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REVIEW ARTICLE

Role of *Carica papaya* in Thrombocytopenia

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Abstract

Background: *Carica Papaya,* commonly referred to as Papaya, has historically been utilised in various medicinal practices for its bioactive constituents. Thrombocytopenia is a medical condition characterised by a lack of platelets, leading to the probable onset of bleeding complications and many related concerns. **Aim:** *C. papaya* contains several bioactive compounds that have been thoroughly investigated for their potential effects on platelet function and production. Papain, chymopapain, carpaine, and many flavonoids are significant constituents. These compounds possess anti-inflammatory and antioxidant properties, and certain studies suggest that they may enhance platelet counts. After this, more research should be done to figure out exactly how these substances affect the pathways that control and make platelets. **Method:** A comprehensive literature assessment was conducted utilising databases from Springer, Elsevier, PubMed, and Science Direct. **Results:** *C. papaya* possesses tropical foliage and promise. Papaya leaves contain phytochemicals. The phytochemicals comprise carpaine, saponins, terpenes, alkaloids, flavonoids, and antioxidants. Papayas, abundant in vitamins and minerals, are low in calories. The leaf of *C. papaya* possesses distinctive therapeutic and medicinal properties for treating thrombocytopenia, as evidenced by scientific research. Minerals and secondary metabolites in the leaves, such as quercetin and carpaine, help platelets form and stop them from breaking down. **Conclusion:** Thrombocytopenia may arise after treatment, dengue fever, chemotherapy, and many other diseases. Novel and commercial *C. papaya* leaf dosages elevate platelet counts and inhibit breakdown.

Major Finding: Thrombocytopenia is a clinical manifestation that refers to a low platelet count, *i.e.*, <150 × 103/µL, of blood, resulting in imbalanced hemostasis, which leads to several fatal complications. The causative factors vary greatly, but, as a consequence, they interfere with platelet production and promote destruction, leading to death. *C. papaya* leaf has unique therapeutic and medicinal characteristics against thrombocytopenia, and this is supported by scientific studies. Secondary metabolites and minerals in the leaf, such as carpaine and quercetin, promote platelet production and inhibit platelet destruction.

Keywords: Carpaine, Papain, *Carica papaya*, Saponins, Thrombocytopenia

1. Introduction

Platelet counts are frequently inadequate in individuals who suffer from a multitude of chronic conditions. It is possible that you are suffering from thrombocytopenia if your platelet count is lower than 150 × 109/L. Platelet counts that are lower than 100 × 109/L are considered to be relevant in the field of medicine. When the platelet counts fall within the range of 50 to 100 × 109/L, a diagnosis of mild thrombocytopenia is made. The presence of a platelet count that is lower than 50 × 109/L is indicative of severe thrombocytopenia[1]. The cause of thrombocytopenia can range from relatively modest to life-threatening clinical complications.

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Despite this, mistaken diagnoses of thrombocytopenia sometimes occur, and they may be the result of artifacts that occur in laboratories[2,3]. In the beginning, a complete blood count and a peripheral blood smear of the patient are required to be examined for the presence of thrombocytopenia[4]. Despite the fact that haematology analyser automation has advanced, the analysis of peripheral blood is still considered to be an essential diagnostic tool[5]. An educated interpretation of the data of the total blood count is provided since there are morphological anomalies that cannot be discovered by an automated analyser. This is the reason for the giving of the data. The distinction between thrombocytopenia, which is the result of laboratory errors and thrombocytopenia, which is caused by actual factors, is an extremely important one, as it is essential to make this distinction. Thrombocytopenia is a condition that can be brought on by a variety of disorders, such as cancer, myelodysplastic syndrome, aplastic anaemia, and opportunistic infections[6,7]. There are a number of factors that can contribute to thrombocytopenia, including decreased bone marrow thrombopoiesis and increased platelet sequestration in the spleen. There are a number of factors that can contribute to thrombocytopenia, one of which is an increase in the fragmentation of platelets around the periphery of the blood vessels. A multitude of various disorders, like disseminated intravascular coagulation, thrombotic microangiopathy, and hypersplenism, can kill platelets. As platelets mature, they become more fragile and more prone to breaking when these things occur[8]. Thrombocytopenia can be attributed to three primary causes: platelet sequestration in the spleen, insufficient platelet synthesis by the bone marrow, and rapid platelet breakdown or destruction. It's also possible that a combination of these issues could be the cause of thrombocytopenia. It is possible that individuals who suffer from bone marrow failure disorders, such as aplastic anaemia and myelodysplastic syndrome, do not produce sufficient amounts of thrombocytes. It is also possible for individuals who have bone marrow-related illnesses, such as lymphoma, leukaemia, multiple myeloma, metastases, and bone marrow granulomas, to experience this manifestation. Certain disorders, on the other hand, such as Immune Thrombocytopenia (ITP), DIC, and thrombotic microangiopathies, are responsible for the destruction of a significant number of thrombocytes[9]. Various marketed formulations are available in Table 1. Platelets getting stuck together is a sign of congestive splenomegaly caused by portal hypertension. Some of the conditions that can cause portal hypertension are heart failure, hepatic vein thrombosis, vena cava thrombosis (also known as Budd-Chiari syndrome), cirrhosis (which includes alcoholic liver disease or chronic viral hepatitis), and very rarely, arteriovenous malformation of the splenic veins. Platelets are transported from the circulation pool to the splenic pool and kept there. Platelet sequester is the common name for this procedure. The *C. papaya* is a plant that is a member of the family Caricaceae[10]. It is an herbaceous plant that does not contain any sections that are made of wood. According to the Sanskrit language, for instance, it is referred to as *Erandakarkati*, while in Hindi it is called *Papita*, and in English, it is called *Papaya*. This fruit is the same thing that goes by many names. This plant was imported to India in the 1600s from tropical America, where it was originally found. There are wide leaves on the plant that are placed in a straight line and range in length from fifty to seventy centimetres. On top of that, it produces berries throughout the entire year[11]. The papaya plant, which is officially known as *C. papaya*, is a perennial plant that is native to southern Mexico. However, it is currently growing in tropical places all over the world. A great number of individuals are of the opinion that the fruit of the *C. papaya* species possesses medicinal qualities. The plant's rinds, fruits, branches, roots, leaves, slime, and seeds are only a few of the sections that have been demonstrated to possess biological impacts[12]. It has been discovered by researchers that the leaves of the *C. papaya* plant are beneficial to one's health in a variety of different ways. Most of the fat-soluble vitamins, including vitamins A, D, E, and K, can be found in the leaves of this plant. The amount of vitamins B and C, iron, salt, and calcium that they contain is also rather high. Furthermore, while the plant undergoes growth, it has the capacity to absorb higher quantities of potassium, nitrogen, and calcium, while exhibiting a significantly reduced uptake of phosphorus[13,14]. For the purpose of obtaining a variety of health benefits, the tender leaves of the *C. papaya* plant are prepared and consumed in a manner that is comparable to that of spinach in many Asian countries. Papaya leaf juice has been shown to increase the number of platelets and White Blood Cells

