

Carica Papaya Leaf Extracts – An Ethnomedicinal Boon

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Available online: 1st June 2014

ABSTRACT

Papaya (*Carica papaya* L.) belongs to the family Caricaceae and is one of the most well researched plants. It is used widely due to its medicinal properties. This review aims at presenting the current literature on phytochemical properties of carica papaya leaves and also its uses in indigenous populations and its therapeutic applications and future research directions. For this review literature was compiled from various databases like pubmed, embase, scopus. The Phytochemical analysis of the leaf extract contains saponins, cardiac glycosides, anthraquinones, reducing sugars, flavonoids, alkaloids and tannins. It is used as an antidiabetic, antiinflammatory, anticancer and also to treat dengue and other diseases due to its wide biological activity. Many scientific studies have been conducted to the same end. Yet there is deficiency and opportunity to enlarge the framework of the research to include research in Parkinsonism and oxidant related damage, research in humans regarding use of c. papaya leaves in management of malaria, dengue fever, heart disorders, diabetes and helminthes.

Keywords:

I NTRODUCTION

Use of plants and plant products as medicine has been documented in the history since centuries. Volumes of literature have been written describing the use of various herbs, shrubs and plants. Despite the presence of modern pharmaceutical drugs search still continues for medicinal plants of high therapeutic value to resolve both old and new problems.

Papaya (*Carica papaya* L.) Belongs to the family Caricaceae and is known by different names across various continents. *Carica papaya* is one such well researched plant which has been used for treating many maladies. Originally derived from southern part of Mexico it is essentially a perennial plant and is mainly present in tropics. Many scientific investigations have been conducted to evaluate the biological activities of various parts of *Carica papaya*, including fruits, shoots, leaves, rinds, seeds, roots or latex.¹⁻⁵

Carica papaya leaf has been researched for its medicinal uses. It has been documented in literature for its use by natives of various parts of world and also for its anti-inflammatory, antitumour, antidiabetic effects and many others. This review exclusively focuses on the carica papaya leaf and leaf extracts – its content, ethnic use, toxicity and uses.

METHODOLOGY

Various databases like Pubmed, Ovid, Embase, Scopus and Google scholar databases were electronically searched

for articles focusing on *Carica papaya* leaf, from January 1990 to December 2013. Articles concentrating on the *Carica papaya* leaf were included in the review. Various journals were hand searched by the reviewers. Followed by which only full text articles were included in this review.

Phytochemical content of papaya leaves- Phytochemicals are compounds naturally present in plant and plant parts and the therapeutic uses of these plants can be attributed to the presence of such compounds. Various studies have been reported in the literature documenting the phytochemical content papaya leaves.⁶⁻⁸ Phytochemical analysis has confirmed the presence of alkaloids, glycosides, saponins, flavonoids, phenolics, proteins, amino acids. Presence of tannin in carica papaya leaf has been documented in studies by Eleazu et al 2012 and by Imaga et al 2010. On the contrary a study conducted by Ayoola PB et al., 2010 failed to confirm the presence of tannin in the leaf extracts.

Nutritive value of leaves- Leaves of *Carica papaya* can also be used as a nutraceutical. It contains carbohydrates, minerals and vitamins, lipids and proteins. So it can be used for dual purpose as a nutritional agent and medicinal agent. It has been observed to contain these compounds in varying proportions. Carbohydrates 8.3 %, ascorbic acid 38.6%, protein 5.6%, minerals like magnesium 0.035%, iron 0.0064% and phosphoric acid 0.225% per 100 gm of edible portion.⁸ These components are responsible for its role in coagulation of blood, proper functioning of the

Table 1: These compounds are responsible for various properties and therapeutic uses of carica papaya leaves.⁹⁻¹¹

