



Phytochemistry and nutraceutical properties of *Carica papaya* (Linn.): A review

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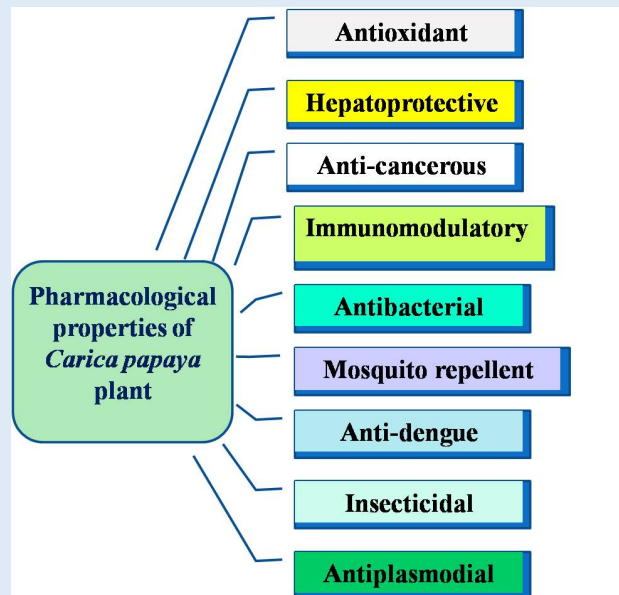
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ABSTRACT

Nutraceuticals derived from a medicinal plant having therapeutic significance are a gift to mankind to acquire healthy life. *Carica papaya* Linn. (aricaceae) commonly known as papaya. It is a significant fruit tree and is found in tropical and subtropical parts of the world. The extract from various parts of plant especially fruit and leaves contains many phytonutrients viz; vitamin A, B1, and vitamin C, calcium hydrate charcoal, phosphorus, iron, protein as well as some endopeptidases like namely papain, glycy endopeptidase, chymopapain, and caricain. The extract of this plant is identified to be efficacious against diversified ailments like malaria, inflammation, digestive disorder, Microbes, Fungi, and many infectious disorders. Its prophylactic and therapeutic values enhance immunity and ensure a healthier life. Each part of this plant has its nutraceutical properties.

Keywords: Nutraceuticals, *Carica papaya*, Papain, Caricain, Chymopapain



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INTRODUCTION

We live in an environment where we are continuously exposed to several xenobiotics in the form of various pollutants, drugs, pesticides, cosmetics, flavorings, fragrances, industrial chemicals, environmental pollutants, food additives, etc. [1]. Many of these chemicals are free radicals, damaging membranes and leading to various diseases [2]. Previous epidemiologic studies have shown that plants, including medicinal and vegetables, play a crucial role in the preventing chronic diseases. They contain bioactive compounds which are responsible for health promotion and disease resistance. It is estimated that one-third of deaths occur due to one or the other pollutant-born diseases like heart diseases, liver-related diseases, cardiovascular diseases, cancer, diabetes, Alzheimer's disease, and age-related functional decline [3- 4]. This may be prevented or cured by the use of appropriate nutraceutical compounds. This evidence suggests that nutraceuticals extracted from plants can significantly reduce the incidence of chronic diseases

because they are rich in antioxidants, vitamins, minerals, and other phytochemicals.

It has been known for a long time that our health depends on what food we eat daily. The current concept of functional foods is a group of foods that positively impact on the individual's health, physical performance, or state of mind, in addition to their nutritious value. Functional foods may be defined as "whole foods along with fortified, enriched, or enhanced foods that are thought to provide benefits beyond basic nutrition and may play an important role in reducing or minimizing the risk of certain diseases and other health conditions." Japan was the first country to develop a specific regulatory approval process for functional foods. Later, the functional food concept rapidly expanded to other parts of the world. Currently, the world's most prominent functional food markets are in Japan, Korea, and the United States, followed by Europe. Functional foods overlap with other terms alongside nutraceuticals

and include “pharmafoods,” “medical foods,” “probiotics,” and “vitafoods.” Functional foods are the foods we consume as part of our daily diet; they are not a capsule, tablet, or powder derived from natural ingredients. With the supplementation of functional foods in our daily diet, we can reduce the onset of specific diseases, control physical and mental disorders, and enhance biological defense mechanisms and recovery from specific diseases.

Nutraceuticals have received considerable interest because of their nutritional and therapeutic values. Nutraceuticals are defined as a food or part of a food product that provides medicinal health benefits, including the prevention and treatment of diseases. Nutraceuticals include isolated nutrients, dietary supplements, genetically engineered “designer” food, herbal products, and processed products such as cereals, soups, and beverages. Antioxidants are a category of nutraceuticals in our foods. Most cells antioxidant defense system consists of two components, an enzymatic component (such as superoxide dismutase, catalase, glutathione peroxidase, etc.) and low molecular weight non-enzymatic antioxidant components (vitamins A, C, E, glutathione, thioredoxin, lycopene, lutein, quercetin, carotenoids, polyphenols, selenium, etc.) which can prevent or slow the oxidative damage to our body cells [5]. Food and food products have several plant polyphenols having high antioxidant properties. These products provide high levels of plant antioxidants to humans. Due to their high antioxidant capacity, these products are helpful to aid in the prevention and treatment of many diseases, such as it reduces tumor growth and cancer, DNA damage, LDL cholesterol levels,

muscular degeneration, cataracts, increasing apoptosis, killing viruses like herpes, treat ulcers and gut inflammation, etc. The uses of nutraceuticals are an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents.

Plant description: *Carica papaya* belongs to the family Caricaceae and has been used as a remedy against a variety of diseases [6]. *C. papaya* is the fourth most traded tropical fruit widely cultivated in tropical regions such as southern Mexico and Central America. It is also known as ‘tree melon’ due to its fleshy nature by the early Europeans. It is also known as papita (in Hindi), pawpaw tree (in English), and Erandkarkati (Sanskrit). Papaya is a major fruit crop known since ancient times as a medicinal and nutritional plant. Papaya is a polygamous species; difficult to identify whether it is female, male, or hermaphrodite. *C. papaya* is considered to be a berry. Its fruit varies in size; it elongates into a globe with a large central cavity. The seeds of the papaya are black, tuberous, and covered by transparent aril. *C. papaya* a widely cultivated and best-known species. The plant is an erect, perennial herb that grows 5 to 10 m (16 to 33 ft) tall with spirally arranged leaves confined to the top of the trunk. The trunk is hollow, green, or deep purple, and leaf scars roughen the base. Latex vessel is present all over the part of this plant. The leaves are hollow, pulpy, green, and also more or less dark purple. Stem and leaves both contain abundant white milky latex. The flowers are small, and numerous, with a yellowish-white color. Inflorescences are cymose type; five-petalled flowers are fleshy, waxy and a bit of fragrant (Figure 1)



Figure 1. *C. papaya* plant and fruit with seed (Source: www.planetayurveda.com/library/papita-carica-papaya/)

Table 1. Plant's Taxonomy

Classification of <i>C. papaya</i> :	
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Brassicales
Family	Caricaceae
Genus	<i>Carica</i>
Species	<i>papaya</i> Linn.

