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CARICA PAPAYA LEAF EXTRACT: A COMPREHENSIVE REVIEW OF ITS PHYTOCHEMISTRY AND ROLE IN THROMBOCYTOPENIA

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ABSTRACT

Carica papaya L. (family Caricaceae) is a tropical fruit plant whose leaves, fruit, seeds and latex have long been used as food and folk medicine. In recent years, the leaf has gained wide public attention because of its popular use for raising low platelet counts during dengue fever. This review summarises the botanical features, phytochemistry and pharmacological profile of papaya, with special emphasis on the role of its leaf extract in thrombocytopenia. The leaf contains piperidine alkaloids such as carpaine, along with flavonoids, phenolic acids, saponins, tannins and glycosides, whereas the fruit is rich in carotenoids and vitamins, the seed in isothiocyanate precursors and the latex in proteolytic enzymes. Laboratory and human reports suggest that the leaf extract supports platelet recovery, which may be linked to protection of blood cells, antiviral action and control of inflammatory mediators. Additional activities such as antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial and antiplasmodial effects have also been described. Toxicity studies in rodents indicate a favourable safety margin at the doses tested. Overall, papaya leaf extract is a promising supportive herbal option, but standardised preparations and well-designed studies are still needed.

KEYWORDS: Carica papaya; papaya leaf extract; thrombocytopenia; dengue; phytochemistry; carpaine; platelet count.

INTRODUCTION

Medicinal plants have gained considerable importance in modern healthcare due to their diverse phytochemical constituents and potential therapeutic properties.[1] Herbal formulations derived from medicinal plants have attracted scientific interest because of their naturally occurring bioactive constituents and potential health benefits.[2] Medicinal plants are used as a form of healthcare in almost every culture, and the folk use of papaya leaf during dengue fits into this wider tradition.[11] Quality control and standardisation are essential for the safety and efficacy of herbal products, which is why a standardised papaya leaf extract is needed for platelet therapy.[13]

Medicinal plants remain an important source of therapeutic leads, and papaya is among the most widely used tropical species in both daily nutrition and traditional practice.[1,2] *Carica papaya* L. is a fast-growing fruit plant of the family Caricaceae, and its fruit, leaves, seeds and latex are all used in food and in household remedies.[3] Apart from its nutritional value, the plant is rich in enzymes, alkaloids and phenolic compounds that are associated with several biological effects.[4,5]

Thrombocytopenia is generally defined as a platelet count below 150,000 per microlitre of blood, and it may arise from reduced platelet production, increased destruction or abnormal pooling of platelets in the spleen.[6] Viral infections are an important cause of low platelet counts because viruses can activate platelets and alter their survival.[7] Platelets also take part in the immune response to viruses, and this makes their loss clinically meaningful in infections.[8]

Dengue is the best-known example, with an estimated 390 million infections occurring every year across tropical and subtropical regions.[9] A fall in platelet number is a regular laboratory finding in dengue and is closely monitored because of the fear of bleeding.[10] No specific antiviral drug is available for dengue, so treatment remains supportive, and this has encouraged interest in herbal options.[10] In many Asian countries, the juice of papaya leaves is taken by the public during outbreaks in the hope of faster platelet recovery.[11,12] Over the last decade, laboratory and human studies have examined this practice, and standardised leaf extract preparations have been developed.[13,14]

This review therefore compiles the botanical background, phytochemistry and pharmacological profile of *Carica papaya*, with special focus on the role of its leaf extract in thrombocytopenia.[13,15]

AIM AND OBJECTIVES

Aim

To present a comprehensive review of the phytochemistry of *Carica papaya* leaf extract and its role in thrombocytopenia, based on published open-access literature.

Objectives

- To describe the taxonomy, distribution and morphology of *Carica papaya*.
- To summarise the phytoconstituents present in different parts of the plant.
- To discuss the role of papaya leaf extract in thrombocytopenia and to outline other reported pharmacological activities.
- To review the traditional medicinal uses, toxicity and safety of the plant.
- To highlight the gaps in current knowledge and the future prospects of papaya leaf extract.

