

Papaya (*Carica papaya* L., Pawpaw)

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INTRODUCTION

Botany

Carica papaya L. is an herbaceous laticiferous tree-like plant that grows to about 10 m in height. It is native to tropical and eastern Central America where seeds that remain viable for a long time in a dried state are transported to different parts of the world. *C. papaya* belongs to the family Caricaceae and is grown in most tropical countries of the world as a food crop (OECD, 2005). It is known by different names in different parts of the world: pawpaw in the UK and Sri Lanka, tepaya in East Malaysia, lechosa in Venezuela, papali in India, and ibepe in the southwest of Nigeria (West Africa). The ripe fruit is the part most commonly consumed. However, the unripe fruit is popular because it produces large amounts of latex, which is rich in enzymes known to be used in a range of applications: industrial, nutritional, and therapeutical (Azarkan et al., 2003). An increasing number of varieties of *C. papaya* are being cultivated throughout the world. Reproductively, the plants are naturally dioecious (having male and female organs on separate plants); however, monoecious (true hermaphrodite) plants are thought to have been cultivated as a result of adaptation after being introduced to different regions of the world. Therefore, some species of *C. papaya* have evolved to become gynodioecious (female organ on some plants and hermaphrodite organs on others) and andromonoecious (male organ and hermaphrodite organs on the same plant). Different cultivars exhibit diverse reproductive morphology (Niklas and Marler, 2007). Many *C. papaya* cultivars grown from several varieties abound in different regions of the world (e.g., the Solo type is the oldest variety and has given rise to “Kapoho Solo,” “Dwarf Solo,” and “Waimanalo”). *C. papaya* cultivars are innumerable and scientists are continuously exploring conventional and modern/advanced plant-breeding techniques—selective, cytogenetical, and biotechnological—to develop new cultivars with desirable fruit characteristics, disease resistance, and increased yield of such other products as *C. papaya* cysteine proteinases and some secondary metabolites, which can be classified as nonvitamin nonmineral (NVNM) nutritional supplements of *C. papaya*. Cultivars like “Kapoho Solo,” which was cultivated in Hawaii, is known for its pear shape, greenish-yellow skin, and sweet taste, while “Sunrise Solo,” cultivated in both Brazil and Hawaii, is known for its orange-red attractive flesh color, precocious low-fruited habit, high sugar content, and desirable flavor. “Pusa Majesty,” which was developed from Pusa-type varieties, is gynodioecious with a medium-sized (1–1.5 kg) fruit. It is known for its high tolerance to viral diseases and root knot nematodes. The CO5 cultivar, which was cultivated in India and developed from Coimbatore-type varieties, has been selected/bred for its high papain production. It consistently produces 14–15 g dry papain per fruit. Studies have developed/documentated *C. papaya* varieties and cultivars in different countries to preserve selected characteristics and more still are being developed in different parts of the world as part of modern agricultural programs seeking improved yield of food and cash crops (Singh and Sudhakar Rao, 2011) (Table 3.32.1).

Origin and Global Distribution of *Carica papaya*

The exact place of origin of *C. papaya* is not known, but the literature reports the presence of *C. papaya* seeds in Panama and the Dominican Republic before 1525. It is believed that cultivation of *C. papaya* spread from here to southern Mexico, Central America, the West Indies, the Bahamas, and Bermuda in 1616 (Morton, 1987). The Spanish are said to have brought seeds of *C. papaya* around 1550 to the Philippines and Malacca, from where the plant reached India and the Kingdom of Naples in 1626. The plant was introduced later in all tropical and subtropical regions of the world (Australia, Hawaii, Sri Lanka, and South Africa) as a plantation crop. In the 1950s, *C. papaya* was brought to Miami and New York from Santa Marta (Colombia),

TABLE 3.32.1 *Carica papaya* Cultivars, Varieties and Country of Origin

Varieties	Cultivars	Countries	Characteristics	References
Solo	Sunrise solo	Brazil, Hawaii	Pear-shaped fruit with a slight neck. Averages 22–26 ounces depending on location. Skin smooth, flesh firm, reddish-orange, sweet, sugar content high. Quality similar to Solo. Seed cavity not as deeply indented as other Solo strains, making seed removal easier. Plant precocious, maturing fruit about 9 months after transplanting, at a height of about 3 feet attractive flavor, taste, sweet, soft, and red pulp	Fabi et al. (2007, 2014), De los Santos de la et al. (2000) and FAO (2003)
	Kapoho solo	Hawaii	Pear-shape, greenish-yellow skin, sweet taste yellow-orange flesh	Wall (2006)
	Frangi or Paiola	Malaysia	Small size, bright yellow skin, sweet taste, pleasant aroma	Oga et al. (2013)
	Dwarf Solo/ Sunset	Hawaii	Solo type. Small to medium-sized, pear-shaped fruit. Orange-red skin and flesh. Very sweet. Dwarf, high yielding plant	De los Santos de la et al. (2000), FAO (2003) and Morton (1987)
	Waimanalo	Hawaii	Fruit round with a short neck, average weight 16–39 ounces. Skin smooth, and glossy, cavity star-shaped. Flesh thick, firm, orange-yellow in colour, flavor and quality high, keeps well. Recommended for fresh market and processing. Fruits of female plants rough in appearance. Average height to the first flower is 32 in.	De los Santos de la et al. (2000), FAO (2003) and Samson (1986)
	Vista Solo	USA	Medium to large fruit depending on climate, 5 in. wide, up to 18 in. long. Skin yellow, flesh orange to yellow-orange. Hardy, compact Solo type producing high quality fruit. Needs fairly hot weather to develop sweetness	De los Santos de la et al. (2000), FAO (2003), Popenoe (1974) and Morton (1987)
Deshaies Plant	NA	Guadeloupe	NA	Ocampo Pérez et al. (2005)
MTQ2	NA	NA	NA	NA
Pusa	Pusa Delicious	India	This is a gynodioecious. The fruits are medium in size with deep orange flesh colour having excellent flavour	Chan and Paull (2008) and Chan (2009)
	Pusa Giant	India	This is a dioecious and bears fruit at one month. height. The plant can withstand strong wind and storm. Fruits have attractive big size and weight ranging from 2.5 to 3.5 kg per fruit used for vegetable and canning industry	Chan and Paull (2008) and Chan (2009)
	Pusa Dwarf	India	This is a dioecious cultivar having dwarf stature and more precocious in bearing. The plants start bearing from 25 to 30 cm. above ground level. Fruit size is medium (1 to 2 kg) and oval in shape. Most suitable for high density orcharding, nutrition garden and kitchen garden	Chan and Paull (2008) and Chan (2009)
	Pusa Majesty	India	This is a gynodioecious line. The fruits are medium in size and round in shape. Fruit flesh solid in texture and yellowish in colour having good keeping quality tolerant to viral diseases	Chan and Paull (2008) and Chan (2009)

TABLE 3.32.1 *Carica papaya* Cultivars, Varieties and Country of Origin—cont'd

Varieties	Cultivars	Countries	Characteristics	References
	Pusa Nanha	India	It is a dioecious line, dwarf and precocious. Fruiting starts at a height of 40 cm within 239 days of planting with the total height of the plant as 130 cm. Fruit medium to small, oval, seed cavity 12 × 8 cm. and flesh 3.5 cm thick of blood red to orange colour with TSS (6.5%–8.0%) resistant to lodging (Pusa series release from IARI, New Delhi)	Chan and Paull (2008) and Chan (2009)
Coimbatore	CO1	India	It is a selection from progenies of cv. Ranchi. Plants are dwarf and fruits are borne within 1.2–1.5 m. from the ground level. Fruits are medium sized and sweet with golden yellow skin and orange coloured flesh	Chan and Paull (2008) and Chan (2009)
	CO2	India	It is a pure line selection from a local type. The plant is medium-tall in height. Fruits are oblate and large in size; skin yellowish green, flesh orange coloured, soft and moderately juicy. It is a good table fruit and high papain yielder	Chan and Paull (2008) and Chan (2009)
	CO3	India	This is a hybrid between Co-2 × Sunrise Solo. It is a tall vigorous plant. The fruit is medium-sized, sweet with good keeping quality	Chan and Paull (2008) and Chan (2009)
	CO4	India	This is a cross between Co-1 × Washington. Plant medium-tall. Fruit large, flesh thick, yellow with purple tinge, taste sweet and good keeping quality. (Co-1 to Co-4 are released from TNAU, Coimbatore)	Chan and Paull (2008) and Chan (2009)
	CO5	India	It is a selection from Washington and isolated for its high papain production. It produces consistently 14–15 g dry papain/fruit. It gives 75–80 fruits/tree in 2 years with an average yield of 1500–1600 kg dried papain/ha	Chan and Paull (2008) and Chan (2009)
Fairchild	NA	NA	It was introduced by the US Department of Agriculture in 1938 and named after Dr. David Fairchild. The fruit weighs about 4 pounds, 8–9 in. long by 5–6 in. and is rounded-oblong in shape. The fleshy portion is thick with a large edible portion. The flavor is medium cressy combined sweetness. The pulp is an attractive orange yellow, smooth texture and cold resistant than most other varieties tested	Annegowda and Bhat (2016)
Kissimmee	NA	NA	NA	
Coorg honey	Sekaki	NA		Chan (2001)
	Eksoitika	NA	NA	Chan (2001) and Farouk-Ildnan et al. (2013)
Madagascar	NA	NA	NA	Caro et al. (2000)

Puerto Rico, and Cuba by Albert Santo, an Italian entrepreneur. *C. papaya* began being grown as a food crop at the commercial scale in southern and central Florida around 1959. Today, farmers in Hawaii, tropical Africa, the Philippines, India, Ceylon, Malaya, and Australia are the largest commercial producers of *C. papaya* in the world (Nakasone and Paull, 1998).

