

Review Article

POTENTIAL ROLE OF CARICA PAPAYA AND THEIR ACTIVE CONSTITUENTS IN THE PREVENTION AND TREATMENT OF DISEASES

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ABSTRACT

Natural products or products from the plant source show pivotal role in the diseases prevention and treatment since ancient. Numerous plants and their ingredients such as *Nigella sativa*, *curcumin*, olive and dates fruits have proven health promoting effects. In this vista, Papaya (*C. Papaya* family Caricaceae) is a medicinal plant that has been extensively used in traditional medicine due to their versatile approach in diseases treatment and prevention. The health-promoting activities of papaya and their constituents are recognized due to antioxidant activity. *C. Papaya* holds a range of valuable constituents such as vitamin, flavonoids and minerals in the different parts of plants and each constituent shows role in the disease management. Earlier reports have proven that *C. papaya* fruits and its ingredients shows role in health management via prevention of the pathogenesis of diseases. Its leaf juice also contains significant constituents, and they shows very effective role in the management of dengue fever with platelet increasing property. In this review, we aimed to evaluate the applications of papaya in cancer, diabetes, wound healing, malaria, dengue fever and other various disease prevention and treatment.

Keywords: *Carica papaya*, Antioxidant activity, Anti-inflammatory activity, Health management.

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INTRODUCTION

Formulations based on plant products have been used in diseases treatment and prevention since ancient time. Natural products have upper hand over synthetic drugs because they have fewer side effects and also does not alter physiological and biochemical pathways. In this vista, Papaya (*C. Papaya L.*) belongs to the family Caricaceae, commonly used in the diseases cure and management worldwide, especially in tropical and subtropical parts of the world. Different parts of *C. Papaya* such as leaves, barks, roots, latex, fruit, flowers, and seeds are used in folk medicine to treat varieties of diseases [1]. It also contains various important constituents such as vitamins, including A, E and C which are a rich source of antioxidant and minerals such as magnesium and potassium, vitamin B pantothenic acid and folate and fiber [2]. The antioxidant activity of papaya shows role in the neutralization of free radical generation and finally prevent the pathogenesis. On the other hand, fiber is one of the valuable constituents, which shows role in the reduction of cholesterol. In addition, Papaya latex is the chief source of the cysteine proteinases including papain, chymopapain, glycol endopeptidase and caricain and levels of proteinases differ in different part such as fruit, leaves, and roots [3]. The fruits parts have papain, which helps in digestion, and also used to tenderize meat [4]. Overall, papaya and their constituents act as a miracle in diseases cure and prevention through modulation of various activities including antioxidant, anti-inflammatory, anti-tumor and hepatoprotective effect. Earlier results confirmed that *C. The papaya* seed, water extract has powerful antioxidant activity in H₂O₂ oxidative stress-induced human skin Detroit 550 fibroblasts [5]. Other finding results showed that anti-inflammatory activity of the seeds of *C. papaya* and effect of the methanolic extract showed inhibition ranged from 57.1% to 64.2% is lower than 85.7% standard anti-inflammatory drugs such as aspirin [6]. An important study results suggest a potential importance of papaya latex as an anthelmintic against patent intestinal nematodes of mammalian hosts [7]. This review summarizes the studies based on *in vitro* and *in vivo* on the papaya in the diseases prevention and treatment.

General description of *C. Papaya* plant

C. Papaya short-lived, single-stemmed/ unbranched, hollow, herbaceous perennial with different height ranged 10 to 30 ft. It

belongs to the plant kingdom, *Carica L* genus, and a member of the Caricaceae family. It is one of the most popular and economically significant plants in the world [8] and genus *C. Papaya* Linn is the most widely cultivated and well-known species of the four genera of the family belong to Caricaceae [9]. The exact region of origination is not fully documented, but it is believed that it originates from tropical America, southern Mexico and nearby Central America.

