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REVIEW ARTICLE

Nutritional and therapeutic potentials of *Carica papaya* Linn. seed: A comprehensive review

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Abstract

The health benefits and nutritional value of pawpaw or papaya (*Carica papaya* Linn.) are well established. The entire papaya plant—including the leaves, fruit, bark, root, juice, seeds and latex - is used for dietary, medicinal and other purposes. However, papaya seeds are the under-exploited part since they are typically seen as waste after the edible fruits have been processed and consumed. Hence, the aim of this review is to document the nutraceutical and therapeutic potential of *Carica papaya* seeds with a view of enhancing its prospect in drug development. The following title search criteria were used "*Carica papaya*" OR "Papaya" OR "Pawpaw OR C. papaya" AND "seed" OR "seed oil"; while "fruits OR leaves OR stem OR root OR juice OR latex" were excluded. The articles used for this research were limited to the original research articles and those written in English Language only. The seeds which are often seen as waste products offer countless possibilities for developing new nutritional supplements and medicines due to the huge vital micronutrients and a variety of secondary metabolites that have been reported to be embedded in them. Papaya seeds contain beneficial phytochemicals such as carotenoids, flavonoids, alkaloids, phytosterols and tocopherols. These substances, have intriguing nutraceutical qualities and are important in the treatment and amelioration of several medical disorders. Benzyl glucosinolates, caricin, fatty acids, crude fibre, carpaine, glucotropaeolin, benzyl isothiocyanate, crude protein, benzyl thiourea, hentriacontane, ß-sitostrol and enzymes (myrosinase and papain) were discovered as nutritional components in papaya seeds. Papaya seeds may be used medicinally as antioxidant, antidiabetic, anti-ulcerogenic, anti-liver cirrhosis and menstrual cycle modulator.

Keywords

Carica papaya; nutritional value; antidiabetic; anthelminthic; nephroprotective

Introduction

Carica papaya Linn. is a tropical fruit indigenous to Mexico, Brazil and Panama in Central America (1-2). There are numerous common names for *Carica papaya*, including papaya, pawpaw, mamao, chichpu, papita and melon tree (3). Pawpaw is known as "ibepe," "okwere" and "gwanda" in Nigeria by the Yoruba, Igbo and Hausa tribes respectively (4). With 4 genera worldwide, the most notable fruit in the *Caricaceae* family is papaya (Fig. 1). In India, the genus *Carica* Linn. is characterized by 4 species; the most popular and commonly grown is *C. papaya* Linn. (5). It is widely renowned for its food, dietary and medicinal benefits worldwide (6). *C. papaya* seeds are usually

tiny, black, spherical and coated with a gelatinous aril; however, this may vary according to species (7).

Fig. 1. *C. papaya* fruit with the seeds.

Once the edible fruits of *C. papaya* have been processed and consumed, the seeds are typically considered as waste products (8). *C. papaya* seed is becoming more popular due to its therapeutic properties (6). It can be eaten and has a spicy and pungent flavour. It is occasionally pulverized and utilized as an alternative to black pepper (9). Consumption of the seed offers an inexpensive, safe, natural, easily accessible monotherapy and preventive method against intestinal parasitosis. The seeds contain benzylisothiocynate, the main antihelminthic (Fig. 2). Benzyl glucosinolates, caricin, fatty acids, crude fibre, carpaine, 1,2,3,4-tetrahydropyridin-3-yl-octanoate, glucotropaeolin, benzyl isothiocyanate, crude protein, benzyl thiourea, hentriacontane, ß-sitostrol and enzymes (myrosinase and papain) are found in papaya seeds (10). Papaya seeds are used medicinally as a carminative, anthelmintics. These are used in menstrual cycle stimulation and have anti-fertility, anti-implantation and abortifacient characteristics. The seeds also work as male fertility inhibitor, a counterirritant and are used in the treatment of liver cirrhosis (11, 12). Papaya seed's anthelmintic properties have primarily been linked to the alkaloid carpaine and the benzyl thiourea (13). Benzyl isothiocyanate (BITC) has been discovered to be the most effective bioactive compound in *C. papaya* seeds. It can potentially harm the endometrium, consequently rendering the uterus infertile and negatively affecting implantation (14).

The vital micronutrients and a variety of secondary metabolites are abundant in *C. papaya* seeds have been credited with its therapeutic uses. The papaya seeds are promising nutraceuticals with anti-diabetic, anti-inflammatory, anti-fertility, anti-tumour, nephroprotective and hepatoprotective agents. Therefore, this review aimed at highlighting the nutritional values, pharmacological uses, chemical composition, prospective uses of papaya seeds and papaya seed oil.