BOTANICAL DESCRIPTION

Taxonomy

Table 1: Taxonomic classification of *Carica papaya*.[1,16]

Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta (Angiosperms)
Class	Magnoliopsida (Dicotyledons)
Order	Brassicales
Family	Caricaceae
Genus	Carica
Species	*Carica papaya* L.[16]
Common names	Papaya, pawpaw (English); Papita (Hindi); Papai (Marathi)[1]

Papaya is placed in the order Brassicales, and the small family Caricaceae is related to the mustard and caper groups in molecular classification.[16] The accepted botanical name of the species is *Carica papaya* L., as maintained in the Kew plant database.[16] The plant is known by several common names across regions, and papaya and pawpaw are the most widely used English names.[1]

Distribution

Papaya is believed to have originated in the lowlands of Mesoamerica, where early domestication took place.[17] From there it spread through the tropics and subtropics and is now grown commercially in many countries, with India, Brazil and Mexico among the leading producers.[18]

Morphology

Habit: Papaya is a short-lived, fast-growing and mostly unbranched tree-like herb that commonly reaches five to ten metres in height, and it has a soft, hollow stem marked by scars of fallen leaves.[3]

Leaf: The leaves are large and are arranged spirally near the top of the trunk on long hollow petioles, and the blade is deeply palmately lobed and may be about 50 to 70 cm across.[19] The upper surface is dark green and smooth, while the lower surface is paler with prominent veins.[19]

Flower: The species shows different sex forms, namely male, female and hermaphrodite plants, and this variable sex expression strongly affects fruit shape and commercial cultivation.[17] Male flowers are small and funnel shaped and are borne on long hanging clusters, whereas female flowers are larger and waxy and occur singly or in small groups.[3]

Fruit: The fruit is a large fleshy berry that is oval to pear shaped, green when unripe and yellow to orange when ripe, and its sweet pulp is rich in carotenoids.[4]

Seed: The central cavity of the fruit holds numerous small, round, black seeds, each covered by a gelatinous coat, and the seeds have a peppery taste owing to their isothiocyanate content.[4]



Figure 1: *Carica papaya* plant with unbranched trunk, spirally arranged palmate leaves and clustered fruits[3]



Figure 2: Ripe fruit (whole and longitudinally sectioned) and palmately lobed leaf of *Carica papaya*[4,19]

PHYTOCHEMISTRY

The chemical makeup of papaya differs from one plant part to another, and the table below gives a plant-part-wise overview of the main groups of compounds reported.[4,19]

Table 2: Plant-part-wise major phytoconstituents of *Carica papaya*.[4,19]

Plant Part	Major Phytoconstituents
Leaves	Piperidine alkaloids (carpaine), flavonoids, phenolic acids, saponins, tannins, glycosides, proteins and minerals.[13,19]
Flowers	Phenolic compounds and flavonoids with antioxidant potential.[20]
Fruit	Carotenoids, phenolic acids, vitamin C, fibre and minerals.[4]
Seeds	Glucosinolate-derived isothiocyanates (benzyl isothiocyanate), fatty acids and phenolics.[4]
Latex	Proteolytic enzymes such as papain, chymopapain and caricain.[3]
Root	Carposide and myrosin.[2]

Leaves

The leaves contain piperidine alkaloids, among which carpaine is the principal and best-studied compound.[13] The carpaine content of leaf samples has been measured by analytical methods and is known to differ between samples, which is important when preparing standardised extracts.[13] Preliminary screening of leaf powder shows the presence of alkaloids, flavonoids, tannins, saponins and glycosides.[19] Another study of the leaves also reported nutrients such as protein and minerals along with these secondary metabolites.[19]

Saponin-enriched leaf extracts have been prepared and were found to carry antioxidant and anticancer capacity.[15] Chromatographic profiling of leaf preparations showed that the method of preparation changes the balance of flavonoid and phenolic components, which in turn influences biological activity.[21] A review on oxidative stress mentions phenolics such as quercetin, kaempferol and caffeic acid as important antioxidant constituents of papaya.[5] Metabolite profiling of leaves by NMR spectroscopy has further shown that the leaf contains a wide range of primary and secondary metabolites.[4,15]

