Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

**E-ISSN:** 2278-4136
**P-ISSN:** 2349-8234
JPP 2017; 6(1): 424-429
Received: 24-11-2016
Accepted: 25-12-2016

**Dr. Neethu S Kumar**
Assistant Professor, Post Graduate Department and Research Centre of Botany, Mahatma Gandhi College, Thiruvananthapuram, Kerala, India

**Sreeja Devi PS**
Post Graduate and Research Centre, Department of Botany, Mahatma Gandhi College, Kesavadasapuram, Thiruvananthapuram, Kerala, India

**Correspondence**
**Dr. Neethu S Kumar**
Assistant Professor, Post Graduate Department and Research Centre of Botany, Mahatma Gandhi College, Thiruvananthapuram, Kerala, India

# The surprising health benefits of papaya seeds: A review

**Dr. Neethu S Kumar, Sreeja Devi PS**

**Abstract**
The study mainly focused on the secret behind the papaya seed against cancer. Papaya (*Carica papaya* Linn.) is well known for its exceptional nutritional and medicinal properties throughout the world. The whole plant including its fruit, leaves, seed, root, bark, juice and latex obtain from papaya plant used as nutritionally, medicinally and for various other purposes. A papaya in vitro study shows that it will treat many cancer cell line and papaya physiochemical having anticancer activities. Papaya is rich in enzyme papain which is effective against cancer. Papain breaks down the fibrin cancer cell wall and protein into amino acid form. Other than papain it also contain lycopene which highly reactive towards oxygen and free radical. Isothiocyanate contained in papaya seed, work well for colon, breast, lung, leukemia and prostrate cancer. These enzymes capable of inhibiting both formation and development of cancer cell.

**Keywords:** Papain, Lycopene, anticancer

## 1. Introduction
Papaya belongs to a small family caricaceae having four genera in world. The genus *carica* L. is represented by four species in India, of which *Carica papaya* L. is the most widely cultivated and the best-known species (Jean *et al*., 2011) [24]. It is commonly known as Papaya Melon tree, Pawpaw or Papau, Kapaya, Lapaya, Papyas, Papye, Tapayas, Fan mu gua, papita, arand- kharpuja, papayabaum and papaya (Bhattachrjee, 2001) [10]. The taxonomical classification includes Kingdom (Plantae), Order (Brassicales), Family (Caricaceae), Genus (*Carica*) and Species (*papaya*). Papaya is probably originated in southern Mexico and Costa Rica, subsequently got introduced in Australia, Hawaii, Philippines, Sri Lanka, South Africa, India and all tropical and subtropical regions. It is growing both commercially and in home garden (Marotta *et al.*, 2006) [32]. A study conducted by University of Florida researchers Nam Dang and colleagues in Japan has documented papaya's powerful anticancer properties and its impact on numerous lab-grown-tumors.
The papaya seed contain fatty acids, crude protein, crude fibre, papaya oil, carpaine, caricin, glucotropaeolin, benzyl glucosinolates, benzyl Isothiocyanate, benzyl thiourea, hentriacontane, ß-sitostrol, caressing and an enzyme myrosin. The seeds and the pulp of *Carica papaya* contain benzyl glucosinolate which can be hydrolyzed by myrosinase to produce benzyl isothiocyanate. Seed extracts have profound bactericidal activity. The seeds of unripe fruits are rich in benzyl isothiocyanate, a sulphur containing chemical that has been reported to be an effective germicide and insecticide. These substances are important for plant natural defense mechanisms (El Moussaoui *et al.*, 2001) [16]. Medicinal uses of papaya seed are carminative, anti-fertility agent in males, counter irritant, as a paste in the treatment of ringworm, psoriasis, emmenagogue, vermifuge, liver cirrhosis and abortifacient. Seed juice is used for bleeding piles, enlarged liver and pectoral properties. Seed paste is used as anthelmintic, stimulation of menstruation or abortion.
*Carica papaya* seeds were approved and confirmed in some studies for their effective anthelmintic properties against nematodes found in animals (Chota A., 2010) [13]. Chinoy *et al.*, (2006) [12] proved the anti-fertility, anti-implantation and abortifacient properties of extracts from papaya seeds. It has been established in males that the seeds of *C. papaya* are potential anti-fertility drugs (Lohiya *et al*., 2005) [30]. Pawpaw seeds are used to produce an indigenous Nigerian food condiment called 'daddawa', the Hausa word for a fermented food condiment (Dakare, 2004) [15]. Fermented seeds have no effects on litters of rats (Abdulazeez *et al.*, 2009) [1], whereas, those effects were apparent when the unfermented extract was administered (Abdulazeez, 2008) [2]. Anthelmintic activity of papaya seed has been predominantly attributed to carpaine (an alkaloid) and carpasemine (later identified as benzyl thiourea). Carpaine has an intensively bitter taste and a strong depressant action on health.