Compound	Properties
Tannins	astringent properties, wound healing property
Saponins	precipitates and coagulates red blood cells, hemolytic activity, cholesterol binding properties and expectorant action
Alkaloids (carpaine, pseudocarpaine, piperidine alkaloids like , dehydrocarpaine I and II)	basic natural products, analgesic, antispasmodic and anti-bacterial properties, antimalarial (contains quinine)
Flavonoids	Antiallergic, anti inflammatory, treatment of capillary fragility, free radical scavenger, platelet aggregation, microbes, ulcers, hepatotoxins, viruses and anti cancer or tumor (Okwu, 2004). Flavonoids are potent water soluble antioxidants and free radical scavengers which prevent oxidative cell damage, have strong anticancer activity and protect against the different levels of carcinogenesis
Cardiac glycosides	Digitalis like action on heart
Amino acids	Antisickling property as it protects cell from oxidative damage (a reason for sickle cell crises)

*C. papaya leaf also contains phenolics such as protocatechuic acid, p-coumaric acid, caffeic acid, 5,7-dimethoxycoumarin, chlorogenic acid, kaempferol and quercetin, Papain, chymopapain, cystatin, tocopherol, ascorbic acid, cyanogenic glucosides, glucosinolates, nicotinic acid and tocopherol.*⁹⁻¹¹

heart and nervous system and the normal contraction of muscles, antibacterial, metabolism of water, promoting digestion, assimilation, osmosis, functioning of the pituitary gland, the pineal gland and the brain, promoting hepato-renal function, combating anaemia, helping in normal growth

Toxicity- Concerns about the toxicity of papaya leaves have been addressed in two studies one conducted by Halim et al 2011¹⁷ and other by Afzan A et al 2012.¹⁸ Both the studies have assessed the acute and sub acute oral toxicity of papaya leaf extract on Sprague Dawley rats. It was observed that that on administration of acute dose of 2000mg/ kg of carica papaya extract did not cause any acute adverse effects or death though it caused dehydration as was observed by increased hemoglobin, haematocrit, total protein levels. Similarly in the other study in which leaf extract from 'Sekaki' *C. papaya* cultivar was administered to the Sprague dawley rats it has been observed that carica papaya is safely tolerated at a dose which is fourteen times higher than the normal dosage used in traditional medicine in Malaysia.

Yet side effects like Stomach trouble, purgative effects and abortion may result from consumption of the dried papaya leaves (Morton, 1987). In ulcerogenic study, it has been observed that lower doses (100 mg/Kg) do not cause gastric irritation but dose of 800 mg/kg can produce gastric effect that is similar to a standard ulcerogenic dose of indomethacin.

Carica papaya leaf extract is a complex of many constituents like glycosylated flavonols, esterified phenolics, organic acids, carpaine alkaloids and other yet unknown compounds. A detailed investigation about the toxicity and tolerance in humans are necessary in the future due to such nature of *C. papaya* leaf extract.

Uses of papaya leaves- Myriad of uses of Carica papaya leaf extracts have been documented in the literature. Multitude of scientific studies has been conducted for the same.

Antitumor and immunomodulatory property of carica papaya leaf- Carica papaya leaf extracts have also been

used for a long time as an aboriginal remedy for various disorders, including cancer and infectious diseases. Various in-vitro studies have been conducted on cell lines to assess this antitumor efficacy of papaya leaves.

All of them have shown the inhibitory action of leaf extracts against the proliferative responses of the solid and hematopoietic tumor cell lines. This action has been demonstrated in against the solid tumor cell lines derived from cervical carcinoma (Hela), breast adenocarcinoma (MCF-7), hepatocellular carcinoma (HepG2), lung adenocarcinoma (PC14), pancreatic epithelioid carcinoma (Panc-1), and mesothelioma (H2452), haematopoietic cell lines, including T cell lymphoma (Jurkat), plasma cell leukemia (ARH77), Burkitt's lymphoma (Raji), and anaplastic large cell lymphoma (Karpas-299), breast cancer cell line (T47D), stomach cancer cell lines(AGS), pancreatic cancer cell line (capan-1), colon cancer cell line(DLD 1),ovarian cancer cell line(dov-13), lymphoma cell line (karpas), neuroblastoma cell line (T98G), uterine cancer cell line (hela), T-cell leukemia cell line (CD26 negative and negative jurkat), T- cell lines (H9, jurkat, molt-4, CCRF-CEM, HPB-ALL), Burkitt lymphoma cell lines, chronic myelogenous leukemia cell lines (K562), cervical carcinoma cell line (hela), hepatocellular cancer cell line (hepg2 and Huh-7) and lung adenocarcinoma cell lines (PC-14).¹⁹