Flowers

Flower extracts have been reported to contain phenolic and flavonoid compounds and to display antioxidant and antibacterial effects.[20] A comparison of several plant parts found that phenolic content and antioxidant strength differ among them.[22]

Fruit

The ripe fruit pulp contains carotenoids and phenolic acids, and their levels change during cold storage.[4] In red-fleshed fruit, carotenoid pigments accumulate steadily during ripening and give the pulp its colour.[4] The fruit is also a source of vitamins, minerals and dietary fibre, which add to its nutraceutical value.[4]

Seeds

The seeds are noted for glucosinolate-derived isothiocyanates, of which benzyl isothiocyanate (BITC) is the prominent member, and this compound is responsible for their sharp taste.[4] NMR-based profiling has compared the metabolites of seeds with those of leaves and showed clear differences in their chemical profiles.[4,15]

Latex, Root, Stem and Bark

The milky latex of unripe fruit and green parts is a rich source of the proteolytic enzymes papain and chymopapain, which are used in food and pharmaceutical industries.[3] The root is reported to contain the compounds carposide and myrosin.[2] Studies using different solvents on all parts of the plant showed that phenolic content, antioxidant power and antibacterial potential depend on both the plant part and the solvent used.[23]

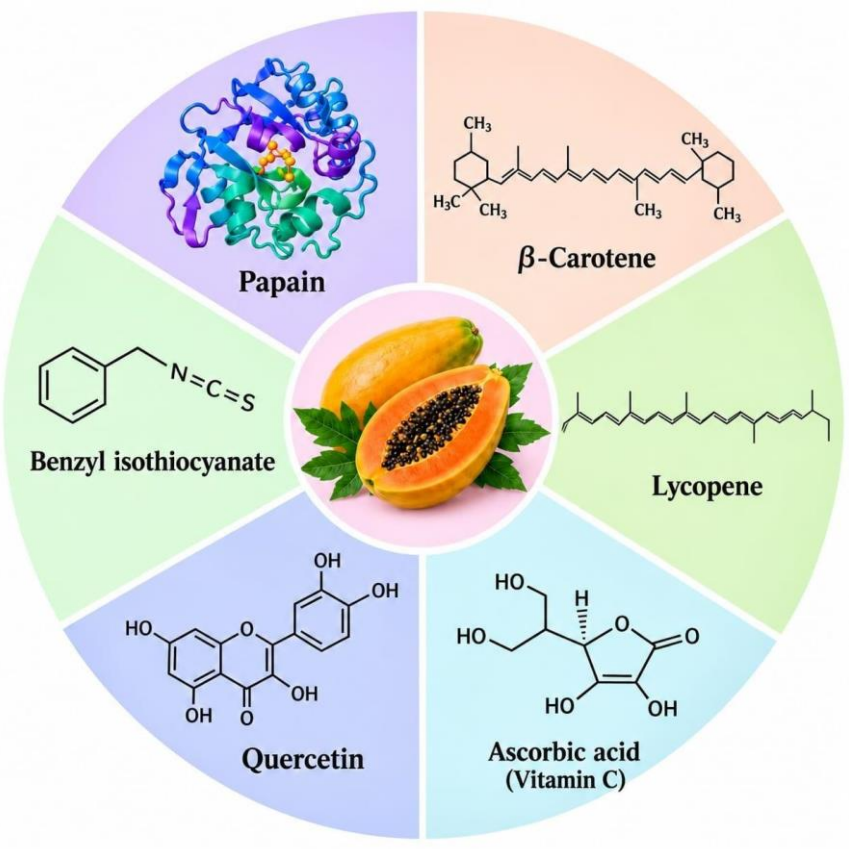

Figure 3: Chemical structures of the major bioactive constituents of *Carica papaya* – papain, β-carotene, lycopene, benzyl isothiocyanate, quercetin and ascorbic acid[4,5,57]

PHARMACOLOGICAL ACTIVITIES

Role in Thrombocytopenia and Dengue (Main Activity)

Thrombocytopenia in dengue is multifactorial and involves suppressed platelet production in the bone marrow, platelet activation and clearance, and immune-mediated destruction.[10] Activated platelets in viral disease can interact with immune cells and release inflammatory mediators, which links platelet loss with disease severity.[8] For this reason, an agent that supports platelet recovery without harmful effects is attractive for supportive care in dengue.[13]

