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Phytomedicinal Chemistry and Pharmacognostic Value of *Carica papaya* L., Leaf

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***Carica papaya* L. leaves contain potent secondary metabolites, such as alkaloids, phenolics, flavonoids, saponin, tannins, glycosides, and other crucial phytochemicals. The leaf is a source of several vitamins conferring it an anti-oxidant property. The leaf is also rich in dietary minerals and essential fatty acid. The fresh leaf extracts are used as a possible remedy for dengue viral infections in Asian countries. This review compiles the knowledge about the physiochemicals, phytochemicals, and biochemicals of *Carica papaya* L. leaves. This includes the identified chemical structures of alkaloids, phenolic, flavonoids, linoleic, and linolenicacids. Additionally, it covers up-to-date information on in-vitro anti-cancer and anti-gout and in-vivo anti-microbial properties, anti-oxidant, anti-sickling, hepatoprotective, hypolipidemic, hypoglycemic, and anti-gout effects.**

Keywords: Fresh leaves, Phytochemicals, Dietary minerals, Vitamins, Anti-oxidant and bio-activity.

Carica papaya L. is commonly known as pawpaw tree. It is a nutraceutical plant. All plant parts have vital immunostimulative and antioxidant effects. The Indian traditional medicinal system prescribes its leaf extract to control dengue viral infections. In other Asian countries, it is also used as a remedy for the same[1]. The leaf contains a mixture of chemicals, which can be described broadly as physiochemical, phytochemicals and biochemicals.

Physiochemicals

The physiochemical nature of the dried leaf has following contents in % w/w: Total Ash (17.4), Acid insoluble ash (13.3), Water soluble ash (3.25), Sulfated ash (27.05), Ethanol soluble extractive (8.4), Water-soluble extractive (17.7), Moisture content (5.70), Crude fat (2.8+0.3), Crude fiber (23+0.1), Crude protein (29.5+0.1), and Carbohydrate (35.9+0.3)[2].

Phytochemicals

It contains alkaloids, phenols, flavonoids, saponin, tannins, and glycosides. They could be described as follows:

Alkaloids

The significant phytochemicals of *Carica papaya* L. leave are bitter tasting alkaloids (1,300–1,500 ppm). It is in the form of carpaine (150–4,000 ppm) (Figure 1), pseudocarpaines, macrocyclic piperidine, dehydrocarpaine I and II (1000 ppm), and nicotine (102.8 ppm)[3].

Carpaine

Its molecular formula is $C_{28}H_{50}N_2O_4$ (Figure 1), which accounts for a molecular mass of 478.70g/Mol. It is used to reduce cardiovascular problems, act as amebicide and was found to inhibit *Mycobacterium tuberculosis* under in-vitro assay condition[4].

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Phenolic acids

The leaf contains phenolic acids such as protocatechuic acid (Figure 2), coumaric acids, caffeic acid (Figur3), chlorogenic acid, and coumarin (Figure 4)[5,2]. These are known as esterified phenolic compounds[6]. These compounds are linked with malic acid by an ester linkage.

Protocatechuic acid

It is 3,4-dihydroxybenzoic acid($C_7H_6O_4$) (Figure 2). It is a type of antioxidant polyphenol.

***p, m, o*-Coumaricacids and caffeicacid**

Coumaric acids are hydroxyl derivatives of cinnamic acid (Figure 3). *p*-Coumaric acids possess anti-oxidant property, which results in the inhibition of the low density lipoprotein oxidation[7].

p-Coumaric acid (3) R_1=R_3=R_4=H, R_2=OH
m-Coumaric acid (1a) R_1=OH, R_2=R_3=R_4=H
o-Coumaric acid (1b) R_1=R_2=R_3=H, R_4=OH
Caffeic acid (5) R_1=R_4=H, R_2=R_3=OH

Chlorogenic acid

It is a polyphenol compound, belongs to the family of esters of hydroxyl cinnamic acids, and has antioxidant effects.The molecular formula is $C_{16}H_{18}O_9$ (Figure 4). Molecular mass is 354.31g mol^{-1}. This can form an ester linkage with caffeic acid and quinic acid.

Coumarin

Its molecular formula is $C_{11}H_{10}O_4$ (Figure 5) and the molecular weight is 206.19gmol–1.

Flavonoids

Flavonols (0–2,000 ppm) are the types of flavonoids. The leaf contains kaempferol and quercetin and other glycosylated flavonols such as manghaslin, clitorin, nicotiflorin, and rutin[6].

Kaempferol and Quercetin

Kaempferol ($C_{15}H_{10}O_6$) and quercetin ($C_{15}H_{10}O_7$) (Figure 6) are main flavanols present in *Carica papaya* L. leaves.

Kaempferol (6) R1=R2=R3=R4=OH, R5=H
Quercetin (7) R1=R2=R3=R4=R5=OH

Other Phytochemicals

Tannins (5,000–6,000 ppm), phytosterol, cardiacglycosides, saponin glycosides, iridoids, anthraquinones, and organic acids such as malic acid, minor quantities of various malic acid derivatives and quinicacid are present in the leaves[6].