Chemical composition/active components of *C. Papaya*

C. Papaya contains valuable constituents in the different parts of the plants such as fruits, leaves, and seeds with different proportions. The Phytochemical analysis of the leaves showed that the leaves hold saponins, cardiac glycosides, and alkaloids whereas tannin were absent [10]. An important study confirmed the leaves of *C. Papaya* contained phenolic acids as the main compound, whereas chlorogenic acid was found in trace amounts, compared to the flavonoids and coumarin compounds [11]. Fruits contain important types of vitamins, flavonoids, and various other minerals. The ripe fruit is said to be a good source of vitamins such as A and C and calcium [12]. The pawpaw is a good source of vitamin C with different amount according to maturation stages [13-14]. Constituents are different in red fleshed papaya and fleshed yellow papaya. As per the earlier report, the total lycopene content of red fleshed papaya was notably higher than that of yellow fleshed fruit [15]. Papaya seed also contains important types of constituents and such ingredients shows role in the health prevention and treatment. An important study confirmed that seed is a good source of proteins, lipids, and crude fiber and observed appreciable quantities of calcium and phosphorus in the seeds; however, the presence of toxicants, such as glucosinolates, was also noticed [16].

Therapeutics role of *C. Papaya* and their ingredients in the prevention and treatment of diseases

C. Papaya has medicinal value in the health management due to a rich source of vitamins, carbohydrate and essential minerals in different parts of the plants. As per literature information, parts such as seeds, fruits, and leaves has therapeutics implications in the diseases cure since ancient time and also holds a key position in traditional medicines. The importance of papaya in diseases cure is presented below based on earlier *Invivo* and *in vitro* findings;

Antioxidant activity

Natural products or plant products are a good source of antioxidant and show vital role in the diseases cure and prevention. An important study results have shown that *C. papaya* seed, water extract has powerful antioxidant activity in H₂O₂ oxidative stress-induced human skin Detroit 550 fibroblasts and additionally finding also confirms that extract is not toxic, decreases cell death, ensures Ca²⁺ homeostasis, and counteracts mitochondrial dysfunctionality [5].

Another study was performed to evaluate the antioxidant and cytotoxic potential of extracts of fruits and seeds and study results proved that both ethyl acetate fractions from the fruits and seeds of *C. Papaya* are high in antioxidant activities with IC₅₀ values of 30.61 µg/ml and 25.97 µg/ml and cytotoxic with LC₅₀ of 163.96 µg/ml and 142.27 µg/ml respectively [17].

C. Papaya leaf aqueous extract effects on alcohol-induced acute gastric damage was analyzed and finding of the study revealed that the gastric ulcer index was significantly reduced in rats pretreated with CPL extract as compared with alcohol treated controls. Additionally, results also confirmed that CPL extract showed some protection with a reduction in plasma lipid peroxidation level and increased erythrocyte glutathione peroxidase activity [18].

Anti-inflammatory activity

Numerous plants or isolated derivatives from the plant source shows role as anti-inflammatory via modulation of various activities [19-20]. Currently used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) produce intestinal tract ulcers and other complications in the stomach. An important study showed anti-inflammatory activity of seeds of *C. papaya* and methanolic extract showed inhibition ranging from 57.1% to 64.2% is lower than 85.7% of aspirin, a standard anti-inflammatory drug [6].

Analgetic activity

Numerous natural products or products from plant source shows an analgetic effect without any complications. In this vista, *C. Papaya* also shows the important role as analgetic activity. A study was performed to investigate the analgetic activity of *C. Papaya* leaves extracts in mice model using acetic acid-induced pain and finding revealed that all extracts such as n-hexane, ethyl acetate, and ethanol at the doses of 0.175, 0.35 and 0.70 mg/kg bw showed significant analgesic activity as compared to control group [21].

Wound healing effect

Numerous plants/their constituents show an important role in the wound healing. A study was performed to evaluate the aqueous extract of *C. papaya* fruit for its wound healing activity in streptozotocin-induced diabetic rats using excision, and dead space wound models and results revealed that extract-treated animals exhibited a 77 % reduction in the wound area as compared to controls that were 59% [22].

Another study was performed to evaluate the wound healing potential of aqueous extract of roots and results confirmed that latex treated animal's exhibit 89.40 % reduction in wound area as compared to controls which were 80.38 % and furthermore extract-treated wounds are found in epithelial faster as compared to controls [23]. Another study also confirmed the papaya leaf aqueous extract has health benefits effect as wound healing activity in rats [24].