(WBC) in the bloodstream, which in turn promotes the healing of the liver and helps to maintain normal blood coagulation. Several investigations have indicated that *C. papaya le*aves, thanks to their phytochemical makeup, have the capacity to decrease the difficulties related to thrombocytopenia in patients[15]. Many of the currently available anticoagulants (like coumarins and heparin) and antiplatelet medicines (like aspirin) have their origins in chemical compounds[16]. As a consequence of this, we proposed doing research on the potential antithrombotic capabilities of *Tinospora cordifolia*. *Tinospora cordifolia* is a huge, *Menispermaceae* family member that is smooth, long-lasting, and climbs. Leaves are shed by it. It has a significant presence across the entirety of India and South Asia. In addition, there are several other names for it, including *gurcha* in Hindi, *amruthu* in Malayalam, *amrutha balli* in Kannada, *guduchi* in Marathi, and in Sanskrit. Numerous health benefits are associated with it, including hepatoprotective, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-stress, antileprotic, antimalarial, and immunomodulatory effects[17,18].

2. Botanical Description

All botanical descriptions are available in Table 2. An injury caused the Carica plant to sprout branches, and the entire plant is made up of a white latex material that can be found throughout its entirety. This material can be found throughout the entire plant. The stem is hollow and has a cylindrical shape with a diameter ranging from 10 to 30 cm. When grown to its full potential, the papaya plant can reach heights of anywhere between two and ten meters. Arborescent and perennial in nature, this herb grows in trees. The majority of the time, it has a single trunk; nevertheless, there are situations in which there are leaf scars and spongy-fibrous tissue that are extremely obvious. Additionally, it has a complex and extensive network of roots that reaches far and wide. The leaves are arranged in a spiral pattern, and they are clustered together in the middle of the stem. Both of these characteristics are characteristic of the plant. One meter is the maximum length that the petiole can grow to. It is hollow and has a colour that is either greenish or purplish-green. It is feasible for the petiole to reach this length. The leaf blade is palmate in form and has seven deep lobes. It is spherical in shape and has a diameter that spans from 25 to 75 cm. It is

Table 1. Marketed formulation of *C. papaya*

Company name	Brand name	Dosage form	References
Rochway	Papaya leaf extract capsules	All of the dry leaves that make up the capsule are finely powdered and come from natural papaya components.	10
Rochway	Papaya leaf extract – 500 ml	Papaya leaf extract that is dry and 100% bio-fermented from *C. papaya*	11
Herbal *Papaya*	Papaya Leaf (Paw Paw Twig) Extract (alcoholfree)	Sixty vegetable capsules made from dried Papaya leaf	12
Iowa Select Herbs LLC	Papaya leaf extract 4 oz (120 ml)	An extract of Papaya leaves in liquid form	13
SidoMuncul Herbal	Sari Daun Pepaya	For every capsule, there is 500 mg of dried extract of *Caricae* folium, also known as Papaya leaf.	14
Celebration Herbals	This product is an herbal tea, which is manufactured only from papaya leaves. There is no caffeine in it. The container measures 1.33 ounces (38 g) and includes 24 tea bags.	(Papaya leaves that have been fermented) Tea bags	15,16
Micro Lab Limited	Caripill	Extract of dried *C. papaya* leaves contained in a tablet	17

Table 2. Botanical Classification of the plant *C. papaya* Linn.

Domain	Flowering plant	References
Kingdom	Plantae	21
Sub Kingdom	*Tracheobionta*	22
Class	*Magnoliopsida*	23
Subclass	*Dilleniidae*	24
Super division	*Spermatophyta*	25
Phyllum	*Steptophyta*	21
Order	*Brassicales*	22
Family	*Caricaceae*	23
Genus	*Carica*	24
Botanical name	*C. papaya* Linn.	25

smooth on the surface of the leaf, in addition to having a heavy veining pattern. An extensive and profound tooth pattern can be found on each of the lobes. The blossoms are funnel-shaped, yellow in colour, and not particularly huge. They have the appearance of funnel clouds. They are able to be located in the crevices between the leaves, either alone or in clusters. There are three sorts of flowers: flowers that are female, male flowers, and flowers that are hermaphrodite. Female flowers are between three and five cm in length and have a vast pistil that is functional; nevertheless, they do not have stamens. Female flowers are identified by their size. They possess an ovary that is oval in form. Flowers that are male are placed on tall panicles that dangle from the ceiling and feature ten stamens that are clustered in two rows. In this particular instance, the only trace of the gynoecium that is present is a pistillode. Female hermaphrodite flowers are bigger than male flowers and include an ovary that is made of five carpellate structures. However, the appearance of these blossoms is contingent upon the time of year or the age of the tree. The *C. papaya* plant has a remarkable ability to survive in many geographical zones, stretching from tropical climes to moderate latitudes. Even Nevertheless, it is essential to cultivate the plants in locations that are not only warm and sunny but also protected from the wind, in order to provide the best possible conditions for their growth. A world in which everything is ideal would have an elevation that is lower than 1500 meters. The consequences of strong winds may be damaging, particularly for soils that are unable to compensate for the loss of considerable volumes of transpiration[19,20].

