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REVIEW

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Bioactive constituents from *Carica papaya* fruit: implications for drug discovery and pharmacological applications

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Abstract

Carica papaya, commonly known as papaya, is a fruit recognized for its substantial medicinal potential, primarily due to its wide range of bioactive compounds. This review thoroughly examines the pharmacological implications of these constituents and highlights their potential applications in drug discovery and therapy. Papaya is abundant in vitamins (A, C, and E), minerals, enzymes, and phytochemicals such as flavonoids, phenolic acids, carotenoids, and alkaloids, all of which contribute to its antioxidant, anti-aging, anti-inflammatory, and anticancer effects. The fruit demonstrates significant activity against diabetes, obesity, cardiovascular diseases, and gastrointestinal disorders. This review also discusses how environmental factors, including temperature, light, soil quality, and rainfall, impact the phytochemical composition of papaya, thereby influencing its medicinal properties. Both in vitro and in vivo studies have highlighted the therapeutic potential of papaya-derived compounds in various health conditions, including cancer, diabetes, wound healing, and cardiovascular health. Additionally, we explore papaya's role in promoting gut health and its antimicrobial properties against bacterial and viral pathogens. In conclusion, the diverse pharmacological activities of papaya's bioactive compounds position it as a valuable candidate for further research and development in drug discovery and therapeutic applications.

Keywords Bioactive compounds, Botany, *Carica papaya*, Drug discovery, Medicinal properties, Nutritional value, Phytochemicals

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Introduction

Carica papaya, widely known as papaya (Europe and Spain), pawpaw (Australia), mamao (Brazil), fruit de bomba (Spain), tree melon (Europe), and lechosa (Spain), is recognized for its significant medicinal properties and is frequently utilized in alternative medicine. It belongs to the Caricaceae family and is an important fruit crop cultivated across various climatic zones, including tropical, subtropical, and temperate regions. Its major producers include Australia, India, Brazil, Hawaii, Nigeria, Malaysia, and China (Fig. 1) [1].

Medium-sized papayas are rich in a variety of vitamins, minerals, antioxidants, and other beneficial nutrients [2]. The widespread use of *C. papaya* in traditional medicine can be attributed to its diverse phytochemical

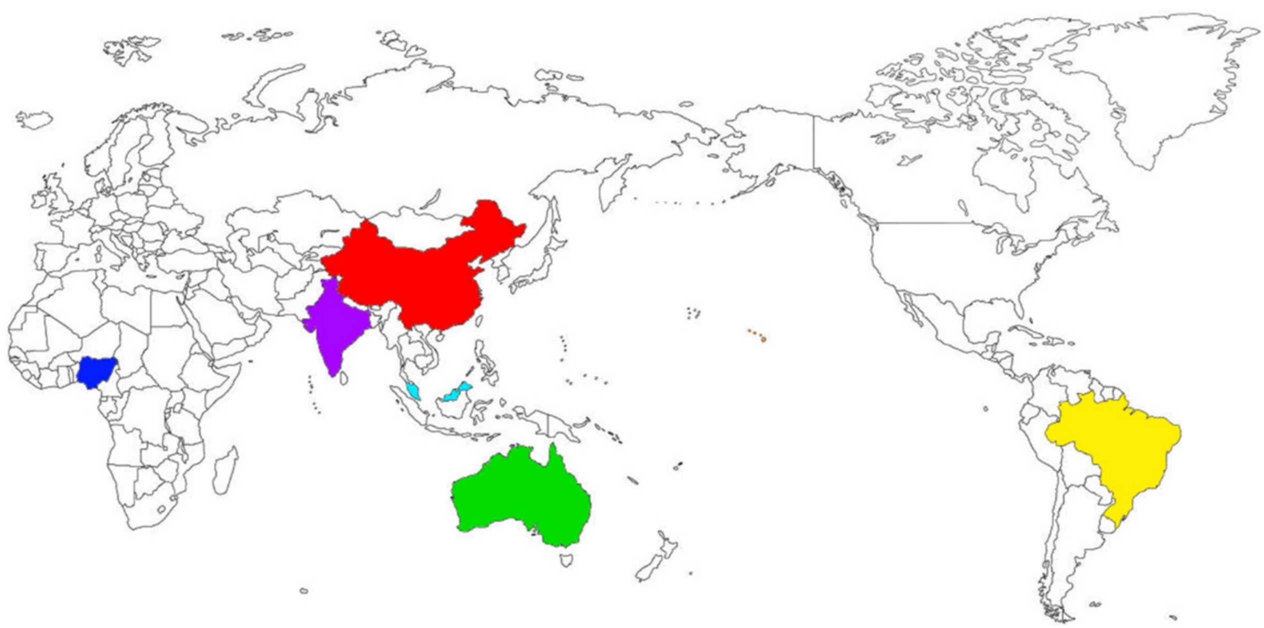

Fig. 1 Global distribution of *Carica papaya*

composition. These bioactive compounds include steroids, tannins, saponins, terpenoids, phenols, proanthocyanidins, flavonoids, anthraquinones, alkaloids, and cardiac glycosides (Table 1) [3].

The medicinal properties of papaya are further enhanced by its enzymatic content. The enzyme papain, present in papaya, is known for its ability to improve gut transit time and is used to treat allergies, trauma, and skin lesions [4]. Moreover, proteolytic enzymes in papaya, such as chymopapain, exhibit antifungal, antibacterial, and antiviral properties. Caricain, endopeptidase papain III and IV, glutamine cyclotransferase, peptidase A and B, lysozymes and glycyl endopeptidase are also two more enzymes present in papaya with therapeutic abilities against fever, asthma, colica, beriberi and jaundice [5]. It is found that, papaya-derived chemopapain is marketed as a medication to treat sciatica. Papaya latex has bacteriostatic properties against a variety of pathogenic organisms and has been employed as a vermifuge [6]. The ascorbic acid concentration of papayas varies; some, like the Waikapu variety, have higher levels than others. Higher ascorbic acid, or vitamin C, varieties may provide more health advantages, like increased immunity and decreased inflammation. Because of their higher antioxidant content, some papayas might be more beneficial in managing diseases and maintaining overall wellness [7]. A variety of phenolic components, including quercetin, caffeic acid, p-coumaric acid, gallic acid, and ferulic acid, are found in papaya. These compounds function together to give the fruit a high total phenol content, which in turn helps to defend against chronic diseases and protect antioxidants [8]. Papaya pulp and seed extract is used to treat various diseases including dengue, beriberi, and colic also. In folk medicine, papaya is used as a therapeutic drug owing to its various bioactivities, including anticancer, wound healing, and hypolipidemic properties. Papaya pulp and seed extract is used to treat hypertension, ringworms, arthritis, and gastrointestinal disorders. Further, papaya pulp and seed extracts, known for their anti-inflammatory activity, can help reduce reactive oxygen species (ROS) and improve mitochondrial membrane activity [9]. Notably, papaya seed extract is used as an alternative treatment for female *Candida vaginitis*. Additionally, studies have shown that papaya seed extract can act as a contraceptive by reducing human sperm motility. Furthermore, the extracts possess anthelmintic properties that can expel worms and have been associated with inducing abortion, highlighting their diverse medicinal potential [10].

The review aimed to extensively investigate the pharmacological significance of phytochemicals produced from *C. papaya.* The purpose of this study was to emphasize the medicinal potential of papaya's bioactive ingredients by collecting and assessing previous data. Furthermore, this paper investigates how climatic variables influence the phytochemical makeup of papaya, consequently influencing its therapeutic capabilities. This review's findings are intended to pave the way for future research into utilizing the therapeutic qualities of papaya for drug discovery and pharmacological applications.

Table 1 Phytochemical composition of papaya seed, fruit, and peel [8]

Bioactive components	Seed	Fruit	Peel	Source Cultivar
Total phenolic	0–30.32	0.02–1263 (mg GAE/100 g FW)	3.92–4.84 (mg GAE/g)	India, Solo
Tannin	0.25–10.60 mg/100 g	129.1 mg GAE/100 g FW	0.63–87.07 (mg/meq of tannic acid)	Africa, Chile, India, Indonesia
Phytic acid	19.77–26.32 (g/100 g DW)	–	–	Africa
Phytic phosphorus	5.57–7.43 (g/100 g DW)	–	–	Africa
Oxalate	2–8 mg/100 g	0.45–57 (g/100 g)	–	Africa
Myricetin	–	0.03–3 (mg/100 g FW)	–	Fiji, Mexico, Hawaii, Hawaiian, Maradol
Morin	–	2 (mg/100 g FW)	–	Fiji, Hawaiian
Total flavonoid	0.9–59.54 (mg GAE/100 g FW)	0.02–126 (mg GAE/100 g FW), 333.1 (mg/g)	1264.0 (mg/kg)	India, Indonesia, Malaysia
kaempferol	–	0.01–2 (mg/100 g FW)	–	Fiji, Hawaii, Mexico, Africa
Deoxyquercetin	–	–	–	India
Quercetin	–	0.04–2 (mg/100 g FW)	–	Africa, Malaysia, Mexico, Maradol
Anthocyanin	–	0.06 (mg/C-3-G 100 g FW)	–	Fiji, Hawaiian
Alkaloid (carpaine)	14.54 (mg/g)	–	8.29 (mg/100 g DW)	Malaysia, Indonesia
Caffeic acid	N/G	46.0–175.5 mg/100 g DW	–	Africa, Fiji, Mexico, Maradol, Hawaiian
Ferulic acid	–	130.3–277.49 mg/100 g	–	Mexico, Maradol
Luteolin	–	0.02 (mg/100 g FW)	–	Hawaii
Saponins	–	26–83 (mg Aes/g FW)	–	Australia
Lycopene	–	113–4138 (µg/100 g)	–	–
Zeaxanthin	–	19–27 (µg/100 g)	–	–
Lutein	–	93–318 (µg/100 g)	–	–
Cystine	–	–	–	–
Phenylalanine	–	–	–	India
Tocopherol	–	–	–	India
Coumarin	146 (mg/g)	–	–	India
Luteolin	–	0.02 (mg/100 g FW)	–	Hawaii
Chlorogenic acid	–	< 0.001 (mg/g DW)	–	Africa
Saponins	–	26–83 (mg Aes/g FW)	–	Australia
Proanthocyanidins	–	–	–	–
Total polyphenols	–	51–59 (mg GAE/100 g)	–	–
Lycopene	–	113–4138 (µg/100 g)	–	–
Zeaxanthin	–	19–27 (µg/100 g)	–	–
Lutein	–	93–318 (µg/100 g)	–	–
Cystine	–	–	–	–
Homocysteine	–	–	–	–
Methyl nonyl ketone	–	–	–	India
Cafeoyl alcohol	–	N/G	–	Africa, Mexico, Maradol
Phenylalanine	–	–	–	India
Stearic acid (%)	4.5	–	–	Africa
Palmitoleic acid (%)	0.21	–	–	Africa
Palmitic acid (%)	13.5	–	–	Africa
Myristic acid (%)	0.24	–	–	Africa
Eicosenic acid (%)	0.28	–	–	Africa
Arachidic acid (%)	0.39	–	–	Africa
Linolenic acid (%)	0.23	–	–	Africa
Linoleic acid (%)	2.9	–	–	Africa
Oleic acid	72.5	–	–	Africa

