



INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation

Journal Home Page: www.ijrps.com

Carica Papaya Leaf Extracts: A Novel Herbal Drug in Cancer Treatment

Rajashri R¹, Mahathi Neralla², Rinku George², Santhosh Kumar M P^{*1}, Arthi Balasubramaniam³¹Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospital, Chennai-600077, Tamil Nadu, India²Department of Oncology, Oral Cancer Institute, Saveetha Dental College and Hospital, Chennai-600077, Tamil Nadu, India³Department of Community Dentistry, Saveetha Dental College and Hospital, Chennai-600077, Tamil Nadu, India

Article History:

Received on: 11.09.2019

Revised on: 10.12.2019

Accepted on: 15.12.2019

Keywords:

Cachexia,
Head and neck cancer,
oral cancer,
Papaya leaf,
Treatment,
Herbal drug

ABSTRACT

With the continued increase in Cancer incidence and deaths, traditional clinical therapies like surgery, radiation, chemotherapy, immunosuppression alone are not enough to counteract cancer due to their cost and its associated side effects, thus emphasizing the need for a novel intervention plan. Hippocrates's (5th century BCE) quote "Let food be thy medicine, and let thy medicine be thy food" is well popular all over the world and thus food was chosen to enhance health and emotional wellbeing that caused the change in trend in the market for natural products that help in combating cancer. Cancer statistics showed that the consumption of diets rich in fresh fruits and vegetables is inversely associated with cancer incidence, which leads to study plant-based dietary antioxidants and its therapeutic role in cancer, which was underestimated in the past. This review is about the potential benefits of leaf extracts of Carica papaya in treating various cancers of the body; and its implication in the management of oral cancers.



*Corresponding Author

Name: Santhosh Kumar M P

Phone: +91-9994892022

Email: santhoshsurgeon@gmail.com

ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11i2.2038>

Production and Hosted by

IJRPS | www.ijrps.com

© 2020 | All rights reserved.

INTRODUCTION

Amongst the 36 cancers known worldwide, Oral cancer stands 11th with a higher incidence in low and middle-income countries (LMIC's). India accounts for 20% of all the oral cancer cases and 25% for its associated deaths. Cancers of the oral cavity and oropharynx are the commonest among

the head and neck cancers, with 90% of them being squamous cell carcinoma.

The main risk factor for oral cancer is the consumption of tobacco products, others being excessive alcohol use and dietary deficiencies. These habits account for more than 90% of oral cancers. It can be prevented by eliminating tobacco consumption, limiting alcohol use and increasing the intake of fruits and vegetables. A healthy diet rich in fruits and vegetables reduces the incidence of cancers in general by 40-50%. In High-income countries (HIC's), lack of fruits and vegetables may account for 15-20% of oral cancers, which is likely to be higher in LMICs. Projections indicate that the estimated number of incident cases of all cancers (a lip, oral cavity, salivary glands and oropharynx), both sexes, all ages will rise to more than 1.8 million from 2018 to 2040 as depicted in Figure 1 and Figure 2. The estimated deaths from 2018 to 2040 of all cancers, both sexes, all ages are 1.45 million, as depicted in Figure 3 and Figure 4 (Bray *et al.*, 2018).

Estimated number of incident cases from 2018 to 2040, lip, oral cavity, both sexes, all ages

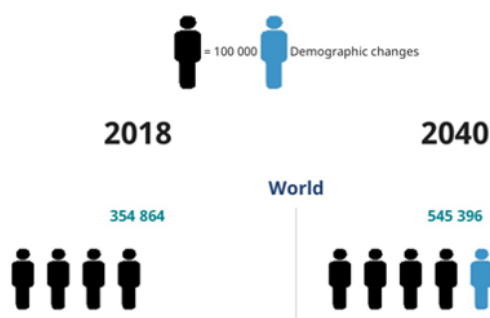


Figure 1: Lip and oral cavity cancer incidence

Estimated number of incident cases from 2018 to 2040, oropharynx, both sexes, all ages

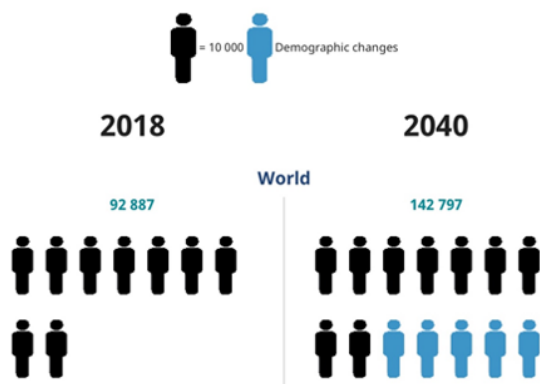


Figure 2: Oropharynx cancer incidence

Estimated number of deaths from 2018 to 2040, lip, oral cavity, both sexes, all ages



