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Research Article **Biochemistry**

Clinico-Hematological profile in dengue fever patients treated with papaya juice and Neelavembu Kudineer

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ABSTRACT

Dengue is an acute viral infection with potential fatal complications. In this study, analysis the biochemical parameters in healthy, dengue fever and dengue fever subjects treated with papaya leaf and Nilavembu kudineer were evaluated. Papaya juice and Neelavembu kudineer treatment to Dengue fever subjects reduce the oxidative stress evidenced by decreased oxidative markers and improve the hematological parameters. These results suggest that use of Papaya juice and Neelavembu kudineer treated subjects possess potential antiviral property against the dengue virus family such as *Flaviviridae*. The potential activity of Papaya juice and Neelavembu kudineer due to the phytotherapetic phytochemicals present in it. Studies suggested that the Papaya juice and Neelavembu kudineer is the best medicine to cure dengue fever.

Keywords: Dengue fever, Papaya juice, Nilavembu kudineer, *Flaviviridae*, Virus

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INTRODUCTION

Dengue is an acute viral infection with potential fatal complications. Dengue fever was first referred as “water poison” associated with flying insects in a Chinese medical encyclopedia in 992 from the Jin Dynasty (265-420 AD). The word “dengue” is derived from the Swahili phrase Ka-dinga pepo, meaning “cramp-like seizure”. The first clinically recognized dengue epidemics occured almost simultaneously in Asia, Africa, and North America in the 1780s. The first clinical case report dates from 1789 of 1780 epidemic in Philadelphia is by Benjamin Rush, who coined the term “break bone fever” because of the symptoms of myalgia and arthralgia . The term dengue fever came into general use only after 1828. Dengue viruses (DV) belong to family *Flaviviridae* and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4. DV is a positive-stranded encapsulated

RNA virus and is composed of three structural protein genes, which encode the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein and seven non-structural (NS) proteins. It is transmitted mainly by *Aedes aegypti* mosquito and also by *Ae. albopictus*. All four serotypes can cause the full spectrum of disease from a subclinical infection to a mild self limiting disease, the dengue fever (DF) and a severe disease that may be fatal, the dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) (Gupta *et al.*,2012).

The World Health Organization (WHO) says, "The female mosquitoes lay their eggs in water containers in and around the homes, and other dwellings. These eggs will develop, become larvae, and further develop into adults in about 10 days."Incurring in tropical and sub-tropical parts of the world, dengue fever is severe, flu-like illness that affects infant, young children, and adults. It spreads apidly, and in the event of epidemic, it will affect a large number of people and eventually cause the loss of lives. Another cause for alarm: More than 2.5 billion people (or 40 percent of the world's population), including 1 billion children lives in areas where there is a risk of dengue transmission.

In recent decades, the incidence of dengue fever has risen sharply in the past two decades. Dengue is an endemic in India. A total number of 10,000 cases were reported in Tamil Nadu from June 2012 to December 2012. The incidence and prevalence of dengue fever is quite prominent in tropical and subtropical regions of the world which includes Southeast Asia. It is a viral-caused disease spread by mosquito – *Aedes aegypti female mosquito* (the primary vector). The severity of the disease varies from asymptomatic infections, to a febrile fever, or potentially life-threatening dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).

Dengue fever is usually a self-limited illness, and only supportive care is required. Acetaminophen may be used to treat patients with symptomatic fever. Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids also used. However, all of these medications are associated with side effects. So the peoples are moving towards for the treatment of dengue with safe medicine. Herbal medicines are potential source for the development of new antiviral drugs, since they can be selected on the basis of their ethno medicinal use, for example, against infection. These plants produce a variety of chemical constituents with the potential to inhibit viral replication and compounds from natural sources are of interested as possible sources to control viral infection. In this study, analysis the biochemical parameters in healthy, dengue fever and dengue fever subjects treated with papaya leaf and Nilavembu kudineer were evaluated.