Table 1 (continued)

Bioactive components	Seed	Fruit	Peel	Source Cultivar
L Glutamic acid	–	–	–	India
Dimethoxy phenol	–	–	–	India
p-Coumaroyl alcohol	–	–	–	India
Coumaroylquinic acid	–	–	–	
Dicoumarol	–	–	–	
Coumarin	146 (mg/g)	–	–	India
Tocopherol	–	–	–	India

Papaya botany and cultivars

Botany and taxonomy

The fruit of *Carica papaya* varies in size, often extending toward a rounded shape with a large central cavity. Its seeds are black, textured, and sometimes coated with a translucent aril. *C. papaya* is widely cultivated across different regions and is a tall, perennial plant, reaching heights of approximately 5–10 m (16–33 feet). Its leaves are arranged in a spiral pattern and cluster only at the top of the stem. The trunk, which is hollow and green or occasionally a dark purple, displays prominent leaf scars around its base. Latex vessels are visible throughout the plant. The leaves are hollow, fleshy, and exhibit green and dark purple shades. Both the leaves and stems secrete a substantial amount of milky white latex. The small flowers are abundant and have a yellowish-white hue (Fig. 2) (Table 2) [11].

Fig. 2 Botanical characterization of *Carica papaya* [7]

Table 2 Papaya taxonomy [11]

Kingdom	Plantae
Phylum	Magnoliophyta
Class	Magnoliopsida
Subclass	Dillenildae
Order	Brassicales
Family	Caricaceae
Genus	Caroca
Species	Carica Papaya Linn

Papaya cultivars

Papaya is grown globally as a variety of cultivars, each with distinct attributes in terms of size, nutrient content, flavor, and regional adaptability. Below is an overview of some notable papaya cultivars classified (Fig. 3) based on their names rather than their regions of origin (Table 3) [12].

Climate and growing condition of *C. papaya* and its impact on phytochemical quality

Temperature

Papaya thrives in tropical and subtropical climates where the temperature range is 21–33 °C (70–91°F). Temperature plays a substantial function in determining the growth, development, and phytochemical composition of papaya. Excessively high and low temperatures can negatively affect the plant, thereby affecting fruit quality [21].

High temperatures exceeding 33 °C (91°F) can cause significant stress in papaya plants [21]. Heat stress often leads to reduced growth rates, flower drops, and potential damage to fruits, including sunburn. Prolonged exposure to high temperatures can degrade essential phytochemicals such as vitamin C and carotenoids, thereby diminishing the nutritional quality and antioxidant properties of the fruit. In contrast, temperatures below 21 °C (70°F) can cause chilling injuries. These injuries might appear as water-soaked lesions on the fruit and leaves, hampering leaf expansion and causing an overall deceleration of growth. Cold stress can also disrupt the synthesis and accumulation of vital phytochemicals such as phenolic compounds and flavonoids, thus reducing the antioxidant activity and nutritional value of the fruit [10].

Seasonal variations influence the growth and phytochemical quality of papayas. During the warm seasons of spring and summer, papayas generally exhibit higher growth rates and improved fruit sets because increased sunlight and warmth promote photosynthesis and nutrient uptake. These conditions often lead to an enhanced concentration of phytochemicals, such as lycopene and beta-carotene, thereby improving the nutritional profile of the fruit. Conversely, growth tended to slow during the cooler autumn and winter seasons. Significant drops in temperature during these periods may necessitate protective measures such as mulching or greenhouse cultivation to safeguard plants. Although cooler temperatures may reduce the overall phytochemical content, they can sometimes induce the production of stress-related compounds such as certain flavonoids as a plant response mechanism [22].

Light

Light intensity

Papayas thrive under full sunlight and require at least 6–8 h of direct sunlight each day. High light intensity promotes robust photosynthetic activity, leading to vigorous growth and higher fruit yield. Adequate light exposure is essential for the synthesis of key phytochemicals, including carotenoids and flavonoids, that contribute to the nutritional value and antioxidant properties of fruits. Increased light intensity can raise the concentration of these chemicals, improving the overall phytochemical quality of the fruit. However, excessive light intensity, particularly in regions with extremely high solar radiation, can lead to photooxidative stress. This stress can damage the chlorophyll and other cellular structures, resulting in reduced photosynthetic efficiency and potential sunburn of the fruit [23].

Light quality

The quality of light, particularly its wavelength, also plays a vital role in the development and phytochemical composition of papaya. Blue and red light are the most effective wavelengths for photosynthesis and influence various physiological processes in plants. Blue light is crucial for vegetative growth, leaf expansion, and chlorophyll synthesis, whereas red light promotes flowering and fruit development. Light quality can affect the accumulation of specific phytochemicals in papaya. For example, exposure to blue light has been associated with increased levels of chlorophyll and antioxidant compounds, which enhance the nutritional quality of fruits. In contrast, red light stimulates the production of carotenoids such as beta-carotene and lycopene, which are vital for fruit color and health benefits [24].

Photoperiod

Photoperiod, or duration of light exposure, influences the flowering and fruiting cycles of papaya. Papayas are day-neutral plants, meaning that they do not have strict photoperiod requirements for flowering. However, consistent and adequate light exposure is necessary to maintain healthy fruit growth and production. In regions with short daylight hours, supplemental lighting can be used

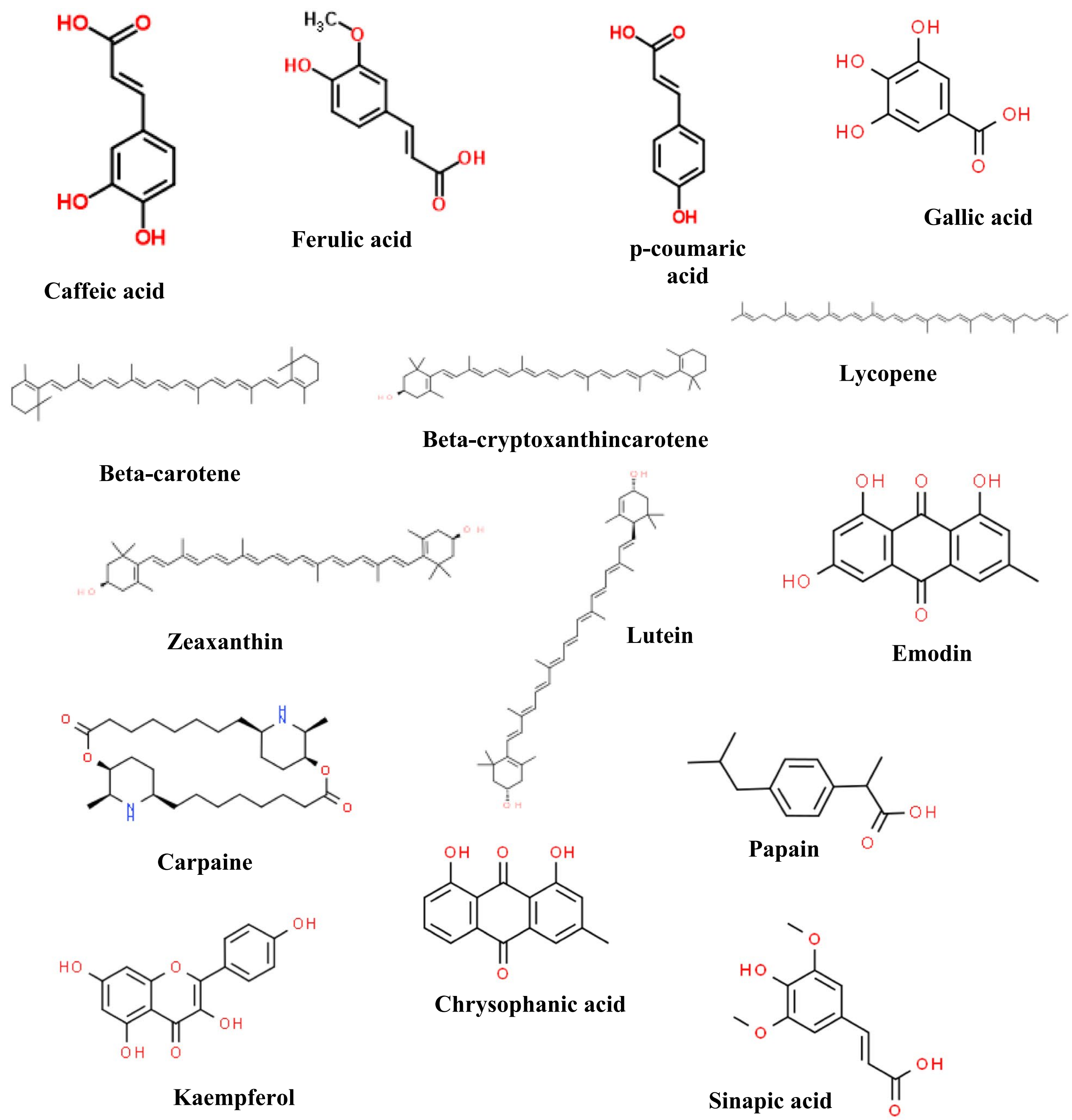

Fig. 3 Bioactive compounds present in *Carica papaya* fruit with medicinal properties

to extend the photoperiod and ensure sufficient light for optimal growth [24].