Anti-microbial activity

Current treatment in health management based on antibiotic is effective, but also causes antibiotic resistance. In this regards, medicinal plants shows effective role in the control of bacterial growth. A study was made on the root extracts using water and organic solvents to examine the antibacterial activity against some pathogenic bacteria and results revealed that aqueous extracts did not show significant activity, whereas organic extracts showed significant activity with the methanol extracts demonstrating the highest activity against the test bacteria. Furthermore, extracts demonstrated higher activities against all the gram-negative bacteria than the gram-positive bacteria tested, with the highest

activity (14 mm zone of inhibition) demonstrated against *Salmonella typhi* [25]. Another study was performed to evaluate the antibacterial activity of aqueous, chloroform extract of leaves and aqueous, methanolic extract of seeds and results confirmed that aqueous and methanolic extract of seeds were effective to inhibit the bacterial pathogens, whereas the chloroform extract of the leaves did not show any inhibition against the bacteria and the aqueous leaf extract was powerful to inhibit them [26]. Antibacterial activity of extracts of *C. Papaya* fruit was evaluated using isolates from wound culture and results showed that extracts established antibacterial activity and this was more prominent with alcohol extracts than that of water [27]. Additionally, *Staphylococcus aureus* was the most susceptible with a minimum inhibition concentration (MIC) of 1:64 whereas *Enterococcus faecalis* showed least sensitive [27].

Finding revealed that high antimicrobial activity of the extracts of *C. papaya* in petroleum ether with a Minimum Inhibitory Concentration (MIC) of 2 mg/ml as against 4 mg/ml and 6 mg/ml for standard drugs including flerflacine and cefuroxime [28]. Additionally, extracts in 1% HCl and ethanol showed antimicrobial activity against the gram positive and negative organisms, whereas water extract was active against *Escherichia coli* and *S. aureus* [28]. An important study was performed to investigate the antibacterial activity of ripe and unripe *C. Papaya* on selected micro-organism and seed extracts from the fruit showed inhibition as *B. cereus* > *E. coli* > *S. faecalis* > *S. aureus* > *P. vulgaris* > *S. flexneri* [29].

Gastroprotective effect

Numerous agents such as food ingredients, microorganism and drugs are one of the main culprits in gastric ulcer/complications. Plant products show anti-ulcer effect, but the exact mechanism is not understood completely. The anti ulcerogenic activities of *C. Papaya* extract on aspirin-induced ulcer in rats was evaluated, and the results showed that *C. Papaya* may exert its gastro protective effect via free radical scavenging action [30].

A study was performed to evaluate the Gastroprotective effects of aqueous *Carica papaya* seed extract on ethanol induced gastric ulcer in male rats and results showed that the extract protected the gastric mucosa against ethanol effect and extract significantly reduced the gastric juice volume and gastric acidity in a dose-dependent manner when compared with the control [31].

Hepato-protective effect

A study was performed to evaluate the hepato protective effects of *C. Papaya* against carbon tetrachloride (CCL 4) induced hepatotoxicity and compared it with that of vitamin-E and results confirmed that *C. Papaya* and vitamin E showed significant hepato protection against CCL4 induced hepatotoxicity, but *C. Papaya* showed more significant changes in ALP level than vitamin E [32].

The experiment was made to examine the hepato protective effect of *C. papaya* leaves against ethanol, and anti-tubercular drug-induced liver damage and results revealed that hepato protective activity was evident by the significant reduction in the levels of all serum markers in both models [33].

Other finding results confirmed that pretreatment with medium and high doses of *C. Papaya* extracts such as 250 and 500 mg/kg p. o significantly reversed the elevated serum enzyme markers in animals treated with Thioacetamide [34].

Another important study was performed to examine the antihepatotoxic activity of ethanol, and aqueous extracts of *C. Papaya* and results confirmed that ethanol and aqueous extracts of *C. Papaya* showed remarkable hepato protective activity against CCL4 induced hepatotoxicity [35].