Global *C. papaya* production in 2014 was about 12.7 million tonnes (FAOSTAT, 2016), which is about a 32% increase over world total *C. papaya* production in 2004. The quantity of *C. papaya* produced in different geographical regions in

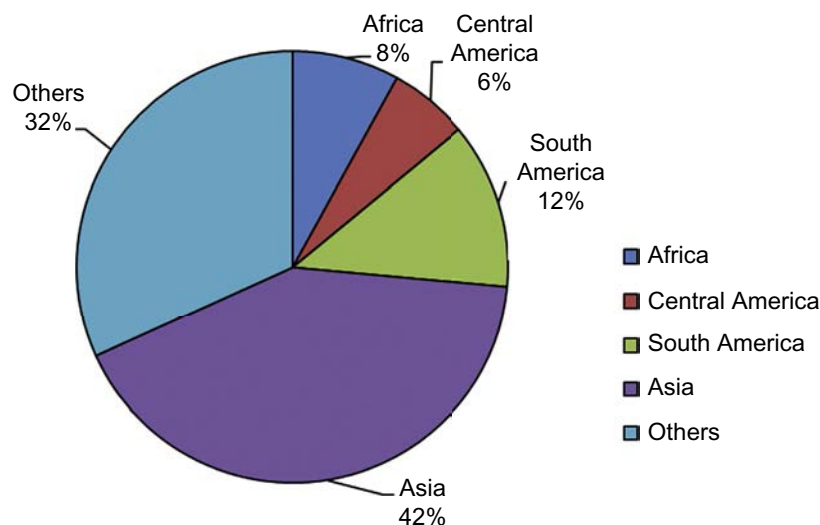


FIG. 3.32.1 Quantity of *Carica papaya* fruit produced in different geographical regions in 2014. Food and Agriculture Organization of the United Nations, Statistics (FAOSTAT, 2016).

2014 is illustrated in Fig. 3.32.1. Asia remains the world's largest producer of *C. papaya*, mainly India (Brazil runs it a close second). Countries like Nigeria, Indonesia, and Mexico also contributed significantly to world total production and along with other countries figures in the list of the top-10 producing countries of the world in 2014 (Table 3.32.2). Importantly, the volume of *C. papaya* production is dependent on factors relating to national agricultural policies, as well as land, pest, and disease control in different countries.

Traditional Uses of *Carica papaya*

C. papaya is a popular plant used traditionally by people of several nations. It has widely reported nutritional and health benefits (Anuar et al., 2008; Nayak et al., 2007; Starley et al., 1999). The ripe fruit is the part of the plant most commonly eaten and is a rich source of nutrients. Decoctions of unripe fruit and of leaves are also widely used in folkloric medicinal preparations. In most ethnomedicinal reports, *C. papaya* is used as a component of herbal mixtures containing other herbs.

TABLE 3.32.2 Total Production (tonnes) and Area (hectares) of Papaya in the Top-Ten Producing Countries of the World in 2014

Country	Production (thousand tonnes)	Area (thousand hectares)
India	5,639,300 million	133,360
Brazil	1,603,351 million	32,031
Nigeria	850,000	94,200
Indonesia	840,121	9,384
Mexico	836,370	14,533
Dominican Republic	704,786	2,676
Congo	220,483	13,043
Philippines	172,628	7,918
Venezuela	165,102	8,664
Thailand	157,571	4,320

Culled from Food and Agriculture Organization of the United Nations, Statistics (FAOSTAT) Database, 2016.

In Nigeria the plant is used by traditional medicine practitioners in the management of diabetes (Gbolade, 2009) and malaria, and in fungal and helminthic infections (Okpe et al., 2016). In Cameroon, it is a component of Nefang, a popular antimalarial herbal mixture (Tarkang et al., 2015). Leaf decoctions are used as anticancer remedies by aboriginal Australians (Nguyen et al., 2013) and as an abortifacient in India. Thus, the traditional use of *C. papaya* seems to be well established. One of the proximate implications of this is that there is increasing scientific interest in evaluating the pharmacologic and therapeutic potential of the plant and its components.

***Carica papaya*: An Important Source of Nonvitamin Nutritional Supplements**

C. papaya has been classified as an herb because of its hollow nonwoody stem. The current definition of a dietary supplement according to the Dietary Supplement and Health Education Act (DSHEA) of 1994 enacted by the US Congress includes vitamins, minerals, herbs, botanicals, amino acids, concentrates, metabolites, constituents, extracts, or a combination of any of these ingredients. In addition, the ingredients must carry a label showing it is a dietary supplement intended for ingestion and not to be traded as conventional food or the main ingredient in a food. The Act separately mentions vitamins, minerals, complex botanics (herbs and extracts), and simpler ones (amino acids, concentrates, metabolites, constituents, or mixtures of these) to show that all such plant-derived bioactive natural products fall under the class of NVNM nutritional supplements (Scarborough, 2004). Hence, extracts, juice, parts of whole plants processed in certain ways, and natural products isolated from different parts of *C. papaya* added to regular food to improve its nutritional value or taken to prevent the development of diseases and improve body structures/functions are NVNM dietary supplements of *C. papaya*. The comprehensive list of NVNM dietary supplements found in various parts of papaya, their potential nutritional benefit, specific sources, and references are contained in Table 3.32.3. The NVNM components found in papaya include different classes of proteins, secondary metabolites, and parts of the whole plant from both ripe and unripe fruits, latex, roots, and leaves.

Therapeutic Potential of *Carica papaya* Nonvitamin Nonmineral Components

There is considerable interest in the use of functional foods, botanicals, and herbals to maintain human well-being. *C. papaya* is a popular component of many traditional medicines and has been used to treat bacterial, fungal, and plasmodial infections. It is also used as a component of diabetic preparations in Nigeria. Scientific reports and clinical studies have evaluated and documented the therapeutic potential of *C. papaya* under various experimental conditions (Table 3.32.4). Generally, only a few clinical studies have evaluated the therapeutic efficacy of *C. papaya* in humans. These clinical studies have used different parts of the plant making generalizations on some of the actions difficult. More importantly, all these studies are small, randomized, usually open-labeled clinical trials. While no large randomized, double-blind clinical trials have yet been conducted, these studies including systematic reviews generally provide robust evidence of safety and efficacy warranting further clinical studies to ascertain clinical efficacy.

Clinical Efficacy of Carica papaya in Dengue Fever

Dengue fever is a neglected tropical disease with no current drug approved for its management. Thrombocytopenia is a common pathological feature and may predict disease severity. *C. papaya* is a promising candidate for dengue therapy primarily because of its ability to improve platelet count. A recent systematic review of clinical studies evaluating the safety and efficacy of *C. papaya* in dengue fever provides evidence in support of the possible therapeutic efficacy of the plant in improving platelet counts in dengue fever patients (Charan et al., 2016). This review included four studies that were mainly small, randomized clinical trials evaluating the efficacy of formulations of *C. papaya* leaf extract (Charan et al., 2016). In a double-blind randomized clinical trial (Kasture et al., 2016), leaf extract significantly improved platelet count in dengue fever patients receiving the extract compared with controls. Thus, dengue fever is a clinical condition where *C. papaya* has interesting therapeutic potential that requires evaluation in larger randomized clinical trials.

Several possible mechanisms by which *C. papaya* improves platelet count have been suggested. Chinnappan et al. (2016) evaluated the ability of *C. papaya* leaf extract to inhibit platelet aggregation after exposure to dengue-infected plasma. They concluded that the action of *C. papaya* leaf extract on platelet count is dengue specific. However, the specific effect of *C. papaya* leaf extract on dengue requires further evaluation.

Therapeutic Potential of Carica papaya in Microbial Infections

Though there is a wide armamentarium of antibacterial agents available for the treatment of bacterial infections, the specter of the emergence of bacterial strains resistant to current antibiotic chemotherapy looms large. Thus, continuous

TABLE 3.32.3 NVNM Component of *Carica papaya* Plants, Processing and Therapeutic Potentials