MATERIALS AND METHODS

A total of 20 consecutive dengue fever patients were enrolled in Rohini Hospital, Thanjavur between November 2012 and December 2012 (two consecutive monsoon seasons), where they were receiving periodic checkups. They were aged between 20 and 40 years. Equal number of subjects with normal physical and mental health was selected to serve as a control subject in the age group of 20 to 40. Patients were interviewed and examined with an objective of identifying the symptoms and signs associated with current febrile illness, associated co-morbidities and other baseline characteristics. This was followed up with basic blood tests (biochemical and haematological), urine analysis, chest X-ray and ultrasound abdomen. An IgM and IgG antibody against dengue was detected using a commercial enzyme-linked immunoassay kit (Panbio, Brisbane, Australia). Additional tests like IgM antibodies for leptospirosis (Panbio, Brisbane, Australia), smear for malaria, blood culture, urine culture, d-dimer, partial thromboplastin time, endoscopy, *etc.*, were done on clinical suspicion. Informed written consent was obtained from all stable patients and from the closest relative of patients who were critically

Group I : Normal subjects
Group I : Dengue fever subjects
Group II: Dengue fever confirmed patients and treated with Papaya juice and Neelavembu kudineer (Course of treatment was 15 days)

Random venous blood samples were collected from both the groups, 3-4 ml whole blood samples were collected in plain screw capped polypropylene tubes, coated with heparin while remaining 2 ml was collected in eppendoff polypropylene micro tubes containing EDTA. Blood samples of Group II patients were collected before and after treated with Papaya juice and Neelavembu kudineer for 15 days.

BIOCHEMICAL ESTIMATIONS

Reduced glutathione was estimated by method of Moron *et al* (1979). Malondialdehyde was estimated by the thiobarbituric acid assay method of Beuge and Aust (1978). Haemoglobin was estimated by Cyanmethaemoglobin method (Dacie and Lewis, 1968) (Beacon Diagnostic Kit). Serum sodium was estimated by colorimetric method of Maruna & Trinders (1958). Serum potassium was estimated by method of Maruna (1957). To determine

the total erythrocyte and leucocyte count by haemocytometry (Oche and Kolhatkar, 2000).

Statistical analysis

The results were presented as mean ± SD. Data was statistically analyzed using student "t" test. P.values set as lower than 0.001, 0.01 and 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

The present study was carried out to analyze the various biochemical parameters in normal and dengue fever patients. The observation made on different subjects of normal and dengue fever patients were compared as follows.

Table I - Shows the levels of MDA in normal and dengue fever subjects. MDA was significantly increased in dengue fever patients when compared to normal and treated subjects.

Table II - Shows the levels of GSH in normal and dengue fever subjects. GSH was significantly decreased in dengue fever patients when compared to normal and treated subjects.

Table III - Shows the levels of Hb in normal and dengue fever subjects. Hb was significantly decreased in dengue fever patients when compared to normal and treated subjects.

Table I- The levels of MDA in normal, treated and dengue fever subjects

Subjects	MDA (mg/dl)
Normal	1.15 ± 0.26
Dengue fever	2.79 ± 0.78*
Dengue fever treated subjects	1.45 ± 0.18

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P< 0.001)

Table II- The levels of GSH in normal, treated and dengue fever subjects

Subjects	GSH (µg/dl)
Normal	8.08 ± 1.59
Dengue fever	2.69 ± 0.52*
Dengue fever treated subjects	7.56 ± 0.84

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.10)

Table III- The levels of Hb in normal, treated and dengue fever subjects

Subjects	Hb (gm/dl)
Normal	16.26 ± 1.65
Dengue fever	9.56 ± 1.51*
Dengue fever treated subjects	14.84 ± 1.74

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.001)

Table IV- The levels of platelet in normal, treated and dengue fever subjects

Subjects	Platelet (cu.mm)
Normal	3,25,466 ± 4000
Dengue fever subjects	62,166 ± 1705*
Dengue fever treated subjects	3,80,459 ± 3800

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.001)

Table IV - Shows the levels of platelet in normal and dengue fever subjects. Platelet was significantly increased in dengue fever patients when compared to normal and treated subjects.

Table V - Shows the levels of Hematocrit in normal and dengue fever subjects. Hematocrit was significantly increased in dengue fever patients when compared to normal and treated subjects.