The effective management of light conditions is crucial for maximizing the phytochemical quality and yield of *C. papaya*. Choosing locations with adequate sunlight exposure and minimal shading from other structures or plants, utilizing shade nets or reflective mulches to moderate excessive light and heat, especially in high-radiation areas, implementing artificial lighting in greenhouse settings or regions with shorter daylight hours to ensure consistent light exposure, and planting papaya with other crops that provide partial shading and protect against excessive light and heat stress can enhance both the growth and phytochemical quality of papaya, ensuring a nutritious and marketable product [25].

Table 3 Most popular papaya cultivars in the world and their ascorbic and total carotenoid concentrations

Papaya cultivar	Country of origin	Ascorbic acid content	Total carotenoid concentration	References
Kapoho	Hawaii	45.4 mg/100 g	29.9 mg/100 g	[13]
Laei Gold	Hawaii	51.3 mg/100 g	48.2 mg/100 g	[13]
Rainbow	Hawaii	43.6–84.9 mg/100 g	57.4–84.9 mg/100 g	[14]
Rainbow/ Hybrid-line	Hawaii	43.6–75.9 mg/100 g	NA	[14]
Sunrise and Kphybrid	Hawaii	87.6–262 mg/100 g	68.3–84.9 mg/100 g	[13]
Sunrise	Hawaii	55.6 mg/100 g	45.6 mg/100 g	[14]
Sun Up	Hawaii	45.3 mg/100 g	20.4 mg/100 g	[13]
Pococi Costa Rican	Costa Rica	NA mg/100 g	132–166 mg/100 g	[15]
Red lady	Florida	153.8 mg/100 g	NA mg/100 g	[16]
Maradol	Mexico	25.1–58.6 mg/100 g	30.84–85.8 mg/100 g	[17]
Local-1(Yellow fleshed)	Sri Lanka	NA mg/100 g	75.84 mg/100 g	[18]
Local-2 (Red fleshed)	Sri Lanka	NA mg/100 g	152.92 mg/100 g	[18]
Local-1	Bangladesh	8.09–31.0 mg/100 g	20.8–33.8 mg/100 g	[12]
Hortus gold	Nigeria	68–96 mg/100 g	NA mg/100 g	[19]
Kamiya	Hawaii	N/A	N/A	[20]
Waimanalo	Hawaii	N/A	N/A	[20]
Solo	Hawaii, Barbados	N/A	N/A	[20]
Caribbean red	Mexican	N/A	N/A	[20]

Soil

Soil texture and drainage

Papaya plants prefer well-drained soils with a loamy texture that provides a balance between sand, silt, and clay. Appropriate drainage is crucial because papayas are highly susceptible to root rot under waterlogged conditions. Sandy loam soils are ideal because they offer good drainage while retaining adequate moisture and nutrients. However, heavy clayey soils can hinder root development and water movement, leading to poor growth and increased susceptibility to disease [26].

Soil pH

The optimal soil pH for papaya cultivation is 5.5–7.0. Soils within this pH range facilitate the availability and uptake of essential nutrients such as phosphorus, potassium, and nitrogen. Acidic soils (pH < 5.5) can lead to nutrient deficiencies, particularly of calcium and magnesium, whereas alkaline soils (pH > 7.0) can result in micronutrient deficiencies, especially of iron and zinc. Maintaining soil pH within the optimal range is vital for maximizing nutrient availability and ensuring healthy plant growth [27].

Nutrient management

Papaya plant species require a well-balanced supply of macro- and micronutrients to thrive and produce fruit. The three essential macronutrients are K, P, and N. N stimulates leaf development and overall plant vigor and is necessary for vegetative growth. Although too much nitrogen might produce luxury foliage with poor fruit set, too little nitrogen can cause stunted growth and leaf browning [28]. P is important for root development, flowering, and fruiting. Adequate phosphorus levels enhance the plant's ability to establish a strong root system and produce high-quality fruit. K is crucial for water regulation, enzyme activation, and the overall health of plants. Potassium deficiency leads to poor fruit quality, reduced disease resistance, and decreased productivity [6].

Although they are found in smaller amounts, micronutrients such as Mg, Ca, Fe, Mn, and Zn are vital. These nutrients are specifically involved in the synthesis of chlorophyll, enzyme activity, and hormone regulation, among other physiological activities [28].

Organic matter

Incorporating organic matter into soil improves its texture, structure, water-holding capacity, and fertility. Organic matter, such as compost or well-decomposed manure, enhances soil aeration and microbial activity, thereby promoting healthy root development and nutrient uptake. It also aids in the slow release of nutrients, ensuring a consistent supply to papaya plants over time [29].

Soil health and microbiology

Healthy soil with a rich microbial ecosystem supports the growth and phytochemical quality of papayas. Beneficial soil microorganisms, including mycorrhizal fungi and N-fixing bacteria, facilitate nutrient cycling and enhance plant nutrient uptake. Practices including crop rotation, reduced tillage and cover cropping can help preserve soil health and microbial diversity, resulting in more resilient and productive papaya plants [30].

Rainfall

Rainfall is a critical environmental factor significantly affecting the growth, development, and phytochemical composition of *C. papaya*. Papayas are generally well-suited to tropical and subtropical regions where consistent and adequate rainfall supports their growth. The optimal annual rainfall for papaya cultivation ranges from 1000 to 2000 mm (40–80 inches). Consistent rainfall is essential as it helps to maintain soil moisture levels, which are crucial for nutrient uptake and overall plant health. In regions with irregular rainfall patterns, supplemental irrigation may be necessary to ensure that plants receive adequate water throughout their growth cycle [31].

Insufficient rainfall can adversely affect papaya plants. Water stress resulting from inadequate rainfall hampers plant physiological processes including photosynthesis and nutrient uptake, leading to reduced growth rates, smaller leaves, and poor fruit set. The lack of sufficient moisture also affects the synthesis and accumulation of phytochemicals, resulting in lower levels of essential compounds, such as vitamins, carotenoids, and flavonoids. Additionally, in areas with low rainfall, there is a risk of increased soil salinity due to a lack of leaching. High soil salinity impairs root function and nutrient absorption, further stressing the plant and reducing its ability to produce and accumulate phytochemicals that negatively affect fruit quality [32].

CO_2

Carbon dioxide (CO_2) is a vital component of photosynthesis, the process by which *C. papaya*, like all green plants, converts light energy into chemical energy. The concentration of CO_2 in the atmosphere directly influences the rate of photosynthesis, plant growth, and ultimately the phytochemical quality of papaya fruit [20].

Elevated CO_2 levels had several beneficial effects on papaya plants. Increased CO_2 concentrations enhance photosynthetic efficiency, leading to higher biomass accumulation and faster growth rates. This increase in photosynthesis also contributes to a greater fruit yield and potentially improves fruit size and quality. Furthermore, elevated CO_2 levels can enhance the water-use efficiency of papaya plants. At higher CO_2 levels, stomata do not need to open as widely, reducing water loss through transpiration and allowing the plant to conserve water, which is particularly advantageous in drought-prone regions. Moreover, elevated CO_2 levels can influence the phytochemical composition of papaya fruits. Studies have shown that increased CO_2 can enhance the concentration of certain beneficial phytochemicals such as carotenoids, vitamin C, and phenolic compounds [33].

Nutritional and phytochemical profile of *C. papaya*

Nutritional value of papaya

Carica papaya (*C. papaya* L.) is highly regarded for its nutrient density, offering minimal calories alongside a wealth of essential minerals and vitamins. Commonly, this fruit is particularly rich in calcium, iron, potassium, fiber, niacin, thiamine, vitamin C, riboflavin, and vitamin A. Another investigation highlights that the unripe pulp is low in fat and contains high carbohydrate levels, with about 42% starch and 15% sugar [34]. Conversely, the ripe fruit contains 32 kcal, with 0.1 g of iron, 89% water content, 0.10 g of fat, 0.60 g of protein, 0.50 g of minerals, 0.80 g of fiber, along with 3 mg of niacin, 3 mg of sodium, and 0.73 mg of vitamin E, as well as 2700 µm of total carotene and 7.20 g of carbohydrates, which also includes 888 µm of β-carotene [35–37]. According to the USDA National Nutrient database, 100 g of fresh orange-hued *C. papaya* offers 39 kcal, along with 0.61 g of ash, 0.14 g of fat, 0.61 g of protein, 9.81 g of total carbohydrates, 1.80 g of fiber, and 88.80 g of water. The fruit is known for its high vitamin C content, magnesium levels, and vitamin A precursors such as β-cryptoxanthin and β-carotene [13]. Additionally, *C. papaya* seeds consist of 32.5% total carbohydrates, 24.3% proteins, and 25.3% fatty oils [12]. While the fruit is predominantly high in carbohydrates, it remains low in both fat and protein [34, 38]. The nutritional profile of the fruit can vary based on factors such as cultivation conditions, ripeness at harvest, and the specific variety [39]. As common nutrition values are like above, there are little differences between the proximity composition among papaya varieties (Table 4).

Phytochemical profile of papaya

Phenolics

Quercetin, caffeic acid, p-coumaric acid, gallic acid, and ferulic acid are phenolic compounds present in papaya, known for their potent antioxidant properties. These phenolic compounds help neutralize free radicals, thereby reducing oxidative stress and lowering the risk of chronic diseases such as cancer and cardiovascular disorders. Furthermore, their antioxidant effects contribute to supporting the immune system and minimizing inflammation [8].