Anti-ulcerogenic effect

A study was performed to investigate the anti-ulcerogenic and antioxidant activities of aqueous extract of *C. papaya seed* against indomethacin-induced peptic ulcer in male rats and results revealed that *C. papaya* seed extract significantly increased gastric pH and percentage of ulcer inhibition relative to indomethacin-induced ulcer rats [36].

Anti-tumor/cancerous activity

Plants products or constituent of the plants shows therapeutics role in the cancer prevention and treatment [37]. In this regards, papaya and their valuable constituents have a significant role in the cancer management. An important study examined the effect of aqueous-extracted *C. papaya* leaf fraction on the growth of various tumor cell lines and on the anti-tumor effect of human lymphocytes and results showed that growth inhibitory activity of the CP extract on 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) in a dose-dependent manner. In addition, CP extract inhibited the proliferative responses of haematopoietic cell lines, including T-cell lymphoma (Jurkat), plasma cell leukemia (ARH77), Burkitt's lymphoma a (Raji), and anaplastic large cell lymphoma (Karpas-299) [38].

Anti-diabetic/hypoglycemic activity

Diabetes mellitus and its linked complication are major health problem worldwide. Oral hypoglycemic drugs are effective and useful in the treatment, but also show adverse complications. Natural products show an important role in the management of diabetes mellitus and complications. A vital study was performed to evaluate the antihyperglycemic and hypolipidemic activity of aqueous extract of leaves of *C. Papaya* Linn and the results confirmed that extracts showed a significant reduction in blood glucose level and serum lipid profile levels with 400 mg/kg body weight in alloxan-induced diabetic rats when compared with the control [39]. Another study results have shown that aqueous extract of *C. Papaya* with 0.75 g and 1.5 g/100 ml significantly decreased blood glucose levels in diabetic rats and also decreased cholesterol, triacylglycerol and aminotransferases blood levels [40]. Earlier investigators have reported the antihyperglycemic effect of unripe mature fruits and seeds of *C. Papaya* [41-4239-40] [17,18].

Anti-nephrotoxicity effect

Experimentation was made to evaluate the nephro protective role of ethanolic extract of the papaya seed and pumpkin seed and the results confirmed that ethanolic extract of both sides showed protection against cisplatin-induced nephrotoxicity and antioxidant studies such as nitric oxide scavenging activity, lipid peroxidation in kidney also supported the nephro protective activity of both types' seeds [43]. A study was performed to evaluate the protective effect of the aqueous seed extract of *C. Papaya L.* On gentamicin-induced hepatotoxicity and nephrotoxicity, and the result had shown that administration of aqueous extract before gentamicin exposure prevented severe alterations of biochemical parameters and disruptions of liver and kidney structures [44].

Diuretic effects

An important study finding showed that root extracts of *C. Papaya*, when given orally to rats at a dose of 10 mg/kg, confirmed significantly increased urine output, which was 74%, of the effect of an equivalent dose of hydrochlorothiazide [45].

Anti-malaria effect

Human malaria is one of the major health problems worldwide. However, safe and effective mode of treatment is needed to control malaria and its complications. In this vista, numerous medicinal plants have confirmed their role in the control of malaria.

A study results have shown that concentrations such as 25, 50,100 and 150 µg/ml of ethanol leaf extracts exhibited promising inhibitory activity against the CQ-sensitive strain with IC 50 values 40.75%, 36.54%, 25.30%, and 18.0% and in CQ-resistant 50.23%, 32.50%, 21.45%, and 23.12% against *P. falciparum* [46]. The earlier study was conducted to evaluate the platelet increasing property of *C. Papaya* leaves juice in patients with dengue fever and which is a randomized controlled trial of 228 patients that confirmed a significant increase in platelet count and dengue hemorrhagic fever after administration of *papaya* leaf juice [47].

Another study reported the positive role of *C. Papaya* leaves in the treatment of dengue and results showed that thrombocyte count

increased from 28000/micro liter to 138000/micro liter after administration of *C. Papaya* leaves at the end of five days [48].

