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Papaya Leaf Extract and its Role in Fighting Dengue and Cancer

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ABSTRACT-
Papaya (Carica papaya L.) is a tropical fruit widely cultivated for its nutritional, medicinal, and industrial applications. Rich in vitamins A, B, and C, calcium, iron, and the enzyme papain, papaya exhibitsdiverse therapeutic properties. The leaves,fruit, seeds, and latex contain bioactive compounds such as alkaloids, flavonoids, saponins, glycosides, and tannins, which provide antioxidant, antibacterial, anti-inflammatory, hypoglycemic, and anticancer benefits. Papaya leaf extracts have been studied for their potential in managing dengue by increasing platelet counts, improving digestion, and boosting immunity. These extracts also show promise in cancer treatment and managing metabolic diseases with minimal toxicity. The phytochemical diversity of papaya underscores its significant role in traditional medicine and modern healthcare, making it a valuable resource for treating a range of conditions, including digestive disorders, infections, and chronic diseases like cancer and diabetes

Keyword : Papaya, Carica papaya L., tropical fruit, medicinal properties, bioactive compounds, vitamins (A,B, C), calcium, iron, papain, antioxidant, antibacterial, anti-inflammatory, hypoglycemic, anticancer, papaya leaf extract, dengue, platelet count, immunity, digestion, phytochemicals, alkaloids,flavonoids, saponins, glycosides, tannins, traditional medicine, modern healthcare, metabolic diseases, cancer treatment.

I. INTRODUCTION

The image you shared discusses papaya, a tropical fruit found in various regions around the world. It highlights the health benefits of papaya leaves and extracts, which are used as dietary supplements to enhance the immune system, increase platelet counts, and improve digestion. The leaves, stems, and fruits are consumed as both food and medicine. The leaves are also prepared as medicinal teas to guard against infections.

Papaya is a fruit known for its many health benefits. The leaf extracts of papaya contain compounds with antibacterial properties that help prevent bacterial growth. Studies have also shown that these extracts may improve blood platelet function and have hypoglycemic effects, making them potentially helpful for managing diabetes with low toxicity. Additionally, papaya contains lycopene, a substance that has shown anticancer activity. For example, papaya juice and pure lycopene have been found to kill liver cancer cells, while papaya seed extracts have demonstrated effectiveness against leukemia cells. Moreover, lycopene in papaya may also be beneficial in fighting prostate cancer.

FigNo.01:Caricapapaya leaf

FigNo.02:Caricapayaya fruit

Papaya, which belongs to the small Caricaceae family, is a plant with many uses. Its fruits, leaves, and latex are widely used for medicinal purposes and in various industries. One important compound derived from papaya is papain, which is used in brewing, winemaking, textile, and tanning industries. Papaya is also rich in a variety of phytochemicals, including polysaccharides, vitamins, minerals, enzymes, proteins, alkaloids, glycosides, fats, oils, lectins,

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and saponins, all of which contribute to its numerous health benefits and industrial applications. flavonoids, sterols, etc. Papaya, a juicy and attractive fruit, belonging to Caricaceae is scientifically known as papaya Linn. it's grown in various parts of the earth, including India, tropical America and Europe. It is commonly mentioned as Papaya, Pawpaw or papau, Kapaya, Lapaya, Papyas, Papyc, Tapayas, Fan mu gua. Papaya plant is laticeferous as they contain specialized cells mentioned as laticifers. Lactifiers secrete latex and d dispersed throughoutmost plant tissues papaya is actuallyshort lived Indian tree. within the historic times, Lit was considered as an exotic fruit thanks to its buttery tasteand appearance. Papayawas the firstgenetically modified fruit consumedby citizenry for its nutritional e and medicinal properties. Plant derived drugs widely used to treat cancer. However, their dose associated side effects, and toxicity to non-tumor tissues negatively affect their utility. As a result, alternative cancer treatments that have little to no impact on healthy tissues are highly desirable. A currently useful strategy used to evaluate herbal extracts is to see in vitro (Hoelder et al., 2012) for his or her selective anti-proliferative activities against cancer cells as compared to normal cells. The papaya plant could also be a nutritionally abundant source of vitamins A, B and C and also an honest source ofcalcium and iron. Itcontains the enzyme papain, which aids digestionand is used to treat ulcers and a number of microbial diseases, with higher doses being especially effectiveagainstgram-negativebacteria. The photochemical investigation suggested thatyoung leaves contain alkaloids, saponin, tannin, flavonoid and glycosides, hence have therapeutic properties like antibacterial, anti-inflammatory, hypoglycaemic antitumor and many others. antiviral,

Papaya, scientifically known as Carica papaya, is a juicy and nutritious fruit from the Caricaceae family. It is grown in many parts of the world, including India, tropical America, and Europe, and is commonly known by different names like Pawpaw, Kapaya, and Fan mu gua. The papaya plant produces latex through specialized cells called laticifers, and its latex has various uses. Papaya is rich in vitamins A, B, and C, as well as calcium and iron, making it a valuable source of nutrition. It also contains papain, an enzyme that helps with digestion and is used to treat ulcers and microbial infections. Additionally, young papaya leaves are packed with compounds like alkaloids, flavonoids, and glycosides, which provide therapeutic benefits such as antibacterial, anti-inflammatory, hypoglycemic, and anticancer properties. Papaya was also the first genetically modified fruit consu the leaves of papaya are among the most valuable parts used for medicinal purposes. Whenused in a hot fomentation, papaya leaves can help increase breast milk production in nursing mothers. An infusion of fresh leaves is often gargled to treat conditions such as tonsillitis, ulcerative stomatitis, and gingivitis. Applying a lotion made from the leaves can stop bleeding and shrink hemorrhoids. Additionally, tender papaya leaves are consumed as spinach, while dried leaves are smoked and inhaled as a tobacco substitute to relieve asthma.