Carotenoids

Carotenoids are another significant group of phytochemicals in papaya that are responsible for its vibrant orange color. Major carotenoids such as beta-carotene, lycopene,

Table 4 Proximate composition of different varieties of papaya fruit according to their maturation stage

Sample	Papaya cultivar	Carbohydrate	Protein	Lipid	Moisture	Fiber	References
Mature fruit	Kapoho	44.16%	NA	NA	NA	NA	[38, 40, 41]
	Rainbow/Hybrid-line	NA	0.743 (g/100 g)	NA	87.1 (g/100 g)	0.632 (g/100 g)	
	Maradol	NA	NA	0.34 (g/100 g)	87.46 (g/100 g)	NA	
	Local-1(Yellow fleshed)	16%	1.14%	0.5%	88.5%	1.3%	
	Local-2 (Red fleshed)	17.9%	1.14%	0.2%	88.45%	1.05%	
Green papaya	Kapoho	NA	NA	NA	0.36%	NA	[14, 42]
	Rainbow/Hybrid-line	NA	NA	NA	NA	NA	
	Maradol	NA	NA	Na	Na	NA	
	Local-1(Yellow fleshed)	14.9%	0.43%	0.2%	87.2%	1.1%	
	Local-2 (Red fleshed)	15.25%	0.41%	0.11%	88.07%	1.25%	
Ripe fruit	Kapoho	NA	NA	NA	NA	NA	[42, 43]
	Rainbow/ Hybrid-line	NA	NA	NA	NA	NA	
	Maradol	NA	NA	NA	NA	NA	
	Local-1(Yellow fleshed)	23.5%	2.012%	0.37%	94.41%	1.01%	
	Local-2 (Red fleshed)	20.3%	1.9%	0.27%	92.70%	0.9%	

and beta-cryptoxanthin provide substantial health benefits [44]. Beta-carotene, a precursor of vitamin A, promotes vision, immune function, and skin health. Lycopene, known for its potent antioxidant activity, is associated with a reduced risk of prostate cancer and cardiovascular diseases. Beta-cryptoxanthin contributes to respiratory health and enhances the overall antioxidant capacity of fruits [45, 46].

Lutein and zeaxanthin

Papaya is rich in carotenoids like lutein, zeaxanthin, and xanthophyll, which play a crucial role in maintaining eye health. These compounds accumulate in the retina, where they shield tissues from light-induced oxidative damage, helping to prevent conditions such as cataracts and age-related macular degeneration (AMD). Their protective effects on retinal cells contribute to preserving visual acuity and supporting long-term eye health [47, 48].

Glucosinolates

Glucosinolates, although present in lower concentrations than in cruciferous vegetables, still contribute to the health benefits of papaya. Compounds such as glucotropaeolin are broken down into isothiocyanates and indoles, which have been studied for their anticancer properties. These metabolites help detoxify carcinogens, inhibit cancer cell proliferation, and promote apoptosis, thus enhancing the potential of the fruit as a functional food with cancer-preventive properties [49].

Alkaloids

Papaya contains several alkaloids, including carpaines and pseudocarpaines, that have various pharmacological effects. Carpaines have demonstrated cardiovascular benefits by lowering the heart rate and blood pressure and exhibiting diuretic effects. In addition to their medicinal value, pseudocarpaines provide antimicrobial and anti-inflammatory benefits [12].

Polysaccharides

Polysaccharides in papaya such as pectin and cellulose are essential for digestive health. Pectin, a soluble fiber, regulates bowel movements and prevents constipation, whereas cellulose, an insoluble fiber, supports healthy gut flora and regularity. These polysaccharides also exert prebiotic effects that improve digestive health and enhance nutrient absorption [50, 51].

Enzymes

Enzymes present in papaya, particularly Papain, chymopapain A and B, endopeptidase papain III and IV glutamine cyclotransferase, peptidase A and B and lysozymes, have notable digestive and therapeutic properties. Papain is a proteolytic enzyme that aids in protein digestion and improves nutrient absorption. It is also used in medicine for its wound-healing and anti-inflammatory properties. Similar to papain, chymopapain is used to treat digestive disorders and reduce inflammation [6, 52].

Vitamins

Papaya is a source of essential vitamins, including E, C, A, and folate. Vitamin C (Ascorbic acid) acts as a powerful antioxidant that enhances the immune system, promotes skin health, and supports wound healing. Ascorbic acid is a water-soluble vitamin found in fruits that is needed for metabolic activities such tissue formation and hormone production. It is also an effective antioxidant that reduces oxidative stress vitamin C also works synergistically with other vitamins and is essential for rebuilding vitamin E, which increases its antioxidant properties [12]. Vitamin A, derived from beta-carotene, is vital for immune function, vision, and skin health. Folate, also known as vitamin B9, is particularly important during periods of rapid growth, such as pregnancy, as it is necessary for DNA synthesis and repair [12].

Other phytochemicals

In addition to these major groups, papaya contains other beneficial phytochemicals. Flavonoids such as kaempferol offer antioxidant and anti-inflammatory benefits. Saponins provide antimicrobial and immune-boosting effects, whereas organic acids such as malic acid and citric acid enhance flavor and have preservative properties. Terpenoids, such as alpha-pinene and limonene, have been found in papaya. These compounds have been shown to exhibit anti-inflammatory, antimicrobial, and anticancer effects [53]. Terpenoids contribute to the medicinal value of the fruit and support overall health. Steroids in papaya, such as beta-sitosterol, are known for their role in cholesterol management and their anti-inflammatory effects. Lowering low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular illnesses are two benefits of beta-sitosterol. Steroids also contribute to the anti-inflammatory properties of papayas, thereby enhancing their therapeutic potential. Anthraquinones, such as chrysophanol and emodin, have notable laxative and antimicrobial effects. These compounds promote bowel movement and may be beneficial for treating constipation. Additionally, anthraquinones possess antimicrobial properties that contribute to their ability to combat infections [54].

Pharmacology of papaya derived bioactive compounds in vitro and in vivo

The papaya (*C. papaya*) fruit is renowned for its diverse array of bioactive constituents, which have been shown to confer numerous pharmacological benefits (Fig. 4). This section explores these substances' pharmacological actions both in vitro and in vivo, focusing on their therapeutic potential under various health conditions (Table 5).

Anti-inflammatory activity

C. papaya exhibits significant anti-inflammatory properties, which are closely tied to its antioxidant activity across various parts of the fruit. Research has demonstrated that aqueous papaya seed extract reduces nitric oxide (NO) radicals in a cell-free in vitro assay. At a concentration of 150 μg/mL, the extract also inhibits the release of lysosomal enzymes and stabilizes human red blood cell (RBC) membranes [55]. Furthermore, a

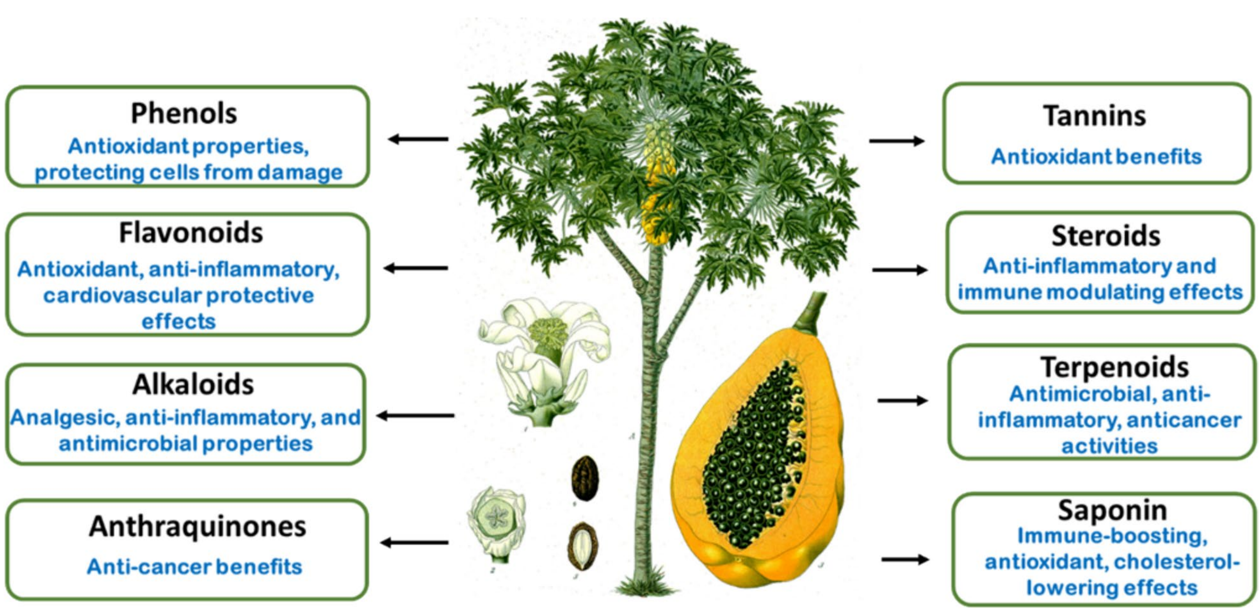

Fig. 4 Pharmacology of *Carica papaya* derived bioactive compounds

Table 5 Summary of studies related to potential medicinal properties of papaya in vitro and in vivo