3. Profiles of Nutrition and Phytochemical Applications

According to the findings of a study, *C. papaya* has a significant amount of potassium (223 mg/100 g of fresh fruit), in addition to high quantities of salt, calcium, phosphorus, zinc, iron, copper, manganese, and magnesium. All phytochemicals and applications of *C. papaya's* available in (Figure 1). It is widely acknowledged that papayas are among the most important fruits due to their high levels of several nutrients, including vitamin A, vitamin C, vitamin B1, vitamin B2, thiamine, folate, riboflavin, niacin, calcium, potassium, iron, and fibre. Although it is low in calories, it is rich in a wide variety of vitamins and minerals with a high concentration. Roughly sixty per cent of the fruit that is present in every one hundred grams is mature fruit. There are 200 kilojoules of energy contained in one hundred grams of papaya. The material may contain three primary sugars: sucrose (48.3 g/100 g), fructose (21.9 g/100 g), and glucose (29.8 g/100 g). To put that into perspective, one hundred grams of fresh fruit has around 108 mg of ascorbic acid, which is a greater concentration than the 67 mg that are found in one hundred grams of oranges. Things that change quickly, like hydrocarbons, alcohols, terpenes, aldehydes, ketones, esters, benzyl isothiocyanate, and organic acids, are what give a product its taste and smell. These chemicals are responsible for the sensory properties that are present. Other than that, ethyl acetate, ethyl 2-methylbutanoate, and ethyl hexanoate have been linked to strawberry-like smells. Aliphatic and volatile hydrocarbons are the chemical groups that are present in substantial numbers and play a significant part in contributing to the scent. These chemical groups are among the important chemical groups that are considered to be present. Significant quantities of these hydrocarbons can also be found in the environment. In papayas, particularly Solo *C. papaya* cultivars, which contain 94% of the material, the volatile chemical known as linalool may be found in exceptionally high proportions. Some papaya varieties have even more of the ingredient than others. Taiwanese varieties feature a large quantity of the oxide cis-linalool, which

is the second most prevalent component. Linalool is the second most abundant component. The Taiwan cultivars, on the other hand, have a substantial amount of methanol[25]. A lot of studies have shown that when the fruit is fully ripe, there are a lot more aromatic compounds like 3-methylbutanol, butanol, terpineol, and benzyl alcohol. Researchers have discovered 103 distinct esters in papaya, with methyl butyrate being the most frequently discovered[26,27]. Fruit may contain numerous compounds, including benzyl isothiocyanate and terpene hydrocarbons. Linalool is just one of the many chemicals that can be found in fruit. The highest levels of butanol, 3-methylbutanol, benzyl alcohol, and α-terpineol can be found in the third stage of maturity. The concentration of this substance directly relates to the fruit's maturity level[28]. It is generally agreed that the colour of the flesh of the *C. papaya* fruit is an important characteristic in terms of the nutritional content of the fruit[29]. The fruit is considered mature once it becomes more pliable and changes from an amber to an orange hue. Its characteristics distinguish it from other types. This fruit has a taste similar to cantaloupe. "There is a slight hint of muskiness present, and it possesses both a sweet and juicy quality simultaneously"[30]. The Total Soluble Solids (TSS) rate in the flesh of this fruit might range anywhere from 10% to 11.5%, depending on the specific circumstances. On the other hand, it is believed that the skin contains a lower concentration of phenolic compounds as the fruit approaches maturity. In fresh fruit, the amounts of caffeic acid, p-coumaric acid, and ferulic acid run from 175.51 mg/100 g to 112.89 mg/100 g, 229.59 mg/100 g, and 277.49 mg/100 g, respectively. But as the fruit ages, it gives off more vitamin C and the pigments β-cryptoxanthin and lycopene. Within a single 100 g, the quantity of lycopene might range anywhere from 0.36 mg to 3.40 mg. Vitamin C has between 0.28 mg and 1.06 mg of α-tocopherol and between 0.23 mg and 0.50 mg of β-carotene per 100 grams. Vitamin C concentrations range from 25.07 mg to 58.59 mg per 100 g. Numerous scientific investigations have been carried out in order to investigate the biological characteristics of various components of the papaya plant, including the roots, shoots, leaves, seeds, and slime, as well as the fruits. There are a lot of different

