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BOTANICAL ORIGIN, CONSTITUENTS & USES OF MEDICINAL PLANTS USED TO CURE DENGUE FEVER

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Purpose: The aim of this study is to determine various possible plants that are having anti-dengue activity which can be further employed to determine the active biological ingredient responsible for this activity and can be extracted for its practical use as there is no specific treatment for dengue but dengue fever is spreading at an alarming rate worldwide affecting millions of people every year and is complicated by Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).
Method: A systematic review of the available literature was conducted for the papers published up to year 2015. This article reviews various plants having anti-dengue activity along with their biological and geographical origin.
Conclusion: Constituents derived from medicinal plants may be used for cure and control of this disease. Need of the hour is to develop a drug that is safe, effective, non-toxic, can increase platelet count and has efficacy against all serotypes. Structural analysis of their active constituents may lead to the development of effective anti-dengue drugs.

Key words: Dengue, warning signs, herbal drugs, anti-dengue medicinal plants, biological origin

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INTRODUCTION

Dengue is an arthropod-borne viral infection, which is one of the serious international public health concerns in modern era. It flourishes primarily in urban and semi-urban areas **[1]**.

Objective of the study is to review what possible plants are having anti-dengue activity which can be further employed to determine active biological ingredient responsible for this activity and can be extracted for its practical use.

EPIDEMIOLOGY

Pakistan's first outbreak of DHF occurred in 1994 in Karachi. Subsequently, another outbreak turned out in Baluchistan in 1995. In 2003, ten cases, four deaths in Haripur were confirmed as well **[2]**.

In Rawalpindi, from September to November 2008, forty-nine positive cases were detected. Out of which twenty-three were reported at Benazir Bhutto Hospital and twenty-six were at Holy Family Hospital **[3]**.

Millions of people in the world get affected by this disease every year **[4, 5]**. It is more prevalent in tropical and sub-tropical regions **[6]**. Traveling repeatedly to the endemic areas spreads it to the previously unaffected areas **[7, 8]**. Dengue hemorrhagic fever, a lethal complication of dengue fever, was first documented in the 1950's, during the dengue epidemics in the Philippines and Thailand, but at present Dengue Hemorrhagic Fever (DHF) has become a principal cause of hospitalization and death among children in various Asian countries **[1]**.

ETIOLOGY

Dengue fever can be caused by four different serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. Infection caused by any of the one dengue serotype can produce life-long immunity to that serotype but only limited protection to other serotypes. Dengue viruses are members of the genus *Flavivirus* and family *Flaviviridae*. It is single stranded RNA virus having an icosahedral neucleocapsid enclosed in an envelope **[9, 10]**.The incidence of each serotype causing Dengue Hemorrhagic Fever/ Dengue Shock Syndrome is in descending order of: type II, III, IV and I **[11]**. Dengue virus is carried by the vector, *Aedes aegypti.* The female Aedes mosquitoes acquire the virus from already infected person when it feeds

on that person. After 8-12 days, the mosquito becomes infective and can transmit the virus to another human through its bites throughout its life **[9, 10]**. Female Aedes mosquito ingests the Dengue virus from the blood of infected humans during feeding. The virus then infects the mid-gut of mosquito and consequently spreads throughout its body within 8 to 12 days **[12]**. Disease transmission is most common due to climate related factors because mosquitoes commonly breed in stagnant water, and a warm ambient temperature is vital requirement for adult feeding behavior and mortality, development rate of larvae, and degree of virus replication **[13-15]**. Outbreaks occur predominantly in the rainy season and during the dry summer months, together with the increase in population of *Aedes* mosquito **[16, 17]**.

SYMPTOMS

Dengue fever can be presented by a large variety of symptoms; essentially starts from asymptomatic to a life threatening Dengue Hemorrhagic Fever (DHF) to Dengue Shock Syndrome (DSS) **[18]**.

The symptomatic phase of this disease is divided into three phases including; febrile phase, critical phase and recovery phase. Symptoms appearing in febrile phase are high fever, retro-orbital headache, arthralgia, myalgia, malaise, nausea and vomiting and this phase lasts for 5-7 days **[19, 20]**. At the end of the febrile phase, inflamed throat, lymphadenopathy, and tender hepatomegaly may be observed. In most of the cases, there is recovery phase just after the febrile phase and the entire disease may disappear as a simple febrile state. Factor responsible for diagnosis of dengue at this point is continuous fall in platelet count. Normally the platelet count is greater than 250,000/microlitre and in dengue fever it is observed to be less than 100,000/microlitre within the period of 2-3 days. In some of the cases, level of platelets reduced to as low as 5000/microlitre or less. Within 5 days of fever, IgM antibodies against the virus start appearing in serum **[21]**. Within 3-7 days of the fever, critical phase can begin at any time. Extravasation of fluid due to increased capillary permeability is the basic pathophysiological characteristic of critical stage **[22]**. Sometimes atypical signs like massive bleeding, hepatitis and encephalitis may develop in patients with DF but without any sign of fluid leakage, thus it should not be considered as DHF **[23]**.The critical phase disappears after 1 or 2 days. Throughout the critical phase, fluid balance must be regulated carefully. As the critical phase starts, fever reduces normally. Critical phase may also be accompanied by shock due to the reasons including, excessive fluid leakage with no sufficient intake and internal bleeding **[19]**. Symptoms appearing in shock include perspiration, abdominal pain, continual vomiting, agitation, postural dizziness and decreased urine output **[23]**.

