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REVIEW ON THE ANTIOXIDANT AND IMMUNOSTIMULANT ACTIVITY OF CARICA PAPAYA LINN. LEAF EXTRACT AND ITS EFFECTIVITY

***Abhishek Parasar and Priyanka Choudhury**

Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam, 781017.

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***Corresponding Author**
Abhishek Parasar
Girijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam, 781017.

ABSTRACT

Papaya is a powerhouse of nutrients and is available throughout the year. It is rich source of three powerful antioxidant vitamin C, vitamin A and vitamin E. the minerals, magnesium and potassium, vitamin B pentothenic acid and folate and fibre. In addition to all this, it contains a digestive enzyme called papain that effectively treat causes of trauma, allergies and sports injuries. The fruit is an excellent source of beta-carotene that prevents damage caused by free radicals that may cause some forms of cancer. Antioxidants are substances that may protect your cells against the effects of free radicals. Free radicals are molecules produced when your body breaks down food, or by environmental exposures like tobacco smoke and radiation. Free radicals can damage cells, and may play a role in heart disease, cancer and other diseases. Studies suggest that a diet high in antioxidants from fruits and vegetables is associated with a lower risk of cancer, cardiovascular disease, Parkinson's disease and Alzheimer's disease. A plant-based diet protects against chronic oxidative stress-related diseases. Immunostimulants are considered as an alternative for antibiotics, which will boost the immunesystem of the cultured organism, thus effectively countering the assault of pathogens. The use of plant materials as immunostimulant will be an eco-friendly approach for the control of pathogens. This review focuses on the antioxidant and immunostimulant activities of papaya leaf extract.

KEYWORDS: Antioxidant, Immunostimulant, *Carica papaya*, Pharmacological activities, Phytochemistry.

1. INTRODUCTION

Antioxidants are substances that may protect your cells against the effects of free radicals. Free radicals are molecules produced when your body breaks down food, or by environmental exposures like tobacco smoke and radiation. Free radicals can damage cells, and may play a role in heart disease, cancer and other diseases. Studies suggest that a diet high in antioxidants from fruits and vegetables is associated with a lower risk of cancer, cardiovascular disease, Parkinson's disease and Alzheimer's disease. A plant-based diet protects against chronic oxidative stress-related diseases. Dietary plants contain variable chemical families and amounts of antioxidants. It has been hypothesized that plant antioxidants may contribute to the beneficial health effects of dietary plants. Our objective was to develop a comprehensive food database consisting of the total antioxidant content of typical foods as well as other dietary items such as traditional medicine plants, herbs and spices and dietary supplements.

Since ancient times, the medicinal properties of the plant materials improve the quality and nutritional value of plants has been investigated in the recent scientific form. While, flavonoids are a group of polyphenolic developments throughout the world, due to their potent compounds with known properties, which include free antioxidant activities. The antioxidants have been reported to have radical scavenging, inhibition of hydrolytic and oxidative to prevent oxidative damage caused by free radical.[1]

Immunostimulants stimulate the immune system. The term immunostimulant can be used interchangeably with immunomodulator, adjuvant, and biological response modifier. Immunostimulators can be in the form of drugs or nutrients. They stimulate the monocyte-macrophage system and thereby modulate the immune system of the body. *Lactobacillus* spp., *Streptomyces* spp., *Aspergillus* spp., etc., can be used as immunostimulants. There are two main categories of immunostimulators**:** specific and non-specific.[2]

Specific immunostimulators provide antigenic specificity in immune response and include vaccines and antigens. For specific immune response, hosts must have had prior exposure to an antigen after which recognition and subsequent activation occurs through co-ordinated action of B-lymphocytes and T-cells. B-lymphocytes play a large role in the humoral immune response, in contrast to

cell-mediated immune responses which are governed by T-cells.

Non-specific immunostimulators act irrespectively of antigenic specificity to enhance the immune response of other antigens or to stimulate components of the immune system without antigenic specificity, such as glucans and the synthetic drug levamisole. Many endogenous substances are non-specific immunostimulators. For example, glucans and mannans possess non-specific immunostimulatory effect. β-glucan is a polymer of glucose consisting of a linear backbone of β-1,3 linked D-glucopyranosyl residues with varying degrees of branching from the C6 position.[3]

2. METHODOLOGY

Various databases like Pubmed, Ovid, Embase, Scopus, Sci-hub and Google scholar databases were electronically searched for articles focusing on *Carica papaya.* Articles concentrating on the *Carica papaya* leaf were included in the review. Various journals were hand searched by the reviewers. Followed by which only full text articles were included in this review.

2.1 Plant Profile

Papaya is a powerhouse of nutrients and is available throughout the year. It is rich source of three powerful antioxidant vitamin C, vitamin A and vitamin E. the minerals, magnesium and potassium, vitamin B pentothenic acid and folate and fibre. In addition to all this, it contain a digestive enzyme called **papain** that effectively treat causes of trauma, allergies and sports injuries. The fruit is an excellent source of beta-carotene that prevents damage caused by free radicals that may cause some forms of cancer.[4]

2.1.1. Taxonomical Classification

The papaya belongs to a small family-Caricaceae, having four genera in the world. The genus Carica Linn. Is represented by four species in India, of which C. papaya Linn. is the most widely cultivated and best known species. The taxonomical classification includes

Kingdom: Plantae
Order: Brassicales
Family: Caricaceae
Genus: Carica
Species: C. papaya.[5,6]

