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Review

Carica papaya L.: A Tropical Fruit with Benefits beyond the Tropics

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Abstract: *Carica papaya* L. (*family: Caricaceae*), also known as 'papaya,' is a tropical American fruit tree. Due to the bioactive components (carpaines, BITC, benzyl glucosinolates, latex, papain, zeaxanthin, choline, etc.) in its seeds, leaves, and fruits, it is revered for its excellent antioxidant, digestive, and nutraceutical benefits. Papayas are high in vitamins A, B, C, E, and K, folate, pantothenic acid, zeaxanthin, lycopene, lutein, magnesium, copper, calcium, and potassium. Being rich in fiber, antioxidants, and vitamin C, it lowers the cholesterol in the arteries; prevents arthritis; reduces aging, cancer, macular degradation, risk of cardiovascular diseases, and stress; increases platelet count; controls dengue fever; facilitates digestion, and lowers body weight. Papaya leaf extract, with many in vitro and case studies in combination therapies with modern medicine, especially for cancers and many other viral diseases, has been found to be an efficient cure. Humans have cultivated papaya cultivars for millions of years because of their significant commercial, medicinal, and agronomic value. Several reports have been published on the genetic modification of papaya for resistance to abiotic (herbicide, Al toxicity, etc.) and biotic stressors (PRSV, mites, Phytophthora, etc.), delaying ripening, and improving shelf life. However, most of these traits have not been introduced globally to all commercial papaya varieties. Unraveling the genetics of papaya has shed light on various domestication impacts, evolutionary patterns, and sex determination in fruit tree crops. It also serves as a potential step toward developing new cultivars to fight climate-oriented stress. Furthermore, extensive research on the stability of the 'transgene' across generations, and the 'yield-penalty' caused by the transgene, is required. Thus, meticulous crop improvement research on commercial papaya cultivars is necessary for long-term food and health security. This review article encompasses information on the traditional and modern medicinal uses, nutritional properties, phytochemistry, diseases and etiology, post-harvest measures, genomics, biotechnological strategies (for papaya improvement), and value-added products of papaya for food and health security.

Keywords: papaya ring spot virus; nutraceutical; phytochemistry; bioactive compounds

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1. Introduction

The papaya tree (*Carica papaya* L.) is a tropical American fruit tree. It is grown worldwide in tropical and sub-tropical climates. According to a recent papaya production report (2020), India is the world's largest producer of papaya, generating 13.9 million tonnes (mt) per year, or 43% of global papaya production. In contrast, the United States is the world's largest consumer of papaya. *Carica* has been classified under various families, including *Passifloraceae*, *Cucurbitaceae*, *Bixaceae*, and *Papayaceae*, but it is now placed under the *Caricaceae* family, which includes 35 latex-producing species divided into four genera:

Carica, *Jarillaand*, *Jacaratia*, and *Cyclicomorpha* [1]. Some species previously attributed to *Carica* have been reclassified and are now assigned to *Vasconcella* [2].

Carica papaya L. originated in southern Mexico, the Philippines, and Central America [3,4]. The Caribbean coast of Central America, Argentina, Chile, and southern Mexico were identified as the origins of papaya, resulting from natural hybridization between *Carica peltata* and other wild species [5]. Papaya is domesticated in tropical and sub-tropical regions of the world (Asia, Africa, Oceania, and North America). According to FAOSTAT 2020, the chief producers are India, Brazil, Mexico, Indonesia, and Nigeria. Figure 1 shows the origin, distribution, and cultivation of papaya. In 2011, researchers from the Philippines reported the development of PRSV-resistant papaya by crossing papaya with *Vasconcella quercifolia*. Papaya fruits are natural gifts, possessing a large proportion of vitamins, macro and micro minerals, bioactive substances, and secondary metabolites. In addition to fruits, the leaves, stems, seeds, and other plant parts are high in alkaloids and flavonoids, which have antimicrobial and medicinal properties. Their numerous medical benefits have been discovered over the years, making papaya a plant of considerable therapeutic relevance. Endopeptidases, papain, caricain, and proteinase enzymes found in papaya latex are important industrial enzymes used in many commercial applications.

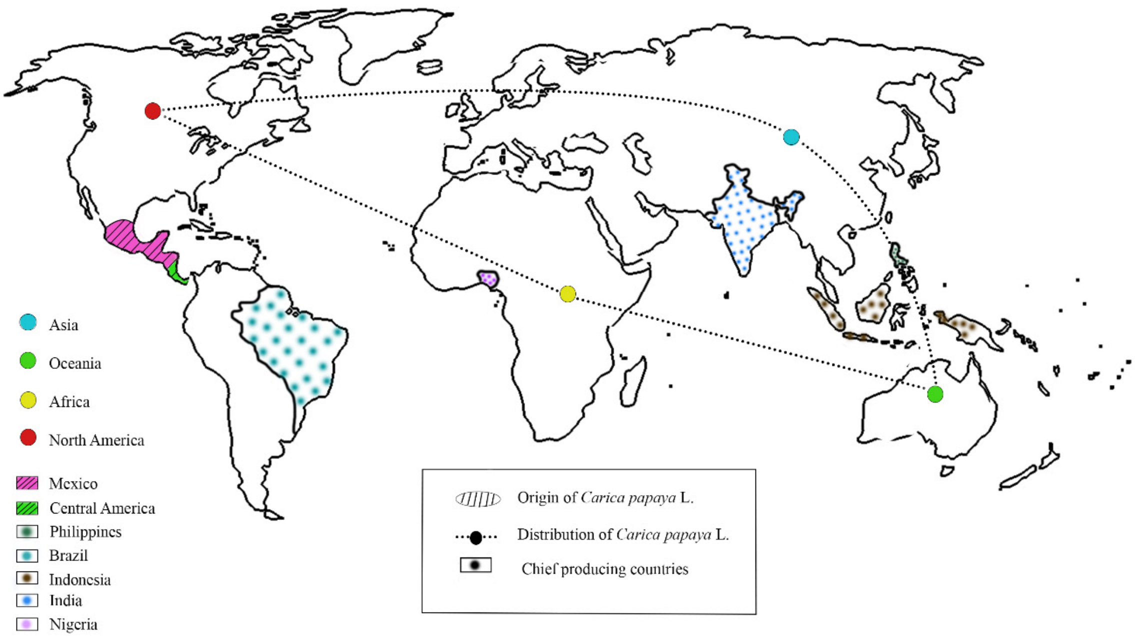


Figure 1. *Carica papaya*: World map showing the origin, distribution, and the chief production countries.

The objective of this review article is to summarize the current state of knowledge on various aspects of papaya, such as nutrition, phytochemistry, use of papaya derivatives in traditional and modern medicine, disease pathologies and post-harvest control measures, genomics, and advancements in the genetic modification of papaya, and commercially available value-added products. The investigators in this work mainly intend to deliver an in-depth view of past studies and accomplishments in the broader conceptual aspects of Papaya, which could help promote and progress a new scope of research with reconciled information. All the topics covered focus on the integrated and aggregate data from several reliable databases that describe the accomplished milestones in the gradual evolution of the crop from its origin and contribution to biotechnology.

2. Botanical Description

Papaya is a tropical, semi-wood, rapid-growing herbaceous plant. The stem is usually hollow, solitary, and straight with conspicuous leaf scars. The plant shows apical dominance, branching is infrequent throughout the lower part of the stem unless the apical meristem is completely removed, and the top part bears a crown of large petiolate, deeply lobed leaves [6]. The leaves are large, palmately lobed, spirally organized, and clustered at the crown. In Malaysian cultivars, leaf arrangement and structure differences have been reported [7]. Papaya varieties can be distinguished based on their leaf structure, stomatal shape, number of central leaf veins, number of lobes at the leaf margins, wax coating on the leaf surface, and petiole color.

Papaya can grow in three sexes: female, male, and hermaphrodite (flowers with both male and female reproductive organs). The shape of the fruit also varies among different varieties. Some are oval to nearly round, elongated, club-shaped, pyriform, and have variable weights of up to 9 kg [8]. The unripe fruit has a lot of white latex, a hard skin, and is green in color, but the ripe fruit is light or deep yellow-orange, thick, succulent, with orange or red juicy flesh, and has a sweet aroma. Several gray to black colored seeds are partially connected to the flesh by white, soft, and fibrous tissue in the adult ripened fruits. Two forms of papaya cultivars are often grown. One is called 'red papaya', with orange or red flesh, and the other, ' yellow papaw', is a large fruit. 'Caribbean Red', 'Sunrise', and red-fleshed 'Mardol' papayas are commonly sold in U.S. markets in Mexico and Belize. Few of the most popular cultivated variety in India is 'Red Lady' (orange-red flesh), which is used for processing; 'Washington', a table variety ranging from 1.5–2 kg with yellow pulp; and the 'Coorg honeydew' cultivar (orange flesh, great flavor), which is valuable for processing and daily consumption.

'Co-1' is a dwarf cultivar that yields exquisite orange-yellow fruits with spherical flesh. 'Co-2' is obovate, medium-sized, and has firm red flesh. The 'Co-3' hybrid ['Co-1' (♀) × 'Washington (♂)'] yielded medium-sized fruits (1.2–1.5 kg) with a yellow flesh and a purple hue, suitable for home gardening.

