Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/6641
DOI URL: http://dx.doi.org/10.21474/IJAR01/6641

RESEARCH ARTICLE

CARICA PAPAYA: A BOTANICAL TREATMENT FOR PATIENTS WITH DENGUE VIRUS INFECTION.

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Manuscript Info

Manuscript History

Received: 02 January 2018
Final Accepted: 04 February 2018
Published: March 2018

Keywords:-
Dengue, Carica papaya, flavovirus serotypes.

Abstract

Dengue is a mosquito borne viral disease caused any one of four closely related but antigenically distinct flavovirus serotypes, DENV 1 through 4. Its spectrum ranges from asymptomatic infection to dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), and may lead to patient death. It is known that the platelet count drops in dengue patients after the first three days of fever and the gradually increases after the seventh day or drop further with derangement of other clotting factors to develop into dengue hemorrhagic state [1]. Dengue Haemorrhagic Fever (DHF), a potentially lethal complication, was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Dengue fever is now an international public health concern, affecting individuals from countries even where the disease is not prevalent, especially spread by global travellers from endemic areas to non-endemic areas [2].

Despite the advancement of knowledge and technology in the field of medicine, no sure cure or vaccine has yet been devised to combat the dengue virus, which has the ability to create a viral epidemic of epic proportions. The aim of this review is to capture the progress made in elucidating the botanical compounds responsible for anti-DENV activity of *Carica papaya*.

Introduction:-

The use of plants for medicinal purposes dates back to ancient times. The papaya plant (*Carica papaya* Linn.) is known for its nutritional value throughout the world, and the leaves have been used in folk medicine for centuries, for various diseases. During the last few decades, research has validated its medicinal use in treating several conditions. Some of Its beneficial effects include anti-inflammatory, wound healing, anti-tumour and immune-modulatory effects, antioxidant, antifungal [3], antimicrobial [4,5], hypoglycemic [6]. Leaves of *Carica papaya* are non-toxic and safe for oral consumption [7]. Of importance, is the use of this leaf in patients with Dengue fever.

Dr. Sanath Hettige, in 2008 conducted the first documented pilot study in 12 patients (a mix of adult and pediatric patients), confirmed with dengue fever during a dengue outbreak in Sri Lanka. The patients were administered non-diluted *C. papaya* leaf juice in two doses every 8 hours. Blood samples and clinical conditions were assessed before and after administering the juice. Drugs which were likely to alter the platelet count were not administered on these patients. The platelet counts and the total white cell counts had increased in all patients within 24 hours after administering papaya leaf juice. Five patients reported that an itching haemorrhagic skin rash (platelet count < 100000) disappeared within two days of treatment. [8]

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Isolated case studies have shown that Carica papaya leaf extracts have successfully improved platelet counts within 5 consecutive days of administration. [9,10] When taken twice a day papaya leaf juice helps to increase white blood cells and platelets, normalizes clotting, and repairs the liver. [11]

Subenthran et al., in 2013 showed via gene expression that the Arachidonate 12-lipoxygenase (ALOX-12) and Platelet-Activating Factor Receptor (PTAFR) genes was higher expressed among leaf extract treated patients as compared to the non-treated patients. While the PTAFR gene is responsible for increased platelet production and aggregation, ALOX 12, a platelet specific gene, is known to be associated with increased megakaryocyte production as well as its conversion to platelets through 12-HETE mediated pathway which in turn leads to increased platelet production. [12] A significant increase in the mean platelet count was noted after 40 hours and 48 hours of leaf juice consumption. The PTAFR gene which is known to be responsible for increased platelet production and aggregation was expressed 13.42-folds among the patients who consumed the juice as compared to the control group indicating that the juice had played an important role in addressing the arresting of bleeding tendencies among these patients. [13]

According to Senthilvel, based on bioinformatics tools, it was shown that the flavonoid quercetin, isolated from the leaves would exert anti-Dengue activity. The study analysed the activity of compounds in *Carica papaya* leaf extracts against NS2B-NS3 serine protease of DENV2 virus. Quercetin showed potential inhibitory activity against NS2B-NS3 serine protease. Further ADME and toxicity risk assessment strongly suggested that quercetin did have marked antiviral activity against DENV2 virus by blocking the viral assembly mechanism of DENV2 virus.[14] Nugroho in 2017 [15], identified seven flavonoids which included quercetin 3-(2*G*-rhamnosylrutinoside), kaempferol 3-(2*G*-rhamnosylrutinoside), quercetin 3-rutinoside, myricetin 3-rhamnoside, kaempferol 3-rutinoside, quercetin and kaempferol were isolated from the leaves of *C. papaya*. [16]

Head and Lauter in 1956 reported the presence of flavonols, tannins, organic acids, alkaloids [17], trace unsaturated sterols [18] and glycosides [19]. Other studies have also shown the presence of saponins, flavonoids, phenols, protein, amino acid, steroid, anthraquinones and terpenoids [20]. These leaves are also rich sources of vitamins such as thiamine (B1), riboflavin (B2), ascorbic acid (C), and minerals such as calcium, magnesium, sodium, potassium and manganese.[21]

Based on the positive outcomes of various research, Akhila and Vijayalakshimi, in 2015 attempted to further characterise constituents, using Liquid Chromatography-Mass Spectroscopy (LCMS). Identified constituents are provided in Table 1.[22]

1: COMPOUNDS IDENTIFIED IN PAPAYA AQUEOUS EXTRACT

Compond name	Molecular mass
Tocopherol	430.72
Ascorbic acid	176.13
Carpaine	466.71
Deoxykaempferol	270.25
Kaempferol	286.24
Deoxyquercetin	286.25
Quercetin	302.24
Dicoumarol	336.31
Coumaroylquinic acid	338.32
Coumarin	146.15
Folic acid	441.41
Cystine	121.16
Homocysteine	135.19
Cysteine sulphoxide	177.22
L Glutamic acid	147.13
p- Coumaroyl alcohol	150.18
dimethoxy phenol	154.17
umbelliferone	162.15
phenylalanine	165.19
Caffeoyl alcohol	166.18
Methyl nonyl ketone	170.30

Conclusion:-

Treatment for dengue is usually symptomatic. Some cases require platelet transfusions and fluid management [23]. One of the most disturbing aspects of the problem of dengue is that there are no effective antiviral agents available to treat dengue complications. Though symptomatic treatment works in most mild cases, some cases progress to complications very fast and this often make it difficult to save the life of the patient. The most severe form of dengue is the hemorrhagic form, This may be the reason a lot of effort has been put into mediating this specific symptom.

As yet research and several clinical trials have indicated that *C. Papaya* leaves can be used in addition to existing treatment, especially in patients with DHF, by increasing the platelet count, and shortening the hospitalisation period. Being easily available and affordable, the use of papaya leaves seems to be occurring indiscriminately, where available. Sarala and Pakinkar in 2014, and Ansari in 2016 [24], both expressed concern that besides a handful of clinical trials and with capsules containing the extract in India, there is no consistent data available on the mode of preparation, pharmacokinetic properties and he absorption of the active ingredient. However, further investigations are required to gain insight into standardizing this very promising treatment.

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