Eraṇḍachirbhit, Vṛkṣacirbhiṭa, Gopālakarkaṭi – These names compare papaya to Ricinus communis (castor, Eraṇḍa) and Luffa species (gourd, karkaṭi) due to similar morphological features, such as leaf shape and structure.

1. **Viṣapatra**–This term highlights the presence of potentially toxic substances in papaya leaves.
2. **Nalikādal, Nālaparṇi** – These names describe the plant's long, hollow leaf stalks (Nāla refers to hollow, Parṇi or Dal refers to leaves).
3. **Kṣīrasravā**–This synonym refers to them ilk sap that oozes from the papaya plant.
4. **Śuklapuṣpi**–This describes the plant's white flowers.
5. **Kumbhaphalā, Madhukarkaṭi** – These names are specific to the fruit, which is considered aphrodisiac and tonic in Ayurvedic tradition. It is said to balance the three doshas—Vāta, Pitta, and Kapha—which represent the fundamental physiological forces in the body.

Plants and plant-based products have been used for preventing and treating various human diseases since ancient times. It is estimated that around 80% of the global population relies on plants for primary healthcare. In India, approximately 45,000 plant species are known to have medicinal properties. Natural products or compounds extracted from plants play a significant role in healthcare practices.

Natural compounds derived from plants offer significant advantages over synthetic drugs, such as being cost-effective, easily accessible, and having minimal side effects. Numerous studies have documented the use of medicinal plants in managing various diseases. One such plant is Caricapapaya Linn. from the Caricaceae family,

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native to Central America and southern Mexico, but commonly cultivated in India for its medicinal properties. The papaya plant is perennial, typically unbranched, with smooth stems and long-stalked leaves with 5–6 lobes, capable of growing up to 20 meters tall. Various parts of the papaya plant, including the fruit, bark, roots, seeds, peel, pulp, and leaves, have multiple therapeutic uses. Nutritionally, papaya is rich in vitamins A, B, and C, and isalso a good source of calcium and iron. It contains the enzyme papain, which aids in digestion and is effective in treating ulcers and certain microbial infections, particularly those caused by gram-negative bacteria.

Papaya has been recognized for its medicinal properties, with various parts of the plant offering therapeutic benefits. The seed extract contains benzyl isothiocyanate (BITC), which has bactericidal, bacteriostatic, and fungicidal properties. Papaya is also known for its strong antioxidant activity, helping to neutralize free radicals and prevent diseases.

The latex of the papaya plant contains enzymes such as papain, glycyl endopeptidase, chymopapain, and caricain, with varying concentrations in different parts of the plant. In recent years, papaya leaves have gained attention for their medicinal uses. They have beenused traditionally to treat ailments like fever, asthma, jaundice, and beriberi. Various methods of preparing papaya leaf extract (PLE) include aqueous, ethanol, and methanol extracts, as well as freeze-driedjuice, all of which are used to prevent diseases.

Pharmacognosy:
Kingdom:Plant
Genus:Carioca
Order:Brassicales
Species:C.Papaya
Family:Caricaceae

Phytochemical Studied-

The popularity of herbs in traditional medicine often stems from their higher likelihood of containing pharmacologically active compounds compared to woody plants. Among the various plant parts used, leaves are the most commonly utilized. For instance, the leaves of Carica papaya L. are notable for containing several alkaloids such as carpaine, pseudocarpaine, and dehydrocarpaine I & II. Carpaine, which was first isolated in 1890, has demonstrated antitumor properties in vitro against various cancer cell lines including mouse lymphoid leukemia L1210, lymphocytic leukemia P388,and Ehrlichascites tumor cells. Additionally, it has shown anti-tubercular activity against Mycobacterium tuberculosis H37 Rv, though it is also known to be a heart poison that lowers pulse frequency and depresses the central nervous system. Carpaine is also recognized for its potent amoebicidal properties.

Pseudocarpaine, an isomer of carpaine, differs only in the configuration at the alcoholic carbon atom, affecting its melting point and optical rotation. The leaves of Carica papaya are also reported to contain other bioactive compounds such as choline, carposide, anthraquinone, vitamin C, and vitamin

E. These molecules contribute to a broad range of biological activities. Furthermore, the leaves accumulate insulin, tannins, and additional alkaloids that might be responsible for their medicinal effects.

Additionally, seven flavonoids have been identified in Carica papaya leaves, including quercetin, kaempferol, and their various glycosides, which have been evaluated for their antioxidant activities. The flavonol types include manghaslin, clitorin, rutin, and nicotiflorin, while the alkaloid fraction consists of five isolated piperidine alkaloids.

However, the extractive yields from the leaf tissue are lower compared to other plant parts suchasripe and unripe fruits. Chemical analyses of the leaves from Carica papaya grown in semi-arid zones have been conducted using Energy Dispersive X-ray Fluorescence (EDXRF), which is a reliable, accurate, and non-destructive method for element analysis. Results showed that oxygen (87%),calcium (4.47%), magnesium (3.37%), and potassium (1.49%) were present in the highest amounts, with trace elements like silicon, aluminum, phosphorus, chloride, sulfur, stannous, and strontium also detected. Heavy metals such as zinc, manganese, copper, and rubidium were found in very small quantities, while elements like vanadium, titanium, cobalt, and tantalum were absent.