3. Nutritional Benefits

Papaya is known as a "common man's fruit" because of its low cost and excellent nutritional value. Phytonutrients are present in papaya leaves, and unripe and ripe fruits [9]. Papaya is adored among all other fruits for its thiamine, folate, riboflavin, niacin, vitamins A, B1, B2, and C, and fiber content. It has been placed in the top five fruits (together with kiwi, watermelon, grapefruit, and guava) based on nutritional scores [10,11]. It does not have fat and protein content and is thus low in calories (energy value: 200 kJ/100 g). The principal sugars include glucose (29.8 g/100 g), sucrose (48.3 g/100 g), and fructose (21.9 g/100 g). Chemical assessment of papaya revealed the presence of essential elements, such as potassium (223 mg), sodium (8 mg), phosphorus (10 mg), calcium (20 mg), iron (0.25 mg), zinc (0.08 mg), copper (0.05 mg), manganese (0.04 mg), and magnesium (21 mg) per 100 g of fresh ripened fruit. Papaya fruits also contain folate (37 μg), thiamin (0.023 mg), riboflavin (0.027 mg), niacin (0.357 mg), pantothenic acid (0.191 mg), and macular carotenoids (1.2–6.4 mg), such as β-carotene and β-cryptoxanthin, along with major pigments such as lycopene (5.7 mg) per 100 g of fresh fruit.

4. Traditional and Modern Medicinal Uses

Papaya is known as a "quasi-drug," owing to its pharmaceutical properties and has been utilized as a folk medicine to heal various disorders [12]. In Africa, papaya pulp is used in hospitals to cure burns and heal wounds [13]. Papain (EC: 3.4.22.2) is a crucial enzyme in drug development and has a variety of biological and commercial activities. The fruit latex of unripe papaya contains chymopapain, which is used to treat herniated lower lumbar vertebrae [14]. Another component, lycopene, prevents various types of cancer.

The fermented fruit of the papaya plant has potential nutraceutical significance as a source of antioxidative components, such as vitamin C, citric and malic acids, and glucose [15]. The efficacy of a mixture of papain and urea has been scientifically proven for enzyme wound debridement. Papaya latex helps treat dyspepsia and is applied topically to treat burns, scalds, diarrhea, and whooping cough [16]. Unripe papaya fruit is a valuable remedy for impotence and ulcers, and reduces menstrual unevenness, thereby assisting in menstrual flow [17]. Antioxidant and immunostimulant substances are thought to be present in fruits. By clearing out infection, mucus, and pus, papaya juice helps alleviate colon infections. The presence of vitamins A and C aids in the improvement of eyesight, prevention of early blindness in children, prevention of flu or cough, and strengthens the immune system of children suffering from colds regularly. Besides the benefits mentioned above, fresh green papaya leaves can also be used as antiseptics, whereas brown leaves are a great tonic for blood-purifying activity. Figure 2 depicts the health benefits of papaya latex, leaves, roots, flower seeds, and raw and ripe fruits.

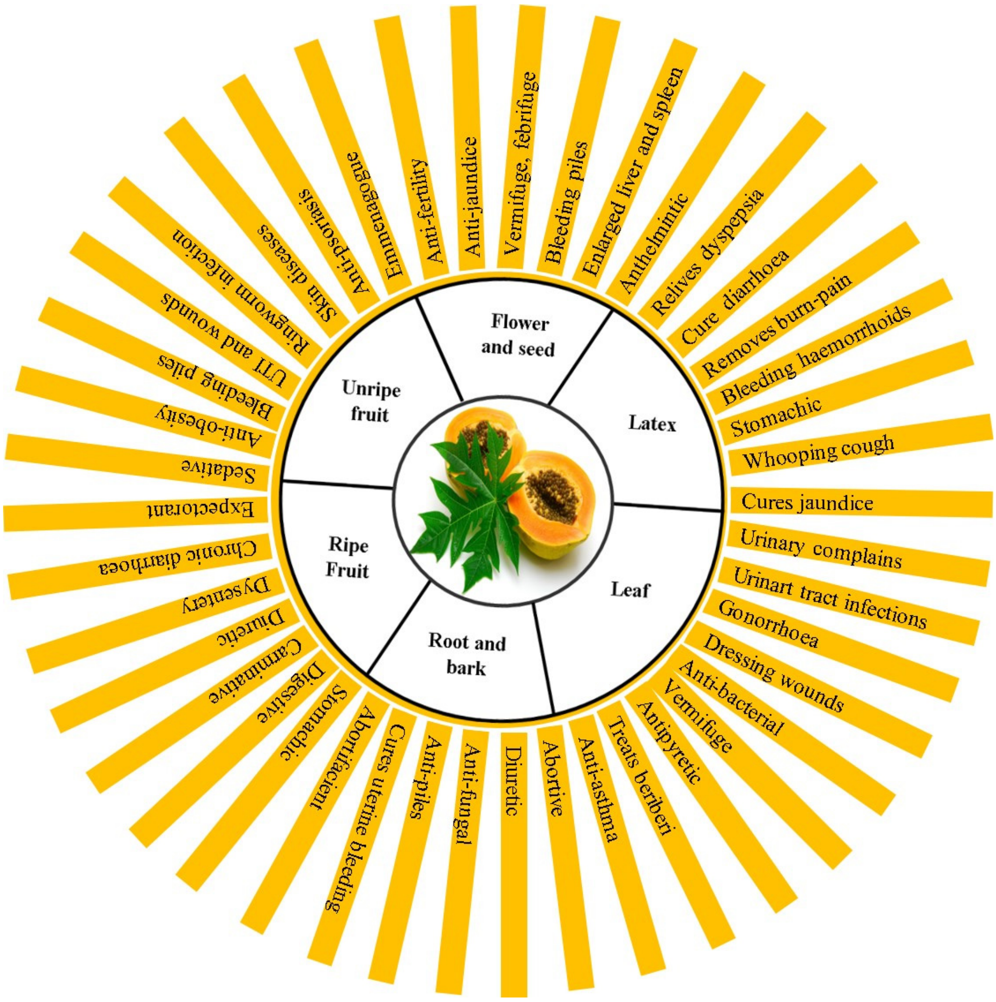


Figure 2. Health benefits of papaya (*Carica papaya* L.) plant parts.

5. Papaya Leaf Extract for Disease Management

As discussed in the above sections on the modern medicinal uses and pharmacological properties of papaya, the papaya leaf extract plays a prominent role in managing human diseases compared to all other vital products and compounds obtained from the remaining plant parts. The bioactive components of the leaf extract are of nutritional, medicinal, and therapeutic importance against a wide variety of human diseases, including lethal viruses, which are currently a global threat to the future [18].

Since the early years of extraction of papaya leaf extract, many methods have been developed, including water, ethanol, methanol, and freeze-dried papaya leaf juice. The therapeutic properties of the leaf extract are mainly due to the presence of alkaloids, glycosides, tannins, saponins, steroids, and flavonoids in papaya leaves [19,20]. It may treat the most prevalent hair dandruff condition, has a synergistic effect on spleen and liver enlargement, and removes venom from snakebites. It is effective in a wide range of pathological conditions. The leaves are exceptionally high in iron and can be used to treat growth-related problems, tuberculosis, and anemia, as well as a cleanser in herbal medicine. The compounds present in the leaf extract interact with a wide range of cellular substrates, including activities such as suppression of DNA synthesis, downregulation of harmful gene expression, upregulation of anti-inflammatory genes, modification of cell signaling pathways, and cleavage of several proteins that have therapeutic activity in a wide range of disease treatments [21]. Many improved therapies are available in modern medicine for cancer treatment based on the location and intensity of phases, such as surgery, chemotherapy, radiotherapy, immunotherapy, and vaccination. However, *Carica papaya* leaf extract can be used in combination therapy to prevent and regulate the subsequent proliferation of malignant cells [22]. Several studies on the action of papaya leaf extract on in vitro cancer have shown that it decreases cancer cell proliferation [23–25].

However, Nisar et al. (2011) found that papaya leaf extracts could be used to treat dengue fever [26]. Papaya leaves can be used for malaria treatment owing to the presence of several alkaloids, including quinine, which has been proven to be an anti-malarial agent [27]. The 'chikungunya' vector is another causal agent that poses a health risk. The combination of papaya leaf extract with spinosad (a bacterial insecticide) has proven to be a helpful and environmentally friendly treatment. The larvicidal and pupicidal effects of this bacterial insecticide dominate the vector. Papaya methanolic leaf extract has a significant larval and pupal mortality rate [28]. Additionally, the Table 1 summarizes scientific reports on the pharmaceutical properties (using human and animal models) of papaya latex, fruit (ripe or unripe), leaf, root, flower, and seed extracts.

Table 1. Pharmacological properties of *Carica papaya*.

