

## A review on papaya leaf extract used to increase in platelets

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Submitted: 15-15-2023

Accepted: 25-12-2023

### I. INTRODUCTION

*Carica papaya* is a member of the Caricaceae and is a dicotyledonous, polygamous, and diploid species. It originated from Southern Mexico, Central America, and the northern part of South America. It is now cultivated in many tropical countries such as Bangladesh, India, Indonesia, Sri Lanka, the Philippines, and the West Indies including Malaysia. Malaysia is known to be one of the top 5 papaya exporting countries. The papaya fruit is globally consumed either in its fresh form or the form of juices, jams, and crystallized dry fruit. The ripe fruit is said to be a rich source of vitamin A, C, and calcium. There are many commercial products derived from the different parts of the *C. papaya* plant, the most prominent being papain and chymopapain, which is produced from the latex of the young fruit, stem, and the leaves. *C. papaya* leaves have been used in folk medicine for centuries(1).



**Fig. 1 Papaya leaf**

*Carica papaya* is an herbaceous, non-woody, tree-resembling plant that belongs to the Caricaceae family. The common name of this evergreen plant is papaya, which has spinally arranged broad leaves (50–70 cm) and bears fruit throughout the year. *C. papaya* is a perennial plant that is native to Southern Mexico and is currently distributed throughout tropical areas worldwide. *C. papaya* fruit has been considered a quasi-drug, and the biological activities of its various parts, including leaves, fruits, shoots, roots, rinds or latex, and seeds, have been proved by several investigations. *C. papaya* leaves have shown multiple therapeutic effects. Its leaves contain high amounts of fat-soluble vitamins (A, D, E, and K); vitamins B and C; and minerals such as iron, sodium, and magnesium. In addition, potassium, nitrogen, and calcium are more absorbed during plant growth, and phosphorus is less extracted. In a few Asian countries, the young *C. papaya* leaves are steamed to eat, similar to spinach, for health benefits. *C. papaya* leaf juice plays a role in liver repair and normalizes clotting by increasing the platelet and white-blood-cell count. Several studies have proved the potential of *C. papaya* leaves in preventing the complications of thrombocytopenia, due to its phytochemical profile. As a result, this review was produced to investigate the most recent studies on *C. papaya* leaves in terms of alleviating thrombocytopenia effects.(2)

## Thrombocytopenia

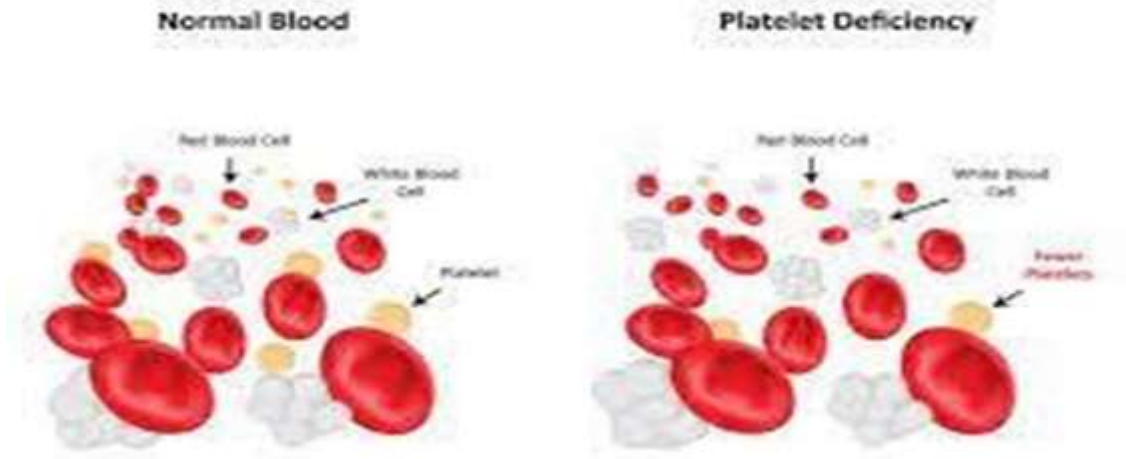


Fig. 2 Thrombocytopenia

constipation. Its seeds can be pounded and then ingested to treat intestinal worms. Toothache, corns and warts can be treated by topically

applying its sap. Recently, the *C. papaya*, particularly its leaf part, has attracted wide attention for its potential use in dengue treatment.

### Diagnosis of Therombocytopenia

## DIAGNOSIS OF THROMBOCYTOPENIA

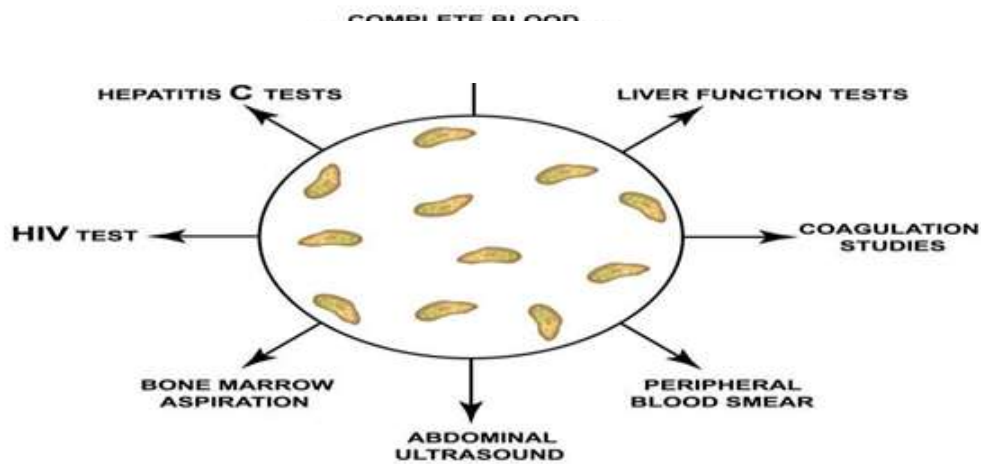


Fig. 3 Diagnosis of Thrombocytopenia

Thrombocytopenia is a hematological condition that is characterized by lower platelets