Papaya leaves are known for their impressive range of medicinal properties, offering significant health benefits. One of the key advantages of papaya leaves is their high antioxidant potential, measured at an impressive 90%. Heavy metals such as zinc, manganese, copper, and rubidium were found in very small quantities, while elements like vanadium, titanium, cobalt, and tantalum were absent. Papaya leaves are

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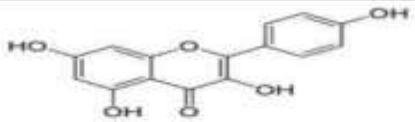
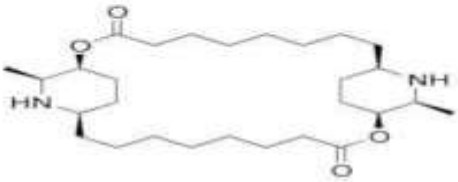
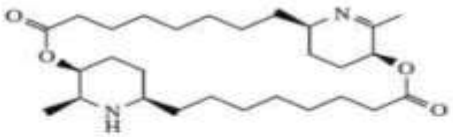
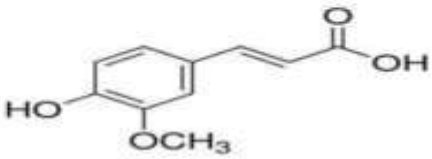
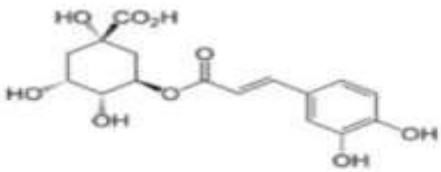
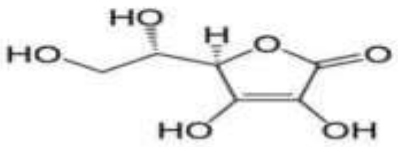
known for their impressive range of medicinal properties, offering significant health benefits. One of the key advantages of papaya leaves is their high antioxidant potential, measured at an impressive 90%. Antioxidants play a crucial role in neutralizing harmful free radicals in the body, thereby protecting cells from oxidative damage and reducing the risk of chronic diseases. Additionally, papaya leaves are rich in trace minerals like iron, zinc, manganese, chromium, and copper, all of which are important for various biological functions, including enzyme activation, red blood cell production, and immune support.

Chemical Constituent-

Chemical constituent	Structure
Kaempferol	
Carpaine	
Dehydrocarpaine I	
Ferulic acid	
Chlorogenic acid	
Vitamin C	

Pharmacognostical Study:

Carica papaya L., known as papaya, papaw, or pawpaw in various regions, is a fast-growing, semi- woody tree with a short lifespan. It is distinguished by its leaf characteristics and is predominantly cultivated in tropical and subtropical areas such as Hawaii, Australia, and Southeast Asia. Major producers include India, Mexico, Indonesia, Thailand, and Nigeria. Historically, papaya spread from Mexico and Panama to the Caribbean, the Philippines, and eventually to other parts of Asia. which can reach up to 12 meters in height, has a milky latex and produces melon-like fruits year-round. The papaya plant is used traditionally for its various medicinal properties; its latex contains the

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enzyme papain, utilized in meat tenderization and treating conditions like wounds, dyspepsia, and psoriasis. Additionally, the root infusion has been used for treating venereal diseases, piles,

The papaya tree, or Carica papaya, is a slender, single-stemmed plant that typically growsbetween15 and 30 feet tall. Its leaves are arranged in a spiral pattern at the top of the tree, while the lower trunk displays scars where previous leaves and fruits have grown

The leaves are broad and lobed, usually having seven lobes and measuring around 50 to 70 cm (20 to 28 inches) in diameter. Papaya trees are dioecious, meaning they have separate male and female plants. Male flowers have fused stamens and petals, while female flowers possess a superior ovary and five twisted petals. Both flower types grow in the leaf axils and have a sweet scent, especially in the evening.

The tree produces large, berry-like fruits that range from 10 to 30 cm in diameter and 15 to 40 cmin length. Belonging to the Caricaceae family, papayas contain latex in all parts of the plant. The papaya tree reaches a height of 5 to 10 meters (16 to 33 feet) and has distinct scars on its lower trunk where leaves and fruits were once attached. Microscopic studies of the leaves reveal various tissues such as the epidermis, collenchyma, parenchyma, sclerenchyma, xylem, and phloem.

Table1Medicinalusesofdifferentpartofpapayaplant Plant	Medicinal use
Ripefruit.Heartdiseaseandstroke:Papayacontainsantioxidantslikevitamin A,vitaminC,and vitamin E that may reduce the risk of heart disease and stroke. Cholesterol:Papaya'sfibermayhelplowercholesterol. Bloodpressure:Papayacontainspotassium,whichcanbehelpfulforpeoplewithhighbloodpressure. Visionandeyehealth:Papayacontainscarotene,whichmayimprovevisionandpreventnight blindness. It also contains zeaxanthin, which filters out harmful blue light rays. Immunesystem:Papayaisagoodsourceofvitamin Candvitamin A,which canhelpboostthe immune system. Bonehealth:PapayacontainsvitaminK,whichimprovescalciumabsorption Cancer: Papaya may help prevent or delay certain cancers Digestion: Papaya's fiber and water content can help with digestion and prevent constipation. Papaya also contains enzymes like papain and chymopapain that can help with digestion and reduce inflammation. Skinhealth:Papayacontainsalpha-hydroxyacids(AHAs)thatcanhelpremovedeadskincellsand rejuvenate skin tissues. This can help prevent wrinkles, sagging, and dull skin.	
Greenfruit–Nutrient-richBoostsimmunesystem	Digestive health, Anti-inflammatory properties,Weightmanagement,Skinhealth,Supportscardiovascularhealth,,Menstrualpainrelief Latex–papayalatexisveryusefulforhealingdyspepsiadiarrhea,bleedinghemorrhoids,and whooping cough
Leaves-Treatingdenguefever:Papayaleafextractshavebeenshowntohelptreatdenguefeverin clinical studies. Increasingplateletcounts:Papayaleafextractscanincreaseplateletcounts,whichcanhelpnormalize blood clotting. Improvingimmunity:Papayaleavescontainnutrientsthatcanhelpimproveimmunity Treatingdigestiveissues:Theenzymesinpapayaleavescanhelpwithdigestion,bloating,and indigestion. Improvingbloodsugarcontrol:Papayaleaves mayhelpimprovebloodsugarcontrol.	
Flowers-Bloodsugarcontrol:Papayaflowerscan helpcontrolbloodsugarlevelsindiabetic patients. Bloodpressure:Papayaflowerscanhelpstabilizehighbloodpressureandthinthebloodtohelpthe heart pump normally Hearthealth:Papayaflowerscanhelppreventheartdisease. Weightloss:PapayaflowerscontainvitaminsA,B,andC,whichcanhelpreducebodyfat. Respiratoryproblems:Amixtureofpapayaflowerextractsandhoneycanhelptreatrespiratory problems like coughs and hoarseness Seeds-Digestivehealth:Papayaseedsareagoodsourceoffiber,whichcanhelpwithconstipation and other digestive issues	

