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REVIEWARTICLE

A POTENT ANTICANCER AND ANTIOXIDANT ACTIVITY OF CARICA PAPAYA – A REVIEW

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ABSTRACT

In this review paper, we discussed about the anticancer and antioxidant activity of *Carica papaya* (Paw Paw). Papaya is commonly known for its food and nutritional values throughout the world and it is most commonly consumed by peoples.The properties of papaya fruit and other parts of the plant are also well known in traditional system of medicine.The whole plant of Papaya can be used as it contains many biologically active compounds such as papain and chymopapain which are helpful in digestion and are effective against cancer.Cancer is the most dangerous and commonly prevailing disease in humans due to many factors such as change in lifestyle, occupational and environmental exposure and exposed to UV radiation, air pollution, use of tobacco products, etc.Prevention is always better than cure.So,we can prevent and treat this dangerous disease by utilizing naturally available sources to avoid costly treatments. Papaya is more suitable and has effective anticancer and antioxidant property.

INTRODUCTION

Carica papaya Linn., generally known as papaya, Pawpaw or Papau, Papaya Melon tree, Kapaya, Lapaya, Papyas, Papye, Tapayas, Fan mu gua, is one of the world's most important fruit and it belongs to the small family Caricaceae.The genus carica linn is represented by four species in India, of which *Carica papaya* linn. is most widely cultivated and best-known species.Papaya is commonly known for its food and nutritional values throughout the world. Originally derived from the southern part of Mexico, *Carica papaya* is a perennial plant, and it is presently distributed over the whole tropical area. In particular, *Carica papaya* fruit circulates widely, and it is accepted as food or as a quasi-drug.The different parts of the *Carica papaya* plant including leaves, seeds, latex and fruit exhibited to have medicinal value. The different parts such as fruit, leaf, stem,latex,flowers obtained from Papaya are used for medicinal and various other purposes.The stem, leafand fruit of papaya contain plenty of latex. The latex from unripe papaya fruit contain enzymes papainand chymopapain (SheikhFauziya*et al*., 2013; Natarjan*et al*., 2014; Emmy*et al*., 2015; Noriko*et al*., 2010; Silvana Albertini*et al*., 2015; Vijay*et al*., 2014; Farhan*et al*., 2014; Quan*et al*., 2013; Pierson*et al*., 2012; Tatyasaheb*et al*., 2014; Runnie*et al*., 2004; Mahmood*et al*., 2005; Corral-Aguayo*et al*., 2008 and Okeniyi, 2007). The whole plant of papaya contain enzyme Papain, Lycopene, Isothyocynate, important Mineral (Copper and Magnesium), Vitamins (vitamin A and vitamin C,Vitamin B6,Riboflavin,Thiamin,Vitamin K), Carbohydrates, Carotenoids, Flavonoids and other phenolic compounds are plant derived compounds with antioxidant activities by scavenging free radicals and represent a special group of nutritional supplements. Food rich in these antioxidants plays a key role in the prevention of oxidative stress based diseases.

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Papain, an enzyme rich in Papaya, 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 (SheikhFauziya*et al*., 2013; Meshram*et al*., 2014; Elisa*et al*., 2014; Godson, 2012). Fruits are rich in antioxidants such as flavonoids, anthocyanins,carotenoids, and vitamins [18,19,20].Experiments have shown that *C. papaya* have antioxidant,anthelmintic,antimutagenic, antiprotozoan, antibacterial, antifungal, antiviral, antiinflammatory, antihypertensive, hypoglycaemic, hypolipidemic, wound healing, antitumor, free-radical scavenging, antisickling, neuroprotective, diuretic, abortifacient, and antifertility activities (Meshram, 2014; Rajarajeswaran*et al*., 2011; Thao*et al*., 2013; Lim, 2012; Krishna*et al*., 2008; Maisarah asmah, Krishna, 2008; Parle,*et al*., 2011; Singh*et al*., 2010; Mahmood*et al*., 2005; Emeruwa, 1982; Rimbach*et al*., 2000; Gupta*et al*., 2000; Udoh*et al*., 1999; Eno, *et al*., 2000 and Singh*et al*., 2010). Epidemiological data available have shown the effectiveness of consuming fresh fruits and their juice on overcoming certain degenerative diseases including cancer, cardiovascular diseases, aging, arthritis, andothers (Annegowda*et al*., 2014; Rui Hai*et al*., 2004). Medicinal plants play important roles in preventing various diseases and have received much attention from many researchers over the last few decades. Studies on the antioxidant contents of fruits and vegetables are increasing because natural antioxidant consumption has been found to be related with decreased risk for cancer and heart diseases (Zuhair Radhi*et al*., 2013; Maisarah*et al*., 2013).Cancer is the second leading cause of death and is becoming the leading one in old age. It has been estimated that by 2030 the number of new cancer cases will increase by 70% worldwide due to demographic changes alone.