It is present not only in papaya fruit and seed but also in its leaves. Benzyl isothiocyanate (BITC), the main bioactive compound in *C. papaya* seeds (Kermanshai *et al.*, 2001) [25] has been shown to be responsible for the anti-fertility effect (Adebiyi *et al.*, 2003) [4]. BITC is capable of damaging the endometrium, making the uterus non-receptive and, thus, affecting adversely the implantation (Adebiyi *et al*., 2003) [4].

Seeds are also a rich source of amino acids; scented oil was extracted, used in treatment of sickle cell disease and poisoning related disorders (Saran and Choudhary, 2013) [45,46]. Papain is used in food processing to tenderize meat, clarify beer and juice, produce chewing gum, coagulate milk, prepare cereals, and produce pet food, also to treat wool and silk before dying, de-hair hides before tanning, adjunct in rubber manufacturing and proteolytic enzymes (papain and chymopapain). Papaya seeds are rich source of amino acids especially in the sarcotesta. A yellow to brown, faintly scented oil was extracted from the sundried, powdered seeds of unripe papayas at the Central Food Technological Research Institute, Mysore, India. White seeds yielded 16.1% and black seeds 26.8% and it was suggested that the oil might have edible and industrial uses. Air dried papaya seeds with honey showed significant effect on human intestinal parasites without significant side effect. Consumption of papaya seed is cheap, natural, harmless, readily available, mono-therapeutic and prevent against intestinal parasitosis especially in tropical communities.

Under diverse agro-climatic conditions of North Bihar, the autumn sown crop is best suited for seed production (Ram and Ray, 1992; Singh *et al.*, 2010) [42, 48]. Quality seed production suffer from several limiting factors including physiological disorders. Different nutrient deficiencies of boron, zinc and sulphur and environmental stresses cause several physiological disorders such as bumpy fruit which may lead to deformed/discolored seeds. Discolored seeds, vivipary seeds (Saha, 2007; Saran *et al.*, 2013a) [44] and white seeds (disturbed sarcotesta) were identified as new physiological disorders of papaya under diverse agro-climatic conditions of India. During seed development period, proper temperature also plays an important role. Keeping a fore-mentioned facts in mind, the present study was conducted on the varietal screening for bumpiness; morphology and economics of bumpy fruits, deformed/discolored seeds, vivipary and white seeds (disturbed sarcotesta) and relationship between temperature and disorders (deformed seed and vivipary).

Increasing anecdotal reports of its effects in cancer treatment and prevention, with many successful cases, have warranted that these pharmacological properties be scientifically validated. A bibliographic search was conducted using the key words "papaya", "anticancer", and "antitumor" along with cross-referencing. No clinical or animal cancer studies were identified and only seven in vitro cell-culture-based studies were reported; these indicate that *C. papaya* extracts may alter the growth of several types of cancer cell lines. However, many studies focused on specific compounds in papaya and reported bioactivity including anticancer effects. This review summarizes the results of extract-based or specific compound-based investigations and emphasizes the aspects that warrant future research to explore the bioactives in *C. papaya* for their anticancer activities.

According to the Journal of Ethno pharmacology published on the 17th of February, 2010, international doctors and researchers from US and Japan have discovered that enzymes found in Papaya Leaf Tea have dramatic cancer-fighting properties against a broad range of tumors. A study conducted by University of Florida researchers Nam Dang and colleagues in Japan has documented papaya's powerful anticancer properties and impact numerous lab-grown-tumors. Another important use of the papaya seed could prevent or possibly even treat food poisoning. The seeds of papaya are believed to have strong anti-bacterial and anti-inflammatory effect on our digestive system. Studies have shown that an extract made from papaya seed is effective in killing *E.coli*, Salmonella, Staphylococus and other dangerous bacterial infections. There are even reports of using papaya seeds to successfully treating viral infections such as Dengue fever in parts of Central America like Costa Rica.

**2. Anti-amoebic activity**

The study suggested that the cold macerated aqueous extract of matured papaya seeds (100 µ/mL) showed significant anti-amoebic activity against *Entamoeba histolytica*.

**3. Anti-ulcer activity**

Aqueous seed extract of *C. papaya* at the dose of 50 mg/ kg and 100 mg/kg against alcohol induced acute gastric damage and blood oxidative stress in rats. The gastric acidity was significantly reduced in rats treated with 100 mg/kg of the extract.