Figure 3: Lip and oral cavity cancer-related deaths

Estimated number of deaths from 2018 to 2040, oropharynx, both sexes, all ages

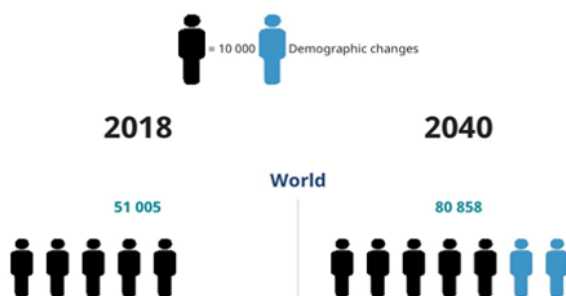


Figure 4: Oropharynx cancer-related deaths

MATERIALS AND METHODS

Due to associated side effects and high cost of treatment with the present treatment modalities, and stable increase in the incidence of new cancer cases and cancer mortality, the quest to search for cheaper and effective alternatives began leading to an increased interest in traditional herbal therapeutics using plants and their derivatives. Papaya leaves have been used for the treatment of malaria ([Krishna et al., 2008](#)), asthma ([Gamulle et al., 2012](#)), dengue fever ([Ahmad et al., 2011](#); [Subenthiran et al., 2013](#)), vitamin B1 deficiency ([Vien and Thuy, 2012](#)), including cancer in many parts of the world ([Heena and Sunil, 2019](#); [Soubra et al., 2016](#)). It also has shown anti-proliferative and cytotoxic activities against colorectal ([Lohsoonthorn and Danvivat, 1995](#)) and gall bladder cancers ([Pandey and Shukla, 2002](#)), prostate cancers [Shahar et al. \(2011\)](#), cervical cancer ([Siegel et al., 2010](#)) and breast cancers ([Zhang et al., 2009](#); [García-Solís et al., 2009](#)), while its extracts from seeds and the fruit show activity against MCF-7, HepG2, HL-60 cancer cells (breast, liver, leukemia, respectively) ([Jayakumar and Kanthimathi, 2011](#)).

Benefits of Carica Papaya

Papaya is remarkably known for its nutritional and therapeutic properties all throughout the world. Enzymes like Papain, Lycopene, Isothiocyanate, Vitamins, Minerals, Carotenoids, Flavonoids and Carbohydrates are present in the entire plant that is capable of feeding and nourishing the human body and immune system ([Nakamura et al., 2007](#)). Every part of the plant, including its leaves, fruits, seeds, bark, latex and its juice are used as a medicine, thus serving as a nutraceutical plant. Its leaves can also be consumed like spinach by steaming as used in some parts of Asia ([Recio et al., 2012](#)).

Immune defense mechanisms are activated by

inflammatory conditions and under constant stimuli, chronic inflammation occurs, triggering the production and development of pro-inflammatory cytokines, transcription factors and oncogenes (Pan *et al.*, 2010). Immune inflammatory components: Immunoglobulins, T-cells and antioxidants are triggered by chronic inflammatory conditions (Gupta *et al.*, 2012). Pathophysiology of cancer is dependent on Oxidative stress and inflammation mechanisms and that being the case, anti-inflammatory and immunomodulatory activities of plant extracts and their metabolites counteract them (Aravindaram and Yang, 2010; Yogiraj *et al.*, 2014). The papaya leaf juice improves the antioxidant defense and is thus being recognized as a promising antioxidant.

There have been no human clinical trials and no in vivo cancer studies that have been conducted with extracts of *Carica papaya* so far in the literature. In a patent application, the high efficacy of extracts or brew of different parts of papaya in water has been demonstrated for the prevention, treatment or improvement of many types of cancers like lung, stomach, colon, pancreatic, liver, ovarian, neuroblastoma and other solid cancers, or lymphoma, leukemia and other hematological cancers. Numerous case studies have been reported as experimental examples, but data is limited. A case of a 47-year-old female with stomach cancer metastasized to the pancreas, drank approximately 750 mL of papaya leaf extract every day (Concentrated 750 mL of one dried papaya leaf boiled in a wooden vessel with 3L of water) for two periods of 90 days each and with a gap between the two periods. The pancreatic metastases disappeared and there was a drop in the tumor marker (carcinoembryonic antigen) to 2.3 from 49 and alpha-fetoprotein to 2.0 from 369, with no subsequent relapse. Long-term survival was observed after drinking papaya leaf extracts in 5 lung cancer patients, 3 stomach cancer patients, 3 breast cancer patients, 1 blood cancer patient, 1 liver cancer patient, and 1 pancreatic cancer patient, but these reported cases lack specific data (Yogiraj *et al.*, 2014).