The leaf juice of papaya is a popular folk remedy for dengue fever in several Asian countries, and this practice first attracted the attention of researchers.[11] A case report from Pakistan described a rise in platelet, white cell and neutrophil counts in a dengue patient after the use of aqueous leaf extract.[24] Another case report documented increasing thrombocyte counts in dengue patients who consumed papaya leaves.[25] Leaf juice was later studied in a randomised study of patients with dengue fever and dengue haemorrhagic fever, in which the platelet count rose faster in the treated patients than in the control group.[26] Capsules of leaf extract were also examined in Indonesian patients for their effect on platelet count and haematocrit.[13] A multicentre, double-blind and placebo-controlled study of a standardised leaf extract reported benefit in platelet counts along with good tolerability.[14]

Laboratory work supports these reports.[27,28] Administration of leaf extract to mice produced higher platelet counts, which agrees with the folk claim.[27] Aqueous leaf extract was found to inhibit dengue virus replication in cell culture and to augment platelet counts in rodent models.[13,15,28] In dengue-infected AG129 mice, freeze-dried leaf juice reduced the production of inflammatory cytokines, indicating a possible role in limiting the immune over-reaction of the disease.[29] A metabolically characterised aqueous leaf extract also counteracted experimentally induced thrombocytopenia in rats and showed immunomodulatory effects.[28] In addition, leaf extracts stabilised the membranes of red blood cells (RBC) against induced damage in vitro, which suggests a protective action on blood cells.[30]

The exact mechanism is not yet settled, but the proposed explanations include promotion of platelet formation or release, protection of platelets from destruction and membrane damage, antiviral action, and suppression of excess inflammation.[13,15,28] The compounds responsible have not been fully identified, although alkaloids such as carpaine and several phenolic compounds are often suggested as contributors.[13] Systematic reviews of human studies point towards a favourable trend in platelet counts, but they also note small sample sizes, differing preparations and risk of bias, so firm conclusions cannot yet be drawn.[31] Another meta-analysis likewise stressed the need for more rigorous trials with a standard extract.[32]

Basis of Low Platelet Count in Dengue

In dengue, platelet loss results from the combined effect of reduced production in the bone marrow, activation of platelets by the virus and the immune response, and their faster removal from the circulation.[10] Activated platelets bind to immune cells and release inflammatory mediators, so the fall in platelet number runs parallel to the severity of the disease and the risk of bleeding.[8,10] Since no antiviral medicine is available, any agent that supports platelet recovery without harm is of interest as supportive care.[10,13]

Evidence from Animal Studies

Feeding a papaya leaf suspension or leaf extract to mice raised the count of circulating thrombocytes, which agrees with the folk use of the leaf.[27] In mice given carboplatin to suppress the bone marrow, leaf extract reduced the fall in

platelet count and increased the expression of the thrombopoietic cytokine interleukin-11, which points towards an action on platelet formation.[33] Aqueous leaf extract also raised platelet counts in rodent models of induced thrombocytopenia and showed antiviral action against dengue virus in cell culture, so both the supportive effect and the virus-directed effect have been seen.[13,15,28] Freeze-dried leaf juice lowered inflammatory cytokines in dengue-infected mice, which may help to limit the immune over-reaction that accompanies platelet loss.[8,29]

Evidence from Studies in Dengue Patients

In the case reports, patients with dengue who took aqueous leaf extract or fresh leaves showed a rising platelet count over the following days.[24,25] In the randomised study of patients with dengue fever and dengue haemorrhagic fever, the leaf juice was given for a short course and the platelet count rose faster in the treated patients than in the control group.[26] Capsules of leaf extract were examined for their effect on platelet count and haematocrit, which shows that a measured dosage form is possible.[13] The multicentre, double-blind and placebo-controlled study of a standardised extract is the most carefully designed report discussed here, and it recorded benefit in platelet counts with good tolerability.[14] Systematic reviews of these reports show a favourable trend, but they point to small sample sizes, different preparations and risk of bias.[31,32]

