REVIEW ARTICLE
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Potential of medicinal plants to treat dengue

Dulanjalee Neelawala, Sanjaya Rajapakse and Wikum Widuranga Kumbukgolla

Department of Biochemistry, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka, Anuradhapura 50000, Sri Lanka.
Corresponding author: Dulanjalee Neelawala, e-mail: dulanjaleen1@gmail.com
Co-authors: SR: sanjayakiri@gmail.com, WWK: kumbukgolla@yahoo.com
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Abstract

Dengue is a major public health challenge worldwide, particularly in tropical areas. Nearly 390 million infections and 22,000 deaths occur every year. At present, there are no specific therapeutics available to treat dengue; however, possible treatment procedures are explained in the traditional medical systems (TMSs), such as Sri Lankan TMS, Indian Ayurvedic, Unani, and Siddha TMS. In these TMSs, medicinal plants have been used in several ways against dengue, such as virocides, larvicides, and mosquito repellents. Therefore, medicinal plants inherit biologically active compounds/lead compounds that are yet to be identified chemically and physiologically. Herein, we discuss the possible applications of crude plant extracts and isolated phytochemicals from medicinal plants such as quercetin, sulfated galactomannans, flavonoids, and glabranine in controlling dengue. Moreover, medicinal plant-based therapeutics can be safer, cost-effective, and non-toxic. Therefore, this paper reviews the medicinal plants that are used in TMSs to manage dengue, the phytochemicals they contain, and mode of action of these phytochemicals such as virocides, larvicides, and mosquito repellents.

Keywords: dengue, *in silico*, larvicides, phytochemicals, virocides.

Introduction

Dengue is a life-threatening arboviral disease, with nearly 390 million cases annually and high mortality worldwide [1]. According to the World Health Organization records, around 22,000 deaths occur due to dengue annually, especially in pediatric patients [2]. The first evidence of dengue was in a Chinese medical encyclopedia of 265–420 AD, in which the dengue has been denoted as “poison water combined with flying insects.” Subsequently, the most famous dengue fever outbreaks occurred in 1635 and 1699 in the Caribbean region. In South Asia, the first dengue epidemic in Sri Lanka occurred in the period from 1965 to 1968, causing 51 dengue hemorrhagic fever cases and 15 deaths, while the largest epidemic occurred in 2017, causing 186,101 cases [3]. In India, until 2015, Delhi has experienced eight dengue outbreaks since 1967, with the last epidemic reported in 2006 [4].

The usage of medicinal plants in treating infections started in the prehistoric period. The ancient Unani manuscripts, Egyptian papyrus, and Chinese writings provide written evidence of this practice. Furthermore, Unani Hakims, Indian Vaiydas, and Mediterranean cultures have been using medicinal plants for 4000 years. The traditional medical systems (TMSs) in Asia utilize medicinal plants to manage dengue. Medicinal plants contain lead compounds/phytochemicals that have the potential to act as virocides and larvicides against the dengue virus and mosquito repellents against the dengue vector mosquitoes. Moreover, with advancements in modern technology, the usage of medicinal plants is increasing as a constituent of *in silico* drug development and anti-dengue vaccine production.

The medicinal plants used in different TMSs as virocides, larvicides, and mosquito repellents, mode of action of phytochemicals isolated from these medicinal plants, and use of plant-based lead compounds in *in silico* drug development and anti-dengue vaccine production are discussed in this review.

Medicinal Plants used in TMSs to Treat Dengue

The TMSs that use medicinal plants for anti-dengue treatment are especially popular in Asian countries such as India, Malaysia, China, Thailand, and Sri Lanka. The usage of medicinal plant preparations to treat dengue may have several advantages over commercial anti-dengue, such as safety, cost-effectiveness, and non-toxicity [5]. Anti-dengue properties of some medicinal plants used in different TMs are described in Table-1 [6-22].

Virocidal and Immunomodulatory Activities of Medicinal Plants

The medicinal plant extracts contain different phytochemicals that can be used to treat dengue. These extracts or molecules can act as virocides and immunomodulators.

