



The Anti-Viral Potential of Medicinal Plants and Herbal Formulations for the Treatment of Dengue Fever

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Abstract

From the existence of human civilization, medicinal plants and herbs have been used for various purposes all over the world. Some of the plants with medicinal activities have played crucial roles in the management of the health care system. Nowadays, dengue fever has become a major concern for governments and the world health organization due to its mortality and morbidity in tropical and sub-tropic regions. The need for therapeutic plants for the treatment of Dengue fever is more urgent compared to the past. In past, medicinal plants have been used due to their therapeutic activity for the treatment of vector-borne diseases such as Malaria. Demand for natural medicine is increasing due to its best efficacy and safety. Additionally, natural medicines are also cost-effective as compared to synthetic medicines. This review aims to describe the medicinal plants distributed all over the world with the best therapeutic potential for the treatment of this ailment. Furthermore, pathogenesis, characteristics of a disease, and prevalence are also described in this review. It has been demonstrated from recent and current studies that natural medicine and plants having medicinal activities are considered safe and better treatments for all diseases.

Keywords: Dengue; Pathogenesis; Medicinal Plants; Herbal Formulation

Introduction

Dengue fever also known as backbone fever is a viral disease caused by the dengue virus (DENV). There are four varieties of dengue viruses. Dengue Virus is a member of the Flaviviridae family, which also includes yellow fever, West Nile disease, and Japanese encephalitis. The Aedes mosquito bite causes dengue disease. Dengue virus was isolated for the first time by Hotta in 1942 from Japan [1]. In recent decades, the prevalence of the dengue virus has grown and it has spread to more than a hundred countries. It has been demonstrated from the recent surveys that about 50 million dengue cases have been reported and 2 million people live in dengue-

endemic countries [2]. In Thailand and the Philippines, the first dengue hemorrhagic fever was reported in 1950 [3]. This virus is composed of three different types of proteins named Enveloped protein, membrane protein, and non-structural protein subsequently. Enveloped protein is found on the viral surface, membrane protein is considered highly important for the formulation of viral particles and non-structural protein participates in viral replication and has seven subtypes [4-6]. It is characterized by fever, arthralgia, myalgia, and headache. Fever can last 5-7 days, but extreme physical and emotional exhaustion is accompanied by the disease [7]. In certain cases, respiratory and gastrointestinal signs are also there in dengue fever. The incubation period

for this disease is 3-8 days.

In the past medicinal plants have been used for the treatment of various ailments. Demand has been increasing for substances with antiviral potential to treat viral infections. Dengue fever has become resistant to some anti-viral and there is an increased need to treat this fever with natural phytochemical constituents possessing strong anti-dengue potential. Plant-based medicines are considered safe, better, cheaper, and non-toxic as compared to synthetic drugs. To date, 31 different phytochemicals have been found to have anti-dengue activity. Some of these chemicals have been tested scientifically and can be used safely against dengue fever. In this article, I have described the anti-viral and anti-dengue activity of some medicinal plants which help us to treat dengue fever.

Medicinal plants Possessing Anti-dengue activity

Due to the non-toxic effect, the use of natural plants and plant-based medicine has been increasing to treat various ailments. In the following section, I have enlisted the medicinal plants from various species that have been reported for their anti-dengue activity. Additionally, some isolated compounds and their role in medicine have been described.

Alternantheraphiloxeroides

This plant is commonly known as Alligator weed and belongs to the *Amaranthaceae* family. It is cultivated in Australia but has its origin in South America. Its potential against dengue fever was analyzed by in vivo studies. It has been demonstrated that it has strong potential against the dengue virus [8].

Andrographis Paniculate

This annual herb belongs to the *Acanthaceae* family. This erect herb is native to Sri Lanka and India. It is widely cultivated in Southeastern Asia and Malaysia. It is bitter. Methanolic extract of this herb was investigated by in vitro studies. It was demonstrated by that study that the methanolic extract of this plant has a strong anti-viral potential [9].

Azadirachta Indica

This fast-growing herb grows in tropical and sub-tropical regions and is native to India and Pakistan. It belongs to the *Meliaceae* family. The final height of this tree ranges from 15-20m. Anti-viral activity of *Azadirachta indica* leaves was evaluated by both in vivo and in vitro studies. It was shown by the studies that possess a strong inhibitory effect against

the virus and is non-toxic [10].

Boesenbergia Rotunda

This herb is used for both culinary and medicinal purposes and belongs to the *Zingiberaceae* family. It is commonly known as China ginger. It is cultivated throughout Southeast Asia. The extract of this herb was investigated against dengue virus protease. It was demonstrated by analyzing the result of studies that it has a strong anti-viral potential [11].