2.1.3. Morphology

Papaya plant is ordinarily grown as a single-stemmed plant with a crown of enormous palmate leaves rising from the tip of the trunk, however, the plant might turn into multistemmed once broken. Under optimal condition, papaya trees can reach 8-10 m in height but in cultivation, they are usually destroyed once they reach heights that make difficult to fruits harvesting.[7,8,9] Investigation of morphological and fruiting characteristics of anther-derived triploid papaya, estimate the usefulness in commercial fruit production and breeding. In conclusion, anther-derived triploid papaya segregated into dwarf, semi-dwarf and tall trees. The diploid control did not differ significantly from the triploid strains in most morphological features.[10]

(i) ***Roots:*** The roots of papaya plant are whitish cream in colour and young roots exhibit well-differentiated endodermis, epidermis, cortex and generally dense and nonaxis.[11]

(ii) ***Stem:*** The stem has soft, hollow, and cylindrical trunk ranges from 30 cm diameter at the base to about 5 cm diameter at crown. Papaya normally grows as a single-stemmed tree with a crown of huge palmate leaves expanding from the apex of the trunk, but trees may become multi-stemmed when damaged.[7,8,9]

(iii) ***Leaves:*** The leaves are 50 to 70 cm wide and hence large. The plant consists of large palmate leaves having 5-9 pinnated lobes with diverse width from 40-60 cm, shows spiral arrangement and groups are together in the upper part of fully grown trees. Leaf blades are dorsiventrally situated and may extended from 30-105 cm long with a hollow stalk of a leaf grows almost horizontally and gifted with abundant starch endodermis, that may be significant for cavitation resorting.[12] The leaf possesses palisade parenchyma and epidermis that are made of an only single layer of the cell, but squishy mesophyll consists of 4-6 cells layer. Leaves are rich in reflective grains and druses (calcium oxalate crystals). The leaves of papaya are hypostomatic (having stomata on underneath), with anisocytic stomata or no subsidiary cells. The leaves are illuminated by sunlight, have a stomatal density around 400/mm sq. can be modified through environmental conditions like water, temperature, and light.[13,14] Microscopy of the leaf showed the presence of epidermis, collenchyma, and parenchyma, sclerenchyma, pith, xylem and phloem, and pith was found to be absent.[15,16] Morphological observation of *C. papaya* leaf with ventral and dorsal view depicted in Fig. (1).

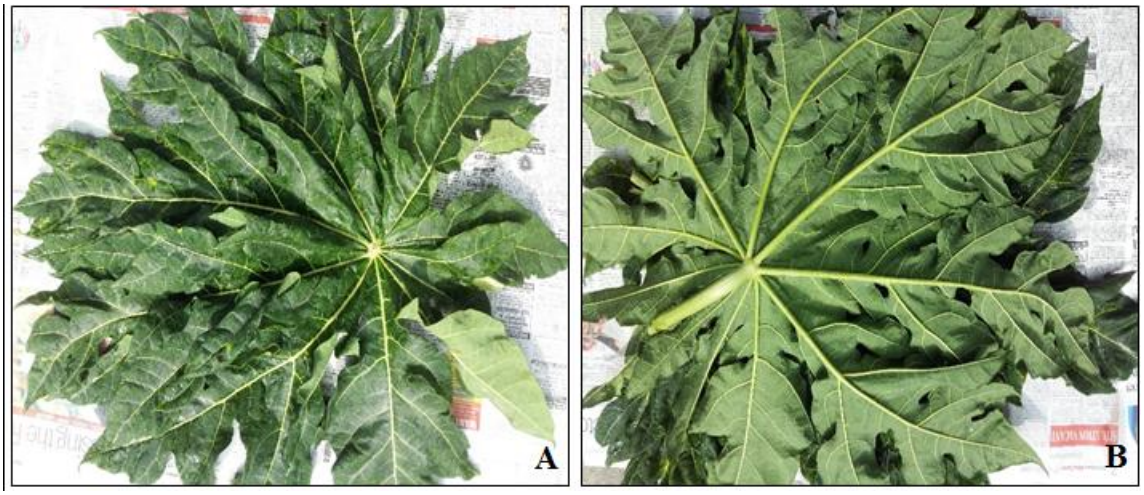

Fig. 1: A. Depicted the ventral view. B. Dorsal view.

(iv) ***Flowers:*** The flowers of *C. papaya* are occasionally known as 'trioecious' that means different plants support either female, male or bisexual flowers. Female papaya has pear-shaped flowers when not opened, male papaya possesses small flowers supported by long stalks while bisexual flowers are tubular in form. Mostly bisexual plants are better and preferred than male or female plants.[17] The flowers are actinomorphic, bracteolate, and immobile in the cluster and arranged along a single central axis. The androecium is epipetalous (borne on the petals or corolla) formed of ten stamens in two whorls. The anthers are introrse (turned inwards) and bilocular. The calyx has five lobes that are small and united (gamosepalous) and corolla composed of five petals that are gamopetalous, longer and yellow in colour. In case of female flowers, androecium is not present, it consists of an ovary and stigma. The pistillate or female flowers are sub-sessile and bracteolate. The androecium is absent in pistillate flowers and gynoecium is sessile. The style is very short with a five-lobed stigma and ovary is superior, having an indefinite number of seeds.

Fig. 2: Flower of *C. papaya*.

