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The Potential Health Benefits of Papaya Seeds

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Abstract: *Papaya (Carica papaya) is a tropical fruit having commercial importance because of its high nutritive and medicinal value. Papaya seeds are traditionally used by human beings from centuries to heal many illnesses. Papaya seeds contains antioxidants and antimicrobial virtues which gives protection against harmful free radicals and reduce rate of cancer and heart disease. Papaya seeds contain a variety of essential macro and micronutrients. The papaya seeds contain large amounts of nutrients, including fibre which is effective for combating constipation and other digestive problems. Seeds can be used to treat health complications such as urinary tract infection, candidiasis and sepsis. Papaya seeds are sometimes used in salads and can even be used as a substitute for black pepper. Products developed from papaya seeds are considered to be nutritionally rich with diverse sources of all nutrients. Papaya seeds have the potential to produce oil with nutritional and functional properties highly similar to olive oil. The papaya seed, and products may be useful for bio-fuel, medicinal and industrial purposes. Therefore, Papaya seeds are usually thrown away but their proper utilization can lead to the development of novel drug in medicine and considered as safe for consumption. 'In this review subtopics covered are nutritional and Phytochemicals composition, antioxidant effect, antibacterial Activity, anthelmintic effect, Phytochemicals with Anticancer activity, Lycopene and isothiocyanate applications in papaya, papaya seed products and in vivo animal studies.'*

I. INTRODUCTION

The first literary reference to papaya fruit dates back to 1526, when they were found in the Caribbean coast of Panama and Colombia and described by the Spanish chronicler Oviedo Hankinson S E. It 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. [1] 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. The taxonomical classification includes Kingdom (Plantae), Order (Brassicales), Family (Caricaceae), Genus (Carica) and Species (papaya).[1] Papaya (Carica papaya) is a tropical fruit having commercial importance because of its high nutritive and medicinal value. Papaya cultivation had its origin in South Mexico and Costa Rica. The papaya is believed to be native to southern Mexico and neighboring Central America. It is currently cultivated in Florida, Hawaii, Eastern British Africa, South Africa, Sri-Lanka, India, Canary Islands, Malaysia and Australia. It is now present in every tropical and subtropical country.

Though it resembles a tree, a papaya plant is actually an overgrown herb, known as an herbaceous perennial. Eventually, it grows to 20 to 30 feet, producing melon-like oval fruits six to 20 inches long.[2] Carica Papaya is commonly known as papaya, pawpaw and in Hindi it is called Papita. The Sanskrit name is Chirbhita. Carica papaya, is a huge herbaceous plant, resembling a tree and belonging to the Caricaceae (papaya) family, originated in Central America and is now grown in tropical areas world-wide for its large, sweet, melon-like fruits. Papayas are spherical or pear-shaped fruits. They have flesh that is rich orange in color with either yellow or pink hues.[18]

Papaya seeds constitute 15%–20% mass of fruit that represent a considerable amount of papaya fruit waste in processing units. Papaya seeds have the potential to produce 30%–34% oil with nutritional and functional properties highly similar to olive oil. [9] Papaya seeds are small, round, black colored, encased in a gelatinous coat in the inner cavity of the fruit having a strong flavor similar to black pepper and small amounts of it are beneficial for overall health. The seeds contain large amounts of nutrients, including fibre (22g %) which is effective for combating constipation and other digestive problems. [18]. Papaya seeds are usually thrown away but their proper utilization can lead to the development of novel drug. papaya seed (both ripe and unripe) is an effective candidate as a potential drug against human pathogenic bacteria and demands isolation of active ingredients. Seeds of C. papaya L. have the traditional use to treat food poisoning caused by bacteria. The C. papaya seed extracts have potential antibacterial property with mild cytotoxic activity.[4]

BITC(benzyl isothiocyanate)is a bioactive substance present in the papaya seed that has been studied among different areas due to its wide applications. BITC applications ranged from vascular relaxation to inhibition of cancer proliferation.[10]

Carica papaya seeds are usually known to be effective in treating *Entamoeba histolytica*. Studies showed that a single oral dose of Caricapapaya seeds water extracts of up to (0.1ml /mice/day) reduced parasite appearance in feces and disappear completely at the 8th day compared with metronidazole the cysts parasite continued till 10th day. [3] Different parts of Carica papaya possess anti-inflammatory effects. Studies show that Aqueous extract of Carica papaya seeds significantly reduced NO radical by 69.4% in a cell free assay in vitro. Meanwhile, the aqueous extract at a concentration of 150 $\mu\text{g/mL}$ inhibited the release of lysosomal enzymes and stabilized human red blood cell membrane by 22.7%. [8] Papaya seed extract exhibit anticancer activity in acute promyelotic leukemia HL-60 cells. Papaya seeds can be effective in inhibiting prostate cancer cells proliferation and may be a good nutraceutical for preventing and treating prostate cancer in men. [6] Papaya seeds are edible and have a peppery, bitter flavor. They are sometimes used in salads and can even be used as a substitute for black pepper.