Bioactive phytochemicals in different medicinal plants

Medicinal plant resources provide various phytochemicals with different anti-dengue virocidal

Table-1: Anti-dengue properties of some medicinal plants used in different TMSs.

TMS	Medicinal plant	Type of extract	Anti-dengue activity	References
Sri Lankan TMS	*Carica papaya*	Aqueous extract	Optimization of clotting time and elevation of the platelet count	[6]
	Euphorbia hirta	Petroleum ether extract	Antipyretic activity, elevation of the platelet count, and prevention of bleeding	[7]
	Ocimum sanctum	Methanol extract	Larvicidal activity	[8]
Indian Ayurvedic	*Tinospora cordifolia*	Leaf extract	Antipyretic and anti-inflammatory properties	[9]
	Ocimum tenuiflorum	Leaf extract	Anti-inflammatory properties	[10]
	Zingiber officinalis	Root extract	Larvicidal activity	[11]
	Carica papaya	Aqueous extract	Optimization of clotting time and elevation of the platelet count	[6]
Siddha medicine	*Andrographis paniculata*	Methanol extracts	Virocidal activity against the dengue virus DENV-1	[12]
	Vetiveria zizanioides	Ethyl 4-(4-methylphenyl) -4-pentenoate extract	Inhibition of dengue NS2B-NS3 protease and prevention of the viral assembly	[13]
	Plectranthus vettiveroides	Root extract	Antipyretic properties	[14]
	Santalum album	Essential oils	Anti-dengue virocidal activity	[15]
	Cyperus rotundus	Essential oils	Ovicidal and larvicidal activity	[16]
	Zingiber officinale	Root extract	Larvicidal activity	[11]
	Piper nigrum	Fruit ethanolic extract	Larvicidal activity	[17]
Unani medicine	*Carica papaya*	Aqueous extract	Optimization of clotting time and elevation of the platelet count	[6]
	Euphorbia hirta	Petroleum ether extract	Antipyretic activity, elevation of the platelet count, and prevention of bleeding	[7]
Not specified	*Alternanthera philoxeroides*	Petroleum ether extract	Anti-dengue virocidal activity	[18]
Not specified	*Hippophae rhamnoides*	Ethanol and water extracts	Virocidal activity against the dengue virus DENV-2	[19]
Not specified	*Cladogynos orientalis, Rhizophora apiculata, Flagellaria indica, Houttuynia cordata*	Dichloromethane and ethanol extracts	Virocidal activity against the dengue virus DENV-2	[20]
Not specified	*Alternanthera philoxeroides*	Petroleum ether extract	Anti-dengue virocidal activity	[18]
Not specified	*Hypericum mysorense*	Extracts from different plant parts	Anti-dengue virocidal activity	[21]
Not specified	*Usnea complanta*	Extracts from different plant parts	Anti-dengue virocidal activity	[21]
Not specified	*Hypericum hookerianum*	Extracts from different plant parts	Anti-dengue virocidal activity	[21]
Not specified	*Quercus lusitanica*	Methanolic seed extract	Virocidal activity against the dengue virus DENV-2	[22]

TMSs=Traditional medical systems

mechanisms such as inhibition of virus replication in the host, prevention of virus adsorption in the host cells, and prevention of the entry of the virus in the host cells. Different phytochemicals contain different molecular compounds such as alkaloids and carbohydrates. Alkaloid phytochemicals can inhibit replication of the dengue virus [23], while carbohydrate phytochemicals including glycosphingolipids, sulfated glycosaminoglycans, and lectins prevent cell entry of the virus [24].

In a study in India, in 2016, Mishra found three main phytochemicals that possess anti-dengue properties: Flavanones, dicoumarols, and terpins [25]. The flavanones belong to the class of flavonoids. Frabasile *et al*. revealed that citrus flavonoid naringenin can prevent infection of all four dengue virus serotypes in Huh7.5 cells [26]. Table-2 summarizes the different phytochemicals in medicinal plants and their modes of action [5,27-34].