(v) ***Fruits:*** Plant fruits are massive oval in shape and occasionally known as pepo-like berries because they resemble melon by having a central seed cavity. Fruits are borne axillary on the main stem, mostly singly; however, sometimes in clusters. Fruit pulp has organoleptic (texture, colour and aroma), chemical (total soluble solids, acidity, balance amount of sugars and organic acids) and digestive properties.[18] Plant individual fruits mature in 5-9 months, depending on cultivator and temperature. Fruits weight from 0.5 up to 20 lbs are green until ripe, turning yellow or red-orange and fruit flesh is yellow-orange to pinkish orange on its maturity. Fruits are berries with seeds within the fruit cavity and the form of the fruit may vary from oval to spherical. The layout of *C. papaya* fruit with longitudinal section with seeds depicted in Fig. (**3**). Microscopy of the unripe fruit showed a thick cuticle, laticifers, epicarp parenchyma, mesocarp endocarp and calcium oxalate crystals.[19,20.21]

Fig. 3: Layout of the *C. papaya* fruit with longitudinal section showing the fruit seeds.

(vi) *Seeds:* Generally, papaya plant grown up from the seeds. Plant seeds are blackish to brownish in colour, straight embryo, and fleshy endosperm and cotyledons are oblong and flat. The internal cavity of the fruit contains numerous black seeds, coated with a mucilaginous substance. The seeds are edible, having a sharp, spicy taste including antibacterial properties protect from the toxin-induced kidney failure.[22]

Fig. 4: Seeds of *C. papaya.*

2.1.4. Local Names: Arabic(fafay, babaya); Bengali(pappaiya, papaya); Burmese(thimbaw); Creole (papayer, papaya); Filipino(papaya, lapaya, kapaya); French (papiller, papaya, papayer); German(papaya, melonenbraum); Hindi(papaya papeeta); Indonesian (gedang, papaya); Javanese(kates); Khmer (lhong, doeum lahong); Lao(Sino-Tibetan) (houng); Luganda (papaali); Malay (papaya, betek, ketelah, kepaya); Sinhala (pepol); Spanish(figuera del monte, fruta bomba, papapa, papaita, lechosa); Swahili (mpapai); Tamil (pappali, pappayi); English (bisexual pawpaw, pawpaw tree, melon tree, papaya); Thai (ma kuai thet, malakor, loko); Tigrina(papaya); Vietnamese(du du).[23,24,25]

2.1.5. Chemical Constituent: The different parts of papaya such as fruit, fruit juice, seed, root, leaves, bark, latex contain various chemical constituents, which are shown as below

- Fruits- Protein, fat, fiber, carbohydrates, minerals: calcium, iron, vitamin C, thiamine, rivoflavin, niacin, and carotene, amino acid, citric acid and malic acid (green fruits), volatile compounds: benzylisothiocynate, cis and trans 2,6-dimethyl-3,6 epoxy octen-2-ol, alkaloids, carpaine.
- Juice- N-butyric, n-hexanoic and n-octanoic acids; lipids; myristic acid, palmitic acid, palmitic acid, stearic acid, linolenic acid, oleic acid.
- Seed- Fatty acids, crude protein, crude fibre, papaya oil, carpaine, carcin, glucotropacolin and an enzyme myrosin.
- Roots- Carposides and enzyme myrossin.
- Leaves- Alkaloids carpain, pseudocarpain, dehydrocarpine I and II, choline, vitamin C and E, carposide.
- Bark- Glucose, Fructose, sucrose, xylitol, beta-sitosterol.
- Latex- Papain, chemopapain, peptidase A and B, lysozymes.

***Table 1: Carica papaya* is a pack of enzymes.[26,27]**

PHYTOCONSTITUENTS	***Carica papaya* PART**
Enzyme: Papain, chymopapain	Unripe fruit
Carotenoid: B carotene, crytoxanthine	Fruits
Carposide	Roots
Glucosinolates: Benzyl isothiocynate, papaya oil	Seeds
Minerals: Ca, K, Mg, Zn, Mn, Fe	Shoots, leaves
Monoterpenoids: Linalool, 4-terpinol	Fruits
Flavanoids: Myrecetin, kaemferol	Shoots
Alkaloids: Carpinine, carpine, vitamin C and E	Leaves

The compound responsible for various properties and therapeutic uses of *Carica papaya* leaves are.[28,29]

Compounds	Properties
Tanins	Astringent properties, wound healing properties
Saponins	Precipitates and coagulates red blood cells, hemolytic activity, cholesterol binding properties and expectorant action.
Alkaloids (carpaine, pseudocarpaine, piperideine alkaloids like dehydrocarpaie I and II)	Basic natural products, analgesic, antispasmodic, and anti-bacterial properties, antimalarial (contains quinine)
Flavanoids	Antiallergic, anti-inflammatory, treatment of capillary fragility, free radical scavenger, platelet aggregation, microbes, ulcers, hepatoxins, viruses, and anti-cancer or tumor. Flavonoids are potent water-soluble antioxidants and free radical scavengers which prevent oxidative cell damage, have strong anti-cancer activity and protect against the different levels of carcinogenesis.
Cardiac glycoside	Digitalis like action on heart
Amino acid	Anti-sicking property as it protects cell from oxidative damage (a reason for sickle cell crises)

Table 2: Parts of *Carica papaya* Plant With Ethnomedical USES.[30,31-39]