One of the mechanisms in inhibition of proliferation was observed to be the capability of carica papaya leaf extract in induction of cell death, apoptosis. The carica papaya leaf extract has a potential of activating caspases 3 and 7 which are pro apoptotic in nature. In study of rumiyati et al conducted in similar lines it was observed that there was induction of apoptosis via the mitochondrial pathway: in breast cancer cells treated with the protein fraction (derived from c.papaya leaves), the tumor suppressor gene p 53 expression was increased by about 59.4% and antiapoptotic factor Bcl-2 protein expression was decreased by approximately 63% in comparison to control cells.

Table 2: Use of papaya leaves by various indigenous populations –Indigenous populations usually cure their sick using various plant products. So it would pave way for future research to understand the various uses of papaya leaves by different populations.¹²⁻¹⁶

Name of the place	Uses of carica papaya leaves
East indies	Young leaves are cooked and eaten like spinach. Crushed leaves may be used to tenderize meat. Also functions as a Vermifuge and a primitive soap substitute in laundering. Dried leaves have been smoked to relieve asthma or as a tobacco substitute.
Ghana	Purgative for stomach troubles Abortifacient
Ivory coast	Purgative for horses Treatment of genitor urinary ailments
Nigeria	Relief in nausea(during pregnancy)
French Guiana	Leaf are prepared in combination with Quassia amara, Euterpe oleracea and Citrus sp for the treatment of malarial fever
Ethiopia	Antimalarial
India	Heart tonic, febrifuge, vermifuge, colic fever, beri beri, abortion and asthma
Phillipines	Rheumatic complaints
Australia	Stomach troubles and cancer
carribean region	To treat high blood pressure
Bangladesh	Rheumatoid arthritis, constipation, jaundice, diabetes, dermatitis, hurt
Others	Packages of dried, pulverized leaves are sold by "health food" stores for making tea (used as tumour destroying agent) The fresh green tea acts as antiseptic and dried leaves are best as a tonic and blood purifier Also used as digestive system promoter, chronic indigestion, weight loss, obesity, arteriosclerosis, high blood pressure and weakening of heart Diuretic and Antihelminthic

Similarly In 2010, Otsuki et al² observed in their study that along with induction of apoptosis other reason for the antiproliferative activity was ability of papaya extract to increase the production of Th1-type cytokines, such as IL-12p40, IL-12p70, INF, and TNF- as well as the expression of 23 immunomodulatory genes in peripheral blood mononuclear cells. The active components with growth inhibitory effect on tumor cells and immunomodulatory effects were identified to be located in the fraction with molecular weight lower than 1000.

In the leaves of Carica papaya, components previously reported to potentially have anti-tumor activity include tocopherol²¹, lycopene²², flavonoid²³, and benzyliothiocyanate²⁴.

Despite this evidence regarding the anti tumor effect of carica papaya leaf extract there is need for human trials regarding the same.