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Anti-inflammatory:Papayaseedscontaincompoundsthatmayhelpreduceinflammation,whichcan be helpful for people with arthritis and other inflammatory conditions
Liverhealth:Someresearchsuggeststhatpapayaseedsmayhelpprotecttheliver. Immune system: Papaya seeds may help strengthen the immune system.
Parasites:Papayaseedshavebeenusedasanaturalremedytotreatintestinalparasites Cholesterol: Papaya seeds may help regulate cholesterol.
Roots/Barks-Treatingulcers:Papayaleaveshavebeenusedtotreatulcers Treating hypertension: Papaya leaves have been used to treat hypertension
Treatinghemorrhoids:Papayarootsortheirextractshavebeenusedtotreathemorrhoids. Treating syphilis: Papaya roots or their extracts have been used to treat syphilis
Treatinguterinecancer:Papayarootsortheirextractshavebeenusedtotreatuterinecancer.

Therapeutic application of papaya leaf extract-

Papaya leaf extract (PLE) has been recognized for its medicinal properties and its role in the treatment of various human diseases. This is largely attributed to its rich content of phytochemicals, minerals, and vitamins. Throughout history, PLE has been used in traditional medicine for managing a wide range of ailments, and modern scientific research has supported these claims. Studies have demonstrated that PLE contains compounds with antioxidant, anti-inflammatory, and immune- boosting properties, making it effective in treating conditions such as dengue fever, malaria, and certain types of cancer. Its ability to promote platelet production, reduce oxidative stress, and enhance overall health makes it a promising natural remedy. Moreover, PLE's potential for disease prevention, as revealed through recent scientific investigations, further highlights its significance in both traditional and modern medicinal practices. By contributing to overall immune system support and aiding in the recovery from various illnesses, PLE continues to be a valuable natural resource inhealth and wellness.

Mechanism of action papaya leaf in health management-

Papaya leaf, derived from the Carica papaya plant, has been used in traditional medicine for centuries due to its various therapeutic properties. The health benefits of papaya leaf can be attributed to the presence of bioactive compounds such as flavonoids, alkaloids, phenolic acids, and enzymes like papain, chymopapain, and carotenoids. These compounds work synergistically to produce a range of medicinal effects, making papaya leaf an important component in natural health management.

One of the most notable properties of papaya leaf is its potential to boost the immune system. This is primarily due to the presence of papaya leaf extract, which has been shown to enhance the production of white blood cells, including T-cells and macrophages, that help combat infections. The antioxidants present in papaya leaves, such as vitamin C and carotenoids, also help in reducing oxidative stress and inflammation in the body, thereby promoting overall immune function and supporting the body's natural defense mechanisms.

Papaya leaf has also gained attention for its role in managing blood platelet levels, especially in conditions like dengue fever. Studies have shown that papaya leaf extract can help increase platelet count in individuals with low platelet levels, likely by stimulating the production of megakaryocytesin the bone marrow, the cells responsible for producing platelets. This makes papaya leaf particularly beneficial in treating viral infections like dengue, where platelet levels tend to drop dramatically, potentially leading to complications.

In addition to its effects on the immune system and blood cell production, papaya leaf is known for its digestive benefits. The enzyme spa pain and chymopa pain in papaya leaf aid in the breakdown of
proteins, improving digestion and nutrient absorption. These enzymes can be particularly beneficialfor individuals suffering from digestive disorders, such as indigestion, bloating, and irritable bowel syndrome (IBS). Moreover, the anti-inflammatory properties of papaya leaf help soothe the digestive tract, reducing discomfort and promoting gut health.

Therapeutic application of carica papaya leaf Anti-cancer activity-

Papaya is widely recognized for its medicinal properties, particularly in preventing and treating alimentary canal disorders, intestinal

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parasite infections, and as a natural sedative and diuretic. Additionally, it is used to relieve nerve pain (neuralgia) and treat elephantoid growths—large, swollen areas of the body caused by parasitic worm infections affecting the lymphatic system. One of the key compounds found in papaya is papain, which is often used as a meat tenderizer. Research suggeststhat papaya consumption may reduce the risk of gallbladder and colorectal cancers. In relation to diabetes, preliminary studies indicate that daily consumption of fermented papaya over two monthscan lower blood glucose levels in diabetics.

Papaya has also been linked to a reduced risk of Human Papilloma virus (HPV) infection. Studies like those conducted by Otsuki et al. have highlighted papaya's traditional use and its purported anticancer properties, establishing its reputation as a tumor-destroying agent. The presence of saponins in papaya leaves supports its cytotoxic effects, while vitamin C contributes to its use inherbal medicine for treating prostatic adenocarcinoma. Moreover, papaya juice has demonstrated ant proliferative effects on liver cancer cells. Lycopene, one of the most abundant carotenoids in papaya, is central to its biosynthetic pathway, becoming more active during the ripening stage. Researchers like Armando have illustrated papaya's protective effects against atrophic arthritis, renal failure, and prostatic adenocarcinoma. Papaya also exhibits potent antioxidant properties, neutralizing free radicals and offering protection against various types of cancer, including breast cancer, prostate cancer, atherosclerosis, and coronary artery disease.