S. No.	Parts	Ethnomedical uses	Type of recipe
1	Leaves	a. To treat a tumour, weakening of heart, high blood pressure, malaria dendue, jaundice, obesity, overweight, chronic indigestion, arteriosclerosis, urinary infection, gonorrhea, abortion, fever, asthma, bacterial & viral diseases. b. Anti-anemic agent and body cleanser. c. Used as tonic & blood purifier	Decoction of fresh leaves. Yellow and brown leaves decoction. Decoction of dried leaves.
2	Flower	a. Jaundice, emmenagogue, febrifuge, and pectoral properties.	Decoction of dried flowers
3	Fruits	a. To treat ulcer, impotency. b. Laxative, void heart attack or stroke.	Unripe fruit ripe fruit.
4	Seeds	a. Cures piles, typhoid, intestinal worms, poisoning related disorders, sickle cell diseases, clear nasal congestion, detoxify the liver, protected kidneys from the toxin. b. To shown anthelmintic bacterial anti-amoebic activities. c. Bleeding piles and enlarged liver and pectoral properties.	Seeds powder. Decoction of seeds extract. Decoction of seed juice.
5	Latex	Anthelmintic relieves a whooping cough, dyspepsia, burns pain, bleeding haemorrhoids, stomachic and diarrhoea	Crude latex decoction
6	Roots	Syphilis (infusion), bronchitis, cough, respiratory diseases, renal, urinary bladder problem, effective purgative & analgesia	Root sap or decoction.
7	Stem bark	Sexually transmitted diseases (STD), jaundice, sore teeth, anti-fungal, anti-haemolytic activities	Decoction of stem bark

Table-3: Leading phytochemicals isolated and characterised from *C. papaya* plant.[40,41-46]

S. no.	Plant Parts	Phytochemical Constituents (structures)
1	Leaves	Carpaine Anthraquinone Ferulic acid Caffeic acid *p*-Coumaric acid *n*- Hexadecanoic acid (palmitic acid)
2	Fruit	Benzyl-β-D-glucoside Benzyl isothiocyanate β-Cryptoxanthin β-Carotene Butanoic acid (butyric acid) *cis*-Linalool oxide *trans*-Linalool oxide Caricapinoside
3	Seeds	Benzyl isothiocyanate Linoleic acid Oleic acid Palmitic acid Carpaine Benzyl glucosinolate Benzylthiourea Hentriacontane β-Sistosterol 1,2,3,4-Tetrahydropyridin-3-yl-octanoate
4	Bark	β-Sistosterol
5	Juice	*n*-Butyric acid *n*-Octanoic acid Linoleic acid Myristic acid Palmitic acid Stearic acid Oleic acid Vaccenic acid *n*-Hexanoic acid

Table 4: Phytonutrients content in leaves, unripe fruit and ripe fruits of *C. papaya* plant.

S. No.	Phytonutrients	Plant parts (per 100g)		
		Leaves	Unripe Fruits	Ripe Fruit
1	Calories	79 cal.	26 cal	46 cal
2	Vitamin A	18,250 SI	50 SI	365 SI
3	Vitamin B_1	0.15 mg	0.02 mg	0.04 mg
4	Vitamin C	140 mg	19 mg	78 mg
5	Calcium	353 mg	50 mg	23 mg
6	Hydrate charcoal	11.9 g	4.9 g	12.2 g
7	Phosphorus	0.0g	16 mg	12 mg
8	Iron	0.8 mg	0.4 mg	1.7 mg
9	Protein	8.0 g	2.1 g	0.5 mg
10	Water	75.4 g	92.4 g	86.7 g

2.1.6. Ecology: C. papaya grows satisfactorily in a wide range of areas from the equatorial tropics to temperate latitudes. However, it must be grown in warm, sunny sites sheltered from wind; preferably below 1500 m. Strong winds are detrimental, particularly on soils that cannot make up for large transpiration loss. C. papaya is not frost hardy; exposure to frost or cold wind usually results in leaf damage and subsequent death of the tree. Roots are very sensitive to waterlogging, and even short periods of flooding can kill the plant.

2.1.7. Biophysical Limits: Altitude: 0-1 600 m, mean annual temperature: (15) 21-33 deg. C, Mean annual rainfall: 1000-2000 mm.

2.1.8. Soil Type: A well-drained, permeable, well aerated, root-knot nematode free, fertile loamy soil, preferably rich in organic matter with neutral reaction (pH 6-7) is ideal for papaya growth.

2.1.9. Geographical Distribution: Papaya exotic ranges are United States of America, Mexico, Costa Rica; while natives ranges are Grenada, Colombia, Democratic Republic of Congo, Nicaragua, Jamaica, Australia, Bahamas, Malaysia, Eritrea, Fiji, Ecuador, Guadeloupe, Netherlands Antilles, Dominica, Barbados, Brazil, Kenya, Indonesia, Martinique, India, Montserrat, Singapore, Dominican Republic, Cambodia, Cameroon, Philippines, Peru, Puerto Rico, Antigua and Barbuda, New Zealand, Cuba, Sri Lanka, Solomon Island, Uganda, Chile, Haiti, Laos, St Lucia, Nigeria, Papua New Guinea, Myanmar, Tonga, Samoa, Sudan, South Africa, Thailand.