Medicinal Property	Description	Treatment and Results	Reference
Anti-cancer	The aqueous extract increases the survival chances from cancers affecting the body's vital parts like lungs, intestines, liver and blood.	Brewed extract of 50 times dilution with RPMI showed positive results for cell death in cancerous cell lines like AGS (stomach), Capan-1 (pancreas), Karpas (lymphoma), MCF-7 (breast).	[29]
	Invitro treatments showed cytotoxic effects against benign, malignant cells of prostate origin.	Leaf extract (1–0.1 mg/mL) showed inhibitory and cytotoxic effects on prostate cell lines (RWPE-2, HPR-1, BPH-1, PC-3, DU-145 and LNCap) after 72 h of treatment.	[25]
	The component of leaf extract reduced adhesion and invasion of metastatic cancer cells in the extracellular matrix.	Leaf juice (3–30 μg/mL) was used for adhesion in PC-3 cells on wells with type 1 collagen and fibronectin. Dose dependant effect on anti-adhesion was observed.	[30,31]
	Suppression of DNA synthesis and inhibiting the proliferation of cancer cell lines in-vitro. AGS(stomach), DLD-1 (colon), MCF-7 (Breast), DOV-13 (Ovarian)	Suppressed DNA synthesis due to suppression in ^{3}H-thymidine incorporation was observed by applying papaya extracts at (1.25–27 mg/mL) concentrations post 24 h exposure.	[31]
	Decrease in production of Interleukins-2,4 and Increased production of cytokines like TNF-α (tumour necrosis factor)	0.125–0.5% papaya extract application to human peripheral blood mononuclear cells (PBMC) showed a decrease in interleukins and enhancement of cytokines.	[23]
Immunomodulatory	Strong effects of immunomodulation effects are observed in the cancer cell lines.	Immunomodulatory effects were observed after treating the Wistar rat and albino mice through aqueous papaya extract (50–150 mg/kg).	[32–34]
	Leaf extract mediated through ethanol had induced the TNF-α in lipopolysaccharide (LPS) induced dendritic cells	TNF-α in imDC (lipopolysaccharide (LPS) induced dendritic cells) was higher when treated along with papaya leaf extract (200 ng).	[35]
	Methanol-mediated papaya leaf extract had reported a decrease in the secretion of pro-inflammatory interleukins in human peripheral blood mononuclear cells (PBMC).	PBMCs stimulated by LPS at 0.1 μg/mL treated with the leaf extracts were analysed using ELISA and have shown positive inhibition of pro-inflammatory interleukins.	[36]
	The aqueous extract had increased the rate of Immunoglobulins IgG and IgM in acrylamide intoxicated mice trials.	Gastro gavaging fruit extract of 250 mg/kg orally in 0.05% acrylamide-induced Wistar albino mice showed an increase in immune functions (IgG and IgM).	[37]

Table 1. *Cont.*

Medicinal Property	Description	Treatment and Results	Reference
Anti-dengue virus	Oral administration of leaf extract significantly increased the count of platelets, RBC, and WBC in mice and humans.	Papaya leaf extract 0.2 mL or 2 g/mouse increased the platelet count from $3.4 \times 10^5/\mu L$ (day 3) to $11.33 \times 10^5/\mu L$ (day 21). RBC count increased from $6 \times 10^6/\mu L$ to $9 \times 10^6/\mu L$.	[38–41]
	The freeze-dried papaya leaf juice has proven to downregulate the inflammatory cytokines in mice infected with (Den-2) dengue virus.	The oral fed (500–2000 mg/kg body wt.) treatment for 3 days increased plasma CCL_2/MCP_{-1} during the viremia peak and downregulation of 8 inflammatory cytokine genes.	[42]
	Controlled trials conducted in patients reported an improvement of mean blood platelets to count with the administration of leaf extract, which had a characteristic of membrane stabilization preventing platelet lysis.	285 subjects with dengue fever were evaluated for treatment with Caripill syrup and showed a significant increase in mean platelet count from day 3 (89,739.31, $p = 0.030$) to day 5 (168,992, $p = 0.023$).	[40,43,44]
Anti-diabetes	The papaya leaf extract has exhibited hypolipidemic and anti-hyperglycemic effects in diabetic rats. Similarly, the aqueous extract released excess insulin from the beta cells and reduced glucose and triacylglycerol concentrations in the blood.	Aqueous papaya extract (0.75 g–3 g/100 mL) has reduced the blood glucose levels in diabetic rats. Islet cells of the pancreas were regenerated and significant positive differences were observed in rats treated with extract compared to control rats.	[45]
	The potential of fermented papaya extract to regulate blood glucose, inflammation, and free radical-induced oxidative damage, which cause liver, bladder, breast, and prostate cancer in type 2 diabetics, may ameliorate detrimental therapeutic effects.	FPP, a certified dietary supplement ISO 9002 produced by yeast fermentation, has antioxidants like superoxide, dimutase, catalase, glutathione peroxidase, therodoxine, and xanthine oxidase, helping in boosting immunity. These prevent the damage (oxidative stress, carcinogenic protein modifications, suppress DNA repair) from existing free radicals.	[46]
Anti-anaemia	Papaya extracts exhibit Antisickling and membrane stabilizing properties. Fragiliograms revealed that leaf extract reduced hemolysis and preserved the integrity of the erythrocyte membrane.	Under high hypoxia, pretreatment of SS cell suspensions with leaf extract reduced sickle cell formation to 0–5% after 40 min compared to untreated SS cell suspensions with >60% sickle cells. These findings point to papaya leaf extract as a potential therapeutic against sickle cell disease.	[33]
	The papaya leaf extract has reduced haemoglobin polymerization and osmotic fragility in human crescent RBCs which could be a potentially viable alternative to the hydroxyurea which is used in the therapy of sickle cell disease	RBCs were induced to sickling by 2% sodium metabisulfite. The percentage of sickle cells dropped from 91.6% to 47.6%, and the polymerization rate was 6×10^{-2} in the presence of hydroxyurea and papaya extract.	[47]

Table 1. *Cont.*

Medicinal Property	Description	Treatment and Results	Reference
Antibacterial	The most potent antibacterial action was found in papaya leaf extract, which significantly inhibited the growth of gram-positive bacteria (*Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*).	60% inhibition activity against bacterial growth has been observed through papaya extract application on Petri dishes. The average zone of inhibition (3.8 to 4 mm) for 75 µL concentration was reported.	[48]
	Papaya leaves extracted with ethanol, methanol, ethyl acetate, acetone, and chloroform were strongly bactericidal against gram-negative bacteria (*Bacillus cereus*, *Klebsiella pneumonia*, *Micrococcus luteus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*).	Phytochemical screening and antimicrobial activity for various solvent extractions of papaya leaf extract were investigated. The chloroform-mediated extract showed more activity against *M. luteus* (15.17 ± 0.29 mm), and acetone extraction showed (11.23 ± 0.25 mm) against *C. albicans.*	[49]
Gastroprotective	Aqueous extract of Carica papaya leaf (CPL) decreased alcohol-induced acute stomach damage and blood oxidative stress in rats. The extract-treated rats had a lower stomach ulcer index than alcohol-treated controls, which could serve as an efficient therapeutic agent for treating gastritis and oxidative stress.	500 mg/kg of aqueous CPL extract induced mucous production and HCO3- in the stomach and has successfully protected the gastric mucosal lining of mice against haemorrhages caused by alcohol.	[50]
	The treatment of rats with experimental stomach ulcers with papaya leaf extract mediated by ethanol resulted in a considerable diminution in ulcers. The ulceration, volume of stomach acids, and pH of rats with aspirin-induced stomach ulcers increased.	The experiment involved rats induced by artificial ulcers and oedema and pellet granuloma were orally fed with 25–200 mg/kg of papaya leaf extract. Significant ($p < 0.05$) reduction in the symptoms was observed.	[51]

6. Phytochemistry

The presence of volatile compounds in papaya, such as alcohols, terpenes, aldehydes, organic acids, ketones, esters, and benzyl isothiocyanate (BITC), is responsible for its sensory characteristics, such as scent and flavor [52]. However, ethyl hexanoate, ethyl 2–methyl butanoate, and ethyl acetate are all linked to fruit scent [53]. Linalool is the most prevalent volatile component in 94% of solo papaya varieties [54]. Aromatic chemicals such as butanol, terpineol, and 3–methyl butanol are abundant during the mature stage [55], whereas methyl butyrate is the most abundant of the 103 esters in papaya [56].

Phytochemicals have been reported in different parts of the papaya plant, including the roots, shoots, heartwood, bark, leaves, fruits, fruit latex, juice, and seeds. In total, 166 volatile and non-volatile compounds belonging to the chemical classes of terpenoids, flavonoids, alkaloids, carotenoids, vitamins, and glycosides have been reported. The most important phytochemicals used are listed in Table 2.

LC-MS analysis of several papaya plant extracts revealed the presence of sinapic acid–O–hexoside, cyaniding–3–O–glucose, 5–hydroxy caffeic quinic acid, 5–hydroxy feruloyl quinic acid, acetyl *p*–coumaryl quinic acid, quercetin–3–O–rhamnoside, syringic acid hexoside, peonidin–3–O–glucoside, and methyl feruloyl glycoside [57]. It has been reported that an extract of papaya leaves processed with hexane possesses antiplasmodial effects [58]. Four of the nine chemicals were flavonols, whereas the other five were alkaloids. Papain was isolated and characterized from ripened fruits to investigate its catalytic capabilities and potential usage in wine stabilization [59].

Table 2. Leading phytochemicals isolated and characterized in *C. papaya* plant.