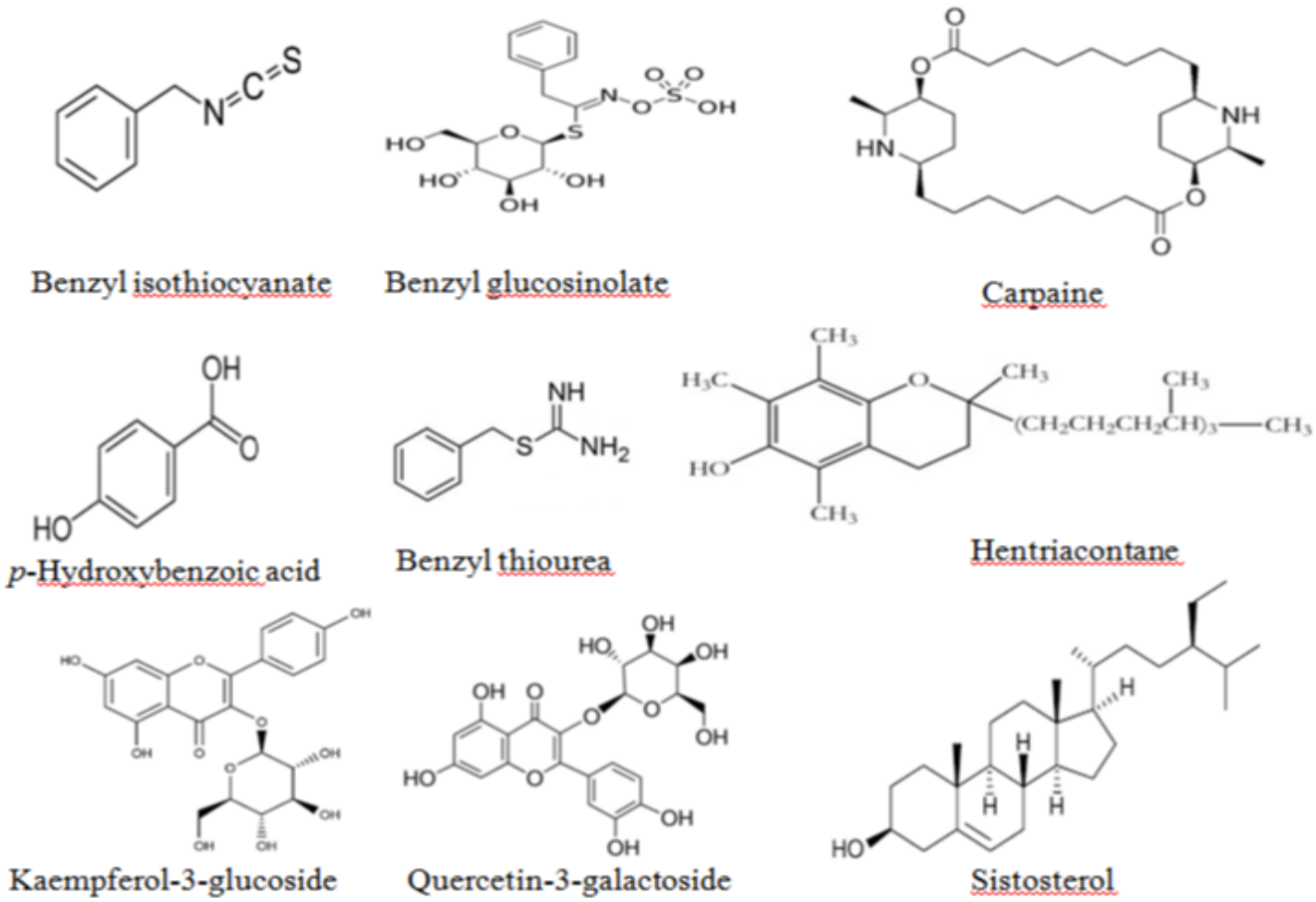

Fig. 2. Compounds isolated from *C. papaya* seeds.

Materials and Methods

Research articles were downloaded from databases such as Scopus, PubMed, Web of Science and google scholar. The keywords used for searching the appropriate articles related to the title were "*Carica papaya*" or "Papaya" or "Pawpaw" or "*C. papaya*" AND "seed" OR "seed oil", however, "fruits, leaves, stem, root, juice, latex" were excluded. The articles used for this research were limited to the original research articles and those written in English Language only.