**4. Anthelmintic**

The dried papaya seeds gives as elixir with honey have shown significant effect on the human intestinal parasites, without significant side effects. Benzylisothiocynate, present in seeds is the chief anthelmintic.

**5. Effect on smooth muscles**

Ethanol extract of papaya seeds at 0.1-6.4 mg/mL showed concentration dependent inhibition of jejunam contraction and found significantly irreversible. Thus the extract is capable of weakening the contractile capability of isolated rabbit jejunam.

**6. Administration dependent antioxidant effect**

Seeds are the less exploited part thus this study is aimed at assessing the antioxidant activities of the *C. papaya* seeds water extract against hydrogen peroxide ($H_2O_2$) oxidative stress in human skin Detroit 550 fibroblasts. *C. papaya* seeds water extract is not toxic and acts as a potent free radical scavenger, providing protection to Detroit 550 fibroblasts that underwent $H_2O_2$ oxidative stress. Study show that (1) the maximum protective effect is achieved by the simultaneous administration of the extract with 1 mmol/L $H_2O_2$; (2) the extract in presence of an oxidative stress does not increase catalase activity and prevents the release of cytochrome C and the inner mitochondrial transmembrane potential loss; (3) the extract is more efficient than vitamin C to hamper the oxidative damage; (4) the purified subtractions of the seeds water extract exert the same antioxidant effect of whole extract. In conclusion, *C. papaya* seed water extract is potentially useful for protection against oxidative stress.

**7. Immuno- modulatory activity**

Chemical constituents of the *C. papaya* seed extract and its bioactive fraction were examined in vitro using lymphocyte proliferation assays and complement-mediated haemolytic assay.

**8. Selected studies on pharmaceutical application of *Carica papaya* on laboratory animals**

The effects of *Carica papaya* on laboratory animals have been reported as remarkable antifertility natural medicine

(Owoyele *et al.*, 2008 & Lohiya *et al*., 2006) [37, 29]. Treating rats with papaya extract in a dose of 200 mg/kg/day for periods of 1 and 8 weeks revealed pronounced hypertrophy in sperm characteristics and its ultra-structure. Rats treated with a lower dose of 50 mg/kg showed mild hypertrophy and hyperplasia effects in the mentioned characteristics. However, gradual degeneration of the Sertoli cells, Leydig cells germinal epithelium and germ cells were also been reported (Manivannan *et al.*, 2009) [31]. These findings were strongly supported by other studies in which rats were given oral doses of 50, 100, 250, and 500 mg/kg methanolic extract of *C. papaya* seeds for 28– and 90–day periods (Lohiya *et al.*, 2006) [29]. It was found that in the rats treated with doses of 50, 100 mg/kg of the extract the density of the sperm decreased whereas in the rats treated with the dose of 500 mg/kg levels for the same period, the interval total sperm motility was inhibited. Similar findings were reported in dose–dependent study in which suppression of aqueous *C. papaya* seed extract on sperm motility in mice was investigated and revealed that with high dosages of the extract, decrease in both sperm count and viability were observed (Verma *et al.*, 2006) [58].

Aqueous extract of *C. papaya* seeds at doses of 100–400 mg/kg/day was investigated for its effects on hypolipidemic, cardioprotective parameters in normal male Wistar rats for 30 days (Adeneye *et al.*, 2009) [5]. Three groups of rats were orally administered either with extract of *Carica papaya* seed at doses of 100, 200, and 400 mg/kg/day of the extract or 0.1 mg/kg/day of glibenclamide or 10 ml/kg/day of distilled water (control) for a period of 30 days. The results showed that *Carica papaya* extract significantly ($p$<0.05) lowered the total cholesterol, serum triglyceride, fasting blood glucose and significantly ($p$<0.05) reduced the density of lipoprotein cholesterol in a dose dependent manner compared to the untreated control rats. A single oral dose at 2,000 mg/kg or 5,000 mg/kg of methanolic and aqueous extracts of whole unripe extract of *Carica papaya* seeds were tested for their toxic effects in rats and they did not elicit signs of toxicity in the treated animals (Ezike *et al.*, 2009) [17]. This study was in a good agreement with the previous investigated study (Lohiya *et al*., 2006) [29]. It was also found that rats orally administrated with methanolic extract of *Carica papaya* seeds daily for long term affected sperm parameters of the rats such as motility, viability and count (Goyal *et al.*, 2010) [19]. Recently, extract of *Carica papaya* leaves was investigated for its toxicity (Halim *et al.*, 2011) [21]. In the study, Sprague Dawley rats received fixed doses of 5, 50, 300 and 2000 mg/kg of the extract and observed for 14 days. The given doses even at the higher level (2000 mg/kg) did not produce mortality or significant changes in body weight or food and water consumption. The investigated rats did not show signs of toxicity and no deaths were observed. In addition, normal relative weights of the internal organs were observed. However, significant increases in hemoglobin (HGB), hematocrit (HCT), red blood cell (RBC) and total protein were recorded indicating dehydration.

