

A Critical Review of *Carica papaya* L.: Phytochemistry, Pharmacological Evidence, Safety and Therapeutic Potential

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Abstract: *Carica papaya* L. is a widely cultivated tropical plant used as food and as a source of enzymes, alkaloids, phenolics, carotenoids, vitamins and other bioactive constituents. The pharmacological literature includes studies on antioxidant, anti-inflammatory, antimicrobial, wound-healing, metabolic, cardiovascular and platelet-related effects, but the strength of evidence differs markedly among plant parts and preparations [1,5–12]. This critical review organizes the evidence by plant part and links reported constituents with experimental outcomes, clinical observations, safety findings and standardization needs. Particular emphasis is given to papaya leaves because they have attracted substantial research in dengue-associated thrombocytopenia, while latex is considered separately because of its proteolytic enzymes [2,15–17,37–39]. Recent literature also indicates that leaf developmental stage can influence phytochemical composition and bioactivity, which has implications for reproducibility of herbal preparations [4]. The review further considers recent evidence on fruit bioactives, leaf nutritional and phytochemical characterization, cancer-related research, antiviral literature and papain safety evaluation [3,30,39,40,49]. Overall, papaya is best viewed as a promising botanical resource whose therapeutic translation depends on standardized raw material, chemically characterized extracts, appropriate dose definition, reliable safety evaluation and well-designed human studies rather than on plant-level claims alone [1–4,27,38,39]

Keywords: *Carica papaya*; papaya leaf; papain; carpaine; phytochemicals; antioxidant; thrombocytopenia; dengue; herbal medicine; standardization.

Abbreviations

ACE, angiotensin-converting enzyme; CPLE, *Carica papaya* leaf extract; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRAP, ferric reducing antioxidant power; GC-MS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; ROS, reactive oxygen species; TLC, thin-layer chromatography; UHPLC-HRMS/MS, ultra-high-performance liquid chromatography-high-resolution tandem mass spectrometry.



Graphical abstract: evidence-oriented view of *Carica papaya* L.

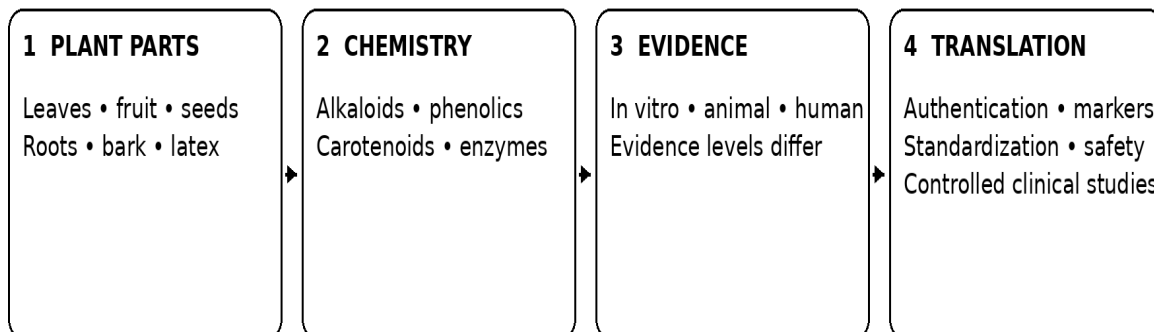


Figure 1. Graphical abstract summarizing the plant-part, phytochemical, evidence and translational framework used in this critical review.

I. INTRODUCTION

Carica papaya L. belongs to the family Caricaceae and is cultivated throughout tropical and subtropical regions. Its soft, generally hollow stem, large palmately lobed leaves and rapidly developing fruits make the species recognizable, while latex-containing tissues distinguish it from many common fruit crops [5,10,38,39]. Historical use has involved the fruit, leaves, seeds, roots, bark, and latex, but these tissues are not chemically interchangeable and should not be treated as a single medicinal material [7–12,38].

The scientific interest in papaya arises from the combination of nutritional value and specialized metabolites.

Fruit contains vitamin C, provitamin-A carotenoids and phenolic compounds, whereas leaves are reported to contain alkaloids such as carpaine and pseudocarpaine together with phenolic and flavonoid constituents and micronutrients. Seeds contain fatty acids and glucosinolate-derived compounds, while latex is a rich source of cysteine endopeptidases such as papain, chymopapain, caricain and glycyl endopeptidase [9–14,39,47].

A major problem in the literature is heterogeneity. “Papaya extract” may refer to material from a different plant part, cultivar, maturity stage or extraction process. Dose, route, extraction solvent and marker chemistry may also vary. Such differences can change composition and biological response, making direct comparison difficult [1,2,27,37–39]. Therefore, a useful review should separate evidence by plant part, preparation and study level rather than simply listing therapeutic activities.

The present review was designed around this principle. It integrates the supplied review papers with targeted literature identified from major biomedical and scientific databases, while explicitly distinguishing traditional observations, in vitro results, animal studies and human clinical evidence. This approach is intended to reduce overstatement and to identify where the evidence is sufficiently reproducible to justify pharmaceutical or nutraceutical development [1–4,27,37–40].

Review objectives

- To summarize the botanical and pharmacognostic profile of *C. papaya*.
- To map major phytochemicals to specific plant parts and preparations [9–14,30,39].
- To synthesize pharmacological findings with attention to evidence level and experimental limitations [1–3,27,38,40].
- To examine clinical evidence, especially leaf preparations in dengue-associated thrombocytopenia [41–44].
- To assess safety, herb–drug interaction concerns and standardization priorities [2,27,49].



II. REVIEW APPROACH AND BOTANICAL CONTEXT

2.1 Review approach

This manuscript is a narrative, publication-oriented critical review rather than a registered systematic review. The supplied review papers were treated as the primary historical source base. Recent and higher-value literature was then checked through PubMed and publisher platforms, with attention to review articles, experimental studies, clinical trials and safety-focused publications. Searches centered on combinations of “*Carica papaya*,” plant part names, phytochemistry, dengue, thrombocytopenia, antioxidant, anti-inflammatory, antimicrobial, cancer, diabetes, wound healing, safety and herb–drug interactions [1–4,27,37–40].