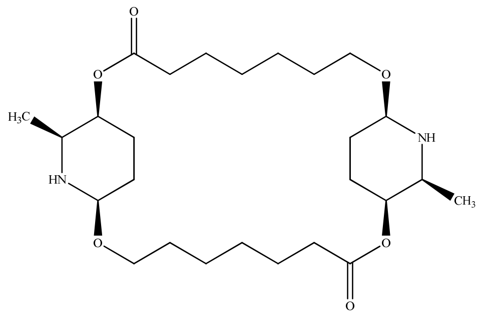
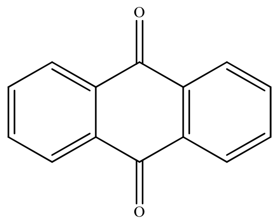
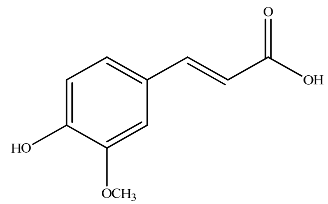
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
1.	Leaves	Carpaine		[33,57,60–62]
		Anthraquinone		
		Ferulic acid		

Table 2. *Cont.*

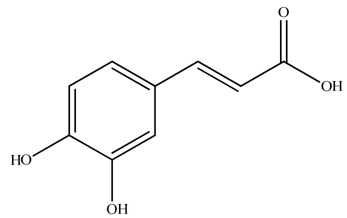
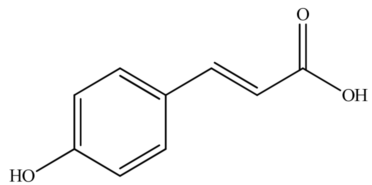
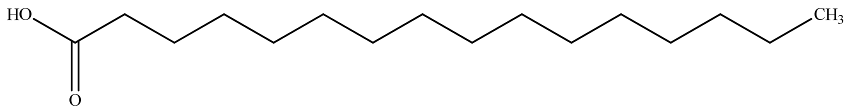
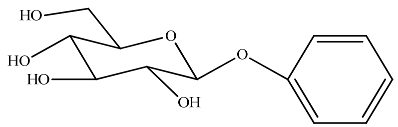
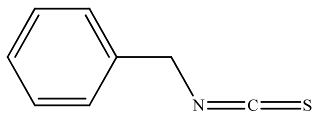
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		Caffeic acid		
		Nicotinic acid		
		n–Hexadecanoic acid (palmitic acid)		
2.	Fruit	Benzyl–β–D–glucoside		[61,62]
		Benzyl isothiocyanate (BITC)		

Table 2. *Cont.*

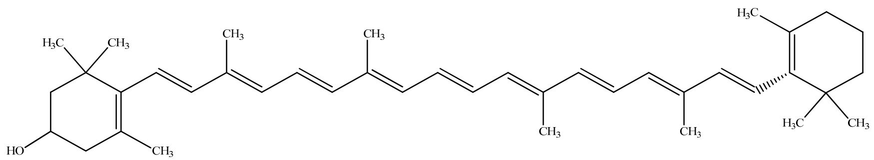
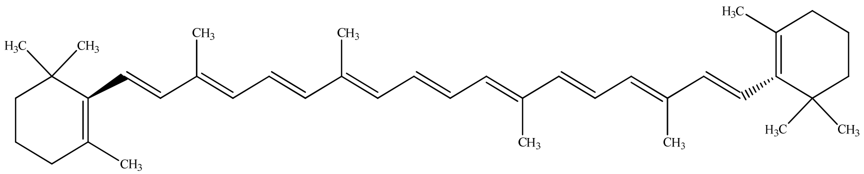
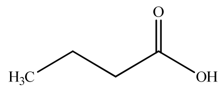
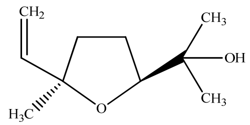
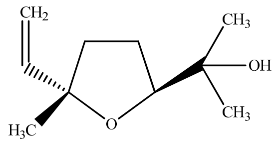
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		β–Cryptoxanthin		
		β–Carotene		
		Butanoic acid (butyric acid)		
		Cis–Linalool oxide		
		Trans–Linalool oxide		

Table 2. *Cont.*

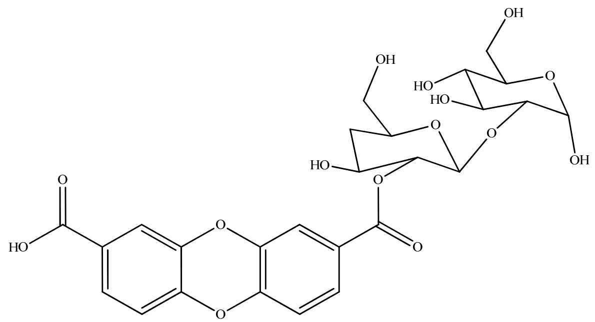
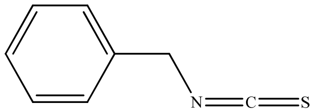
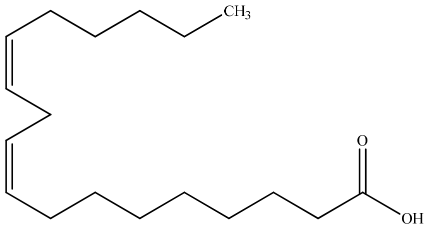
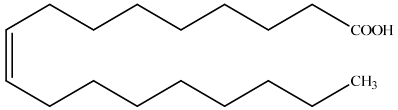
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		Caricapinoside		
3.	Seeds	Benzyl isothiocyanate		[60–64]
		Linoleic acid		
		Oleic acid		

Table 2. *Cont.*

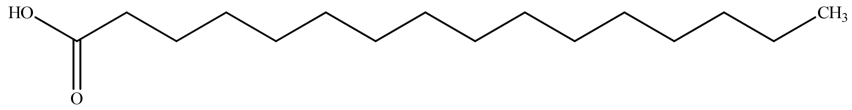
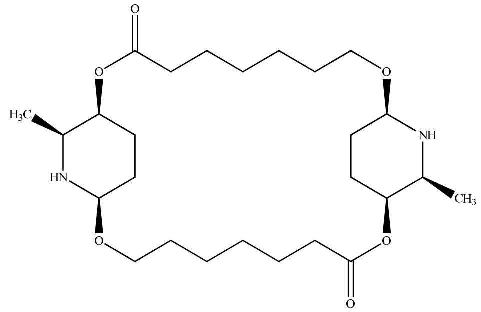
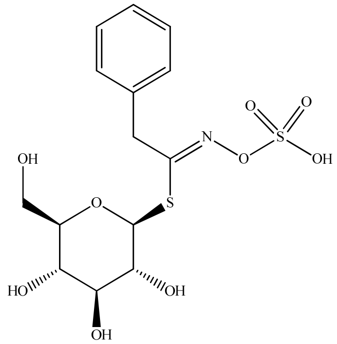
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		Palmitic acid		
		Carpaine		
		Benzyl glucosinolate		

Table 2. *Cont.*

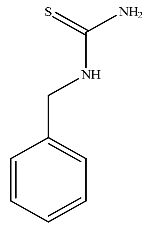
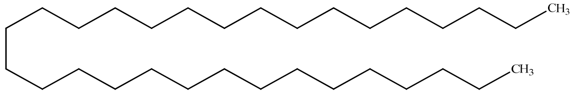
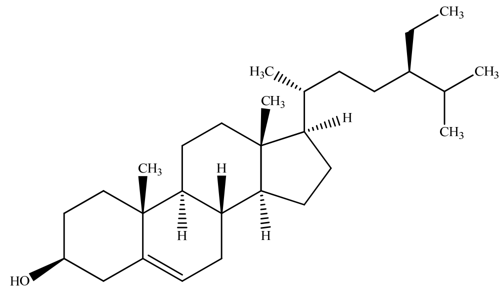
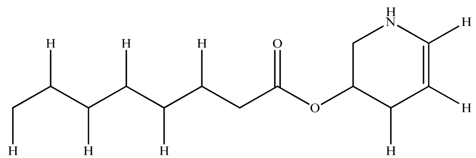
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		Benzylthiourea		
		Hentriacontane		
		β–Sitosterol		
		1,2,3,4–Tetrahydropyridin–3–yl–octanoate		

Table 2. *Cont.*

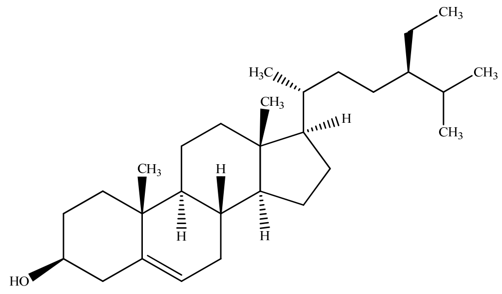
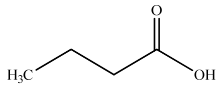
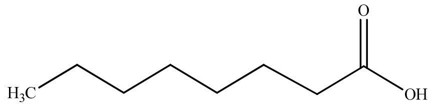
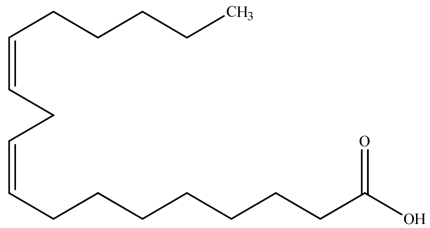
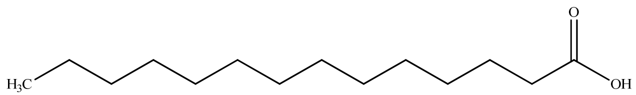
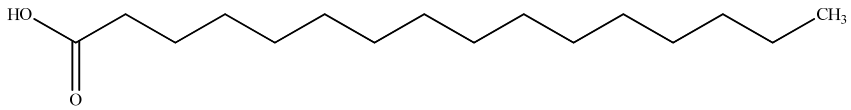
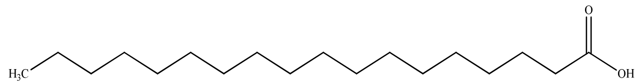
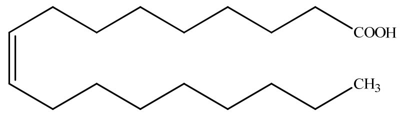
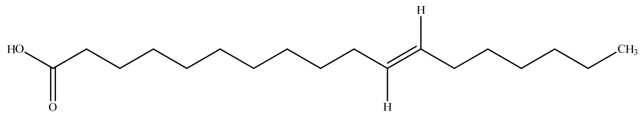
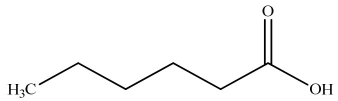
S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
4.	Bark	β–Sitosterol		[61]
5.	Juice	n–Butyric acid		[61,62]
		n–Octanoic acid		
		Linoleic acid		
		Myristic acid		