Phytochemistry of *C. papaya*: The plant contains different chemical constituents such as antioxidant nutrients (e.g., Carotene, vitamin C and flavonoids), vitamins B (e.g., pantothenic acid), minerals (e.g., potassium and magnesium), and fibers. Papaya leaves have vitamins (vitamins C and E), Alkaloids, carpaine, pseudocarpain, caproside, choline, and dehydrocarpain. Fruits contain biomolecules such as (protein, fats,

carbohydrates), minerals, vitamins, volatile compounds, alkaloids, and glycosides (Table 1). Papaya juice mainly contains palmitic acid, stearic acid, linolenic acid, myristic acid, n-hexanoic, and N-butyric acid. The plant is lactiferous because it has specialized cells known as lactifers which secrete latex (milky material) disperses it throughout most plant tissue. Drenth et al., 1968 [7] reported that papain is the most important proteolytic

enzyme extracted from the raw fruit of the papaya plant. Azarkan et al., 2003 [8] experimental results showed that latex constituents might vary in fruit, roots, and leaves. As the papaya fruit ripens, the amount of lactifers cells that produce latex decreases. Huet et al., 2006 [9] reported a lipase (a hydrolase and naturally immobilized biocatalyst) that was unstable for the essential lipolytic activity in papaya latex. Wall et al., 2021 [10] reported

that papaya is a rich source of the three strongest antioxidants, vitamin C, vitamin A, and vitamin E sequentially, and the minerals K and Mg; the vitamin B includes; B5 and folate; it contains high content of fibers. The root of the papaya plant also contains myrosin and caproside enzymes. Seeds contain chemical constituents such as benzyl isothiocyanate, carpain, fatty acid, protein, fibers, myrosin enzymes, and carcaine

Table 2. Phytochemicals present in different parts of *C. papaya* plant.

Plant parts	Phytochemicals
Leaves	Papain, chymopapain, cystatin, tocopherol, alkaloid carpain, dihydrocarpain I and II, carposide, vitamin C and E
Fruit	Ascorbic acid, fibers, sugar, protein, fiber, mineral: calcium, phosphorous, Iron, vitamin C, thiamine, riboflavin, niacin, and carotene, amino acid, citric acid and malic acid (green fruit), volatile compound: benzyl isothiocyanate, cis and trans 2,6- dimethyl-3,6 epoxy-7 octen2-ol.
Root	Myrosin and caproside
Seed	Benzyl isothiocyanate, carpain, fatty acid, protein, fibers, myrosin enzymes and carcaine.
Flower	Phalobatanine, flavinoids

Bio-pharmacological activity of c. Papaya: *Papaya* is a tropical fruit with commercial importance because of its high nutritive and medicinal value. The traditional system of medicine such as Ayurveda, Siddha, and Unani have mentioned the pharmacological and medicinal properties of *C. papaya* plant. It is widely used to treat blood pressure, dyspepsia, constipation, warts, sinuses, expel, antimicrobial, diabetes, inflammation, anticancer, and malaria. The papaya plant is a reliable source of nutrition as well as a phototherapeutic agent by using a unique mode of preparation and subsequently by consuming its parts. It is estimated that nearly 80% of the

population depends upon the traditional system of medicine as a primary healthcare modality in resource-constrained healthcare settings [11]. Jain, 1994 . [12] reported that in India, about 45,000 plant species have been reported to possess medicinal properties. *Papaya* comprises a hepatic enzyme - papain that efficiently treats basic causes like allergies, trauma, and sports injuries. This plant has many pharmacological such as anticancer, antimicrobial, anti-dengue, antipyretic, insecticidal mosquito repellent, and wound healing properties (Table 2). The detailed pharmacological properties of the papaya plant are explained below.

Table 3. Pharmacological properties of different parts of *C. papaya* plant.

Sr. No.	Plant's part	Pharmacological activities	References
1.	Leaf	Antibacterial, Antiviral, Antitumor, Hypoglycemic, Anti-Inflammatory, Anti Dengue	[13]
		Malaria, Jaundice	[14]
		Chikungunya	[15]
		Anticancer, Antiproliferative, Antimetastatic	[16]
		Increase Breast Milk, Constipation, Gonorrhoea, Fracture Healing, Indigestion, Yellow Fever, Tonsillitis, Ulcerative, Stomatitis, Gingivitis	[17]
		Sickle Cell Anemia	[18]
2.	Root	Antibacterial	[19]
		Antiulcer	[20]
3.	Flower	Urine Problem, Dyspepsia	[21]
		Anticancer	[22]
		Antioxidant, Cytotoxic, Chemo preventive	[23]
4.	Latex	Vital Lipolytic Activity	[24]
		Anti-Helminthic, Dyspepsia, Diarrhea, Bleeding Hemorrhoids, Whooping Cough, Anti-inflammatory, Anti-Sickling Activity, Anticoagulant Effect	[25]
		Antiviral, Antibacterial, Antioxidant, Anticancer	[26]
		Antiulcer	[27]
5.	Seed	Anticancer	[28]
		Nephroprotective Activity, Kidney Protector	[14]
		Antifertility, Contraceptive, Anthelmintic, Anti-inflammatory, Analgesic, Antimicrobial, Antioxidant, Diabetes Mellitus, Sickle Cell Disease	[29]
		Typhoid	[25]
		Antiparasitic Activity	[30]
6.	Peel	Muscle Relaxant	[14]
		Antibacterial, Antioxidant, Anticancer, Induced Apoptosis, Wound Healing Property	[29]
7.	Stem bark	Antibacterial, Antiviral	[31]
		Jaundice, Sore Teeth, Antifungal, Antihemolytic Activity	[32]
8.	Fruit	Anthelmintic, Anti Protozoan, Antibacterial, Antifungal, Antiviral, Anti-inflammatory, Free Radical Scavenging, Anti-Sickling, Neuroprotective, Diuretic, Abortifacient, Hypoglycemic, Hypolipidemic, Antihypertensive, Wound Healing, Antitumor, Antifertility, Anticancer, Stroke Prevention, Antiulcer, Blood Cholesterol Control	[29]
		Antioxidant Activity	[33]