Evidence was grouped into four broad levels: traditional or ethnomedicinal reports; in vitro and chemical assays; animal or other preclinical studies; and human clinical evidence. This distinction is important because a positive radical-scavenging assay or cell-line experiment cannot by itself establish clinical efficacy. Similarly, a clinical platelet response in dengue should not be generalized to unrelated disease indications [2,3,40–44].

2.2 Taxonomic position

Rank	Classification	Reference
Kingdom	Plantae	[5,38,39]
Order	Brassicales	[5,38]
Family	Caricaceae	[5,10,38]
Genus	<i>Carica</i>	[5,38]
Species	<i>Carica papaya</i> L.	[5,38,39]

2.3 Geographical distribution and cultivation

The species is native to tropical America, particularly the Mesoamerican region, and has become established widely across tropical and subtropical agriculture. Literature sources describe cultivation in India and other Asian, African and American regions. Environmental conditions influence growth, fruit quality and, potentially, phytochemical accumulation; therefore, geography and cultivation practice can contribute to inter-study variability [5,8,38,39].

2.4 Why plant-part separation matters

The same scientific name can represent chemically different materials. Leaf preparations are dominated by a different mixture from fruit pulp, seeds or latex, and extraction can selectively enrich different chemical classes. A publication that reports “activity of papaya” without a clear plant part, preparation and chemical description has limited value for product standardization or reproducibility [2,27,37–39].

III. BOTANICAL AND PHARMACOGNOSTIC PROFILE

Papaya is commonly described as a short-lived, rapidly growing, herbaceous or semi-woody perennial. The stem is erect and typically hollow; leaves form a crown near the upper part of the stem and possess long petioles with deeply divided laminae. Flowers may be staminate, pistillate or hermaphroditic, and sex expression is affected by genotype and environmental conditions [5,38,39].

The fruit develops near the crown and may be rounded, pear-shaped or elongated. Mature fruits contain orange-yellow pulp and numerous black seeds within a central cavity. Papaya latex is present in laticiferous tissues, especially unripe fruit and leaves, and contains proteolytic enzymes that contribute to both biological and industrial importance [8,10,39,47].



Morphological and plant-part photographs of *Carica papaya* L.

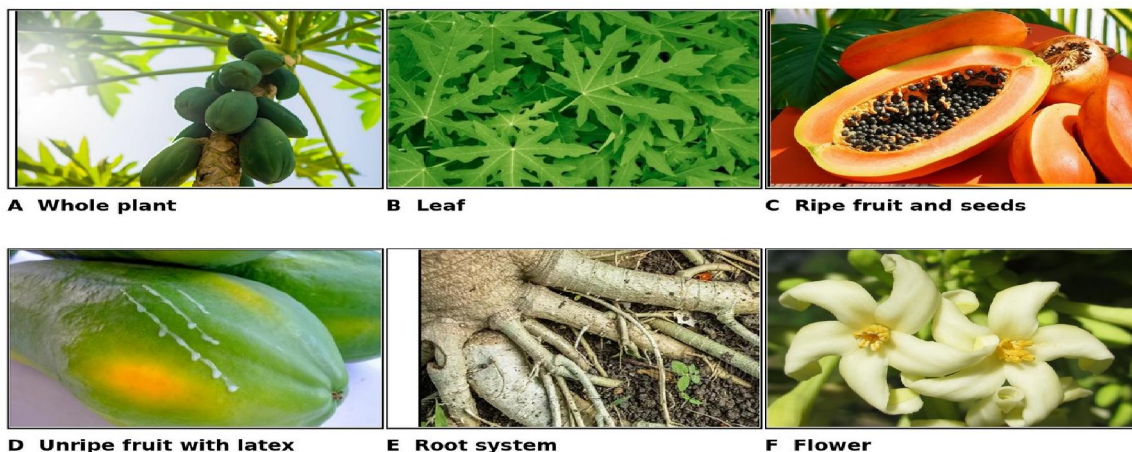


Figure 2. Representative morphological features of **Carica papaya* L.*: whole plant, leaf, ripe fruit and seeds, unripe fruit with latex, root system and flower. Photographs supplied for the present manuscript.

From a pharmacognostic perspective, leaf identity can be supported by macroscopic and microscopic characters and by physicochemical evaluation. Published quality-standard work has emphasized parameters such as organoleptic characteristics, ash values, extractive values and preliminary phytochemical profiles, illustrating the need for authenticated raw material before biological testing [13,14].

Key botanical implications for pharmacological studies

- Plant part should always be stated explicitly.
- Maturity and developmental stage can alter chemical composition [4].
- Cultivar and growing environment may contribute to compositional variation [38,39].
- Latex-containing preparations require separate safety consideration because of proteolytic enzymes and potential irritation [41,47,49].

IV. PLANT PARTS AND PHYTOCHEMICAL CONSTITUENTS

The phytochemical distribution of *C. papaya* is highly tissue dependent. The supplied literature consistently identifies leaves as a source of alkaloids and phenolic and flavonoid constituents, fruits as nutrient- and carotenoid-rich tissues, seeds as lipid- and glucosinolate-containing material, and latex as an enzyme-rich secretion [9–14,30,37–39,47].



