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A REVIEW ON SIDDHA FORMULATION ADATHODAI MANAPPAAGU IN THE MANAGEMENT OF DENGUE FEVER

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ABSTRACT

Dengue fever is the major alarm of the recent past specifically in the tropical and subtropical regions of the world. The thrombocytopenic complication of dengue hemorrhagic fever stands aloof with no drug or vaccine except for intravascular fluid replacement. The *Siddha* system of medicine has an enormous literature evidence of herbal medicines which are time-tested and clinically practiced in day to day life in South India. Hence it is high time for researchers to prove the scientific validity for these traditional claims for the present day alarming medical needs such as Dengue Hemorrhagic fever (DHF). *Adathodai manappaagu* is one such combination though commonly used for respiratory disorders in children yet claimed by *Siddha* literature to have a challenging potential against hemorrhagic conditions. This is a literature review of *Adathodai manappaagu* towards the treatment of dengue fever, analyzing its prospective through various latest researches thereby to derive an hypothesis of intervention of *Adathodai manappaagu* in Dengue hemorrhagic fever (DHF) for further future studies in this perspective.

KEYWORDS: Herbal medicine, Dengue fever, Justicia Adhathoda, Adhathoda vasika, DHF, Thrombocytopenia.

INTRODUCTION

Dengue fever is an essential concern area of Government and world health organization(WHO).[1] It is the most prevalent mosquito born viral infection affecting 2.5

billion people across the globe. An estimated 5 million people with DHF require hospitalization each year and a significant population of severely affected are children.[2] There is no standard vaccine or drug against this infection till now as the four serotypes of DENV does not provide cross protection against each other due to antibody dependent enhancement effect.[3] As dengue associated mortality is usually linked with DHF and DSS, close surveillance of this phase, which may need intervention of prevention of thrombocytopenia is crucial along with treatment modalities like intravascular fluid replacement and maintenance of good haemodynamic stability. Since no such synthetic drug to combat the thrombocytopenic complication has been implemented till now, the scenario has created a great demand for the search of plant based alternative solution which is safer and efficient to conflict this grave disease.

Nature has sustained to prompt drug designers. Various compounds that may prove to be therapeutically effective still remain unexplored scientifically. *Siddha* system of medicine stands as an oasis of ancient literature with indiscriminate symptoms of various diseases and their treatments. Though they are not emphasized with present day medical terminologies and techniques, a critical evaluation of *Siddha* medicines derived from nature"s flora and fauna provides us a way out for today's inexplicable diseases that are devoid of any medications and measures. Hence it is the high time for researchers to explore, evaluate and extract these traditional medicines to curtail the grievances caused by infections like dengue. *Adathodai* is a significant herb mentioned in *Siddha* literature and is advocated for any condition that associated with bleeding tendency (*Ratha pitham*). *Ratha pitham* is the condition explained in *Siddha* texts as the copious escape of blood from vessels through the nine openings of the body (Bleeding/hemorrhage).That is why the plant is also called by other vernacular names such as *Ratha pitha vakkini* and *Ratha pitha poondu* [4]. *Adathodai manappaagu* is a formulation consisting of this single herb *Adathodai* processed in palm jiggery. This article analyses the possible intervention of *Adathodai manappaagu* in dengue associated complication and its prevention.

Pathogenesis of dengue

Dengue fever is a vector borne infection caused by *Flavivirus* and transmitted by female *Aedes egyptii* mosquito. The virus incubates about 8-10 days in the intestinal tract of the infected mosquito. When mosquito bites human, the Dengue virus(DENV) infects the immature dendritic cells of the skin and migrate to the regional lymph nodes and present viral

antigens to the T cells, initiating the cellular or humoral immune response promoted by the salivary proteins. Replication of virus also takes place in liver, spleen, parenchymal cells, macrophages and peripheral blood monocytes. The clinical symptoms such as fever, malaise, headache, bodypain, rashes are early symptoms of Dengue infection. Later during defervescence symptoms of Dengue hemorrhagic fever(DHF)such as bleeding, thrombocytopenia, bleeding tendencies occur resulting in ascites, pleural effusion etc. The most severe form of Dengue is Dengue shock syndrome (DSS) which is presented with clinical warning signs such as severe and continuous abdominal pain, restlessness or somnolence, persistent vomiting, sudden reduction in temperature (fever to subnormal) associated with profuse perspiration, loss of strength and fainting can be indicators of plasma extravasation and immense shock.[5]