The process of cancer development is due to genetic and epigenetic alterations which leads to disruption in basic biological functions, such as cell division, differentiation, angiogenesis (Swathi Sudhakar*et al*., 2015; Stavridi*et al*., 2010; Chuu*et al*., 2011; Hoffman-Censits, 2013; Higano*et al*., 2014; Sartor*et al*., 2013). Projections indicate that the deaths over the world from cancer will rise to more than 13.1 million in 2030.The purpose of this review is to conduct a literature search to unveil the scientific evidence that *C. papaya* may be of use in the treatment and prevention of cancer (Thao*et al*., 2013). Thus, *Carica papaya* has different properties and has wide appications.This review only focusses on the anticancer and antioxidant activity of *C.papaya.*

Chemical Composition of *Carica papaya*Linn

The whole plant of papaya can be used as medicine. The chemical composition of various parts of *Carica papaya* is given in the Table 1(Vijay*et al*., 2014; Krishna*et al*., 2008; Jean Bruneton, 1999; The Wealth of India, 1992; Nadkarni, 1954;Aravind*et al*., 2013).

Result showed that there was considerably variation in the antioxidant activities where it ranges from the lowest of 58% to the highest of 91% where the orders of the antioxidant activity are as follow: α-tocopherol > unripe fruit > young leaves > ripe fruit > seed (Maisarah*et al*., 2013).Papaya seeds might be used as natural antioxidants (Kaibing Zhou*et al*., 2011).

Free Radical Scavenging Capacity

Papaya has many phenolic groups which may scavange free radicals. Aqueous extract of papaya leaves shows anti-oxidant activity. The fiber of papaya is able to bind cancer-causing toxins in the colon and keep them away from the healthy colon cells. These nutrients provide synergistic protection for colon cells from free radical damage to their DNA (Vijay*et al*., 2014; Aravind*et al*., 2013; Karabhari Rekha Bhaskar, 2014). Astaxanthin, zeaxanthin, and lutein are excellent lipid-soluble antioxidants that scavenge free radicals, especially in a lipid-soluble environment. Carotenoids at sufficient concentrations can prevent lipid oxidationand related oxidative stress.

Table 1. Chemical composition of various parts of *Carica papaya*

S.NO	PART	CONSTITUENTS
1	Fruit	Protein, fat, fibre, carbohydrates, minerals, calcium, phosphorus, iron, vitamin C, thiamine,riboflavin, niacin, and caroxene, amino acid, citric acids and molic acid (green fruits), volatile compounds : linalol, benzylisothiocynate, cis and trans 2, 6-dimethyl-3,6 expoxy-7 octen-2-ol. Alkaloid, α; carpaine, benzyl-β-d glucoside, 2-phenylethl-β-D-glucoside, 4-hydroxyl -phenyl-2-ethyl-B-D glucoside and four isomeric malonated benzyl-β-D glucosides,Carotenoids:B carotene,crytoxanthin, Monoterpenoids:Linalool,4-terpinol
2	Juice	N-butyric, n-hexanoic and n-octanoic acids, lipids; myristic, palmitic, stearic, linoleic, linolenic acids-vaccenic acid and oleic acids
3	Seed	Fatty acids, crude proteins, crude fibre, papaya oil, carpaine, benzylisothiocynate, benzylglucosinolate, glucotropacolin, benzylthiourea, hentriacontane, β-sistosterol, caricin and an enzyme nyrosin, Glucosinolates:Benzyl isothiocynate, papaya oil
4	Root	Arposide and an enzyme myrosin, Carposide
5	Leaves	Alkaloids: carpain, pseudocarpain and dehydrocarpaine I and II, choline, carposide, vitamin C and E
6	Bark	β-sitosterol, glucose, fructose, sucrose, galactose and xylitol
7	Latex	proteolytic enzymes, papain and chemopapain, glutamine cyclotransferase, chymopapain A, B and C, peptidase A and B and lysozymes
8	Shoot	Flavonoids: Myricetin,kaemferol
9	Unripe fruit	Enzyme : Papain,chymopapain