Plant-part-oriented phytochemical map

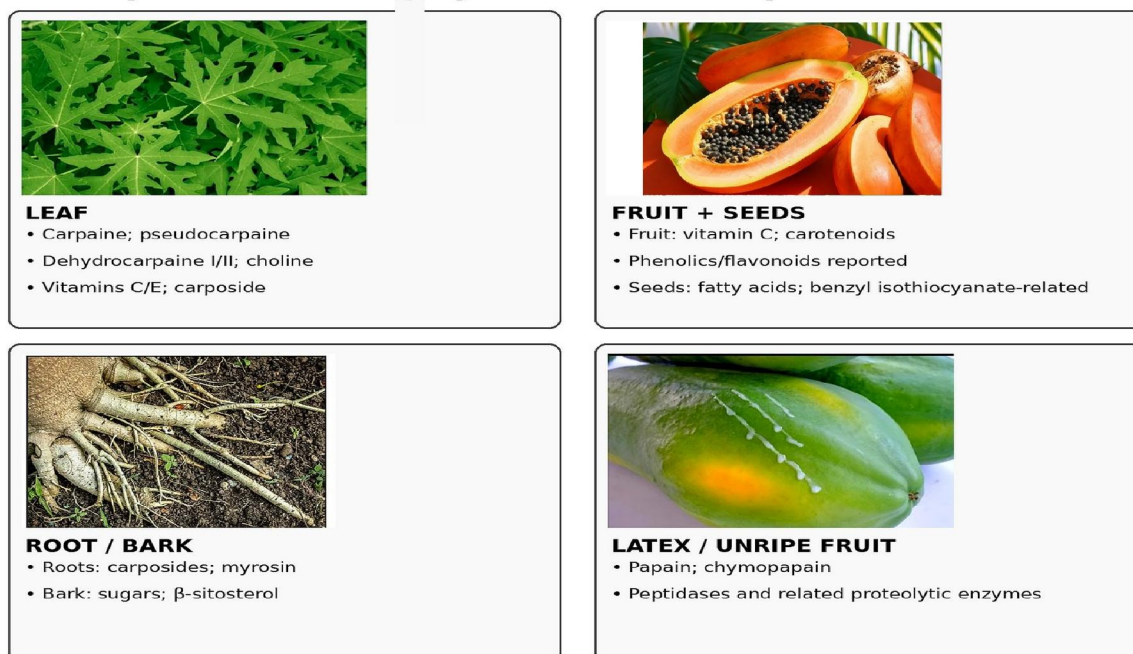


Figure 3. Plant-part-oriented phytochemical map of *C. papaya*. The listed constituents represent compounds or constituent classes reported in the reviewed literature; composition is preparation- and plant-part-dependent [9–14,30,37–39].

This distribution supports a central interpretation of the review: biological activity should not be attributed to the whole plant without specifying which tissue and which preparation were examined. For example, the proteolytic activity of papain belongs to the latex enzyme fraction, whereas platelet-related leaf research is associated with a chemically different matrix that includes alkaloids and other metabolites [15,16,47].

V. PHYTOCHEMICAL GROUPS: FROM MOLECULES TO BIOLOGICAL RELEVANCE

5.1 Alkaloids and related constituents

Carpaine and related alkaloids are repeatedly reported from leaves and have attracted attention in experimental studies of platelet-related and other biological effects. However, activity observed with an alkaloid fraction does not establish that one isolated alkaloid accounts for the entire action of a crude leaf preparation. Matrix effects and coexisting constituents remain important considerations [13–16,38].

5.2 Phenolics, flavonoids and carotenoids

Phenolic acids and flavonoids, including compounds such as caffeic, ferulic, gallic and related phenolics, are widely discussed in papaya literature because of redox-related and anti-inflammatory activities. Fruit carotenoids contribute to color and nutritional value, while flavonoids and phenolics are also detected in leaves. Recent work confirms substantial phytochemical and antioxidant capacity in papaya leaves using DPPH and FRAP assays [23–26,30,39].

5.3 Proteolytic enzymes

Papaya latex contains cysteine endopeptidases including papain, chymopapain, caricain and glycyl endopeptidase. These enzymes underpin important industrial uses and also explain why latex should not be treated as a simple extension of fruit or leaf pharmacology [47]. A 2026 EFSA safety assessment of papain as a food enzyme further illustrates the relevance of defined enzyme preparations, exposure assessment and manufacturing controls when papaya-derived enzymes move into regulated products [49].



Plant part	Representative constituents	Interpretive significance	Refs.
Leaves	Carpaine; pseudocarpaine; dehydrocarpaine I/II; choline; phenolic/flavonoid constituents	Frequently investigated for antioxidant, anti-inflammatory and platelet-related effects	[13–16,28,30]
Fruit / pulp	Vitamin C; carotenoids; phenolics/flavonoids; dietary nutrients	Major nutritional contribution; redox and metabolic research	[8–12,26,39]
Seeds	Fatty acids; glucosinolate-derived compounds; benzyl isothiocyanate	Anthelmintic, antioxidant and other experimental applications	[30,37,45]
Latex / unripe fruit	Papain; chymopapain; caricain; glycyl endopeptidase	Proteolytic and industrial relevance; separate safety considerations	[47,49]
Roots / bark	Carposides/myrosin; β -sitosterol and sugars reported in reviews	Traditional and preclinical antimicrobial/other investigations	[5,12,18,38]

Overall, the chemistry supports a multi-component interpretation, but it also highlights the need for marker-based profiling before two preparations are compared or considered therapeutically equivalent [27,37–39].

VI. NUTRITIONAL COMPOSITION OF THE FRUIT

Papaya fruit has nutritional importance independent of its medicinal literature. Published reviews describe it as a water-rich fruit providing carbohydrate, dietary fibre, vitamin C, provitamin-A carotenoids and minerals, with comparatively low fat and protein content [8–12,37–39]. The exact nutrient profile varies by cultivar, maturity and growing conditions, which cautions against treating one analytical value as universal for all papaya fruit.