Bioactivity	Bioactive Compounds	In Vitro and In Vivo Studies	How Papaya is Involved in Bioactivity	References
Antioxidant	Flavonoids (kaempferol, myricetin, quercetin), Phenolic acids (caffeic acid, ferulic acid), Rutin	Neutralizes free radicals, reduces oxidative stress	Inhibits free radicals, reduces oxidative stress, increases antioxidant enzyme activities, and enhances skin elasticity	[51, 52]
Anti-inflammatory	Tocopherols, Quercetin, Flavonoids, Phenolic acids, β-carotene, Lycopene, Benzyl isothiocyanate (BiTC), and Vitamin C	In vitro: Inhibition of lysosomal enzyme release and stabilization of red blood cell membranes. In vivo: Reduction in inflammation markers oxidative stress in rats fed a high-fat diet	Enhances AMPK activation, inhibits COX-2 expression, reduces pro-inflammatory cytokines, and upregulates antioxidant enzyme activities	[54–56, 67]
Anti-cancer	Papain, Flavonoids, Phenolic acids, Vitamin C, β-carotene, Lycopene	In vitro: Induction of apoptosis in HepG2 liver cancer cells, cytotoxic effects on A549 lung cancer cells. In vivo: Reduced tumor growth in lung cancer mouse model and chemically induced liver cancer rats	Inhibits tumor cell proliferation, induces cell cycle arrest and apoptosis, suppresses angiogenesis and metastasis	[63, 97–99]
Prostate cancer management	Papain	In vitro: Induction of cell cycle arrest and apoptosis in PC3 prostate cancer cells. In vivo: Reduced prostate tumor growth and PSA levels in xenograft mouse model	Modulates PI3K/Akt pathway, enhances ROS generation, and promotes apoptosis in cancer cells	[64]
Anti-diabetic	Flavonoids, Phenolic acids, Ethyl acetate, Hexane extract, Kaempferol, Quercetin, Caffeic acid	In vitro: Inhibition of α-glucosidase and α-amylase enzymes, antioxidant activities. In vivo: Reduced postprandial glucose levels and improved insulin sensitivity in diabetic rats	Enhances glucose uptake, inhibits carbohydrate-digesting enzymes, reduces oxidative stress, improves antioxidant defenses, and protects β-cells	[65–67]
Anti-obesity	Dietary fiber, Enzymes (Papain, Chymopapain), Antioxidants (Vitamin C, Flavonoids, Carotenoids)	In vivo: Reduced body weight gain and adipose tissue accumulation in animal models of obesity	Promotes satiety, reduces lipid accumulation, improves lipid profiles by lowering LDL and triglycerides while increasing HDL, and enhances insulin sensitivity	[62, 72–74]
Gut health	Proteolytic enzymes (Papain, Chymopapain), Dietary fiber, Flavonoids, Phenolic acids, Vitamin C	In vitro: Enhanced proliferation of beneficial gut bacteria, inhibition of pathogenic bacteria. In vivo: Improved gut barrier function and reduced gut permeability in animal models	Aids in protein digestion, promotes beneficial gut bacteria growth, reduces inflammation, strengthens gut barrier function, and enhances digestion	[92–96]
Cardiovascular health	Antioxidants (Vitamin C, Flavonoids, Carotenoids), Potassium, Papain	In vitro: Inhibition of LDL oxidation, reduction of pro-inflammatory cytokines. In vivo: Improved lipid profiles and reduced atherosclerotic lesions in animal models	Neutralizes free radicals, reduces oxidative stress and inflammation, improves lipid metabolism, enhances endothelial function, and lowers homocysteine levels	[82, 84–86]
Antibacterial and antiviral	Papain, Chymopapain, Flavonoids, Alkaloids, Vitamin C	In vitro: Inhibition of bacterial pathogens and viral replication. In vivo: Reduced bacterial load and viral load, improved survival rates in animal models	Disrupts microbial cell walls, inhibits protein synthesis and nucleic acid replication, boosts immune response, enhances pathogen defense mechanisms, and neutralizes free radicals	[90, 91]
Wound healing	Papain, Chymopapain, Flavonoids, Phenolic acids, Vitamin C, Selenium	In vitro: Antioxidant action against H_2O_2-induced oxidative stress in fibroblasts. In vivo: Enhanced wound healing with increased collagen synthesis and vascularization	Proteolytic enzymes debride necrotic tissue, promote granulation, enhance collagen deposition and epithelialization, reduce inflammation, and regulate antioxidant enzymes	[76, 79, 80]

Table 5 (continued)

Bioactivity	Bioactive Compounds	In Vitro and In Vivo Studies	How Papaya is Involved in Bioactivity	References
Anti-aging	Flavonoids, Phenolic acids, Rutin, Vitamin C, Carotenoids, Papain	In vitro: Inhibition of H_2O_2-induced endothelial cell death, reduction of MMP expression, enhancement of antioxidant defenses. In vivo: Improved skin elasticity and reduced wrinkles in human trials	Suppresses ROS, reduces skin erythema via NF-κB and AP-1 signaling, protects skin cells from oxidative stress, increases collagen synthesis, and enhances skin health	[51, 75]

fermented papaya preparation (FPP) has been shown to inhibit Akt and p38 phosphorylation induced by H_2O_2, downregulating the MAPK pathway, which suggests a mechanistic basis for its anti-inflammatory effects [56]. Fermentation improves papaya's anti-inflammatory and anti-diabetic qualities by changing its chemical composition, making the beneficial chemicals more accessible and effective. Fermentation uses microbial activity to break down complex chemicals into smaller ones, allowing for better absorption and more effective interaction with cellular anti-inflammatory mechanisms. This mechanism boosts the concentration of small-molecule antioxidants and other substances that can neutralize reactive oxygen species (ROS), which are major causes of inflammation and cell death. Furthermore, fermentation appears to improve papaya's modulation of important signaling pathways involved in inflammation, such as the MAPK pathways (ERK, Akt, and p38), which control cellular responses to oxidative stress and inflammatory stimuli. Fermented papaya preparation (FPP) inhibits pro-inflammatory pathways more efficiently than unfermented papaya by decreasing protein phosphorylation [57].

Papaya fruit aqueous extracts have also been found to lower the production of reactive oxygen species (ROS) and reduce the secretion of pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) at a dosage of 2 mg/mL. In addition, they enhance the activity of antioxidant enzymes, which contributes to their protective effects against inflammation [58]. These antioxidant properties are key in mitigating oxidative stress, a critical factor in the inflammatory response [59].

In vivo studies further support the anti-inflammatory potential of papaya. For example, papaya juice has demonstrated anti-obesity effects in rats fed a high-fat diet by reducing inflammation and oxidative stress. This was achieved through the upregulation of superoxide dismutase (SOD) levels and a reduction in lipid peroxidation, ROS generation, PPAR-γ expression, and serum malondialdehyde (MDA) [56]. Additionally, the methanolic extract of *C. papaya* showed possible anti-inflammatory effects in Wistar albino rats exposed to egg albumin-induced inflammation. Similarly, the aqueous extract of papaya seeds significantly reduces inflammation in rats with formalin- and carrageenan-induced pedal edema [56].

The anti-inflammatory effects of papaya are further supported by its rich content of antioxidants. Papaya fruit extracts are high in flavonoids and phenolic compounds that act as free radical scavengers and metal ion chelators, helping to neutralize oxidative stress [60]. Phytochemicals such as tocopherols and quercetin activate AMP-activated protein kinases (AMPK) while inhibiting COX-2 expression, which also contributes to anti-inflammatory effects [39]. Papaya fruits, including both the pulp and seeds, contain additional anti-inflammatory compounds like vitamin C, lycopene, β-carotene, and benzyl isothiocyanate (BiTC). These compounds work synergistically to suppress pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1. Additionally, the polyphenols in *C. papaya* further enhance its antioxidant capacity, increasing antioxidant enzyme activity and supporting its anti-inflammatory and overall health-promoting properties [61].

Anticancer activity

It is estimated that one in three people will have cancer at some point in their lives, making it a global public health concern that can impact anybody [62]. Globally, there are about 32.50 million documented instances of cancer [63]. By binding to the chemicals that cause colon cancer and keeping healthy colon cells away from them, fibers from *C. papaya* have been found by Yogiraj et al. [36] to have the potential to prevent colon cancer. Together, these fibers shield the DNA of colon cells from harm caused by free radicals. Men who consumed lycopene-rich fruits and vegetables, such *C. papaya*, were 82% less likely to develop prostate cancer than men who consumed foods low in lycopene [37].

Nguyen et al. [62] investigated the antiproliferative properties from pure lycopene on human liver cancer cells and breast cancer cell lines, together with lycopene extracted from papaya and watermelon juices. Lycopene has been shown to influence cell cycle regulation and apoptosis. In cancer cells, lycopene can arrest the cell cycle, particularly in the G1 phase, by downregulating cyclins and cyclin-dependent kinases (CDKs) that are critical for cell cycle progression. This arrest prevents the cells from entering the S phase, where DNA replication occurs, thereby halting cancer cell proliferation. Lycopene also upregulates pro-apoptotic proteins (such as Bax) and downregulates anti-apoptotic proteins (such as Bcl-2), leading to the release of cytochrome c from mitochondria and the activation of caspases, which are proteases that drive the apoptosis process [64]. Papaya juice and pure lycopene had IC_{50} values of 20 mg/mL and 22.8 μg/mL, respectively, and both increased cell death in the Hep G2 liver cancer cell line. However, neither pure lycopene nor papaya juice affected the lifespan of MDA-MB-21 breast cancer cells. The growth of either cell line was unaffected by the papaya juice's derived lycopene. The extracted lycopene's lack of effectiveness has been attributed to a variety of causes, including a faulty extraction method, lycopene's sensitivity to light and oxidation, and microbial contamination after treatment [65].