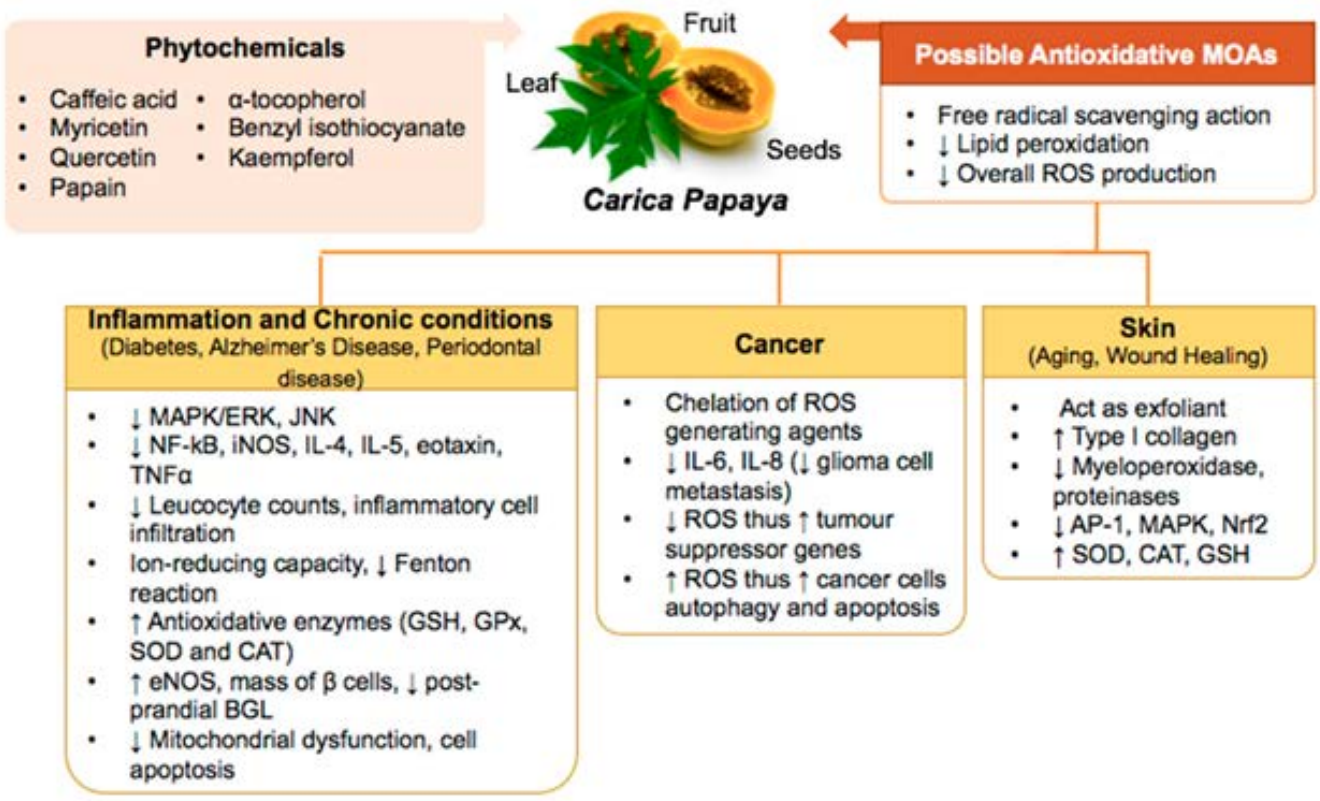


Figure 1. Phytochemical and application of *C. papaya*.

chemicals in the plant that can affect different types of cells in different ways. For instance, you may find linal in the fruit's flesh. Together with the alkaloids carpaine and pseudocarpaine, the leaves also contain dehydrocarpaine I and II. This plant has Classes II and III chitinases, cysteine endopeptidases, and glutaminyl cyclases in its shoots. Glutaminyl cyclases are in its latex, and it has quercetin and kaempferol in its shoots. The roots contain cyanogenic compounds[31-35]. All tissues contain both benzyl glucosinolate and the breakdown product benzyl isothiocyanate. The extracted metabolite undergoes a chemical examination to determine the identities of each of these components.

4. Platelet Physiology

The initial stage of stopping bleeding, known as platelet stimulation, consists of three stages. Adhesion, stimulation, and aggregation are the three stages that make up the process. Platelets may adhere to the subendothelial surface, the bottom layer of injured blood artery walls. There is a protein known as von Willebrand Factor (vWF) that assists these cells in adhering to one another. Once this structural change is done, the platelets start making factor V, serotonin, fibrinogen, white blood cells that connect to blood vessels, adenosine diphosphate and triphosphate, fibrinogen, and other substances. Clopidogrel simultaneously halts both platelet activity and aggregation by establishing a persistent binding to the P2Y12 adenosine diphosphate receptor. It is possible for glycoprotein IIb/IIIa receptors to attach to platelets when the shape of the platelet undergoes a change. When these receptors come into contact with fibrinogen, they trigger the reversible process of platelets adhering to each other. Intravenous administration of antiplatelet medications like tirofiban, eptifibatide, and abciximab can prevent fibrinogen from attaching during this specific period. The third stage releases arachidonic acid, which then transforms into thromboxane A2. This process generates a platelet plug, a persistent grouping of platelets. Because it alters thromboxane A2 in an irreversible way, aspirin plays a significant role in the way it operates. Because they are responsible for the production of the phospholipid membrane that completes the coagulation process, platelets are of utmost significance[36].

5. Pathophysiological Mechanisms Involved in Thrombocytopenia

Pathophysiological mechanisms that produce thrombocytopenia and haemorrhagic events are discussed in Figure 2. There is a wide range of factors that might contribute to a low platelet count in an individual. A few examples of these are low platelet counts, haemorrhage, reduced platelet production, increased platelet loss, increased platelet sequestration, and increased platelet disintegration. In Intensive Care Units (ICUs), low platelet levels can be caused by heparin, GP2b3a inhibitors, alcohol, antibiotics, sepsis, major bleeding, and microangiopathic hemolytic anaemias such as Thrombocytopenic Thrombotic Purpura (TTP), Hemolytic Uremic Syndrome (HUS), and Disseminated Intravascular Coagulation (DIC)[37]. When it comes to the efficient management of thrombocytopenia in intensive care units, it is absolutely vital to have a firm grasp of the numerous processes and the genesis of the condition. An example of this would be the utilisation of platelet transfusion as a treatment for low platelets that are the consequence of substantial bleeding. On the other hand, plasmapheresis is the therapy of choice for conditions such as transfusion-resistant TTP and HUS. There are several ways to treat Heparin-Induced Thrombocytopenia and Thrombosis (HITT), such as finding out what caused the condition right away, stopping medications that interact with heparin, and starting treatment with different blood thinners, like direct thrombin inhibitors. There are a number of factors that might slow down platelet synthesis, including aplastic anaemia, infections, cancer, inadequate nutrition, and substances like alcohol or narcotics that harm the bone marrow[38]. The spleen stores 33% of the body's platelets. Platelets have the ability to travel about in the body for anywhere between seven and 10 days, depending on the physiological conditions involved. If you have cirrhosis or portal hypertension, your spleen may clog, making platelet growth after a transfer harder. A process known as rapid destruction and consumption is responsible for the deaths of a significant number of patients who are receiving treatment in intensive care units. Such a condition is comparable to sepsis and DIC. There are many things that can happen during sepsis that can cause a low platelet count, including hem