Antifertility effect

An important study has confirmed that oral administration of crude ripe papaw seeds at 100 mg/kg body weight for 8 w showed degeneration of the germinal epithelium and germ cells, a reduction in the number of Leydig cells and the presence of vacuoles in the tubules [49].

Another study results revealed that oral administration of the aqueous extract of *C. Papaya* (Linn.) seeds at all dose regimens tested such as 50 mg/kg; 100 mg/kg and 800 mg/kg body weight altered the normal sequence of the estrous cycle, whereas showed no effect on ovulation and the number of ova shed [50].

A finding result reported that cholesterol levels in testes were notably decreased by the *C. Papaya* seed extraction indicating decreased mobilization towards androgenesis and in this manner inhibition of spermatogenesis in the testis [51].

Earlier study results revealed the extract such as chloroform extract of the seeds leads to azoospermia without adverse toxicity after 90 d of treatment in langur monkeys and sperm functional tests confirmed the voided spermatozoa after 30 and 60 d of treatment were in the infertile range [52].

Anti-amoebic activity

Experimentation was performed to evaluate the Anti amoebic activity of methanol extract of mature seeds based on *in vitro* on axenic culture of *Entamoeba histolytic* and results revealed that MIC of seed extract was >62.5 µg/ml as compared to <0.8 µg/ml for metronidazole [53].

Anxiolytic and sedative effects

Various medicinal plants or their constituent's shows role as Anxiolytic and sedative effects. A study was performed to evaluate the anxiolytic and sedative effects of ethanolic *C. papaya* pulp extract in mice, and the results confirmed that extract at 100 mg/kg showed Anxiolytic effect [54].

Anti-obesity effect

Numerous plants and their product, including *C. Papaya* has confirmed the anti-obesity effect. A study was designed to evaluate the anti-obesity potential of aqueous fruit extract of *C. papaya L.* on high-fat cafeteria diet (HFD) fed obese rats and study finding revealed that the BMI, body weight, organ weight of the liver, kidney and spleen were significantly decreased in the treated groups than in the HFD group animals. Furthermore, Finding of the study also confirmed that serum Glucose, Triglycerides, Total cholesterol, LDL-Cholesterol, and VLDL-Cholesterol were significantly decreased, whereas HDL-Cholesterol was elevated in the treated groups in a dose-dependent manner as compared to the HFD group [55].

Safety and toxicities of papaya

Various medicinal plants and their constituent's shows role in disease prevention and treatment at certain doses. Overdose or improper dose causes complications and alters various biological activities. However, safe dose of any plants or products is a very important in the health management. A study was performed to investigate the toxicity of CP leaf extracts on Sprague-Dawley rats and results revealed that *C. Papaya* leaf juice did not show any toxicity effect [56].

Another study was performed about acute and chronic oral toxicity study on the aqueous and ethanol leaf extracts of *C. Papaya* in Wistar rats and results demonstrated that no deaths or signs of acute oral toxicity were recorded. Additionally, oral sub-acute and sub-chronic toxicity included hypoglycemia, hypolipidemia, and hyperglycemia, increased AST, BUN values in aqueous and ethanol extract experimentations respectively [57].

CONCLUSION

Since ancient times, papaya plants or their products have been used in diseases treatment worldwide. Numerous studies based on *in vivo*

and *in vitro* have confirmed their role in disease prevention through modulation of the various process such antioxidant, anti-inflammatory, anti-diabetic and immunomodulatory activity. Platelet increasing property of *C. Papaya* leaves have been confirmed and show a vital role in the management of malaria and dengue fever. In spite of numerous therapeutic implications of *C. Papaya*, detailed studies based on animal model and clinical trials are needed to standardize the safe dose of leaf juice, seeds and fruits and its mechanism in disease prevention.