Antioxidant potential: The enzymatic antioxidant defense systems are the natural protectors against reactive oxygen species produced during metabolism or due to external factors. The presence of bioactive molecules in *C. papaya* impedes the impact of reactive oxygen species accounting for the biological effect via antioxidant and/or free radicals scavenging activities. Exogenous intake of antioxidants from animal/ plant sources can help the body by scavenging free radicals effectively [34]. Literature showed a significant reduction in the level of GSH. Activity of catalase and superoxide dismutase were observed during high free radical concentration. This suggests an increased utilization of this antioxidant enzyme with subsequent depletion to counter the increased level of free radicals in these tissues. EL-Ballal and EL-Manankhly, 1998 [35] reported that a decrease in the activity of GST and other antioxidant enzymes in rat brains was found on subsequent exposure to acrylamide as the source of free radical formation. Sadak, 2012 [36] reported that administration of papaya fruit extract in combination with acrylamide restored the activity of this enzyme in all tissues. It was because *C. papaya* contains antioxidant phytochemicals, such as vitamin C, β -carotene, lycopene, and vitamin E, all of which acts as an antioxidant and subsequently decreases the consumption of these antioxidant enzymes to combat oxidative stress. A small double-blind, placebo-controlled study observed a significant enhancement of the individual's antioxidant defense system when a fermented extract of *C. papaya* was administered to elderly patients without major diseases [37]. Haramaki et al., 1995 [38] explored that oral administration of fermented Papaya Preparation (F.P.P.) decreased lipid peroxidation and increased the superoxide dismutase activity in the rat. The same group of authors also reported that the antioxidant action of papaya could be exerted through different mechanisms, such as by scavenging of hydroxyl radicals, by metal

chelation, by an effect on antioxidant enzymes, or by reaction with peroxy radicals.

Hepatoprotective effect: Papaya is used as a natural remedy for abnormal digestion in tropical countries. The clinical examination revealed the beneficial effect of papaya for a patient with heartburn, constipation, and symptoms of irritable bowel syndrome (IBS) after eating. Mantok, 2005 [39] reported that tea is prepared with the green leaf of papaya; it enhances digestion and aids in the treatment of ailments of chronic disorders such as chronic indigestion, obesity, overweight, arteriosclerosis, high blood pressure, and weakening of the heart. The aqueous and ethanol extract of dried fruit of papaya showed hepatoprotective activity in rats against CCl₄-induced hepatotoxicity. The aqueous (500 mg/kg of body weight) and ethanolic (500 mg/kg of body weight) extract of *C. papaya* plant showed hepatoprotection by lowering the biochemical parameter such as SGOT, SGPT, alkaline phosphatase, serum, bilirubin. Papaya is used daily to ensure a good supply of vitamin C and A, which is beneficial for good health. especially for eyesight and can help prevent early age blindness in youngsters. Sadak, 2012 [36] reported that *C. papaya* extract (CPE) has a hepatoprotective effect against carbon tetrachloride intoxicated rats. It may be mediating its protective effects either by decreasing the metabolic activation of carbon tetrachloride, acting as a chain-breaking antioxidant for scavenging free radicals or by combining these effects. Janatuinen et al., 2002 [40] reported that celiac disease, an immune-mediated encephalopathy of the small bowel, is caused by indefinite sensitivity to dietary prolamins present in gluten. Genetically susceptible individuals can minimize with supplementation of plant extract.

Anticancerous effect: Currently, cancer is one of the most fatal diseases in the world WHO claims that cancer currently kills more people than all coronary heart diseases. Since ancient times, plant and plant-based products have been working to prevent many human diseases. Tripathi and Tripathi, 2003 [41] reported that approximately 80% population of the world depends directly on plants for primary health care. Papaya is commonly used as human caloric herbal medicine, being a good source of nutrients and available throughout the year. Some parts of papaya contain phytochemicals that have the ability to bind with a toxin that causes cancer in the colon and keeps them away from healthy colon cells. Fiber present in papaya fruit provides a synergistic shield for colon cells from free radical damage. *C. papaya* leaf extract has also been used from ancient times as an aboriginal remedy for various disorders-including cancer and infectious diseases. Among all types of cancer disorders, breast cancer is the most prevalent form of cancer, and extract from *C. papaya* leaves showed anti-breast cancer activity [42- 43]. Other studies also showed that the extract of *C. papaya* has a variety of constituents that have anticancer properties and are used in the treatment of breast, liver, blood, pancreatic, skin, and prostate cancer [44- 45]. In animal models of cervical cancer, the ethanol leaf extract of papaya reduced the cancer cell proliferation index and boosted cancer cell apoptosis. Additionally, it might improve the expression of the P-53 gene and NF-KB [46]. Egeh et al., 2022 [28] reported that aqueous and methanolic extracts of *C. papaya* seeds could stop human breast cancer cells from proliferating. In another study, the administration of papaya seed extract to Acute promyelocytic leukemia HL-60 cells showed antitumor activity. Papaya seeds have been shown to be useful in preventing male prostate cancer [30]. The plant contains the enzyme papain, which also has an anti-cancerous effect. Papain covers the

tumor cells and breaks down fibrin, converting them into amino acids.

Additionally, papaya contains isothiocyanate, which also works against cancers of the breast, prostate, pancreas, lungs, leukemia, and colon [47]. Wang et al., 2006 [48] reported that the heating procedure to prepare the decoction could potentially affect the heat-labile compound, leading to a change in the bioactivity and an observed increase in the antiproliferative effect in comparison to natural material. Nguyen et al., 2013 [49] reported that animal cancer studies based on *in vitro* cell-culture indicate that papaya extracts may inhibit the growth of cancerous cells due to specific compounds showing anticancer effects. It has also been reported that the pure lycopene from papaya fruit showed anti-proliferative activity in the human liver and breast cancer cell lines [50]. These studies suggest that papaya has a direct antitumor effect on many types of cancers and, therefore, could be functional in possible therapeutic strategies in the fight against cancers.