Results and Discussion

Nutritional Value of *C. papaya* Seed

C. papaya seeds have been shown to contain 25-33% lipid, 29-30% crude protein, 14-19% carbohydrate, 7.8-9% crude fibre, 9-11 % crude ash. *C. papaya* seeds have been reported to contain sodium, potassium, phosphorus, iron, calcium and magnesium levels that range from 9.00 to 98.33 mg/100 g, 13.70 to 244.37 mg/100 g, 9.00 to 1156.00 mg/100 g, 0.17 to 26.58 mg/100 g, 2.52 to 1821.00 mg/100 g and 0.52 to 93.17 mg/100 g respectively (10,15-19). Vitamins and minerals are needed for optimal physiological and metabolic processes. Iron, copper and zinc contents of papaya seeds were greater than watermelon seeds. Likewise, the magnesium level of the watermelon seeds is within the range reported for papaya seeds, while the iron content of melon seeds reported as earlier was higher than the iron constituent of papaya seeds (16). Additionally, it was showed that pawpaw seeds contained beta carotene (65.64 IU/100g), niacin (0.26 mg/100g), thiamine (0.05 mg/100g) and vitamin C (111.73 mg/100g) (17). The seed coat has a comparatively low moisture level, but significantly higher ash content. The seed coat provides both livestock and humans with a good source of protein and fibre, because studies have shown that it has a relatively higher protein and crude fibre content. Dietary fibres can reduce cholesterol levels and eliminate toxins from the digestive system (20). When compared to oil, the seed coat has a modest fat content and energy value. Humans can get all the energy they need from the seed coat by consuming no more than 1000 g of it each day. Papaya seeds are significant in human diets because they have nutraceutical benefits and are full of vitamins and macronutrients. The seeds' high fat, protein and carbohydrate content make them suitable as supplement to existing energy sources for undernourished human populations and animal feedstock (21). Phytochemicals such as carotenoids, phytosterols, tocopherols and phenolics are abundant in papaya seeds. In general, phytochemicals have a variety of advantageous features, including the inhibition of tumour growth, protection against cellular injury and lowering the incidence of non-communicable diseases (22). Amino acids are known to be abundant in papaya seeds; hence it can be explored in feed formulations (10).

Nutritional, industrial and pharmacological value of *C. papaya* seed oil

C. papaya seed oil has a hue that ranges from light to dark yellow. The oil has a pH of 5.6, melting point of 47 ^{0}C, 0.22% moisture content, 0.6% crude fibre, energy value of 525 kcal/100 g, saponification value of 32.9 (mg KOH/g), free fatty acid of 0.278 (mg KOH/g), 0.451 μM/g thiobarbiturate value and refractive index of 1.47 (23, 24). Papaya seed oil has found its applications in industrial, pharmaceutical and biofuel production. The high energy value of *C. papaya* seed oil might make it suitable for use as biofuel (24). Products made from papaya seed oil are marketed as cosmetics and are usually used as antioxidants, skin exfoliators and lightening cream (15). Papaya seeds oil is used as a medication for sickle cell illness and problems linked to the poisoning. The free fatty acid value of the seed oil is rather low, indicating it does not easily go rancid, because of the nature of free fatty acids (18, 24). The oil has a low thiobarbiturate value, which suggests that the lipid peroxidation in the oil is low, indicating that it contains high amount of antioxidants. Therefore, the oil might shield cells from oxidative damage (24). The oil is high in oleic acid and triacylglycerol. Oleic acid and other important fatty acids, such as lipophilic polyphenols. Oleic acid is renowned for its anti-inflammatory properties and may potentially confer beneficial effects on tumour-related genes (25). There are further reports of palmitic, arachidic, linolenic, and stearic acids in the seeds. Compared to other oil seeds, papaya seeds are more economically appealing for industrial use due to their high lipid content (21). It is a good source of unsaturated fatty acids; its nutritional values are comparable to olive oil (25). Before papaya seed oil is commercially used in food markets or the food industry, more research will be needed to determine whether it is edible. However, papaya seed oil is a great option for use in the industries due to its triacylglycerol profile and fatty acid content (Table 1). This could immediately contribute to the reuse and recycle of a significant number of the seeds, consequently reducing agro waste on a global scale.

Pharmacological value of *C. papaya* seed

Papaya seeds are considered as promising nutraceutics, studies have shown that it has pharmacological potential in the following areas.

Antidiabetic Potential

It has been reported that papaya seeds have great potential in managing diabetes (Table 2). Reports are on the significant antidiabetic activity of ethyl acetate fraction of the crude extract of *C. papaya* seeds (CPS) through *in vitro* inhibition of intestinal α-glucosidase and α-amylase when compared to other fractions (29). When these enzymes are inhibited, only a small amount of glucose is absorbed into the bloodstream, preventing a post-meal plasma glucose increase (31). They reported that sub-fraction K had low IC_{50} values and moderately inhibited α-glucosidase and α-amylase (29). Furthermore, metabolites in CPS might conserve the function of beta-