count ( $<150 \times 10^3$  cells/ $\mu$ L of blood) and is often a multi-factorial disease . Thrombocytes,

commonly known as platelets, are blood cells (either nucleated or anucleated) produced in marrow with a normal range of  $(150-450 \times 10^3)$  cells/ $\mu\text{L}$  of blood. The platelets play a significant role in the physiological system of the body, especially in vascular injury reactions. Platelets forestall the excessive blood loss after injury by forming a structural plug. The various receptors are present in the layers of plug for collagen, ADP, vessel divider von Willebrand factor, and fibrinogen. (2)

The platelets have an average life span of 8–10 days, where two-thirds of the platelets

are in blood and one-third is in the spleen. The major causes of thrombocytopenia include increased destruction, splenic sequestration, and decreased production of platelets by bone marrow. The causative agents implicate a variety of types of thrombocytopenia, such as drug-induced thrombocytopenia, idiopathic thrombocytopenic purpura, HIV induced, dengue, liver cirrhosis, leukemia, chikungunya, hepatitis C virus, malaria, and various infections. The incidence of thrombocytopenia in adults is 3.3/100,000 annually, with a prevalence factor of 9.5 per 100,000 adults. (2)

Drug profile :-

Domain :-	Flowering plant
Kingdom :-	Plantae
Sub Kingdom :-	Tracheobionta
Division :-	Magnoliophyta
Class :-	Magnoliopsida
Subclass :-	Dilleniidae
Phyllum:-	Steptophyta
Order :-	Brassicales
Family :-	Caricaceae
Genus :-	Carica
Botanical Name :-	Carica papaya Linn

Parts of papaya plant and its medicinal uses :-



Fig. 4 parts of papaya plant and its medicinal

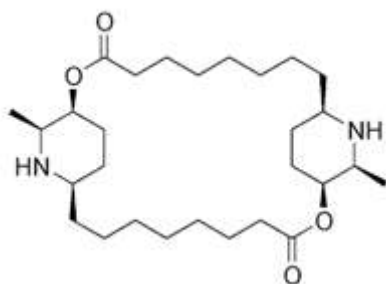
Plant Parts	Medicinal uses
Ripe fruit	Sinuses, chronic forms of skin indurations in Caribe, Philippines; Chronic skin ulcers in Jamaica Stomachic, digestive, diuretic, expectorant, sedative and tonic, bleeding Piles and dyspepsia in India
Green fruit	Malaria, hypertension, diabetes mellitus, hypercholesterolemia
Latex	Dermatitis and psoriasis in Africa, Asia, Europe
Leaves	Heart tonic, febrifuge, vermifuge, colic, dengue fever, beriberi, abortion, asthma India, Stomach troubles, cancer in Australia
Flowers	Jaundice, cough, hoarseness, bronchitis, laryngitis, and tracheitis in Asia
Seeds	Anti-fertility. Antimicrobial, fungicidal, carminative, counter irritant

Chemical constituent's :-

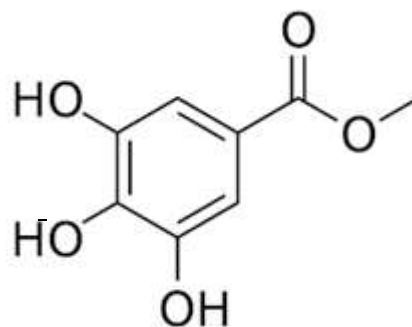
The leaves contain multiple bioactive components as follow –

(3)

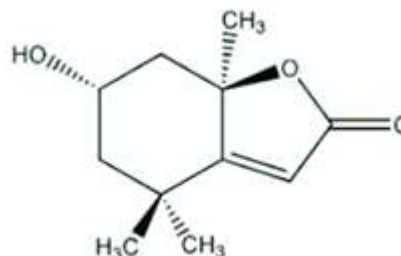
1) Carpaine :- It was separated as a white crystalline.



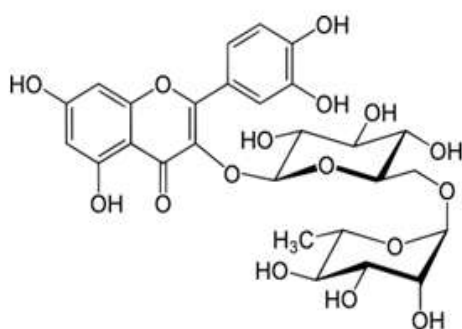
2) Methyl gallate :- It was separated as a whitish grey powder.