Immunomodulatory properties: Medicinal plants are a potential source of immunomodulatory agents [51]. Immunomodulation is the regulatory adjustment in the body's immune system caused by agents that activate or suppress its function. Different parts of the papaya plant indicate that they have significant medicinal potential and immunomodulatory properties. According to reports, papaya leaf tea extract positively impacts the immune system. However, the mechanism of cell function is unclear. Fatima and Shahid, 2018 [14] reported that aqueous leaf extract at dosages of 400 and 800 mg/kg given orally for 14 days to wistar rats showed potential as an immunomodulatory agent. Recently, Singh et al., 2020 [13] also reported that papaya leaf extract has strong immunomodulatory and anti-inflammatory activities on cancer cell lines. The immunomodulatory activities of *C. papaya* leaf juice and

extracts have been proven by its ability to modulate cytokine production, enhance phagocytic activity and increase splenocyte proliferation [52]. *In vitro* and *in vivo* studies have shown that papaya extracts and papaya-associated phytochemicals possess anti-inflammatory and immunomodulatory properties [53]. Several studies have shown significant anti-inflammatory and immunomodulatory activities of different parts of the papaya plant by different mechanisms. Although the extent of maturation, cultivar type, different parts of the plant, and extraction method may affect the levels of anti-inflammatory and immunomodulatory activities due to variations in bioactive phytochemicals. Norahmad et al., 2019 [54] reported that *C. papaya* leaf juice treatment enhances the production of proinflammatory cytokines in the plasma and the liver of AG129 mice infected with a laboratory strain of dengue virus.

Antibacterial activity: The seeds of papaya are edible and have a sharp, spicy taste. Seeds are sometimes ground and used as a substitute for black pepper. Dried papaya seeds look quite similar to peppercorns and can be used in just the same way. Experimental results showed that *C. papaya* seeds have antibacterial properties and are effective against *E. coli*, *Staphylococcus*, and *Salmonella* infections. Chandra et al., 2011 [55] reported that aqueous, n-hexane and ethanolic extract of *C. papaya* has potent antibacterial activity against *Escherichia coli*, *Pseudomonas auruginasa*, *Bacillus subtilis* and *Staphylococcus aureus* bacteria, and detected that these three extracts were able to inhibit all the tested bacteria. Among the three extracts, ethanolic and n-hexane extract had the highest inhibition against *S. aureus*, while aqueous extract had maximum inhibition against *B. subtilis*, *P. auruginasa*, and *E. coli*. Arvind et al., 2013 [56] reported that *C. papaya* seeds have antibacterial activity and have the capacity to protect the kidneys from toxin-induced kidney failure as well as eliminate intestinal

parasites. Mangalanayaki and Nirosha, 2013 [57] examined the antibacterial activity of *C. papaya* leaf using ethanol and ethyl acetate solvents against *Streptococcus pneumonia*, *Bacillus cereus*, *E. coli*, *S. aureus*, and *P. aeruginosa* bacteria by diffusion method and found antibacterial impact. Suresh et al., 2008 [58] reported that papaya leaf extract showed antibacterial activity against gram-positive and gram-negative bacteria. In an experiment Tewari et al., 2014 [59] showed that methanolic leaf extract of *C. papaya* exhibited antimicrobial activity versus *Candida albicans*, *E. coli* and *Staphylococcus aureus*. These studies showed that *C. papaya* has antibacterial activity.

Anti-dengue effect: Dengue is a panic disease affecting people all over the place with approximately 50 to 100 million cases every year. Dengue is caused by the dengue virus (DENV) 1-4, belongs to the Flaviviridae family, and is transmitted by the *Aedes albopictus* mosquito. Dengue fever is mainly fought by a combination of vector control, personal protection, and disease management. At that time, there were no specific antibiotics or approaches in terms of vector control, personal protection, and disease management by drugs. After some time, identifying the most affordable and effective anti-dengue drugs was essential and unavoidable. Herbal medicine is an alternative approach to treating dengue. *C. papaya* leaf extract significantly increased the platelets count, which decreased during dengue infection. DENV1, DENV2, DENV3, and DENV4 exhibited dengue dandy fever (DF) or a break bone (fever, lymphadenopathy, muscle, headache) followed by dengue hemorrhagic fever (DHF) (abdominal pain, vomiting, nausea, sore throat), thrombocytopenia and finally bleeding in the mucous membrane and sometimes predisposed to spontaneous ocular hemorrhages. Ranasinghe et al., 2012 [60] experiment reported that the papaya leaf contains important properties to stabilize the membrane, protect

blood cells against stress-induced destruction and can prevent platelet lysis in dengue patients. Ranasinghe et al., 2012 [60] also reported that the juice of papaya leaves has possible beneficial effects in treating patients with dengue viral infection. Papaya leaf extracts showed potential in membrane stabilization in vitro hemolytic assay.

Anti-plasmodial activity: World health organization in world malarial report (2008) estimated that infection and mortality from malaria per year is 500 million and 2.7 million, respectively. 90% of these infections occur in Africa. 1.3% per annum in endemic areas reduces economic growth due to malaria causes. Karunamoorthi et al., 2014 [61] estimated that nearly half of the world's population is at risk of contracting malaria, with sub-Saharan Africa being the riskiest area. Karunamoorthi et al., 2012 [62] reported that Malaria is quite endemic world's poorest regions. Malaria is often referred to as a disease of poverty and a cause of scarcity. Adjanohoun et al., 1996 [63] reported that the mature papaya leaves are widely used to treat splenomegaly and malaria, while the fruit is often used against anemia, which malaria can also cause. Melariri et al., 2020 [64] experiment result showed that ethyl acetate extract from the papaya leaves has greater anti-plasmodial properties, an IC_{50} of 2.96 ± 0.14 $\mu\text{g/ml}$ compared to the activity of the fractions and isolated compounds. It is hypothesized that leaves of *C. papaya* are effective as an antimalarial agent due to the presence of alkaloids [65].

Mosquito repellent properties: Mosquitos are responsible for many diseases, including arboviruses which are responsible for yellow fever, dengue hemorrhagic fever, epidemic polyarthritis, several form of encephalitis, and bancroftian filariasis [66- 67]. Hag et al., 1999 [68] reported that the intensive use of chemical insecticides led to the development of a resistant insect

population, resulting in bio-amplification in the food chain and contamination. *C. papaya*, the single species in the genus *Carica*, is widely cultivated, and experimental findings explore those different parts of the *C. papaya* plant that can be used as a Mosquito repellent agent. Mello et al., 2008 [69] reported that the papaya plant is used as a remedy against various of diseases caused by mosquitoes. Crude and solvent extracts of seed extract of *C. papaya* were investigated for anti-mosquito potential, including larvicidal, pupicidal, adulticidal, smoke toxicity, and repellent activities against *Culex quinquefasciatus* and *Anopheles stephensi*, the vector of filaria and malaria, respectively. Results showed repellency against both mosquito species in adult females with 78% and 92% protection, respectively [70]. The seed extract of *C. papaya* showed repellency against both mosquito species with 78% and 92% protection, respectively. Utomo and Margo, 2013 [71] reported that papaya seed extract is more effective in killing larvae of *Anopheles* species. To date, the scientific community has tested thousands of traditional repellants to identify the potential plant-based mosquito/insect repellent. These findings suggest that papaya extracts possess remarkable pupicidal, larvicidal, adulticidal, and repellent activity against various vector mosquito species. Many key challenges and problems lie ahead for advancing the ideal commercial insect repellent from the plant as a source. The content of secondary metabolites in the leaves and seeds of papaya in the form in which the main works alkaloids inhibit the body's metabolic processes in larvae, interfere with growth hormone, and digest the protein in the larval body and turn it into peptone derivatives that will host larvae as food shortage and eventually die.