Papaya native ranges are Costa Rica, Mexico, US.[9]

3. **Biochemical and Chemical Analysis**

The detailed and extensive biochemical and chemical investigations of *C. papaya* have been examined and characterized the large number of constituents in different parts. The biochemical analysis of *C. papaya* dried leaves analysed for Ca2+, Mg2+, Na+, K+, Cl^- and Li+, and results indicate that leaves contained high potential constituents which curried the number of diseases,[17] and the fruit showed the existence of K+ (223 mg/100 g) amount, besides that Na+, Ca2+, P, Zn2+, Fe2+, Cu2+, Mn2+, and Mg2+ in a considerable quantity. The energy value of papaya fruit is 200 kJ.100 g-1, keeping this view that sucrose value contained (48.3 g), glucose (29.8g) and fructose (21.9 g), respectively.[47] Study of Saeed *et al.*[48] publicized that *C. papaya* fruit pulp possess the minerals such as Fe3+, Ca2+, Na+, K+, P, Zn2+, Cu2+, Mg2+, Mn2+, Co2+, while Cd2+ and Pb3+ were absent. However, fruit pulp contained the chemical compositions such as starch (43.28%), sugars (15.15%), crude protein (13.63%), moisture content (10.65%), fiber (1.88%) and fat (1.29%). In view of chemical examination, the literature reveals the presence of altogether 166 volatile and non-volatile chemical constituents in different parts of *C. papaya* plant. Resulted, isolated and identified constituents mainly belong to the terpenoids, flavonoids, alkaloid, carotenoids, vitamins and glycosides class. Different parts of papaya plant such as roots, shoots, heartwood, bark, leaves, fruits, fruits latex, juice and seeds contained various compounds associated with different chemical class presented in Table **2**. Table **3** demonstrate the leading isolated and characterized constituents from different parts of papaya plant. Investigation of Zunjar *et al.*[49] revealed that phenolic compounds present in different plant extracts were separated and identified as 5-hydroxy feruloyl quinic acid, acetyl *p*-coumaryl quinic acid, quercetin-3-*O*-rhamnoside, syringic acid hexoside, 5-hydroxy caffeic quinic acid, peonidin-3-*O*glucoside, sinapic acid-*O*-hexoside, cyaniding-3-*O*-glucose and methyl feruloyl glycoside by LC-MS technique. Akhila and Vijayalakshmi analysed the phytochemical profile of young leaves of papaya extract using LC-MS, and identified 21 chemical constituents belonging to the alkaloids, phenolics, flavonoids and amino acids.[50] Another study of Julianti *et al*.[51] on papaya plant extract examined by HPLC-based activity profiling exhibit the antiplasmodial activity. Resulted, fractionated hexane extract contains the total nine compounds, four are flavonols and remaining five are alkaloids. Esti *et al*.[52] analysed papain from ripe fruit and from papaya latex was characterized, in comparison with stem bromelain, under wine-like conditions, with the aim to evaluate their applicability for white wine stabilization. The resulted papain from latex showed a significantly higher and stable catalytic activity in fruit papain and stem bromelain, retaining after 7 days, about 50% of its initial activity. Sancho *et al.*[53] conducted the qualitative and quantitative analysis of major phytochemicals using HPLC-MS. Conclusively, analysis demonstrated that papaya fruit flesh and skin contain vitamin C, phenols, and carotenoids which are bioactive compounds that protect the body from oxidative stress, reducing the risk of cardiovascular diseases and some types of cancer.[52] Burdick.[54] in 1971, analyzed the presence of carpaine , a major alkaloid in all of the green parts of papaya plant and as well as in the seeds. Phytochemical analysis of the ethyl acetate fraction of the methanol extract of the unripe fruit extract of *C. papaya* led to the isolation and identification of a new anti-sickling agent named as caricapinoside (IUPAC Name: 8(2-*O*-β- D-4, 5-anhydroglucitoyl 1→2glucopyranosyl carbonyl) dibenzo [b,e].[1,4] dioxine-2-carboxylic acid). The structure was elucidated by the application of MS, 1D, and 2D-NMR spectroscopic analyses and by comparison with literature data.[55-56] Zunjar and his co-worker.[57] examined the bioactive compound carpaine that was isolated and purified by chromatographic methods and its structure was confirmed by single crystal X-ray diffraction. The results showed that alkaloid-based carpaine has good biological activity. Investigation of volatile compounds analyzed by Canini *et al.*[58] showed the quantitative presence of phenolic acids as the main compound, while chlorogenic acid found was in trace amounts identified by GC-MS. The quantities detected were 0.25 $mg.g^{-1}$ (dry leaf) for caffeic acid, 0.33 $mg.g^{-1}$ for *p*-coumaric acid and 0.11 $mg.g^{-1}$ for protocatechuic acid. However, kaempferol and quercetin were 0.03 and 0.04 $mg.g^{-1}$, respectively. The study by Vuong *et al.*[59] analyzed the optimized conditions for the extraction of saponins from papaya leaves and assessed their antioxidant and antipancreatic cancer activity. Optimization was achieved using response surface methodology. Saponins and total phenolic compounds were measured for free radical scavenging, ion reducing capacity, and anti-pancreatic cancer activity. Besides that, Pino *et al.*[60] in their study reported the presence of 166 volatile compounds that were identified in fruit aroma analyzed by GC/GC-MS, which showed methyl butanoate, ethyl butanoate and 3-methyl-1-butanol as the major

components. Fairly, wide ranges of different types of compounds were detected belonging to the esters, alcohols, aldehydes, ketones, terpenoids, *etc*. Another GC-MS study by Upgade and Bhaskar.[61] from the down South Indian region identified 24 volatile compounds and *n*-hexadecanoic acid was found to be in a higher percentage (14.73%). Furthermore, a study on plant seed essential oil was conducted using GCMS, that represented benzyl isothiocyanate (99·36%) as a major constituent.[62] Nakamura *et al.*[63] conducted a study on papaya seed and edible pulp and separated the contents of benzyl isothiocyanate and corresponding to glucosinolate as benzyl glucosinolate or glucotropaeolin identified and quantified. In continuation, Tang.[64] described that macerated papaya seeds and pulp contain benzyl isothiocyanate, produced by the enzymatic hydrolysis of benzyl glucosinolate by thioglucosidase. Moreover, the study by Barroso *et al.*[40] investigated the composition of papaya seed oil extracted with supercritical fluid and analysed by GC-MS and NMR. The study evaluated and efficated the presence of benzyl isothiocyanate.