Table 2. *Cont.*

S.No.	Plant Parts	Chemical Constituent	Chemical Structure	Reference(s)
		Palmitic acid		
		Stearic acid		
		Oleic acid		
		Vaccenic acid		
		n–Hexanoic acid		

Sancho et al. (2011) used HPLC–MS to determine the presence of vitamin C, phenols, and carotenoids in papaya fruit flesh and skin [65]. The human body is protected from oxidative stress by these substances, which lowers the risk of cardiovascular diseases and some types of cancer. Caprine, a significant alkaloid present in all green sections and seeds of *C. papaya*, was discovered by Burdick (1971) [60]. The anti-sickling substance 'caricapinoside' was found in phytochemicals extracted from the ethyl acetate fraction of an aqueous extract of *C. papaya* unripe fruit [66].

To investigate volatile chemicals, Canini et al. (2007) used quantitative phenolic acid analysis (GC–MS) [67]. Chlorogenic acid was recorded at trace levels, and 0.25 mg/g (dry leaf) caffeic acid, 0.33 mg/g *p*–coumaric acid, 0.11 mg/g protocatechuic acid, 0.03 mg/g kaempferol, and 0.04 mg/g of quercetin was also observed. GC–MS and NMR analyses of papaya seed oil extracted with supercritical fluid revealed the presence of BITC [64].

7. Papaya Diseases and Etiology

Papaya has always been a revenue-generating crop for farmers in tropical and subtropical regions, after commercial horticultural crops, such as bananas and mangoes. Unripe raw fruits are consumed as culinary vegetables, whereas ripe fruits are consumed as table fruits. The overall global production amounts to 13.89 million tonnes [68]. Bacteria, viruses, fungi, and nematodes incur losses in production every year, and post-harvest losses due to infections caused during storage and transport of this fruit tend to be a severe constraint [69] (Figure 3).

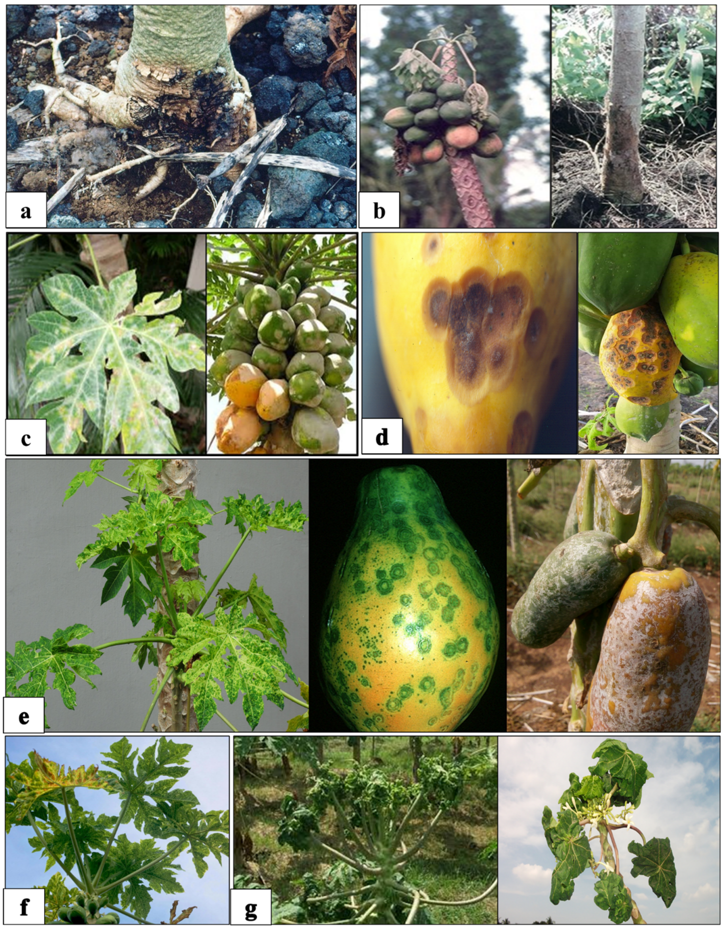


Figure 3. Fungal and viral disease in papaya. (**a**) Stem rot in papaya due to *Pythium aphanidermatum.* (**b**) Infected stem and malformed apical portion caused by *Phytophthora palmivora.* (**c**) Infection in leaves and fruits caused by *Oidium caricae.* (**d**) Fruits affected by fungus *Colletotrichum gloeosporioides.* (**e**) Ring-shaped spots on leaves and fruits due to PRSV. (**f**) Leaves affected by PMV and (**g**) curly leaves symptoms due to PLCV.

7.1. Foot Rot/Stem Rot (Fungi: Pythium Aphanidermatum)

Soil-borne fungal pathogens of the oomycetes class are usually found in waterlogged and humid conditions. Water-soaked lesions form at the base of the stem, decaying the tissue and transforming it into a black necrotic area [70]. Because of an insufficient water supply and nutrients through the main stem, the fruits of diseased plants become deformed and shriveled. Pathogenicity occurs predominantly during the monsoon season when a seedling or plant encounters oospores, sporangia, or hyphae that can live in the soil and degrade organic materials.

Control measures: Avoid waterlogging and follow a ring irrigation system. During planting, apply 15 g of *Trichoderma viride* mixed with manure near each plant root. Drenching copper oxychloride at 3 g/L of water every 15 days from planting and applying the paste of copper oxychloride to the rotted area.

7.2. Collar Rot/Soft Fruit Rot (Fungi: Phytophthora Palmivora)

Soil-borne fungi of the oomycetes class cause widespread diseases in nations such as India, Sri Lanka, Indonesia, Australia, Malaysia, Hawaii, Taiwan, Brazil, and Spain. Lesions form at the base of the stem, which could be below or above the ground, resulting in yellow wilted leaves [71]. Higher soil temperatures and inadequate drainage aid in the spread of this disease. Lower leaves and fruits shrink and fall prematurely because of the white mycelial coat [72]. Fungi produce zoospores (infective and motile) and chlamydospores (dormant), which can become active at high temperatures and spread by wind and flowing water [73].

Control measures: Grow papayas where they have never been previously cultivated. Use disease-free seedlings, drenching copper oxychloride 3 g/L mixed with organic manure in the pit near each plant's root.

7.3. Powdery Mildew (Fungi: Oidium Caricae)

Originally described in 1898 in Brazil, this fungal pathogen classified under Leotiomycetes, was later detected in all other subtropical climates, and papaya was the only host for this organism. The fungus has no saprophytic phase in its life cycle and can be detected only in living plants [74]. High humidity, moderate light, rainfall, and temperature promote disease spread, resulting in minor fuzzy spots on leaves and the spread of white powdery mycelia all over senescent leaves, leading to chlorosis and leaf fall [75]. The fruits of older plants become deformed and distorted; however, young plants suffer severe damage. The fungus develops asexual spores known as conidia and globose sexual spores known as ascospores [71].

Control measures: Spraying the trees with chemicals after disease incidence. 0.1% tridemorph, 0.25% wettable sulfur, or 0.05% dinocap.

7.4. Papaya Anthrocnose (Fungi: Colletotrichum Gloeosporioides)

Many early studies mentioned this fungus of Sordariomycetes class as an important disease-causing agent in citrus, mango, and several other hosts. This disease is distinguished by sunken patches of varied colors on plant parts such as leaves, stems, and fruits, which enlarge and eventually cause wilting and withering of the plant [76]. *C. gloeosponoides* has an asexual or anamorphic phase, in which conidia grow and proliferate anthracnose by rain or irrigation water in warm conditions. Conidia generate typical structures known as appressoria and acervuli, which aid fungal penetration into host plant cells [77].

Control measures: Chemical spraying of either 2 g/L cholothalonil at 10–15 day intervals with 2 g/L Mancozebat at 10-day intervals, or carbendazim 1 g/L at every 45-day interval.

7.5. Papaya Ring Spot (Virus: Papaya Ring Spot Virus, PRSV)

PRSV is a single-stranded positive-sense RNA virus that belongs to the Potyvirus genus and is classified under the Potyviridae family. PRSV is more catastrophic to *Papayaceae*, *Chenopodiaceae*, *Cucurbitaceae*, and *Caricaceae* family members [78]. It was first identified in 1949 as a destructive virus of the papaya crop in the Hawaiian Islands. By 1992, it had destroyed 100% of papaya production in East Asian countries and Hawaii [3]. Aphids serve as vectors for PSRV infection and induce symptoms, such as vein cleaning and young leaf yellowing. Moist and oily streaks on the stem, chlorosis on the root lamina, vein clearing, and mosaic patches on the leaf surface are the leading causes of yield loss. Fruits develop distinct ring-spot patterns with concentric rings, and these spots degrade the quality and taste [79].