The C. papaya seed oil is stable upon storage, and possesses little or no cellular injury (that is, low toxicity) when consumed. Both the seed coat and the oil possess reasonable antioxidant properties, this gives credence to their potential nutritional and health benefits. The seed coat may equally be developed into edible coatings or packaging materials for shelf-extension of agro-crops. [7]. the seed, and the fermentation product may be useful for bio-fuel, medicinal and industrial purposes. [5] Fermentation greatly improved the nutritional value of the seed, which was revealed by assessing the chemical composition of Carica papaya seeds. [28] With this brief description an attempt is made to write a review on potential health benefits of papaya seeds.

A. Nutritional Composition

Nutritional Composition of papaya seeds per 100g.

Component	Values[18]	Values [12]	Values [24]
Energy	374.47 kcal	212.7kcal	-
Crude fiber	21.96g%	2.1 g	8.02 \pm 0.026
Carbohydrate	31.94g%	43.6g	19.70 \pm 0.093
Crude fat	26.36g%	3.1g	28.61 \pm 0.029
Crude protein	2.33g%	2.6g	27.41 \pm 0.029
Moisture content	10.5%	-	11.02 \pm 0.025
Ash content	6.91%	-	5.21 \pm 0.289

Values are mean \pm standard deviation of triplicate determinations

Micronutrient composition of papaya seeds.

Components	Seeds[12]	Percentage [24]
Potassium	344mg	720.83 \pm 0.289
Phosphorous	241.5mg	-
Magnesium	10.4mg	-
Iron	0.2mg	4.20 \pm 0.012
Calcium	54.4mg	6.43 \pm 0.029
Vitamin C	11.7mg	-
Zinc	-	6.41 \pm 0.029
Vitamin B3 (Niacin)	0.26mg	-
Vitamin B2 (Riboflavin)	0.05mg	-
Vitamin B1 (Thiamin)	0.05mg	-
Beta-carotene	65.64 IU	-

B. Phytochemical Compounds

Phytochemical characterization conducted revealed that C. papaya seeds contained flavonoids, tannins, reducing sugars, alkaloids, phenols, saponins, and terpenoids in organic and aqueous extract of dried seeds of papaya. The seeds of papaya are reported to contain crude proteins, crude fibre, fatty acids, papaya oil, carpaine, benzylisothiocynate, benzylthiourea, glucotropacolin, benzylglucosinolate, hentriacontane, β -sistosterol, caricin and an enzyme nyrosin. [11]

Evaluating the oil extracted from the seeds, the main quantified fatty acid was oleic acid (71.30%), followed by palmitic (16.16%), linoleic (6.06%), and stearic acids (4.73%). The predominant tocopherols were α and δ -tocopherol, with 51.85 and 18.9 $\text{mg}\cdot\text{kg}^{-1}$, respectively. The β -cryptoxanthin (4.29 $\text{mg}\cdot\text{kg}^{-1}$) and β -carotene (2.76 $\text{mg}\cdot\text{kg}^{-1}$) were the quantified carotenoids, and the content of total phenolic compounds was 957.60 $\text{mg}\cdot\text{kg}^{-1}$. [12]

II. HEALTH BENEFITS

A. Antioxidant Property

Free radical causes many chronic health problems. Antioxidants can help us by preventing the formation of free radicals. A study conducted shows that *C. papaya* seeds water extract has a potent antioxidant activity in H₂O₂ oxidative stress-induced human skin Detroit 550 fibroblasts. The results suggest that the extract is not toxic, acts as a potent free radical scavenger, decreases cell death, ensures Ca²⁺ homeostasis, more efficient than vitamin C to hamper the H₂O₂ oxidative damage and counteracts mitochondrial dysfunctionality in oxidative stress-damaged Detroit 550 fibroblasts. [33] the papaya seeds are proven to contain antioxidants by the results given in DPPH, FRAP, and TPC tests.[49] The antioxidant potential of the *C. papaya* seeds was also determined by using DPPH free radicals scavenging method and BHT used as a standard. The degree of decolourisation indicates the potency of the plant extracts in scavenging the free radicals. [13] Phytate had been reported to possessed antioxidant activity. The high phytin levels of the unripe seeds can be attributed to its use in preference for the ripe *Carica papaya* seed in medicinal medicine for curing diseases. [14]