Mosquito Repellent and Larvicidal Activity of Medicinal Plants

Aedes aegypti is the primary vector mosquito of the dengue virus, while *Aedes albopictus* acts as a secondary vector in cooler climates [35]. Some medicinal plants contain aromatic essential oils and compounds that can act as mosquito repellents and larvicides. These essential oils and compounds are usually produced by plants for protection against microorganisms and other harmful organisms. Therefore, studies have been performed to validate the use of these compounds as dengue vector mosquito repellents and larvicides.

In Argentina, medicinal plants are widely used as mosquito repellents and larvicides. In a study in Argentina, Gillij *et al*. assayed the mosquito repellent activity of several medicinal plants and found that of 12 aromatic plants, three (*Baccharis spartioides*, *Rosmarinus officinalis*, and *Aloysia citrodora*) were

Table-2: Mode of action of phytochemicals extracted from medicinal plants.

Medicinal plant	Phytochemicals	Mode of action	References
Psidium guava	Quercetin	Elevation of the platelet count and prevention of bleeding and mRNA formation of the virus DENV-2	[5]
Mimosa scabrella and *Leucaena leucocephala*	Sulfated galactomannans	Anti-dengue virocidal activity	[27]
Tephrosia madrensis, Tephrosia viridiflora, and *Tephrosia crassifolia*	Flavonoids, glabranine, and 7-O-methyl-glabranine	Anti-dengue virocidal activity	[28]
Ocimum sanctum	Eugenol and ursolic acid	Anti-dengue viral and antipyretic activities	[29]
Azadirachta indica	Azadirachtin	Inhibition of the replication of DENV-2	[30]
Red seaweed *Gymnogongrus torulosus*	D-galactose	Optimum dengue inhibitory activity in the phase of virus adsorption in the host cells by interfering between the virus particles and cell receptors	[31]
Meristiella gelidium	Carrageenan	Anti-dengue virocidal activity	[32]
Marine algae *Cladosiphon okamuranus*	Fucoidan, a sulfated polysaccharide	Virocidal activity against the virus DENV-2	[33]
Cyclohexenyl chalcone	4-hydroxypanduratin A and panduratin	Higher inhibitory activities against DENV-2 and NS3 protease	[34]

effective against *Aedes* [36]. Several other studies revealed the ability of medicinal plants to act as mosquito repellents and larvicides. *Ocimum sanctum,* commonly known as the holy basil, contains phytochemicals such as eugenol, caryophyllene, alpha-farnesene, and farnesyl acetone that are effective against dengue vector mosquitoes [37]. Eugenol belongs to the class of allylbenzene and contains an allyl chain substituted with guaiacol, while caryophyllene is a natural bicyclic sesquiterpene that is a constituent of many essential oils. Govindarajan *et al*. showed that eugenol and caryophyllene have acute toxicity against the third instar larvae of *A. albopictus* [38]. *Eclipta prostrata* and *Annona squamosa* have better larvicidal activities [39].

The leaf and stem/bark extracts of *Jatropha curcas*, *Citrus grandis*, and *Tinospora rumphii* are effective against larvicidal activities. Alkaloids, flavonoids, and steroids in *J. curcas* and alkaloids, saponins, tannins, flavonoids, and steroids in *C. grandis* and *T. rumphii* are toxic to the third instar larvae of *A. aegypti* [40].

Medicinal Plants as a Constituent of *In Silico* Drug Development

There are many sources of information on medicinal plants. Therefore, it is difficult for plant-based researchers to identify the potential medicinal plants to develop novel anti-dengue drugs. However, multi-target drug designing and bioinformatic approaches, such as computational methods (*in silico* methods), are becoming popular [41,42].

Some *in silico* methods used in drug development processes are molecular docking, structure-activity relationship (SAR), quantitative SAR (QSAR) models, and pharmacophore techniques. In these methods, the drug target molecules are identified by employing bioinformatics tools. Phytochemicals are matched with their viral targets to find interactions between the drug and the disease-producing agents and reveal the treatment. The atomic-level structural information can be obtained using the docking, SAR, and QSAR methods.