Proposed Mechanisms of Action

Promotion of platelet formation is one proposed mechanism, and the rise in interleukin-11 expression in treated mice supports this idea.[13,33] Protection of existing platelets and other blood cells is a second proposed mechanism, and the stabilisation of red blood cell membranes against induced damage supports it.[28,30] Antiviral action is a third mechanism, which was seen when aqueous leaf extract inhibited dengue virus replication in cell culture.[13,15,28] Control of inflammation is a fourth mechanism, because the extract reduced cytokine production in infected mice.[29] The compounds responsible are not fully identified, but the alkaloid carpaine and phenolic compounds are suggested contributors, which is why the carpaine content is used as a marker of quality.[13] The forms studied so far include fresh leaf juice, aqueous extract, capsules and a standardised extract, and the lack of one uniform preparation is the main obstacle in comparing the studies.[13]

Application of Papaya Leaf Extract in Raising White Blood Cell Count

Dengue lowers the white blood cell and neutrophil counts along with the platelet count, and these counts are followed in patients during the illness.[10,24] In the case report from Pakistan, the platelet, white cell and neutrophil counts rose after the use of aqueous leaf extract.[24] Aqueous leaf extract given to normal rats increased the total white blood cell, lymphocyte, neutrophil and thrombocyte counts without raising the liver enzymes AST and ALT.[34] Long-term oral leaf extract in rabbits kept the white cell and neutrophil counts slightly above those of the control group and also improved red cell indices, which indicates a stimulant effect on blood formation.[34] Leaf juice prevented the fall in white blood cell count in mice given carboplatin, a drug that depresses the bone marrow, and this protection was dose dependent.[33] In the same type of carboplatin mouse model, leaf extract reduced the fall in total white cell count and raised it in the treatment group, which supports a bone marrow-protective action.[33]

Thus, papaya leaf extract is used to support the recovery of platelet, white cell and neutrophil counts in dengue, but it remains an adjunct to, and not a replacement for, medical care.[12,24] Therefore, papaya leaf extract should be viewed as a promising supportive option and not as a replacement for medical care in dengue.[12]

Antioxidant Activity

Extracts from different parts of papaya show radical-scavenging capacity in laboratory assays, and this effect is linked to their phenolic content.[22] A review on oxidative stress concluded that papaya extracts and their phytochemicals help to neutralise free radicals and support cellular antioxidant defence.[5]

Anti-inflammatory and Immunomodulatory Activity

Published evidence indicates that papaya constituents can modulate inflammatory mediators and immune responses, as summarised in a dedicated review.[35] A methanolic extract of the seeds reduced experimentally induced inflammation in animals.[36]

Anticancer Activity

An aqueous extract of the leaves inhibited the growth of several tumour cell lines and enhanced the production of Th1-type cytokines in cell-based studies.[15] The method of leaf preparation was found to affect cytotoxicity against human squamous cell carcinoma cells.[21] A review of anticancer reports on papaya has also discussed the role of its leaf, seed and fruit constituents.[15]

Antidiabetic Activity

Leaf extract lowered blood glucose in streptozotocin-induced diabetic rats, and this effect was accompanied by the presence of phenolic and flavonoid compounds.[37] A review on metabolic syndrome has also discussed the benefits of papaya on blood sugar and lipid disturbances.[38]

Antimicrobial Activity

Leaf extracts have shown inhibitory activity against pathogenic bacteria in laboratory tests.[39] Extracts of various plant parts prepared in different solvents showed variable antibacterial potential, and flower extracts were also found to be active.[20,23]

Antiplasmodial Activity

Carpaine, the major leaf alkaloid, has been described as an antiplasmodial compound, and its quantification in leaves is important for the development of standardised material.[13] The antimalarial potential of the leaf is also discussed in a review on therapeutic applications of leaf extract.[40]

