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PAPAYA (*CARICA PAPAYA*): SOURCE MATERIAL FOR ANTICANCER

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ABSTRACT
Papaya (*Carica papaya* Linn.) is well known for its exceptional nutritional and medicinal properties throughout the world. The whole plant including its leaves, fruits, seed, bark, latex and their juice are use as medicine. Papaya is considering as Nutracuitical fruits duo its multifaceted properties. The whole plant of papaya contain enzyme Papain, Lycopene, Isothyocynate, important Mineral, Vitamins, Carbohydrates, Carotenoids, Flavonoids. These important nutritious fruits feed the body and immune system. 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. Isothyocynate effective against breast, lung, colon pancreas, prostate as well as leukemia. These enzymes capable of inhibiting both formation and development of cancer cell.

Key Words: *Carica papaya, Anticancer, Physiochemical, Papain, Lycopene, Isothyocynate*

INTRODUCTION
The papaya tree is belonging to small family caricaceae having four genera in world. The genus carica linn is represented by four species in India, of which *Carica papaya* linn. is most widely cultivated and best-known species (Jean *et al*., 2001). Papaya belongs to *Caricaceae* family. Scientific name of papaya is *Carica papaya*. It is commonly known as Papaya Melon tree, Pawpaw or Papau, Kapaya, Lapaya, Papyas, Papye, Tapayas, Fan mu gua (Bhattachrjee, 2001).
The fruit, leaves and latex obtain from papaya plant used medicinally and for various other purposes. Papain, major chemical compound extracted from fruit and stem latex is used in brewing and wine making and in textile and tanning industries (CSIR, 1992).
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 (Mike, 2012).
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.
Papaya is small, erect, usually unbranched, fast-growing tree growing 3-6 meters high. Trunk is soft and grayish, marked with large petiole-scars. Leaves are somewhat rounded in outline, 1 meter broad or less, palmately 7-or 9-loabrd, each lobe pinnatelyincised or lobed. Petioles are stout, hollow, and about 1 meter long. Male flowers are in crowded cluster, straw-colored, and fragrant. Corolla tube is slander, about 2cm long. Female flowers are in short, axillary spikes or racemes, the petal 7cm long or less. Fruit is Indehiscent, subglobose, obovoid or oblong-cylindric, 5-30cm long, fleshy and yellowish or yellow-orange when ripe, containing numerous black seeds which are embedded in sweet pulp (Nadkarni, 1954).

MATERIALS AND METHODS
Origin and Distribution
Papaya is probably originated in southern Mexico and Costa Rica, subsequently it was crop introduce in Australia, Hawaii, Philippines, Srilanka, Southafrica, India and all tropical and subtropical regions. It is growing both commercially and in home garden. (Marotta *et al*., 2006).

Table 1: Nutritional value

Constituents	Ripe Papaya	Green Papaya
Water	89.1	92.6
Protein	8.26 g	10.8 g
Total lipid	0.93 g	1.35 g
Ash	4.59 g	6.76 g
Carbohydrates	86.2 g	81.1 g
Total DF	11.9 g	27.0 g
Sugar	NR	NR
Mineral		
Macronutrient		
Sodium	128.4 mg	283.8 mg
Potassium	1238 mg	2743 mg
Magnesium	229.4 mg	635.1 mg
Phosphorus	NR	NR
Calcium	146.8 mg	432.4 mg
Micronutrient		
Iron	12.84 mg	8.11 mg
Copper	0.18 mg	0.14 mg
Zinc	0.92 mg	0
Manganese	NR	NR
Selenium	NR	NR
Vitamins		
Vitamin C,	568.8 mg	391.9 mg
Thiamin	0.28 mg	0.54 mg
Riboflavin	0.28 mg	26 mg
Niacin	2.80 mg	4.05 mg
Pantothenic Acid	NR	NR
Vitamin B-6	NR	NR
Total Folate,	NR	NR
Folate	NR	NR
Vitamin B-12	NR	NR
Vitamin A	NR	NR
Vitamin E	NR	NR
Vitamin K	NR	NR
Carotene	7,807 µg	0
Cryptoxanthin	NR	NR
Lutein + Zeaxanthin	NR	NR