**10. Studies on morphological and quantitative traits**

The observations were recorded from December, 2008 to May, 2013. The average monthly temperature was recorded from IARI RS Pusa observatory. Morphological observations were recorded for fruit surface, seed attachment, seed color, seed surface, sarcotesta, removal of sarcotesta and vivipary in both varieties namely, Pusa Dwarf and Pune Selection-3. The fruits of Pusa Dwarf were observed with vivipary and morphological observation for fruit surface, seed attachment, seed color, seed surface, seed size, sarcotesta and removal of sarcotesta during fruit harvesting (initia-tion of colour turning stage) and seed extraction. The data were also recorded on the total number of seeds/fruit, number of normal seeds/fruit, number of deformed seeds/fruit, white seeds/fruit, vivipary seeds/fruit, deformed seeds (%), seed harvest (%) and economic losses (Rs/ha) in Pusa Dwarf at seed crop harvesting (December to May) due to deformed seed disorder in autumn crop. Each fruit was cut into two equal halves for observing the incidence. The deformed/discolored seeds were recorded by counting the seeds in different categories. An economic loss was estimated by calculating the seed yield per unit area in kilograms. Loss was estimated by observing seed harvest (normal and deformed percent) in particular months and multiplied by our sale price (at Rs. 40,000/kg). Relationship between average monthly temperatures, time of fruit harvest and seed disorders, namely, deformed seed and vivipary seeds from December to May were shown during the study years.

**11. The cytotoxic effect of *C. papaya* extract has been tested in various cancer cell lines in vitro studies summarized in table**

| Cancer Cell Line | Treatment | Result | Reference |
|---|---|---|---|
| Acute promyelotic leukemia HL-60 cells | *n*-hexane extract of papaya seed or pulp (0.1– 100 _g/mL),Pure benzyl isothiocyanate (10 _M) | Extract of seed: Dose dependently inhibited the superoxide generation (IC50 = 10 _g/mL) and the viability of cells (IC50 = 20 _g/mL), comparable to that of pure benzyl isothiocyanate. Extract pulp had no effects at 100g/mL | Nakamura *et al.*, 2006 [35] |

**9. Phytochemicals in *C. papaya* with Reported Anticancer Activities**

*Carica papaya* contains a broad spectrum of phytochemicals including enzymes (in the latex), Carotenoids (in fruits and seeds), alkaloids (in leaves), phenolics (in fruits, leaves, and shoots), glucosinolate (in seeds and fruits) (Krishna *et al.*, 2008; Parle *et al*., 2011) [27, 40]. Some important phytochemicals found in *C. papaya* are Lycopene, Betacarotinoid, Benzyl isothiocyanate, Betacryptoxanthin, Benzylglucosinolate, chlorogenic acid, caffeic acid, protocatechuic acid, Quercetin etc. Among more than 5000 compounds from plants that have been identified to be associated with anticancer properties (Huang *et al*., 2009) [23], three groups of bioactive compounds-phenolics, Carotenoids, and glucosinolate-have attracted considerable interest in anticancer studies. Pure compounds of these three groups have been extensively researched in vivo and in vitro studies on many types of cell lines for their potential effects in cancer treatment and prevention. These bio actives act via multiple mechanisms such as cancer cell signalling, proliferation, apoptosis, migration, invasion, as well as angiogenesis and carcinogen elimination (Huang *et al*., 2009; Zhang *et al*., 2004; Thornalley *et al*., 2002; Nakamura *et al*., 2006; Wu *et al*., 2009; Navarro *et al*., 2011; Wahle *et al*., 2011; Soobrattee *et al*., 2006; Tanaka *et al*., 2012; Van Breemen *et al*., 2011) [23, 62, 52, 35, 60, 36, 59, 49, 51, 57] to exhibit in vitro and in vivo

anticancer activities.