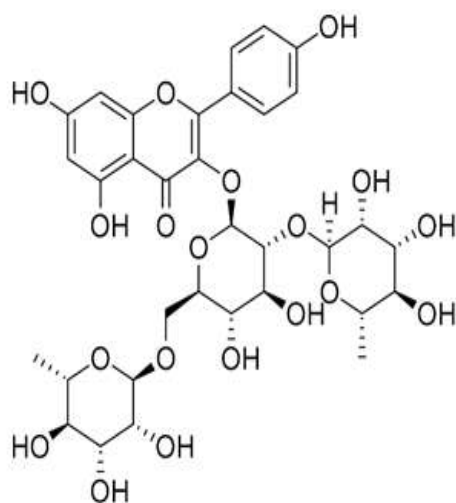
3) Loliolide :- It was separated as a white amorphous powder



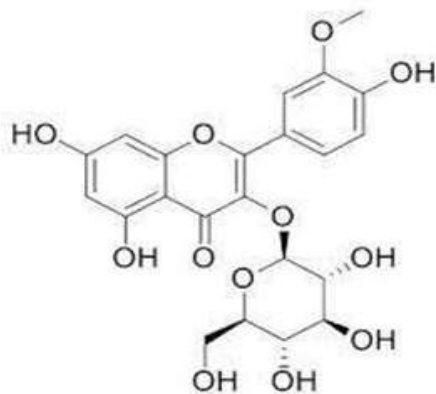
4) Rutin :- (quercetin-3-O-rutinoside or sophorin or rutoside)  
It was separated as a yellow powder



5) Clitorin  
(kaempferol 3-O-(2'',6''-di- $\alpha$ -Orhamnopyranosyl)- $\beta$ -glucopyranoside)] :- It was separated as a yellowish powder.

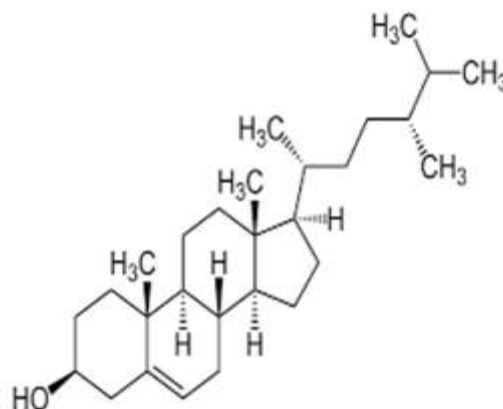


6) isorhamnetin 3-O- $\beta$ -D-glucopyranoside :- It was separated as a yellowamorphous powder.



7) Campesterol :- Campesterol is a member of phytosterols , a 3-beta sterol , a 3betahydroxy Delta 5 steroid and a C28 steroid . It has role as a

mouse metabolite . it derives from a hydride of a campestane.



Phytochemical Screening :-

*C. papaya* L. contains a high concentration of phenolic compounds and minerals, which appear to be responsible for its high antioxidant capacity and may help to prevent and cure ailments . The phytochemical analysis is required to investigate the pharmacological potential of plant extracts and their fractions. The phytochemical screening of fruit and leaves extracts of *C. papaya* reveals the presence of alkaloids, flavonoids, cardiac glycosides, saponins, phenols, tannins, and terpenes. Iskandar and Mustarichie investigated the pharmacognostic parameters of the Indonesian Pharmacopeia of *C. papaya*. The major phytocomponent, 2-ethyl-1-hexanol, in *C. papaya* leaf extract in terms of relative abundance originated from Padang (92.50%), Bandung (76.78%), and Sumedang (32.17%) .(2)

The ethanolic leaf extracts of *C. papaya* showed the greatest levels of total phenols ( $49.24 \pm 2.16$  mg GAE equivalent/g) and flavonoids ( $47.16 \pm 2.15$  mg Rutin equivalent/g) (20). The most active extracts were ethanolic leaf extracts ( $25.8 \pm 0.5$  mm), ethanolic fruit extracts ( $24.5 \pm 0.1$  mm), and methanolic leaf extracts ( $25.8 \pm 0.5$  mm) ( $23.4 \pm$ mm). The lowest activity was found in the aqueous leaves extract ( $10.5 \pm 0.6$  mm). Aqueous extracts showed significantly decreased fungal toxicity when compared to extract prepared using organic solvents. Three dilutions of *C. papaya* leaves and fruit extracts (10, 100, and 1000 g/mL) were made to investigate brine shrimp cytotoxicity. Anticancer components in the form of essential phytonutrients were discovered in the plant extracts. Plant extracts with an LD50

of 1000 g/mL were physiologically active, but those with an LD50 > 1000 g/mL were not (non-toxic).(2)

Similarly, Sarjono et al. reported that the ethanol extract of *C. papaya* leaves contains quinines and steroids. Endophytic bacteria in symbiosis with *C. papaya* leaves produced flavonoids, alkaloid compounds, saponins, triterpenoids, and tannins, all of which exhibit antioxidant properties. Flavonoids such as

hesperidin, kaempferol, naringenin, routine, and quercetin were discovered to have the highest antioxidant activity in *C. papaya* leaves. Furthermore, the presence of saponins and alkaloids in complex media binds free radicals. Proteolytic enzymes (papain, Caricain chymopapain), alkaloids (carpasemine, carpain), sulfur compounds (benzyl isothiocyanate), triterpenes, flavonoids, oils, and organic acids are all found in *C. papaya* seeds and leaves .(2)