6.1 Selected nutritional features

Parameter	Representative information	Comment	Refs.
Water	High water content	Supports low energy density of fresh ripe fruit	[9,10,37,39]
Carbohydrate	Predominant macronutrient	Amount changes with maturity	[8–10,36,39]
Dietary fibre	Present in pulp	Contributes to food value and digestive relevance	[9,10,37]
Vitamin C	Relatively rich source	Important antioxidant micronutrient	[9,10,39]
Provitamin-A carotenoids	β -carotene, β -cryptoxanthin and related pigments	Contribute to fruit color and vitamin A activity	[9,10,39]
Minerals	Potassium, magnesium and other minerals	Varies with cultivar and cultivation conditions	[10,30,39]

6.2 Maturity and processing

Maturity affects the balance among starches, sugars, organic acids, pigments and textural components. The unripe fruit contains higher starch and latex-related material, while ripening shifts the fruit toward softer tissue and greater sugar and pigment expression [8,36,39]. Processing can also alter phytochemical availability; therefore, “fresh fruit,” juice, puree, dried material and seed preparations should be considered distinct matrices in research and product development [8,49].



6.3 Food and nutraceutical relevance

The fruit is used in fresh consumption and in processed foods such as juices, purees, jams, jellies and other preparations. Reviews also describe potential use of underutilized tissues and by-products, which is relevant to sustainable valorization of papaya processing streams [8,10,48,49]. The nutritional and functional-food perspective should, however, remain separate from claims of treatment efficacy for disease unless supported by appropriate clinical evidence.

Interpretive point

A nutrient-rich fruit can contribute to a healthy diet without implying that concentrated extracts have equivalent safety or efficacy. This distinction is important when discussing dietary papaya alongside pharmacological preparations [37–39].

VII. PHARMACOLOGICAL ACTIVITIES I: ANTIOXIDANT, ANTI-INFLAMMATORY AND ANALGESIC EFFECTS

7.1 Antioxidant activity

Antioxidant activity is among the most frequently reported properties of papaya-derived preparations. Leaf, fruit and seed extracts have been assessed using DPPH, FRAP and cellular oxidative-stress models. A recent leaf study quantified phenolics, flavonoids and tannins and confirmed antioxidant activity, while seed water extract protected cultured fibroblasts from hydrogen-peroxide-associated oxidative damage [25,30,32,39]. These findings support biological plausibility but remain dependent on the assay system and extraction conditions.

7.2 Anti-inflammatory and analgesic activity

Experimental work with ethanolic leaf extract demonstrated reduced paw oedema, granuloma formation and formaldehyde-associated inflammation in rat models, while an experimental analgesic study reported activity of hexane, ethyl acetate and ethanol leaf extracts in mice [21,28]. A broader 2025 review also consolidates anti-inflammatory evidence from several plant parts and emphasizes that many observations remain preclinical [1].

7.3 Representative evidence

Activity	Preparation / model	Key finding	Evidence level	Refs.
Antioxidant	Leaf extracts; DPPH/FRAP	Redox-scavenging activity with measurable phenolic/flavonoid content	In vitro	[25,30]
Antioxidant	Seed water extract; human fibroblasts	Protection against H ₂ O ₂ -associated oxidative stress	Cellular	[32]
Anti-inflammatory	Ethanolic leaf extract; rat models	Reduced oedema and granuloma formation	Preclinical	[21]
Analgesic	Leaf extracts; mouse pain model	Significant analgesic response across extracts tested	Preclinical	[28]

A recurring limitation is that chemical antioxidant capacity does not automatically translate to clinical antioxidant benefit in humans. Extract concentrations, absorption, metabolism and tissue exposure must be established before therapeutic claims are made. This is especially relevant when studies use highly concentrated laboratory extracts that differ from traditional preparations [1,2,27,37].



7.4 Mechanistic interpretation

The most defensible interpretation is that several constituent classes may contribute simultaneously through radical-scavenging, modulation of inflammatory mediators and changes in cellular redox status. The literature supports a multi-component hypothesis more strongly than a single-compound explanation for most crude preparations [1,24,27,39].

VIII. PHARMACOLOGICAL ACTIVITIES II: ANTIMICROBIAL, ANTIFUNGAL AND ANTHELMINTIC EFFECTS

8.1 Antibacterial and antifungal activity

Antibacterial activity has been reported for root extracts and for leaf-derived preparations against a range of organisms. Experimental work with *C. papaya* roots and leaves suggests that activity depends on extraction solvent and the organisms tested [18,33]. A 2025 analytical study of leaves also reported antimicrobial effects against several laboratory strains, alongside measurable phenolic and flavonoid content [30]. Latex has demonstrated antifungal activity in work that linked inhibition of *Candida albicans* to latex proteins and glycosidic enzymes [47].

8.2 Anthelmintic activity

Papaya seeds and latex have longstanding ethnomedicinal associations with worm expulsion. Experimental studies provide a mechanistic basis for these claims: benzyl isothiocyanate was strongly associated with anthelmintic activity in seed extracts, while latex produced dose-related reductions in intestinal nematode burdens in animal models [45,46]. These studies are valuable because they connect specific chemical or enzyme-rich preparations with measurable biological outcomes, but they do not establish safety or effectiveness for human self-treatment.

Plant material	Experimental evidence	Interpretation	Refs.
Roots	Antibacterial assays on extracts	Supports exploratory antimicrobial activity	[18]
Leaves	Bacterial assays; phenolic/flavonoid-rich material	Activity varies with extraction and organism	[30,33]
Latex	Fungal growth inhibition; enzyme-associated activity	Protein/enzyme fraction may contribute	[47]
Seeds	Nematode viability assays; benzyl isothiocyanate correlation	Provides chemical candidate for anthelmintic action	[45]
Latex	Rodent / pig intestinal nematode models	Dose-related reduction in worm counts	[46]

8.3 Translational cautions

In-vitro antimicrobial activity is often reported at concentrations that may not be achievable safely in human tissues. The active fractions may also be unstable or dependent on extraction and storage. Consequently, antimicrobial data are best interpreted as evidence for further compound isolation, mechanism studies and formulation development rather than as a direct substitute for standard antimicrobial therapy [1,3,37–39].

The antimicrobial section also illustrates the value of plant-part specificity: the chemistry and likely mechanism of a protein-rich latex preparation are not equivalent to those of a leaf polyphenol-rich extract. This distinction should be preserved in future publications and regulatory dossiers.