4. Pharmacological Activities

- **Antithrombocytopenic Activities**: Carpaine is reported to exhibit potent activity in sustaining platelet counts up to $555.50 \pm 85.17 \times 10^9$/L on busulfan induced thrombocytopenic Wistar rats exhibiting no acute toxicity. In order to determine the platelet count increasing potency *Carica papaya* L. leaf extract a study was carried in a murine model. Results were very significant as increased platelet and RBC count in the test group compared to that of controls was observed. Starting from day 3 ($3.4\pm 0.18 \times 10^5$/mil) the platelet count increased to almost fourfold higher at day 21 (11.3×10^5/mil) in test group which was almost more than double in comparison to control. The RBC also increased significantly. Hence, through this study, the conclusion was made to appreciate the recommendation of *Carica papaya* L. leaf extract to boost thrombopoiesis and erythropoiesis in humans and animals where these cell lineages have been compromised.[66] Regarding the role of *Carica papaya* L. leaves in a patient suffering from dengue fever, a case study has also been discussed. The 45-year-old patient suffering from dengue fever was administered with 25 ml aqueous extract of *Carica papaya* L. leaf twice a day for 5 consecutive days. Pre and post-treatment blood samples were analysed for platelet count, WBC, and neutrophils. PLT count increased from 55×10^3 µl to 168×10^3 µl. Hence threefold increase in PLT, twofold in WBC and 70% increase in neutrophils were observed. So, it was concluded from patients feeling and blood reports that *Carica papaya* L. leaves aqueous extract exhibit potential activity against dengue fever.
- **Analgetic Activity:** The three extracts of leaves of *Carica papaya* L. have been evaluated for their analgesic activity in mice model having acetic acid-induced pain (Siegmund method). These three extracts (*n*-hexane, ethyl acetate, and ethanol extracts) exhibited significant analgesic activity at all the three dose levels (0.175, 0.35 and 0.70 mg/kg bw orally) when compared to aspirin (taken as the standard drug).
- **Antiplasmodial Activity:** Leaf extracts of *Carica papaya* L. exhibit high antiplasmodial activity with low cytotoxicity. This activity is shown by three alkaloids. Compounds were tested for bioactivity *in-vitro* against four parasites (*Trypanosom brucei rhodesiense*, *Trypanosoma cruzi*, *Leishmania donovani*, and *Plasmodium falciparum*), and in the Plasmodium berghei mouse model. This study concludes that the antiplasmodial activity of papaya leaves was confirmed and might be linked to alkaloids. Among these alkaloids, carpaine was highly active and selective *in-vitro*.
- **Antitumor and Immunomodulatory Activity:** A study has been completed to assess the antitumor and immunomodulatory activity of *Carica papaya* L. leaf aqueous extract. In this study, the effects of *Carica papaya* L. extract on the proliferative response of tumour cell lines were observed. Through [3H] thymidine incorporation the cytotoxic activities of human peripheral blood mononuclear cells (PBMC) were also assessed. Results were indicative of significant growth inhibitory activity of this extract on tumour cell lines. As far as PBMC concerned the leaf extract reduced the production of IL-2 and IL-4. The expression of immunomodulatory genes was enhanced by this extract. Index markers of immunomodulatory effects were also found. Conclusively this study revealed that the *Carica papaya* L. leaf extract may mediate a Th-1 type shift in the human immune system. The extract may potentially provide a link for treatment of carcinoma, allergic disorders and serve as immuno-modulator in human. The antiproliferative response of *Carica papaya* L. leaf juice has been assessed on a range of cell lines representing benign hyperplasia, tumorigenic and normal cells of prostate origin. A time course analysis of before and after *in-vitro* digestion and of the molecular weight-based fraction of leaf juice showed significant antiproliferative response. The cytotoxic effect of medium polarity fraction of leaf juice (0.03-0.003 mg/mL) was seen on all prostate cells excepting of the normal cells. The medium polar fraction has also been found to inhibit migration and adhesion of metastatic PC-3 cells. The S phase cell cycle arrest and apoptosis were thought to be a possible mechanism for these activities on the basis of flow cytometric study. Hence this study reports about the antiproliferative and antimetastatic properties of *Carica papaya* L. leaf extract against prostatic diseases including PCa. Proliferative Activity of Saponin-Reducing *Carica papaya* L. leaves extracts on human lung fibroblast cell (IMR90) has also been studied.
- **Antidiabetic Activity:** A study regarding the assessment of antidiabetic activity of *Carica papaya* L. leaf extract was carried out in an experimental rat model. The chloroform extract which consists steroid and quinines was administered at various dose levels in streptozotocin-induced diabetic and non-diabetic rats. After 20 days of treatment, the sacrifice was done and

the biochemical study was carried out. There was a significant reduction in serum glucose, trans-aminases and triglyceride observed in diabetic rats after the administration of *Carica papaya* L. leaf chloroform extract. This study concludes the potential activity of *C. papaya* leaf to treat the symptoms of diabetic patients.