Table 1. Nutritional content of *C. papaya* seed and oil

Nutrients	Function	Reference
Minerals		
Sodium	Conduction of nerve impulses, muscle contraction, maintenance of fluids and mineral balance	(10, 16, 19)
Potassium	Regulation of heart function and water retention	(10, 16, 19)
Phosphorus	Important for growth, repair, and maintenance of cells	(10, 17, 19)
Iron	Formation of haemoglobin, myoglobin, transferrin and other hemoproteins	(10, 16)
Calcium	Bone formation, muscle contraction, blood clotting and regulation of hormone actions	(10, 16, 19)
Magnesium	Carbohydrate metabolism, enhancement of insulin and glucose levels in diabetics	(10, 16, 19)
Copper	Maintenance of integrity of connective tissues	(16, 19)
Zinc	Wound healing, boosting of immune system, regulation of gene expression and metabolism of macromolecules	(16, 19)
Vitamins		
Tocopherols	Serves as antioxidants and protects cells from damage caused by free radicals	(10, 19)
Niacin	Converts nutrients to energy, aids in cell signalling and DNA repair	(10, 19)
Beta carotene	Serves as precursor of vitamin A, also protects against free radical damage	(10, 19)
Thiamine	Helps in energy metabolism	(10, 19)
Vitamin C	Aids in wound healing, immune defence and biosynthesis of collagen	(10, 19)
Fatty Acids		
Oleic acid	Antioxidant, anti-inflammatory and anti-tumour	(18, 21, 25)
Linoleic acid	Maintains membrane fluidity	(10, 18)
Triacyl glycerol	Energy production, storage and insulation	(25)
Stearic acid	Cosmetics emulsifier	(10, 18)
Myristic acid	Surfactant in soap, detergent and textiles	(18)
Phytochemicals		
Carotenoids	Antioxidants and photo protector	(10)
Phytosterols	Lowering of LDL-cholesterol and total cholesterol from the body. Also serves of components of biological membranes	(18)
Phenolics	Antioxidants, anti-inflammatory and anticancer	(10)
Others		
Fibre	Reduction of cholesterol levels and eliminate toxins from the digestive system	(10, 15-17, 20)
Protein	Growth, repair and building of body cells	(10, 15-17)
Carbohydrate	Source of energy	(10, 15-17)

cell of pancreas and repress the actions of α-amylase and α-glucosidase (28). A significant hypoglycemic effect has also been attributed to flavonoids, quercetin, steroids, quinones and kaempferol through the regeneration of pancreatic beta cells and increased insulin production. Hexadecanoic acid, methyl ester, 11-octadecenoic acid, methyl ester, n-hexadecanoic acid and oleic acid were found to be the main antidiabetic components in CSE, and it is hypothesized that these substances could act in conjunction to have antidiabetic effects (28). It was reported that antidiabetic effects of 400 mg/kg b.w. of aqueous CPS on alloxan-induced diabetic rats (26). They reported that papaya seed extract restored kidney and liver functions to normal rate that is comparable to those of non-diabetic rats. Biochemical parameters were significantly altered in the untreated diabetic group. It was reported that antidiabetic potential of 100 and 200 mg/kg of *C. papaya* seeds on streptozotocin-induced diabetic male Sprague-Dawley rats (27). They reported that it significantly reduced blood glucose, elevated liver enzymes and lipid profiles in animal model.

Nephroprotective Potential

The papaya seed extract (PSE) has demonstrated nephroprotective properties (Table 3). Methanolic papaya seed extract dose, dependently inhibited $KBrO_3$-induced nephrotoxicity in rats, this demonstrates the protective effects of papaya seeds. It was reported that 600 mg/kg b.w. of methanolic PSE ameliorated potassium bromate-induced nephrotoxicity (32). Investigations are on the nephroprotective role of ethanolic papaya seed extract in Swiss albino mice, using 10 mg/kg/day cisplatin to induce nephrosis and 100 mg/kg/day ethanolic PSE to protect against cisplatin-induced nephrotoxicity (33).

The ethanolic PSE extract significantly improve liver and kidney functions. It was also reported the nephroprotective effects of aqueous PSE on paracetamol-induced nephrotoxicity in rats (34). The results of their investigation demonstrated that daily pre-treatment with 500 mg/kg and 750 mg/kg PSE for 7 days offered nephroprotection in the paracetamol renal-damaged. The extract reversed the changes generated in kidney structure, protecting against the harmful effects of

Table 2. Antidiabetic activity of papaya seeds

Model	Dosage	Significance	Reference
Alloxan-induced diabetic rat model	400 mg/kg aqueous papaya seed extract for 28 days	Reduced blood glucose levels	(26)
Streptozotocin-induced diabetic rat model	100 and 200 mg/kg aqueous papaya seed extract for 14 days	Dose-dependent decrease in blood glucose levels	(27)
Streptozotocin-induced diabetic rat	250, 500 and 1000 mg/kg body weight	Ethyl acetate fraction significantly reduced postprandial glucose levels in diabetic rats	(28)
In vitro α-glucosidase and amylase inhibitory activities	Twenty microliters of 20–100 mg/mL	Ethyl acetate fraction D showed maximum inhibition of α-amylase (84.56 ± 0.23%) and glucosidase (51.81 ± 0.45%) with an IC50 values of 36.86 and 82.33 mg/ml respectively.	(29)
In vitro α- amylase inhibitory activities	200 µL seed extract at 40- 640 µg/mL	Methanol extract of seeds more effective than acarbose (standard drug) with IC_{50} values of 46.99±0.018 µg/mL and respectively.	(30)

