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Carica papaya leaf extract: potential therapeutic effects-a review

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ABSTRACT

Carica papaya (*C. papaya*, family Caricarceae, papaya) is one of the most popular and economically important tropical plants in the world. The plant is rich in bioactive secondary metabolites like alkaloids, phenolics, Carbohydrates, terpenoids, phytosterols, glycosides, flavonoids, carotenoids, tannins, saponins. The plant has been used traditionally for many beneficial effects like pyrexia, diabetes, bacterial and fungal infections, hypertension, beri beri, asthma etc. The strong defensive mechanism of the principal constituents of leaves proved anti-inflammatory and immune-modulatory effects. Leaves contain an alkaloid called carpaine and a glucoside named carposide. Research done extensively on *C. papaya* leaf extract revealed to possess haemopoietic and thrombopoietic activites. Various invittro and in vivo models have been successfully employed to prove the anticancer and anti-dengue effects of C. Papaya. The extract in the form of tablets and syrups is available for the convenient administration. Further more studies are encouraged to be performed on the leaves and leaf extracts for the possible extraction of principal constituents for various therapeutic activities

Keywords: Carica Papaya, Lleaf extract, Anti-dengue, Anti-cancer

NOVELTY STATEMENT OF THE PRESENT REVIEW

Carica Papaya is a traditional plant of tropical regions. It is a popular fruit as the best vitamin-A supplement and in the treatment of various helminthic infections. All parts of the plant have been proved for various activities in vitro. The current review pinpoints the activities of leaf extract exclusively for their inflammatory, anti-oxidant, anti-cancer, anti-dengue, anti-platelet and against few antiviral effects for the future studies to be performed against resistant infections and other diseases for the benefit of the society.

INTRODUCTION

Carica papaya (C. papaya, family Caricarceae, papaya) is one of the most popular and economically important tropical plants in the world [1, 2]. The plant is lactiferous which makes it an abundant source of endopeptidases or proteolytic enzymes like papain, chymopapain, glycyl endopeptidase and carican [3]. The plant also is rich in bioactive secondary metabolites like alkaloids, phenolics, Carbohydrates, terpenoids, phytosterols, glycosides, flavonoids, carotenoids, tannins, saponins. Leaves contain an alkaloid called

carpaine and a glucoside named carposide [4]. All these compounds are responsible for the strong defensive mechanism which fascinated the research scientists. Few phenolic compounds like quercetin, protocatechuic acid, p-coumaric acid, caffeic acid, chlorogenic acid, kaempferol, and 5, 7-dimethoxycoumarin were isolated by GCMS [5].

Beneficial Effects and Therapeutic activates of Carica Papaya Leaf Extract

Some of the traditional claims of efficacy that have been investigated scientifically using animal models and their efficacy have been proven [6, 7]. Recent studies conducted on leaf extract proved to possess anti-sickling (inhibition of sickle cell formation under severe hypoxia conditions) and membrane stabilizing properties [6,8]. The in vitro studies conducted on rats showed increased erythrocyte glutathione peroxidase activity and reduction of plasma lipid peroxidation level thus serving as a good therapeutic agent for protection against gastric ulcer and oxidative stress [6, 7]. It was also reported that the leaf extract possess an ability to modulate inflammatory markers in various cell types exposed to a variety of stressors due to the presence of proteolytic enzymes [9,10]. Studies also showed that *C. papaya* leaf extract may be used as a medicine to boost haemopoiesis and thrombopoiesis when these have been suppressed by disease [11]. The milky juice (latex) is employed as styptic and as debridement when applied as external applications to burns and scalds [10].

The leaf extracts were tested for their natural antibacterial properties against Bacillus stearothermophilus, Listeria monocytogenes, Pseudomonas sp., and Escherichia coli etc [12]. Research showed that the leaf extract possesses angiotensin converting enzyme inhibitory effect and reduced cardiac hypertrophy thus acting as a natural antihypertensive agent [12]. Carica papaya leaf extracts are used as a powerful cardiotonic and also for the treatment of fever, pyrexia, diabetes, gonorrhea, syphilis, inflammation and for dressing foul wounds. Traditionally, the leaf extract was used as analgesia and in the treatment for dyspepsia, colic, pyrexia, beriberi, abortion, hypertension, asthma [13-16] and cancer in Australia.