Primary infections of Dengue are predominantly mild or subclinical and are well tolerated by most of the children and adults. While secondary infection with different form of serotypes and primary infection in children with more virulent serotypes is often accompanied by a tendency to bleed and can lead to severe hemorrhages. The cross reaction between the non structural protein NS1 of the DENV and human platelet and endothelial cells raises the antibodies that damages the host cells.[6]

Current treatment targets and challenges

An optimal drug against DENV should encompass a good safety profile, resolve symptoms rapidly and reduce the risk of severity and achieve comparable inhibition of all four DENV serotypes.[7] Present treatment for dengue aims at two general strategies. The first one is viral targets such as inhibition of viral entry, viral enzymes, viral proteins and the second is the host targets.[8] Regardless of the above strategies, attempts to identify a potential antiviral for the treatment of dengue is being unsuccessful continuously as there are challenges such as presence of four distinct serotypes of DENV which undergo frequent mutations and also a difficulty in finding an appropriate model for induction of infection and to study the protective action of drug, as the available mouse model (AG29) has its limitations such as low viral load and short period of viremia. Development of suitable vaccine for dengue has been ineffective and is attributed to the facts of complex pathology of the illness and the need to robust immune response against all the four serotypes. Also poor understanding of the mechanisms inducing protective immunity against dengue infection poses additional challenge for vaccine development.[9]

Platelets as targets in Dengue

Failure of an optimal drug gratifying the probable viral and host targets and challenges of antidengue therapy, makes us sensible to focus towards the management of thrombocytopenia which is a key to the survival of patients. The hallmark of Dengue infection is Thrombocytopenia which causes Dengue hemorrhagic fever (DHF) and is characterized by a thrombocyte count of <100,000 cells/mm3. The possible mechanisms that have been suggested to be responsible for dengue induced thrombocytopenia are impaired thrombopoiesis due to reduced megakaryopoiesis at the onset of infection and peripheral platelet destruction. This effect could be due to a direct effect of the virus on the megakaryocytes, or on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis. Studies also reveal bone marrow suppression in 2-4 days of DENV infection causing impaired thrombopoeisis[10]. The other mechanism of thrombocytopenia may be due to increased peripheral platelet destruction by the DENV due to an autoimmune reaction, causing lysis of platelets. Abnormal activation and inhibition of platelet aggregation in dengue patients may lead to platelet dysfunction and destruction[11]. The current strategy for the prevention or treatment of severe bleeding in patients with dengue is platelet transfusion. However,recent WHO guidelines do not recommend platelet transfusion for hemodynamically stable patients with thrombocytopenia. Even in patients who exhibit severe bleeding and hemodynamic instability, transfusion of platelets is only to be considered with restrictions [12]. Therefore traditional *Siddha* medicines like *Adathodai manappaagu* that are plant based are gaining immense interest in recent years especially in Tamilnadu , India as a reflection of positive impact of consolidated efforts aimed at the reduction of increasing mortality caused by dengue.

Adhatodai Manappaagu* in *Siddha

The plant *Adhatoda vasica* has been used extensively in the traditional *Siddha* system of medicine of India for over 2000 years.[13] Siddha system of medicine categorizes the medicines into internal (*Ulmarunthu*) and external (*Velimarunthu*) medicines and advocates various methods of purification, preparation, processing and administration of them. One such form of parenteral administration of internal medicines is known as *Manappaagu.* In this method the fresh juice of any part of a plant is taken and mixed with sugar or palm jaggery and heated until it comes to a state of string consistency (Kambipatham) and

stored.[14] In *Adathodai manappaagu* the fresh leaf juice is used for the preparation of *Manapaagu*.