NR= not reported
Source: Puwastien et al., 2000

Table 2: Constituents

Part	Constituents	Image
Fruits	Protien,fat,carbohydratesminerals:calcium,phosohorus,iron,vitamin C, thiamine, riboflavin, niacin, carotene, Amino acid, citric acid and malic acid, voletile compound : linalool, benzylisothyocynate, cis and trans 2,6-dimethyl 3,6 epoxy-7 octen-2-ol,Alkaloid,α carpine, benzyl-β-D gucoside,2-phenyl ehyle-β-D gucoside,4-hydroxyphenyl-2-ehyle-β-D gucoside,	
Juice	N-butyric, n-hexanoic and n-octanoic acid, lipid, myristic, palmitic, stearic, linoleic, linolenic and cis-vasanic and oleic acid	
Seed	Fatty acid, crude protein, crude fibre, papaiya oil, carpaine, benzyl isothiocynate, benzyle glucosinolate, glucotropecolin, benzylethiourea, hentriaconate, β-sitosterol, caricin and enzyme myrosin	
Root	Carposide and enzyme myrosine	
Leaves	Alkaloids carpain, pseudocarpain and dhydrocarpaine 1 and 2 , choline, carposide, , vitamin C and E	
Bark	B-sitosterol, glucose, fructose, galactose and xylitol.	

Latex	Protieolytic enzyme, papain, chemopapain, glutamine cyclotransferase, chymopapain A, B, C, Peptidase A and B and lysozyme.	

Source: Indian Material Medical by KM Nadkarni.
Photochemistry PF Medicinal Plant, 2nd Edn by Jean Bruneton

Table 3: The cytotoxic effect of *C. papaya* extract has been tested in various cancer cell lines in vitro studies summarized intable

Cancer Cell Line	Treatment	Result	Reference
Breast cancer cell line (MDA-MB-231) Liver Cancer cell line (Hep G2) Chang liver cell line (normal cell)	Papaya fruit juice(0.28– 28 mg/mL), Lycopene extracted from papaya juice, Pure lycopene (3– 30 _g/mL)	Pure lycopene and papaya juice inhibited viability of liver cancer cell line Hep G2 (IC50 = 22.8 _g/mL and 20 mg/mL, respectively) but had no effect on breast cancer cells or normal cells. Lycopene extracted from papaya juice did not show any effect on either cell line.	Puwastien *et al., 2000*
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
Breast cancer cell line (MCF-7)	Aqueous extract of papaya flesh (0.01–4% v/v)	Significant inhibitory effect on proliferation of MCF-7 cells (p <0.05)	Garcia-Solis, 2009
Breast cancer cell line (MCF-7) treated with sodium nitroprusside, a nitric oxide donor	Ethanolic extract of papaya pericarp (50–640 _g/mL)	Inhibited cell growth in MCF-7 cells (decrease in cell viability). Scavenged nitric oxide in dose-dependent manner (about 35% of nitric oxide was scavenged by extract at 640 _g/mL)	Jayakumar *et al.*, 2011
Breast cancer cell line (T47D)	Protein fraction containing RIPs isolated from leaves	The protein fraction possessed cytotoxicity: IC50 = 2.8 mg/mL). Induction of apoptosis by regulation of p53 and BCl-2 protein expression (increased by 59.4% and decreased by 63%, respectively).	Hirose *et al., 1998*
Stomach cancer cell line (AGS) Panc0reatic cancer cell line	Aqueous extract of papaya	Papaya leaf extract showed a concentration-dependent anticancer effect on each of the cancer cell lines	Marotto *et al.*, 2006

(Capan-1) Colon cancer cell line (DLD-1) Ovarian cancer cell line (Dov-13) Lymphoma cell line (Karpas) Breast cancer cell line (MCF-7) Neuroblastoma cell line (T98G) Uterine cancer cell line (Hela) T-cell leukemia cell line (CD26 negative or negative Jurkat	leaves(1.25–27 mg/mL)	and suppressed DNA synthesis by suppressing the incorporation of 3*H*-thymidine.	
T-cell lines (H9, Jurkat, Molt-4, CCRF-CEM and HPB-ALL) Burkitt's lymphoma cell lines (Ramos and Raji) Chronic myelogenous leukemia cell line (K562) Cervical carcinoma cell line (Hela) Hepatocellular carcinoma cell lines (HepG2 and Huh-7)	Aqueous extract of papaya leaves (0.625–20 mg/mL)	Inhibited the proliferative responses of both haematopoietic cell lines and solid tumor cell lines. In peripheral blood mononuclear cells, papaya extract reduced the production of IL-2 and IL-4 whereas increased the production of Th1 type cytokines such as IL-12p40, IL-12p70, INF-_, and TNF-_.The expression of 23 immunomodulatory genes was enhanced by the addition of papaya extract.	Otsuki *et al.*, 2010

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). Some important Phytochemicals found in *C. papaya* are Lycopene, Betacarotinoid, Benzylisothyocynate, Betacryptoxanthin, Benzylglucosinolate, chlorogenic acid, caffeic acid, protocatachuic acid, Quercetin, Among more than 5000 compounds from plants that have been identified to be associated with anticancer properties (Huang *et al.*, 2009), 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; Breemen *et al.*, 2008) to exhibit in vitro and in vivo anticancer activities.