More surprisingly, the number of previous in vitro cancer studies for *Carica papaya* is also limited, with only several cell culture-based studies. Papaya preparation is used as a food supplement in treating conditions like thalassemia, cirrhosis, stroke, Alzheimer's disease, Parkinson's disease, diabetes and aging (Aruoma *et al.*, 2010). The cytotoxic effect of *C. papaya* extract has been tested in various cancer cell lines in In Vitro studies (Nguyen *et al.*, 2013).

RESULTS AND DISCUSSION

Juice of *Carica papaya* leaves has been widely used in treating dengue and malaria with favorable results. Ingestion of papaya leaves is not needed to elicit its antiproliferative nature and hence they are widely tested for anticancer activity. They have been shown to exhibit an anticancer effect on the development of various cancer cell lines in vitro, like MCF-7, HepG2, HL-60 and solid tumor. Hence, further studies involving papaya leaf juice are warranted towards other cell lines, including oral squamous cell carcinoma. It is the presence of carotenoids, phenolics, and glucosinolates in papaya that exhibit these potential anticancer activities (Nguyen *et al.*, 2013).

Many in vitro cell studies have discovered various bioactive compounds that modulate immune-inflammatory markers with papaya leaves and papaya seeds extracted using both water and ethanol or methanol.

Leaves and seeds have similar anti-oxidation activity profile even with differing phenolic and flavonoids content. Of all the papaya fractions, ethanolic extracts of papaya have greater anti-oxidation activity compared to aqueous extracts. This is attributed to the solubility of polyphenol's chemical structure (Hadadi *et al.*, 2018). Similarly, leaf juice extracts have demonstrated stronger cytotoxic effect than brewed decoction as the bioactive compounds in papaya being temperature sensitive and can be heat-inactivated.

The enzyme papain in papaya is responsible for the anticancer activity. The fibrin in the cell wall of cancer cells is broken down and converted to the protein end products, i.e., amino acids. Papaya also contains oxygen and free radical reactive lycopene. Isothyocyanate, too, is effective against various cancer cell lines. Thus, these compounds inhibit both the formation and development of cancer cells.

CONCLUSIONS

Three groups of bioactive compounds —phenolics, carotenoids, and glucosinolates — have attracted considerable interest in anticancer studies. Although the evidence is limited, there are indications that *Carica papaya*, with its abundant bioactive phytochemicals, can be used for treating various types of cancers. But human clinical trials are yet to be performed to confirm these findings. Even though survival was observed in patients with lung cancer, stomach cancer, breast cancer, pancreatic cancer, liver cancer and blood cancer after drinking papaya leaf extract; its anticancer effects in oral cancer has not been explored in detail. Cell cul-

ture and animal studies, as well as clinical trials, need to be conducted to determine doses for the consumption of different parts of papaya for oral cancer treatment, prevention and validation of the findings.