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Jaiswal P, Kumar P, Singh VK, Singh DK. Carica papaya linn: a potential source for various health problems. J Pharm Res 2010;3:998-1003.
- Vij T, Prasha Y. A review on medicinal properties of Carica papaya Linn. Asian Pac J Trop Dis 2015;5:1-6.
- Anuar NS, Zahari SS, Taib IA, Rahman MT. Effect of green and ripe Carica papaya epicarp extract on wound healing and during pregnancy. Food Chem 2008;46:2384-9.
- Samson JA. Tropical Fruits." 2nd ed. Longman Scientific and Technical Publication; 1986. p. 256-69.
- Panzarini E, Dwikat M, Mariano S, Vergallo C, Dini L. Administration dependent antioxidant effect of carica papaya seeds water extract." J. Evidence-Based Complementary Altern Med 2014. doi: 10.1155/2014/281508. [Epub 2014 Mar 25]
- Amazu LU, Azikiwe CCA, Njoku CJ, Osuala FN, Nwosu PJC, Ajugwo AO, Enye JC. Antiinflammatory activity of the methanolic extract of the seeds of Carica papaya in experimental animals. Asian Pac J Trop Med 2010;3:884-6.
- Satrija F, Nansen P, Murtini S, He S. Anthelmintic activity of papaya latex against patent *Heligmosomoides polygyrus* infections in mice. J Ethnopharm 1995;3:161-4.
- Ong H, Chua S, Milow P. Ethnomedicinal plants used by the temuan villagers in kampung jeram kedah, negeri sembilan, Malaysia. Ethnomed Plants 2011;5:95-100.
- Krishna KL, Paridhavi M, Jagruti AP. Review on nutritional, medicinal and pharmacological properties of Papaya (*Carica papaya* Linn.). Nat Prod Radian 2008;7:364-73.
- Ayoola PB, Adeyeye A. Phytochemical and nutrient evaluation of Carica papaya (pawpaw) leaves. Int J Res Rev Appl Sci 2010;5:325-8.
- Canini A, Alesiani G, D'Arcangelo, P Tagliatesta. Gas chromatography-mass spectrometry analysis of phenolic compounds from Carica papaya L. leaf. J Food Compos Anal 2007;20:584-590.
- Nakasone HY, Paull RE. Tropical Fruits, CAB International, Wallingford, NY, USA; 1998.
- Bari L, Hassen P, Absar N, Haque ME, Khuda MIIE, Pervin MM, et al. Nutritional analysis of two local varieties of papaya (*Carica papaya*) at different maturation stages. Pak J Biol Sci 2006;9:137-40.
- Hernandez Y, Lobo MG, Gonzalez M. Determination of vitamin c in tropical fruits: a comparative evaluation of methods. Food Chem 2006;96:654-64.
- Schweiggert RM, Steingass CB, Heller A, Esquivel P, Carle R. Characterization of chromoplasts and carotenoids of red-and yellow-fleshed papaya (*Carica papaya* L.). Planta 2011;234:1031-44.
- Marfo EK, Oke OL, Afolabi OA. Chemical composition of papaya (*Carica papaya*) seeds. Food Chem 1986;22:259-66.
- Khor ES, Wong NK. Potential antioxidant and cytotoxic properties of secondary metabolite extracts from carica papaya fruits and seed. Int J Pharm Pharm Sci 2014;6:220-4.
- Indran M, Mahmood AA, Kuppasamy UR. Protective effect of Carica papaya L leaf extract against alcohol-induced acute gastric damage and blood oxidative stress in rats. West Indian Med J 2008;57:323-6.
- Rahmani AH, Aly SM. Nigella sativa and its active constituent's thymoquinone shows pivotal role in the diseases prevention and treatment. Asian J Pharm Clin Res 2015;8:48-53.
- Rahmani AH, Albutti AS, Aly SM. Therapeutics role of olive fruits/oil in the prevention of diseases via modulation of anti-oxidant, anti-tumour and genetic activity. Int J Clin Exp Med 2014;7:799-808.
- Hasimun P, Suwendar, Ernasari GI. Analgetic activity of papaya (*Carica papaya* L.) Leaves extract. Procedia Chem 2014;13:147-9.