Control measures: Use of healthy or disease-free seedlings. Identifying the symptoms at early stages and culling out the infected plants, using yellow sticky traps for aphids, crop rotation with maize or sorghum to evade the aphids, and avoiding planting the crops of the *Cucurbitaceae* family.

7.6. Papaya Mosaic (Virus: Papaya Mosaic Virus, PMV)

Papaya mosaic virus (PMV), a member of the genus *Potexvirus* and the family *Flexiviridae*, is a rod-shaped, single-stranded RNA plant virus that was initially detected in 1962 as a threat to papaya crops after PRSV [80]. Its morphological and structural properties resemble those of the tobacco mosaic virus [81]. Infected plants exhibit significant deformation and string-shaped mosaic patterns on their leaves, causing them to be stunted, as well as water-soaked sores on their stems. PMV has a high impact on the production of native varieties and rapidly spreads even in transgenically produced PRSV-resistant cultivars [82].

Control measures: Use healthy seedlings and exercise caution when handling plants during intercultural operations. Roughing out diseased plants and immediately burning them. All intercultural operating tools should be sterilized with sodium hypochlorite solution.

7.7. Papaya Leaf Curl (PLCV)

Papaya leaf curl virus (PLCV), a geminivirus belonging to the *Geminiviridae* family with single-stranded DNA (ssDNA) as its fundamental genetic component, was first discovered in India in 1939 [83]. The virus is transmitted by the whitefly (*Bemisia tabaci*), which was discovered and proven by Saxena et al., 1998 [84]. This viral disease significantly impacts commercial sectors, such as pharmaceutical firms that rely on papaya leaves. This disease is distinguished by the inward or downward curling of the leaves, which resembles an inverted cup shape. The leaf surface becomes hard and leathery textured with thick veins, resulting in stunted growth, defoliation, and failure to blossom and set fruits [85].

Control measures: Roughing out the infected plants immediately and using systemic insecticides against the vector. Cultivation of *Solanaceae* crops on the same land should be avoided.

8. Post-Harvest Diseases of Papaya

Post-harvest diseases of papaya cause significant revenue losses. Owing to improper handling and transportation, most disease outbreaks occur before they reach the market [86]. Fruits with a thin outer coat and a fleshy core are very susceptible to diseases such as Rhizopus rot, Fusarium rot, Anthracnose rot, Aspergillus rot, stem end rot, and black rot.

The fungus *Mycosphaerella caricae* causes dry rot and stem-end rot of papaya, mainly through damage or cuts on the fruit. A rigid layer of tissue with wrinkles was observed on the outer layer of the fruits, followed by translucent edges and brown lesions [87]. The fungus *Phomopsis* sp. induces wet rot in papaya, causing tissue softening and discoloration in the infected area during the early stages of infection. A spot is usually observed in the center of a wet lesion, which develops into a hollow cavity and white mycelial growth on the surface [88]. Charcoal rot is a common disease of pulse and oil crops such as soybean, sesame, peanut, cowpea, chickpea, green gram, and cluster bean, but it also affects crops such as cotton, maize, sorghum, and papaya. The causal organism is *Macrophomina phaseolina* (Tassi) goid, a fungal pathogen from the Ascomycetes class. Ripe fruits are particularly vulnerable to this fungus, with pycnidia entering through incisions, insect bites, or abrasions during transit and spreading infection. Sclerotia and pycnidia produced by the fungus result in black-to-brownish patches on the skin [89]. *Alternaria alternata* (Fr) Keissl is a fungal pathogen that causes papaya fruit rot and brown leaf spots. The infection is most visible on the outer skin of fruits, where black spores and circular ring patterns can be observed. Older leaves are a source of infection, forming brown lesions that spread to other fruits during transport and storage [90].

Stem end rot in papaya fruits is a common disease caused by the combined effects of numerous pathogens. This can differ among species of *Phomopsis*, *Fusarium*, *Rhizopus*, *Botruodiplodia*, *Mycosphaerella*, *Ascochyta*, *Alternaria*, and other organisms [91]. During harvest, the pathogen enters the fruit via cuts and wounds in the peduncle region and fruit. Abnormalities such as dark lesions, soaked lesions, rough black patches on the skin, wrinkles, yellowing, spore patterns, and a carpet of white mycelium can be noticed on the infected fruit [92]. During transportation and extended storage, it rapidly spreads to other fruits. Negligence in storage conditions may also result in infections in the fleshy portions of fruit, where *Fusarium*, *Penicillium*, *Cladosporium*, and bacteria *Enterobacter cloacae* and *Erwinia herbicola* have been found to cause purple streaks and yellowing of the mesocarp [93].

Control measures: The majority of post-harvest diseases are caused by harvesting activities, wherein the microbial inoculum is transferred from damaged plants to healthy fruits. To prevent further disease spread, diseased fruit should be removed and discarded as early as possible. Handling during harvest and post-harvest should be performed with caution to avoid physical damage to the fruits. The use of sterilized wares or inoculum-free packaging materials, as well as proper fruit arrangement, could decrease mutual stress on the fruits. Spraying healthy fruits with contact fungicides such as 2 g/L chlorothalonil or mancozeb before rainfall and 7–10 days after harvesting will reduce the spread of diseases. Pre-harvest treatment with 2% enhanced freshness formulations (EFF) using hexanal as an active ingredient resulted in delayed maturity, color change, ripening, and reduced post-harvest disease incidence [94].

Although pre-harvest chemical sprays offer protection, subsequent treatments with synthetic chemicals, such as post-harvest fungicidal spray containing 0.2% hexaconazole, propiconazole, copper oxychloride, zineb, benomyl, chlorothalonil, or 0.1% carbendazim, would aid in preventing post-harvest infections [95,96]. Using natural oils from lemongrass, mint, castor, cinnamon, and thyme as fruit-coating materials has reduced the incidence of Anthracnose and Rhizopus rot [97,98]. Hot water dips, dry heated air, and heat vapor treatment at 49 °C significantly reduced fruit ripening and increased the shelf life of papaya [99,100]. Papaya fruits were treated with chitosan, aloe, papaya leaf extract [101], or chitosan with carbonate salts of ammonium ($(NH_4)_2CO_3$) and sodium (Na_2CO_3) to reduce post-harvest infections [102]. A hypoxic storage system (20 mm Hg at 10 °C, 90–98% relative humidity) of the fruits during lengthy shipments and freight resulted in reduced disease development, and no change in the texture or quality of fruits has been observed after this pressure or controlled atmospheric storage conditions [103].

Temperature and storage conditions significantly affect the spread of post-harvest diseases. Even temperatures during transit and storage are recommended to supply high-quality fruits. In contrast, temperature alterations may cause early ripening of fruits, soft flesh, color changes, and decay [93]. The summarized packages of various preharvest and post-harvest methods, together with environmentally friendly measures, will prevent infections and meet global nutritional demands through delicious papaya fruits.

9. Papaya Genomics

Papaya (*Carica papaya* L.) belongs to the flowering plant taxa classified under the order Brassicales and the family Caricaceae, with six genera and 35 species [104]. Carica was subsequently partitioned into two genera: *Vasconcellea* with 21 species and *Carica* with one species called papaya [105,106]. *Vasconcellea* and *Carica* have the same chromosome number, 2n = 2x = 18, that is, nine pairs of chromosomes with varied sizes, seven of which are metacentric and two of which are submetacentric, according to karyotypic studies [107]. Chromosome 1 is distinct and responsible for the determination of sex, thus categorized as a sex chromosome, and the remaining chromosomes are responsible for vegetative function confirmed based on studies performed with the help of fluorescent in situ hybridization (FISH) and bacterial artificial chromosomes (BAC) [108,109].

Papaya serves as an excellent model organism to study the evolutionary patterns of tree crops, their genetic resources, and variations in the genome structure, and proposes developmental strategies as its sequenced is comparably small, around 372 Mb [110], and has already been mapped [105]. The traditional whole-genome shotgun sequencing method was used to study the genetic arrangement of papaya, yielding 372 Mb of sequenced data, of which 271 Mb (nearly 70%) accounts for assembled contigs (contiguous sequences with overlapping data sets), and the remaining portion is scaffolds (including contigs and gaps) [111]. Genome annotation revealed the presence of 24,746 genes, which is proportionally less than that in other important crop genomes, such as rice (34%), Arabidopsis (20%), and grapes (19%) [112–114]. The advent of sequencing technology, primarily next-generation sequencing (NGS), has had a significant positive impact on the total genome sequencing of several crops, with papaya standing out as the fifth flowering crop after Arabidopsis, poplar, rice, and grape [115]. Single nucleotide polymorphism (SNP) markers were employed in conjunction with NGS to obtain 23,318 scaffolds (>200 bp lengths) in two commercially established varieties ('Eksotika' and 'Sekaki') and previously mapped 'Solo' papaya from Hawaii. These SNP markers could be useful in developing novel breeding programs using marker-assisted selection approaches in the future [116]. Wu et al. (2017) presented evidence for the establishment of the recessive *y* gene and its selection in red-fleshed papaya following domestication [117]. Haplotyping analyses have shown that the recessive *y* allele originates in wild cultivars. Genetic variability studies have confirmed a considerable reduction in recessive *y* alleles compared to dominant *Y* alleles in yellow-fleshed cultivars (wild and cultivated) [117].