Categories of NVNM	Plant parts	Processing/Usage	Application	References
Extract	Root	Blended/ pulverized/ soxhlet extraction	Antibacterial	Doughari et al. (2007) and Tiwari et al. (2011)
	Stem	Grinded/pulverized	Antibacterial, antimicrobial	Nirosha and Mangalanayaki (2013), Sumathi and Gowthami (2014)
	Leave	Blended, pulverised, crushed, lyophilization, soxhlet extraction, liquid extraction	Antimalarial, antimicrobial, antiproliferative, antidiabetes, antioxidant, wound healing, antitumor, antithrombocytopenic, anticancer, antihyperglycaemic, antiinflammatory	Kovendan et al. (2012a,b), Baskaran et al. (2012), Pandey et al. (2017), Indran et al. (2008), Juárez-Rojop et al. (2014), Imaga et al. (2010), Anuar et al. (2008), Vuong et al. (2013, 2015), Alabi et al. (2012), Otsuki et al. (2010), Zunjar et al. (2015), Sasidharan et al. (2011) and Owoyele et al. (2008)
	Fruit	Grinded, macerated, homogenizing, fermentation, liquid extraction	Antihepatotoxic, antibacterial, antisickling, antioxidant, antiinflammatory	Raj Kapoor et al. (2002), Ocloo et al. (2012), Mojisola et al. (2008), Nafiu and Rahman (2015a,b)
	Seed	Pulverized, grinded, liquid extraction	Hepatoprotection, antihypoglycemic, antioxidant, antiinflammatory	Adeneye et al. (2009), Adeneye and Olagunju (2009), Kothari and Seshadri (2010) and Amazu et al. (2010)
	Pulp/Juice/Latex	Blended	Anxiolytic	Kebebew and Shibeshi (2013)
Whole plant parts	Root	Decoction, boiled	Abortifacient, diuretic, checking irregular bleeding from the uterus, piles, antifungal activity	Krishna et al. (2008) and Aravind et al. (2013)
	Stem	Decoction	Jaundice, antihemolytic activity, STD, store teeth (inner bark), antifungal activity	Krishna et al. (2008) and Aravind et al. (2013)
	Leave	Cut into small pieces, squeeze, and filter	Tumour-destroying agent, Young leaves as vegetable, Jaundice (fine paste), urinary complaints & gonorrhea (infusion) dressing wound fresh leave, antibacterial	Nwofia and Okwu, 2015, Krishna et al. 2008 and Aravind et al. (2013)
	Fruit	Eaten raw	Round worm infection, dyspepsia, constipation, amenorrhoea, stomachic, digestive, carminative diuretic, dysentery and chronic diarrhea, expectorant, sedative and tonic, relieves obesity, bleeding piles, wound of urinary tract, ringworm and skin disease psoriasis	Burkill (1985), Krishna et al. (2008) and Aravind et al. (2013)

TABLE 3.32.3 NVNM Component of *Carica papaya* Plants, Processing and Therapeutic Potentials—cont'd

Categories of NVNM	Plant parts	Processing/Usage	Application	References
	Seed	Chew, pounded and crushed	Intestinal worms, clear nasal congestion, carminative, emmenagogue, vermifuge, abortifaciant, counter irritant	Elizabeth (1994), Krishna et al. (2008) and Aravind et al. (2013)
	Pulp/Juice/Latex	Incision, pressing, milled	Antioxidant, antifungal, anthelmintic, warts, sinusitis, eczema, cutaneous tubercles, bleeding piles and enlarged liver and pectoral properties, anathematic, relieves dyspepsia, cures diarrhea, pain of burn and topical use, bleeding hemorrhoids, stomachic, whooping cough	Mehdipour et al. (2006), Giordani et al. (1996), Adu et al. (2009), Calvache et al. (2016), Satrija et al. (1995), Aravind et al. (2013), Krishna et al. (2008) and Nafiu et al. (2016)
Isolated fraction	Root (Nicotine, Carposide, Myrosine)	Isolation and characterization	Antibacterial	Krishna et al. (2008)
	Stem (Papain, Myricetin, Kaempferol, Quercetin)	Isolation and characterization	Antioxidant analgesic antipyretic hypoglycemic	Anibijuwon and Udeze (2009), Baskaran et al. (2012) and Krishna et al. (2008)
	Leave (Quercetin, Kaempferol, Quercetin-3-rutinoside, Myricetin-3-rhamnoside, Kaempferol-3-rutinoside, Papain, Chymopapain, Caricain, Glycylendopeptidase, Carpaine, Carpinine, Pseudocarpaine, Dehydrocarpaine I and II, Nicotine, Choline, Bispiperidine, Caffeic acid, P-coumaric acid, Chlorogenic acid, Tryptophan, Methionine, Lysine, Cystatin, Saponins, Tannins, Anthraquinolones, reducing sugars, steroids)	Isolation and characterization	Peroxynitrite scavenging activity, antitumor anticancer analgesic antiinflammatory diuretic amoebicide antibacterial antispasmodic, antimalarial heart depressant antihelmintic, antioxidant, antioxidant analgesic antipyretic hypoglycemic	Nugroho et al. (2017), Aravind et al. (2013), Baskaran et al. (2012), Burdick (1971), Krishna et al. (2008), Tuffley and Williams (1951), and Baskaran et al. (2012)
	Fruit (Danielone, isopropyl 5- β -Dglucopyranosyloxy-2-hydroxybenzoate, methyl β -D-glucopyranoside, α -linolenic acid, Chitinase, Carpaine)	Isolation and characterization	Antimicrobial, antioxidant	Echeverri et al. (1997), Galang et al. (2016), Krishna et al. (2008), Aravind et al. (2013)
	Seed (Myrosin, Carpaine, Caricin, β -sitosterol, Carpasemine)	Isolation and characterization	Cytotoxic	Krishna et al. (2008) and Aravind et al. (2013)
	Pulp/Juice/latex proteinases (papain, chymopapain, and papain proteinases A and B), N-butyric, n-hexanoic and n-octanoic acids, lipids; myristic, palmitic, stearic, Linoleic, Linolenic and C is -vaccenic and oleic acids	Isolation and characterization	Proteolytic, antiinflammatory, antioxidant, antioxidant Analgesic antiinflammatory antibacterial antiviral antifungal anticancer antiallergic aid in digestion laxative assist wound healing boost platelets	Milivoevich (1978), Mezhlumyan et al. (2003), Gazetov and Kalinin (1990), Aravind et al. (2013), Broke (2013)

TABLE 3.32.4 Therapeutic Potential of *Carica papaya* in Clinical and Experimental Studies

Papaya preparation used in study	Route of administration – dose	Findings	References
Crude ethanolic extract of unripe <i>C. papaya</i> fruit	Intravenous, 20 mg/kg	Extracted significantly lowered mean arterial pressure in animal models of hypertension	Eno et al. (2000)
Methanolic extract for <i>C. papaya</i>	Oral, 100 mg/kg twice daily for 30 days	Extract lowered blood pressure in spontaneously hypertensive rats	Brasil et al. (2014)
Standard fermented <i>C. papaya</i>	Oral – 0.2 g/kg	8 weeks administration to db/db mice improved macrophage function ant wound site	Collard and Roy (2010)
<i>C. papaya</i> leaf aqueous extract	Oral – 0.75, 1.5, 3 g/100 mL	All doses exhibited glucose lowering effect and raised insulin levels in streptozotocin induced diabetic rats	Juárez-rojop et al. (2012)
<i>C. papaya</i> fruit aqueous extract	Oral 100 mg/kg/day for 10 days	Wound area was significantly reduced in STZ-induced diabetic rats compared to control. Wound epithelialized faster in extract treated rats	Nayak et al. (2007)
<i>C. papaya</i> leaf aqueous extract	Oral 100, 200 and 400 mg/kg for 21 days	In alloxan-induced diabetic rats, only 400 mg/kg dose resulted in significant hypoglycemic effect	Maniyar and Bhixavatimath (2012)
Fermented <i>C. papaya</i>	Oral, 6 g/day for 14 weeks	No significant changes in fasting blood glucose and glycated hemoglobin during supplementation period	Somanah et al. (2012)
Standardized fermented <i>C. papaya</i> gel	Topical 7 g/day for 10 days	In this human study, clinical symptoms of gingivitis were improved as well as inflammatory marker reduction was achieved	Kharaeva et al. (2016)
Ethanolic extract of <i>C. papaya</i> leaves	Oral, 100 mg/kg	Significant hypoglycemic effect in STZ treated mice	Sasidharan et al. (2011)
<i>C. papaya</i> leaf juices	Oral, juice extracted from 50 g of leaves, administered once daily for 3 days	Ability to induce platelet production in dengue patients	
<i>C. papaya</i> leaf extract tablets	Oral, 1100 mg 3 times daily for 5 days	Rapid induction in rise in platelet number in 30 patients who received standard therapy plus c papaya treatment compared to control that received standard therapy alone	
<i>C. papaya</i> ethanol leaf extract capsules	Oral, 550 mg	Capsules shortened hospitalization stay and induce rise in platelet count	
<i>C. papaya</i> leaf extract capsule	Oral 500 mg once daily for 5 days	Leaf extract raises platelet count in dengue fever patients without side effect	
Fermented <i>C. papaya</i>	Oral, 4.5 g twice a day for 90 days	Significant improvement in skin features such as elasticity, evenness and moisturization. Effect is associated with changes in cyclophilin A and CD147 genes	Bertuccelli et al. (2016)
<i>C. papaya</i> leaf extract	Oral, three times daily for 5 days	<i>C. papaya</i> leaf extract accelerates rise in platelet count	Kasture et al. (2016)
Fermented <i>C. papaya</i>	Oral, 3- or 9 g daily for 30 days	Dose-dependent increase in natural killer cytotoxicity	
<i>C. papaya</i> seed	Oral	Effective stool parasite clearance	Okeniyi et al. (2007)
Fermented <i>C. papaya</i>	Oral, 500 mg/kg for 92 days	Improvement in key antioxidant enzyme activity and reduced liver peroxidation	Somanah et al. (2016)
Fermented <i>C. papaya</i>	Oral (150, 300, 450 mg/kg) or intraperitoneal (1600/4000 mg/kg)	Suppressed tumorigenesis on balb/mice	Murakami et al. (2016a,b)

efforts in search of novel antibacterial agents subsist. Phytochemicals, especially essential oils, have been shown to exhibit antimicrobial properties on many strains including multidrug-resistant strains when used alone or in combination as synergists/potentiators of less effective products (Ohene-Agyei et al., 2014). The main classes of phytochemicals with recognized antibacterial activity (phenols and phenolic acids, quinones, flavones, flavonoids and flavonols, terpenoids and essential oils, alkaloids, polyamines, isothiocyanates, and glycosides) are detected in varying amounts in different parts of *C. papaya*. Several lines of evidence are in support of the potential use of *C. papaya* parts in bacterial infections. Although an early study reported lack of microbiocidal activity against bacterial strains, recent studies have continued to show *C. papaya* antibacterial activity (Asghar et al., 2016; Mbosso Teinkela et al., 2016; Yismaw et al., 2008). Asghar et al. (2016) reported the in vitro antibacterial activity of several extracts of the pulp, leaf, stem, and roots of *C. papaya* against multidrug-resistant strains of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*. Ethanolic extract of *C. papaya* seem to be the most active. Ethanolic extract of the sap was also found effective against *S. aureus* (Mbosso Teinkela et al., 2016). There seems to be a dearth of quality peer-reviewed studies that have examined the antibacterial activity of *C. papaya* in experimental animal models. This notwithstanding, human clinical studies have evaluated the plant's antimicrobial effects.