Adhatoda vasica (L.) Nees (family Acanthaceae) is an evergreen, perennial shrub commonly of 1–2.5 m high. The leaves are lanceolate, opposite, 10–15 cm long and 4 cm wide and is also known under the common name Malabar nut tree .The flowers are white, pink or purple. The plant grows throughout the Indian peninsula in wastelands in a variety of habitats and soil upto an altitude of 1350 m. The leaves, flowers, fruits and roots are extensively used for treating bronchitis, cold, cough, whooping-cough and chronic bronchitis and asthma, as sedative-expectorant, antispasmodic and as anthelmintic. Since ancient times various preparation of leaves were used for bleeding and hemorrhagic conditions in Southeast Asia.[15]

Ethanobotanical information of ingredients of *Adathodai manappaagu*

S.No	Botanical name	*Justicia adhatoda*	*Borassus flabellifer*
1	Tamil name	Adathodai	Panai vellam
2	Common vernacular names		
3	English	Malabar nut	Palm tree
4	Hindi	Adosa	Tari
5	Sanskrit	Vasaka	Guda
6	Malayalam	Adalodakam	Pana
7	Family	Acanthacea	Arecacea
8	Parts used	Leaf	Jaggery
9	Suvai	Kaippu	Inippu

Phytochemical constitution of *Adhathodai manapaagu*

The Phytochemical analysis of *Justicia adhatoda* leaves show the presence of phenols, tannins, alkaloids, anthroquinone, saponins, flavanoids and reducing sugars. The pharmacologically most studied clinical component of *Justicia adhatoda* is a bitter quinozoline alkaloid vasicine which is present in leaves, roots and stem. Apart from vasicine, several alkaloids such as vasicinone, vasicinol, adhatodine, adhvasinone, betaine, steroids, and alkanes are also present. The chemical compounds found in *Justicia adhatoda* includes essential oil,fats, resins, sugar, gum, aminoacids, proteins and vitamin C.[15] Among other Jaggeries, Palm Jaggery gains its significance due to its high nutritive value. Palm jaggery is processed from unfermented palmyrah tree saps and its nutritional composition contains protein - 0.35%, fat (ether extraction) 0.17%,minerals - 0.74%, carbohydrates - 90.60%, calcium -0.06%, phosphorus - 0.06%, iron - 2.5 (mg/gm),nicotinic acid - 5.24 (mg/100 gm),

vitamin B1 -24.0 (mg/100 gm), Riboflavin - 432.0 (mg/100 gm)and Vitamin C - 11.0 (mg/100 gm).[16]

Recent researches on *Adatoda vasika*

The complications of Dengue such as DHF/DSS results due to constant interplay between the viral factors, host genetics and host immune factors. The common findings of DHF/DSS are Thrombocytopenia caused by the impairment of hematopoietic function. On repeated oral and intramuscular administration of vasicine hydrochloride resulted in a dose related increased in platelet count in normal rats, mice, rabbits and dogs. This increase in platelets was also associated with significant hyperplasia of megakaryocytes in the bone marrow. The findings disclosed vasicine to be a promising phytoconstituent for the control of capillary haemorrhages and for correction of drug induced bone marrow depression.[17] Vasaka exhibited marginal increase in the WBC count to the extent of 16%. Vasaka showed statistically significant protective effect against cyclophosphamide induced myelosuppression to an extent of 80%[18] Effect of alcoholic extract of plant leaf (500 mg/kg, p .o.) on hematological profile, spleenic lymphocytes and peritoneal macrophages was studied 5, 10, 15 and 20 days after treatment in swiss albino mice. Its effect on macrophages phagocytic index, *E.coli* induced abdominal peritonitis and SRBC induced delayed type hypersensitivity was also evaluated. Plant showed significant increase in total WBC, blood lymphocytes, splenic lymphocytes and peritoneal macrophages. It also showed significant protection against *E. coli* induced abdominal peritonitis.[19]

Various extracts of Adhatoda vasica was administered at a dose of 400mg/ Kg orally for 8 days which significantly inhibited the adhesion of neutrophils to nylon fibres which stimulates the process of margination of cells in the blood vessels indicating the fact that adhadhota reduces the number of neutrophils thus decreasing the phagocytosis action and inhibit release of various enzymes, showed inhibitory effect on T Lymphocytes and mediators that make inflammation.[20] Both alkaloids vasicine and vasicinone in combination showed bronchodilatory activity. Vasicine showed bronchodilatory activity comparable to theophylline both invitro and invivo.[21] Furthermore, in other studies it has been shown that vasicine is a very effective oxytocic agent in human beings and stopping post-partum haemorrhage.[22]