IX. PHARMACOLOGICAL ACTIVITIES III: ANTIDIABETIC, CARDIOVASCULAR AND HEPATOPROTECTIVE EFFECTS

9.1 Antidiabetic activity

Papaya leaves have been evaluated in streptozotocin-induced diabetic rat models. Aqueous leaf extract reduced blood glucose and improved selected biochemical parameters, while a later study using chloroform leaf extract reported



reductions in serum glucose, triglycerides and transaminases [31,28,38]. These studies establish preclinical activity but do not define a human therapeutic dose or confirm disease-modifying efficacy in patients.

9.2 Cardiovascular and antihypertensive activity

A standardized methanolic papaya extract produced antihypertensive effects in experimental models and was associated with reduced ACE activity and improved baroreflex responses. Chemical analysis identified phenolic acids and flavonoids in the tested preparation [23]. Earlier work similarly described blood-pressure-lowering effects of papaya fruit juice in animal hypertension models [34]. The more standardized design of the later work illustrates why chemical characterization strengthens interpretation of pharmacological results.

9.3 Hepatoprotective effects

Seed and fruit-derived preparations have been investigated in chemically induced hepatic injury models. Experimental findings suggest reductions in markers of hepatic injury and oxidative stress, but the literature remains dominated by animal studies [20,35,39]. These results are compatible with the broader antioxidant and phenolic profile of papaya but should not be interpreted as proof of efficacy for human liver disease.

Activity	Preparation / model	Main observation	Evidence limit	Refs.
Antidiabetic	Leaf aqueous/chloroform extracts; diabetic rats	Reduced blood glucose and selected biochemical abnormalities	Animal evidence	[28,31]
Antihypertensive	Standardized methanolic extract; hypertensive rats	Reduced ACE activity; improved baroreflex-related measures	Animal evidence	[23]
Blood-pressure effect	Fruit juice; hypertensive rats	Depression of blood pressure reported	Animal evidence	[34]
Hepatoprotective	Seed/fruit preparations; toxicant-induced injury	Improved biochemical and tissue markers	Animal evidence	[20,35]

9.4 Shared mechanistic theme

Across these indications, oxidative stress, inflammatory signaling and metabolic regulation are frequently proposed as common pathways. Such overlap is biologically plausible but should not be used to infer that one papaya preparation will treat all related diseases. The appropriate next step is controlled research using standardized preparations and predefined pharmacodynamic outcomes [1,27,38–40].

X. DENGUE, THROMBOCYTOPENIA AND PLATELET-RELATED EVIDENCE

Papaya leaf preparations have received unusual clinical attention in dengue-associated thrombocytopenia. Preclinical work reported platelet-related effects of leaf extracts and carpaine-containing alkaloidal fractions in thrombocytopenic animal models [15,16]. Human studies subsequently examined leaf juice or standardized leaf extract as an adjunct to usual dengue management [17,42–44].

10.1 Human clinical studies

An open-label randomized trial involving 228 patients reported a faster rise in platelet counts in the papaya-leaf-juice group compared with controls, with differences emerging during the first two days of observation [17]. A multicenter double-blind placebo-controlled study in 300 patients also reported a platelet-count benefit during treatment and described mostly mild gastrointestinal complaints [43]. In a separate pilot study of adults with severe thrombocytopenia, standardized leaf extract was associated with increased platelet counts and was reported to be well tolerated [44].



10.2 Meta-analytic interpretation

A 2016 systematic review and meta-analysis pooled four trials involving 439 subjects and concluded that papaya leaf extract was associated with platelet-count improvement, while emphasizing the need for larger high-quality trials [41]. A later systematic review and meta-analysis similarly evaluated the available dengue trials and showed that platelet outcomes varied according to time point and study characteristics [42–44]. These findings support continued investigation but do not justify replacing standard dengue supportive care with an unstandardized home preparation.

10.3 Why standardization remains central

Clinical evidence cannot be transferred reliably from one extract to another unless the preparation is chemically characterized. Leaf age, extraction method, drying, storage and marker profile may influence biological response [2,4,27,38]. This makes dengue one of the clearest examples of why phytochemical standardization and clinical trial reproducibility must progress together.

XI. ANTICANCER, IMMUNOMODULATORY, WOUND-HEALING AND GASTROPROTECTIVE RESEARCH

11.1 Anticancer evidence

Papaya has attracted anticancer interest because extracts and specific phenolic compounds show activity in cell-based models. Early review work noted that the evidence was largely in vitro and that clinical or animal cancer evidence was limited at that time [7,40]. Experimental studies summarized in later reviews describe effects of papaya-derived preparations on tumor-cell growth and immune-related responses, while proposed molecular pathways include modulation of oxidative stress, apoptosis and related signaling processes [40]. These findings justify further research but do not establish papaya as a cancer treatment.

11.2 Immunomodulatory observations

Seed extract and leaf preparations have shown immunomodulatory signals in cell-based and experimental systems. One study found changes in lymphocyte proliferation and complement-mediated responses with seed fractions, suggesting that more than one constituent may contribute [37]. Such findings are mechanistically interesting but require careful separation of immunomodulation from clinical efficacy.

11.3 Wound-healing activity

Aqueous fruit extract promoted faster wound closure and greater granulation-tissue and hydroxyproline measures in diabetic rats, while recent leaf-senescence work suggests that aged or withered leaf preparations may display stronger wound-healing activity in cellular models than fresh material [22,4]. These data provide a useful example of how plant developmental stage could become a quality variable in future topical formulations.

11.4 Gastroprotective activity

Papaya seeds and other plant parts have been investigated in ethanol- or drug-induced gastric injury models. Review literature summarizes reductions in lesion severity, gastric acidity or oxidative damage in preclinical systems [37,38]. These effects are promising for further study, but gastrointestinal activity should be separated from the established nutritional role of whole fruit and from safety concerns associated with concentrated seed preparations.