Antioxidant capacity

Antioxidant activity of *Carica papaya* decreases the risk of oxidative damage to tissues(Mahmood*et al.,* 2005; Mikhalchik*et al*., 2004). Antioxidants are the substances that can prevent or retard the oxidation of easily oxidisable materials such as fat, the functions of which are generally based on their abilities to scavenge reactive free radicals in food (Karabhari Rekha Bhaskar*et al*., 2014).The leaves of papaya have been shown to contain many active components that can increase the total antioxidant power in blood (Noriko*et al*., 2010; Seigler*et al*., 2002). Fermented papaya preparation (FPP) has defined antioxidant and immune-modulating potentials. The ability of FPP influence signaling cascades associated with cell growth and survival presents a rational for chemopreventive adjunct that can be used in combination with traditional redox based therapies that target oxidative stress in the cancer micro environment.Yoshino *et al*. providesample evidence that FPP is one such antioxidant (Okezie*et al*., 2014; Yoshino*et al*., 2009). Antioxidant functions are associated with decreased DNA damage, diminished lipid peroxidation, maintained immune function and inhibited malignant transformation of cells (Maisarah*et al*., 2013; Gropper*et al*., 2009).

The free radical scavenging activity of the fruit extract was analyzed by using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (Rui Hai*et al*., 2004; Piyawan Surinrut*et al*., 2005; Rampraba, 2015)Osato *et al*., reported antibacterial and oxidant activities of unripe papaya and they correlate the bacteriostatic activity of papaya with its scavenging action on superoxide and hydroxyl radicals,which could be part of the cellular metabolism of such enteropathogens (Mahmood*et al*., 2005; Osato*et al*., 1993).

Role of phytochemicals in the prevention of cancer

Phytochemicals occur naturally in plants and they are responsible for colour and organoleptic properties,such as the deep purple of blue berries and red for tomatoes. Previous reports have indicated that phytoconstituents in fruits and vegetables may reduce the risk of cancer possibly due to dietary fibers, polyphenols, antioxidants and anti-inflammatory effects (Saidu*et al*., 2013)**.** The papaya showed that the plants contained some phytochemical compounds which possess good antimicrobial properties on the test clinical isolates used in the

study. The phytochemical analysis of the plant showed that the flower contain saponin, Tannin, Alkaloids and Flavonoids.
This finding can be attested to the work of Sikanda *et al*. (2013) who also reported similar finding and also stated the effect of these phytochemical as a good antimicrobial agent on different test organism (Ekaiko Marshall*et al*., 2015; Sikandar *et al*., 2013). Cells in humans and other organisms are constantly exposed to a variety of oxidizing agents, some of which are necessary for life. These agents may be present in air, food, and water, or they may be produced by metabolic activity within cells. The key factor is to maintain a balance between oxidants and antioxidants to sustain optimal physiological conditions.Overproduction of oxidants can cause an imbalance, leading to oxidative stress, especially in chronic bacterial, viral, and parasitic infections (Liu, 1995).

Oxidative stress can cause oxidative damage to large biomolecules such as lipids, proteins, and DNA, resulting in an increased risk for cancer and Cardio vascular disease (Liu, 1995; Ames, 1991; Ames *et al*., 1993). To prevent or slow the oxidative stress induced by free radicals, sufficient amounts of antioxidants need to be consumed. Fruits, vegetables, and whole grains contain a wide variety of antioxidant compounds (phytochemicals), such as phenolics and carotenoids, and may help protect cellular systems from oxidative damage and also may lower the risk of chronic diseases (Sun*et al*., 2002; Chu*et al*., 2002; Adom*et al*., 2002; Wang*et al*., 1996; Vinson*et al*., 2001 and Adom*et al*., 2003). Strong epidemiological evidence suggests that regular consumption of fruits and vegetables can reduce cancer risk. Block *et al*. (1992) reviewed 200 epidemiological studies that examined the relationship between intake of fruits and vegetables and cancer of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary. In 128 of 156 dietary studies, the consumption of fruits and vegetables was found to have a significant protective effect.The risk of cancer was 2-fold higher in persons with a low intake of fruits and vegetables than in those with a high intake. Significant protection was found in 24 of 25 studies for lung cancer. Fruits were significantly protective in cancer of the esophagus, oral cavity, and larynx.
Fruits and vegetable intake was protective for cancer of the pancreas and stomach in 26 of 30 studies and for colorectal and bladder cancer in 23 of 38 studies. A prospective study involving 9959 men and women in Finland showed an inverse association between the intake of flavonoids and incidence of cancer at all sites combined (Knekt*et al*., 1997). After a 24-y follow-up, the risk of lung cancer was reduced by 50% in the highest quartile of flavonol intake (Rui Hai,2004).