paracetamol. In another research report, it was demonstrated the nephroprotective effect of aqueous PSE in carbon tetrachloride (CCl_4) induced toxicity (11). Before being challenged with 1.5 ml/kg b.w. of 20% CCl_4, three groups of rats were orally pre-treated with 100 to 400 mg/kg b.w. for 7 days. Additionally, the effect of dose of 400 mg/kg was assessed over a time-course of 3 hrs at, 0hr, 1 hr, 3 hr and 6 hr after CCl_4 administration respectively. Their results demonstrated that intraperitoneal injection of CCl_4 caused a considerable rise in serum levels of urea, creatinine and uric acid and histological alteration. However, advancements in the observed biochemical variables were greatly decreased in a dose-dependent manner following administration of PSE. The extract provided the greatest nephroprotection, lasting up to 3 hrs post-CCl_4 exposure and at 400 mg/kg/day PSE. Advancements in the renal histology lesions brought on by CCl_4 poisoning confirmed this biochemical evidence (11). Reports are also on the nephroprotective effect of the 200 mg/kg b.w. of aqueous PSE on gentamicin-induced nephrotoxicity in rats (35). Aqueous extract of the seed normalises biochemical parameters and kidney structures (35).

Antitumour Potential

Tumours are caused by an unregulated cell cycle, which leads to uneven tissue mass growth (36). Cells' irregular development manifests as either malignant or non-cancerous tumours. Reports are on the anti-tumour properties of papaya seeds on various cancer cells. It also showed cytoprotective properties against inflammation and oxidative stress (37). The mechanisms for anti-tumour effect of papaya seed extract include ability to maintain cell's mitochondrial viability, antiproliferative, reduction of intracellular reactive oxygen species levels and mediation of pro-inflammatory cytokine secretory levels (tumour necrosis factor-a, interleukin-6, monocyte chemo attractant protein-1. At 2 mg dry weight ml^{-1}, *in vitro* cultures of the extracts of seeds from ripe and unripe fruit showed cytoprotective effects and notably decreased levels of oxidative stress in hydrogen peroxide-exposed human pre-adipocytes (SW872) and hepatocellular carcinoma cells (HepG2) (37), human lung cancer (H69), where the seeds showed an antiproliferative effect against H69 cells in an *in vitro* culture in a dose-responsive manner of 50 µg/ml, 100 µg/ml, 250 µg/ml, 500 µg/ml of methanol and hexane for 24 hrs. At the most elevated concentration

Table 3. Nephroprotective potential of *C. papaya* seeds

Model	Dosage	Significance	Reference
Potassium bromate-induced nephrotoxicity rat model	100, 200, 400 and 600 mg/kg methanolic Papaya seed extract for 48 hrs	Prevented renal damage	(32)
Cisplatin-induced Nephrotoxicity in mice	100 mg/kg ethanolic papaya seed extract	Decreased elevated biochemical parameters	(33)
Paracetamol- induced nephrotoxicity rat model	500 and 750 mg/kg aqueous papaya seed extract	Reversed changes generated in kidney structure	(34)
Intraperitoneal Carbon tetrachloride-Induced nephrotoxicity rat model	100-400 mg/kg aqueous papaya seed extract for 7 days	Improved renal histological lesions	(10)
Gentamicin-induced nephrotoxicity	200 mg/kg aqueous papaya seed extract	Prevented severe alterations of biochemical parameters	(35)

of methanol and hexane (500 µg/ml), 76% and 62% were viable (38). It was reported the anti-tumour effects of papaya seeds on the prostate cancer (PC-3) cell line (39). The white and black seeds from unripe papaya and ripe papaya respectively, were taken from the fruit and extracted using water, 80% methanol and hexane. An assay for the growth of WST-1 cells was used to investigate the cytotoxic effects of seed extracts. PC-3 cells' proliferation was dramatically reduced by water extracts from *C. papaya* white seeds and methanolic extracts of the black seeds. The aqueous extract from white seeds, however, promoted PC cell growth. Compared to white seeds, black seeds have a much higher concentration of polyphenols. The evidence suggests that while white papaya seeds promoted the growth of prostate cancer, black papaya seeds had an anticancer effect on PCs. The high quantity of polyphenols in black seeds may be the cause of their anti-tumour properties. They posited that the consumption of white papaya seeds should be avoided, while the consumption of black papaya seeds should be encouraged due to their potential to slow the growth of prostate cells (39). It was reported the anti-proliferation potential of aqueous extract of papaya seed in breast cancer cells using a WST-1 assay (40). Hence, the aqueous PSE induced little to moderate cytotoxic effects only on ER-negative breast cancer cell lines. They proposed that the seed's anti-tumour properties were due to the presence of benzyl isothiocyanate (BITC) and the high antioxidant activity of the seed. Myrosinases found in papaya seeds catalyse the production of isothiocyanates by hydrolysing glucosinolate. Benzyl isothiocyanate (a compound found in papaya seed) has been reported to induce protective autophagy in cancer cells through inhibition of mammalian target of rapamycin (mTOR) signalling. Inhibition of mTOR has been reported to increase the expression of autophagy-related genes (*Atgs*), such as *Atg8* (LC3) and the kinase activity of *Atg1.* It has also been reported to target mitochondria and trigger ROS -dependent apoptosis in cancer cells. Papain has been reported to cleave peptide bonds containing basic amino acids, especially those containing arginine, lysine and residues after phenylalanine. Hence, papain acts by destroying fibrin-protective coating of many cancer cells. Other mechanisms involve activating tumour-suppressor genes, deactivating oncogene products transcriptionally, cell cycle regulation and appropriate cell death, decreasing oxidative damage by scavenging free radicals and impeding the commencement of lipoxygenase reaction by chelating with ROS-generating agents (36).