Research area	Representative evidence	Current interpretation	Refs.
Anticancer	Cell-line studies; aqueous leaf fractions	Mechanistically promising but largely preclinical	[40]
Immunomodulation	Seed extract; lymphocyte/complement assays	Multiple fractions may contribute	[37]



Wound healing	Fruit extract in diabetic rats; aged leaf cellular models	Suggests tissue-repair potential	[22,4]
Gastroprotection	Seed/leaf preparations in experimental ulcer models	Preclinical evidence; dosing needs definition	[37,38]

XII. CLINICAL EVIDENCE AND TRANSLATIONAL RELEVANCE

Among the therapeutic themes reviewed, dengue-associated thrombocytopenia has the clearest human evidence base. The existence of randomized trials does not automatically settle the clinical question because preparations, dosing schedules, study populations and endpoints differ [41–44]. Outside dengue, the literature is much more heavily weighted toward in vitro and animal studies [1,3,38–40].

12.1 Evidence map

Activity	In vitro experimental	Preclinical	Human evidence	Interpretation	Refs.
Antioxidant	Strong	Moderate	Limited	Useful pharmacological basis; clinical benefit unproven	[25,30,32,39]
Anti-inflammatory	Moderate	Moderate	Limited	Promising preclinical signal	[1,21,28]
Antimicrobial	Moderate	Moderate	Minimal	Supports discovery/formulation research	[18,30,33,47]
Dengue / platelets	Moderate	Strong	Multiple trials	Most clinically investigated indication	[15,16,41–44]
Antidiabetic	Limited	Moderate	Limited	Needs controlled human studies	[28,31,38]
Antihypertensive	Limited	Moderate	Limited	Needs standardized preparation and clinical validation	[23,34]
Anticancer	Moderate	Limited/variable	Insufficient	Primarily exploratory	[40]
Wound healing	Moderate	Moderate	Limited	Candidate for topical/formulation research	[4,22]

12.2 Translation requires defined interventions

Clinical translation is stronger when the investigational product is chemically defined, manufactured reproducibly and compared with appropriate control treatment. For papaya, the intervention should specify plant part, cultivar or source, processing stage, extraction solvent, drug-to-extract ratio, marker compounds, dose, duration and storage conditions [2,27,37–39]. Without these details, replication is difficult and apparently conflicting results may simply reflect different products.

12.3 Human evidence matrix

Study	Design / population	Preparation	Main reported outcome	Ref.
Subenthiran et al.	Randomized, 228 dengue patients	Leaf juice for 3 days	Faster platelet rise than controls	[17]



Kasture et al.	Double-blind, placebo-controlled, 300 patients	CPLE tablets for 5 days	Greater platelet increase; few GI events	[43]
Sathyapalan et al.	Randomized pilot, severe adult thrombocytopenia	CPLE	Higher platelet increase by day 3; good short-term tolerability	[44]
Charan et al.	Systematic review/meta-analysis	Clinical trials	Potential platelet benefit; need stronger evidence	[41]
Rajapakse et al.	Systematic review/meta-analysis	Clinical trials	Effect depends on timing and study heterogeneity	[42]

Interpretation: human evidence is concentrated in dengue-associated thrombocytopenia; these findings should not be generalized to all papaya preparations or all therapeutic indications.

Evidence hierarchy for interpreting papaya claims

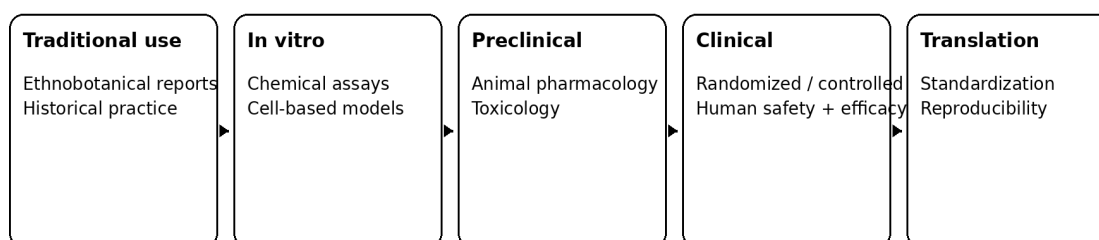


Figure 5. Evidence hierarchy used for critical interpretation of *C. papaya* claims. Traditional reports, laboratory findings, animal studies and clinical observations are treated as distinct evidence levels [2,41–44].

For pharmaceutical science students and researchers, this evidence hierarchy provides a practical rule: a biologically interesting extract is a research candidate first; therapeutic positioning comes later, after reproducible chemistry, pharmacology, safety and clinical evaluation are established.

XIII. SAFETY, TOXICOLOGY AND HERB–DRUG INTERACTIONS

Safety should be assessed separately for each plant part and preparation. A systematic scoping review of C. papaya leaf identified 41 relevant articles, including clinical and preclinical evidence. Short-term leaf juice or standardized aqueous extract was generally tolerated in the studied adult populations, with gastrointestinal symptoms among the more common reported adverse effects; the review also identified concerns for long-term use and possible herb–drug interactions [2].

13.1 Pregnancy and latex-related concerns

Unripe fruit and latex deserve particular caution because papaya latex contains proteolytic enzymes and can show contractile effects in isolated smooth-muscle systems [47]. Historical reviews and experimental literature have therefore advised caution with unripe or latex-rich preparations in pregnancy [7,8,38]. The available evidence is not sufficient to define a universally safe medicinal dose of latex-containing material, so concentrated preparations should not be equated with ordinary dietary intake of ripe fruit.

13.2 Herb–drug interactions

The strongest compiled evidence for papaya leaf interactions is preclinical. Reported interaction candidates include oral hypoglycemic drugs such as metformin and glimepiride, digoxin, ciprofloxacin and artemisinin [2]. Because the causative compounds were not consistently identified, the practical lesson is not that every papaya product will interact with every drug, but that concentrated leaf preparations should be evaluated when used with narrow-therapeutic-index or metabolically sensitive medicines.