Hepatoprotective Activity

Liver injury produced by carbon tetrachloride, in which reactive free radicals start lipid peroxidation of liver cells, is the standard rat model used to test the hepatoprotective action of papaya.[41] Ethanol and aqueous extracts of dried papaya fruit showed remarkable protection in this model, and the protection was judged from serum AST, ALT, alkaline phosphatase, bilirubin and gamma-glutamyl transpeptidase together with liver histology.[41] In a second rat study, the aqueous extract of dried fruit gave more significant protection than the ethanol extract, and it lowered the raised enzyme levels and reduced necrosis and degenerative changes in the liver.[41] The aqueous pulp extract was also studied when given before, during and after carbon tetrachloride injury, and its protection was assessed through markers of oxidative stress, inflammation, fibrosis and apoptosis.[41] The seed extract reduced liver injury in rats as well, its antioxidant and anti-inflammatory effects were linked with improved liver and kidney functions, and it caused

no adverse effects in healthy rats given it for 12 weeks.[42] These findings suggest that the hepatoprotective action of papaya rests mainly on antioxidant protection of liver cells.[41,42]

Gastroprotective (Anti-ulcer) Activity

Aqueous and methanol extracts of unripe papaya fruit reduced the ulcer index in ethanol-induced and indomethacin-induced gastric ulcer in rats, with the aqueous extract more effective against ethanol and the methanol extract more effective against indomethacin.[43] The same extracts inhibited intestinal motility, and this cytoprotective and antimotility action may account for the anti-ulcer property of the unripe fruit.[43] The methanolic extract of papaya seed reduced the gastric lesions caused by ethanol and indomethacin and also healed the chronic ulcers produced by acetic acid.[44] In the pylorus-ligation model the seed extract increased mucus production and decreased gastric acidity, and sulfhydryl compounds such as glutathione were involved in the protection.[44] Aqueous seed extract also protected male rats against ethanol-induced gastric ulcer and reduced the volume of gastric juice.[44] The seed extract showed no signs of toxicity at a single dose of 2000 mg/kg in rats, which supports its safety margin as a gastroprotective agent.[44]

Anthelmintic Activity

Papaya seeds are used in folk practice to expel intestinal worms, and the seeds are noted for benzyl isothiocyanate, a glucosinolate-derived compound.[4] In a pilot study, children with intestinal parasites who received an elixir of air-dried papaya seeds with honey cleared their stool of parasites more often than children given honey alone.[45] Benzyl isothiocyanate was found to be the chief or sole anthelmintic compound in papaya seed extracts when they were tested on the nematode *Caenorhabditis elegans*.[4] Heat-treated seed extracts lost their activity, and the activity returned when a myrosinase-containing fraction of the seed was added, because this enzyme releases benzyl isothiocyanate from its glucosinolate precursor.[4] The human data are limited to a small pilot study, so wider testing of seed preparations is still needed.[45]

Hypolipidaemic Activity

Papaya has been discussed for its benefit on the lipid disturbances that accompany metabolic syndrome.[38] In alloxan-induced diabetic rats, the aqueous leaf extract showed a hypolipidaemic effect along with its blood glucose lowering action.[46] The fibre and antioxidants present in the fruit are considered to contribute to the control of lipid levels.[4,38] As both the leaf and the fruit show this action, the effect appears to depend on the phenolic and antioxidant content of the plant.[5,46]

Wound Healing Activity

Papaya has been tested on excision, incision and dead space wound models in rats, and these tests measure the speed of wound closure and the hydroxyproline content of the new tissue.[47] The extract of unripe fruit given at 100 mg/kg daily for ten days increased wound healing in streptozotocin-induced diabetic rats, in which healing is normally poor.[47] An ethanol extract of papaya seeds also promoted wound healing in a rat model, which supports the folk use of the seeds on wounds.[47] The latex, which is rich in digestive enzymes, healed burn wounds in rats in a time comparable to silver sulfadiazine cream, although it caused bleeding in a few animals.[48] The proteolytic enzymes of the latex, namely papain and chymopapain, might clean wounds by digesting dead tissue, and this is the likely basis of its use on burns.[3,48]