Carica Papaya

It is an unbranched tree belonging to the *Caricaceae* family. This fast-growing tree is widely cultivated in Mexico. This tree has its origin in Central America. The leaves of these plants have been used in traditional medicine for the treatment of dengue fever. The aqueous extract of the leaves of this tree was investigated to test the anti-viral activity. The results of the study indicated that ethanolic extract from the leaves of this plant exhibited strong potential against dengue fever and have strong anti-viral activity [12,13].

Cladosiphon Okamuranus

This brown seaweed belongs to the *Chordariaceae* family and is found naturally in Japan. An important phytochemical of this plant known as sulfated *polysaccharide fucoïdan* was found to exhibit strong anti-viral potential against dengue fever.

Castanospermum Austral

Castanospermum austral is commonly known as black beans or Moreton Bay chestnut. This flowering plant belongs to the *Fabaceae* family. This evergreen large plant is native to Queensland in Australia. The anti-viral activity of the important phytochemical constituent "*castanospermine*" belonging to this plant was investigated by in vitro assay. Whitby, et al. [14] demonstrated that according to studies, *Castanospermine* may impair the folding of some viral proteins by blocking the removal of the terminal glucose residue on N-linked glycans in dengue virus may impair the folding of some viral proteins by blocking the removal of the terminal glucose residue on N-linked glycans in dengue virus, according to studies [14].

Cissampelos Pareira

Cissampelospareira is commonly known as velvetleaf. It is a flowering plant belonging to the *Menispermaceae* family. The anti-dengue efficacy of an extract of *Cissampelospareira* aerial parts was patented by Bhatnagar and colleagues

[9]. Their research focused on the anti-dengue action of *Cissampelospareira* extracts, as well as medicinal formulations containing *Cissampelospareira* extracts. In a traditional experiment, methanolic extracts of *Cissampelospareira* showed antiviral efficacy against all strains of dengue virus, with PRNT50 values ranging from 1.2-11.1 g/mL.

Euphorbia Hirta

Euphorbia hirta commonly known as the Asthma plant is a member of the *Euphorbiaceae* family. In ethanolic-producing thrombocytopenic rat models, Apostol, et al. investigated the platelet-raising activity of *Euphorbia hirta* plant decoction. After 7 days of dosing, 100mg/kg of the lyophilized decoction of *E. hirta* improved platelet count in ethanol-induced thrombocytopenia. The anti-

thrombocytopenic action was maintained after repeated administration of the plant decoction. The active element in *E. hirta*, lowering polyphenols, is thought to be responsible for increasing platelet count.

Gastrodiaelata

Gastrodiaelata is a well-known and significant Chinese medicinal herb in the *Orchidaceae* family. Qui H [15] and Tong [16] et al. extracted *Dglucans* from *Gastrodiaelata* and produced sulfated derivatives, which were tested for anti-dengue activity against the dengue 2 viruses. With an EC (50) value of 0.68+/-0.17 micron/mL, these sulfated D-glucan derivatives substantially inhibited dengue 2 virus infections, primarily interfering with virus adsorption, at an early stage of the virus cycle [15].

Medicinal Plant	Family	Chemical constituent	Anti- dengue Activity
<i>Alternantheraphiloxeroides</i>	<i>Amaranthaceae</i>	petroleum ether extract	Has Strong Anti-Viral Activity
<i>Andrographis paniculate</i>	<i>Acanthaceae</i>	Methanolic Extract	antiviral inhibitory effect on DENV-1 by an antiviral assay based on cytopathic effects.
<i>Azadirachta indica</i>	<i>Meliaceae</i>	Aqueous Extract	inhibit the replication of DENV-2
<i>Boesenbergia rotunda</i>	<i>Zingiberaceae</i>	Compound Extract	Has good competitive inhibitory activities towards DENV-2 NS3 protease
<i>Carica papaya</i>	<i>Caricaceae</i>	Aqueous Extract of leaves	It possesses potential activity against DF by increasing the platelet (PLT) count, white blood cells (WBC) and neutrophils (NEUT)
<i>Cladosiphonokamuranus</i>	<i>Chordariaceae</i>	Fucoidan	Has Inhibitory Effect against dengue virus
<i>Castanospermum austral</i>	<i>Fabaceae</i>	Castanospermine	inhibited dengue virus infection at the level of secretion and infectivity of viral particles
<i>Cissampelospareira</i>	<i>Menispermaceae</i>	Alcoholic Extract	Has inhibitory Effect on the replication of dengue virus
<i>Euphorbia hirta</i>	<i>Euphorbiaceae</i>	Leaves extract	Has potential anti-viral activity & increases platelets count
<i>Gastrodiaelata</i>	<i>Orchidaceae</i>	Polysaccharides	It possesses potential activity against DF by increasing the platelet (PLT) count, white blood cells (WBC) and neutrophils (NEUT)
<i>Hippophaerhamnoides</i>	<i>Elaeagnaceae</i>	Leaves extract	inhibit the replication of DENV-2
<i>Lippacitriodora</i>	<i>Verbenaceae</i>	Essential oil	It has inhibitory effect on dengue virus serotype replication
<i>Mimosa scabrella</i>	<i>Fabaceae</i>	Galactomannans extracted from seeds	Has Inhibitory Effect against dengue virus
<i>Phyllanthusurinaria</i>	<i>Phyllanthaceae</i>	Leaves extract	It has inhibitory effect on dengue virus serotype replication
<i>Quercuslusitanica</i>	<i>Fagaceae</i>	Methanolic Extract	inhibit the replication of DENV-2
<i>Rhizophoraapiculata</i>	<i>Rhizophoraceae</i>	Ethanolic Extract	inhibit the replication of DENV-2
<i>Zostera marina</i>	<i>Zosteraceae</i>	Methanolic Extract	Has Inhibitory Effect against dengue virus