B. Antimicrobial Property

The seeds of papaya irrespective of its fruit maturity stages have bacteriostatic activity on gram positive and negative organisms which could be useful in treating chronic skin ulcer. [22] Ethyl acetate extract of *C. papaya* seeds exhibit promising antimicrobial activities which is attributable to secondary metabolites present in the seeds.[15] *Proteus mirabilis* and *Vancomycin-resistant enterococci* were highly inhibited. Seeds of the plant can be used to treat health complications such as urinary tract infection and sepsis caused by *Proteus mirabilis* and *Vancomycin-resistant enterococci*, respectively. Candidiasis could be treated using extracts of papaya seeds. [15] Studies have demonstrated that the extract from papaya could induce apoptosis in *C. albicans* cells significantly. The results indicated a role of the extract as a novel drug for cardiac diseases which is a rich and high-purity source of BITC. [17] A study dealt with the antibacterial activity of aqueous, methanolic extract of seeds of *Carica papaya* var. *pusa dwarf* through agar well diffusion assay against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. coli* and *Salmonella typhi*, results indicated that it's effective to inhibit the bacterial pathogens.[30] Different parts of papaya have been used to prevent or treat a number of diseases. Oil extract of papaya seed have shown antifungal activity. The fatty acids identified in the seed extracts of papaya (from ripe fruit) were able to reduce the number of *Trypanosoma cruzi* parasites in mice. The methanolic extract of the seeds also showed antifungal activity against *Aspergillus flavus*, *Candida albicans* and *Penicillium citrinum*. [16]

C. Anthelmintic Property

C. papaya extracts can serve as a source of chemical substance for use in The development of effective anthelmintic agents.[38] Laboratory studies were carried out for anthelmintic Potency of *Carica papaya* seeds, as prevalence of Ascariasis is high among rural areas in Indonesia. The Infusa of papaya (*Carica papaya* L.) seed has anthelmintic effect against *Ascaris suum* in vitro.[39] The seeds of *Carica papaya* has reasonable pharmacotherapeutic properties against intestinal nematodes of sheep hence it could serve as an anthelmintic agent.[35] *C. papaya* seed extracts have comparable anthelmintic potency to Thiabendazole and that aqueous forms were more efficient than powdery forms when administered in Red Sokoto goats as an alternative to anthelmintic to synthetic dewormers in rural areas in controlling helminthosis. [36] Studies show that groups of chicks treated with *Carica* seed has obtained 100% of reduction rate while Lcp(Citrate of piperazine mixed to water) obtained 69.23%. It can be concluded that papaya seed reduces significantly parasitic population in pullets' gut.[37]

D. Phytochemicals with Anticancer activity

Papaya seed extract exhibited anticancer activity in acute promyelotic leukemia HL-60 cells at IC 50 of 20 µg/mL whereas papaya pulp extract did not have any effect even at a concentration of 100 µg/mL. Papaya seeds can be effective in inhibiting prostate cancer cells proliferation and may be a good nutraceutical for preventing and treating prostate cancer in men. [16]

E. Lycopene and isothiocyanate applications in papaya

Preliminary research suggests lycopene may reduce the risk of macular degenerative disease, serum lipid oxidation, and cancers of the lung, bladder, cervix, and skin. Antioxidants and Antimicrobial virtues give protection against harmful free radicals and reduce rate of cancer and heart disease and the most efficient carotenoid antioxidant is Lycopene.[46] Papaya juice and pure lycopene, a component present in papaya, caused cell death in the liver cancer cell line, Hep G2, with the half maximal inhibitory concentration (IC 50) of 20 µg/mL and 22.8 µg/mL, respectively. [16] Papaya seed is a rich source of biologically active isothiocyanate, especially benzylisothiocyanate, and its precursor, glucosinolate.