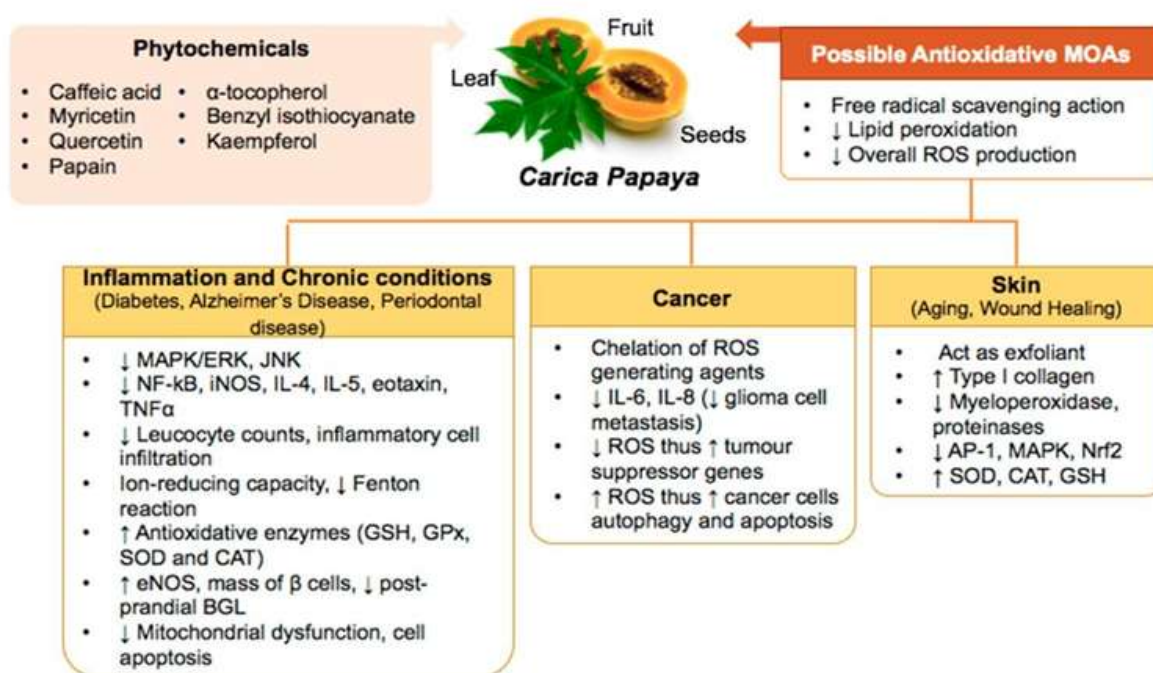


Figure 1. Role of oxidative stress in different medical conditions.

Pharmacological action :-

*C. papaya* is tremendously efficient in different types of ailments cure due to availability of wide varieties of phytoconstituents in almost all parts of plant. (3)

➤ Antioxidant activity :-

Oxidative stress tends to be the most critical risk factor, as it results in many life-threatening diseases. The crude extract of *C. papaya* leaves can reduce oxidative stress. An experimental study was monitored in Swiss mice with cyclophosphamide-induced oxidative stress who received 500 mg/kg BD of *C. papaya* leaf extract for 15 days. Studies exhibited that

*C. papaya* leaf extract was beneficial against oxidative events, and it prevented damage . Research is going on to find new

sources of antioxidants of natural origin which are safe and economically viable. According to a study hexane fraction of *C. papaya* male flower shows a good antioxidant activity .

➤ Antibacterial activity :-

Pathogenesis by bacteria has become a major challenge, along with its more resistant responses to treatment drugs. The antibacterial activity of *C. papaya* leaf extracts was observed against *S. aureus*, *B. subtilis*, *E. coli*, and *S. typhi* by using the agar well-diffusion method. The results illustrated the higher activities against tested bacteria with *E. coli* being the maximum. Methanol CPLE fractionation yielded seven fractions, out of which five fractions exhibited the highest activity against *E. coli*. Hence, *C. papaya* leaf extracts can be used in the treatment

of urethritis, gastroenteritis, wound infections, and typhoid fever . Oleic acid isolated from the seed and was tested for its chemo-preventive action on live fish which was infected with pathogenic bacteria named Klebsiella PKBSG14 and it was found that drug bioavailability increases with an increase in oleic acid .

➤ Anti-malarial activity :-

In South Asian nations, the usage of *C. papaya* leaf for antimalarial purposes is commonly recognized. In vitro testing was used to assess the effectiveness of *C. papaya* leaf extracts against *Plasmodium falciparum* 3D7 and Dd2 strains. The dichloromethane extract from papaya leaves showed considerable antimalarial efficacy. Bioassay-guided fractionation resulted in a more active carpaine isolate with IC50 values of 2.01 ± 0.18 g/mL (4.21 m) and 2.19 ± 0.60 g/mL (4.57 m) against both strains. The leaf extract was shown to be non-toxic to healthy, uninfected human red blood cells, due to its high selectivity. Antimalarial activity was, therefore, demonstrated in this investigation . Swiss mice infected with *Plasmodium berghei* NK65 were given methanolic leaf extract of *C. papaya* to assess if it has antimalarial properties. Six groups of six mice were made from 36 mice in total, with Group A and B acting as normal and disease controls, respectively. Groups C and D received chloroquine (10 mg/kg BW) and artesunate (10 mg/kg BW), whereas Groups E and F received methanolic leaf extract from *C. papaya* at 400 and 600 mg/kg BW, respectively. The *C. papaya* extract decreased parasitemia by 56.76 and 75.53% at 400 and 600 mg/kg BW, respectively, during a curative test, whereas chloroquine and artesunate reduced parasitemia by 92.86 and 90.67% at 10 mg/kg BW, respectively. The extract substantially lowered WBC count and raised HGB and HCT concentration in the treated mice as compared to untreated infected animals. The study discovered that the methanolic leaf extract of *C. papaya* has antimalarial properties .