- **Antimicrobial activity:** In order to investigate the antimicrobial activity of different extracts of leaves of *Carica papaya* L it was observed that the ethanol, methanol, ethyl acetate, acetone, chloroform, petroleum ether, hexane and aqueous extract showed activity against bacteria and fungus. Among these extracts, the chloroform extract was found more active against *Micrococcus luteus* bacteria whereas acetone extract was more active against *Candida albicans* fungus. Hence it was concluded that extracts of *Carica papaya* L. leaves possess antibacterial and antifungal activity against several human pathogenic bacterias and fungi. The 20% aqueous and alcoholic extracts of leaf were screened for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (George *et al*., 1947). Carpine isolated from plant exhibited slight inhibitory activity against *M. tuberculosis* H37Rv. The leaf extract inhibited the growth of ring worm causing fungi, *Epidermophyton floccosum* (52.37%), *Trichophyton mentagrophytes* (24.3%) and *Microsporum gypseum* (20.32%).[79] The aqueous extract of leaves showed 30 and 40 percent mycelia inhibition of *Aspergillus flavns* and A versicolor respectively and mycelia inhibition of skin disease causing fungi *Trichophyton rubrum* and *Epidermophyton floccosum*. The aqueous leaf extract in another study showed growth and spore production of three fungal pathogens of rice, *Pyricularia oryzae, Drechslera oruzae* and *Corticium sasakii*. The three phytopathogenic fungi: *Colletotrichum gloeosporioides*, *R. stolonifer* and *Fusarium spp.* were subjected for assessment of the antifungal activity of *Carica papaya* L. leaf and seed extracts (Seed ripe extract, Seed unripe extract). Among them, the broadest action spectrum was exhibited by the leaf extract. The MIC 50 (minimum inhibitory concentration 50) for the leaf extract was found to be >10 mg ml^{-1} for *C. gloeosporioides* and 0.625 mg $ml^{-1}$for *Fusarium spp.* Approximately 20% mycelial growth inhibition was observed in both. Hence the ethanolic extracts from leaves of *Carica papaya* L. may be taken as a potential antifungal agent having the source of secondary metabolites. The antifungal activity of aqueous extracts of leaves has also been found against *Colletotrichum gloeosporioides*. The antimalarial activity of *Carica papaya* L. leaves extract has also been established through a study. During this study, the activity of ethanol extract on blood stages of CQ sensitive and CQ resistant strains against *Plasmodium falciparum* (target species) was assessed. The highest larval mortality was observed in first to fourth instars larvae and pupae were evaluated. The plant extract exhibited moderate to good antiparasitic effects. In four concentrations the extract showed promising inhibitory activity against the CQ sensitive strain and in CQ resistant to *P. falciparum*. The result concluded that the *Carica papaya* L. leaf ethanol extract has the potential to be used as an ideal eco-friendly approach for the control of vector mosquitoes 48. Leaves are reported to support the growth and development of the larvae of the pest Diacrisia oblique. An alcoholic extract of the leaves was found to inhibit the growth of *Neurospora crassa* whereas the extracts of leaves and fruits show antibacterial activity against several bacteria. The alcoholic extract of the leaves also possesses molluscicidal activity against *Bulinus globosus*.
- **Anthelmintic Activity:** After performing epidemiological survey for relevance of guinea worm infection it was found to be 2.85% and more common in males. A paste of leaves of the plant with opium and common salt applied for 3 days was helpful in relief of symptoms and easy extraction of worms from the body. The leaf extract of papaya showed light mortality against meloidogyne incognito and *Rotylenchulus reniformis* nematodes.
- **Central and Cardiovascular Effects:** The alcoholic extract of leaves (10 mg/kg ip) showed dose dependent sedative effect in male rats. The extract (5 mg/kg ip) induced central muscle relaxation. The extract at dose of 50 mg/kg ip completely protected the rats against pentylene-tetrazol induced seizures, while 50 percent protection was observed with dose of 5 mg/kg ip. The extract at dose of 100 and 200 mg/kg ip showed 100% protection against maximum electroshock induced convulsions. The behavioural effects of extract were associated with an initial desynchronization of EEG and increased activity of EMG. The leaf extract showed cholinesterase activity. The major alkaloid found in leaves carpaine has been reported for cardiovascular effects using Wistar rats. Increased dosage of carpaine showed progressive decrease in systolic, diastolic, and mean arterial blood pressure. Atropine sulphate (1 mg/kg) or propranolol hydrochloride (8 mg/kg) also did not change the circulatory response to carpaine. Capaine in 2 mg/kg dosage is reported to reduce cardiac output, stroke volume, stroke work, and cardiac power, but has no effect on total peripheral resistance. So, it can be said that caprine affects the myocardium.
- **The Anti-inflammatory Activity:** The ethanolic extract of *Carica papaya* L. leaves have been also investigated for its anti-inflammatory activity in rats using paw oedema (carrageenan test), formaldehyde induced arthritis models and cotton pellet granuloma. Experimental animals were treated with 25 - 200 mg/Kg (orally) of the extracts or saline (control group) and the reference group was given indomethacin 5 mg/Kg bw. The ulcerogenic activity of the extract was also investigated. It was observed that there was a significant ($p<0.05$) reduction in paw oedema in the carrageenan test. A significant reduction in the amount of formation of granuloma (from 0.58 ± 0.07 to 0.22 ± 0.03 g.) was also observed. The extract exhibited a significant reduction in persistent oedema from the 4^{th} day to the 10th day of the investigation was observed in formaldehyde arthritis model. Slight mucosal irritation has also been seen at high doses of extract. Conclusively

the anti-inflammatory activity of *Carica papaya* L. leaves has been established.