Scientific research on aqueous leaf extract showed antitumor activity by the induction of apoptosis and growth inhibitory activity. In addition it was also reported to increase the production of Th1 type cytokines such as the interleukins 1L 12p40 and IL 12p70, interferon (IFN Y) and tumour necrosis factor (TNF α) and expression of 23 immuno-modulatory genes in peripheral blood mononuclear cells [11]. A study conducted using aqueous and ethanolic extracts of C. papaya leaves were found to be more effective in inhibiting the proliferation in pancreatic cells [11]. The effects of Carica papaya leaf extracts have previously been reported being tested on the growth of different cancer cell lines: breast, stomach, lung, pancreatic, colon, liver, ovarian, cervical, neuroblastoma, lymphoma, leukaemia and other blood cancers. And the leaf extracts were found to exert in vitro cytotoxicity on human squamous cell carcinoma [13, 14].

Three groups of bioactive compounds identified by Huang et al., 2009 have attracted considerable interest in anticancer studies: phenolics, carotenoids and glucosinolates that are available in carica papaya leaves. Pure compounds of these three groups have been extensively researched in *in vivo* and *in vitro* studies on many types of cell lines for their potential effects in cancer treatment and prevention. These bioactives act *via* multiple mechanisms, such as cancer cell signalling, proliferation, apoptosis, migration and invasion, as well as angiogenesis and carcinogen elimination [13]. Various doses of leaf extracts have been tested in vitro for the mechanism of anticancer activity on different cell lines [15-18] as shown in the table: 1

Table: 1. Mechanism of anticancer activity studied using leaf extracts

Type of cancer cell line	Type and dose of leaf extract	Results	Reference
• Stomach cancer cell line (AGS) • Pancreatic cancer cell line (Capan1) • 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 leukaemia cell line (CD26 negative or negative Jurkat)	Aqueous extract of papaya leaves (1.25–27 mg/mL)	Papaya leaf extract showed a concentration-dependent anticancer effect on each of the cancer cell lines, and suppressed DNA synthesis by suppressing the incorporation of 3H-thymidine	Morimoto et al., 2008
• T cell lines (H9, Jurkat, Molt-4, CCRF-CEM and HPB-ALL) • Burkitt's lymphoma cell lines (Ramos and Raji) • Chronic myelogenous leukaemia cell line (K562) Cervical carcinoma cell line (Hela) • Hepatocellular carcinoma cell lines (HepG2 and Huh-7) • Lung adenocarcinoma cell line (PC14) • Pancreatic epithelioid carcinoma cell line (Panc-1)	Aqueous extract of papaya leaves (0.625–20 mg/mL)	Inhibited the proliferative responses of both haematopoietic cell lines and solid tumour cell lines. In peripheral blood mononuclear cells, papaya extract reduced the production of IL-2 and IL-4, and increased the production of Th1 types cytokines, such as IL-12p40, IL-12p70, IFN-γ and TNF-α. The expression of 23 immunomodulatory genes was enhanced by the addition of papaya extract.	Otsuki et al., 2010

• Mesothelioma cell lines (H2452, H226, and MESO-4) • Plasma cell leukaemia cell line (ARH77) • Anaplastic large cell lymphoma cell line (Karpas-299) • Breast adenocarcinoma cell line (MCF-7) • Mesothelioma cell line (JMN) • Pancreatic adenocarcinoma cell line (Capan1)			
Human pancreatic cancer cells (Mia-Paca2 and ASPC-1)	Saponin-enriched water and ethanolic extracts (100 µg/mL)	Ethanolic extracts were more effective than or at least as effective as the chemotherapeutic agent, gemcitabine.	(Vuong et al., 2015)
Breast cancer cell line (T47D)	Protein fraction containing ribosome-activating proteins 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%	Rumiyati, 2006

The studies also showed that the leaf extract possesses a dengue-specific neutralizing effect on dengue viral-infected plasma that may exert a protective role on platelets [19, 20]. The findings revealed quercetin has potential inhibitory activity against NS2B-NS3 serine protease with marked antiviral activity against DENV2 virus as an effective anti-dengue compound [19, 20]. The activities of leaf extracts of Carica Papaya are represented as shown in the table: 2 [21-27].