In the molecular docking method, phytochemicals are matched with the protein targets of the dengue virus [43]. The most effective targets of the dengue virus are NS5 RNA-dependent RNA polymerase, NS5 methyltransferase, NS3 protease, NS3 helicase, and envelope glycoprotein [44]. NS4B in DENV-1, DENV-2, and DENV-4 has binding sites for phytochemicals such as epicatechin, catechin, eupatoretin, cianidanol, laurifolin, glabranin, and DL-catechinare [45]. NS2b/NS3 protease of DENV-1, DENV-2, and DENV-3 is good binding sites for antiviral ligands [46].

Suganya and Mahendran, in 2016, performed a study to design *in silico* actives against the dengue virus using new plant actives. In that study, 75 medicinal plant actives were subjected to QSAR and molecular docking procedures. Eleven inhibitory compounds against NS5 and eight inhibitory compounds against NS3 were identified using the QSAR method, while 13 inhibitory compounds against NS5 and three inhibitory compounds against NS3 were identified using the molecular docking method [47].

The multitarget drug designing shows better results with effective drug actives that can act simultaneously with the targets [48]. The least binding energy in the molecular docking analysis shows stronger docking between the ligands and viral targets [47]. NS3 and NS5 act as protective, non-structural, multifunctional proteins, and creating various enzymatic activities, which allow the development of drugs acting on all four serotypes of DENV [49]. Qaddir *et al*. [50] found novel DENV inhibitors such as derrisin, mundulinol, and isopomiferin from the medicinal plant *Silybum marianum* and narlumicine and oxysanguinarine from *Fumaria indica* using the absorption, distribution, metabolism, excretion, and toxicity analysis and docking method. *Sonneratia alba* can synthesize silver nanoparticles, which can be used to produce environment-friendly nanoformulations, which have shown better activity against DENV and dengue vectors [51].

Alkaloid, rohitukine, has exhibited better interaction against NS5 dengue antigen [52].

Usage of Medicinal Plants for Anti-Dengue Vaccine Production

The development of anti-dengue vaccine started with clinical trials in 1970 [53]. However, there are no licensed anti-dengue vaccines available commercially [54]. An effective and safe anti-dengue vaccine with long-term action is required due to the rapid spread of dengue in the tropics [55]. However, there are several impediments that make it hard to develop a vaccine that is effective against all four serotypes. Some of them are the vast epidemiological distribution of the four DENV serotypes, complex immunoprotective and/or immunopathogenic responses following natural infection or vaccination, and a lack of validated animal models [56]. The complex immunopathogenic responses of dengue may have been caused by antibody-dependent enhancement [57-59], and cytokine storm resulted from the activation of cell-mediated immunity [60], complement activation [61], and development of autoimmunity. Furthermore, manufactured vaccines occasionally show enhanced pathogenicity instead of protection [62].

Medicinal plants would provide a better option to overcome these impediments because plant-derived vaccine production is cheaper, efficient and requires easy techniques compared to those used in animal-based vaccine production. [63]. Another advantage of plant-based vaccine production is that the processes involved in vaccine production, such as fermentation, purification, cold storage, sterile delivery, and transportation, are inexpensive [64].

Dengue antigen protein-encoding genes can be incorporated in the genetic material of the plant tissues. The particle bombardment gene delivery method and chloroplast transformation through biolistic particle delivery system are popular gene delivery techniques for good quality plant-derived vaccine production. Furthermore, transformation through genetically modified plant virus and *Agrobacterium*-mediated gene transferring techniques are currently used to produce vaccines. Recent advances in plant-derived vaccine production are biolistics, electroporation, agroinfiltration, sonication, and polyethylene glycol treatment [65].

Conclusion

Many medicinal plant extracts and ingredient compounds have shown promising inhibitory activity against dengue based on the aforementioned data. The structure-activity relationship of these active compounds can be determined with the *in silico* approach. Moreover, the *in silico* modeling of drugs can be conducted using the lead templates of active plant-based compounds. Development of a vaccine against dengue is a challenge, and several previous approaches have failed. However, plant-based vaccines could be less toxic and more cost-effective. Therefore, novel plant-based drug development initiatives are important in controlling dengue.

Authors' Contributions

WWK stipulated the hypothesis. DN and SR conducted a literature survey. The manuscript was written by WWK and DN. All authors read and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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