Lycopene

Papaya has an abundance of cancer fighting lycopene. It is a key intermediate in the biosynthesis of many important carotenoids, such as beta-carotene and xanthophylls.Men consuming lycopene-rich fruits and vegetables such as papaya, tomatoes, apricots, pink grapefruit, watermelon, and guava were 82% less likely to have prostate cancer compared to those consuming the least lycopene-rich foods (Vijay*et al*., 2014; Aravind*et al*., 2013; Karabhari Rekha Bhaskar, 2014Aswani*et al*., 2012). Papaya is considered a good source of lycopene, with average values ranging from 0.36 to 3.4 mg/100 g FW, being ranked number 4 of overall foods in the USDA nutrient reference database, after red guava, water melon and tomatoes (Emmy*et al*., 2015).

Benzyl Isothicyanate

Papaya is one of the few examples known of a plant containing both glucosinolates and cyanogenic glucosides (Williams*et al*., 2015). It is rich in benzyl isothiocyanate (BITC) which may provide potential for use in chemoprevention of cancer. It has been suggested that the anti-carcinogenic effects of isothiocyanates are related to their capacity to induce phase II enzymes such as glutathione S-transferase, nicotinamide adenine dinucleotide phosphate and quinine reductase (Cavell*et al*., 2011; Nakamura*et al*., 2000). The glucosinolates are known to be degraded into isothiocyanates by enzymatic action of plant-specific myrosinase or intestinal microbiota in the human body (Basu*et al*., 2008). It suggested that the extract containing BITC and other phytochemical(s) may potentially provide the means for the treatment and prevention of selected human diseases such as cancer, and may also serve as immunoadjuvants for vaccine therapy (Emmy*et al*., 2015; Noriko*et al*., 2010).

Beta Carotene

The fruit is an excellent source of beta carotene that prevents damage caused by free radicals that may cause some forms of cancer (Aravind*et al.,* 2013).

Saponin

Saponins can recognize cancer cells, because cancer cells have cell membranes and structures are different from normal cells. Cancer cell membranes contain more compounds such as cholesterol. Saponins can bind cholesterol contained in the membrane of cancer cells, thereby disrupting membrane permeability (Marline Nainggolan*et al*., 2015; Sung and Rao, 1995). Saponins also reduce the occurrence of reactive oxygen species such as H2O2 and inhibit signaling pathways phosphatidyl inositol-3 kinase which may be the reason for the prevention of damage chromosome (Marline Nainggolan and Kasmirul, 2015; Pawar*et al*., 2001).

Flavonoid

Flavonoid compounds inhibit cell proliferation in various human cancer cells through the inhibition of oxidative processes that can lead to cancer initiation. This mechanism is mediated decrease xanthin oxidase enzyme,Cyclooxygenase (COX) and Lipooxygenase (LOX) required in the process prooxidation thereby delaying cell cycle.Flavonoids also inhibit the expression of topoisomerase I and II enzymes that play a role in catalyzing DNAscreening. Topoisomerase enzyme inhibitor complex will stabilize DNA topoisomerase and cause cuts and damage (Marline Nainggolan and Kasmirul, 2015; Ren*et al*., 2003).

Proteolytic enzymes: Papain and chymopapain

Proteolytic enzymes have a long history of use in cancer treatment.In 1906,John Beard,a Scottish embryologist,reported on the successful treatment of cancer using a pancreatic extract in his book The Enzyme Treatment of Cancer and its Scientific Basis.Proteolytic enzmes have been promoted by numerous alternative cancer practitioners for many years,but most

recently by Nicholas Gonzalez,M.D., who is evaluating the benefit of proteolytic enzymes in patients with advanced pancreatic cancer in a large-scale study, funded by the National Institute of Health's National Center for Complementary and Alternative Medicine, with collaboration from the National Cancer Institute. This larger trial is a follow-up to a smaller study that showed dramatic improvements in these patients.Once absorbed the body prevents digestion of proteins in blood and other body tissues by producing anti-proteases. The production of these anti-proteases is critical to the mechanism of action of proteolytic enzymes.These anti-proteinases block the invasiveness of tumor cells as well as prevent the formation of new blood vessels (angiogenesis).Proteolytic enzymes exert a number of other interesting anticancer mechanisms including the mechanism of metastasis (the spread of cancer) and the enhancement of the immune response.The Papain enzyme is similar to pepsin, a digestive enzyme in our body. Both papain and chymopapain can help lower inflammation and improve healing from burns (Aravind*et al*., 2013; Michael, 2001; Gonzalez *et al*., 1999).