➤ Anti dengue activity :-

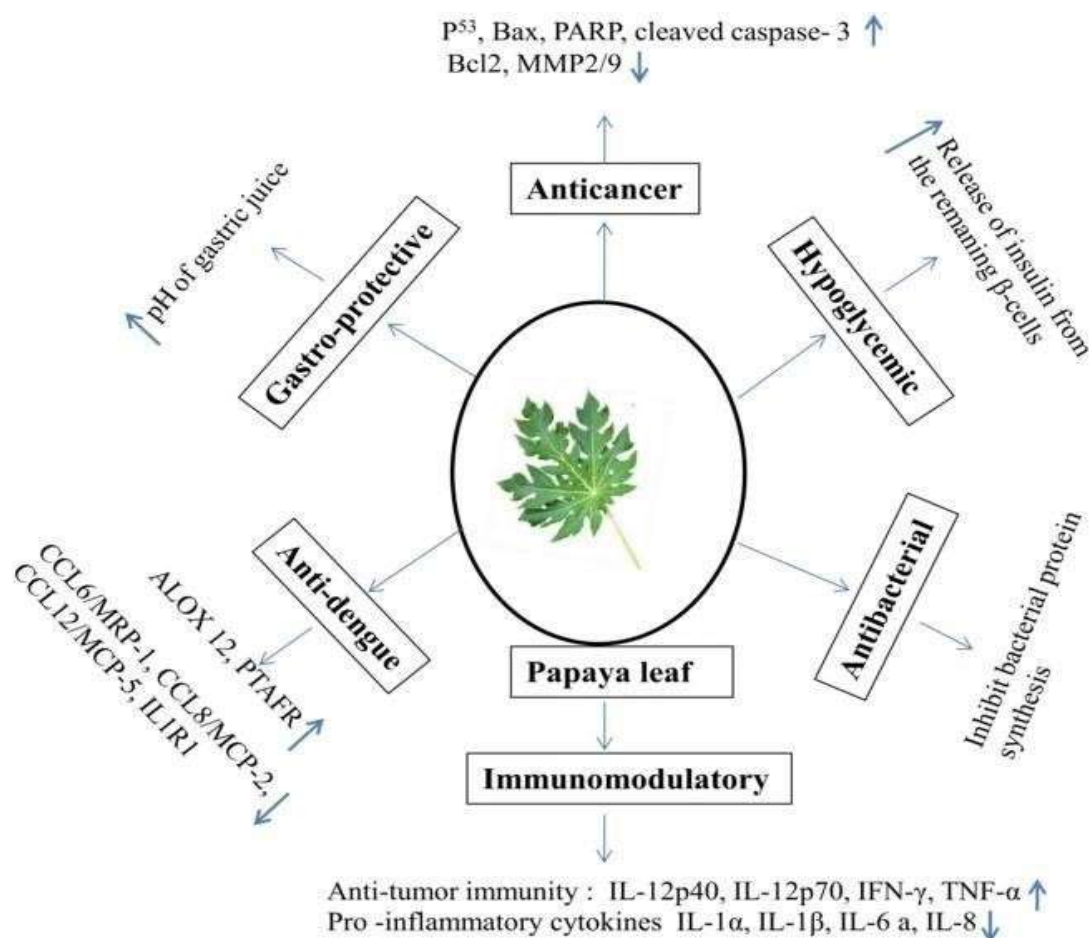
Dengue is an arboviral disease caused by dengue virus of the Flaviviridae family. Dengue fever occurs due to the infection transmitted by infected *Aedes aegypti* mosquito as a carrier of this virus . The

occurrence of this disease has increased by almost 30-fold in the previous three decades especially in developing countries. A number of infections caused by dengue virus ranges from 50 to 100 million per year , and every year, there is a new outbreak of dengue being reported. This viral infection leads to thrombocytopenia condition in infected patients . The most common reason for thrombocytopenia is the poor production of platelets by the bone marrow, minimal survival of platelets, and sequestration of the platelets by the leptospirosis, malaria, dengue, and other viral infections. Major quantitative or qualitative dysfunction and reduction in the platelet count is the cause of mucocutaneous bleeding in the patients . The platelet count drops below the normal level to an extent depending upon severity of viral infections. Moreover, viral fever is generally a self-limited illness which requires supportive care for complete recovery.

➤ Anticancer activity :-

Cancer is a huge group of diseases which can affect any organ of the human body with abnormal body cell growth. Cancer is also commonly known by the name of malignant tumour, and the cells affected by this disease have a tendency to spread from the originating organ to others very rapidly. Nowadays, cancer is one of the major causes of death worldwide, with 9.6 million estimated deaths due to this lethal disease in a year . Prostate, lung, colorectal, liver, and stomach cancers are commonly found in males, while breast, colorectal, thyroid, lung, and cervical cancers are the most reported in females . The burden of this disease is continuously growing in the world, exerting tremendous emotional and financial strain on patients, their families and health systems, especially in low- and middle-income countries. Alternative therapy includes different plant extracts and their bioactive ingredients responsible for tremendous health improvement, including the prevention and treatment of cancer in many countries .