Mechanism of action–

Papaya leaf extract has shown potential as an anticancer agent by modulating the immune system and enhancing the production of Th1 cytokines, including interleukin-12 (IL-12), interferon-gamma (IFN-gamma), and tumor necrosis factor-alpha (TNF-alpha). Research suggests that papaya leafextract may inhibit cancer cell growth most effectively in fractions with a molecular mass below1000. Additionally, the extract contains antioxidant, antibacterial, and phenolic compounds, though its precise mechanism of action remains unclear. Papaya juice and lycopene, a key compound found in papaya, demonstrated cytotoxic effects on Hep G2cancercells with IC50 values of 20µg/mL and 22.8 µg/mL, respectively, inducing necrobiosis. In acute promyelotic leukemia HL-60 cells, papaya seed extract exhibited anticancer activity at 20 µg/mL, while papaya pulp extract had no effect even at the same concentration. Although no human clinical trials have been conducted yet, some cancer patients, including those with liver and stomach carcinoma, have reported improved survival after consuming papaya leaf extract. Additionally, papaya may offer therapeutic benefits for prostatecancer due to its lycopene content.

Anti-cancer effects of papaya leaf extract-

Cancer is one of the most lethal diseases globally, arising from the uncontrolled division of genetically unstable cells. It is a significant cause of death worldwide. Among the various types of cancers affecting humans, such as colon, cervical, liver, stomach, lung, pancreatic, and breast cancers, lung cancer is the most prevalent among males, while breast cancer is the leading type among females. Currently, depending on the type, stage, and location of the cancer, there are several treatment options available, including surgery, chemotherapy, radiotherapy, immunotherapy, vaccinations, and combination therapies. Of these, chemotherapy is a widely used treatment, particularly for highly metastatic cancers. Chemotherapeutic drugs, such as irinotecan, vinblastine, doxorubicin, oxaliplatin, melphalan, carboplatin, cisplatin, cyclophosphamide, docetaxel, vincristine, and paclitaxel, have proven to be significantly effective against a wide range of cancers. These drugs often show promising results either alone or in combination with other cancer therapies.

However, despite their effectiveness, chemotherapeutic drugs come with several limitations, suchas limited bioavailability, high toxicity, lack of specificity, and rapid clearance from thebody. They are frequently associated with adverse side effects, including high cytotoxicity, neutropenia, sensory neuropathy, cardiovascular toxicity, pulmonary and hematologic toxicity, gastrointestinal toxicity, diarrhea, and nephrotoxicity. Due to these drawbacks, researchers have increasingly focused on exploring alternative cancer treatments that come with minimal or no side effects. Extensive research has identified plant extracts and their derived analogs as a promising alternative to conventional cancer therapies. These natural compounds have shown potential for treating cancer without the noticeable side effects commonly observed with traditional chemotherapeutic drugs during therapy.

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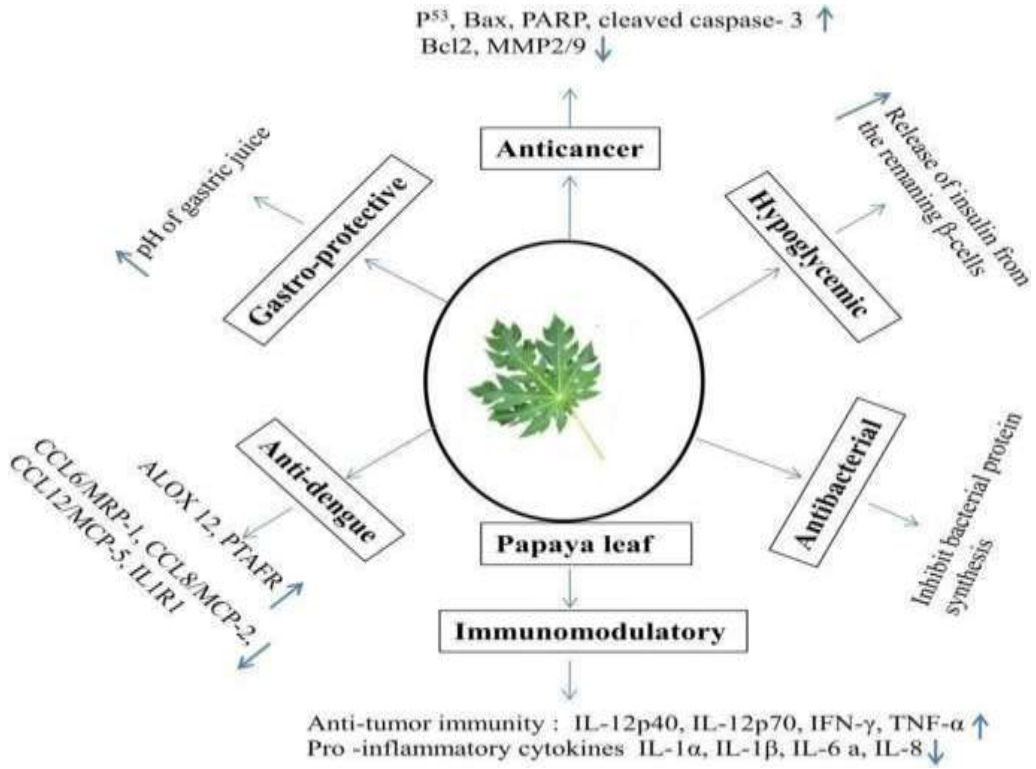

Fig.04 Therapeutic Benefits of Carioca papaya

Bonem arrow suppression-

The isolation of viral RNA from the bone marrow of dengue-infected individuals, along with the observation of hypocellularity and inhibited megakaryocyte maturation in the early stages of the disease, indicates a suppressive effect of the dengue virus on bone marrow, which contributes to thrombocytopenia. This suppression can occur either directly, through damage to progenitor and stromal cells, or indirectly by altering cytokines in the bone marrow that influence megakaryocyte differentiation. Megakaryopoiesis, the process by which megakaryocytes and platelets are formed, has been shown to be suppressed in both in vivo and in vitro studies involving dengue infection. In particular, the DENV-envelope protein domain III (DENV-EIII) was found to impair megakaryopoiesis in mice, while progenitor cells from murine bone marrow and human cord blood showed similar suppression. Autophagy dysfunction has been proposed as a potential mechanism behind this suppression. Furthermore, dengue virus type 4 (DV-4) was observed to alter the proliferative capacity of human bone marrow progenitors, and studies have shown that the virus inhibits the propagation and differentiation of CD34+ progenitors into megakaryocytes, causing apoptotic cell death.