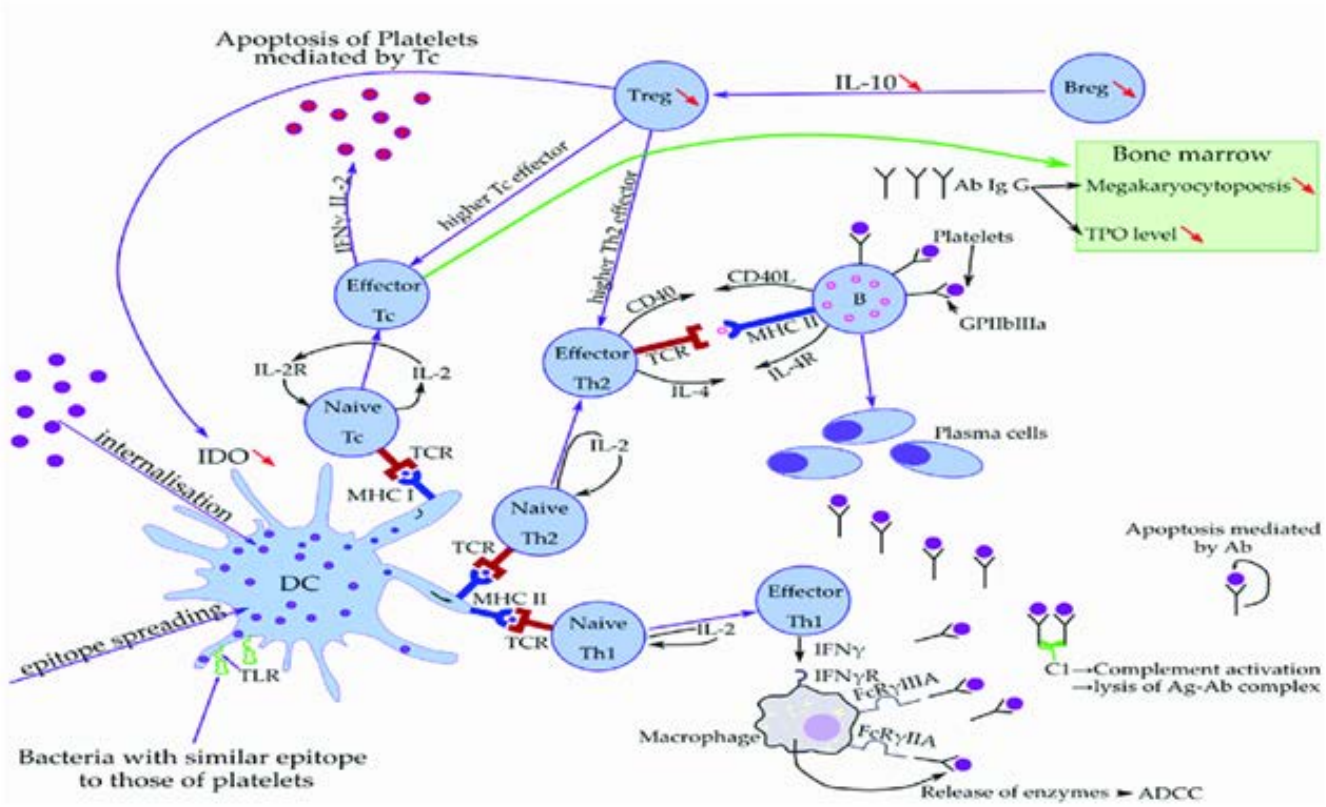


Figure 2. Pathophysiological mechanisms that produce thrombocytopenia and hemorrhagic events.

phagocytosis, activation of the complement system, loss of ADAMTS13 protein, and release of histones[39].

6. In the Treatment of Thrombocytopenia, *C. papaya's* Mechanism of Action

Through the reduction of platelet disintegration, the leaf of the *C. papaya* plant has the potential to be an effective treatment for thrombocytopenia. Some of the compounds found in the leaves of the *C. papaya* plant are termed flavonoids, and they have the ability to attach to proteases, which are essential for developing viruses. Thrombocytopenia, *C. papaya's* mechanism of action is shown in Figure 3. The components of viruses, known as proteases, are the ones that are accountable for their reproduction and functioning. This strategy effectively prevents the virus from reproducing, leading to a positive outcome. By using this strategy, it is possible to keep haematocrit levels at normal levels while simultaneously lowering the quantity of platelet disintegration. Additionally, the leaf extract has been shown to be able to remove free radicals and act as an antioxidant, which prevents damage and lowers the amount of bleeding and haemolysis that happens. Also, these extracts boost the production of platelets by making ALOX-12 and PTFAR enzymes work much better (15:13 and 13:14, respectively). This leads to a rise in the production of platelets. It has been demonstrated that the presence of carpaine and quercetin in papaya leaves can stimulate the production of platelets, protect them from injury, and maintain the integrity of the platelet membrane. Controlling the activation of genes and inhibiting the action of viral proteases are the means by which these effects are achieved[40].

7. Other Therapeutic Potentials of *C. papaya* Leaf

For thousands of years, the medicinal benefits of *C. papaya* leaf have been recognised. The leaf possesses therapeutic properties that can effectively treat a wide range of illnesses. These curative roles include.