In a phase 2 randomized clinical trial, children with stool-confirmed microbial infections were treated with *C. papaya* extract (Okeniyi et al., 2007). This regimen was found to be safe in these children. A recent study conducted by Fujita et al. (2017) further corroborates this finding showing that *C. papaya* reduces the number of firmicutes, *Clostridium scindens* and *eggerthella lenta*, and boosts immune activity by modulating bacterial clearance from the gut.

It has been suggested that papaya exerts a proteolytic effect on bacteria by producing a coagulum that immobilizes microorganisms and improves the efficiency of phagocytic cells thereby protecting the host against bacterial infections (Gurung and Škalko-Basnet, 2009; Wimalawansa, 1981). The antimicrobial properties of papaya are also connected with its alkaloid and carpaine content (Hewitt et al., 2002).

Therapeutic Potential of *Carica papaya* in Aging

There is evidence suggesting the efficacy of *C. papaya* as an antiaging agent in humans. The study of Bertuccelli et al. (2016), a double-blind, randomized clinical trial, evaluated the antiaging effects of oral supplementation with a fermented papaya preparation (FPP). The FPP caused marked improvement in skin quality and integrity in treated patients compared with those without FPP. This antiaging effect was further corroborated by significant change in the gene expression of proteins involved in skin integrity.

Therapeutic Potential of *Carica papaya* in Wound Healing

Wound healing is a complex process that involves several cells and mediators (Velnar et al., 2009). Traditionally, it is thought to occur in nonlinear phases including inflammation, proliferation, and remodeling (Broughton et al., 2006). Wound impairment is a major pathological condition in the clinic. Wound healing may generally be impaired as aging progresses and by pathological conditions such as diabetes mellitus (Brem and Tomic-Canic, 2007; Greenhalgh, 2003).

Several plants have been evaluated for their ability to promote wound healing including several parts and components of *C. papaya*. *C. papaya* dried latex was shown to promote wound healing in a mouse burn model (Gurung and Škalko-Basnet, 2009). Water extract of the fruit also possesses wound-healing potential as it shortens the period of reepithelialization in diabetic wounds in mice (Nayak et al., 2007). The seeds (Nayak et al., 2012) and unripe fruit (Nafiu and Rahman, 2015a) were reported to promote wound healing in an excision wound model. These animal studies provide a scientific basis for further evaluation of this effect in human studies. The pulp of *C. papaya* fruit is a major component of burn dressings in the Pediatric Burn Unit of the Royal Victoria Hospital in the Gambia. Experience of this preparation shows it prevents wound infection and appears to aid shedding of necrotizing tissue in the wound. The preparation is well tolerated by children (Starley et al., 1999). The study by Murthy et al. (2012) shows that in cesarean patients receiving partially ripe *C. papaya* wound dressings, incision wounds healed faster. This randomized, open-labeled study shows the superiority of *C. papaya* over hydrogen peroxide in rapid induction of development of healthy granulation tissue and comparable safety of the *C. papaya* preparation. Several factors may play a role in the wound-healing effect of *C. papaya*. Wound healing requires recruiting fibroblasts to the wound site which play important roles in tissue repair. *C. papaya* has been reported to induce the expression of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF- β 1) (Nafiu and Rahman, 2015b), factors that promote recruitment of fibroblasts to the wound, thereby promoting the healing process. The wound-healing properties of *C. papaya* may also be related to its antibacterial activity (Dawkins et al., 2003; Yismaw et al., 2008). Bacterial infections are known to alter the course of wound healing by prolonging the inflammatory state.

Therapeutic Potential of Carica papaya in Periodontitis

A fermented papaya preparation was evaluated for its clinical efficacy in periodontitis patients. In this randomized open-labeled clinical trial, *C. papaya* effectively lowered inflammatory cytokines improving clinical indices including disease severity, bleeding, and depth of cavity (Kharaeva et al., 2016). This study is a proof-of-concept study supporting further evaluation of *C. papaya* in larger randomized double-blind clinical studies. Tadikonda et al. (2017) also reported the antiplaque and antigingivitis efficacy of a dentifrice containing papain and other related phytochemicals in a randomized controlled clinical trial. When compared with a standard dentifrice among patients undergoing fixed orthodontic treatment, papain-containing dentifrice reduced plaque and gingival indices. The study concluded that the test dentifrice can be used as a home-based adjunct to clinical therapy in orthodontic patients.

Therapeutic Potential of Carica papaya in Diabetes Mellitus

C. papaya has been used as a traditional agent in the management of diabetes (Gbolade, 2009). Scientific evidence further suggests the antidiabetic potential of *C. papaya*. In animal models of diabetes, *C. papaya* was reported to lower blood glucose (Juárez-Rojop et al., 2012; Maniyar and Bhixavatimath, 2012; Sasidharan et al., 2011) and increase beta cell area suggesting regenerative capacity. A recent evaluation of *C. papaya* in diabetes shows that it restores basal insulin levels in diabetic animals. While these studies suggest the plant effects may be attributable to beta cell regeneration, in vitro studies have reported other potential antihyperglycemic effects including antiglucosidase activity (Loh and Hadira, 2011; Obboh et al., 2014). Furthermore, the usefulness of *C. papaya* may extend beyond its glucose-lowering effect. Two studies in animals report the wound-healing properties of the extract in diabetic wounds (Collard and Roy, 2010; Nayak et al., 2007). The antidiabetic effect of *C. papaya* has subsequently been evaluated in human patients. In this human study, *C. papaya* shows antidiabetic potential due to its hypoglycemic effect (Somanah et al., 2012). These studies showed that *C. papaya* may be beneficial in diabetes therapy and warrants further studies in larger populations.

Therapeutic Potential of Carica papaya in Hypertension

A few scientific reports have evaluated the antihypertensive potential of this plant. Eno et al. (2000) found that intravenous administration of *C. papaya* reduced mean arterial pressure in renal and deoxycorticosterone acetate-induced hypertension in male Wistar rats. In another study, Brasil et al. (2014) reported *C. papaya* had an antihypertensive effect in spontaneously hypertensive rats. While Eno et al. (2000) suggest the effect may be via adrenoceptor antagonism, the studies by Brasil et al. (2014) suggest angiotensin-converting enzyme inhibitory activity corroborating earlier in vitro studies reporting angiotensin-converting enzyme inhibition by the plant (Loh and Hadira, 2011). These studies point to the potential of *C. papaya* in hypertension. There is need to evaluate this pharmacologic effect in human patients.

Therapeutic Potential of Carica papaya in Cancer

C. papaya has been demonstrated to possess excellent in vitro antiproliferative activity in various cancer cell lines including breast, lymphocyte, and human peripheral mononuclear cells. It is a potential source of anticancer agents (Nguyen et al., 2013, 2015; Pandey et al., 2017). Animal chemopreventive studies further demonstrate the chemopreventive potential of *C. papaya* (Pathak et al., 2014). Somanah et al. (2016) also reported the ability of fermented *C. papaya* to modulate hepatocellular carcinoma in mice. Murakami et al. (2016a) also showed *C. papaya* tumor-suppressive activity in vivo.

Antisickling Potential of Carica papaya

A very early report suggested the antisickling potential of unripe *C. papaya* (Thomas and Ajani, 1987). Thereafter, the use of *C. papaya* in thalassemias was evaluated. Fermented papaya preparations improved red blood cell sensitivity to hemolysis and oxidative stress markers in a mouse model of beta thalassemia and in patients (Amer et al., 2008; Fibach and Rachmilewitz, 2010). In another in vitro study, which evaluated the antisickling effect of plants, *C. papaya* showed promising antisickling effects as it significantly prevented the sickling effect of 2% sodium metabisulfite (Nurain et al., 2016).

Pharmacological Properties of *Carica papaya*

The use of *C. papaya* in humans is based on some pharmacological actions that are associated with disease prevention and therapeutic targets. Pathological factors such as tissue oxidative damage, inflammation, immune disorder, and microbial infections form the bases and underlying changes leading to the development of most diseases. Therefore, this section focuses

on the antioxidant, antiinflammatory, and immunomodulatory properties of *C. papaya* and its products. The antimicrobial property of *C. papaya* was discussed in the “Therapeutic potential of *Carica papaya* in microbial infections” section.