**12. Papaya is Rich Source of Enzyme Papain which is Effective against Cancer**

Papain is an endolytic plant cysteine protease enzyme which is isolated from papaya (*Carica papaya* L.). It preferentially cleaves peptide bonds involving basic amino acids, particularly arginine, lysine and residues following phenylalanine. (Menard *et al*., 1990) [33] The unique structure of papain gives its functionality that helps to understand how this proteolytic enzyme works and it's useful for a variety of purposes. (*Carica papaya* L.).

Many cancer cells having a protective coating of fibrin. That is why they go undetected for many months and years. Papain breaks down that fibrin coat of cancer cell wall. So ultimately it helps diagnose cancer cells.

**13. Mechanism of Functions of Papain**

The mechanism in which the function of papain is made possible is through the cysteine-25 portion of the triad in the active site that attacks the carbonyl carbon in the backbone of the peptide chain freeing the amino terminal portion. As this occurs throughout the peptide chains of the protein, the protein breaks apart. The mechanism by which it breaks peptide bonds involves deprotonation of Cys-25 by His-159. Asparagine-175 helps to orient the imidazole ring of His-159 to allow this deprotonation to take place. Although far apart within the chain, these three amino acids are in close proximity due to the folding structure. It is though these three amino acids working together in the active site that provides this enzyme with its unique functions. Cys-25 then performs a nucleophilic attack on the carbonyl carbon of a peptide backbone. (Menard *et al*., 1990; Tsuge *et al*., 1999) [33, 55] In the active site of papain, Cys -25 and His -159 are thought to be catalytically active as a thiolate imidazolium ion pair. Papain can be efficiently inhibited by peptidyl or non-peptidyl N-nitrosoanilines. (Guo *et al*.,1995) [20]. The inactivation is due to the formation of a stable S-NO bond in the active site (Snitroso- Cys25) of papain. (Xian *et al*., 2000) [61]

**14. Papaya is a Store-House of Cancer Fighting Lycopene**

Lycopene is a member of the carotenoid family, which is synthesized by many plants and microorganisms. It is a highly unsaturated open straight chain hydrogen compound consisting of 11conjugated and 2 unconjugated double bonds (Stahl *et al*., 1992; Knachik *et al*., 2002; Rao *et al*., 2006) [50, 26, 43]. The red color of many fruits and vegetables is due to the presence of lycopene. Because of the presence of double bonds in the structure of lycopene, it can exist in both the cis and Trans isomeric forms. Lycopene is present in foods primarily in the all-trans isomeric form, (Cliton, 1998) [14] However, it can undergo monoor poly-isomerization by light, thermal energy, and chemical reactions to the cis isomeric form. It is highly stable at high temperatures and can be stored. (Agrawal *et al*., 2001) [6].

**15. Isothiocyanate Found in Papaya Restore the Cell Cycle to Eliminate Cancer**

Organo-sulfur compounds called isothiocyanate are found in papaya. In animal experiments, isothiocyanate protects against cancers of the breast, lung, colon pancreas, and prostate, as well as leukemia, and they have the potential to prevent cancer in humans. Isothiocyanate have shown that they are capable of inhibiting both the formation and development of cancer cells through multiple pathways and mechanisms (Barbara, October-2008) [8]. Researchers in Japan clarified the mechanisms of action in a type of isothiocyanate found in papaya known as BITC. That underlies the relationship between cell cycle regulation and appropriate cell death. When cancerous cells die on schedule, they are no longer a problem. The researchers established that BITC exerted cancer cell killing effects that were greater in the proliferating cells than in the quiescent cells. Cancer cells that are proliferating are much more dangerous than cancer cells that are in a state of dormancy (Barbara, 2009) [9].

**16. Conclusion**

*Carica papaya* is an important and promising natural medicinal plant which could be utilized in several pharmaceutical and medical applications because of its effectiveness, availability and safety. The papaya plant has been touted by traditional hearlers for counties as source of powerful medicine. Slice open a papaya and see hundreds of shiny black seeds that all need to get there start in life from the nutrition found in the fruit. Papaya promotes immune system. Papaya is potent cancer fighter that is highly effective against hormone related to cancer as well as other cancer. Papaya can stop the growth of cancer cell, halt metastasis and normalize cell cycle. Fruit and seed disorders in papaya cause great economic losses in seed production during autumn sown crop. We observed that Pune Selection-3 and Pusa Dwarf were the most susceptible germplasm lines for bumpy fruit and deformed seed disorders, while vivipary and white seeds (disturbed sarcotesta) are a serious economic problem only in Pusa Dwarf. The challenges that Indian Agriculture faces in the coming years remain enormous. The seed production in papaya with 100% genetic purity is difficult because of dioecious nature of the plant. Therefore, the seed should be produced either strictly under controlled condition or in an isolated area.

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