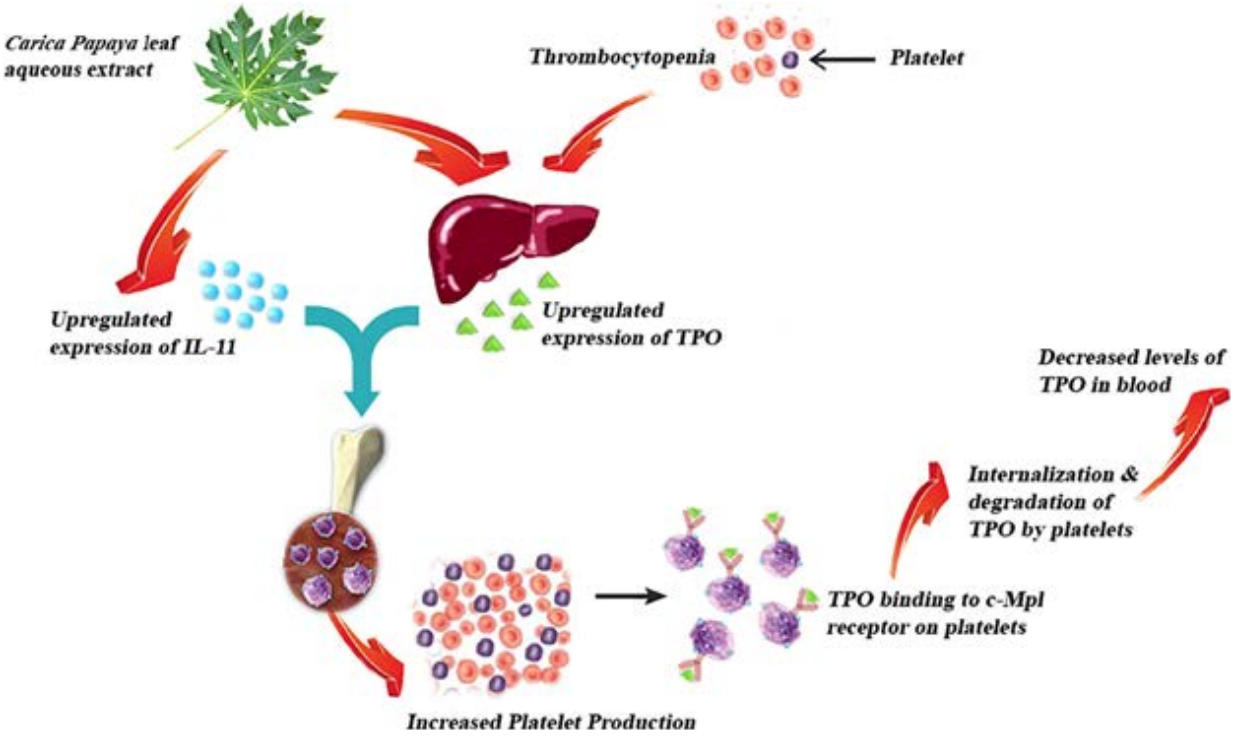


Figure 3. In the treatment of thrombocytopenia, *C. papaya* mechanism of action.

7.1 Immunomodulatory Activity

Deliberately lowering the immune system's defences is within reach. Immunomodulation entails this. The purpose of this study was to determine if AG129 mice infected with a clinical form of DENV-2 (DMOF015) might have their immune systems suppressed by using Freeze-dried *C. papaya* Leaf Juice (FCPLJ). We observed the infected individuals for three days to determine the effects of oral administration of 500 or 1000 mg/kg/day of FCPLJ. We detected increased concentrations of GM-CSF, GRO-alpha, IL-1 beta, IL-6, MCP-1, and MIP-1 beta in the plasma of ill mice. Mice that were unharmed had lower concentrations of these substances in their plasma. We also noted reductions in viral RNA and IL-6 levels in hepatocytes. We demonstrated that the FCPLJ could influence the immune system in a dengue disease model that does not kill rats[41]. Six Wistar rats were assigned to each group to assess the efficacy of *C. papaya* leaf in routine immunological treatment. We administered oral dosages of pure mature leaf to the rats daily for three consecutive days. There were three doses: 0.18, 0.36, and 0.72 mL/100 g BD. The peritoneal macrophages' bacterial-eating behaviour and associated cytokine responses were examined in this study using varying concentrations of Mature Leaf Concentrate of *C. papaya* (MLCP). Additionally, they investigated the process of splenocyte and bone marrow cell growth *in vitro*. Given orally by gavage, MLCC increased the number of several cell types, including leukocytes, platelets, lymphocytes, bone marrow cells, and monocytes. Levels of pro-inflammatory cytokines, particularly TNF and IL-6, decreased significantly when rats were administered the maximum dosage of MLCC. When the MLCC was given by mouth at all three dosage levels, it greatly increased the number of peritoneal macrophages in rat tissue. *In vitro*, the MLCC enhanced the rat PMS's innate immune response, leading to the activation of Th1 cells and improving the PMS's capacity to take in foreign particles. Scientists found that a small amount of MLCC (31.25 g/mL) helped Bone Marrow Cells (BMC) grow in a lab dish. At concentrations of 31.25 and 62.5 g/mL, it aided the growth of Stem Cells (SC). Both of these operations occurred in the laboratory. However, at concentrations of 500 and 1000 g/mL, cytokine levels were altered, and BMC and SC were negatively affected. Oral administration of MLCC revealed its immunomodulatory effects[42].

7.2 Antimalarial Activity

C. papaya is a common remedy for malaria among South Asian populations. *C. papaya* leaf extracts were tested *in vitro* for their efficacy against Plasmodium falciparum strains 3D7 and Dd2. The efficiency of a papaya leaf dichloromethane extract in treating malaria was quite high. A more effective version of carpaine was identified by researchers through the use of bioassay-guided separation. It was discovered that the half-life of this particular carpaine type was 2.19 ± 0.60 g/mL (4.57 m) and 2.01 ± 0.18 g/mL (4.21 m) for the two forms. The fact that the leaf extract had no negative effect on human red blood cells that were clear of viruses was one of its most distinctive features. Experiment findings demonstrated the presence of antimalarial action. The methanolic leaf extract of *C. papaya* was administered to Swiss mice after they had been infected with Plasmodium berghei NK65 in order to study its potential antimalarial effects. We divided the 36 mice into 6 distinct groups. Those in Group A served as controls for the healthy individuals, while those in Group B served as controls for the sick persons. Both Group C and Group D were administered artesunate and chloroquine at doses of 10 mg/kg body weight, respectively. We administered both of these dosages to the participants. Groups E and F were present. We administered a methanolic extract of *C. papaya* leaves (400 mg for one and 600 mg for the other) to them. We administered a mixture of leaf extract and methanol to Groups E and F. People who were given 400 mg/kg BD of *C. papaya* plant extract had 56.76% fewer blood bugs, and people who were given 600 mg/kg BD had 75.56% fewer. When administered at dosages of 10 mg/kg BD, artesunate reduced parasite numbers by 92.86% and chloroquine by 90.67%. In contrast to its effects on white blood cell count, the extract substantially raised hematocrit and haemoglobin levels in the mice that received it. Mice that were afflicted but showed no signs of responding to therapy were also mentioned. Experiment results showed that a methanolic extract of *C. papaya* leaves could destroy malaria eggs[43,44].