Table: 2. Studies conducted on platelet count using Carica Papaya Leaf Extract

S.No	Type of Extract	Dose and route of administration	Results	References
1	Ethanol	Oral-25–200 mg/kg	Significant ($p < 0.05$) reduction in carrageenan-induced paw edema, granuloma (cotton pellet induced) and inflammation in arthritic rats.	(Bamidele V.Owoyele et al. 2008)
2	Aqueous	Oral-100–200 mg/kg	Leaf extract found to contain alkaloids, tannins, cardiac glycosides and saponins. Extract displayed significant ($p < 0.05$) anti-inflammatory effect in rats (using acetic acid-induced writhing response and formalin test).	Adeolu and Vivian 2013
3	Juice	Oral - 0.2 ml, 7 d	Platelet count was enhanced after 21 d (5.53×10^5/µl to 11.3×10^5/µl) in mice. Increment in RBC count also observed (6×10^6/µl to 9×10^5/µl)	(Dharmarathna et al. 2013
4	Ethanol (70%)	Oral - 1.1g, twice daily, 12 d	Significant ($p < 0.05$) increment in platelet count was observed in dengue fever patients (male and female)	Fenny et al. 2012

5	Juice	Oral - 150 ml, daily, 5 d	Increment in thrombocytes (28×10^3/µl to 138×10^3/µl) and WBC (3000/µl to 7800/µl) in male dengue fever patient	(Osama et al. 2014,
6	Juice	Oral - 25 ml, twice daily, 5 d	Increment in platelets (55×10^3/µl to 168×10^3/µl), RBC (5.0×10^6/µl to 5.3×10^3/µl), WBC (3.7×10^3/µl to 7.7×10^3/µl) and PMN (46.7% to 78.3%) in male dengue fever patient	Ahmad et al. 2011
7	Juice	Oral - 0.72 ml/100 g	Both mature and immature leaves displayed platelet enhancing property with no signs of toxicity and stress in rats	Achini et al. 2012
S.No	**Type of Extract**	**Dose and route of administration**	**Results**	**References**
8	Juice	Oral - 50 g, daily, 3 d	Mean platelet count enhanced in dengue fever patients at 40 h of first dose. *ALOX12* (ΔCT mean = 16.02, FC = 15.00) and *PTAFR* genes (ΔCT mean = 14.87, FC =13.42) highly expressed	Soobitha et al. 2013

Dose and dosage regimen play a vital role in the therapeutic activity of the constituent. Also excess doses may cause toxic effects and on toward reactions. Considering the history of the usage of leaves for various effects, the leaf extract is formulated as syrups and tablets as stable and convenient oral dosage forms. Currently leaf extract in the form of syrup or tablets are successfully being used in the control of the progression of cancer and also in the improvement of platelet count which is the major cause in the adverse effects of dengue.

CONCLUSION

The leaves of Carica Papaya, a traditional tropical plant has been studied extensively for its chemical constituents like endopeptidases, alkaloids, phenolics, Carbohydrates, terpenoids, phytosterols, glycosides, flavonoids, carotenoids, tannins, saponins. The presence of all these compounds revealed various potential therapeutic effects like immune-modulatory and anti-inflammatory effects, anticancer, anti-dengue etc apart from its traditional uses like antihypertensive, wound healing, malaria, fungal infections, asthma, diabetes, ulcers, eczema, helminth infections etc. Further studies are still encouraged to prove the possible therapeutic efficacy of leaf extracts of Carica Papaya against various antiviral agents and other diseases as natural treatment against dreadful diseases.

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