DISCUSSION

Intervention *of Adhatoda in DHF/DSS*

It has been estimated that the primary vessels of Dengue viral propogation are monocytes. The activated dengue infected monocytes stimulates the cytokines and chemokines such as TNFαand interleukins and cause apoptosis. These factors are known to compromise the integrity of vascular endothelial cell layer due to the loss of barrier function leading to vascular leakage the hallmark of severe dengue disease.[23] It has been reported that following SRBC challenge for 9 days, the cytokines and chemokines were increased. But pretreatment with *Adhatoda vasica* leaf extract reduced the monocyte chemotactic protein MCP-1 which is the key molecule in terms of chemotaxis and activation of macrophages which favours the release of TNFα and interleukins. Also a study on the plant *Adhatoda vasica* has shown immunostimulatory activity by potentiating humoral as well as cellular immunity.[24] Targeting host factors and adverse sets of immune and non immune host molecule involved in disease pathogenesis may help to control infection triggered worsening of physiological homeostasis and enables the body to control virus itself.

Hence we can arrive at an hypothesis that *Adathodai manappaagu* interferes at the chemotactic stage of the binding of Dengue virus with the monocytes by reducing the monocyte chemotactic protein (MCP) thereby, reducing the release of apoptoptic factors such as cytokines and chemokines preventing the loss of barrier function and vascular leakage in the vascular endothelium. The *manappaagu* form of *Adathodai* significantly owes its grandeur for the presence of Palm jaggery (*Panai vellam*) and its nutritive value as it is enriched with iron and vitamin C. It also compliments for the thrombocytopenic complication of DHF since iron therapy causes an increase in megakaryocytes and an increase in platelet count in a study.[24] Also, Vitamin C facilitates the absorption of iron, strengthens the collagen of blood vessels, connective tissues preventing their damage and enhances the body's defence mechanism by strengthening the immune system.[25]

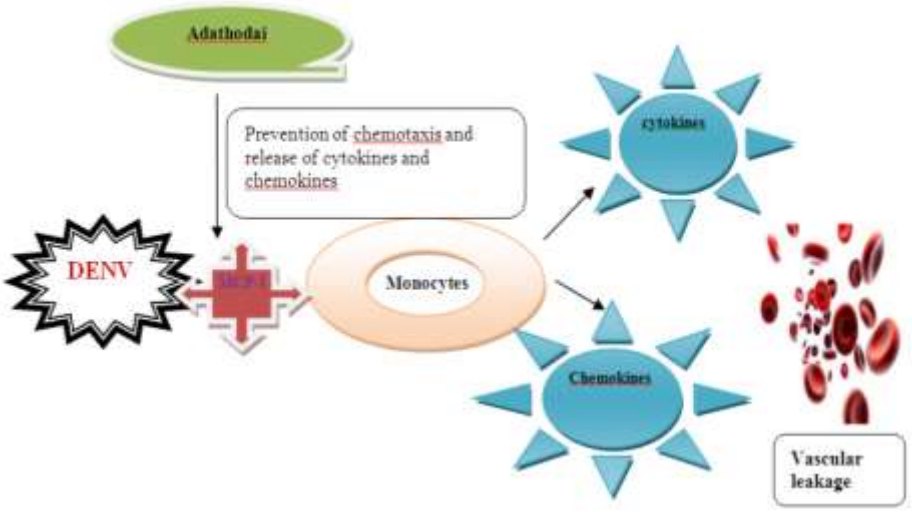

Fig-1: Intervention of Adathodai in DHF/DSS

Toxicity profile

Autopsy and histo-pathological examination did not reveal any abnormalities on vascicine administration in experimental rats. However intraperitoneal administration of vasicine in rats (5 and 10mg/kg body weight) showed an abortifacient effect after 7 days of pregnancy. There was no teratogenic effect of vasicine in a study involving rats and rabbits. [22] Repeated oral administration of vasicine daily for 6 months was carried out in rats and monkeys by pahwa et al., 1987 and the major organs, clinical chemistry and histopathology was observed for general toxicity studies. Leaf showed significant hepatoprotective effect at doses of 50 to 100 mg/Kg on liver damage induced by galactosamine in rats.[12]

CONCLUSION

The above critical review about *Adhatodai Manappaagu* emphasise that it is potentially safe, easily accessible, simple *Siddha* formulation which may interfere in the treatment of Dengue through the prevention of chemotaxis and release of cytokines and chemokines thereby preventing the vascular leakage which is a major threat for the mortality of dengue hemorrhagic fever. Further, clinical trial and pharmacodynamic targets of this formulation has to be evaluated for global recognition of this simple *Siddha* herbal formulation in the management of dengue hemorrhagic fever(DHF).

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