Antifertility Activity

The chloroform extract of papaya seeds, given orally to langur monkeys for 360 days, decreased the sperm concentration, completely inhibited sperm motility and led to azoospermia after the 90th day of treatment.[49] Sperm characteristics returned to nearly the pretreatment values 150 days after the treatment was stopped, so the effect was reversible.[49] The extract is thought to act on the developing germ cells, possibly through the Sertoli cells.[49] A compound isolated from the seeds, 1,2,3,4-tetrahydropyridin-3-yl-octanoate, decreased the motility and viability of rat spermatozoa and increased the abnormal forms.[49] These findings make papaya seed a candidate for male contraceptive research.[49]

Antihypertensive Activity

The crude ethanol extract of unripe papaya fruit lowered the mean arterial blood pressure in normotensive, renal hypertensive and DOCA-salt hypertensive rats.[50] At 20 mg/kg given intravenously, the extract produced about 28% more fall in blood pressure than hydralazine in the hypertensive groups.[50] The effect was lost in rats pretreated with propranolol, which indicates that beta-adrenergic mechanisms are involved.[50] In spontaneously hypertensive rats, a standardised methanolic extract of papaya given at 100 mg/kg twice daily for 30 days lowered blood pressure to a level similar to that of enalapril.[51] The extract inhibited angiotensin converting enzyme, improved baroreflex sensitivity and reduced cardiac hypertrophy, so its action resembles that of ACE-inhibitor drugs.[51]

Nephroprotective Activity

The aqueous seed extract of papaya was tested against kidney injury produced by carbon tetrachloride in Wistar rats, using oral doses of 100 to 400 mg/kg given for 7 days before the toxin.[52] The rise in the measured biochemical markers of kidney injury was reduced in a dose-related manner, and the highest dose of 400 mg/kg gave maximum protection that lasted up to three hours after exposure to the toxin.[52] The kidney histology showed matching improvement, and the protection is believed to be mediated by antioxidant or free radical scavenging constituents of the seed.[52] In the rat study of seed extract against liver injury, kidney function improved as well, which gives further support to its renal protective action.[42]

Analgesic Activity

The aqueous leaf extract of papaya was tested in mice by the acetic acid-induced writhing test, in which pain is measured by counting the abdominal constrictions.[53] Intraperitoneal doses of 30, 100 and 300 mg/kg significantly reduced the number of constrictions without impairing the motor coordination of the mice in the Rotarod test.[53] This indicates a peripheral antinociceptive action and not a general depression of the nervous system.[53] The ethanolic leaf extract at 100, 300 and 600 mg/kg given orally also reduced the writhing movements in mice, and its effect was of similar potency to paracetamol.[53]

Digestive Activity

Papaya is widely used as a natural remedy for indigestion, and its digestive action is credited to the proteolytic enzymes of the fruit and the latex.[3,54] In a double-blind placebo-controlled study, volunteers with long-standing indigestion took 20 ml of a papaya preparation daily for 40 days.[54] The preparation was assessed for constipation, bloating, heartburn and painful straining during bowel movements, and the authors concluded that it helps to maintain the physiology of the digestive tract.[54] The benefits were no longer observed after the washout phase, which shows that the preparation has to be taken regularly.[54]

TRADITIONAL USE

In folk medicine, different parts of papaya have been used to treat digestive complaints, wounds, skin problems, fever and malaria, as compiled in reviews of its traditional uses.[1,2] The ripe fruit is eaten as a nutritious food and a mild digestive aid, while the latex has been applied to the skin and used as a source of digestive enzymes.[3] Papaya leaf juice is used by the general public in South and South-East Asia for dengue fever, which is the most talked-about modern use of the plant.[11] A summary of the plant also lists the use of leaves, roots and seeds in a number of home remedies.[3] The seeds have shown wound-healing effects in a rat model, which supports their folk use on wounds.[47]

TOXICITY AND SAFETY

In an acute oral toxicity study in rats, a single high dose of leaf extract caused no mortality or evident signs of toxicity.[55] In a 28-day repeated-dose oral study in rats, the leaf extract did not cause serious toxic effects at the doses tested, which supports the safety of oral leaf extract on repeated administration.[56] In the multicentre study of a standardised extract, the preparation was well tolerated by patients.[14] The latex contains proteolytic enzymes, so persons who are sensitive to papaya or latex should avoid its use.[3] Review authors point out that long-term safety data in humans and standard dosing guidance are still limited.[13]