13.3 Enzyme safety and regulated food use

Papain-containing enzyme preparations represent a different regulatory question from whole-plant extracts. A 2026 EFSA assessment describes papain, chymopapain, caricain and glycyl endopeptidase as components of food-enzyme preparations derived from unripe papaya latex and evaluates their safety in the context of defined manufacturing and exposure conditions [49]. This reinforces the value of preparation-specific risk assessment.

Safety issue	What the literature indicates	Practical implication	Refs.
Short-term leaf use	Generally tolerated in studied short courses	Do not extrapolate to long-term use	[2]
GI effects	Nausea, vomiting or GI discomfort reported	Monitor symptomatic intolerance	[2,43]
Liver / long-term concerns	Animal evidence raises concern	Avoid unsupported chronic use; study hepatic safety	[2]
Pregnancy / latex	Experimental contractile activity and historical caution	Avoid concentrated unripe/latex preparations in pregnancy	[7,8,47]
Drug interactions	Preclinical interactions reported with several medicines	Review concomitant medicines before use	[2]
Papain enzyme preparations	Defined food-enzyme safety assessment available	Use exposure- and product-specific evaluation	[49]

XIV. STANDARDIZATION AND QUALITY CONTROL

Standardization is one of the most important unresolved issues in the papaya literature. Different cultivars, harvest stages, leaf ages, extraction solvents, extraction times, drying methods and storage conditions may generate chemically distinct products [2,4,13,27,37–39]. Consequently, comparing biological results without comparing chemical identity is unreliable.

14.1 Proposed quality-control sequence

Proposed standardization workflow for *C. papaya* botanical products

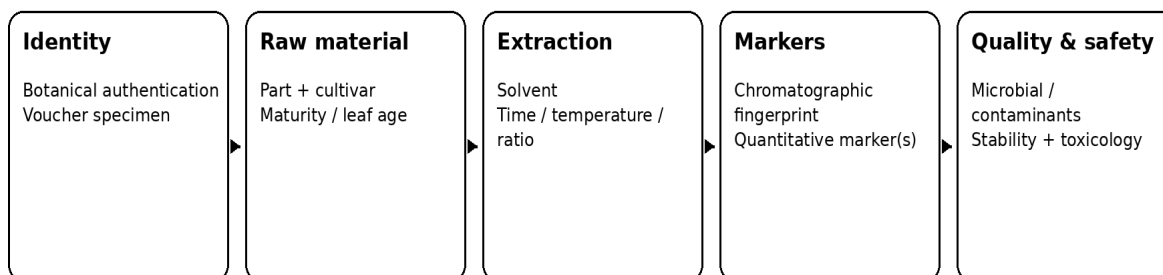


Figure 6. Proposed standardization workflow for development of **C. papaya** botanical preparations, integrating botanical identity, raw-material controls, extraction parameters, marker profiling and final quality/safety testing [13,14,27,38,49].

14.2 Minimum quality attributes

Quality domain	Minimum consideration	Why it matters	Refs.
Botanical identity	Authenticated species; voucher specimen	Prevents misidentification	[13,14]



Plant part	Leaf, fruit, seed, latex, root or bark clearly defined	Different chemistry and safety	[2,9,38]
Developmental stage	Maturity / leaf age recorded	Can alter phytochemical profile	[4,39]
Extraction	Solvent, ratio, time, temperature and drying specified	Controls extract composition	[27,37–39]
Chemical markers	Chromatographic fingerprint + quantitative markers	Supports batch-to-batch reproducibility	[1,13,14,23,39]
Contaminant control	Microbial, heavy-metal and other contaminant testing	Protects patient/consumer safety	[13,30]
Stability	Defined storage and shelf-life testing	Controls degradation during use	[27,49]

14.3 Leaf age as a critical quality attribute

Recent work shows that leaf senescence can reshape the specialized-metabolite profile and alter antioxidant, wound-healing and inflammatory responses in experimental systems [4]. The implication is practical: “leaf extract” may be too broad a specification for a reproducible botanical medicine. Future monographs and clinical studies should record developmental stage or leaf age where appropriate.

A good standardization strategy therefore begins before pharmacological testing. Authentication, defined raw material, controlled extraction and marker analysis should be part of the study design rather than added after biological differences are observed [13,14,27].

XV. PHARMACEUTICAL, NUTRACEUTICAL AND INDUSTRIAL APPLICATIONS

Papaya has a dual identity as a food crop and a source of materials with pharmaceutical, nutraceutical, food-processing and industrial relevance. Fruit is consumed fresh and processed into juices, purees and other foods, while latex-derived enzymes are used in food and technical applications because of their proteolytic properties [8,39,47–49].

15.1 Papain and enzyme technology

Papain and related papaya latex proteases are among the most established industrially relevant constituents. The latex contains multiple cysteine endopeptidases, and enzyme fractionation studies have demonstrated the complexity of this proteolytic system [47]. This provides a stronger translational pathway than many whole-plant pharmacological claims because the active material can be characterized and manufactured as a defined enzyme preparation.

15.2 Functional foods and nutraceuticals

Recent reviews emphasize the nutritional value of fruit, seeds, leaves and other tissues and discuss the possibility of using papaya material in functional-food systems [37,38]. A 2025 leaf study additionally documented measurable protein, carbohydrate, phenolic, flavonoid, tannin and mineral content, together with antioxidant and antimicrobial activity [30]. Such findings support ingredient-development research, provided that dose, safety and intended use are clearly distinguished from drug claims.

15.3 By-product and waste valorization

Papaya processing generates peels, seeds and other residues that can potentially be valorized. Comprehensive reviews describe applications of fruit peels in food, cosmetic, environmental and material-related settings, while seeds and other tissues have been explored as sources of bioactive or industrially relevant compounds [48]. This broader perspective is valuable because a circular bioeconomy approach can improve the utilization of the crop without requiring every by-product to be positioned as a therapeutic agent.