Thrombopoietin (TPO), a key cytokine involved in regulating megakaryocyte production, is typically released in response to low platelet counts. It binds to its receptor and activates signaling pathways, such as JAK and STAT, to promote megakaryocyte production. In the early stages of dengue, increased levels of TPO have been observed, indicating a decline in megakaryopoiesis at this point in the disease. Moreover, DENV antigens have been detected in infected stromal cells, which likely leads to changes in cytokine profiles. For example, the cytokine TGF-β, which has been foundat elevated levels in dengue patients, is known to reduce pro-platelet production. This further supports the notion that dengue virus infection disrupts normal bone marrow function and megakaryopoiesis, contributing to the development of thrombocytopenia in affected individuals.

Destruction of platelets-

The destruction of platelets in dengue infection is driven by molecular mimicry between viral proteins, such as NS1, prM, and E, and host components like platelets, endothelial cells, and blood clotting molecules. This mimicry plays a

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significant role in platelet destruction through either direct mechanisms, such as the cross-reactivity of antibodies, or indirect mechanisms involving theformation of aggregates with leukocytes or endothelial cells. Antibodies produced against these viral proteins can trigger various harmful processes, including macrophage activation, platelet dysfunction, coagulation deficiencies, and the destruction of endothelial cells. Notably, IgM antibodies generated against NS1 viral proteins have been found to induce peripheral platelet destruction or cell lysis, and they can inhibit platelet aggregation. These IgM antibodies are present in higher quantities in patients with Dengue Hemorrhagic Fever (DHF) compared to those with Dengue Fever (DF), and DHFpatients also exhibit increased platelet lysis.

Additionally, dengue infection prompts endothelial cells to become activated, leading to platelet adhesion and activation, as well as the expression of P-selectin on the surfaces of these cells. The presence of P-selectin facilitates the interaction between activated platelets and leukocytes, resultingin the formation of platelet-leukocyte aggregates, such as platelet-monocyte and platelet-neutrophil complexes. These aggregates, in turn, contribute to the development of thrombocytopenia.

Role of blood coagulation factors-

Disseminated intravascular coagulation (DIC) is a critical complication often activated during dengue virus (DENV) infection. The virus induces a hyper activation of both fibrinolysis and the coagulation system, leading to significant alterations in coagulation and fibrinolytic parameters (da Costa Barros and de-Oliveira-Pinto, 2018). In patients with dengue hemorrhagic fever (DHF) who develop DIC, several coagulation-related abnormalities have been observed. Low platelet counts in these patients are commonly linked to decreased levels of prothrombin, fibrinogen, factor VIII, plasminogen, and antithrombin activities. Additionally, prolongation of partial thromboplastin time (PTT) and prothrombin time (PT) has been documented, indicating impaired blood clotting (Funahara et al., 1987).

Platelets as a target for viral replication-

Dengue virus (DENV) has been linked to platelet activation and replication within platelets, indicating that platelet clearance may involve DENV-exposed platelets interacting with CD14+CD16+ monocytes, even ifthe virus doesn'tdirectly infect the platelets (Kar etal., 2017). Studies have shown that intact platelets can replicate all four DENV serotypes (Rondina and Weyrich, 2015), and platelets can replicate the virus at both 37°C and 25°C, with saturable binding to DENV,producing infectious viral particles (Simon et al., 2015). DENV RNA has also been detected in platelets,specifically CD61+cells, in blood samples from denguepatients and experimentally infected rhesus monkeys. Moreover, DENV antigens have been found in vesicles of various sizes and in nuclear cells within platelets (Noisakran et al., 2012). Additional studies have identified DENV-likeparticles,antigens, and RNA in association with platelets(Noisakranet al., 2009a;2009b). DENV is thought to induce platelet activation, mitochondrial dysfunction, and apoptosis by targeting DC-SIGN receptors on platelets (Hottz et al., 2013; Hottz et al., 2018). These mechanisms contributeto the development of thrombocytopenia during dengue infection.

Immunomodulatory effect of papaya leaf extract-

The experimental evaluation of various parts of the papaya plant has revealed its significant medicinal properties, particularly in the treatment of numerous pathological conditions such as wound healing, cardiovascular diseases, dengue fever, and cancer. Recent studies have highlighted the immunomodulatory, antitumor, and anti-inflammatory effects of papaya leaf extract (PLE) on cancer cell lines and peripheral blood mononuclear cells (PBMCs). PLE has been shown to regulate cytokine production, enhancing anti-tumor immunity by up regulating Th1 type cytokines such as IL-12, TNF-α, and IFN-γ, while down regulating Th2 type cytokines like IL-4 and IL-2. This shift from a Th2 to a Th1 response suggests its potential use in treating Th2-mediated allergic conditions and as a vaccine adjuvant.