REFERENCES

- Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B. H., Mohammad, I., Fazal, L. 2011. Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pacific journal of tropical biomedicine*, 1(4):330-333.
- Aravindaram, K., Yang, N. S. 2010. Anti-Inflammatory Plant Natural Products for Cancer Therapy. *Planta Medica*, 76(11):1103-1117.
- Aruoma, O. I., Hayashi, Y., Marotta, F., Mantello, P., Rachmilewitz, E., Montagnier, L. 2010. Applications and bioefficacy of the functional food supplement fermented papaya preparation. *Toxicology*, 278(1):6-16.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., Jemal, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 68(6):394-424.
- Gammulle, A., Ratnasooriya, W. D., Jayakody, J., Fernando, C., Udagama, P. V. 2012. Thrombocytosis and Anti-inflammatory Properties, and Toxicological Evaluation of *Carica papaya* Mature Leaf Concentrate in a Murine Model. *Online International Journal of Medicinal Plants Research*, 1(2):21-30.
- García-Solís, P., Yahia, E. M., Morales-Tlalpan, V., Díaz-Muñoz, M. 2009. Screening of the antiproliferative effect of aqueous extracts of plant foods consumed in México on the breast cancer cell line MCF-7. *International Journal of Food Sciences and Nutrition*, 60(sup6):32-46.
- Gupta, S. C., Hevia, D., Patchva, S., Park, B., Koh, W., Aggarwal, B. B. 2012. Upsides and Downsides of Reactive Oxygen Species for Cancer: The Roles of Reactive Oxygen Species in Tumorigenesis, Prevention, and Therapy. *Antioxidants & Redox Signaling*, 16(11):1295-1322.
- Hadadi, S. A., Li, H., Rafie, R., Kaseloo, P., Witiak, S. M., Siddiqui, R. A. 2018. Anti-oxidation properties of leaves, skin, pulp, and seeds extracts from green papaya and their anti-cancer activities in breast cancer cells. *Journal of Cancer Metastasis and Treatment*, 4(5).
- Heena, D., Sunil, T. 2019. *Carica papaya*: Potential Implications in Human Health. *Current Traditional Medicine*, 5(4):321-336.
- Jayakumar, R., Kanthimathi, M. S. 2011. Inhibitory effects of fruit extracts on nitric oxide-induced proliferation in MCF-7 cells. *Food Chemistry*, 126(3):956-960.
- Krishna, K. L., Paridhavi, M., Patel, J. A. 2008. Review of nutritional, medicinal and pharmacological properties of papaya (*Carica papaya* Linn.). *Indian Journal of Natural Products and Resources*, 7(4):364-373.
- Lohsoonthorn, P., Danvivat, D. 1995. Colorectal Cancer Risk Factors: A Case-control Study in Bangkok. *Asia Pacific Journal of Public Health*, 8(2):118-122.
- Nakamura, Y., Yoshimoto, M., Murata, Y., Shimoishi, Y., Asai, Y., Park, E. Y., Nakamura, Y. 2007. Papaya Seed Represents a Rich Source of Biologically Active Isothiocyanate. *Journal of Agricultural and Food Chemistry*, 55(11):4407-4413.
- Nguyen, T. T. T., Shaw, P. N., Parat, M. O., Hewavitharana, A. K. 2013. Anticancer activity of *Carica papaya*: A review. *Molecular Nutrition & Food Research*, 57(1):153-164.
- Pan, M. H., Lai, C. S., Ho, C. T. 2010. Anti-inflammatory activity of natural dietary flavonoids. *Food & Function*, 1(1):15-15.
- Pandey, M., Shukla, V. K. 2002. Diet and gallbladder cancer: a case-control study. *European Journal of Cancer Prevention*, 11(4):365-368.
- Recio, M. C., Andujar, I., Rios, J. L. 2012. Anti-Inflammatory Agents from Plants: Progress and Potential. *Current Medicinal Chemistry*, 19(14):2088-2103.
- Shahar, S., Shafurah, S., Shaari, N. S. A. H., Rajikan, R., Rajab, N. F., Golkhalkhali, B., Zainuddin, Z. M. 2011. Roles of diet, lifetime physical activity and oxidative DNA damage in the occurrence of prostate cancer among men in Klang Valley, Malaysia. *Asian Pacific Journal of Cancer Prevention*, 12(3):605-611.
- Siegel, E. M., Salemi, J. L., Villa, L. L., Ferenczy, A., Franco, E. L., Giuliano, A. R. 2010. Dietary consumption of antioxidant nutrients and the risk of incident cervical intraepithelial neoplasia. *Gynecologic Oncology*, 118(3):289-294.
- Soubra, L., Nureddin, H., Omar, A., Saleh, M. 2016. Factors Associated with Hypertension Prevalence and Control among Lebanese Type 2 Diabetic Patients. *International Journal of Pharmacy and Pharmaceutical Sciences*, 8(10):153-153.
- Subenthiran, S., Choon, T. C., Cheong, K. C., Thayan, R., Teck, M. B., Muniandy, P. K., Ismail, Z. 2013. *Carica papaya* Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever. *Evidence-Based Complementary and*

Alternative Medicine, pages 1–7.

- Vien, D. T. H., Thuy, P. T. 2012. Research on the biological activity of some extracts from Vietnamese *Carica papaya* leaves. *ASEAN Journal of Chemical Engineering*, 2:43–51.
- Yogiraj, V., Goyal, P. K., Chauhan, C. S., Goyal, A., Vyas, B. 2014. *Carica papaya* Linn: an overview. *International Journal of Herbal Medicine*, 2(5):1–08.
- Zhang, C. X., Ho, S. C., Chen, Y. M., Fu, J. H., Cheng, S. Z., Lin, F. Y. 2009. Greater vegetable and fruit intake are associated with a lower risk of breast cancer among Chinese women. *International Journal of Cancer*, 125(1):181–188.