7.3 Antiviral Efficacy

Viruses have caused awful illnesses that people have passed on to one another for many decades. The pharmaceutical industry has made great strides in understanding the mechanics and targeting of antiviral medicines. While these innovations have revolutionised the field, they have also increased the immune resistance of viruses. Due to the difficulties experienced in finding a solution, the focus of treatment has shifted from synthetic drugs to natural cures. There is no text. Scientific studies have shown that the papaya leaf of the *C. papaya* plant is crucial for viral production. Studying dengue-infected mice, researchers found that freeze-dried CPLJ was far more effective in reducing viremia and NS1 levels[45]. Researchers discovered this during the investigation. This study involved inoculating AG129 mice with novel dengue virus strains originating from New Guinea C (DEN-2). Mice were not a suitable host for these novel strains. In the three days after the first dosage, the subjects were orally administered freeze-dried CPLJ at doses of 500 mg/kg/day and 1000 mg/kg/day. When CPLJ was freeze-dried, researchers discovered twenty-four distinct compounds. Oral administration of CPLJ to diseased AG129 mice also decreased mortality. To show that *C. papaya* leaf can fight viruses, we did another *in vitro* experiment with C6/36 cells that were infected with DENV-1. The experiment relied on plates. It was qRT-PCR that was used to test the four infected samples that were treated with *C. papaya* leaf extracts, along with a test sample that was not infected. We used the general real-time RT-PCR technique for dengue to determine the concentration of DENV-1 RNA. This method's chemical sensitivity is 1 x 10^1 copies/M1. Eight standard dilutions of the positive control were used, along with one positive control, one negative control, and a positive control that was generated by an analytical system. Cell shape assays revealed that *C. papaya* leaf extract dilutions ranging from 1/16 to 1/512 were safe. We determined that the most effective dilutions for treating an experimental DENV-1 sickness were between 1/32 and 1/256. Two of the study's control groups did not have DENV-1 infection, but the positive control did. The qRT-PCR results showed that all three of them had DENV RNA. Four samples were treated with DENV-1 and different amounts of papaya leaf extracts. The fifth and final sample did not have any DENV RNA in it. Tests have demonstrated that *C. papaya* leaf extract inhibits DENV-1 infections. Researchers recently studied the antiviral properties of silver nanoparticles synthesised from *C. papaya*

leaf extract. The research utilised kidney Vero E2 cell lines. Following aqueous and non-aqueous extractions, the process involved generating and analysing silver nanoparticles. We used molecular docking simulations to look at the therapeutic chemicals in *C. papaya* leaf extract and see how they might interact with the viral NS5 protein. We found that the methanol extract of *C. papaya* leaves yielded the silver nanoparticles with the greatest action potential. The nanoparticles have an IC_{50} value of 9.20 µg/mL. This compound, 5,7-dimethoxy coumarin, binds to the NS5 protein very well, making it the best ligand. Findings suggest that MCPLE silver nanoparticles considerably slow dengue virus-type growth[46].

7.4 Properties that Reverse Cancer

The *C. papaya* plant's leaves have the potential to halt the spread of many cancers, according to scientific studies. We tested how harmful papaya leaf and its many byproducts are to different kinds of cells, such as prostate cancer cells, normal prostate cells, and benign hyperplasia cells. Consumption of leaf juice for 24, 48, or 72 h induced apoptosis, halted cell development and ended the S phase of the cell cycle, according to laboratory experiments. There was a wide range of results, from 0.1 mg/mL to 1 mg/mL. We sorted the chemicals based on their molecular weight, confirming the inquiry's findings. Researchers found that the medium-polar part of the leaf juice effectively stopped invasive PC-3 cells from sticking to it and moving on it. A substitute for surgery was the administration of ethanol solutions containing papaya and moringa leaves to the rats. The primary objective of the therapy was to halt the proliferation of malignant cells. There is substantial evidence that a dose of 150 mg per kg of body weight effectively inhibits the development of cancer cells[47,48].

7.5 Action against Diabetes

The high incidence of diabetes and the harmful side effects of synthetic pharmaceuticals have prompted more research for safe, cost-effective alternatives. Researchers used alloxan to test whether the ethanolic extract from *C. papaya* leaves could help treat diabetes in rats that had been given a substance that causes it. Group A served as the positive control and Group B as the negative control, both to provide benchmarks. Group C received glibenclamide, whereas Groups D, E, and F were administered dosages of 200, 400, and 600 mg/kg BD, respectively, of an ethanolic leaf extract from *C. papaya* leaf. Over two weeks, there was a notable decrease ($p<0.05$) in blood sugar levels following the oral administration of extracts. Despite an increase in HDL levels, there was a significant drop in triglycerides, total cholesterol, and Low-Density Lipoprotein (LDL) plasma levels. After that, HDL levels increased. Researchers investigated the potential of *C. papaya* leaf juice as a diabetic treatment. The experiment exposed mice to alloxan, which led to the development of diabetes. Five sets of six individuals participated in the experiment. Participants in Groups I and II each received 0.1 mL of a vehicle solution for the positive and negative samples. Solution Bas Group III received 600 grams of glibenclamide based on their body weight. In contrast, 250 milligrams per kilogram of body weight was administered to Group V and 500 mg/kg of body weight to Group IV. Lipid pro Biochemical markers, lipid profiles, and blood glucose levels that are linked to the risk of heart disease and the start of artery disease were found to be significantly lower ($p<0.05$) after 28 days of medication use. It should be mentioned that there was a substantial increase in the serum HDL levels ($p<0.05$). Inhibition of angiogenesis. We call this process angiogenesis when new blood vessels sprout from preexisting ones. A set of binary switches controls whether to encourage or inhibit blood vessel development. Developing cancer is one of the possible outcomes of the process change. Molecular docking was used to find the possible binding sites for the angiogenic receptors VEGFR1 and VEGFR2 and to see how bioactive compounds in leaves interact with these receptors. The primary objective of the study was to identify possible receptor-binding sites. Us An aqueous leaf extract could successfully implement the chorioallantoic membrane egg-yolk angiogenesis model. This completes the task. There is evidence that the blood capillaries' width, length, and interconnectedness are all reduced by the *C. papaya* plant's leaf. Furthermore, research indicates that some compounds, such as quercetin, ascorbic acid, lycopene, and riboflavin, are reduced when the leaf is removed. These findings supported the study's conclusions. It also