Insecticidal effect: Papaya leaf extract has a lethal effect on *Aedes spp.* larvae. However, further study is essential

to determine the accurate dose of these extracts as a larvicide —the effect of these extracts on the larvae of other species is still necessary to be studied. Refai et al., 2013 [72] reported that the negative effect of the prolonged use of chemical insecticides; it is imperative to study natural insecticides derived from plants as an alternative to larvicides. Natural larvicides, including cyanide, saponin, tannins, flavonoids, steroids, alkaloids, and essential oils, have been reported to have larvicidal effect. Karunmoorthi, 2011 [73] reported that vector control is a cornerstone in the fight against vector-borne diseases, particularly malaria. Karunmoorthi et al., 2012 [62] reported that insecticides are considered a potent weapon in order to enhance agricultural productivity and boost the significant public health indices too. Experimental results suggested that higher flavonoid content in papaya leaf extract was highly toxic to aphids as its LC₅₀ value at 72 hr. Field bioassays also proved the extract's efficacy against these pests more than a week under greenhouse conditions. Results recommended that papaya leaf extracts be used as a safe biological pesticide and showed moderate to high toxicity towards the sucking pests of rose [74]. In an experiment to see the insecticide properties of the seed extracts of four cultivars of *C. papaya* (Maradol, Mammee, Yellow, and Hawaiian), an insect diet based on the seeds of *C. papaya* given to the first larval stage of *Spodoptera frugiperda*. Extracts from seeds of the Maradol, Mammee, and Yellow cultivars of *C. papaya*, followed by extracts from the Hawaiian cultivar, were applied at concentrations of 10, 100, and 1000ppm, were toxic on *S. frugiperda* larvae (50-70% corrected mortality rate) [75]. Ethanolic extract of papaya leaf could be formulated as a potent natural insecticide to control populations of German cockroaches that have been resistant to synthetic insecticides [76].

CONCLUSION

It is well known that they are available in the form of natural fruit, leaves, and their phytochemicals are able to

cure fatal diseases. Given increasing awareness about health and increased use of phytochemicals in the prevention and treatment of common and severe diseases, there is need to explore the possibilities of including fruit in our daily diet. Papaya is used as a nutraceutical to treat/prevent many diseases/disorders, including cancer. Traditionally it has also been used for various purposes like contraception, medicine for acne, menstrual pain reducer, and appetite enhancer. The present survey findings suggest that the papaya plant parts contain many powerful activities such as hepatoprotective activity, anti-cancerous activity, Anti plasmodial, anti-dengue, and antitrichomonal. It is also exhibited potential as an antiseptic, anti-inflammatory, contraceptive activity, and management of sickle cell anemia, and heart diseases. To evaluate the possible therapeutic application of these phytochemicals, extensive in vivo or vitro studies are required before going on to clinics. *C. papaya* is used as food or as a quasi-drug to prevent/treat various ailments through social media.

Abbreviations: LDL: Low-Density Lipoprotein, GSH: Reduced Glutathione, GST: Glutathione S-Transferases, FPP: Fermented Papaya Preparation, IBS: Irritable Bowel Syndrome, CCl₄: Carbon Tetrachloride, SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic Pyruvic Transaminase, CPE: *Carica Papaya* Extract, WHO: World Health Organization, NF-KB: Nuclear factor kappa B, DENV: Dengue virus, DHF: Dengue Hemorrhagic Fever, IC₅₀: Half Maximal Inhibitory Concentration, LC₅₀: Lethal Concentration Causing Death in 50%

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REFERENCES:

- Patterson AD, Gonzalez FJ, Idle JR.: Xenobiotic metabolism: a view through the metabolometer. *Chem Res Toxicol* 2010, 23(5): 851-860. DOI: <https://pubs.acs.org/doi/10.1021/tx100020p>
- Pham-Huy LA, He H, Pham-Huy C.: Free radicals, antioxidants in disease and health. *Int J Biomed Sci* 2008, 4(2):89-96. DOI: PMID: PMC3614697.
- Singh P, Kakkar P, Singh RL.: Protective Effect of *Trigonella foenum-graecum* and *Foeniculum vulgare* Mature Leaf Against t-BHP induced Toxicity in Primary Rat Hepatocytes. *J Exp Food Chem* 2016a, 2:111. DOI: <http://dx.doi.org/10.4172/2472-0542.1000111>
- Singh P, Singh RL, Kakkar P.: Antioxidant, DNA Damage Protective and hepatoprotective Activities of *Amorphophallus campanulatus*. *Int J Pharm Pharm Sci* 2016b,8(3):330-338.
- Singh P, Vishwakarma SP, Singh RL.: Evaluation of Antioxidant, Oxidative DNA Damage Protective and Antimicrobial Activities of *Foeniculum vulgare* Plant. *J Med Plant Res* 2013, 4(35):2551-2563. DOI: <https://doi.org/10.5897/JMPR2013.5120>
- Alabi OA, Haruna MT, Anokwuru CP, Jegede T, Okegebe HV, Esan.: Comparative studies on antimicrobial properties of extracts of fresh and dried leaves of *Carica papaya* (L) on clinical bacterial and fungal isolates. *Adv Appl Sci Res* 2012, 3 (5):3107-3114.
- Drenth J, Jansonius JN, Koekoek R, Wolthers HM, BG.: Structure of papain. *Nature*.1968, 218: 929-932. DOI: <https://doi.org/10.1038/218929a0>
- Azarkan AM, Moussaoui E, Wuytswinkel D van, Dehon G, Looze Y: Fractionation and purification Analyt Technol of the enzyme stored in the latex of *Carica papaya*. *J Chromatogr B Biomed Appl* 2003, 790:229-238. DOI: [https://doi.org/10.1016/s1570-0232\(03\)00084-9](https://doi.org/10.1016/s1570-0232(03)00084-9)
- Huet J, Looze Y, Bartik K, Raussens V, Wintjens R, Boussard P.: Structural Characterization of the papaya cysteine proteinases at low pH. *Biochem Biophys Res Commun* 2006, 341:620-6. DOI: <https://doi.org/10.1016/j.bbrc.2005.12.210>
- Wall MM.: Ascorbic acid, vitamin A, and mineral composition of banana (*Musa sp.*) and papaya (*Carica papaya*) cultivars grown in Hawaii. *J food Compos Anal* 2021, 19(5):434-445. DOI: <http://dx.doi.org/10.1016/j.jfca.2006.01.002>
- Singh P, Vishwakarma SP, Singh U, Shukla M, Singh R, Singh RK, Singh RB, Wilson DW and Singh RL.: Quantification and Evaluation of Antioxidant Activity of Some Bioactive Phytochemicals in Different Medicinal Plants. *Open Nutr J* 2012, 5:179-186. DOI: <http://dx.doi.org/10.2174/1876396001205010179>.
- Jain SK.: Ethnobotany and research in medicinal plants in India. *Ethanobot Search New Drugs* 1994, 185:153-168. DOI: <https://doi.org/10.1002/9780470514634.ch11>
- Singh SP, Kumar S, Mathan SV, Tomar MS, Singh R, Verma PK, Kumar A, Kumar S, Singh RP, Acharya A.: Therapeutic application of *Carica papaya* leaf extract in the management of human diseases. *DARU J Pharm Sci* 2020, 28(2):735-744. DOI: <https://doi.org/10.1007%2Fs40199-020-00348-7>
- Fatima U, Shahid S.: Pharmacological Activities of *Carica papaya* Linn. *J Basic Appl Sci* 2018, 14:210-216. DOI: <http://dx.doi.org/10.6000/1927-5129.2018.14.33>
- Hariono M, Julianus J, Djunarko I, Hidayat I, Adelya L, Indayani I, Auw Z, Namba G, Hariyono P.: The Future of *Carica papaya* Leaf Extract as an Herbal Medicine Product. *Molecules* 2021, 26:2922. DOI: <https://doi.org/10.3390/molecules26226922>
- Pandey P, Walpole C, Shaw PN, Cabot PJ, Hewavitharana AK, Batra J.: Bio-Guided Fractionation of Papaya leaf juice for Delineating the Components Responsible for Selective Anti-proliferative Effects on Prostate Cancer cells. *Front Pharmacol* 2018, 9:1319. <https://doi.org/10.3389/fphar.2018.01319>
- Priyadarshi A and Ram B.: A Review on pharmacognosy, phytochemistry and pharmacological activity of *Carica papaya* leaf. *Int J Pharm Sci Res* 2018, 9(10):4071-4078. DOI: <http://dx.doi.org/10.13040/IJPSR.0975-8232>.
- Upko GE, Owalabi MA, Image NOA, Oribayo OO, Ejiroghene AJ.: Effect of *Carica papaya* aqueous leaf extract on pharmacokinetic profile of ciprofloxacin in rabbits. *Trop J Pharm Res* 2016, 16(1):127-134. DOI: <https://doi.org/10.4314/tjpr.v16i1.16>
- Wemambu, DJ Ajose and Eni CC.: Antibacterial Effect of *Carica papaya* root extract on some selected pathogens from clinical isolates. *ACTA Sci Microbiol* 2018, 1(7):6-10.
- Manokar P, Agilan S, Deepika E, Sridhar N.: Evaluation of Antiulcer Activity of *Carica papaya* root. *Int J Allied Med Sci Clin Res* 2019, 7(2): 509-514.
- Sivarajah N.: Medicinal Uses of *Carica papaya*. *Int J Sci Res* 2017, 6(5): 2770-2772.
- Nainggolan M and Kasmirul.: Cytotoxicity Activity of Male *Carica papaya* flowers on MCF-7 Breast Cancer Cells. *J Chem Pharm Res* 2015, 7(5): 772-775.