Table V- The levels of Hematocrit in normal, treated and dengue fever subjects

Subjects	Hematocrit (mm)
Normal	3.83 ± 0.46
Dengue fever	4.66 ± 0.81*
Dengue fever treated subjects	3.21 ± 0.23

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.05)

Table VI - Shows the levels of sodium in normal and dengue fever subjects. Sodium was significantly increased in dengue fever when compared to normal and treated subjects.

Table VI- The levels of sodium in normal, treated and dengue fever subjects

Subjects	Sodium (M.equ/l)
Normal	135 ± 3.49
Dengue fever	167.37 ± 30.44*
Dengue fever treated subjects	138.45 ± 3.21

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.001)

Table VII - Shows the levels of potassium in normal and dengue fever subjects. Potassium was significantly decreased in dengue fever patients when compared to normal and treated subjects.

Table VII- The levels of potassium in normal, treated and dengue fever subjects

Subjects	Potassium (M.equ/l)
Normal	5.75 ± 0.68
Dengue fever	2.18 ± 0.35*
Dengue fever treated subjects	4.89 ± 0.57

Values were expressed as mean ± SD.* Significantly different from normal and treated subjects (P<0.05)

Table VIII - Shows the count of WBC and RBC in normal and dengue fever subjects. WBC and RBC count were significantly decreased in dengue fever when compared to normal and treated subjects.

Table VIII - WBC and RBC count in normal, treated and dengue fever subjects

Subjects	WBC (cu.mm)	RBC (cu.mm)
Normal	9033 ± 605.53	4.33 ± 0.33
Dengue fever	36.468 ± 2,682*	2.0 ± 0.12*
Dengue fever treated subjects	10,235 ± 756	4.12 ± 0.24

Values were expressed as mean ± SD.

* Significantly different from normal and treated subjects (P<0.001).

DISCUSSION

The World Health Organization (WHO) defined Dengue Fever as an acute febrile illness of 2-7 days duration sometimes with two peaks having the following manifestations of abrupt onset of fever accompanied by headache, myalgia, malaise and other constitutional symptoms with high index of suspicion based on period, population & place with absence of convincing evidence of any other febrile illness. While DHF manifest with dengue fever signs and symptoms with a drop in platelet count to below 100,000/mm3 and an increase of 20% or more in the hematocrit with probable or con rmed case of dengue infection and hemorrhagic tendencies (Ahsanullah *et al*., 2000)

The continued emergence of dengue virus infection and its severe disease manifestation has made it a growing public health problem. Shock and bleeding are the two most dreaded complications and factors which may predict its occurrence. A few studies have shown that factors such as hemoconcentration, platelet count less than 50,000/mm3, elevated ALT level and prolonged coagulation factors (Ayyub *et al.,* 2006) can predict spontaneous bleeding. While leukocyte count can be an important prognostic guide in early phase of dengue infection, no studies have been done comparing leukocyte count, platelet count and the incidence of bleeding outcome among these patients. Leukopenia in dengue patients may be caused by virus-induced destruction or inhibition of myeloid progenitor cells. While thrombocytopenia may results from destruction of peripheral platelet or bone marrow megakaryocytes by viruses which consequently reduce the platelet production (Lin *et al*., 1989).

Blood substitutes are products that are designed to replace whole blood (or) red blood cells in the field of transfusion medicine. The search for a clinically useful blood substitute is stimulated by the limitations of blood due to its insufficient supply, safety and costs. There is a lot of concern over the blood-borne pathogens, including hepatitis and human immunodeficiency virus (HIV) that makes development of blood substitutes very attractive. Blood substitutes are those agents that can be administered without any need for blood grouping (or) cross matching. They can be produced in large volumes and stored for longer periods of time. The important properties of blood substitutes are the increase in blood volume, blood flow and oxygen supply to the vital organs. For these reasons it is more appropriate to call these agents as oxygen carrying volume expanders. There are two major groups of blood substitutes that are in advanced stages of

development. They are (i) perthe fluorocarbons (PFC) and (ii) modified hemoglobins (Palaparthy *et al*., 2000).