Antioxidant Properties of *Carica papaya*

Complex metabolic activities involving many enzymes, nutrients, and molecular oxygen to produce the energy needed for normal body functions yield oxidants that at the basal level could impact positively on the body. However, altered tissue metabolism under disease conditions (diabetes mellitus, chronic wound healing, microbial infections, and chronic inflammation-associated diseases) increases oxidant production such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and peroxides. Altered tissue metabolism also suppresses the endogenous antioxidant defense system, a prelude to tissue/cellular oxidative damage. Exogenous antioxidants find relevance in this condition. Studies have shown that phytochemicals such as carotenoids, phenolic acids, flavonols, and flavonols, which are found abundantly in *C. papaya*, play important roles as antioxidant nutritional supplements.

Recently, [Somanah et al. \(2017\)](#) showed that ripe and unripe Mauritian *C. papaya* (Solo-type) seed, peel, and pulp extracts (2 mg/mL) significantly reduced oxidative stress levels in human preadipocytes (SW872) and hepatocellular carcinoma cells (HepG2) exposed to hydrogen peroxide (H_2O_2) by mediating proinflammatory cytokine—such as tumor necrosis factor- α (TNF- α), interleukin (IL-6), and monocyte chemoattractant protein-1 (MCP-1)—secretory levels, reducing intracellular ROS and maintaining mitochondrial viability. *C. papaya* peel water extracts were found to contain the highest total phenolic content and reducing activity, while total flavonoid content and radical scavenging activity was found in 80% ethanolic extract ([Siddique et al., 2017](#)). FPP also induced increased nuclear translocation of nuclear factor erythroid 2–related factor (Nrf2) and release of Nrf2-regulated neuroprotective antioxidants and detoxifying molecules in striatal astrocyte culture. It also suppressed 6-hydroxydopamine–induced dopaminergic neuronal loss in neuron–astrocyte mixed cultures and neuron-rich cultures pretreated with glial-conditioned medium. The protective role of FPP against neurooxidative damage was confirmed in vivo. FPP induced striatal Nrf2 activation and increased the glutathione level in mice treated with FPP for 2 weeks ([Murakami et al., 2016b](#)). The antiaging property of FPP, mentioned above, was also linked to its antioxidant effect on skin tissue ([Bertuccelli et al., 2016](#)).

Antiinflammatory Properties of *Carica papaya*

Inflammation is a component of several diseases including rheumatoid arthritis, asthma, and type 2 diabetes mellitus as well as of wound healing. Papain from papaya latex or unripe pulp produced therapeutic effects in patients with inflammatory disorders and was effective in controlling edema and inflammation associated with surgical or accidental trauma ([Rakhimov, 2000](#)). *C. papaya* leaf ethanol extract significantly reduced carrageenan-induced paw edema and cotton granuloma tissue formation. Similarly, the extract reduced edema in a formaldehyde-induced arthritis model ([Owoyele et al., 2008](#)). Many studies (human and animal) on the wound-healing effect of papaya consistently implicated the antiinflammatory properties of *C. papaya* as the main mechanism for wound healing ([Mikhailchik et al., 2004](#); [Nafiu et al., 2015a,b](#); [Rakhimov, 2000](#)). Ironically, Gupta et al. have used *C. papaya* latex as an inflammagen in a new model of inflammation for testing antiinflammatory drugs ([Sindhu et al., 2017](#)). A latex suspension injected in the hind paw of a rat produced concentration-dependent inflammation similar to carrageenan-induced inflammation, but more responsive to slowly acting antiarthritic drugs. A recent study on a mouse model of allergic airway inflammation showed that *C. papaya* leaf extract reduced inflammatory cell infiltration of the lungs as well as total and differential leukocyte counts in both blood and bronchoalveolar lavage fluid samples. These were associated with *C. papaya*–induced downregulation of inflammatory genes: IL-4, IL-5, eotaxin, TNF- α , nuclear factor- κ B (NF- κ B), and inducible nitric oxide synthase (iNOS) ([Inam et al., 2017](#)). An ethanol acetate fraction of *C. papaya* leaf water extract (500 μ g/mL) was shown to inhibit the release of TNF- α (60.2% inhibition) by human monocytic cells derived from an acute monocytic leukemia (THP-1) following *Porphyromonas gingivalis* lipopolysaccharide activation. The extract was active when compared with dexamethasone and is a major bioactive component in Gencix. Gencix is a toothpaste recommended for the protection of gums and prevention of gingivitis. The antiinflammatory property was linked to the flavonol (quercetin and kaempferol) content of the extract ([Dejoie et al., 2016](#)). A complex fruit/vegetable concentrate (Juice Plus + Orchard, Garden, and Berry Blends), prepared from *C. papaya* and 24 other fruits and vegetables, reduced systemic inflammation in a double-blind, randomized placebo-controlled trial. The subjects were given 6 capsules of the concentrate daily for 8 weeks. The concentrate markedly reduced plasma TNF- α without change in plasma C-reactive protein, especially in subjects with higher baseline systemic inflammation (serum CRP ≥ 3.0 mg/mL). The concentrate also altered the expression pattern of several genes: NF- κ B, 5′-adenosine monophosphate–activated protein kinase (AMPK) signaling, phosphomevalonate kinase (PMVK), zinc finger AN1-type containing 5 (ZFAND5), and calcium-binding protein-39 (CAB39). The concentrate improved blood lipid and metabolic profiles through reduction of systemic inflammation to alleviate the risk of obesity-induced chronic disease ([Williams et al., 2017](#)).

Immunomodulatory Properties of Carica papaya

Enhancing the immune response is an important approach to prevent infection under conditions that can compromise immune cell functions. Studies have shown that *C. papaya*-based products exhibit remarkable immunomodulatory properties, and this has been reviewed by Pandey et al. (2016). Recently, Jayasinghe et al. (2017) used in vitro, ex vivo, and in vivo techniques to establish the immunomodulatory properties of mature leaf concentrate of *C. papaya* (MLCC). They found that oral MLCC considerably increased platelet, total leukocyte, lymphocyte, and monocyte subpopulations and bone marrow cells in rats. The highest MLCC dose tested in the study markedly reduced proinflammatory cytokine (IL-6 and TNF- α) concentrations. The phagocytic index of rat peritoneal macrophages, in vitro and in vivo, increased at all doses tested (0.18, 0.36, 0.72 mL/100 g body weight of rats) with T helper 1 (Th₁)-biased cytokine response elicited in vitro by the MLCC. MLCC (31.25 and 62.5 μ g/mL) also stimulated proliferation of bone marrow cells and splenocytes ex vivo, but induced cytotoxicity of both bone marrow cells and splenocytes at 500 and 1000 μ g/mL via modulation of cytokines. An oral subacute toxicity test, targeting hepatorenal function biomarkers, revealed that MLCC was safe.

C. papaya leaf and seed extracts are most commonly investigated for their immunomodulatory properties. *C. papaya* seed extract enhances mitogen-activated proliferation of lymphocytes. Fractions separated from the seed extract significantly inhibited the classical complement-mediated hemolytic pathway in a study that used lymphocyte proliferation assay and complement-mediated hemolytic assay (Mojica-Henshaw et al., 2003). In another study, it was shown that *C. papaya* water extract upregulates interleukin-12 subunit p40 (IL-12p40), interleukin-12 subunit p70 (IL-12p70), interferon-gamma (IFN- γ), and TNF- α , but inhibits IL-2 and IL-4 to enhance survival of peripheral blood mononuclear cells (PBMC) in the culture supernatant. Using microarray technology and real time polymerase chain reaction, 23 genes classified by gene ontology analysis as immunomodulatory were upregulated following the addition of *C. papaya* extract to the cells. The addition of papaya extract to activated PBMC significantly enhanced cytotoxic activity against cancer cells. The study concluded that *C. papaya* extract may serve as an immunoadjuvant for vaccine therapy (Otsuki et al., 2010). A fermented papaya preparation, when administered on raw 264.7 macrophages in a culture, significantly increased production and expression of nitric oxide (NO) and iNOS, respectively. It also enhanced TNF- α secretion independent of bacterial lipopolysaccharide (Rimbach et al., 2000). *C. papaya* leaf water extract was shown to increase neutrophil adhesion to nylon fibers, which corresponds to the in vivo process of margination (Ghaisas et al., 2012). Unripe *C. papaya* fruit were also reported to markedly enhance immunoglobulin IgG and IgM levels in a rat model of acrylamide-induced oxidative stress (Sadek, 2012). In a comparative study on the immunomodulatory potentials of ripe and unripe, transgenic and native papaya fruits using an ovalbumin-sensitized mouse model, native green and ripe papaya fruit supplementation considerably increased ovalbumin-specific IgG_{2a} titer while native green papaya fruit only decreased ovalbumin-specific IgE (Chen et al., 2011). Human subjects (male and female) fed 100 g fresh papaya fruit for 2 days exhibited decreased Th₁ T-cell phenotypes, but increased Th₂ and T_{regs} T-cell phenotypes in their PBMCs. The increased T_{regs} phenotype of the male sample was markedly associated with IL-1 β level in the in vitro culture supernatant (Abdullah et al., 2011).