While papaya contains glucosinolates and benzyl isothiocyanate (BiTC), which are well-documented for their

Table 6 In vitro anti-cancer activity of papaya fruit

Type of cancer cell line	Papaya sample	Experiment	Results	References
Acute promyelotic leukemia HL-60 cells	Papaya seed or pulp	Papaya seed or pulp n-hexane extract (0.1–100 μg/mL), pure benzyl isothiocyanate (10 μM)	Seed extract: Similar to pure benzyl isothiocyanate, its dose-dependently suppressed the production of superoxide (IC50 = 10 μg/mL) and cell viability (IC50 = 20 μg/mL). At 100 μg/mL, pulp extract showed no impact	[66]
(MDA-MB-231) Breast cancer, (Hep G2) Liver cancer cell line, (normal cell) Chang liver cell line	Papaya fruit juice	Lycopene derived from papaya juice, pure lycopene (3–30 μg/mL), and papaya fruit juice (0.28–28 mg/mL)	Hep G2 liver cancer cell line viability was decreased by pure lycopene and papaya juice (IC50 = 22.8 μg/mL and 20 mg/mL, respectively), however neither breast cancer cells nor normal cells were affected. There was no effect of papaya juice lycopene on either cell line	[65]
Breast cancer cell line (MCF-7)	Papaya flesh	Papaya flesh aqueous extract (0.01–4% v/v)	MCF-7 cell growth is significantly inhibited ($p < 0.05$)	[68, 69]
Breast cancer cell line (MCF-7) treated with sodium nitroprusside	Papaya pericarp	Papaya pericarp ethanolic extract (50–640 μg/mL)	Reduced MCF-7 cell viability by inhibiting cell proliferation. Nitric oxide in a dose-dependent manner (at 640 μg/mL, the extract scavenged ~ 35% of the nitric oxide)	[37, 67, 70]

anticancer properties, a study conducted by Nakamura et al. in 2007 performed a single in vitro investigation comparing n-hexane extracts from papaya seeds and pulp with pure BiTC to evaluate their ability to induce apoptosis and inhibit superoxide production. The results showed that the papaya seed extract effectively reduced superoxide production and decreased cell viability in acute promyelotic leukemia HL-60 cells, achieving results comparable to BiTC (with IC_{50} values of 10 μg/mL for superoxide formation and 20 μg/mL for cell viability). In contrast, the papaya pulp extract did not exhibit similar effects, with an IC_{50} of 100 μg/mL. These findings suggest that the anticancer effects of papaya seed extract may be associated with its content of electrophilic compounds, such as benzyl isothiocyanate [66]. The apoptosis-inducing effects of papaya seed extract are likely attributed to its content of electrophilic compounds like BiTC, which activate apoptotic pathways in cancer cells. These compounds can trigger mitochondrial dysfunction and activate caspase-mediated cell death, thereby promoting apoptosis [66]. In prostate cancer, papaya has been reported to enhance reactive oxygen species (ROS) generation and activate apoptosis through the PI3K/Akt signaling cascade, further supporting its role in promoting cancer cell death [67]. The anticancer effects of papaya are thus strongly linked to its ability to induce apoptosis through both oxidative stress and the modulation of critical apoptotic signaling pathway.

Two experiments investigated the effects of papaya flesh extracts on the viability of the breast cancer cell line MCF-7, alongside extracts from other fruits [68, 69]. The researchers focused on the role of antioxidants in fruits, such as β-carotene, polyphenols, and flavonoids, in inhibiting cell proliferation. Garcia-Solis et al. found that papaya significantly suppressed the proliferation of breast cancer cells [70]. Additionally, Rumiyati et al. reported cytotoxicity with an IC_{50} of 2.8 mg/mL when applying a protein fraction containing ribosome-inactivating proteins isolated from *C. papaya* to the T47D breast cancer cell line [67]. The authors utilized immunocytochemistry to demonstrate that apoptosis is triggered via the mitochondrial pathway. In the treated cells, the expression of the p53 tumor suppressor gene increased by approximately 59.4%, while the expression of the anti-apoptotic protein Bcl-2 decreased by about 63% compared to the controls [67] (Table 6). In addition, *Carica papaya* has demonstrated promising anticancer and chemopreventive activities in a variety of in vitro and in vivo investigations. Its extracts, particularly the fermented papaya preparation (FPP) and aqueous fruit and leaf extracts, have substantial antiproliferative effects on human breast cancer (MCF-7) cells, possibly through the activation of apoptotic pathways and the reduction of tumor growth. Phytochemicals such as flavonoids in papaya function as free radical scavengers, minimize oxidative damage, and chelate ROS-generating substances, lowering cancer incidence in animal models. For example, FPP inhibited DNA fragmentation and enhanced antioxidant enzymes like GPx, SOD, and CAT, while also considerably increasing glutathione and decreasing MDA and ROS levels [56]. These findings suggest that papaya extract induces apoptosis through the mitochondrial pathway by increasing p53 expression and decreasing Bcl-2 levels, which in turn activates pro-apoptotic signals and triggers cell death [69, 70].

Antidiabetic activity

Diabetes is a chronic condition primarily caused by insulin resistance or insufficient insulin production, resulting in hyperglycemia or increased blood glucose levels. Uncontrolled diabetes can lead to a number of microvascular and macrovascular problems that can seriously impair a patient's quality of life [71].

In streptozotocin-induced diabetic rats, the ethyl acetate extract of *C. papaya* effectively reduced postprandial glucose levels, showcasing its ability to modulate carbohydrate metabolism. In vitro, this extract, along with a hexane extract, was shown to inhibit key digestive enzymes, α-glucosidase and α-amylase, which play pivotal roles in the breakdown and absorption of carbohydrates. The hexane extract exhibited slightly higher potency than the ethyl acetate extract in this regard, indicating that the inhibition of these enzymes may be a key mechanism by which papaya helps regulate blood sugar levels. By inhibiting these enzymes, papaya reduces the rate at which carbohydrates are converted into glucose, thus preventing post-meal blood sugar spikes and supporting overall blood glucose control [72].

Fermented papaya preparations (FPP) have beneficial effects in addressing diabetic complications. The fermentation process most likely causes particular biochemical changes in the papaya extract, such as reducing complicated compounds to simpler, more accessible ones. This includes the increase of antioxidant molecules and the activation of proteolytic enzymes such as papain, which help FPP resist oxidative stress. Fermentation can also alter the makeup of bioactive molecules, resulting in enhanced production of antioxidants and chemicals that aid in glucose metabolism and immunological response. These changes help to improve platelet function and minimize oxidative stress, which is essential for managing diabetes and preventing complications [73].

FPP prevent the formation of atherosclerotic plaques, increase SOD levels, and reduce lipid peroxidation at a 50 μg/mL concentration. Additionally, FPP enhanced platelet membrane fluidity and prevented platelet malfunction caused by chronic hyperglycemia [74]. Somanah and colleagues investigated the effect of short-term supplementation with fermented papaya preparation (FPP) on biomarkers of diabetes. The randomized controlled experiment found that consuming 6 g of FPP daily for 14 weeks increased the individuals' antioxidant level and improved the overall health of many organs that were possibly at risk of diabetes impairment [56]. In addition, FPP enhances antioxidant enzyme levels, such as superoxide dismutase (SOD), which reduces oxidative stress—a key factor in diabetes-related vascular damage. Studies also report improvements in liver insulin sensitivity, as indicated by decreased levels of liver enzymes (ALT and AST), as well as better blood glucose control in individuals with diabetes. These findings suggest that FPP may contribute to the regulation of glucose levels while also mitigating complications related to diabetes [74].

Unripe papaya, a common remedy in traditional medicine for managing diabetes, has been found to exert protective effects on pancreatic β-cells, which are critical for insulin production. In diabetic rats, papaya fruit extract has shielded these cells from oxidative damage, supporting β-cell function and insulin secretion. The presence of bioactive phytochemicals in papaya, such as caffeic acid, quercetin, and kaempferol, plays a key role in enhancing the body's antioxidant defenses and protecting β-cells from the damaging effects of hyperglycemia. By improving β-cell function, papaya fruit extract helps to preserve the body's ability to regulate blood glucose levels effectively [56, 75].

Additionally, papaya seeds contain bioactive compounds with anti-diabetic properties. Grind dried papaya seeds to a coarse powder using a household mixer grinder. To extract the dry seed powder, boil it in water. The extract was filtered using Whatman filter paper and dried at 40˚C. The extract was provided orally to streptozocin-induced type II diabetic rats. The aqueous extract of papaya seeds at doses of 100 mg/kg and 200 mg/kg significantly reduced blood glucose levels, improved lipid profiles, and decreased liver enzymes associated with liver damage in diabetic rats. Furthermore, papaya seed extracts exhibited strong inhibition of α-amylase, with an IC_{50} value of 46.99 ± 0.018 g/mL, indicating that these extracts may help control blood glucose by limiting carbohydrate digestion. These findings suggest that papaya seeds may also be effective in the management of diabetes, contributing to improved glucose control and lipid metabolism [56, 76].

Anti-obesity activity

C. papaya fruit has shown significant potential in managing obesity owing to its rich composition of bioactive compounds, including fibers, enzymes, and antioxidants. These compounds contribute to various mechanisms that aid in weight management and overall metabolic health.

The papaya fruit contains enzymes and fibers that play crucial roles in lipid metabolism. These components help reduce lipid accumulation in the body by promoting the breakdown and utilization of fat [77]. Papaya fruit extract can lower the levels of triglycerides, total cholesterol, and LDL cholesterol, while accelerating high-density lipoprotein (HDL) cholesterol. A balanced lipid profile is essential for preventing obesity-related complications and maintaining metabolic health [68].

The dietary fiber in papaya fruit contributes to a feeling of fullness and satiety, which can help reduce overall calorie intake. Fiber slows digestion and prolongs the feeling of fullness, thereby decreasing the likelihood of overeating. Thus, regular consumption of papaya can aid in appetite control and support weight loss [78]. Due to its low glycemic index, papaya is a good option for people controlling their weight. Fiber content in papaya helps to control the blood sugar level by delaying the glucose absorption and preventing the pike of blood sugar level [79]. Some studies suggest that the nutrients in papaya may help improve insulin sensitivity and reduce the risk of developing type II diabetes and obesity. By maintaining stable blood sugar levels and supporting metabolic health, papaya can play a valuable role in diabetes and obesity prevention strategies [79]. Papaya, particularly its pulp and seeds, has shown promise in regulating blood glucose levels and metabolic health. Methanolic extracts of papaya, particularly from green papaya pulp, improve glucose absorption in liver and muscle cells, implying a function in blood glucose control. Papaya includes polyphenolic chemicals, flavonoids, and antioxidants that contribute to its anti-diabetes and anti-obesity properties. Papaya's effect on glucose transporters (GLUT-2 and GLUT-4) promotes glucose homeostasis, and its capacity to prevent triglyceride accumulation in liver cells adds to its metabolic benefits [80].