Immunomodulatory action- Immune system is of vital importance in maintaining the homeostasis and for warding off the diseases that attack humans almost every day. A study was conducted by M. M.Ghaisas et al in 2012 to assess the immunomodulatory action of carica papaya leaf extract, it was observed that c. papaya leaf extract enhanced the adhesion of the neutrophils to nylon fibres which correlated with the margination of cells.²⁵ Similar findings regarding immunomodulatory action of the extract was observed in a study by Osuki et al 2010.² Microarray analyses showed that the expression of 23 immunomodulatory genes, classified by gene ontology analysis, was enhanced by the addition of CP extract. CCL2, CCL7, CCL8 and SERPINB2 were representative

of these upregulated genes, and thus may serve as index markers of the immunomodulatory effects of CP extract. This property of C Papaya leaf can be attributed to its anti-inflammatory, wound healing, anti-hepatotoxic, diuretic, and antihypertensive effect and also for relief in dengue fever.

Anti-inflammatory activity- Use of dried leaves for treatment of fever, pyrexia, diabetes, gonorrhoea, syphilis, inflammation and as dressing for foul wounds, arthritis and rheumatism has been documented in the literature. Reports have shown that the leaves of C. papaya contain many bioactive agents like carpaine, nicotinic acid which may be responsible for the biological activity of the plant. (Duke, 1984; Gill, 1992). There is apparent lack of basic and clinical studies to assess anti-inflammatory action of Carica Papaya leaf extract.

In a study by Osuki et al 2010²⁶ the anti-inflammatory activity of the ethanol extract of C. papaya was established using the carrageenan-induced paw oedema, cotton pellet granuloma and formaldehyde-induced arthritis models. These methods were used to evaluate inflammation at acute, subchronic and chronic stages respectively. The result of the carrageenan test showed that the ethanol extract of C. papaya can inhibit prostaglandins mediated inflammation. It was also postulated that at lower doses the extract might resemble the effect of a cox selective inhibitor. Similarly, in another study conducted by Owoyele BV et al 2008²⁷ it was observed that carica papaya leaf extract significantly reduced paw edema, amount of granuloma, thereby substantiating the anti-inflammatory activity of leaf extracts.

Arthritis- Two studies using the formaldehyde model has demonstrated anti-arthritic activity of papaya leaf extract. The trend of the anti arthritic activity of the extract closely resembled that of the standard drug Indomethacin.^{26, 27}

Granulomatous tissue formation- Studies have demonstrated that the extract of *C. papaya* leaf produces significant inhibition of granulomatous tissue formation. This indicates that the extract can inhibit sub chronic inflammation in which various types of cellular migration are (e. g. fibroblast) involved.^{26,28}

Sickle cell disease- *C. papaya* leaf extract has been advocated to assist in relieving the pains associated with sickle-cell crisis and also may prevent opportunistic infections in sickle cell disease. Oxidative stress ensuing from lipid peroxidation of erythrocyte membranes is a leading sign of sickle cell crisis phenomenon. In a study conducted by Imaga et al 2010, phytochemical screening of carica papaya leaf extract confirmed the presence of folic acid, vitamin B12, alkaloids, saponins, glycosides, tannins and anthraquinones. This study also showed that each of these plants extracts contained flavonoids and the antioxidant vitamins A and C. Intake of carica papaya leaves supplies some of the required amino acids like glycine, cysteine and glutamic acid, for glutathione production, as well as the antioxidant nutrients needed to protect the red blood cell membrane from lysis and destruction. The reported antisickling activity of the leaf extracts may in part be as a result of the presence of precursors for GSH biosynthesis present in abundance in the extract. Along with this the presence of magnesium is known to reduce erythrocyte dehydration in patients with sickle cell disease and is indicated in several transport systems (De Franceschi et al., 1997). This was an in vitro research on methanolic extracts of the leaf for anti sickling and membrane stabilizing using rbc from non crises state patient and confirmed the membrane stabilizing and prevention of sickle cells formation under severe hypoxia. Similarly in other study *C. papaya* leaves extracted from Soxhlet extraction method with five different solvents like hexane, chloroform, ethyl acetate, butanol and water. On comparison of two concentrations of extract 10 mg/ml was more effective than 5 mg/ml. butanol extract showed maximum antisickling property at 10 mg/ml and ethyl acetate had maximum activity at 5 mg/ml.^{7,29}

Antihelminthic- Antihelminthic action of papaya leaves has been reported in a study conducted by Shaziya Bi and Goyal P.K et al 2012 in mice.³⁰ It has been assessed that papaya has a definite antihelminthic action on *A. Caninum* a nematode infecting dogs. The anthelmintic efficacy of Papaya might be due to presence of proteolytic enzyme such as papain, chymopapain and lysozymes in the latex as well as in leaves.