Dietary Supplements and Drug Interactions

In the last decade, plant-derived dietary supplements have become a common alternative to medical remedies throughout the world for a number of reasons: increased cost of medical care; belief that phytochemicals are natural and safe; lack of strict guidelines for development; approval, use, and reports of enhanced efficacy with concomitant use of plant-derived dietary supplements and drugs (Ernst, 2005; Iwu et al., 1999; Sahoo et al., 2010). This means patients are now using plant-derived dietary supplements at the same time as allopathic drugs for improved therapeutic efficacy. However, in recent years there has been an increasing number of reports on complications emanating from interactions between drugs and dietary supplements secondary to excessive pharmacological actions (adverse events) or constrained bioavailability of drugs (treatment failure). Most plant phytochemicals when ingested either as food or dietary supplements mimic drugs and are capable of interfering with the bioavailability and bioactivity of other drugs and food (nutrients) taken together or separately as they share the same metabolic pathways. Dietary supplements from *C. papaya* are no exception to such interactions as they are capable of modifying the absorption, distribution, metabolism, and excretion (ADME) properties of drugs through their effects on drug-metabolizing and transporting proteins in the body (Rodríguez-Fragoso et al., 2011).

Interactions Between Carica papaya and Drugs

Studies have reported potential interactions between *C. papaya* and different drugs. Most reported cases are at the preclinical level and their clinical significance cannot be confirmed; however, some cases show that interactions between *C. papaya* and drugs have raised serious concern about clinical implications (Rodríguez-Fragoso et al., 2011). The mechanisms under-

lying the interactions between *C. papaya* and drugs depend on two principal groups of factors: drug factors (pharmacokinetic or ADME properties of the drug, pharmacodynamics or drug/body interaction, and physical/biochemical interactions between papaya and drugs) and factors relating to characteristics of the constituent parts of *C. papaya* ingested (plant part, species, geographical origin, maturity, manufacturing processes, storage conditions, and seasonal variability). Additive interactions between *C. papaya* phytochemicals and drug actions can be beneficial (enhanced pharmacological actions) or detrimental (adverse reactions and treatment failure). Drugs, *C. papaya* dietary supplements, phytochemicals, their mode of interactions, and implications for body/structure functions are presented in [Tables 3.32.5 and 3.32.6](#).

TABLE 3.32.5 Plants and Bioactive Principles That Form the Starting Point for Modern Drugs

Plant of origin	Bioactive principle	Pharmacological benefit	Remark and references
<i>Artemisia annua</i>	Artemisinin	Antimalaria	A sesquiterpene lactone found to be effective against all the malaria-causing protozoan organisms in the genus <i>Plasmodium</i> . The drug is used in the treatment of malaria involving chloroquine-resistant parasites and multidrug-resistant <i>P. falciparum</i> (Guo, 2016)
<i>Atropa belladonna</i>	Atropine	Spasmolytic	An anticholinergic drug used to treat slow heart rate, organophosphate insecticides and nerve gases poisoning and inhibit salivary and mucus glands (Máthé, 2014)
<i>Cinchona succirubra</i>	Quinine	Antimalaria	An alkaloid bioactive phytochemical in the extracts of cinchona which have been used as antimalarial drug since before 1633 (Achan et al., 2011)
<i>Carica papaya</i>	Chymopapain	Antiinflammation (slipped disk)	A cysteine proteinase enzyme used for intradiscal injection in patients suffering prolapsed intervertebral discs (Anibijuwon and Udeze, 2009)
<i>Claviceps purpurea</i>	Ergot alkaloids (ergotamine)	Antimigraine	An ergot alkaloid vasoconstrictor. It is an alpha-1 selective adrenergic agonist and is commonly used in the treatment of migraine disorders (Schardl et al., 2006)
<i>Coffee Arabica</i>	Caffeine	Vasotherapeutics	A central nervous system (CNS) stimulant of the methylxanthine class used to treat bronchopulmonary dysplasia and apnea of prematurity and can enhance cognitive and physical performance (Nehlig et al., 1992)
<i>Erythroxylon coca</i>	Cocaine	Local anesthetics	A strong stimulant of tropane alkaloid class used as local anesthetic and vasoconstrictor (Luft and Mendes, 2007)
<i>Ephedra sinica</i>	Ephedrine	Sympathomimetics and sympatholytics (β-blockers)	alpha- and beta-adrenergic agonist of phenethylamine class. It has central nervous system stimulatory effects and has been used in the treatment of several disorders including asthma, heart failure, rhinitis, urinary incontinence, narcolepsy and depression (Kobayashi and Zhang, 2003)
<i>Theobroma cacao</i>	Theobromine	Vasodilator	A xanthine alkaloid, formerly used in the treatment of angina pectoris, hypertension and as a diuretic, commonly used as a bronchodilator and as a vasodilator (Usmani et al., 2005)
<i>Camellia sinensis</i>	Theophylline		Is a xanthine derivative used as a drug to treat muscle pain in people with peripheral artery disease. It is indicated mainly for asthma, bronchospasm, and COPD (Hansel et al., 2004)

(Continued)

TABLE 3.32.5 Plants and Bioactive Principles That Form the Starting Point for Modern Drugs—cont'd

Plant of origin	Bioactive principle	Pharmacological benefit	Remark and references
<i>Rauwolfia serpentine</i>	Reserpine	Antihypertensives	Reserpine is an adrenergic blocker of indole alkaloid class. It has been used for the control of high blood pressure and psychotic symptoms, though seldomly used nowadays because of its numerous side-effects (Shamon and Perez, 2009)
	Ajmaline	Antiarrhythmics	Ajmaline is an alkaloid belonging to class Ia antiarrhythmic agent. It is used diagnostically to reveal typical findings of ST elevations in patients suspected of having Brugada syndrome (Wolpert et al., 2005)
<i>Physostigma venenosum</i>	Physostigmine	Antidementia	A parasympathomimetic alkaloid, used as an antidote against anticholinergic drug overdoses as it reversibly inhibit cholinesterase activity (Stilson et al., 2001)
<i>Papaver somniferum</i>	Morphine	Analgesics	Morphine alkaloid is a narcotic pain reliever that acts directly on the central nervous system to decrease the feeling of acute and chronic pain
	Papaverine	Spasmolytic	Is an opium alkaloid vasodilator drug, used primarily to improve blood flow in patients with visceral spasm (especially those involving the intestines, heart, or brain), and can be used in the treatment of erectile dysfunction (Kim et al., 2008)

TABLE 3.32.6 Herb-Drug Interactions: *Carica papaya* Phytochemicals and Various Classes of Drugs

<i>C. papaya</i> phytochemicals/ dietary supplements	Molecular target	Interacting drug	Remark and reference
Freeze dried hot aqueous infusion extract	Papaya metal chelation of ciprofloxacin. May also involved inhibition of a member of the influx transporter protein family (organocation transporter polypeptide; OATP.)	Ciprofloxacin	In vivo. Metal cations chelate ciprofloxacin in aqueous solution and limit their antibacterial activity and associated adverse events. <i>C. papaya</i> reduced the bioavailability since it is rich in cation mineral elements.
Fermented papaya preparation	ND. Inhibition of P-gp is proposed in line with an in vivo finding	Glybenclamide	<i>Clinical</i> , fasting and postprandial plasma glucose were significantly reduced both in healthy and diabetic patients. The patients were induced to reduce or suspend their oral antidiabetic drug. FPP could inhibit P-gp to enhance bioavailability of glybenclamide. Dose adjustment of glybenclamide may be required
Ethanol leaves extract	the extract may bind part of glimepiride in GIT thereby delays its absorption	Metformin, glimepiride	In vivo. The extract delayed the hypoglycaemic activity of glimepiride but hastened that of metformin. The extract is thought to bound part of glimepiride or stimulates production and activity of enzymes that degrade it. (Fakeye et al., 2007)

TABLE 3.32.6 Herb-Drug Interactions: *Carica papaya* Phytochemicals and Various Classes of Drugs—cont'd