The plant contains an enzyme, namely papain which is a constituent of papaya and very helpful in cancer treatment. Fibrin breaks down by papain which coats the tumor cells into amino acid. The pigment lycopene is found inside the papain which is highly reactive towards free radical and oxygen.



**Fig. Pharmacological action of papaya leaf**

Mechanism of Action of C. papaya against Thrombocytopenia

C. papaya leaf has been scientifically proved to possess therapeutic potential against thrombocytopenia .

It is evident from various studies that C. papaya leaf increases platelet production by gene expression activity. The activity of certain genes is increased by the action of C. papaya leaf extract, including platelet-activating factor receptor (PTAFR) and arachidonate 12-lipoxygenase (ALOX-12) genes. The high expression of specific genes stimulates the bone marrow to produce more megakaryocytes, these megakaryocytes are the stem cells responsible for platelet production, and, upon maturation, they break up into small fragments called platelets, hence increasing the platelet production and aggregation in circulating blood. (2)

A recent experimental study has shown

that carpaine from C. papaya leaf is responsible for this mechanism of action . C. papaya leaf juice helps to increase the expression of CD110 receptors on the megakaryocytes, which are effective against chemotherapy- induced thrombocytopenia .Thrombocytopenia can also be managed with C. papaya leaf by reducing platelets' destruction. C. papaya leaves contain flavonoids that bind to the viral assembly's proteases, which are the working and replicating units of viruses, to cease viral replication. This process minimizes the platelet destruction and sustains normal haematocrit levels, as elaborated in Figure 2. The leaf extract also exhibits free radical scavenging and antioxidant properties, which impair destruction, thus preventing haemolysis and bleeding. These extracts also enhance the platelet production by increasing the activity of ALOX-12 and PTFAR by 15- and 13-14-folds, respectively .(2)



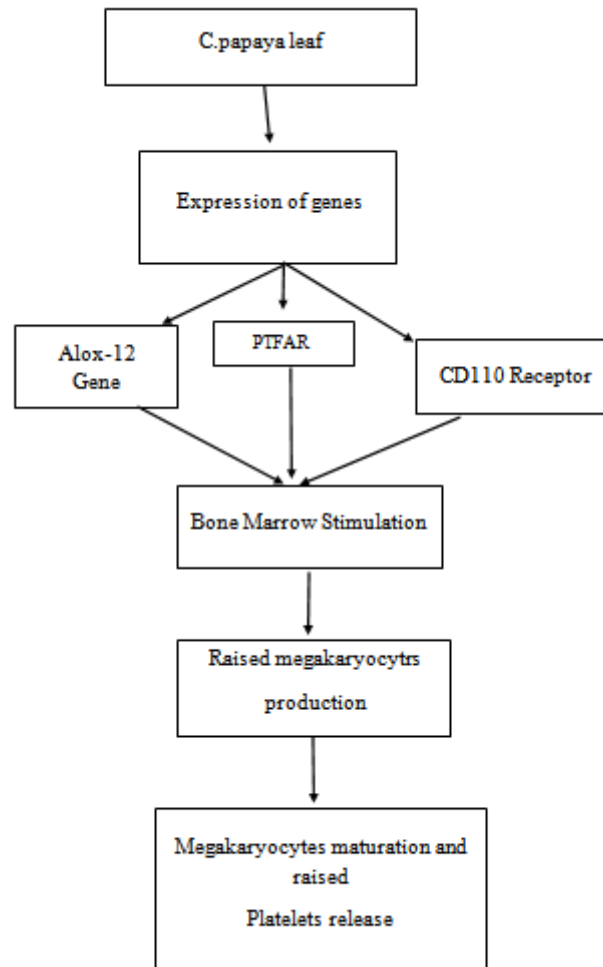


Fig.1 :- Mechanism of action of C. papaya in thrombocytopenia modulation

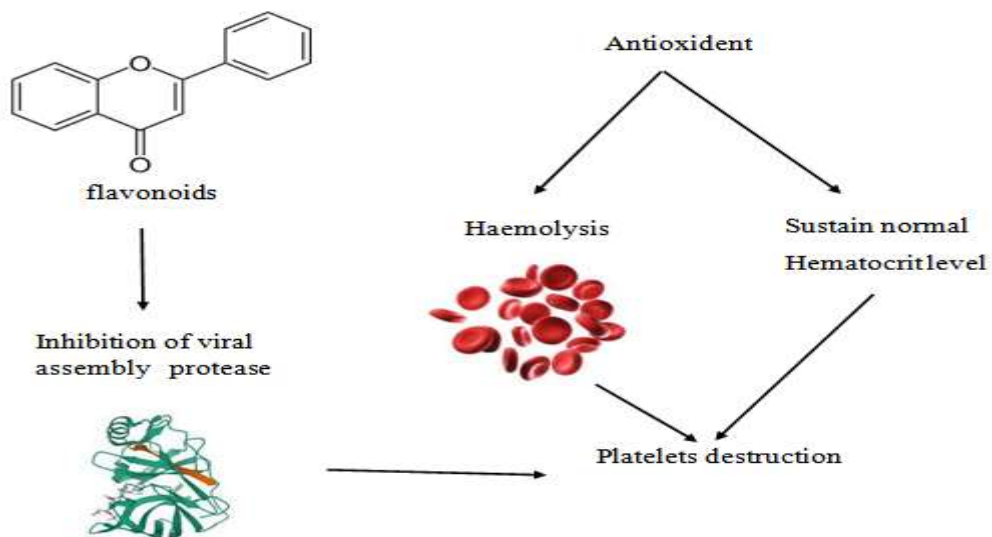


Fig 2 . Role of flavonoids and antioxidants of C. papaya leaf in inhibiting plateletdestruction.