Hypoglycaemic effect of papaya leaf extract-

Diabetes mellitus is a complex metabolic disorder marked by chronic hyperglycemia and impaired insulin production. Its prevalence is rising globally, driven by factors such as unhealthy diets, aging populations, obesity, and sedentary lifestyles, as well as malnutrition-related issues. According to the American Diabetes Association, around 1.3% of the global population was affected by diabetes in 2017. India, in particular, has been identified as the diabetic capital of the world due to its growing number of cases, with the International Diabetes

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Federation projecting an increase in the diabetic population from 40.9 million to 69.9 million by 2025.

Sickle cell anaemia and papaya leaf extract–

glycine, and glutamic acid, along with essential minerals like potassium, magnesium, calcium, iron, manganese, and sodium. These nutrients help protect the RBC membrane from lysis and destruction. Although these findings are promising, further investigations are necessary to fully understand the mechanisms through which PLE prevents sickle cell disease and to evaluate its potential for clinical application.

Antibacterial activity of papaya leaf extract–

Studies on Carica papaya leaf extracts have demonstrated notable antibacterial properties. Research by Suresh et al. revealed that among five plant extracts tested, Carica papaya leaf extract exhibited the highest antibacterial activity. This extract significantly inhibited the growth of several gram-positive bacteria, including Pseudomonas aeruginosa, Bacillus subtilis, and Staphylococcus aureus. However, its effects on gram-negative bacteria such as Klebsiella pneumoniae and Escherichia coli were less pronounced. This reduced effectiveness against gram-negative bacteria is attributed to their thick murein layer in the outer membrane, which hinders the entryof the extract's antimicrobial compounds into the bacterial cells. Additional studies have shownthat Carica papaya leaf extracts, when prepared with solvents like ethanol, methanol, ethyl acetate, acetone, chloroform, or hot water, exhibit strong bactericidal activity against a range of bacteria, including Bacillus cereus, Klebsiella pneumoniae, Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus.

Gastro-protective effects of papaya leaf extract–

Ulcers are a prevalent gastrointestinal disorder affecting a large segment of the global population. They can be triggered by various factors, including smoking, stress, alcohol consumption, nutritional deficiencies, the use of non-steroidal anti-inflammatory drugs (NSAIDs), and infections such as those caused by Helicobacter pylori. Recent research has explored the potential therapeutic benefits of Carica papaya leaf extract (PLE) in treating gastric ulcers. A study by Odo et al. investigated the effects of ethanolic extracts of papaya leaves on experimentally induced gastric ulcers in rats. The results showed a significant reduction in ulcer index and gastric juice volume, along with an increase in the pH of gastric juice in rats with aspirin-induced ulcers, indicating a therapeutic potential for PLE. Furthermore, another study demonstrated that aqueous extracts of papaya leaves were effective in reducing the ulcer index in an alcohol-induced rat model. These findings suggest that PLE may offer a promising therapeutic approach for managing gastric ulcers. However, further research is necessary to gain a deeper understanding of its efficacy and mechanisms of action.

Analgetic activity–

The analgesic activity of three different leaf extracts from Carica papaya L. was evaluated using amice model with acetic acid-induced pain, following the Siegmund method. These extracts—n-hexane, ethyl acetate, and ethanol—demonstrated significant analgesic effects at all tested dose levels (0.175, 0.35, and 0.70 mg/kg body weight, administered orally). The results showed that these extracts provided effective pain relief comparable to that of aspirin, which was used as the standard reference drug.

Antiplasmodial activity–

Leaf extracts of Carica papaya L. have shown significant antiplasmodial activity with minimal cytotoxicity. This effectiveness is attributed to three specific alkaloids found in the extracts. In vitro testing against various parasites, including Trypanosoma brucei rhodesiense, Trypanosoma cruzi, Leishmania donovani, and Plasmodium falciparum, as well as in a Plasmodium berghei mouse model, demonstrated the extracts' potent antiplasmodial properties. The study highlights that the observed antiplasmodial activity of Carica papaya leaves is likely due to these alkaloids, with carpaine being particularly effective and selective in vitro.

Antitumor and Immunomodulatory activity–

A study investigating the antitumor and immunomodulatory effects of Carica papaya L. leaf aqueous extract demonstrated notable findings. The study focused on the extract's impact on tumorcell lines and human peripheral blood mononuclear cells (PBMCs). Results indicated that the extract significantly inhibited the growth of tumor cell lines. Additionally, it reduced the production of interleukins IL-2 and IL-4 by PBMCs and enhanced the expression of 23 immunomodulatory genes, suggesting a shift towards a Th-1 type immune response. This implies potential for Carica

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papaya leaf extract in treating carcinomas, allergic disorders, and serving as an immunomodulator.

Further research assessed the antiproliferative effects of Carica papaya L. leaf juice on various cell lines, including benign, tumorigenic, and normal prostate cells. A time-course analysis of the juice before and after in vitro digestion, along with molecular weight-based fractionation, revealed a significant antiproliferative response. Notably, the medium polarity fraction (0.03-0.003 mg/mL) exhibited cytotoxicity against all prostate cells except the normal cells. This fraction also inhibited the migration and adhesion of metastatic PC-3 cells. Flow cytometric studies suggested that the observed antiproliferative effects might be due to S phase cell cycle arrest and apoptosis.

Overall, these findings highlight the potential of Carica papaya L. leaf extract in addressing prostatic diseases, including prostate cancer (PCa), and underscore its ant proliferative and ant metastatic properties. Additionally, the proliferative activity of saponin-reducing Carica papaya L. leaf extracts on human lung fibroblast cells (IMR90) has also been studied, contributing to the broader understanding of its therapeutic potential.

Antidiabetic activity–

A study was conducted to evaluate the antidiabetic activity of Carica papaya L. leaf extract using an experimental rat model. In this study, chloroform extracts of Carica papaya L. leaves, which contain steroids and quinines, were administered to both streptozotocin-induced diabetic rats and non- diabetic rats at various dosage levels. The treatment lasted for 20 days, after which the rats were sacrificed for biochemical analysis. The results demonstrated a significant reduction in serum glucose levels, transaminases, and triglycerides in the diabetic rats that received the Carica papaya L. leaf chloroform extract. These findings suggest that the extract has a notable potential to alleviate the symptoms associated with diabetes, indicating its possible therapeutic value for managing diabetes in patients.