Findings also provide evidence showing that the papaya seed extract exhibits the same biological effects as does benzylisothiocyanate such as superoxide generation inhibition and apoptosis induction. Also, there have been various studies showing the ability of benzyl isothiocyanate to inhibit chemically induced cancer development or growth of cancer xenografts in vivo. Various isothiocyanates are effective chemo protective agents against chemical carcinogenesis in experimental animals. Papaya seeds can be used for the prevention and medication of inflammation-related disorders, including cancer. [47] BITC(benzyl isothiocyanate) is a bioactive substance present in the papaya seed that has been studied among different areas due to its wide applications. BITC applications ranged from vascular relaxation to inhibition of cancer proliferation.[10]

III. USES OF PAPAYA SEEDS

A. Products Developed

Gastro-free churan balls were prepared by incorporating papaya seed and papaya seed oil and were standardized as natural product with no added preservative, and would help to relieve constipation issues, has an acceptable organoleptic profile and benefit overall health and wellness. Based on the obtained results, it is seen that the product is nutritionally rich with diverse sources of all nutrients. Thus, the product can be used in a defensive nutrition plan with no perceived harm even if consumed in excess. [18] Studies were conducted to produce 'coffee' powder of papaya seeds for drinks; to test the organoleptic properties and the activity as a pancreatic lipase inhibitor. Inhibitor activity for pancreatic lipase was measured relative to anti-obesity drugs of Orlistat (Xenical), using titrimetric method.

The results showed that every 1.42 grams of papaya seeds powder have an inhibitory activity equivalent to 1 tablet (120 mg) of Orlistat. Most of the respondents like with the texture, color, and flavor of the drinks.[31]

Papaya seed oil utilized in high amount such oils could lead to reduced risk of coronary heart disease. Papaya seed oil can be considered as high oleic oil and hence viewed as a healthy alternative to many other vegetable oils. [19] In papaya seed oil, oleic acid(73.79%) was the dominant compound, followed by palmitic (14.38%) and stearic acids (3.58%), linoleic(1.06%). The analytical results showed that papaya seed oil had the potential to become the new oleic-rich oil, suitable for dietary oil products. In addition, the bioactive and phenolic content in papaya seed are also significant, potentially applied to make nature – based products for human beings.[23]

The papaya seed oil had a high oxidative stability (77.97 hours), suggests that crude papaya seed oil may exhibit a desired shelf life. Moreover, lipids with high monounsaturated fatty acid content, such as papaya seed oil, are used in emollient skin care products, bath oils, hair conditioners, and makeup.[21]

The papaya seed flour was characterized by having a high content of protein and fiber, which can be considered an excellent source to nutritionally enhance the products in which it is added. The addition of papaya seed flour in the hamburger formulation not only allows the improvement of the nutritional and technological quality of this widely consumed product, but can also be effective to reduce the environmental impact caused by the improper disposal of industrial waste.[20]

Papaya seed flour bread was made by baking, resulting minerals content such as magnesium(143.00-182.50 mg/100g), calcium(252.60-342.60 mg/100g), phosphorus(73.50-127.30 mg/100g), potassium, iron, sodium, increased as the level of papaya seed flour addition increased. There was an increased trend in the anti-nutritional contents of the bread samples with increased level of papaya seed flour addition.[27]

The analysis carried out on 3 different species of papaya seeds flour indicates the presence of nutrients and functional properties, with high levels of protein and fat, small amounts of carbohydrates and adequate quantities of minerals. Anti nutrients like oxalate, tannins, phytic acid and phytic phosphorus are also found in minute quantities.[25]

Papaya seed fortified porridge had a significant effect on reduction of *Ascaris lumbricoides* burden. It had a better nutritional outcome and effect on child fungal infections than albendazole. Its application as a routine school meal may aid current national school based nutrition and deworming programs in Africa. [48] Studies conducted using papaya seeds flours as value addition in preparing functional papaya seed flour cookies, contained higher amount of protein content and high in the crude fiber than the control wheat cookies and was acceptable, and enhanced nutritional properties, physicochemical characteristics and organoleptic attributes. [26] Incorporation of papaya seeds, watermelon, golden melon, flours into wheat flour for cookies production improved its fiber, ash, protein and virtually all the minerals examined.[22]

A value added product, namkeen developed using Papaya Seed Flour(PSF), gram flour and spices, showed that PSF namkeen was more acceptable than without PSF. The namkeen product made from composite PSF can be a boon to the savoury industry by providing the benefit of variety as well as a nutritive option for consumers.[29]