Papaya is recognized as a trioecious tree species with three plant types: male, female, and hermaphrodites, which is an attractive element for investigating the genetic makeup and evolutionary behaviors of the species. The morphological differences among the three sex types benefit the progression of offspring with ease of reproduction. Male and female plants follow cross-pollination, whereas hermaphroditic plants prefer self-pollination, which is a peculiar commercial cultivating feature. Any stress caused by water and high temperature immediately alters the inflorescence behavior and changes the bisexual flower to male flowers with pollen-bearing stamens, and aborted and degenerated pistils and no fruits [118,119]. Pistil abortion could be caused by improper hormone signal transduction, lack of expression of hormone-related genes, transcriptional factors, or variation in auxin-producing genes between flowers [120].

The use of BAC in gene sequencing studies has been beneficial in revealing information on the XY system of sex determination and in evolutionary studies on sex chromosomes in plants [121,122]. Sequencing of sex chromosomal DNA, when aligned with BAC physical chromosomal maps and comparing the divergence between X and Y genes, has shown homomorphic evidence. In contrast, Y (male-specific regions of Y) resulted in many alterations such as insertions, duplications, deletions, and translocations, and divergence studies between male-specific Y and hermaphroditic Y (Y^h) regions demonstrated that the hermaphroditic trait in plants evolved at the species level in Papaya rather than at the family level in the course of evolution around 2.2 million years [121,122]. Wild varieties of Papaya and *Vasconcellea* relatives are dioecious, have significant genetic variability, and are inter-compatible, facilitating the creation of new hybrids with beneficial traits. Commercially grown papaya cultivars are gynodioecious, with two-thirds of the population being hermaphroditic and one-third female. However, they possess minimal genetic diversity due to their geographical isolation [123,124]. Such genetic dissimilarity prohibits hybridization, demonstrating a major need for trait introgression from wild varieties, embryo rescue to develop new cultivars with diversity, and overcoming compatibility issues [125].

Structural variations (SV) are complex genomic DNA mutations that include gene insertions, deletions, inversions, and transposable elements (TEs) at single genes or many places in the genome. Variations in copy number are also responsible for the size and species expressional behavior [126]. SVs are usually lengthy modifications of DNA and are random in every chromosome, rather than SNPs and indels (short insertions and deletions), which can have a proportional impact on the gene expression of various traits in the species, modifying or developing new biological processes, the association between specific variation and its impact on an individual's phenotypic behavior, and evolutionary and genetic diversity studies.

In the papaya genome, 8083 SVs, 5260 deletions, 552 duplications, and 2271 insertions were found, where 1794 genes overlapped with SVs, with 1350 genes expressed in at least one tissue, highlighting the prominence of deletions during evolution and domestication [127]. The identified SVs showed a co-expressional relationship in several plant tissues and played a vital role in the growth and biotic stress response. SVs genes that influenced environmental tolerance, reproduction, and yield qualities during papaya domestication were identified and summarized using copy number varying gene (CNVs) correlation analysis. Such variability investigations will help to understand the evolution of male to hermaphroditic flowers in papaya.

This papaya genome study revealed many fundamental and interesting facts about papaya and will serve as a foundation for identifying and designing DNA markers for papaya enhancement. It would also aid in phylogenetic and evolutionary studies of other tropical fruit crops and *Brassicaceae* family members [125]. Many genetic markers have been developed to differentiate hermaphroditic and female plants. Hermaphroditic plants grow longer and larger fruits, whereas female plants yield round fruits. Owing to packaging and shipping limitations, the fruits of hermaphroditic plants are preferred over those of females. The use of genetic markers aided in the removal of females during seed production and tissue culture screening [128] and successfully developed two genetic markers for males in papaya using an 8396 bp insertion transposon sequence to identify sex reversal [129]. Morphological papaya sex determination is only viable six months after germination. The application of these modern genetic markers aids in the rapid determination of sex types over several hours. Using such markers in ecological surveys will be extremely valuable for estimating population dynamics based on population sex ratios [130]. Genomics as a whole, in conjunction with proteomics and transcriptomics, could provide a solution for developing new cultivars of tropical fruits to cope with high temperature and drought stress and combat the adverse effects of global warming [131,132].

Genetic diversity and phylogeny investigations, and their organization in wild ancestors, will represent genetic sources that can aid in developing breeding methods for climate-smart cultivars of all crops. Currently, papaya is considered a crop of high agronomic, therapeutic, and economic importance in many aspects that result from its domestication. Further research into the history, evolution, and domestication of these plants is required to counteract future concerns, such as overpopulation, global climate change, and food scarcity and security.

10. Papaya Biotechnology—Crop Improvement

Papaya is amenable to plant transformation; thus, foreign genes can be introduced into the papaya genome using various transgenic procedures such as particle bombardment (biolistic approach) and *Agrobacterium*-mediated transformations [133,134]. After PRSV was eliminated from Hawaiian papaya production in 1994, many PRSV-resistant varieties were developed using traditional methods, but they were not long-term remedies. The use of transgenics has paved the way for improving the production of commercial cultivars against this virus. Papaya was the world's first crop to have transgenic cultivars released for commercial cultivation in Hawaii in 1998 by institutions in the USA [135]. The development of a PRSV-resistant papaya cultivar is based on pathogen-derived resistance (PDR), which includes the DNA sequence from a target pathogen to be engineered and incorporated into the host plant; thus, the host-pathogen interaction in the plant is disrupted by the transgenic protein produced during pathogen attack, which subsequently delays the resistance of plants against the disease [136–138]. Successful expression of the PSRV coat protein has led to the development and release of transgenic PSRV-resistant papaya [139]. The co-cultivation of embryogenic cultures with disarmed *A. tumefaciens* containing a vector with the gene of interest is required for papaya transformation mediated by *A. tumefaciens*. Acetosyringone is a phenolic substance frequently added to bacterial suspensions to increase the virulence of *vir* genes and to improve transformation efficiency [140]. In transgenic papaya, the *GUS* gene (β-glucuronidase gene from *E. coli*) and *GFP* (green fluorescent protein from jellyfish) have been used as reporter genes to distinguish between transgenic and non-transformed tissues [141,142]. The GUS gene encodes a β-glucuronidase enzyme that produces a vivid blue color when combined with a colorless substrate 5-Bromo 4-chloro-3-indolyl-glucuronic acid (X-Gluc). *GFP* has the additional benefit of being a non-destructive screening tool for identifying altered tissues. As an alternative selection system, phospho-mannose isomerase (PMI)/mannose (Man) has been developed to efficiently perform the transformation procedure [143]. Embryogenic cells transformed with the *pmi* gene consistently expressed the PMI enzyme and could use mannose added to the culture medium. Genetic modification of papaya has been performed for biotic and abiotic stress tolerance, qualitative traits, and production of plant-based vaccines. The chitinase gene from *Manduca sexta* has been reported to be helpful in the development of transgenic papaya resistant to mites [144]. In another report, transgenic papaya expressing the agglutin gene from *Galanthus nivalis* was developed by McCafferty et al. (2008) for resistance against spider mites [145]. The stilbene synthase gene (*vst1*) from grapevine was introduced into the papaya genome for resistance against biotic stress caused by *Phytophthora palmivora* [143]. Currently, efforts are being made to develop transgenic papaya resistant to fungal diseases. The *esat*-6 gene from *M. tuberculosis* has also been introduced into the papaya genome to produce vaccines against tuberculosis [146].

The transgenic approach also improved the shelf life of ripe papaya fruit. Papaya has a short shelf life and is highly prone to chilling injuries when stored at low temperatures during long transport [147]. Storage rot can result in significant losses of market value [148]. Fruit ripening in papaya is triggered by a rapid burst of ethylene production, which activates downstream genes responsible for fruit softening [149]. The selection of transgenic markers for sex determination in papaya seedlings is another example of genetic engineering [150]. The bright yellow protein (Eyfp) and a selectable bar gene conferring glufosinate resistance were introduced into embryogenic cells in this study. Transgenic plants with insertions near sex-linked genes are currently being evaluated to develop rapid assays for sex identification in papaya seedlings. Table 3 shows selected reports on papaya crop improvement under various abiotic and biotic stressors.

Table 3. Reports on the development of transgenic papaya.

Source	Gene(s)	Type of Transformation	Useful Trait Introduced	Reference
E. coli; *E. coli* K12	*uidA*; *nptII* gene	Microprojectile-mediated transformation of zygotic/somatic embryos/freshly explanted hypocotyl sections	GUS expression; Kanamycin resistance	[133]
PRSV; *E. coli*; *E. coli* K12	PRV *cp* gene; *uidA*; *nptII* gene	Microprojectile-mediated transformation of immature zygotic embryos	Resistance against PRSV	[151]
PRSV; *E. coli*; *E. coli* K12	PRV *cp* gene; *uidA*; *nptII* gene	*Agrobacterium*-mediated transformation of somatic embryos	Resistance against PRSV	[134]
E. coli; *E. coli* K12	*uidA*; *nptII* gene	*Agrobacterium*-mediated transformation of petioles	GUS expression; Kanamycin resistance	[152]
P. aeruginosa	CSb gene	Particle bombardment-mediated transformation	Al tolerance in tobacco and papaya	[153]
PRSV	Coat protein gene	Particle bombardment-mediated transformation of embryogenic tissues derived from immature zygotic embryos	Resistance against PRSV	[139]
M. tuberculosis	*esat*-6 gene	*Agrobacterium*-mediated transformation	Vaccine against tuberculosis in papaya	[146]
A. victoria	*gpfp*	Particle bombardment -mediated transformation of hypocotyl-derived embryogenic calli	GFP -mediated selection of transformants	[121]
Grapevine (*V. vinifera* L.)	Stilbene synthase gene (*Vst* 1)	Particle bombardment-mediated transformation of papaya embryogenic callus	Resistance against *Phytophthora palmivora*	[143]
M. sexta	Chitinase gene	Microprojectile bombardment of hypocotyl-derived embryogenic calli	Resistance to spider mites	[144]
D. pinnata	Defensin (DmAMP1)	Particle bombardment -mediated transformation of hypocotyl-derived embryogenic calli	Resistance to *Phytophthora palmivora*	[154]
G. nivalis	*G. nivalis* agglutin	Biolistic gene gun-mediated transformation of embryogenic calli	Resistance to spider mites	[145]

11. Value-Added Products of Papaya

Papaya can also be used to create value-added products. Products such as pickles, candy, papaya-mix juices, and face wash are already being sold in the market [155] (Figure 4).