Hippophae Rhamnoides

Hippophaerhamnoides, sometimes known as saw buckthorn, is a spiny deciduous shrub in the *Elaeagnaceae* family. Mounika Jain, et al. [17] studied the anti-dengue activity of *Hippophaerhamnoides* [17]. The anti-dengue activity of this plant's leaf extract was tested in Dengue type 2 virus-infected blood-derived human macrophages as the primary targets. This study found that this extract could maintain cell viability in dengue-infected cells while also increasing TNF- and IFN- levels.

Lippia Citriodora

Lippacitriodora, popularly known as Lemon verbena, is a perennial shrub in the *Verbenaceae* family. Before cell adsorption, the dengue virus was treated with essential oil for 2 hours at 37 degrees Celsius, and studies were done to see if untreated virus reproduction was inhibited in the presence of oil. Treatment of the virus before adsorption on the cell resulted in plaque reduction for all four dengue serotypes. *L. alba* oil had an IC50 of 0.4-32.6 microns/mL, while *L. citriodora* oil had an IC50 of 1.9-33.7 micron/mL. [16].

Mimosa Scabrella

Mimosa scabrella is a multifunctional tree of the *Fabaceae* family. Two galactomannans were obtained by Wollinger, et al. [18] from *Mimosa scabrella* and *Leucaenaleucocephala* seeds. In vitro antiviral properties of these two active compounds were investigated against yellow fever and dengue viruses. At concentrations of 347 and 37 mg-1, in vitro tests in C6/36 cell culture assays revealed inhibitory action against the dengue virus [18].

Phyllanthus Urinaria

Phyllanthusurinaria, often known as chamber bitter or gripe weed, is a member of the *Phyllanthaceae* family. Sau Har Lee, et al. [19] investigated the anti-dengue effect of *Phyllanthusamarus*, *Purinaria*, *Pniruri*, and *P.wastonii* aqueous and methanolic extracts. These species had the highest inhibitory efficacy against DENV2, with more than 90% viral decrease in simultaneous treatment at 250.0 g/mL and 15.63 g/mL, respectively [19].

Quercus Lusitanica

Quercuslusitanica, sometimes known as *Quercusinfectora*, is a member of the *Fagaceae* family. In vitro inhibitory action of *Quercuslusitanica* seed extract was demonstrated by Sylvia, et al. [1]. After treating infected cells with seed extract, the expression of the NS1 protein was shown to be reduced.

Sylvia et al. examined the same plant extract for antidengue activity in 2008. *Quercuslusitanica* seed extract suppressed Dengue type 2 viruses at concentrations of 0.032 to 0.25 mg/m in this investigation.

Rhizophora Apiculata

Rhizophora species can be found in most tropical coastal areas of the western Pacific and eastern Africa. *Rhizophoramucronata*, *Rhizophorastylosa*, and *Rhizophoraapiculata* are the three species that make up this genus. India, Australia, Indonesia, Malaysia, and other countries have *R. apiculata*. T. Ramanathan, et al. investigated the larvicidal effectiveness of *Rhizophoraapicuata* petroleum ether extracts against the *Aedes aegypti* mosquito. With an LC50 of 25.7g/L, the petroleum ether extract of *R. apiculata* is the most effective. In addition, the extract has synergistic larvicidal efficacy with pyrethrum.

Zostera Marina

Zostera marina is a member of the *Zosteraceae* family. Eelgrass is a type of aquatic plant that is endemic to North America and Eurasia. Anti-dengue viral activity has been discovered in a substance derived from the temperate marine eelgrass *Zostera marina* [20].

Conclusion

This review updates and summarizes the several medicinal plants that have been reported to have strong potential against the dengue virus. Many isolated compounds and medicinal plants have shown great potential in clinical trials. The anti-viral and anti-dengue activity of various medicinal plants has been highlighted in various researches. However, some of the medicinal plants have not been explored fully. The formation of new anti-dengue medicine from phytochemical constituents and the isolated compound is highly important to finding more effective drugs for the treatment of resistant dengue fever. For this purpose, the medicinal plants possessing anti-dengue potential should explore and go through additional in vivo, in

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