<i>C. papaya</i> phytochemicals/ dietary supplements	Molecular target	Interacting drug	Remark and reference
GMP certified Standardized <i>C. papaya</i> extract (proteolytic activity > 6000 NFPU/mg papayafruit; Bio Serae LaboratoriesBram, France)	<i>C. papaya</i> reduced intestinal motility to inhibit the intestinal propulsion movements? It could also inhibit drug metabolizing (CYP isoenzymes; CYP3A and CYP2E1) and transporting proteins (P-gp) efflux activity	Amiodarone	In vivo and in vitro. Co-administration of single doses of Amiodarone and <i>C. papaya</i> in rats caused delay in t_{max} but could not alter the amiodarone C_{max} significantly. Thus, <i>C. papaya</i> extract or some of its phytochemical constituents increases the bioavailability of amiodarone through reduced intestinal absorption and inhibition of drug metabolizing and transporting proteins. Repeated administration of <i>C. papaya</i> extract also alters tissue distribution and may contribute to tissue accumulation and the target organ toxicity associated to amiodarone and MDEA
<i>C. papaya</i> fruit juice	Activation or induction of CYP3A4-mediated pre-systemic felodipine metabolism	Felodipine	In vivo. <i>C. papaya</i> reduced bioavailability of felodipine
Papain (complex proteases enzyme mixture)	Potentiate the effect of warfarin	Warfarin	Clinical. Patient developed skin, urinary and gastrointestinal bleeding after ingestion of the complex proteases enzyme mixture (as nonsteroidal antiinflammatory drug) and exhibited prolonged prothrombin time, activated thromboplastin time, and low functional and antigenic levels of prothrombin. Fresh frozen plasma and parenteral vitamin K ameliorated the condition (Perez-Jauregui et al., 1995)
<i>C. papaya</i> extract containing papain	Potentiate the effect of warfarin	Warfarin	The patient was admitted for cardiac surgery with an INR of 7.4 which decreased to 2.0 after withdrawal of both papaya extract (used as weight-loss aid) and warfarin (Shaw et al., 1997)
Ethanoextract of unripe fruit of <i>C. papaya</i>	Potentiation of digoxin effect by inhibition of P-gp efflux activity in Caco-2 cells	Digoxin	In vitro. <i>C. papaya</i> inhibited p-gp mediated transport of 3H-Digoxin on Caco-2 cell monolayers using digoxin as a model p-gp substrate. Therefore, interactions with conventional p-gp substrate drugs are likely to occur on co-administration which may result in altered therapeutic outcomes
Aqueous extract of <i>C. papaya</i> leaves	Inhibition of P-gp efflux activity in the intestinal segment mounted in Ussing chamber	Digoxin	In vivo and ex vivo. <i>C. papaya</i> leaves extract increased the permeability of the P-gp substrate digoxin in the mucosal-to-serosal direction in intestinal segments mounted in Ussing chambers. However, co-administration of the leaf extract of <i>C. papaya</i> and digoxin in rats did not determine a significant increase in the extent of systemic drug exposure
<i>C. papaya</i> aqueous crude leaf extract	ND, pharmacodynamic interaction was suggested. <i>C. papaya</i> antioxidants activity could counteract artesunic acid mediated oxidants production during malaria parasite infection thus, isobolar equivalence reveal antagonism	Artesunic acid	In vivo, co-administration of <i>C. papaya</i> and artesunic acid enhanced antimalarial activity, prolonged the survival time and increased the cure rate compared to artesunic acid alone. Nevertheless, quantitative assessment of synergistic potential of the drug and <i>C. papaya</i> using isobolar equivalence showed that the combinations of artesunic acid and <i>C. papaya</i> are antagonistic (Onaku et al., 2011)

Interactions Between Carica papaya and Anticoagulants/Antiplatelets

There is a dearth of information on the clinical significance of interactions between *C. papaya* and anticoagulants in the body (Rodríguez-Fragoso et al., 2011). However, what little data are available on the potential interaction with anticoagulant drugs have been widely reported (Perez-Jauregui et al., 1995; Shaw et al., 1997). There is little or no information available in the literature characterizing the interaction between *C. papaya* and various classes of anticoagulants, but the interaction between *C. papaya* and warfarin has been described in a few reports. Warfarin, a cheap anticoagulant that has long been used in clinical settings, receives more attention regarding its potential interaction with herbs and foods. Therefore, patients and users of *C. papaya* or *C. papaya*-derived nutraceuticals and dietary supplements for whatever purpose should inform their doctors when taking other classes of anticoagulants.

We found two case reports of the interaction between warfarin and papain in the literature. One was the 1991–95 toxicology review conducted by the National Poisons Information Service in the United Kingdom. Although full details of the case have not been published, the patient reportedly maintained a therapeutic international normalized ratio (INR) while receiving warfarin, but began to take papaya extract containing papain as a weight loss supplement. The patient was admitted later for cardiac surgery with an INR of 7.4 which reduced to 2.0 after withdrawal of both papaya extract and warfarin (Shaw et al., 1997). In another case, a 47-year-old woman ingested an overdose of a nonsteroidal antiinflammatory complex mixture containing pancreatin, bromelain, papain, lipase, amylase, trypsin, alpha chymotrypsin, and rutin. She developed skin, urinary, and gastrointestinal bleeding which was thought to be the effect of a coumadin overdose. The patient exhibited a prolonged prothrombin time during an activated partial thromboplastin time test as well as low functional and antigenic levels of prothrombin. Administration of fresh frozen plasma and parenteral vitamin K to the patient reverted all laboratory and clinical abnormalities back to normal (Perez-Jauregui et al., 1995). The adverse reaction may be connected to components of the drug mixture, although experimental testing and high-performance liquid chromatography analysis revealed that the drug might have been contaminated by coumadin. Until further information about this potential interaction becomes available, patients receiving warfarin should be advised to avoid papain supplementation. The exact mechanisms behind the interaction between *C. papaya* and anticoagulants (warfarin) is not yet known; however, possible mechanisms include potentiation of inhibition of vitamin K-dependent coagulation factor by warfarin as well as inhibition of cyclooxygenase and prostaglandins through its antiinflammatory effect.

There are no clinical or preclinical reports on the interactions between *C. papaya* and any class of antiplatelet drug in the literature. Despite the lack of studies, there is theoretical concern here. *C. papaya* and its bioactive components are widely reported as having antiinflammatory properties and have been shown in many studies to increase platelet counts, reduce platelet aggregation in dengue-infected platelet-rich plasma in vitro, and significantly induce upregulation of platelet-specific genes in patients with dengue fever and dengue haemorrhagic fever. Platelet-type lipooxygenase (ALOX 12) and platelet-activating factor receptor (PTAFR) genes have been shown to influence platelet production and platelet aggregation. There is a need for research here to reveal possible interactions between *C. papaya* and antiplatelet drugs. This will have significant implications for patients suffering thrombotic events, especially those associated with dengue fever. A patient suffering a dengue-associated large-vein thrombotic event was recently reported in Brazil (da Costa et al., 2012).

Interactions Between Carica papaya and Antidiabetic Drugs

The available reports on the interaction between *C. papaya* and antidiabetic drugs are mainly preclinical. Therefore, the clinical significance cannot be ascertained. Coadministration of *C. papaya* ethanol leaf extract with metformin or glimepiride in an alloxan animal model of diabetes led to significant interactions with glimepiride or metformin which affected the hypoglycemic activities of the drugs. The extract delayed the onset of hypoglycemic activity of glimepiride and increased the hypoglycemic activity of metformin. The investigator proposed that the extract might delay absorption of the drug by binding up part of the drug or stimulating production and activity of enzymes that degrade some of the drug, especially in the gut (Fakeye et al., 2007). In a separate study, a fermented papaya preparation was shown to reduce both the postprandial and fasting plasma glucose level to a level that influenced patients who were already on an oral antidiabetic drug (glybenclamide) to reduce the dosage of their oral antidiabetic therapy and even suspend the drug in one patient (Danese et al., 2006). This is a serious clinical concern in patient management. Further studies are needed to elucidate the mechanism behind the interaction.

Interactions Between Carica papaya and Antiarrhythmic Drugs

Antiarrhythmic drugs (cardiac dysrhythmia medications) are a diverse group of drugs that are used in the treatment of abnormal heart rhythms (cardiac arrhythmias) such as atrial fibrillation, ventricular fibrillation, ventricular tachycardia, and atrial flutter. Preliminary studies in animals and in vitro have shown the potential interaction between *C. papaya*

and antiarrhythmic drugs, such as amiodarone and digoxin. Amiodarone is one of the most widely prescribed class III antiarrhythmic agents with a narrow therapeutic index. Coadministration of single doses of amiodarone and *C. papaya* in rats caused delay in the time taken to reach the maximum plasma amiodarone concentration, but did not alter the extent of systemic exposure to amiodarone. However, in rats pretreated with *C. papaya* extract for 14 days, before single-dose amiodarone, the extent of systemic amiodarone exposure was markedly increased while the peak of systemic exposure to amiodarone showed no significant change (Rodrigues et al., 2014). Thus, *C. papaya* extract or some of its phytochemical constituents could have antimotility properties that inhibit intestinal propulsion movements (Ezike et al., 2009), prolong the transit time of drugs, and increase the extent of absorption of amiodarone (Tarirai et al., 2010). In addition, *C. papaya* could have an inhibitory effect on drug-metabolizing (CYP isoenzymes) and transporting protein (P-gp) efflux activity that could be responsible for the increased bioavailability of amiodarone, since amiodarone is known to be a cytochrome p450 (CYP) isoenzyme and a P-gp substrate.

Tissue distribution and resultant change in the tissue-pharmacodynamic effect of a drug is another area of concern in herb–drug interaction. With regard to this, repeated administration of *C. papaya* extract before amiodarone treatment increases the concentration of amiodarone in the lungs and results in greater exposure of heart and lung tissues to mono-N-desethylamiodarone (MDEA), the main metabolite of amiodarone. Therefore, repeated administration of *C. papaya* extract could contribute to tissue accumulation and target organ toxicity associated with amiodarone and MDEA (Rodrigues et al., 2014). Digoxin, a class V antiarrhythmic agent, is commonly used to treat heart failure. *C. papaya* leaf water extract significantly increased (54.50%) the apparent permeability of digoxin in the mucosal-to-serosal direction in intestinal segments mounted in Ussing chambers. However, coadministration of *C. papaya* leaf extract and digoxin in rats did not bring about significant change in the extent of systemic drug exposure (Oga et al., 2013). Note that these reports are taken from preclinical studies which may not represent the clinical experience; however, they do indicate the need for a clinical study to ascertain the clinical significance of the reports.