- **Nephroprotective Activity**: A study dealing with nephrotoxicity of Pb (II) and its amelioration through *Carica papaya* L. leaves powder has been done in experimental rats. In Pb (II) ions 1.000 mg/L i.p administered rats experimental rats the increased levels of serum biochemical parameters and oxidative stress including SGPT, SGOT, urea, creatinine, and malondialdehyde were seen. Whereas pre-treatment with papaya leaves powder reduced the levels of SGPT, SGOT, urea, creatinine, and malondialdehyde significantly, compared to Pb (II) treated group only. Pb (II) exposure induced severe necrosis of kidney cells and swelling of tubular cells whereas pre-treatment with C. papaya leaves powder reduced the damage effects. It has been concluded from this study that pre-treatment with C. papaya leaves powder antidote to serve preventive effects against Pb (II) induced nephrotoxicity in experimental rats.
- **Wound Healing Activity:** The wound healing competence of *Carica papaya* L. leaves powder has been evaluated in an experimental study. Here the propylene glycol was taken as control check and the rate of wound closure; wound contraction, fibroblast cell count, and histology of granulation tissue were the assessment criteria. The insignificant wound contraction was noticed. But significant wound closure and fibroblast cell count were observed in *Carica papaya* L. leaves powder treated group. As a conclusive remark, this study provides a scientific background for leaves of Carica *papaya* L. having remarkable wound healing potential. Due to platelet increasing property of the leaves of *Carica papaya* L., various supplements having it as a content are nowadays being marketed rapidly. On average reviews indicate that various manufacturing techniques used in several marketed C. papaya leaves formulations may degrade the phytochemical which will suppress the beneficial effects of this component. Hence the traditional method of its presentation should be made in practice but it also needs some more updations.
- **Insecticidal and Larvicidal activity:** Konno found that papain, a cysteine protease in latex of Papaya tree (*Carica papaya*, Caricaceae), is a crucial factor in the defence of the papaya tree against lepidopteran larvae such as oligophagous *Samia ricini* (Saturniidae) and two notorious poluphagous pests, *Mamesta brassicae* (Noctuidae) and *Spodoptera litura* (Noctuidae). Leaves of number of laticiferous plants, including papaya and wild fig, *Ficus virgata* (Moraceae), showed strong toxicity and growth inhibition against lepidopteran larvae; though no toxic apparent factors from these species have been reported. When the latex was washed off, the leaves of the lactiferous plant lost toxicity. Latexes of both papaya and the wild fig were rich in cysteine protease activity. E-64, a cysteine protease-specific inhibitor, completely deprived the toxicity of leaves when painted on the surface of papaya and fig leaves. Cysteine protease, such as papain, ficin and bromelain, all showed toxicity. The result suggests that plant latex and the proteins in it, cysteine proteases in particular, provide plants with a general defence mechanism against herbivorous insects. Latex from unripe fruits of *Carica papaya* shows mosquito larvicidal properties.
- **Molluscicidal activity:** *Carica papaya* seed and latex are potential source of botanical molluscicides. *Carica papaya* lyophilised latex is more effective than seeds against *L. acuminata.* The molluscicidal activity of *Carica papaya* seed and latex may be due to the presence of papain. Papain occurs in all parts of the tree except the root. Lyophilised latex from the skin of unripe fruits and pure papain shows about similar toxicity against *L. acuminata* at all exposure period whereas column purified fraction of *Carica papaya* seed shows lower toxicity than lyophilised latex. It is due to the presence of high concentration of papain in *Carica papaya* latex than seed.[65]

5. Toxicity Studies

Available literature reveals no adverse or toxic effects of papaya except for consumption during pregnancy. One study in 2013, suggested that semi-ripe or unripe papaya is unsafe in pregnancy due to high latex content although ripe papaya is safe to eat. Papaya that is unripe contains a latex substance that may cause contractions of the uterus. Papaya or papaya enzymes are sometimes recommended for soothing indigestion, which is common during pregnancy. Although a fully ripe papaya is not thought to be a problem, it is not known for sure if papaya is completely safe during pregnancy. Ismail and his co-workers analysed the sub chronic toxicity effect of the leaf extract of *Carica papaya* in Sprague Dawley (SD) rats. In conclusion, the results suggested that daily oral administration of rats with plant leaf extract for 13 weeks at a dose of up to fourteen times the levels employed in traditional medicine practice did not cause any significant toxic effect.

CONCLUSION

Human have long been using plants as dietary supplements as well as in the treatment of various diseases. Currently many plants are being annually investigated around the world in terms of therapeutic properties. *Carica papaya* plant is used as one of the important traditional plants. The present review systematically analysed the ethnomedicinal uses, phytochemistry and pharmacological activities of *Carica papaya.* The pharmacological research clearly studies that papaya plant parts possess powerful antibacterial, antifungal, anxiolytic and relaxing, hypoglycemic, mosquito larvicidal, anti-cancer, anti-inflammatory, antithrombocytopenic, antihypertensive effect, free radical scavenging, anti- HIV, antihyperlipidemic, anti-sickling, antifertility, antihelmintic, hepatotoxicity, anti-intestinal parasite, anti-ulcer, anti-tubercular, wound healing and nephroprotective activities. The plant exhibited limited toxicological information, but traditionally detailed toxicological investigations are still required to confirm their safe use in human beings. The

pharmacological studies are still insufficient to validate the traditional uses and realise their possible interaction mechanism. Further research should be investigated to expand medicinal and industrial applications of papaya plant.

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