It is often associated with chronic inflammation and oxidative stress, which can exacerbate metabolic disorders. The bioactive compounds in papaya, such as flavonoids, carotenoids, and vitamin C, help in reducing inflammation in adipose tissues, which is essential for avoiding insulin resistance and other metabolic problems linked to obesity. These compounds modulate key inflammatory pathways, such as inhibiting pro-inflammatory cytokines and reducing the activation of inflammatory enzymes like COX-2. By reducing inflammation and improving insulin sensitivity, papaya can play a significant role in managing obesity-related metabolic dysfunction [81].

Papaya fruit improves insulin sensitivity, which is beneficial for the management of diabetes and obesity.

Improved insulin sensitivity improves glucose use, lowers blood sugar levels, and prevents excess fat storage. Papaya extract enhances glucose uptake by cells and inhibits the enzymes involved in carbohydrate digestion, which lowers blood sugar levels after meals [82].

Anti-skin aging activity

Skin aging is characterized by the degradation of the extracellular matrix (ECM), leading to dryness, thinning, uneven pigmentation, and wrinkling. This process is driven by intrinsic aging factors, which are inevitable, and extrinsic aging factors, which can be avoided. Both these factors can act synergistically, leading to premature skin aging. ROS play a critical role in skin aging by inducing oxidative stress and inflammation. Over the past few decades, researchers have focused on strategies to combat skin aging, with *C. papaya* emerging as a potential candidate due to its ability to modulate inflammatory pathways and support collagen synthesis. The bioactive compounds in papaya, such as flavonoids and phenolic acids, help reduce oxidative stress, inhibit inflammatory cytokines, and enhance skin elasticity, thus potentially mitigating the signs of aging [83].

Jarisarapurin et al. conducted an in vitro investigation to examine the effect of unripe *C. papaya* fruit extract on endothelial oxidative stress associated with skin aging. According to this study, active endothelial cells produce oxidative stress and a low-grade inflammatory state, which in turn creates an unfavorable microenvironment that causes dermal fibroblasts to express MMP-1. As a result, type I collagen is significantly lost and ECM breakdown is expedited [56]. At doses ranging from 100 μg/mL to 1000 μg/mL, immature *C. papaya* fruit extract effectively reduced hydrogen peroxide (H_2O_2)-induced endothelial cell death. This protective action is achieved by modulating intracellular stress and enhancing the antioxidant defenses of endothelial cells. Specifically, the extract inhibited nuclear factor kappa B (NF-κB) activity, increased superoxide dismutase (SOD) and catalase (CAT) activities, and reduced H_2O_2-induced overactivation of Nrf2. The extract also demonstrated a dose-dependent ability to scavenge reactive oxygen species (ROS). The uncoupling of the Nrf2/Keap1 complex and the subsequent early translocation of Nrf2 into the nucleus are critical for the activation of the body's antioxidant defense mechanisms. Excessive activation of Nrf2 caused by oxidative stress can lead to the depletion of endogenous antioxidants, accelerating skin aging. Therefore, the ability of unripe *C. papaya* to regulate the NF-κB and Nrf2 pathways helps maintain redox balance and may contribute to preventing premature skin aging [56]. Bertuccelli and colleagues found that taking a sublingual FPP 4.5 g sachet twice daily reduced skin aging biomarkers. While both treatments reduced skin MDA levels, FPP shown more anti-aging efficacy than antioxidant mixtures. Furthermore, FPP increased SOD, NO, and aquaporin-3 (AQP-3), while decreasing the expression of pro-aging cyclophilin-A (CyPA) and CD147 genes. The study suggested that the moderating effects of FPP on AQP-3 and pro-aging variables were critical for considerable improvement in skin health [56].

The potential use of *C. papaya* in cosmetic formulations was demonstrated by Saini et al., who created a perfect *C. papaya* fruit cream using oil and water. This cream possessed a smooth, shiny texture and was steady and homogeneous. This study further confirmed that the anti-aging effects of *C. papaya* fruit are primarily due to its ROS suppression capabilities. The 5% cream formulation was particularly effective in reducing H_2O_2-induced oxidative stress, highlighting its potential as a potent anti-aging product [56].

Collectively, these studies underscore the significant anti-aging potential of *C. papaya* fruit. Its ability to inhibit oxidative stress, modulate key signaling pathways such as NF-κB and Nrf2, and enhance antioxidant defenses highlights its value as a natural ingredient in anti-aging skincare products. By reducing inflammation and promoting collagen preservation, *C. papaya* extract can help mitigate the effects of intrinsic and extrinsic skin aging. Further research, particularly clinical trials, is essential to fully understand and confirm the therapeutic benefits of *C. papaya* extract in the management of skin aging and its potential integration into skincare regimens [83]

Wound healing activity

Oxidative stress is required for wound healing, and *C. papaya* fruits have demonstrated significant potential in this regard. *C. papaya* seeds prevent human skin fibroblasts from oxidative stress-induced apoptosis. An in-depth mechanistic study revealed that papaya extract combats H_2O_2-induced oxidative stress in fibroblasts through radical scavenging, reducing calcium ion influx into the cytoplasm, restoring mitochondrial dysfunction induced by oxidative stress, and preserving the oxidative equilibrium in cells. These actions collectively contribute to enhanced cellular survival and improved wound healing, highlighting C. papaya's therapeutic potential in tissue repair and regeneration [84].

Mikhal et al. emphasized the antioxidant and anti-inflammatory effects of fermented papaya preparation (FPP). The study demonstrated that FPP effectively inhibited superoxide and hydroxyl radicals, as well as total reactive oxygen species (ROS) in the bloodstream. Additionally, it reduced myeloperoxidase (MPO) activity and radical formation at wound sites in vivo. Topical application of papaya fruit extract (5 mg/mL) enhanced wound healing by regulating inflammation, arginine metabolism, and the levels of antioxidant enzymes. The mechanism behind this action was further validated with the inclusion of selenium (Se) in the treatment regimen, which significantly expedited the wound healing process [41]. FPP's ability to regulate inflammation and promote antioxidant defenses, such as increasing catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) levels, was instrumental in accelerating the wound healing process. These findings underscore the therapeutic potential of *C. papaya* in wound healing through its modulation of oxidative stress and inflammation pathways, rather than simply focusing on its antioxidant activity [41].

In an excision wound model, the application of *C. papaya* fruit extract diminished inflammation associated with oxidative damage by enhancing antioxidant enzyme activity, modulating arginine metabolism, and inhibiting cyclooxygenase. This extract contributed to reduced inflammation, augmented collagen synthesis, and improved vascularization at the wound site. Throughout the healing process, the angiogenic factor vascular endothelial growth factor A (VEGFA) remained consistently elevated, while transforming growth factor-beta (TGF-β), a cytokine that aids in fibroblast recruitment, showed increased levels during the inflammatory phase but decreased during the repair phase. Moreover, selenium supplementation in conjunction with the papaya fruit extract directly facilitated increases in TGF-β and VEGFA levels, significantly accelerating the wound healing process [85, 86].

Oral supplementation of FPP at a dose of 0.2 g/kg body weight for eight weeks improve diabetic wound closure by enhancing macrophage respiratory-burst function and induce the production of nitric oxide synthase (iNOS) [87]. Dickerson and colleagues investigated the diabetic wound healing efficacy of FPP in patients with type II diabetes mellitus. The participants received oral FPP (9 g/day for 6 weeks) and discovered that NADPH and cellular ATP levels increased in human monocytic THP-1 cells treated with FPP. Furthermore, FPP increased oxygen utilization and mitochondrial membrane potential in monocytic cells, demonstrating its ability to rectify respiratory burst function and improve diabetics' defense systems against infections. FPP elevated the mRNA expression of Rac2, which was needed for NOX activation and eventually enhanced the respiratory burst in macrophages [56]. Cysteine endopeptidases such as papain and chymopapain shown wound healing activity, which can be related to their proteolytic wound debridement and antibacterial properties. An in vivo investigation utilizing a wound cleaner based on papain confirmed this. The cleanser contains 5 g of papain and α-tocopherol. The results indicated superior collagen deposition and less fluid exudates than betadine cleaner, leading to eschar reduction and faster epithelialization. *Carica papaya* leaf extracts and dressings are less likely to cause harm because they have long been used to heal wounds and certain skin diseases. Several studies have further assured its safety for use. In addition, papaya dressing proved safe to use and suitable in hydrogel composition [56]. Diabetes-related wounds are difficult to heal because of their susceptibility to many types of infections and compromised nitric oxide (NO) levels at the wound site. FPP alters these circumstances, improves the antibacterial effects of macrophages, and restores respiratory burst function [85, 86].

Dickerson et al. examined the effect of FPP on the wound healing ability of patients with type II diabetes. For six weeks, the participants took nine grams of FPP orally, which raised the levels of cellular ATP and NADPH in human monocytic THP-1 cells. Additionally, FPP enhanced respiratory burst function and defensive mechanisms against infections in patients with diabetes by improving oxygen utilization and the potential of the mitochondrial membrane in monocytic cells. FPP increased Rac2 mRNA expression, which is necessary for the activation of NOX and improving the macrophage respiratory burst [88, 89].

Cardiovascular health

C. papaya fruit has shown considerable potential for promoting cardiovascular health because of its rich composition of bioactive compounds, including antioxidants, vitamins, and phytochemicals. These compounds contribute to various mechanisms that protect the cardiovascular system and improve cardiac health [90].

Papaya fruit is abundant in antioxidants, such as vitamin C, flavonoids, and carotenoids, and plays a crucial role in neutralizing free radicals. LDL cholesterol oxidation is a major contributor to the development of atherosclerosis, and antioxidants help prevent it. They also reduced oxidative stress. In vitro studies have demonstrated that papaya fruit extracts effectively inhibit LDL oxidation, thereby reducing the risk of plaque formation in arteries [91].