Papaya is Rich Source of Enzyme Papain which Effective against Cancer

Papain (EC 3.4.22.2) is an endolytic plant cysteine protease enzyme which is isolated from papaya (*Caricapapaya* L.) latex.(Abu-Alruz *et al.*, 2009)It preferentially cleaves peptide bonds involving basic amino acids, particularly arginine, lysine and residues following phenylalanine. (Menard *et al*., 1990) The unique structure of papain gives its functionality that helps to understand how this Protieolytic enzyme works and it's useful for a variety of purposes. (*Caricapapaya* L.) Latex, (Mitchel, 1970).

Figure 1: Papain Structure (Huet J *et al.*, 2006)

Many cancer cells having a protective coating of fibrin. That is why the go undetected for many month and year.

Papain breaks down that fibrin coat of cancer cell wall. So ultimately it helps against the cancer.

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) 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*., 1996; 1998) The inactivation is due to the formation of a stable S-NO bond in the active site (*S*nitroso- Cys25) of papain.(Xian *et al*., 2000)

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 11 conjugated and 2 unconjugated double bonds (Stahl *et al.*, 1992; Knachik *et al.*, 2002; Rao *et al.*, 2006). 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* isomeic form, (Cliton, 1998) However, it can undergo mono- or 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).

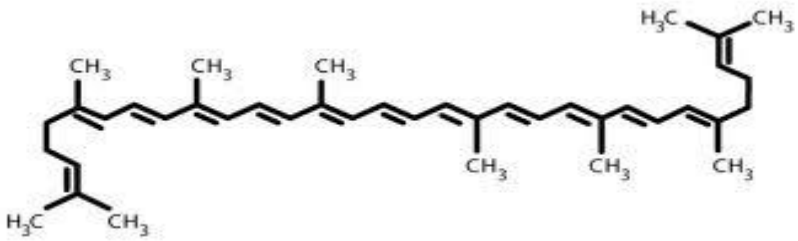

Figure 2: Structure of lycopene (Gali *et al.*, 2002)

Mechanism of Lycopene

Lycopene enhances cell-to-cell communication by increasing 'Gap junctions' between cells (Gali-Muhtasib *et al.,* 2002). Two major mechanisms have been proposed to explain the ant carcinogenic activities of lycopene: non oxidative and oxidative mechanisms. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes and to stop cell division at the G0-G1 cell cycle phase (Obermuller-Jevis *et al.,* 2003). Astorg and colleagues proposed that lycopene-induced modulation of the liver metabolizing enzyme cytochrome P4502E1 was the underlying mechanism of its protection against carcinogen- induced preneoplastic lesions in rat liver. Preliminary *in vitro* evidence also indicates that lycopene reduces cellular proliferation induced by insulin-like growth factors-which are potent mitogens-in various cancer cell lines (Levy, 1995). Regulation of intrathymic T-cell differentiation (immune modulation) was suggested to be the mechanism for suppression of mammary tumor growth by lycopene treatments in SHN retired mice (Nagasava *et al.*, 1995 and Kobayashi *et al.*, 1996). This is an important mechanism by which cells communicate with each other, and helps to ensure proper cell and organ functions. It also prevents uncontrolled growth of cancer cells and modulates cell-cycle progression. The cell cycle is a highly ordered set of events that culminates in cell division. The use of lycopene appears to be a potential anticancer strategy of regulating the cell cycle by inhibiting abnormal cellular growth (Agrawal *et al.,* 1998). Lycopene has been hypothesized to prevent carcinogenesis by protecting critical cellular bimolecular, including lipids, lipoproteins, proteins, and DNA (Matsushima *et al*., 1995; Pool-Zobel *et al.*, 1997; Rao *et al*., 1998).

Isothiocyanate Found in Papaya Restore the Cell Cycle to Eliminate Cancer

Organo-sulfur compounds called isothiocyanate are found in papaya. In animal experiments, isothiocyanate protected 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 them capable of inhibiting both the formation and development of cancer cells through multiple pathways and mechanisms (Barbara, October-2008).

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).

CONCLUSION

Papaya is originally native to southern Mexico and now cultivated in many tropical counties. Sweet and succulent with satiny consistency. Papaya was referring to as the fruit of the angels. 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. This implies that fruit must be power packed. The papaya plant has been touted by traditional hearlers for counties as source of powerful medicine. Papaya not only the delicious fruit but it is loaded with vitamins, Phytochemicals, and several mineral compound and hawing some important enzyme like papain, lycopene, Isothyocynate and some proteolysis enzyme which help to treat health problem. 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 normalized cell cycle.

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