- Nayak SB, Pinto Pereira L, Maharaj D. Wound healing activity of Carica papaya L. in experimentally induced diabetic rats. Indian J Exp Biol 2007;45:739-43.
- Tiwari P, Kmar K, Panik R, Pandey A, Pandey A, Sahu PK. Evaluation of aqueous extract of roots of carica papaya on wound healing activity in albino Rats. J Chem Pharm Res 2011;3:291-5.
- Mahmood AA, Sidik K, Salmah I. Wound healing activity of Carica papaya l. aqueous leaf extract in rats. Int J Mol Med Adv Sci 2005;1:398-401.
- Doughari JH, El Mahmoud AM, Manzara S. Studies on the antibacterial activity of root extracts of Carica papaya L. Afr J Microbiol Res 2007;037-041. Available from: <http://www.academicjournals.org/ajmr>. [Last accessed on 05 Aug 2015].
- Peter JK, Kumar Y, Pandey P, Masih H. Antibacterial activity of seed and leaf extract of carica papaya var. pusa dwarf Linn. J Pharm Biol Sci 2014;9:29-37.
- Akujobi CN, Ofodeme CN, Enweani CA. Determination of antibacterial activity of Carica papaya (paw-paw) extracts. Nigerian J Clin Practic 2010;13:55-7.
- Orhue PO, Momoh ARM. Antibacterial activities of different solvent extracts of carica papaya fruit parts on some gram positive and gram negative organisms. Int J Herbs Pharmacol Res 2013;2:42-7.
- Dawkins G, Hewitt H, Wint Y, Obiefuna PC, Wint B. Antibacterial effects of Carica papaya fruit on common wound organisms. West Indian Med J 2003;52:290-2.
- Ologundudu A, Lawal AO. The antiulcerogenic activity of aqueous extract of Carica papaya fruits on aspirin induced ulcer in rats. Int J Toxicol 2008;5:2.
- Abisola OT, Wahab OA. Gastroprotective activity of aqueous Carica papaya seed extract on ethanol induced gastric ulcer in male rats. Afr J Biotechnol 2012;11:8612-5.
- Sadeque MZ, Begum ZA, Umar BU, Ferdous AH, Sultana S, Uddin MK. Comparative efficacy of dried fruits of carica papaya Linn. and Vitamin-E on preventing hepatotoxicity in rats. Faridpur Med College J 2012;7:29-32.
- Pandit A, Sachdeva T, Bafna P. Ameliorative effect of leaves of carica papaya in ethanol and antitubercular drug induced hepatotoxicity. Br J Pharm Res 2013;3:648-61.
- S Kantham. Influence of carica papaya linn extracts on paracetamol and thioacetamide-induced hepatic damage in rats. Internet J Pharmacol 2009;9:1.
- Raj Kapoor B, Jayakar B, Kavimani S, Muruges N. Effect of dried fruits of Carica papaya Linn on hepatotoxicity. Biol Pharm Bull 2002;25:1645-6.
- Oloyede HO, Adaja MC, Ajiboye TO, Salawu MO. The anti-ulcerogenic activity of aqueous extract of Carica papaya seed on an indomethacin-induced peptic ulcer in male albino rats. J Integr Med 2015;13:105-14.
- Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S, Khan AA. Therapeutic effects of date fruits (*Phoenix dactylifera*) in the prevention of diseases via modulation of anti-inflammatory, antioxidant and anti-tumour activity. Int J Clin Exp Med 2014;7:483-91.
- Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C. Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects. J Ethnopharmacol 2010;127:760-7.
- Maniyar Y, Bhixavatimat P. Antihyperglycemic and hypolipidemic activities of aqueous extract of Carica papaya Linn. leaves in alloxan-induced diabetic rats. J Ayurveda Integrative Med 2012;3:70-4.
- Juárez-Rojop IE, Díaz-Zagoya JC, Ble-Castillo JL, Miranda-Orsorio PH, Castell-Rodríguez AE, Tovilla-Zárate CA, et al. Hypoglycemic effect of Carica papaya leaves in streptozotocin-induced diabetic rats. BMC Complementary Altern Med 2012;12:236.