Interactions Between Carica papaya and Antimalaria Drugs

There is an increasing tendency in patients to take herbs (*C. papaya*) at the same time as antimalaria drugs. This is understandable because malaria remains one of the world's foremost infectious diseases causing the death of children and pregnant women in poor tropical regions including West Africa, India, and Central and South America where traditional medicines (herbs) are as popular as allopathic medicines. Again, as a result of the increasingly resistant malaria parasite concomitant use of alternative (herbs) and allopathic medicines in most developing malaria-endemic countries is on the increase. To date, there has been no clinical case reporting on the interaction between *C. papaya* and any of the antimalaria drugs, despite concerns that the citizens of poor developing countries are most likely taking herbs (including papaya products) at the same time as commonly prescribed antimalaria drugs. The reasons are obvious and relate to the high cost of new and safe antimalaria drug and the belief that herbs (*C. papaya* products) enhance the efficacy of antimalaria drugs. This may be connected to the attitude of patients toward disclosure of previous or concomitant herbal therapy to their doctors. However, preclinical data do show the potential interaction between *C. papaya* and artesunic acid (antimalaria drug). Onaku et al. (2011) showed that coadministration of *C. papaya* and artesunic acid enhanced antimalarial activity, prolonged survival time, and increased the cure rate compared with artesunic acid alone. Nevertheless, quantitative assessment of the synergistic potential of the drug and *C. papaya* using isobologram analysis showed that combinations of artesunic acid and *C. papaya* are antagonistic, despite the fact that artesunic acid enhances its activity.

Interactions Between Carica papaya and Antimicrobial Drugs

C. papaya has been found to interact with antimicrobial drugs. Ciprofloxacin, a quinolone antibacterial drug, is used in the treatment of a wide range of bacterial infections. It is known to be associated with many side effects ranging from altered biochemical markers of hepatorenal function, of the endogenous antioxidant system, of dyslipidemia, to changes in immune system functions. When *C. papaya* and ciprofloxacin are coadministered in rats, elevated oxidative stress and other markers in ciprofloxacin-treated rats are markedly reduced without any adverse event in body organs and erythrocytes. This shows that combined use of *C. papaya* and ciprofloxacin can potentially prevent the side effects commonly experienced by patients on ciprofloxacin treatment alone. This can be linked to the interaction between *C. papaya* and ciprofloxacin. The mechanism behind the interaction is not understood; however, decreased absorption of ciprofloxacin or the direct effect of *C. papaya* leaf extract in the body is suspected (Imaga et al., 2012). In a recent in vivo pharmacokinetic analysis of ciprofloxacin in combination with *C. papaya* leaf water extract, *C. papaya* was shown to reduce the bioavailability of ciprofloxacin by decreasing the rate of absorption and volume of distribution as well as increasing the elimination rate, which confirm an earlier report on the possible interaction between *C. papaya* and ciprofloxacin (Ukpo et al., 2017). In another study, concomitant

use of *C. papaya* seed methanol extract and amoxicillin revealed a potential additive interaction against *E. coli* ATCC 25922 with a fractional inhibitory concentration index of 0.99, but no interaction was observed when used against *S. aureus* ATCC 25923 with a fractional inhibitory concentration of 2.51 (Bridge et al., 2015). Giordani et al. (1997) reported that *C. papaya* latex and fluconazole brought about a synergistic bactericidal effect on *Candida albicans* by enhanced cell wall degradation. Likewise, Adejuwon et al. (2011) and Rakholiya and Chanda (2012) showed a possible synergistic antimicrobial interaction between *C. papaya* root and leaf methanol extract and certain known antimicrobial drugs such as penicillin G, ampicillin, amoxycylav, cephalothin, polymyxin B, rifampicin, amikacin, nilidixic acid, gentamicin, chloramphenicol, and ofloxacin against a wide spectrum of Gram-positive and Gram-negative bacteria, but not with tetracycline.

Interactions Between Carica papaya and Other Herbs/Dietary Supplements

There is increasing awareness of the drug–herb interaction, but little is known about the interaction between herbs and other dietary supplements in the mainstream medical literature. However, it is common practice among traditional medical experts (herbalists) to combine two or more herbs/dietary supplements in an effort to enhance therapeutic efficacy. Many studies have reported the use of combinations of *C. papaya* and other herbs or dietary supplements to achieve enhanced therapeutic efficacy or to multitarget in the healing process.

Interaction Between Carica papaya and Vernonia amygdalina

C. papaya combined with *Vernonia amygdalina* has long been used in folkloric medicine among Nigerian (West Africa) tribes to treat malaria. In an attempt to provide scientific evidence of the therapeutic and synergistic potential (interaction) of this herb–herb combination the leaf water extracts of *C. papaya* and *V. amygdalina* were coadministered in mice infected with *Plasmodium berghei*. The combination markedly reduced the parasite load and at the same time enhanced recovery of hepatic cell damage and hematological parameters (Okpe et al., 2016).

Interaction Between Carica papaya and Flamboyant Bark (Delonix regia)

Delonix regia flamboyant bark extract and *C. papaya* extract have both long been used in folkloric medicine as antimalaria agents, but separately. Recently, Fatmawaty et al. (2017) investigated the potential synergistic interaction between *C. papaya* leaf and flamboyant bark ethanol extracts in *P. berghei*–infected mice. A ratio of 1:1 was found the most efficacious and exhibited synergistic or additive effects in vivo. It had much better antiplasmodial properties than every single-dose plant extract tested in the study.

Interaction Between Carica papaya and Carissa spinarum

A potential synergy has been demonstrated for combined use of methanol extracts of *C. papaya* leaves (MECpL) and *Carissa spinarum* leaves (MECsL) as antimicrobial agent against *S. aureus* using fractional inhibitory concentrations to determine the interactions. Using the same approach, an additive interaction was found for a number of combinations: ethanol extracts of *C. papaya* root (EECpR) and *C. spinarum* bark (EECsB), petroleum ether extract of *C. papaya* leaves (PECpL) and methanol extract of *C. spinarum* root (MECsR), and petroleum ether extract of *Carissa spinarum* leaves (PECsL) and ethanol extract of *C. papaya* seed (EECpS) as antimicrobial agents against *S. aureus*. PECsL and EECpS, EECpR and EECsB, and PECpL and MECsR were also found to have an additive interaction against *E. coli*. However, combinations of EECpR and ethanol extract of *C. papaya* leaves (EECpL), PECpL and MECsR, PECsL and EECpS, and EECsR and EECpL exhibited antagonism when tested against *E. coli* and *S. aureus* respectively (Rubaka et al., 2014).

Interactions Between Carica papaya and Many of the Herbs in Polyherbal Preparations

A polyherbal preparation with *C. papaya* as a major herb component named Nefang has been reported for its potential health benefits. The polyherbal preparation comprises *Mangifera indica* (bark and leaf), *Psidium guajava*, *C. papaya*, *Cymbopogon citratus*, *Citrus sinensis*, and *Ocimum gratissimum* leaves. Tarkang et al. (2013, 2014a,b, 2015) conducted extensive studies into the biological properties of the polyherbal preparation and the constituents of the plants. The various plant components of Nefang, *C. papaya* leaves included, were individually shown to exhibit good antioxidant properties as a measure of therapeutic value in vitro. Additive interaction of the plant components in Nefang in vivo markedly reversed oxidative stress and enhanced the endogenous antioxidant enzyme system to ameliorate alterations in hepatorenal function markers (Tarkang et al., 2013). In vitro sensitivity assessment (on chloroquine-sensitive and multidrug-resistant *P. falciparum* strains) of Nefang component combinations (pairwise) for malaria using isobologram analysis at variable potency ratios showed that *C. papaya*/*O. gratissimum* and *C. papaya*/*C. sinensis* exhibited strong synergism with antiplasmodial

activities greater than five times that of Nefang (Tarkang et al., 2014a). The paired combinations interact in such a way that they enhance antiparasitic activity better than the parent herbal drug (Nefang). These findings were separately confirmed in an in vivo antimalarial activity study on Nefang-treated BALB/c mice and Wistar rats preinfected with *P. berghei* and *Plasmodium chabaudi* (Tarkang et al., 2014b).

Herb–herb interaction or combination therapy has been given considerable attention in the treatment of typhoid. This has long been used in traditional medical practice. Combinations of parts of usually more than two plants are mixed in a decoction for patients. Nkuo-Akenji et al. (2001) and Oluduro and Omoboye (2010) extensively investigated the synergistic antibacterial potentials of different polyherbal formulations commonly prescribed by traditional medical practitioners against different species of *Salmonella* (*S. typhi*, *S. paratyphi*, and *S. typhimurium*) including the multidrug-resistant strains (reviewed in detail by Aliero and Ibrahim (2012)). Many of these herbal combinations, especially those that contained *C. papaya* as one of the important constituent plants, exhibited enhanced antibacterial activities against different species of *Salmonella* better than when they were tested alone.

CONCLUSION

C. papaya is an herbaceous laticiferous plant cultivated in most tropical and subtropical countries of the world. Asia (mainly India) is the largest producer. The plant produces latex rich in papain (a major proteolytic enzyme) and contains phenolics, flavonoids, and alkaloids as the major phytochemicals. These are responsible for the traditional and modern uses of *C. papaya* and its products as nutritional supplements and therapeutic agents under various disease conditions. The established pharmacological properties (antioxidant, antiinflammatory, immunomodulatory, and antimicrobial) of *C. papaya* make it a candidate in the treatment of a wide range of diseases (e.g., dengue fever, gastrointestinal infections, and periodontitis) and for wound healing. Studies have shown that *C. papaya* can interact with standard drugs and other herbal products to cause enhanced therapeutic efficacy, but can bring with it adverse effects or treatment failure. Therefore, patients and medical practitioners should exercise caution when using *C. papaya* and its products as medical remedies.

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