Infection In Vitro and In Vivo. J. Virol. 79, 8699–8706. doi:10.1128/jvi.79.14.8699-8706.2005

World Health Organization (2021a). Dengue and Severe Dengue. Available at: https://www.who.int/news-room/fact-sheets/dengue-and-severe-denguee

World Health Organization (2021b). Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: WHO.
Dhiman et al.

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World Health Organization (2021b). Dengue Situation Updates 2021. WHO. Available at: https://apps.who.int/iris/bitstream/handle/10665/341494/Dengue-20210520.pdf (Accessed May 30, 2021).

Xie, Q., Zhang, B., Yu, J., Wu, Q., Yang, F., Cao, H., et al. (2017). Structure and Function of the Non-structural Protein of Dengue Virus and its Applications in Antiviral Therapy. Curr. Top. Med. Chem. 17, 371–380. doi:10.2174/156802616666160829155327

Xu, G., Dou, J., Zhang, L., Guo, Q., and Zhou, C. (2010). Inhibitory Effects of Baicalein on the Influenza Virus In Vivo Is Determined by Baicalin in the Serum. Biol. Pharm. Bull. 33, 238–243. doi:10.1248/bpb.33.238

Yam-Puc, J. C., Cedillo-Barrón, L., Aguilar-Medina, E. M., Ramos-Payán, R., Escobar-Gutiérrez, A., and Flores-Romo, L. (2016). The Cellular Bases of Antibody Responses during Dengue Virus Infection. Front. Immunol. 7, 1. doi:10.3389/fimmu.2016.00218

Yang, J.-Y., and Lee, H.-S. (2012). Evaluation of Antioxidant and Antibacterial Activities of Morin Isolated from mulberry Fruits (Morus alba L.). J. Korean Soc. Appl. Biol. Chem. 55, 485–489. doi:10.1007/s13765-012-2110-9

Yao, X., Ling, Y., Guo, S., Wu, W., He, S., Zhang, Q., et al. (2018). Tatanan A from the Acorus calamus L. Root Inhibited Dengue Virus Proliferation and Infections. Phytomedicine 42, 258–267. doi:10.1016/j.phymed.2018.03.018

Yogarajalakshmi, P., Venugopal Poonguzhali, T., Ganesan, R., Karthi, S., Senthil-Nathan, S., Krunmuang, P., et al. (2020). Toxicological Screening of marine Red Algae Champia Parvula (C. Agardh) against the Dengue Mosquito Vector Aedes aegypti (Linn.) and its Non-toxicity against Three Beneficial Aquatic Predators. Aquat. Toxicol. 222, 105474. doi:10.1016/j.aquatox.2020.105474

Yu, J. S., Wu, Y. H., Tseng, C. K., Lin, C. K., Hsu, Y. C., Chen, Y. H., et al. (2017). Schisandrin A Inhibits Dengue Viral Replication via Upregulating Antiviral Interferon Responses through STAT Signaling Pathway. Sci. Rep. 7, 45171. doi:10.1038/srep45171

Zandi, K., Teoh, B. T., Sam, S. S., Wong, P. F., Mustafa, M. R., and AbuBakar, S. (2011). Antiviral Activity of Four Types of Bioflavonoid against Dengue Virus Type-2. Virol. J. 8, 560. doi:10.1186/1743-422X-8-560

Zandi, K., Teoh, B. T., Sam, S. S., Wong, P. F., Mustafa, M. R., and AbuBakar, S. (2012). Novel Antiviral Activity of Baicalein against Dengue Virus. BMC Complement. Altern. Med. 12, 214. doi:10.1186/1472-6882-12-214

Zeng, Z., Zhan, J., Chen, L., Chen, H., and Cheng, S. (2021). Global, Regional, and National Dengue burden from 1990 to 2017: A Systematic Analysis Based on the Global burden of Disease Study 2017. EClinicalMedicine 32, 100712. doi:10.1016/j.eclinm.2020.100712

Zhang, J. X., Braakman, I., Matlack, K. E., and Helenius, A. (1997). Quality Control in the Secretory Pathway: the Role of Calreticulin, Calnexin and BiP in the Retention of Glycoproteins with C-Terminal Truncations. Mol. Biol. Cell 8, 1943–1954. doi:10.1091/mbc.8.10.1943

Zhang, Y., Yu, X., Wang, M., Ding, Y., Guo, H., Liu, J., et al. (2021). Hyperoside from Z. Bungeanum Leaves Restores Insulin Secretion and Mitochondrial Function by Regulating Pancreatic Cellular Redox Status in Diabetic Mice. Free Radic. Biol. Med. 162, 412–422. doi:10.1016/j.freeradbiomed.2020.10.320

Zhao, Q., Chen, X. Y., and Martin, C. (2016). Scutellaria Baicalensis, the golden Herb from the Garden of Chinese Medicinal Plants. Sci. Bull. (Beijing) 61, 1391–1398. doi:10.1007/s11434-016-1136-5

Zhou, X., Yang, Z. Y., and Tang, R. C. (2016). Bioactive and UV Protective Silk Materials Containing Baicalin - the Multifunctional Plant Extract from Scutellaria Baicalensis Georg. Mater. Sci. Eng. C Mater. Biol. Appl. 67, 336–344. doi:10.1016/j.msec.2016.05.063

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