41. Olagunja JA, Ogunlana CO, Gbile Z. Preliminary studies on the hypoglycemic activity of ethanolic extract of unripe mature fruits of *Carica papaya*. *Nig J Biochem Mol Biol* 1995;10:21-3.
42. Adeneye AA, Olagunja JA. Preliminary hypoglycemic and hypolipidemic activities of aqueous seed extract of *Carica papaya* Linn in Wistar rats. *Biol Med* 2009;1:1-10.
43. Debnath S, Babre N, Manjunath YS, Mallareddy V, Parameshwar P, Hariprasath K. Nephroprotective evaluation of ethanolic extract of the seeds of papaya and pumpkin fruit in cisplatin-induced nephrotoxicity. *J Pharm Sci Technol* 2010;2:241-6.
44. Nale LP, More PR, More BK, Ghumare BC, Shendre SB, Mote CS. Protective effect of carica papaya l. seed extract in gentamicin-induced hepatotoxicity and nephrotoxicity in rats. *Int J Pharm Biol Sci* 2012;3:508-15.
45. Sripanidkulchai B, Wongpanich V, Laupattarakasem P, Suwansakri J, Jirakulsomchok D. Diuretic effects of selected Thai indigenous medicinal plants in rats. *J Ethnopharmacol* 2001;75:185-90.
46. Kovendan K, Murugan K, Panneerselvam C, Aarthi N, Kumar M, Subramaniam J, Amerasan D, *et al.* Antimalarial activity of *Carica papaya* (Family: Caricaceae) leaf extract against plasmodium falciparum. *Asian Pac J Trop Dis* 2012;2:S306-S311.
47. Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, *et al.* *Carica papaya* leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. *J Evidence-Based Complementary Altern Med* 2013. doi.org/10.1155/2013/616737. [Article in Press]
48. Siddique O, Sundus A, Ibrahim MF. Effects of papaya leave on thrombocyte counts in dengue-a case report. *J Pak Med Assoc* 2014;64:364-6.
49. Udoh P, Kehinde A. Studies on the antifertility effect of pawpaw seeds (*Carica papaya*) on the gonads of male albino rats. *Phytother Res* 1999;13:226-8.
50. Dosumu OO, Akinola OB, Oremosu AA, Noronha CC, Okanlawon AO. Antifertility effects of the aqueous extract of *Carica papaya* (Linn.) seeds on estrous cycle and ovulation of adult cyclic Sprague-Dawley rats. *Niger J Health Biomed Sci* 2008;7:31-3.
51. Lakshman J, Changamma C. Antispermogenic effect of *Carica papaya* seed extract on steroidogenesis in albino rats. *Int J Pharm Pharm Sci* 2012;5:67-9.
52. Lohiya NK, Manivannan B, Mishra PK, Pathak N, Sriram S, Bhande SS, *et al.* Chloroform extract of *Carica papaya* seeds induces long-term reversible azoospermia in langur monkey. *Asian J Androl* 2002;4:17-26.
53. Sarker SK, Begum N, Mondal D, Siddique MA, Rashid MA. *In vitro* study of the antiamebic effect of methanol extract of mature seeds of *Carica papaya* on trophozoites of *Entamoeba histolytica*. *Bangladesh J Pharmacol* 2010;5:45-7.
54. Athesh K, Karthiga D, Brindha P. Anti-obesity effect of aqueous fruit extract of carica papaya L. in rat fed on high-fat cafeteria diet. *Int J Pharm Pharm Sci* 2012;4 Suppl 5:327-30.
55. Kebebew Z, Shibeshi W. Evaluation of anxiolytic and sedative effects of 80% ethanolic *Carica papaya* L. (Caricaceae) pulp extract in mice. *J Ethnopharmacol* 2013;25:150:665-71.
56. Halim SZ, Abdullah NR, Afzan Z, Abdul Rashid BA, Jantan I, Ismail Z. Acute toxicity of *Carica papaya* leaf extract in Sprague Dawley rats" *J Med Plants Res* 2011;5:1867-72.
57. Tarkang PA, Agbor GA, Armelle TD, Ramthe TLR, David K, Ngadana YSM. Acute and chronic toxicity studies of the aqueous and ethanol leaf extracts of *Carica papaya* Linn in Wistar rats. *J Nat Prod Plant Resour* 2012;2:617-27.