Hemoglobin is a tetrameric protein that is responsible for the transport of oxygen to various tissues. Hemoglobin constitutes about 95% of the dry weight of RBC. Normal hemoglobin consists of a globin and . four heme groups and weighs 64 kD. Each heme group in turn contains a protoporphyrin ring and iron. Thus, for normal hemoglobin synthesis, there should be an adequate supply and delivery of iron and synthesis of heme precursors like protoporphyrin and globins. Functionally, hemoglobin has a natural property of carrying and delivering O_2 in a co operative manner and a huge capacity to hold as much as 1.39 ml of O_2 per g of protein. Hemoglobin is considered capable of carrying O_2 outside a red blood cell (RBC). The toxicity and short retention times are the potential drawbacks that demand a modification of hemoglobin. Several modification procedures of hemoglobin have been attempted to improve the physiological properties of the free hemoglobin to function as oxygen carriers. Recent studies indicate that the modified hemoglobin solutions are not simply oxygen carriers but also possess significant pharmacological properties could play a significant role when used as a resuscitative agent (Palaparthy *et al*., 2000).

Erythrocytes, the unique carriers of oxygen are highly susceptible to oxidative stress conditions. The rich polyunsaturated membrane lipids and iron, a potent catalyst for free radical reactions makes erythrocyte a good substrate for oxidative damages. Membrane oxidations do affect the intrinsic membrane properties as well, by altering membrane fluidity, ion transport and loss of enzymic activities of the cell (Chiu *et al*., 1989). As cell membrane is an important target for radical damage, and blood can reflect the liability of the whole animal to oxidative condition erythrocytes have been used extensively for determining the effect of aging in studies concerning the possible involvement of free radicals. The erythrocyte cell membrane has a total negative electric charge, which determines the correct course of many processes like transport of metabolic substrates and products through ionic pumps, carriers and membrane channels, for the transfer of information and mainly to prevent aggregation of erythrocytes from each other (Jovtchev *et al*., 2000).

The study of lipid peroxidation is attracting much attention in recent years due to its role in diseases process membrane lipids are particularly susceptible to lipid peroxidation due to the presence of polyunsaturated fatty acids. It has been implicated in the pathogenesis of a number of diseases and clinical conditions. These include atherosclerosis, cancer etc., Experimental and clinical evidence suggests that aldehyde products of lipid peroxidation can also act as bioactive molecule in physiological and pathological conditions. It is now generally accepted that lipid peroxidation and its product play an important role in liver, kidney, heart and brain toxicity (Lakshmi *et al*., 2005). Malondialdehyde (MDA) is the major aldehyde resulting from the peroxidation of biological membrane polyunsaturated fatty acid. MDA, a secondary product of lipid peroxidation is used as an indicator of tissue damage by series of chain reactions (Ray and Husain, 2002). MDA is one of the indicators of oxidative stress. In the present study, the increased content of MDA in dengue fever subjects as compared with normal and treated subjects, indicates that the increase in oxidative stress and lipid peroxidation in dengue fever subjects.

Glutathione status is a highly sensitive indicator of cell functionality and viability. GSH depletion is linked to a number of diseases states including cancer, neurodegenarative diseases, kidney and cardiovascular diseases. Glutathione is a ubiquitous thiol containing tripeptide, which plays a central role in cell biology. It is implicated in the cellular defence against xenobiotics and naturally occurring deleterious compounds, such as free radicals and hydro peroxides. Kidneys are exposed to various cytotoxic agents before the elimination of these agents in urine. Thus the GSH concentrations in kidney cells are important (Pastore *et al*., 2003). In the present study, decreased content of GSH in dengue fever subjects as compared to normal and treated subjects. The decreased plasma GSH content, implying increased consumption for oxygen radical scavenging activity.

The composition of ICF and ECF is different. The principal intracellular cation is potassium and the main extracellular cation is sodium. ICF has high protein content, whereas the protein content of ECF is almost zero. Proteins have multiple charges on each molecule; at body pH the net charge is negative. After protein, the principal intracellular anions are organic phosphates (e.g. creatine phosphate, ATP) (Atherton, 2006).