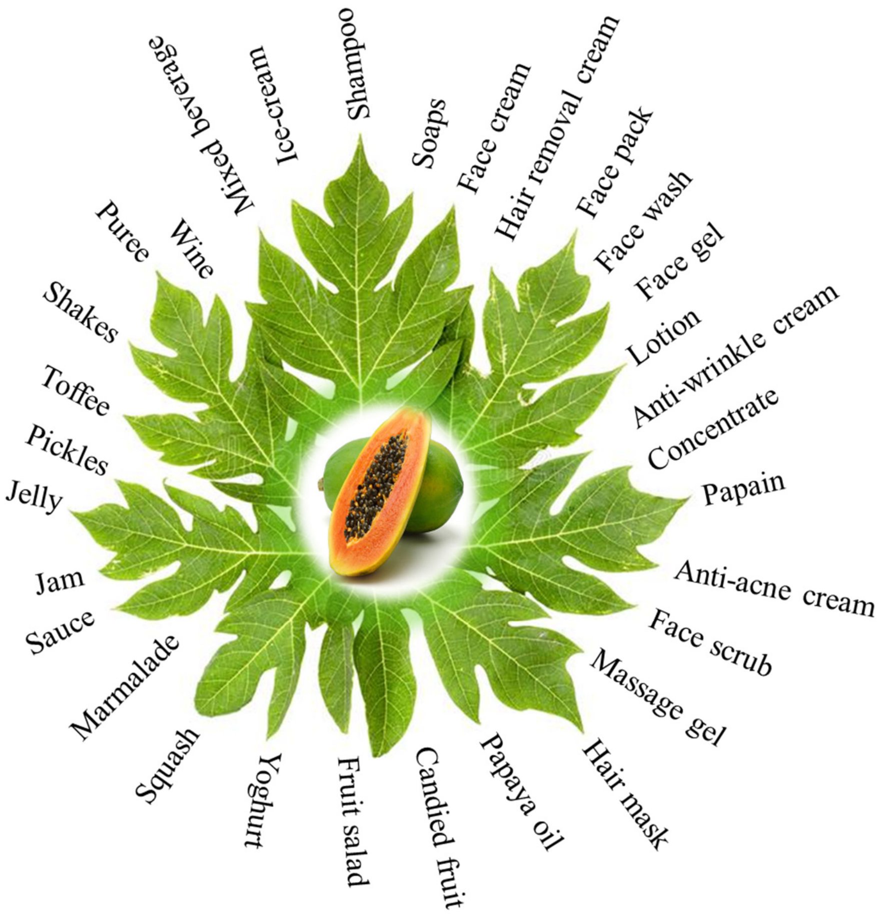


Figure 4. Value-added commercial products of *Carica papaya*.

Papaya milkshake is regarded as one of the most important components of a decent breakfast menu. Thus, there is a continuous and growing demand for papaya in the food and pharmaceutical industries. In this section, we discuss the importance and use of the selected papaya products. They are (i) *Papain*: It is the dried milk of papaya that is collected, treated, packaged, and sold for various industrial uses, including softening meat, oil extraction from Tuna fish, in brewing industry, leather curing, preshrinking of wool, degumming of silk and rayon, in preparation of face cream, dental paste, and wound healing properties [156]. Papain-based proprietary medicinal products are available in the market. It is used in medicine to treat necrotic tissues, skin rashes, renal problems, digestive disorders, dyspepsia, and ring or roundworm infection; (ii) *Papaya candy*: Preparation of papaya candy is a unique strategy to prevent post-harvest loss of papaya fruit which accounts for a loss in millions per annum. Papaya candy is a value-added product that can reduce papaya fruit losses by up to 10%.

To prepare the papaya candy, mature unripe papaya was harvested and streaked to drain the papain. After that, they were peeled (seeds were removed), diced into pieces of uniform size (approx 2–3 cm in dimension), and dipped for one or half-hour in a cold solution containing salt (2 g/100 mL) and calcium chloride (1 g/100 mL). The solution was drained, and the pieces were washed with cold or fresh water. The pieces were then cooked for five minutes along with one-fourth of the sugar (*w/w*), color, and/or flavor (cardamom and/or tulsi and/or lemongrass powder), followed by cooling at room temperature for four hours. Thereafter, more sugar was added (Brix 70°) stepwise, along with a preservative (citric acid: 1–1.5 g/100 mL) and cooked for five minutes. Finally, the syrup was drained, and the candy was dried in the shade, followed by packaging in sterilized containers or polythene bags. These candies are medicinal foods that are very useful in digestion and bowel cleansing. They even lower cholesterol, boost immunity, and protect against arthritis; (iii) *Papaya jelly and jam*: Papaya jellies are relished by all age groups as they are tasty and digestive. To prepare papaya jelly, fully ripe papaya was peeled, and the seeds and inner skin were removed.

Papaya pieces were blended into a puree, which was sieved and poured into a pan kept on a flame. For 200 mL of papaya puree, 100 mL of milk was added, and 1.5 tablespoons of agar-agar powder were added with continuous stirring (to dissolve the agar-agar powder), followed by the addition of sugar and/or 2 tablespoons of condensed milk. The slurry was then poured into molds and maintained at 4 °C for setting. For the preparation of jam, to 200 mL of papaya puree, three-fourths of a cup of sugar was added and continuously stirred on a flame. Thereafter, 10 mL of lemon juice was mixed, and the thick puree (jam) was transferred into a glass container and cooled in a refrigerator; (iv) *Papaya squash:* The initial steps for squash preparation are similar to that of jelly preparation, but agar-agar powder is not added, water (1 kg/kg papaya pulp) is added instead of milk or condensed milk, and only mildly heated to dissolve the sugar (1.8 kg/kg papaya pulp) and citric acid (2.5 g/kg papaya pulp). After straining, potassium metabisulphite (2.5 KMS/lite of squash) was added as a preservative, and the syrup was stored in a bottle. It is diluted with water before serving; (v) *Papaya pickle:* The food item (fruits or vegetables) may be preserved through pickling in common salt and vinegar. Papaya pickles are tasty appetizers and improve the overall flavor of the dinner, similar to any other pickle. It stimulates the production of stomach juices, aiding digestion [157]. The ingredients required for papaya pickle are peeled mature green-papaya pieces, red chili powder, mustard seeds, fenugreek, salt to taste, asafoetida, and vinegar. The mature green papaya was peeled, seeds were removed, cut into pieces, washed with water, boiled, and drained. The pieces were mixed with salt and spices and then stored in vinegar in a jar; (vi) *Papaya face cream*: The common ingredients are papaya enzymes, wheat germ, almond, and sesame oil, which make the skin light, smooth, and youthful. Natural papaya extract in papaya face cream removes dead skin cells, clears blemishes, hydrates and smoothes, and makes the skin spot-free; (vii) *Papaya toothpaste*: Papaya contains the enzyme papain, which loosens the enamel stains and therefore finds application in toothpaste preparation along with mint, pineapple extracts, and other ingredients [158]. Thus, there is a long list of papaya products, some of which are commercialized, and several are routinely used or consumed.

12. Conclusions

Papaya is a widely consumed fruit that consists of several varieties of compounds with pharmacological properties. Papaya fruit is a boon for health-conscious people, particularly for weight management. Apart from fruits, the plant and its parts contain a substantial number of phytochemicals, particularly the leaves, which have been used for traditional medicinal purposes from ancient times to the current era of medicine. This could lead to various therapeutic combinations to address numerous catastrophic disease outbreaks involving multiple viruses and other parasites. Because of domestication, papaya is now widely recognized as a crop with significant agronomic, medicinal, and commercial potential. The history, evolution, and domestication of these plants must be studied in greater depth to address future issues, such as overcrowding, global climate change, and food scarcity and security. The development of new ecologically sustainable practices for the production, post-harvest, and processing of delectable papaya fruits will keep illnesses aside and meet the world's nutritional needs. Therefore, papaya conservation and comprehensive investigations of its phytochemistry, pharmacodynamic characteristics, and kinetics, as well as proper standardization and clinical trials, are essential to fully harness its medicinal potential and effectiveness against diseases, such as dengue and malaria. It also provides the necessity to develop upgraded transgenic cultivars using various transformations with enhanced phytochemical contents in plants or plant parts to meet global needs. Moreover, crop improvement of papaya varieties through transgenic technologies is required to efficiently cope with various biotic stresses, especially PSRV infection.

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