Uses Of Papaya leaf :-

- 1) Can Treat Dengue-related Symptoms One of the most prominent medicinal benefits contained in papaya leaves is its ability to treat some of the symptoms associated with dengue. papaya leaf therapy has very few side effects involved and is said to be much more cost-effective than conventional treatments. (4)
- 2) Maintains blood sugar at reasonable level Papaya leaves are often used in Mexican folk medicine as a natural remedy to treat type 1 and type 2 diabetes and improve control. blood sugar.(4)



- 3) May assist with digestive function Papaya leaf tea and extract is often used as an alternative therapy to ease uncomfortable digestive symptoms, such as bloating, gas, and heartburn (4)
- 4) May Have Anti-Inflammatory Effects Various papaya leaf preparations be commonly used to treat a wide range of internal and external inflammatory conditions, including skin rashes, joint pain, rheumatoid arthritis and muscle aches. (5)
- 5) Papaya leaves support hair and scalp health Topical applications of masks and papaya leaf juice are often used for improving hair growth and scalp health, but evidence is Its effectiveness for these purposes is limited.(5)
- 6) Papaya leaves contain several compounds with antioxidant properties such as flavonoids and vitamin E.(5)
- 7) Papaya leaves for healthy skin Papaya leaves are taken orally or applied topically as a way to help you maintain a soft, clear, and youthful skin. (4)
- 8) Papaya leaves have been used in traditional medicine practices to help prevent and treat no. of platelets in human body and RBC count.



**Fig. uses of papaya**

Marketed Preparation :-

1) Caripill Tablet

It is used to treat digestive disorders such as bloating and chronic indigestion. It is known to improve the digestion of carbohydrates and fats due to the presence of the enzyme called papain. It is also known to help in the treatment of dengue fever due to its ability to improve platelet count, and thus, manage the symptoms.

(6)

Product highlights

Contains carica papaya leaf extract as the active ingredient

- Helps in the process of digestion and treats digestive disorders
- Aids in the treatment of stomach ulcers

- Increases low blood count and helps to fight dengue
- Improves symptoms of dengue such as fever and pain

2) SBL Carica Papaya Mother Tincture :-

SBL Carica Papaya Mother Tincture is an effective homoeopathic remedy used in the treatment of indigestion and other stomach related issues such as loss of appetite. It is a multipurpose health tonic which is used in the treatment of various health issues such as urinary issues, intestinal worms and enlargement of the liver. Contractions in the uterus and irregular periodflow is also addressed using this medicine.

(6)