Anthelmintic Potential

C. papaya seeds (CPS) have been used in traditionally to treat helminths. Several studies demonstrated the ability of PSE to combat internal nematodes in various mammalian hosts. It was reported that PSE was effective in controlling helminthosis in Red Sokoto goat (41). The parasiticidal abilities of the CPS could be explained by the presence of benzyl isothiocyanate (BITC). They reported that 300 mg/ kg body weight/day of CPS extract per day administered to goat completely cleared all the parasites at the 3rd day and was comparable to thiabendazole (standard drug). In a different study, it was reported that when 20 mL elixir of CPS and honey were given to children, 75-100% significant clearance of intestinal worms was seen in the faeces of the children compared to the control group (honey alone) which achieved a clearance of 0-15% within 7 days (42). There were no negative consequences following CPS elixir treatment, hence ingestion of CPS could offer an affordable, natural, safe and easily accessible curative and prophylactics against intestinal parasitosis (42).

Antiulcerogenic Activity

One of the gastrointestinal tract problems that causes ulcers is excessive stomach acid or pepsin secretion, which leads to the erosion of the gastric or duodenal mucosa. In a study by Okewunmi and Oyeyemi (43), 100 mg/kg PSE protected the stomach mucosa from ethanol-induced gastric ulcers. The quantity of gastric juice and gastric acidity were dramatically lowered by the seed extract of *C. papaya* dose-dependently. It was reported that the gastroprotective effect of methanolic PSEs in ethanol and indomethacin-induced acute gastric ulcers and acetic acid -induced chronic gastric ulcers (44). No adverse effects were observed, even at concentrations as high as 2000 mg/kg of the extract. A dose of 30 mg/kg of lansoprazole (standard drug) demonstrated 79% inhibition in the ethanol model, in contrast 82% inhibition exhibited by 500 mg/kg of the methanolic extract of CPS (MECPS) (Table 4). 500 mg/kg of MECPS was reported to display a superior anti-ulcerative effect than 200 mg/kg cimetidine (standard drug), while MECP reduced the ulcerative symptoms by 82%, cimetidine reduced it by 73% (44).

Antifertility Potential

Extracts of CPS have been reported to be effective contraceptives for men and women; hence, it is used in family planning (Table 5). It was reported that 100 mg/kg b.w. of n-hexane extract of CPS administered for 24 days significantly reduced sperm quality (motility, viability, quantity and normal sperm cell morphology) in Wistar rats

Table 4. Anti-ulcerative potential of *C. papaya* seeds

Model	Dosage	Significance	Reference
Ethanol-induced gastric ulcer male rat model	100 mg/kg Papaya seed extract for 48 hrs	Lowered gastric juice and acidity	(43)
In vivo ethanol, indomethacin and acetic acid-induced gastric ulcer rat model	125, 250, 500 mg/kg methanolic papaya seed extract	Decreased gastric lesions and lowered ulcerative symptoms	(44)

(12). It was reported the influence of 14 days of oral administration of chloroform extract of 100 mg/kg b.w. of CPS on oestrous cycle, fertility and serum 17-oestradiol levels in female rats (45). Ten proestrus rats received the same treatment as in the oestrous cycle study for 14 days before coexisting in close quarters with fertile male rats that had not received CPS for 14 days. They reported that the rats' body weight was not significantly affected by CPS, but the ovary's weight decreased significantly, but not that of the uterus. In rats given CPE, serum levels of 17-oestradiol significantly dropped and from the 3rd week of CPS treatment, the oestrous cycle became erratic, with a protracted dioestrous phase in rats. The ovary displayed disarray and deterioration, while the uterus displayed vacuolation and little disarray. They also reported that though the number of litters generated by the extract-treated rats significantly decreased, the weight and morphology of the foetuses did not alter in comparison to the control group (45). Reports are on the isolation of 1,2,3,4-tetrahydropyridin-3-yl-octanoate as the antifertility compound in PSE (46). The isolated compound reduced spermatozoa motility and viability. It was reported that contraceptive ability of papaya seeds in female rats following 7 and 21 days of administration of 200 mg/kg aqueous extract of CPS extract (13). A significant decline in uterine weight and blood progesterone levels was observed, so also, theca cells, granulosa and corpus luteum showed considerable degeneration and mucin granules were lost from the uterine tissues in treated groups when compared to the control which had higher proestrus and dioestrus phases. The dioestrus and proestrus phases of the oestrous cycle of the treated group became longer and more irregular. Aqueous PSE lowered progesterone levels, disrupted oestrus patterns and histologically altered utero-ovarian tissue, which all contributed to antifertility and anti-implantation (13). The proposed mechanism for contraceptive nature of compounds and bioactive agents in *C. papaya* seed such as 1,2,3,4-tetrahydropyridin-3-yl-octanoate was due to feedback inhibition of key enzymes such as aromatase, hydroxysteroid dehydrogenase, hydroxysteroid isomerase etc. which are involved in the synthesising of reproductive hormones.