23. Sianipar MP, Suwarso E, Roshidah R.: Antioxidant and Anticancer Activities of Hexane fraction from *Carica papaya* L. Male Flower. Asian J Pharm Clin Res 2018, 11(3): 81-83. DOI: <https://doi.org/10.22159/ajpcr.2018.v11i3.22382>
24. Saeed Fa, Arshad MU, Pasha I, Naz R, Batool R, Khan AA, Nasir MA, Shafique B.: Nutritional and Phyto-therapeutic Potential of *Carica papaya*: An overview. Int J Food Prop 2014, 17:1637-1653. DOI: <https://doi.org/10.1080/10942912.2012.709210>
25. Yogiraj V, Goyal PK, Chauhan CS, Goyal A, Vyas B.: *Carica papaya* Linn.:An overview. Int J Herb Med 2015, 2(5): 01-08.
26. Samrat AV, Saigeetha S, Mun CY, Abirami S, Purohit K, Cypriyana PJJ, Dhas S, Inbathamizh L, Kumar SS.: Utilization of *Carica papaya* Latex on Coating of SPIONs for dye removal and delivery. Sci Rep 2021, 11:24511. DOI: <https://doi.org/10.1038/s41598-021-03328-2>
27. Chen CF, Chen SM, Chow SY, WeiHan P.: Protective Effects of *Carica papaya* Linn. On the Exogenous Gastric Ulcer in Rats. Am J Chinese Med 1981, 9(3):205-212. DOI: <https://doi.org/10.1142/s0192415x81000275>
28. Ejeh E, Dan VM, Dikwa, KB, Mshelia, AS.: Assessment of the effects of ripe *Carica papaya* seeds extracts on MCF-7 Breast cancer cell lines. ISOR J Biotech Biochem 2022, 8(1): 12-19.
29. Anitha B, Raghu N, Gopenath TS, Karthikeyan M, Gnanasekaran A, Chandrashekrappa GK, Basalingappa KM.: Medicinal Uses of *Carica papaya*. J Nat Ayu Med 2018, 2(6):000144. DOI: <http://dx.doi.org/10.23880/ionam-16000144>
30. Saba S, Pattan N.: The Potential Health Benefits of Papaya Seeds. Int J Res Appl Sci Eng Tech 2022, 10(1):44-50. DOI: <https://doi.org/10.22214/ijraset.2022.39271>
31. Haque M, Chaudhary MGF, Kabir MF, Rashid MA.: Antibacterial Activity and Cytotoxicity of Stem Bark of two common plants of Bangladesh. Int J Nutr Pharmacol Neurol Dis 2015, 5(2):75-81. DOI: <https://doi.org/10.4103/2231-0738.153797>
32. Kaur M, Talnia NC, Kumar A, Stashenko E.: Ethnomedicinal Uses, Phytochemistry and Pharmacology of *Carica papaya* Plant: A Compendious Review. Mini Rev org Chem 2019, 16(5):463-480. DOI: <http://dx.doi.org/10.2174/1570193X15666180816110733>
33. Abhishek K, Kumar MR, Badhusha PAS, Gowda SK, Ajay A, Baby B, Ramesh B.: Ethanobotanical and Biological Activities of *Carica papaya* Linn: A Review. Int J Pharm Drug Anal 2020, 8(8):1-5.
34. Singh P, Singh RL.: Quantification of Phytochemicals Imparting Antioxidant Activities in Commonly Used Vegetables. Int J Appl Sci Biotech 2018, 6(2):107-112. DOI: <https://doi.org/10.3126/ijasbt.v6i2.19636>
35. EL-Ballal SS, EL-Manankhly EM.: Histopathological and ultrastructural evaluation of the effect of nigella sativa on experimentally induced acrylamide neurotoxicity in rats. 8th Science Congress Faculty of Veterinary Medicine Assiut University, Egypt. 1998.
36. Sadek KM.: Antioxidant and immunostimulant effect of *Carica papaya* linn. Aqueous extract in acrylamide intoxicated rats. Acta Informatica Medica 2012, 20(3):180-185. DOI: <https://doi.org/10.5455/aim.2012.20.180-185>
37. Marotta F, Weksler M, Naito Y, Yoshida C, Yoshioka M, Marandola P.: Nutraceutical supplementation: effect of a fermented papaya preparation on redox status and DNA damage in healthy elderly individuals and relationship with GSTM1 genotype: a randomized, placebo-controlled, cross-over study. Ann N Y Acad Sci 2006, 1067:400-407. DOI: <https://doi.org/10.1196/annals.1354.057>
38. Haramaki N, Marcocci L, D'Anna R, Liang-Jun Yan-Hirotsugu Kobuchi, Packer L.: Fermented papaya preparation supplementation: effect on oxidative stress to isolated rat hearts. Biochem Mol Biol Int 1995, 36(6):1263-1268.
39. Montok C.: Multiple usage of green papaya in healing at Tao Garden Health spa and Resort. 2005.
40. Janatuinen EK, Julkunen TA, Kosma RJK, Maki VM, Heikkinen M, Uusitupa M.: M.I.J.No harm from five year ingestion of oats in oeliacdisease. Gastroenterology 2002, 95: 332-335. DOI: <https://doi.org/10.1136/gut.50.3.332>
41. Tripathi L, Tripathi JN.: Role of biotechnology in medicinal plants. Trop J Pharm Res 2003, 2:243-253. DOI: <http://dx.doi.org/10.4314/tjpr.v2i2.14607>
42. 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, 127:760-767. DOI: <https://doi.org/10.1016/j.jep.2009.11.024>
43. Mahendran VS, Sophiya K, Sruthimalvika S, Suganthi B, Sujitha E.: *Carica papaya*: Anticancer activity in MCF-7 Breast cancer cell lines. Int J Pharm Sci Res 2021, 12(1):176-182. DOI: <http://dx.doi.org/10.13040/IJPSR.0975-8232>
44. Parray ZA, Parray SA, Khan JA, Zohaib S, Nikhat S.: Anticancer activities of papaya (*Carica papaya*): A review. Cell Ortho Med Pharma Assoc 2018, 8(4):201-205. DOI: <https://doi.org/10.5667/tang.2018.0020>
45. Sumana S, Kumar GT.: Breaking the Barrier of cancer through papaya extract and their formulation. Anticancer Agents Med Chem 2019, 19(13):1577-1587. DOI: <https://doi.org/10.2174/1871520619666190722160955>