Human studies are lacking for this particular use of papaya leaves.

Dengue- Dengue is a viral disease, spread by mosquitoes of the genus *Aedes*, primarily *Aedes aegypti*, which is today the most important arboviral disease worldwide in terms of morbidity, mortality and economic impact. The symptoms of Dengue hemorrhagic

fever, the most serious form of dengue fever, are hypotension, increased vascular permeability, thrombocytopenia and hemorrhagic manifestations. *Carica papaya* extract has been seen to increase the platelet³¹ count which is lowered in dengue fever. Recently, *Carica papaya* leaves have been successfully employed in folk medicine for the treatment of dengue infections with haemorrhagic manifestations, using suspensions of powdered leaves in palm oil. In an observation by Kala cp in 2012 it was observed that the platelet counts of five dengue patients increased substantially within 24 hours of consumption of papaya leaf extract.³² Similar observations were found in a study conducted on a single dengue patient in Pakistan by Ahmad et al in 2011.³³ Similarly, in a randomized controlled trial conducted in Malaysia on 228 patients it was observed that after forty eight hours of consumption of papaya leaf extract by dengue patients there was a substantial increase in platelet count compared to control group of dengue patients who were on standard treatment. There was also increase in platelet specific genes like ALOX 12 and PTAFR in the experimental group.³⁴

Antidiabetic effect- A single Study has shown that the aqueous extract of *C. papaya* exerted a hypoglycemic and antioxidant effect and improvement in the lipid profile of diabetic rats. In this study effect of carica papaya leaf extract on streptozocin induced diabetes in rats was analysed. In addition, the leaf extract positively affected integrity and function of both liver and pancreas. It is suggested that the aqueous *C. papaya* leaf extract may act by stimulating the few remaining β -cells with the subsequent release of more insulin.³⁵ Human studies are lacking for this particular use of papaya leaves.

Action on heart- Caripaine obtained from the leaves has depressant action on heart (glycoside like action). The cardiac glycosides, therapeutically have the ability to increase the force and power of the heart-beat without increasing the amount of oxygen needed by the heart muscle. They can thus increase the efficiency of the heart and at the same time steady excess heart beats without strain to the organ (David, 1983).¹

Antibacterial- In a study conducted to assess the antibacterial action of carica papaya leaf it has been observed that the extract possesses antibacterial activity against tested gram positive (*Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*) and gram negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacteria. Similarly its action against salmonella typhi, paratyphi and typhimurium has also been documented.¹¹

Gastro-protective and oxidative stress protector –

The effects of *Carica papaya* leaf (CPL) aqueous extract on alcohol induced acute gastric damage and the immediate blood oxidative stress level were studied in rats. It *Carica papaya* leaf may potentially serve as a good therapeutic agent for protection against gastric ulcer and oxidative stress.³⁶

Future directions of research- Need of research in Parkinsonism and oxidant related damage.

Need for research in humans regarding use of c. papaya leaves in management of malaria, dengue fever, heart disorders, diabetes and helminthes.

Research regarding the long term tolerance and toxicity of c papaya leaf extract has to be conducted.

CONCLUSION

Carica papaya is a plant with multitude of uses. It is one of the well researched plants with ethnomedicinal use. Leaves of this plant have been widely used by various indigenous populations. Many scientific studies have been conducted to the same end. Yet there is deficiency and opportunity to enlarge the framework of the research so that all the generations to come can reap the benefits of this ethnomedicinal boon – carica papaya leaf.

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