Hepatoprotective Activity of C. Papaya Seed

The hepatoprotective potential of ethanol extract of *C. papaya* seeds (EECPS) was reported earlier in rifampicin and isoniazid (anti-tuberculosis drugs) induced hepatotoxicity in rats (47). According to the findings, EECPS considerably lowers the levels of ALT, AST, ALP, GGT and bilirubin in the treated groups. A different study carried out reported the hepatoprotective effect of aqueous extract of *C. papaya* seed (AECPS) to minimize the harmful effects of thermally oxidized palm oil (TPO) in rats (49). The rats were fed TPO and AECPS for 28 days. The findings demonstrated that adding *C. papaya* seed extract to a diet high in thermally oxidized palm oil conferred a hepatoprotective effect in treated rats. It was also reported that the hepatoprotective potential of AECPS on CCl_4 induced hepatotoxicity in rats (49). Their result showed effective hepatoprotection was conferred at 400 mg/kg/day of the extract.

Antioxidant Potential

It was reported that strong antioxidant activity in the ethyl acetate fraction (EAF) as well as the n-butanol fraction (NBF) of the CPS extract (50). EAF demonstrated the most potent free radical-scavenging activities of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and hydroxyl groups *in vitro*. The n-butanol fraction showed the greatest $ABTS^{+*}$ radical scavenging activity. The EAF and NBF also showed higher superoxide anion and hydrogen peroxide radical scavenging activities. Also contributing to the antioxidant activities in the EAF and NBF is the high quantity of total phenolics and flavonoids. Zhou and colleagues isolated p-hydroxybenzoic acid and vanillic acid as the bioactive compounds responsible for antioxidant effect in CPS. It was reported that papaya seed extract's antioxidant capacity to hydrogen peroxide-induced oxidative stress in Detroit 550 fibroblasts from human skin (51). Their results showed that *C. papaya* seed water extract is safe and serves as a strong free radical scavenger. They observed that the extract prevents the release of cytochrome C and does not increase catalase activity when the fibroblasts were subjected to oxidative stress. It also lowers cell apoptosis, ensures Ca^{2+} homeostasis, counteracts mitochondrial dysfunctionality and consequently protects Detroit 550 fibroblasts from oxidative stress caused by hydrogen peroxide than vitamin C (the standard antioxidant). It was also reported that methanol and hexane extract of CPS modulated endogenous glutathione, superoxide dismutase, catalase and glutathione peroxidase (GPx) against H_2O_2 induced oxidative stress in HepG2 cells. It was also reported that CPS have potent antioxidant characteristics and can lower DPPH radicals, ABTS, NO_2 and ferric ions because of their diversity of bioactive secondary metabolites (52). Reports are on the isolation of many bioactive chemicals such as 11-octadecenoic acid, methyl ester N, N-dimethyl, n-hexadecanoic acid, oleic acid and methyl ester in the EAF fraction of *C. papaya* seeds (28). N-hexadecanoic acid and oleic acid have been identified in several investigations as possessing antioxidant potential.

Table 5. Antifertility potential of *C. papaya* seed

Model	Dosage	Significance	Reference
Male Wistar rat model	100 mg/kg n-hexane papaya seed extract for 24 days	Reduced sperm quality	(11)
Female rat model	100 mg/kg chloroform papaya seed extract	Decreased ovary weight and irregular oestrous cycle	(45)

Anti-Inflammatory Potential

The protein enzyme papain, isolated from papaya seeds, demonstrated an anti-inflammatory effect of *C. papaya* seeds. Repression of the activities of inflammatory mediators like histamine, prostaglandins, nitric oxide, inflammatory cytokines such as IFN-γ, TNF-α, IL-6 and NF-kβ, platelet-activating factor, and effects on adrenocortical hormone and immunosuppression are some of the mechanisms that possibly underlie its anti-inflammatory activity in acute, sub-acute and chronic experimental models (53, 54). Inflammation is due to the reaction of a cell/tissue to infection, injury, or irritation. It is often characterised by fever, swelling, swelling and pains. During inflammation, mast cells are often mobilised to release histamine. Another plausible explanation for the anti-inflammatory activity of papaya seed could be to the presence of antihistamine compounds in it. These compounds are capable of inhibiting lipoxygenases might be responsible for reducing the production of leukotrienes and consequently delaying inflammation (Fig. 3). Aqueous extract of *C. papaya* notably decreased carrageenan-induced pedal oedema and formalin-induced pedal oedema in rats (54).