had the effect of reducing the quantity of angiogenesis cases that occurred in unhealthy settings[49].

7.6 Antioxidant Activity

Oxidative stress is a big risk factor that leads to many serious illnesses. There is evidence that a product from *C. papaya* leaves may be able to lessen the effects of oxidative stress. Swiss mice underwent a test to investigate the reactive stress that cyclophosphamide causes. Each animal received 250 mg of *C. papaya* leaf extract daily for fifteen days, based on its weight in kg. Studies have shown that the leaf extract of the *C. papaya* plant helps fight oxidative stress and may even help protect DNA from damage[50]. Using Swiss albino mice, this study looked at how antioxidants and antimutagenic substances from *Anastatica hierochuntica*, *Lepidium sativum*, and *C. papaya* extracts worked. EAC-cell injections into the mice's peritoneal cavity caused Ehrlich ascites cancer. However, oxidative stress, chromosomal aberration, DNA breakage, and inflammation went down when all extracts were taken by mouth for seven days at a dose of 500 mg/kg body weight. As stated in the reference, the biomarkers linked to kidney and liver function showed improvement.

7.7 Antibacterial Activity

It is well known that germs can cause diseases, which is a big problem that is made worse by the fact that bacteria are becoming more resistant to medicine. Researchers used the agar well-diffusion method to demonstrate the ability of *C. papaya* leaf extracts to kill S. aureus, B. subtilis, *E. coli, and S. typhi* bacteria. The data revealed that *E. coli* demonstrated the highest effectiveness against the microorganisms under study. The CPLE separation of methanol led to the creation of seven different parts. The five parts that have shown the most effectiveness against *Escherichia coli* are listed below. The green part of the *C. papaya* plant has chemicals that might be able to treat a number of illnesses, such as typhoid fever, wound infections, gastroenteritis, and urethritis. The above factors are what made this happen[51-54].

7.8 Hepatoprotective Activity

The fruit's ethanol and aqueous extracts exhibit notable hepatoprotective effects. However, the hepatoprotective mechanism and the active ingredient responsible for the plant's effects are still unknown.

8. Future Perspective

We have cause to be enthusiastic about *C. papaya* potential as a treatment for thrombocytopenia, but this can only happen with increased funding for research, industry standards, and government support. To maximise papaya's efficacy in treating thrombocytopenia, it is necessary to consider both modern scientific knowledge and traditional wisdom. Important compounds include carpaine, chymopapain, papain, and many flavonoids. Multiple investigations have pointed to these compounds as potential players in the process of elevated platelet counts. Furthermore, these substances have antioxidant and anti-inflammatory properties. Understanding how these substances interact with the pathways responsible for platelet production and regulation may be the focus of future studies.

9. Conclusion

Among the many parts of the tropical papaya plant, which is also called *C. papaya*, are the leaves, which have tremendous potential. It is possible to find several phytochemicals in papaya leaves. These plant compounds contain antioxidants, alkaloids, carpaine, saponins, terpenes, and flavonoids. Even though it's packed with vitamins and minerals, papayas are surprisingly low in calories. You can't go wrong with this fruit for your diet. Volatile chemicals control the fruit's sensory properties, and dynamic substances with diverse effects on tissues are present in the pulp. The condition known as thrombocytopenia occurs when the blood platelet count falls below 150 × 109/L. More than one factor may be contributing to this sickness. It appears that the leaf of the *C. papaya* plant could be particularly effective for treating a wide variety of ailments due to its unique combination of compounds[24,50,52]. There are special things about papaya leaves that make it a good medicine that can help with many health problems, like diabetes, malaria, viral illnesses, cancer, oxidative stress, and weak immune systems. A lot of research has shown that the *C. papaya* leaf can help treat thrombocytopenia. It achieves this by

focusing on certain genes, such as CD110, ALOX-12, and PTFAR. This data is the result of a tremendous deal of scientific investigation. Numerous factors, including drugs, viral illnesses like dengue, chemotherapy, and various medical and physiological conditions, can induce thrombocytopenia. Both the newly developed dosages and the widely available dosages of *C. papaya* leaf are meant to raise the number of platelets in the blood while also stopping them from breaking down. We accomplish this without causing any damage. *C. papaya* leaf contains a number of phytochemicals, including carpaine, flavonoids, and antioxidants, which are considered to be among the most important bioactive components. New studies suggest that the leaf belonging to the *C. papaya* plant might be able to help people who have low platelets. The plant achieves this by reducing platelet disintegration, containing flavonoids that bind to viral assembly proteases, preventing viral replication, and increasing platelet synthesis. In addition, it has antibacterial, anticancer, antiangiogenic, and anti-cancer activities. Urethritis, gastroenteritis, wound infections, and typhoid fever are some of the conditions that might potentially be treated with this substance.

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11. Author Contribution

A. D.: Writing – review and editing, K. S. S.: Writing – original draft, S. M.: Investigation, D. S.: Supervision, S. A. A. M.: Formal analysis, K.. M.: Reviewing manuscript. All authors have read and agreed to the published version of the manuscript.

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