Fibrin

Another useful compound not readily found in the plant kingdom is Fibrin. It reduces the risk of blood clots and improves the quality of blood cells, optimizing the ability of blood to flow through the circulatory system. Fibrin is also important in preventing stoke (Aravind*et al*., 2013).

Anticancer activity

Papaya is one of the few examples known of a plant containing both glucosinolates and cyanogenic glucosides (Emmy*et al*., 2015; Williams*et al*., 2015). It is rich in benzyl isothiocyanate (BITC) which may provide potential for use in chemoprevention of cancer.A study on the anticancer effect of *Carica papaya* in experimentally induced mammary tumours in rats showed that showed that administration of aqueous leaf extract of *Carica papaya* at a dosage of 200 mg/kg body wt showed anticancer effect (Gurudatta*et al*.,2015). Petroleum ether (40-600 C), Chloroform, ethyl acetate and methanol 80% extracts of C. papaya aerial parts were tested for their anti-cancer activity on three cancer cells TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells using a Sulforhodamine B (SRB) assay. Petroleum ether of C. papaya at the concentration of 100µg/ml has shown a significant anticancer effect for MCF7 (breast) cancer cells and showed less anticancer effect for the other two cancer cells while the other extracts have mild anticancer effect on the three cancer cells (Khaled*et al*., 2013; Bhadane Vishal*et al*., 2014).Various parts of *Carica papaya* Linn. (CP)have been traditionally used as ethnomedicine for a number of disorders, including cancer. Study was conducted to examine the effect of aqueous-extracted CP leaf fraction on the growth of various tumor cell lines and on the anti-tumor effect of human lymphocytes. Result showed significant growth inhibitory activity of the CP extract on tumor cell lines. In PBMC, the production of IL-2 and IL-4 was reduced following the addition of CP extract, whereas that ofIL- 12p40, IL-12p70, IFN- γ and TNF- α was enhanced without growth inhibition (Norikoe*t al*., 2010; Bhadane Vishal*et al*., 2014). Recent research on papaya leaf tea extract has demonstrated cancer cell growth inhibition. It appears to boost the production of key signaling molecules called Th1-type cytokines, which help regulate the immune system (Aravind*et al*., 2013). Papaya leaf juice has been consumed by people living on the Gold Coast of Australia, withsome anecdotes of successful cases being reported for its purported anticancer activity (Norikoe*t al*., 2010). A recent study found that papaya leaf extract could prevent growth of cancer cells, including pancreatic cancer – one of the most devastating forms of cancer (Norikoe*t al*., 2010; Scarlett*et al*., 2011). This result suggests that papaya leaf may contain compounds that limit the proliferation of pancreatic cancer cells (Quan*et al*., 2013). The leaf tea or extract has a reputation as a tumor destroying agent (Godson*et al*., 2012; Ayoola*et al*., 2010 and Walter Last, 2008).*Carica papaya* extract inhibited the proliferative responses carcinoma,breast adeno carcinoma,pancreatic epithelioid carcinoma, lung adeno carcinoma, pancreatic epithelioid carcinoma andmesothelioma in a dose-dependent manner (Norikoe*t al*., 2010). Epidemiological studies have shown that increased consumption of fruits is associated with a reduced risk of developing cancer (Rajarajeswaran*et al*., 2011; Block*et al*., 1992).

Conclusion

The vitamins, phytochemicals like lycopene, Isothyocynate, mineral compounds and some proteolytic enzymes like papain and chymopapain are present in papaya and helps to treat health problems.This properties makes papaya as one of the best herbal medicine. Papaya also promotes immune system. Papaya is one of the potent cancer fighting agent and they are highly effective against all kinds of cancer cells and their high antioxidant activity makes papaya to use in various medicinal and cosmetic field.

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