Centaral and cardiovascular effects–

The alcoholic extract of Carica papaya L. leaves demonstrated dose-dependent sedative effects when administered intraperitoneally at a dose of 10 mg/kg in male rats. At a lower dose of 5 mg/kg,the extract induced central muscle relaxation. Notably, a dose of 50 mg/kg provided complete protection against seizures induced by pentylene-tetrazol, while a 5 mg/kg dose offered 50% protection. The extract at doses of 100 and 200 mg/kg completely protected rats from convulsions induced by maximum electroshock. Behavioral observations associated with the extract included an initial desynchronization of EEG and increased EMG activity, indicating significant central nervous system effects. Additionally, the leaf extract demonstrated cholinesterase activity, further suggesting its impact on neurophysiological processes.

The major alkaloid found in Carica papaya leaves, known as carpaine, has been studied for its cardiovascular effects using Wistar rats. Increased dosages of carpaine were found to progressively decrease systolic, diastolic, and mean arterial blood pressure. Notably, the circulatory response to carpaine was not altered by atropine sulfate (1 mg/kg) or propranolol hydrochloride (8 mg/kg). At a dose of 2 mg/kg, carpaine reduced cardiac output, stroke volume, stroke work, and cardiac power, though it did not affect total peripheral resistance. These findings suggest that carpaine specifically influences myocardial function, highlighting its potential impact on cardiovascular health.

The anti-inflammatory activity–

The anti-inflammatory potential of ethanolic extracts from Carica papaya L. leaves was investigated through various experimental models in rats, including the paw edema test using carrageen an, formaldehyde-induced arthritis, and cotton pellet granuloma assays. In these studies, experimental animals were administered the extracts orally at doses ranging from 25 to 200 mg/kg, while the control group received saline and the reference group was given indomethacin at 5 mg/kg body weight. The results demonstrated a significant reduction in paw edema in the carrageen an test, with a notable decrease in the formation of granuloma, from 0.58 ± 0.07 grams to 0.22 ± 0.03 grams, indicating effective anti-inflammatory activity. Additionally, the ethanolic extract significantly reduced persistent edema from the fourth to the tenth day in the formaldehyde arthritis model. However, slight mucosal irritation was observed at higher doses of the extract. Overall, these findings confirm the anti-inflammatory properties of Carica papaya L. leaves, while also highlighting the need to monitor for potential mucosal irritation at elevated doses.

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Nephroprotective activity–

In a recent study investigating the nephrotoxic effects of lead (Pb(II)) and the potential mitigating effects of Carica papaya L. leaf powder, experimental rats were subjected to Pb(II) exposure to assess its impact on renal function and oxidative stress. Rats treated with 1.000 mg/L Pb(II) ions exhibited elevated serum biochemical markers indicative of kidney damage, including significant increases in serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), urea, creatinine, and malondialdehyde levels. These biomarkers reflect both liver and kidney dysfunction as well as oxidative stress. Additionally, histopathological examinations revealed severe necrosis of kidney cells andswellingof tubular cells in Pb(II)-exposed rats, underscoring the extent of renal damage caused by lead toxicity. However, rats pre-treated with C. papaya leaf powder demonstrated a significant reduction in these detrimental effects. Specifically, the pre-treatment group showed markedly lower levels of SGPT, SGOT, urea, creatinine, and malondialdehyde compared to the Pb(II)-treated group. Furthermore, the pre-treatment with papaya leaf powder mitigated the structural damage to the kidneys, as evidenced by reduced necrosis and less swelling of tubular cells. This study concludes that Carica papaya leaf powder holds promise as an effective antidote, providing notable preventive effects against Pb(II)-induced nephrotoxicity.

Wound healing activity–

An experimental study was conducted to evaluate the wound healing efficacy of Carica papaya L. leaf powder. In this study, propylene glycol was used as a control to compare against the effects of the papaya leaf powder. Various parameters were assessed, including the rate of wound closure, wound contraction, fibroblast cell count, and the histology of granulation tissue. While there was only an insignificant effect on wound contraction observed, the Carica papaya L. leaf powder-treated group exhibited notable improvements in wound closure and an increase in fibroblast cell count, which are crucial indicators of effective wound healing. The findings provide a scientific basis for the wound healing potential of Carica papaya L. leaves, highlighting their effectiveness in promoting faster and more efficient wound repair.

Moreover, Carica papaya L. leaves are recognized for their ability to increase platelet count,leading to a surge in supplements containing this ingredient in the market. However, reviews suggest that various manufacturing techniques employed in these products may degrade the phytochemicals responsible for their beneficial effects. This degradation could potentially reduce the therapeutic efficacy of the supplements. Therefore, while traditional methods of preparing and presenting Carica papaya L. leaves have demonstrated significant benefits, there is a need for modernization and refinement in manufacturing processes to preserve the phytochemical integrity and maximize the health benefits of these supplements.

II. CONCLUSIONS

Herbal products, especially those derived from plants like Carica papaya (papaya), are increasingly favored as safer alternatives to synthetic substances, which are often associated with various adverse health effects. The leaves of Carica papaya are a rich source of numerous bioactive compounds that contribute to their wide range of therapeutic properties. Phytochemical analysis has revealed the presence of several active molecules, each potentially responsible for the plant's beneficial biological activities, such as antioxidant, anti-inflammatory, and antimicrobial effects. However, much of the plant's potential remains unexplored, and further research is needed to identify and harness its full medicinal capabilities. Advanced investigative methods could play a crucial role in isolating these active compounds and understanding their mechanisms, opening the door for more targeted and effective therapeutic applications of Carica papaya leaves.

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