Various studies revealed that there is mild to moderate increase in liver enzymes in patients with DF & DHF. It is generally because of ischemic hepatitis caused by long term condition of shock. It does not require any particular treatment, mainly if patient do not have any mark of hepatic encephalopathy. Due to long term state of shock in the patients with DHF, dysfunction of myocardial contractility may occur, mainly because of metabolic acidosis and hypocalcaemia (mostly in DHF grade III and IV) **[23]**.

After the survival from critical phase, the patient will move towards the recovery phase. It arises 2-3 days subsequent to the critical phase. In the recovery phase, extravasated fluid will again penetrate the intravascular compartment **[19]**. There will also be an increased Platelet count. Death can result due to fluid overload but patient may recover and feel better if there is watchful management of fluid volume **[24]**.

TREATMENT

Dengue fever does not have any specific treatment. But patients can survive if there is cautious clinical supervision by skilled physicians and nurses. By means of suitable supportive therapy, death rate may be lessened to nearly 1%. DHF can be managed by maintaining the circulating fluid volume **[1]**. Anti-pyretics, like paracetamol can be used to treat fever. Analgesics can be used to treat arthralgia. Hospitalization is necessarily required for DHF/DSS patient. Rehydrating by oral means of therapy is recommended to prevent dehydration and if patient is not able to take oral therapy then intravenous fluid replacement can be used as a prophylactic to shock in infected individuals. Patient is recommended for platelet transfusion if platelet count is very low or is less than 20,000 or if notable bleeding is there. Non-Steroidal Anti-inflammatory Drugs (NSAIDs) particularly aspirin and ibuprofen should be avoided to prevent worsening of conditions, as well as the drugs that can decrease the platelet count should not be used in dengue **[25]**.

CONTROL OF DENGUE

Vaccination against dengue can be a useful parameter for its control, but there is no vaccine available. Drug therapy is another way to control this disease but is limited due to the unavailability of antiviral against dengue virus **[26]**. In order to develop anti-dengue drug, we have to face various challenges. To be effective clinically, the drug ought to have activity against each serotype and should alleviate the symptoms and decrease the prevalence of severe illness **[27].**

TABLE 1: List of plants with their botanical origin, constituents and uses

Botanical name	Common / English name	Family	Parts used	Geographical Source	Constituents	Anti-dengue Activity	Ref.
Andrographis paniculata	Creat	Acanthaceae	Aerial parts	India, Srilanka. South East Asia	Lactones, diterpenoids, diterpene glycosides, flavanoids, flavanoid glycosides	Anti-dengue against type 1 virus	[28, 29]
Alternanthera philoxeroides	Alligator weed	Amaranthaceae	Whole plant	South America, Bangladesh	phaeophytin a , pheophytin a'. 3beta-hydroxystigmast-5-en-7-one. 24-methylenecycloartanol, cycloeucalenol , phytol	Anti-dengue activity	[2, 30, 31, 32]
Azidarachta indica	Neem	Meliaceae	Leaves	India & Pakistan	Azadirechtine	Dengue VIRUS type 2	[33, 34]
Boesenbergia rotunda	Finger root	Zingiberaceae	Rhizome	Asian countries such as Malaysia, Thailand, Indonesia, India, and China	Flavanoids, cyclohexaneyl Flavanones& theirchalcones. 4-hydroxpanduratin A and panduratin A	Inhibitory activity against type 2 dengue virus	[35, 36, 37, 38]
Boerhaavia diffusia	Spreading Hogweed	Nyctaginaceae	Stem	Africa, Asia, North America, South America	Sterols, alkaloids (Punanavine), Punarnavoside, Lignans, flavonoids and glycosides	Anti-dengue	[39, 40, 41, 42, 43, 44]
Carica papaya	Papaya	Caricaceae	Leaves	America, Mexico, nearly all tropical countries.	Minerals, vitamins A, B, C, and E, chymopapain, papain, beta-carotene	Potent inhibitory activity against dengue fever, increases platelet count, WBCs and neutrophils	[45, 46, 47]
Castanospermum austral	Black Bean	Fabaceae	Seeds	Australia, India, Pakistan, Sri Lanka	Alkaloid; Castanospermine	Anti-dengue	[48]
Chondrus crispus	Carrageen moss	Gigartinaceae	Whole Algae	Ireland Europe	Polysaccharide carrageen, carrageenans	Anti-dengue Viral infections of common cold	[49]
Cissampelos pareira	Velvet leaf	Menispermaceae	extract of aerial parts	Widely distributed worldwide	Alkaloids; hyatinhyatinin, haytidine, bebeerines, chalcone and flavones dimer; cissampeloflavone	Anti-dengue	[50, 51]
Gastrodia elata	Tian Ma or Gastrodia	Orchidaceae	Whole herb	China, Nepal	Phenolic compounds, amino acids, D-glucans	Dengue virus 2 type	[52]
Euphorbia hirta	Tawa-tawa	Euphorbiaceae	Leaves	Java, Sunda, Sumatra, Peninsular Malaysia, Philippines, Vietnam	Polyphenols, reducing sugar, alkaloids, flavanoids, sterols, tannins, triterpenoids	Platelet increasing activity	[47, 53, 54]
Houttuynia cordata	Chameleon	Saururaceae	Whole plant	Native to many Asian countries	Alkaloids, flavanoids, fatty acids, sterols, phenols, essential oils	Anti-dengue	[38, 54, 55]
Hippophae rhamnoides	Sea buckthorn	Elaeagnaceae	Leaf extract	Asia, Europe and North America	Vitamin A,B,C,E,K, flavanoids, lycopene, carotenoids, phytosterols	Anti-viral, Dengue type 2 virus	[56, 57]
Kaempferia parviflora	Karachai Dam	Zingiberaceae	Leaves and stem	Thailand tropical Asia	Borneol, flavanoids.	Dengue 2 type virus.	[58]