Enzyme Source of *C. papaya* seed

Papain and myrosinase are very useful enzymes found in the seeds of *C. papaya*. The anti-inflammatory and immunomodulatory properties of papain are well known for enhancing the body's resistance to infection (55). It cleaves peptide bonds containing basic amino acids preferentially, especially those containing arginine, lysine and residues after phenylalanine. Numerous cancer cells have a fibrin-protective coating that makes them go months or years without being discovered. The fibrin coating on the cancer cell wall is destroyed by papain; hence making the detection of cancer cells possible (56). Myrosinase is responsible for the hydrolysis of benzylglucosinolate contained in *C. papaya* seed to produce BITC (57).

Conclusion

Numerous studies have confirmed pharmacological and nutraceutical potentials of *C. papaya* seed. Papaya seed oil could be included into the formulation of skin and hair care products due to abundant antioxidants, antimicrobial, collagen synthesising agent and enzymes in it which could aid wound healing, photo protection, skin exfoliation, tissue regeneration/rejuvenation. In view of paucity of information on the safety of *C. papaya* seeds and oil; there is a need to carryout comprehensive toxicological studies and establish pharmacokinetics in various animal models and human subjects. This will help in the developments of novel drug candidates and nutraceutics.

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Authors' contributions

RIA conceptualised the study, wrote part of the original draft and revised the final draft. ETO wrote part of the original draft. IOO wrote part of the original draft. KO revised the original draft. MOA supervised the work and revised the final draft. All authors read and approved the final manuscript.

Compliance with ethical standards

Data Availability

Data availability is not applicable as data sets were not generated.

Conflict of interest: None

Ethical issues: None.

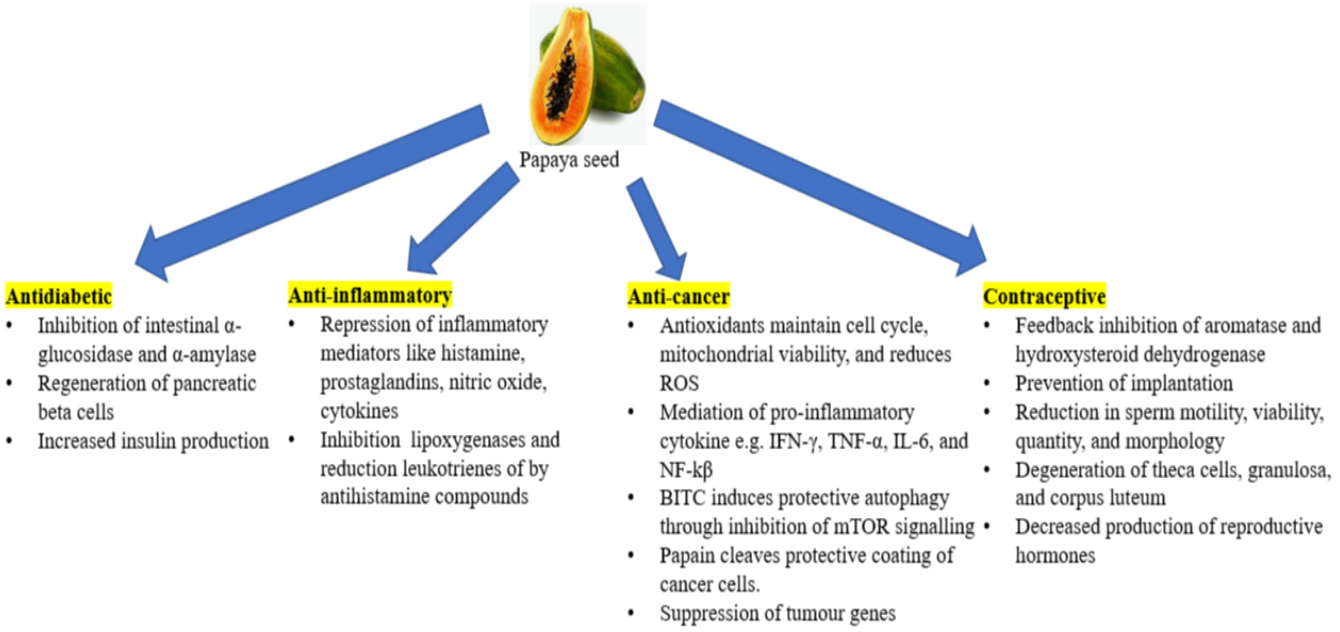

Fig. 3. Mechanism of action of various pharmacological applications of papaya seed.

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