IV. IN VIVO STUDIES ON CARICA PAPAYA SEEDS/ ANIMALS EXPERIMENTS

C. papaya seed extract may possess gastro protective effects against ethanol induced gastric ulcer in rats. C. papaya seed extract reduces gastric secretion and protects gastric mucosa from ethanol noxious effect, which may also be attributed to the active compounds of the extract polyphenols (antioxidant), alkaloids and flavonoids which are widely known as being useful for digestive disorders and disturbances of the gastrointestinal tract.[44][45]

The chloroform extract of the papaya seeds showed contraceptive efficacy without adverse toxicity, mediated through inhibition of sperm motility. [16] Study conducted to assess possible alterations in the serum levels of some key liver functional enzymes and related compounds in doses of aqueous extract of carica papaya seeds in wistar rats, demonstrated possible hepatomodulatory activities of carica papaya seeds with hepatoprotective effects.[41]

The aqueous extract of Carica papaya seeds produced adequate nephroprotective Phytochemicals on albino Wistar rats as evidenced by the reduction in the biochemical parameters and may be useful in preventing kidney damage induced by paracetamol. This supports the folklore use of the plant in renal disorders. Oral administration of C. papaya seed extract prevented ovum fertilization, reduced sperm cell counts, revealed sperm cell degeneration, and induced testicular cell lesion, which could induce reversible male infertility and therefore could be used for pharmaceutical development of a male contraceptive.[42]

Study conducted on hypoglycemic and hypolipidemic effects of the aqueous seed extract of Carica papaya investigated in normal male rats showed that it progressively lowered the FBS(Fasting blood glucose), TG(triglyceride) TC(totalcholesterol), LDL-c(low density lipoprotein cholesterol), and VLDL-c and elevation in HDL-c(high density lipoprotein). Phytochemical analyses revealed the presence of alkaloids, flavonoids, saponins, tannins, anthraquinones, anthocyanosides and reducing sugars. Thus, lending support to its folkloric use in the management of suspected type 2 diabetic patients.[32] Aqueous extract of Carica papaya seed extract has minimal anti-inflammatory and antinociceptive activities with the tested doses in the used animal models, but a better antipyretic activity. [50] Antiamoebic activity of methanol extract of mature seeds of Carica papaya tested in vitro on axenic culture of Entamoeba histolytica using metronidazole as a reference amoebicidal agent, suggests that the mature seeds of C. papaya have antiamoebic effect but less Pronounced than metronidazole.[43]

V. DOSAGE AND TOXICITY

An observation drawn from the study is the relative oral safety of the extract at the dose of 2000 mg/kg. According to Clarke and Clarke (1977), any compound or drug with the oral LD50 estimate greater than 1000 mg/kg could be considered of low toxicity and safe. Arising from this documented fact, CPE at an oral dose of 2000 mg/kg could be considered relatively safe on acute oral exposure.[32]

study determines the toxicity of an aqueous extract of pawpaw (Carica papaya) seed powder to catfish (Clarias gariepinus) fingerlings using static bioassay. The toxicity effect of pawpaw seed powder had a positive correlation with exposure time from 24 to 96 h, for the sharptooth catfish C. gariepinus. Toxic reactions include; erratic movement, air gulping, loss of reflex, molting and discoloration. Maximum admissible toxicant concentrations ranged from 0.1 to 1.29 mg/L (confidence level: 22 - 78.8%). The results showed that concentrations of pawpaw seed powder in excess of 1.29 mg/L can be potentially harmful to C. gariepinus fingerlings.[34]

VI. CONCLUSION

Papaya seeds are famously known to be used as herbs for managing pain, Infections, blood sugar levels, obesity, abdominal discomfort and food poisoning. It is also widely used for treatment of intestinal human pathogens, also posses anticancer, antioxidant, anti-inflammatory, antibacterial, antiparasitic, and anthelmintic properties. Papaya seeds are good source of nutrients, including mono unsaturated fatty acids, fiber, antioxidants and phytochemicals. Papaya Seeds are also known for treatment of diabetes and hypercholesterolemia.

Papaya seeds are determined to be beneficial in the treatment and prevention of intestinal parasites, also readily available, harmless, and cheap. Papaya seeds consumption is recommended not only for their nutritive but their medicinal value. Papaya seeds are used as value addition in many products.

Products developed from papaya seeds are found to be nutritionally rich with diverse sources of all nutrients and have beneficial effects on human health. Therefore, Papaya seeds are usually thrown away but their proper utilization can lead to the development of novel drug in medicine, considered safe for consumption and it is highly nutritious.

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