DISCUSSION

The biological activity of *Carica papaya* depends largely on the plant part and the method of extraction. The leaf is rich in piperidine alkaloids, chiefly carpaine, together with flavonoids, phenolic acids and saponins, whereas the fruit, seed and latex are dominated by carotenoids, isothiocyanates and proteolytic enzymes, respectively, which explains why the leaf has emerged as the main candidate for platelet-related use. Support for a platelet-restoring effect follows a consistent progression from animal experiments to human reports, including a multicentre, double-blind, placebo-controlled study of a standardised extract that reported a favourable platelet response with good tolerability. Because thrombocytopenia in dengue is multifactorial, promotion of platelet formation, protection of blood cells, antiviral action and cytokine modulation have all been proposed as mechanisms, although these were inferred from separate models and the active principle remains unidentified.

The human evidence is still limited by case reports, small studies, non-uniform preparations and risk of bias. Since platelet counts in dengue tend to recover spontaneously, controlled studies with clinically meaningful end points are needed to confirm a true pharmacological effect. The other reported activities rest mainly on cell-based and rodent studies, often with fruit or seed preparations, and cannot be extrapolated to leaf extract. Safety in rodents is encouraging, but long-term human data are lacking, and safety is plant-part specific, as shown by the reversible antifertility effect of seed extract. Papaya leaf extract should therefore be regarded as a promising supportive option and not as a replacement for medical care in dengue.

RESEARCH GAP

The following gaps limit the translation of current findings into an established therapeutic option for thrombocytopenia.

1. Lack of a uniform preparation. Fresh juice, aqueous extract, capsules and standardised extract have all been studied, and carpaine and phenolic content vary between leaf samples.
2. Limited clinical evidence. Human data are mostly case reports and small studies with risk of bias, and large controlled trials are few.

3. Unidentified active constituents. The compounds responsible for the platelet-supportive effect, and their mechanisms in humans, are not yet confirmed.
4. Insufficient human data on dosing, pharmacokinetics and long-term safety.
5. Preclinical nature of other activities. Non-haematological effects rest mainly on cell-based and rodent studies, often with fruit or seed preparations.

FUTURE PROSPECTS

Standardisation of papaya leaf extract on the basis of marker compounds such as carpaine is a priority for reliable product development. Metabolite profiling methods such as NMR can support quality control and help to compare different batches and plant parts. Defined cultivation, harvest and extraction procedures will be needed because the method of preparation changes the chemical profile of the leaf.

Larger, well-designed and properly controlled human studies with a uniform extract are needed to confirm the benefit seen so far. Such trials should use adequate sample sizes, blinded allocation, predefined dosing and clinically meaningful end points in addition to platelet count.

Mechanistic work should identify which compounds act on platelet production, platelet protection and viral replication. Bioassay-guided fractionation of the leaf extract, together with studies of thrombopoietic signalling such as interleukin-11, would help to link specific constituents to specific actions. Pharmacokinetic studies of the principal constituents are also required.

Long-term safety evaluation and clear dosage forms, such as tablets or capsules, will also be necessary before routine clinical use can be recommended. Post-marketing surveillance should accompany any clinical use, and the safety profile of leaf extract should be assessed separately from that of seed and latex preparations.

CONCLUSION

Carica papaya is a nutritionally and medicinally valuable plant whose leaf contains alkaloids, flavonoids, phenolic acids and saponins of pharmacological interest. Available reports suggest that papaya leaf extract can support platelet recovery in thrombocytopenia, especially in dengue, through antiviral, protective and immunomodulatory actions.

Safety studies in animals are reassuring, and human studies report good tolerability. However, the human evidence is limited by small studies, non-uniform preparations and an incomplete understanding of the active constituents and mechanisms. Standardised preparations, mechanistic studies and larger controlled clinical trials are therefore still required, and until then the extract should be regarded as a supportive measure under medical supervision.

LIST OF ABBREVIATIONS

Abbreviation	Full Form
ACE	Angiotensin-converting enzyme
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BITC	Benzyl isothiocyanate
DOCA	Deoxycorticosterone acetate
NMR	Nuclear magnetic resonance
RBC	Red blood cell

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