Chronic inflammation is a significant contributor to cardiovascular disease. The anti-inflammatory properties of papaya, attributed to its high flavonoid and phenolic acid content, help mitigate this risk. These compounds diminish inflammation in the vascular system and stop the synthesis of pro-inflammatory cytokines, which can prevent the worsening of atherosclerosis and other cardiovascular diseases [92].

Regular consumption of papaya has been linked to better lipid profiles. In vivo studies indicate that

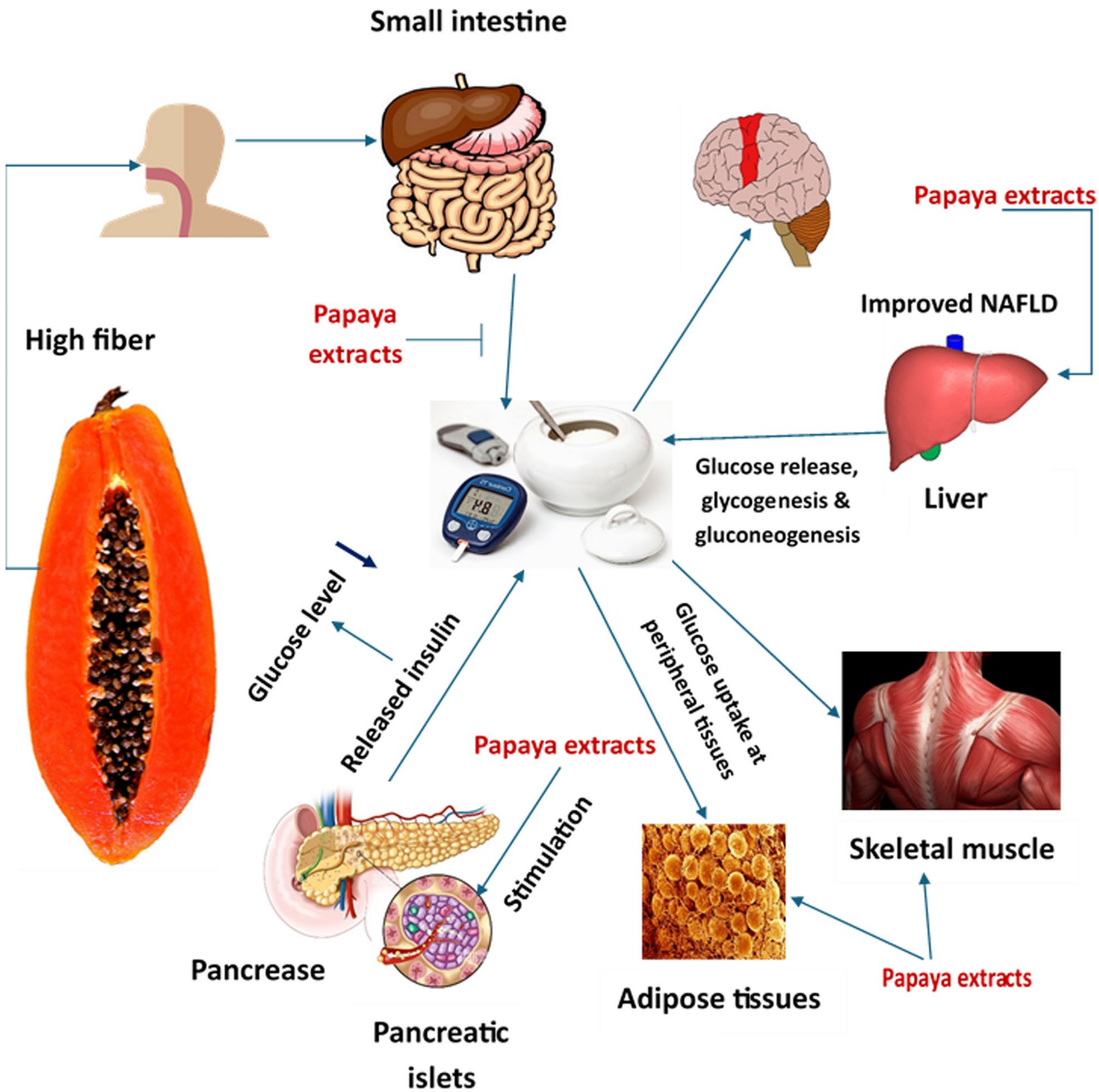

Fig. 5 Anti-diabetic activity of phytochemicals derived from *Carica papaya*

supplementation with papaya fruit extract can raise HDL cholesterol levels while reducing triglycerides, total cholesterol, and LDL cholesterol. Maintaining a balanced lipid profile is crucial for cardiovascular health and reducing the risk of heart disease [69, 93].

The bioactive compounds in papaya, such as papain, have been shown to possess antithrombotic properties. These compounds help prevent blood clot formation by inhibiting platelet aggregation and enhancing fibrinolytic activity. This reduces the risk of thromboembolic events such as heart attack and stroke [94, 95].

Antibacterial and antiviral activity

Multiple studies have highlighted the antibacterial properties of papaya. In vitro experiments have shown that papaya water extract can inhibit the growth of several bacterial pathogens, such as *Escherichia coli, Staphylococcus aureus,* and *Salmonella typhi* [96, 97]. Papaya achieves its antibacterial effects by disrupting bacterial cell walls, blocking protein synthesis, and interfering with nucleic acid replication. The flavonoids and phenolic compounds present in papaya fruits further enhance these effects by disrupting microbial cell membranes and promoting cell lysis.

Papaya leaf, pulp and seed water extracts are effective against several viruses, including dengue, influenza, and herpes simplex viruses. The antiviral mechanisms involve inhibition of viral entry into host cells, disruption of viral replication, and enhancement of the host immune response [98]. For example, papaya has been shown to inhibit the replication of dengue virus by interfering with viral RNA synthesis. Additionally, the high vitamin C content in papaya boosts the immune system, helping the body fight viral infections more effectively. Bioactive compounds in papaya, such as papain and chymopapain, also contribute to its antimicrobial properties. These proteolytic enzymes break down proteins in the pathogens, rendering them inactive. Furthermore, papain has been found to enhances the effectiveness of other antimicrobial agents, suggesting a potential synergistic effect when used in combination with conventional treatments [59, 99].

Impact on gut health

The papaya fruit has a notable impact on gut health because of its rich composition of dietary fiber, enzymes, and bioactive compounds. These components collectively contribute to promoting a healthy digestive system, improving the gut flora balance, and enhancing overall gastrointestinal function [100].

Papaya is renowned for its abundant proteolytic enzymes, particularly papain and chymopapain. These enzymes facilitate the digestion of proteins by breaking them down into smaller peptides and amino acids, which enhances their absorption [101]. This enzymatic activity can alleviate common digestive problems, such as bloating, constipation, and indigestion. Regularly consuming papaya can improve overall digestive function and comfort (Fig. 5).

Additionally, papaya is a rich source of dietary fiber, which is crucial for promoting gut health. Fiber increases stool bulk, promoting regular bowel movements and preventing constipation. It also serves as a prebiotic, encouraging the growth of beneficial gut bacteria, such as *Lactobacillus* and *Bifidobacterium*. Maintaining a balanced gut microbiota is essential for optimal digestive processes and immune function [102].

The fibers and diverse compounds present in papaya function as prebiotics, supplying nourishment that supports the proliferation of beneficial gut bacteria. Research indicates that fermented papaya fruit extracts not only stimulate the growth of these advantageous bacteria but also inhibit the proliferation of harmful strains. This equilibrium fosters a healthy gut microbiome, which is critical for efficient digestion, nutrient absorption, and enhancing the immune system. Furthermore, a well-balanced gut microbiome is vital for preventing gastrointestinal disorders and improving overall health. By incorporating papaya into one's diet, individuals can promote gut health and enhance their overall well-being [103].

Papaya is also abundant in anti-inflammatory agents, including flavonoids and phenolic acids, which effectively reduce inflammation in the gastrointestinal tract. Chronic inflammation in this area can result in various digestive disorders, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) [102]. By alleviating inflammation, papaya contributes to the maintenance of a healthy gut lining, thereby lowering the risk of these conditions. Moreover, its antioxidants, such as vitamins C and E and beta-carotene, play a significant role in shielding the gut lining from oxidative stress. Oxidative stress can damage cells within the gastrointestinal tract, potentially leading to issues like gastritis and peptic ulcers. The antioxidant properties of papaya help neutralize free radicals, thereby promoting gut health and overall wellness [103].

Papaya supports gut barrier function, a vital factor in preventing harmful bacteria and toxins from crossing into the bloodstream, thereby reducing the risk of systemic inflammation and infections. Papain extract from papaya latex enhances intestinal barrier integrity by modulating tight junction proteins and decreasing gut permeability [104]. Additionally, papaya's enzymes and fiber content aid in regulating gut motility, promoting smooth food movement through the digestive tract to help prevent constipation and diarrhea. The soluble fiber in papaya also slows down digestion and absorption, facilitating a gradual release of glucose into the bloodstream, which aids in blood sugar management [101].

Abbreviations

AMD	Age related macular degeneration
ROS	Reactive oxygen species
AP1	Activating protein 1
MMP	Matrix metalloprotein
RBC	Red blood cells
NFkB	Nuclear factor kappa B
FPP	Fermented papaya preparation
IL-6	Interleukin 6
MAPK	Mitogen activated protein kinase
MDA	Serum malondialdehyde
AMPK	Activated protein kinase
BiTC	Benzyl isothocyanate
MCP-1	Monocytenchemorreactant protein-1
SOD	Superoxide dismutase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
LDL	Low density lipoprotein
HDL	High density lipoprotein

ECM Extracellular matrix
MPO Myeloperoxidase
CAT Catalase
GPx Glutathione peroxidase
VEGFA Vascular endothelial growth factor A
TGF-β Transforming growth factor-Beta
iNOS Nitric oxide synthase
IBD Inflammatory bowel disease

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Author contributions
Conceptualization: SCK and DSL; methodology, KHS and JHK; investigation, KHS, KCK and RMTDP; writing—original draft preparation, KHS and JHK; writing—review and editing, JHK and SLK; supervision, DSL; project administration, SCK. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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