Fig. Caripill Tablet



Fig. SBL Carica Papaya Mother tincture

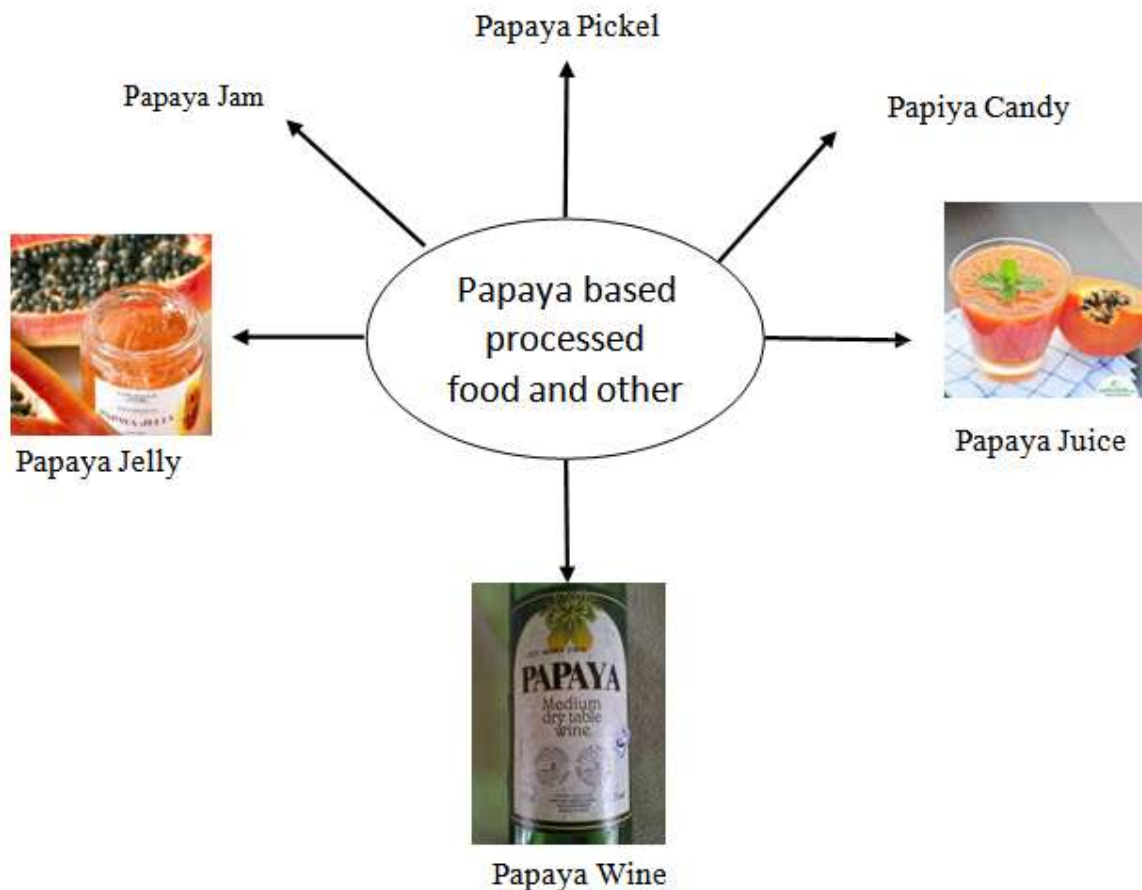


Fig. Other marketed product based on papaya

## II. CONCLUSION :-

C. papaya is a tropical plant with heavenly potentials in its various parts, especially the leaves. The papaya leaves contain various phytochemicals, such as antioxidants, alkaloids, flavonoids, caprine, saponins, terpenes, etc. The present review concludes that C. papaya leaf has a potent therapeutic effect against various diseases, due to its phytochemical profile. The distinctive characteristics of papaya leaf mitigate diabetes, malaria, viral infections, compromised immunity, oxidative stress, and cancer. A large number of research studies prove that C. papaya leaf has an influential role against thrombocytopenia by targeting the ALOX-12, PTFAR, and CD110 receptor genes. The causative agents that induce thrombocytopenia include various drugs, dengue, chemotherapy, and numerous physiological and pathological conditions. The commercially and freshly prepared doses of C. papaya leaf equally increase the blood platelet count, as well as impair the platelet destruction without causing any harm.

The considerable active antithrombocytopenia components of papaya leaf are phytochemicals that include carpaine, flavonoid, and antioxidants. These components directly influence the respective genes, but further investigations are still required to find out the actual component and its mode of action that alleviate thrombocytopenia.

In the recent year's dengue has emerges out as a serious epidemic disease in tropical countries. Unfortunately, death rate is increasing due to its inefficient and improper methods of treatment. At present there are several research organizations (Bill and Melinda Gates Foundation) indulging in discovery of vaccine for dengue. In 2014, phase three trail for dengue was conducted by Sanofi Pasteur on approx. 10,275 children aged 2-14 years in the following countries (Malaysia, Indonesia, Thailand, Philippines, and Vietnam). Meanwhile old herbal formulation which are available in market should to be improvise. There is need of improvisation of available marketed C. papaya leaves

supplements for better treatment. Conflict of interest: The author has declared that no conflicts of interest exist.

#### REFERENCES :-

- [1]. Research Article Carica papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever.
- [2]. Review Delving into the Therapeutic Potential of Carica papaya Leaf against Thrombocytopenia
- [3]. National Institutes of health organisation website  
<https://pubchem.ncbi.nlm.nih.gov/>
- [4]. Review Ethnomedicinal uses, nutritional composition, phytochemistry and potential health benefits of Carica papaya.
- [5]. Phytochemistry, pharmacological activities, nanoparticle fabrication, commercial products and waste utilization of Carica papaya L.: A comprehensive review
- [6]. Use data on TATA 1mg website  
<https://www.1mg.com/otc/sbl-carica-papaya-mother-tincture> and  
<https://www.1mg.com/otc/caripill-tablet-otc223972?wpsrc=Google+Organic+Search>
- [7]. AOAC, (1980). Official methods of analysis. 13th Ed. Washington D.C
- [8]. Atta, K. Bonsu (1999). "The Power of Garlic". Cardiovascular disease prevention Association, Buea, Cameroon.p.72.
- [9]. Bruce, S. and Peter, C. A. (2008). Handbook of environmental physiology of fruit crops. 1 st Ed. p.217.
- [10]. Claude, B. and Paule, S. (1979). The manual of natural living. 1st Ed. Biddles Ltd, pp.98 - 101.
- [11]. David, H. (1983). The new holistic herbal. 3rd Ed. Findhorn press, U.S.A. pp: 241.
- [12]. Desmond, R. Layne (1995)".Pawpaw": New crop factsheet. Department of Horticulture, Poole Agriculture Centre,
- [13]. Nandini, C.; Madhunapantula, S.R.V.; Bovilla, V.R.; Ali, M.; Mruthunjaya, K.; Santhepete, M.N.; Jayashree, K. Platelet enhancement by Carica papaya L. leaf fractions in cyclophosphamide induced thrombocytopenic rats is due to elevated expression of CD110 receptor on megakaryocytes: Carica papaya leaf juice for the treatment of thrombocytopenia. J. Ethnopharmacol. 2021, 275, 114074.
- [14]. Ahmed, M.; Memon, F.; Irum, N.; Dahri, G.M.; Mughal, A.; Kumar, G. Papaya seeds: Their effects on quantitative platelets count in female rabbits. JPUMHS 2020, 10, 47–53.
- [15]. Babu, R.; Kubavat, S.; Poullose, K.P.; Srinivasa, K.P.K.; Handae, S. A randomized, double-blind, placebocontrolled, proof of concept study to assess the safety and efficacy of Carica papaya and Tinospora cordifolia leaf extract (Thrombobliss) in subjects undergoing chemotherapy treatment and subjects with systemic microbia. Int. J. Clin. Trials 2017, 4, 116–121. [CrossRef]