Leucaena leucocephala	White Leadtree	Fabaceae	Seeds	Southern Mexico, Northern Central America and West Indies	Galactomannans	Activity against DENV-1	[59, 60]
Lippia citriodora	Lemon verbena	Verbenaceae	Leaves	South America	Salvigenin, eupatorin, eupafol, hispidulin ,6-hydroxyluteolin, cismaritin, chrysoeriolapygenin. Essential oils; limonene, beta cryophyllene, p-cymene, camphor, linalool, p-pineneandthymol	Anti-dengue	[61]
Mimosa scabrella	Bracatinga	Fabaceae	Seeds	Southeastern Brazil	Carbohydrates Flavanoids Alkaloids Phenols Galactomannans.	Inhibits dengue virus type-2	[60, 62, 63]
Phyllanthus urinaria	Chamber bitter	Phyllanthaceae	Whole plant	South India, South America and China	Kaempferol corilagin, rutin, brevifolincarboxylic acid, isostrictiniin, geraniin, gallic acid andellagic acid	Ethanolic extract shows anti dengue activity	[64, 65]
Piper sarmentosum	Lolot pepper	Piperaceae	whole plant	South east Asia, Vietnam, North America	Ascaricin Alpha-ascarone Beta-sitosterols Vitamin C Vitamin E Carotenes Xanthophylls	Ethanol extract possess larvicidal activity for *Aedesaegypti*	[66, 67]
Psidium guajava	Guava	Myrtaceae	Leaves	Mexico, *Caribbeans*and Central and South America	Flavonol morin, morin-3-O-lyxoside, morin-3-O-arabinoside, quercetin an d quercetin-3-O-arabinoside	Platelet boosting activity	[47, 68]
Quercus lusitanica / Quercus infectoria	Mazuphal	Fagaceae	Seed extract	Greece, Asia, Iran and India	Gallic acid Ellagic acid	Anti viral for dengue virus	[69, 70]
Rhizophora apiculata	Mangrove Kaya-Kandel	Rhizophoraceae	Whole plant	India, Australia, Indonesia, Malaysia	2-(2- ethoxyethoxy) ethanol, butyl cyclohexyl ester, 1,2-Benzenedicarboxylic acid. Octadecamethylcyclononasiloxane, Kaurene	Larvicidal activity	[38, 71, 72, 73, 74]
Tephrosia madrensis	-----	Fabaceae	Leaves and flowers	Tropical and subtropical regions of the world	Flavanoids; Glabranine 7-O-methyle glabranine	Antiviral against dengue virus	[38]
Uncaria tomentosa	Cat's Claw	Rutaceae	Stem bark	South and Central America	Oxindole alkaloids. tannins, flavanoids steroids	Anti-viral activity of hydroalcohoic extract	[38, 75]
Zostera marina	Eelgrass	Zosteraceae	Whole plant	North America and Eurasia	p-sulfoxy-cinnamic acid, zosteric acid	Activity against dengue virus type-2	[76]

CONCLUSION

There is no specific treatment to cure dengue and to prevent its further spread. It is the need of time to develop antiviral for dengue virus to save humanity. Various studies show that different plants have been used to prevent, control and cure dengue. Structural analysis of their active constituents may lead to the

development of effective anti-dengue drugs. Health care system should discourage the use of whole plant or a part of the plant as such to treat dengue, as it may also have toxic components as well. However using appropriate part of the plant, isolation of the most effective constituents, and study of their pharmacological activity, therapeutic effectiveness, therapeutic and lethal dose can help us discover natural remedy against dengue.

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