Extract of *Carica papaya* L. leaves: Standardising its use in dengue fever

Sir,

Currently, the medical fraternity is facing a challenge in treating dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) apart from classical dengue fever (DF). The pathophysiological mechanism by which the virus induces thrombocytopenia is bone marrow suppression due to circulating interleukins as a result of stringent host immune response. The dengue virus is trophic toward the cells of the monocyte macrophage system and endothelium, inducing apoptosis to a larger extent and necrosis to a lesser extent. As a result, the virus infects the vascular endothelium inducing a spontaneous aggregation of platelets to them, culminating in peripheral platelet lysis. The interleukin tumor necrosis factor-C, interleukin-1α, interferon alpha, soluble CD4, soluble CD8, interleukin 2, and interferon gamma A also disrupt the zona adherens of the endothelial cells, causing them to retract and open the intercellular junction, thus increasing vascular permeability. Although platelets play a vital role in maintaining the intercellular junctions of endothelium, endothelial thrombocytopenia in DHF offers no help to the already fragile vascular wall. In the peripheral circulation, premature destruction of platelets is induced by abnormal activation and prevention of normal platelet aggregation and direct infection of the platelets by the virus. Auto immune-mediated destruction of platelets and an interesting concept of immune deviation manifested by immature atypical neutrophil, lymphocyte population, over production of interleukins and deranged T-cell response has been noticed by researchers. The NS1 antigen expressed on the surface of the infected cell mediates complement activation which may also be involved in vascular leakage in DHF/DSS patients.

Oral consumption of *Carica papaya* L. extract leaves is found to increase the platelet levels as early as 24 h with a significant increase in the total white blood cell and neutrophil counts as well. In murine models, the extract combats heat and hypotonicity-induced hemolysis of cells by exhibiting its membrane stabilizing properties in erythrocytes and lysosomes thereby inhibiting the release of proteolytic enzymes. As a sequel, Subenthiran et al. confirmed the lowering of hematocrit levels in dengue patients after administration of the extract. As known earlier, arachidonate 12-lipoxygenase (ALOX 12) also known as the platelet type lipoxygenase (ALOX 12) gene aids in the production and differentiation of megakaryocytes which leads to the production of 12-hydroxyeicosatetraenoic acid and therein production of platelets. Adding on, platelet-activating factor receptor (PTAFR) gene, expressed in megakaryocytes is involved in platelet aggregation. The KNA extracted from the blood of the patients who were administered the extract showed a 15-fold increase in the ALOX 12 gene activity. This gene is platelet-specific and is a direct target of transcription factor RUNX1 in megakaryocytes and platelets. As reported, there was a 13.42-fold increased expression of the PTAFR gene among the patients who were given the extract orally as compared to the control group substantiating the role of papaya extract in platelet aggregation. It has been noted that two components of a viral serine protease, NS2B and NS3, play a pivotal role in viral replication. It is crucial for the production of the polyprotein precursor before the assembly of the viral complex. Researchers screened the flavonoid components of papaya leaves and concluded that quercetin has significant inhibitory activity against NS2B-NS3 serine protease, particularly against Dengue virus serotype 2 and exerts its antiviral property by preventing viral assembly.

The major hurdle in using these leaves for treatment, is the dearth of substantial and consistent findings. Concrete evidence is still lacking as significant number of studies were done on patients solely based on the symptoms alone. As on date, a study in Malaysia and a pilot study in Bengaluru, India were found to have a systematic approach in evaluating the effect of the leaf extract. Although capsules of the extract are currently marketed in India the mode of preparation, pharmacokinetic properties and the absorption of the active ingredient are still grey areas to be addressed. Hopefully in future, this can be meted out by conducting large-scale studies in DF confirmed human subjects in a tertiary hospital set up, standardizing the dosage and period of the intervention.

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**Conflicts of Interest**

There are no conflicts of interest.

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