In a healthy individual, sodium intake and sodium excretion are equal over time. In normal salt intake is 6–18 g(100–300 mmol)/day. Sodium loss occurs via the skin (in sweat) and the gastrointestinal tract, but the principal site of sodium regulation is the kidney, which normally accounts for 95% of sodium output. Sweat is a hypotonic solution containing 5–80 mmol/litre of sodium. Sodium balance is closely

related to ECF volume because sodium is the main extracellular cation. Sodium retention is associated with fluid retention and oedema, and sodium depletion with shrinkage of the ECF volume and hypovolaemia. The regulation of sodium balance in the healthy individual is determined via ECF volume, detected by receptors in the arterial (Atherton, 2006).

The renal mechanisms that affect sodium excretion are glomerular filtration rate (GFR), plasma aldosterone levels, renal tubular mechanisms and renal sympathetic activity, and atrial natriuretic peptide. A spontaneous increase in GFR leads to an increase in sodium load presented to the proximal tubule. Sodium excretion not increased markedly because of 'glomerulotubular balance' whereby the proximal tubule and the loop of Henle increase their rates of sodium reabsorption so that excess losses do not occur.

Normal intake of potassium in food is about 100 mmol/day. About 10% is secreted in the faeces and 90% in the urine. Sweat contains about 5–10 mmol/litre. Plasma potassium levels are influenced by insulin, aldosterone and the catecholamines (sympathetic stimulation). Insulin and the catecholamines both stimulate the Na+/K+-ATPase pump in the cell membrane, and potassium is pumped into the cells, resulting in a fall in plasma potassium (Iain Campbell, 2006)

Acid, bases and salts are collectively called electrolytes. Electrolyte imbalance can leads to serious consequences as it affects the homeostasis of the body. Homeostasis is the process by which the body cells maintain their internal balance in spite of changes in the external environment commonly measured electrolytes are sodium, potassium, calcium, chloride bicarbonate etc., which are good indicators of kidneys function (Cohen and Lemann, 1991). In the present study, we observed the increased level of sodium and decreased level of potassium in dengue fever subjects as compared with normal and treated subjects. This due to antiport transport system of sodium and potassium i.e. the increased excretion of potassium is promoted the reabsorption of sodium.

The human haemopoietic system is extremely sensitive to health and diseases because of the rapid synthesis and destruction of cells with consequent heavy metabolic demands. Haemotological parameters are a sensitive index to change in pathological conditions and can constitute an important diagnostic tool in pathological studies (Callistur, 2001).

In the present study, we observed the decreased level of haemoglobin in dengue fever subjects as compared with normal subjects. This is may be due to inhibition or decreased synthesis of Hb and destruction of cells in dengue fever subjects.

In the present study, we observed the decreased count of RBC and increased count of WBC in dengue fever subjects as compared with normal and treated subjects. The decrease in RBC count in exposed subjects in the present study is indicative of microcytic anemia. It was observed in the study that there was an increase in white blood cell count regardless the period of exposure and may be, only a short exposure period is necessary to stimulate the excess formation of WBC's. Immune responses and reactions may have led to increase in WBC in dengue fever subjects

In the present study, we observed the decreased count of platelet in dengue fever subjects as compared with normal and treated subjects. The decrease in platelet count in dengue fever subjects in the present study is indicative of dengue fever. It was observed in the study that there was decrease in platelet count regardless the period of exposure and may be due to destruction of platelet in dengue fever subjects.

The above results comfimed that the Papaya juice and Neelavembu kudineer treated subjects improve the biochemical and hematological parameters and restored the patients normal life. The potential activity of Papaya juice and Neelavembu kudineer due to the presence of effective phytochemical present in it.

The above results of this study show that Papaya juice and Neelavembu kudineer treatment to Dengue fever subjects reduce the oxidative stress evidenced by decreased oxidative markers and improve the hematological parameters. These results suggest that use of Papaya juice and Neelavembu kudineer treated subjects possess potential antiviral property against the dengue virus family such as *Flaviviridae*. The potential activity of Papaya juice and Neelavembu kudineer due to the phytotherapetic phytochemicals present in it. Studies suggested that the Papaya juice and Neelavembu kudineer is the best medicine to cure dengue fever.

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