15.4 Pharmaceutical development opportunities

- Standardized leaf extract for research into adjunctive management of platelet-related conditions [41–44].
- Marker-defined antioxidant or anti-inflammatory botanical fractions for further pharmacological evaluation [1,23,39].
- Papain-rich enzyme products with defined activity units and controlled exposure [47,49].



- Topical preparations for wound-healing research using standardized fruit or leaf fractions [4,22].
- Functional-food or nutraceutical ingredients based on fruit, seed or leaf matrices with validated safety profiles [30,37,39].

The main development principle is “define the product before comparing the activity.” This reduces the uncertainty created when different laboratories use different raw materials under the same label of “papaya extract” [2,27,37–39].

XVI. CRITICAL SYNTHESIS, RESEARCH GAPS AND FUTURE PERSPECTIVES

16.1 What is relatively well established?

The nutritional value of ripe papaya fruit is well documented, and the broad presence of phytochemical classes across different plant parts is consistently described [9–12,37–39]. Papaya latex is a recognized source of proteolytic enzymes with established industrial relevance [47,49]. Pharmacognostic and physicochemical characterization of leaves has also been reported [13,14].

16.2 What is promising but still preclinical?

Antioxidant, anti-inflammatory, antimicrobial, antidiabetic, antihypertensive, hepatoprotective, wound-healing and anticancer activities are supported by laboratory or animal studies, but the evidence is uneven and often preparation-specific [1,18–26,28,31,33–35,38–40]. The most scientifically useful future studies will therefore use chemical characterization and standardized dosing to determine which findings can be reproduced.

16.3 Where is human evidence most developed?

Papaya leaf preparations in dengue-associated thrombocytopenia have the most substantial human evidence among the reviewed indications, including randomized studies and meta-analyses [41–44]. Even here, product heterogeneity and differences in study design limit direct generalization. The clinical literature should therefore be used to define research priorities rather than to infer equivalence among all papaya leaf products.

16.4 Key research gaps

- Isolation and confirmation of bioactive constituents responsible for clinically relevant outcomes [38,39].
- Pharmacokinetic studies linking marker compounds to exposure and biological effect [1,27,39].
- Long-term safety studies, including hepatic and reproductive endpoints where relevant [2].
- Validated analytical markers and batch-release specifications for standardized botanical products [13,14,27,39].
- Well-designed multicenter clinical trials using chemically characterized interventions [41–44].
- Assessment of cultivar, geography, maturity and leaf-age effects on chemical composition [4,38,39].
- Clear separation between nutraceutical, traditional-medicine and therapeutic-drug claims in future publications [27,37–40].

16.5 Integrated research framework

Integrated phytochemical-to-evidence framework

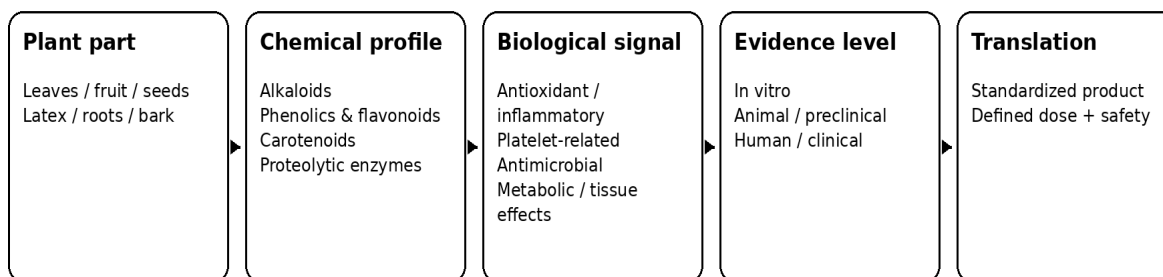


Figure 4. Integrated framework linking plant part, phytochemical composition, measured biological effect, evidence level and potential translation. The framework is intended to reduce overextension of laboratory findings into clinical claims [1–4,27,38–40].



XVII. CONCLUSION

Carica papaya L. is a chemically diverse botanical resource with nutritional, pharmacological and industrial relevance. Its leaves, fruits, seeds, latex, roots and bark should not be treated as interchangeable medicinal materials because their chemical profiles, extraction characteristics and evidence bases differ [9–14,37–39]. The literature supports continued investigation of antioxidant, anti-inflammatory, antimicrobial, metabolic, cardiovascular, wound-healing and platelet-related effects, while the strongest human evidence remains concentrated around selected papaya-leaf preparations investigated in dengue-associated thrombocytopenia [41–44]. Importantly, the existence of experimental or clinical findings for one preparation does not establish equivalent efficacy for another extract, plant part or dosage form.

From a pharmaceutical-development perspective, the central challenge is reproducibility rather than simply the discovery of additional biological activities. Future studies should define authenticated raw material, plant part, cultivar or source, developmental stage, extraction solvent and drug-to-extract ratio; quantify suitable chemical markers; control microbial and chemical contaminants; and report stability and batch-to-batch consistency.

Pharmacokinetic studies should connect marker-compound exposure with biological outcomes, while adequately powered and well-controlled clinical trials should evaluate standardized preparations with predefined endpoints [1–4,27,38,49]. The emerging evidence that leaf developmental stage can alter phytochemistry and bioactivity further supports the need to control harvesting stage when leaf-based products are investigated [4].

Overall, **C. papaya** is best positioned as a promising botanical platform for food, nutraceutical, enzyme and pharmaceutical research rather than as a uniformly established therapeutic agent. Responsible translation will depend on matching the claim to the evidence level, separating traditional use from experimentally demonstrated effects, and applying modern quality-control principles to botanical preparations. Such an approach can improve reproducibility, reduce inappropriate extrapolation and provide a clearer pathway from plant material to scientifically defensible products [1,2,27,38,49].

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Declarations

Funding: To be confirmed by the authors before journal submission.

Conflict of interest: To be confirmed by all authors before journal submission.

Author contributions: To be finalized by the authors according to the selected journal's requirements.

Ethics statement: Not applicable to a narrative literature review.