46. Peristiwati Y, Puspitasari Y, Indasah.: Effects of Papaya leaf Extract on Cellular Proliferation and Apoptosis in Cervical cancer Mice model. *Phytothérapie* 2019, 17:265-275. DOI: <https://doi.org/10.3166/phyto-2018-0096>
47. Wadekar AB, Nimbawar MG, Panchale WA, Gudalwar BR, Lanwar JV, Bakal RL.: Morphology, Phytochemistry and Pharmacological aspects of *Carica papaya*: a review. *GSC Biol Pharm Sci* 2021, 14(03):234-248.
48. Wang CZ, Zhang B, Song WX, Wang A, Ni M, Luo X, Aung HH, Xie JT, Tong R, Che T, Yuan CS.: Streamed American ginseng berry: Ginsenoside analysis and anticancer activities. *J Agri Food Chem* 2006, 54(26):9936-9942. DOI: <https://doi.org/10.1021/jf062467k>
49. Nguyen TT, Shaw PN, Parat MO, Hewavitharana AK.: Anticancer activity of *Carica papaya*: a review. *Mol Nutr Food Res* 2013, 57(1):153-164. <https://doi.org/10.1002/mnfr.201200388>
50. Rahmat A, Rosli R, Zain MWNW, Endrini S, Sani HA.: Antiproliferative Activity of pure Lycopene Compared to Both Extracted Lycopene and juice from *Carica papaya* on Human Breast and Liver Cancer Cell Lines. *J Med Sci* 2002, 2:55-58. DOI: <https://dx.doi.org/10.3923/jms.2002.55.58>
51. Jantan I, Ahmad W, Bukhari SNA.: Corrigendum- Plant-derived immunomodulators: An insight on their preclinical evaluation and clinical trials. *Front Plant Sci* 2018, 9:1178. DOI: <https://doi.org/10.3389/fpls.2015.00655>
52. Razak MAMR, Norahmad NA, Md Jelas NH, Afzan A, Mohamad Misnan N, Mat Ripen A, Thayan R, Zainol M, Syed Mohamed AF.: Immunomodulatory Activities of *Carica papaya* L. Leaf Juice in a Non-Lethal, Symptomatic Dengue Mouse Model Pathogens. *Pathogens* 2021, 10(5):501. DOI: <https://doi.org/10.3390/pathogens10050501>
53. Pandey S, Cabot PJ, Shaw PN, Hewavitharana AK.: Anti-inflammatory and immunomodulatory properties of *Carica papaya*. *J Immunotoxicol* 2016, 13(4):590-602. DOI: <https://doi.org/10.3109/1547691x.2016.1149528>
54. Norahmad NA, Razak MRMA, Misnan NM, Jelas NHM, Sastu UR, Muhammad A, Ho TCD, Jusoh B, Zolkifli NA, Thayan R.: Effect of freeze-dried *Carica papaya* leaf juice on inflammatory cytokines production during dengue virus infection in AG129 mice. *BMC Complement Altern Med* 2019, 19:1-10. DOI: <https://doi.org/10.1186/s12906-019-2438-3>
55. Chandra G, Bhattacharjee I, Chatterjee SK, Ghosh A.: Antibacterial activities of some plant extracts used in Indian traditional folk medicine. *Asian Pac J Trop Biomed* 2011, S165-S169. DOI: [https://doi.org/10.1016/S2221-1691\(11\)60148-2](https://doi.org/10.1016/S2221-1691(11)60148-2)
56. Aravind G, Bhowmik D, Duraivel S, Harish G.: Traditional and Medicinal Uses of *Carica papaya*. *J Med Plants Stud* 2013, 1:7-15.
57. Mangalanayaki R, Nirosha N.: Antibacterial Activity of Leaves and Stem Extract of *Carica papaya* L. *Int J Adv Pharm Biol Chem* 2013, 2(3): 473-476.
58. Suresh K, Deepa P, Harisaranraj R, Vaira A, Achydhnan.: Antibacterial and Phytochemical investigation of the leaves of *Carica papaya* L. *Cynodon dactylon* (L.) Pers., *Euphorbia hirta* L., *Melia azedarach* L. and *Psidium guajava* L. *Ethnobotanical Leaflets* 2008, 12:1184-1191.
59. Tewari BB, Subramanian G, Gomathinayagam R.: Antibacterial Properties of *Carica papaya* (Papaya) Different Leaf Extract against *E. coli*, *S. aureus* and *C. albicans*. *Am J Pharm Pharmacother* 2014, 1(1):025-039.
60. Ranasinghe P, Abeyeskera WP, Permakumara GA, Perera YS, Gurugama P, Guanatilake SB.: In vitro erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extract. *Pharmacogn Res* 2012, 4(4):196-202. DOI: <https://doi.org/10.4103/0974-8490.102261>
61. Karunamoorthi K, Hyung-minK, KaliyaperumalJ, Xavier J, Vijayalakshmi J.: Papaya: A gifted nutraceutical plant – a critical review of recent human health research. *Tang* 2014, 4:1-17. DOI: <https://doi.org/10.5667/tang.2013.0028>
62. Karunamoorthi K, Mohammed M, Wassie F.: Knowledge and Practices of Farmer with Reference to Pesticide Management: Implication on Human Health. *Arch Environ Occup Health* 2012, 67:109-116. DOI: <https://doi.org/10.1080/19338244.2011.598891>
63. Adjanohoun JE, Aboubakar N, Dramane K, Ebot ME, Ekper JA, Enoworock EG, Focho D, Gbile ZO, Kamanyi A, Kamsu JK, Keita A.: Traditional Medicine and Pharmacopoeia. Contribution to ethnobotanical and floristic studies in Cameroon. 1996, (Addis Ababa, Ethiopia: Organisation of African Unity).
64. Melariri P, Campbell W, Etusim P, Smith P.: Antiplasmodial Properties and Bioassay-Guided Fractionation of Ethyl Acetate Extract from *Carica papaya* Leaves in rats. *J Parasitol Res* 2020, 104954. DOI: <https://doi.org/10.1155/2011/104954>
65. Ayoola PB, Adeyeye A.: Phytochemical and Nutrient Evaluation of *Carica papaya* (Pawpaw) Leaves. *Int J Res Rev Appl Sci* 2010, 5: 325-328.
66. Maheswaran R, Sathis S, Igacimuthu S.: Larvicidal activity of leucosaspera (wild.) against the Larvae of *Culex quinquefasciatus* Say and *Aedes aegypti* L. *Int J Integra Biol* 2008, 2(3):214-217.
67. Kamzembe T, Makusha C.: Evolution of mosquito Repellencies of capsicum frutescens, *Carica papaya* and *Cyanodon Dactylon*

- Extracts and Extract Mixtures. Bull Environ Pharmacol Life Sci 2012, 7:34-40.
68. Hag EAEI, Nadi AH, Zaitoon AA.: Toxic and growth retarding effects of three plant extracts on *Culex pipiens* larvae (Diptera: Culicidae). Phytother Res 1999,13:388-392. DOI: [https://doi.org/10.1002/\(sici\)1099-1573\(199908/09\)13:5%3C388::aid-ptr455%3E3.0.co;2-u](https://doi.org/10.1002/(sici)1099-1573(199908/09)13:5%3C388::aid-ptr455%3E3.0.co;2-u)
69. Mello VJ, Gomes MT, Lemos FO, Delfino JL, Andrade SP.: The gastric ulcer prospective and healing role of cysteine proteinase from *caricacandamarcensis*. Phytomedicine 2008, 15:237-244. DOI: <https://doi.org/10.1016/j.phymed.2007.06.004>
70. Chandra G.: Aliphatic Amide from Seeds of *Carica papaya* as Mosquito Larvicide, Pupicide, Adulticide, Repellent and Smoke Toxicant. J Mosq Res 2012, 2(2):8-18. DOI: <http://dx.doi.org/10.5376/jmr.2012.02.0002>
71. Utomo, Margo.: Own power plant-based ingredients of papaya seed powder against death *Aedes aegypti* larvae isolates SALATIGAB2P2VRP laboratory (Proceeding of the National Seminar Uniiimus) 2013.
72. Refai H, Hermansyah, Nau EDAB.: Ujiefektifitas: biolarvasida *Carica papaya* terhadapkematian larva instar iii nyamuk *Aedes aegypti*.
73. Karunmoorthi K.: Vector control: A cornerstone in the Malaria Elimination Campaign. Clin Microbiol Infect 2011, 17:1608-1616. DOI: <https://doi.org/10.1111/j.1469-0691.2011.03664.x>
74. Gupta G, Sharma S, Kumar N.: *Carica papaya* aqueous leaf extracts as potential botanical insecticide against rose aphids (*Macrosiphum rosaeformis* D.). J Entomol Zool Stud 2020, 8:960 – 964.
75. Brito R, Perez-Moreno I, Huerta-de la P, Arturo, Olgúin JF, Marco-Mancebón V.: Insecticidal activity of seed extracts of *Carica papaya* (L.) Against the fall armyworm *Spodoptera frugiperda* (J.E. Smith) (Lepidoptera: Noctuidae). Interiencia 2011, 36: 752-756.
76. Rahayu R, Darmis A, Jannatan R: Potency of Papaya Leaf (*Carica papaya* L.) As Toxicant and Repellent against German Cockroach (*Blattella germanica* L.). Pak J Biol Sci 2020, 23:126-131. DOI: <https://doi.org/10.3923/pjbs.2020.126.131>