Biochemicals

Vitamins

The extracts are very rich in the anti-oxidant vitamins such as vitamin A (7873.4 mg/

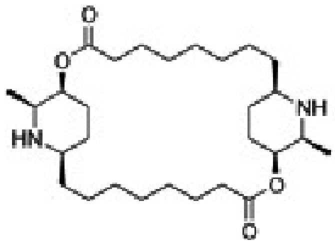

Fig. 1. Structure of carpaine (-13, 26-dimethyl-2, 15-dioxa-12, 25-diazatricyclotriacontane-3, 16-dione)

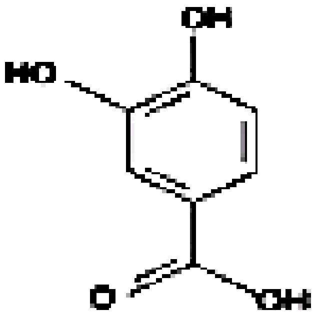

Fig. 2. Structure of protocatechuic acid[5]

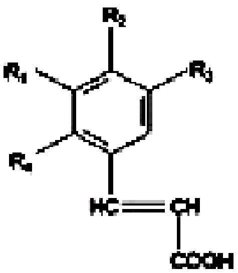

Fig. 3. Structure of coumaric and caffeic acids[5]

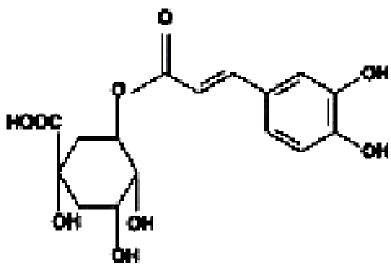

Fig. 4. Structure of chlorogenic acids[5]

kg), folic acid (2.4mg/kg), vitamin B_{12} (2.8 mg/kg), and vitamin C (89.0 mg/kg)[8].

Minerals

The leaf contains Ca (8612.50 mg/Kg), Mg (67.75mg/Kg), Na (1782.00mg/Kg), K (2889.00 mg/Kg), Fe (90.50mg/Kg), Mn (9.50 mg/Kg)[9] and calcium oxalate. Other essential growth-promoting biochemicals are aminoacids such as proline and glutamine, enzymatic proteins such as α-amylase, β-amylase, and carbohydrate such as starch and cellulose.

Fatty acids

Linoleic (Figure 7) acid is an unsaturated omega-6 fatty acid. Linolenic acid (Figure 8) is an omega-3 fatty acid. These two compounds were found to show anti-malarial property in in-vitro biological assay conditions[10].

Pharmacognostics properties of the leaves

Antibacterial activity

The in-vitro activity against clinical pathogens such as *Klebsiella pneumonia, K.oxytocin*, *Enterococcus faecalis*, *Proteus mirabilis*[11], *Escherichia coli, Pseudomonas aeruginosa*[12], *Salmonella typhi*[13], *Salmonella paratyphi A*, *Shigella flexneri*[14], *Streptococcus pyogenes*, *Staphylococcus aureus, Bacillus subtilis,* and *Micrococcus luteus* has been detected in the leaf extract using agar and disk diffusion methods.

Anti-fungal activity

Carica papaya leave extracts have broad spectrum anti-fungal activity against *Aspergillus flavus, Candida albicans, Trichophyton rubrum, T. mentagrophytes*[15,16], *Cryptococcus neoformans, Candida tropicalis,* and *C. kefyr*[17]. *Colletotrichum gloeosporioides, Rhizopus stolonifer*, and *Fusarium* spp.[18] were also inhibited. The dry leaves can control the radial growth of mycelia of *Fusarium verticillioides*[19]. An aqueous extract controlled *Alternaria* sp., *Fusarium* sp., *Pestalotiopsis* sp., and *Rhizopus* sp.[20]

Anti-helminthic

The leaf extract at 5% concentration caused paralysis to the *Pheretima posthuma*, an Indian adult earthworm[21].The healthy leaves were used to cure ascariasis infection caused by a pathogenic form of *Ascaridia galli*[22]and *Ancylostoma caninum* in an *in-vivo* mouse animal model[23].

Antitumor activity

The leaf extracts can block the proliferative responses in cervical carcinoma, breast adenocarcinoma, hepatocellular carcinoma, lung adenocarcinoma, and pancreatic epithelial carcinoma. Apart from these, the leaf extracts also help in protecting the vascular systems and functional systems. It mediated Th1 type shift in human and acted as a potent anti-tumor agent in an in-vitro assay[24].

Immunostimulant activity during DENV viral infection

In a study, a leaf extract was orally administered to the patients to reduce the dengue viral symptoms. It increased the thrombocyte[25]

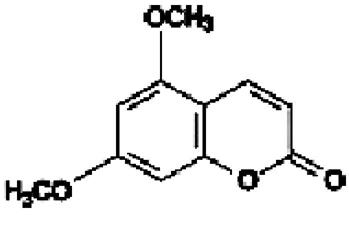

Fig. 5. Structure of 5, 7-dimethoxycoumarin[5]

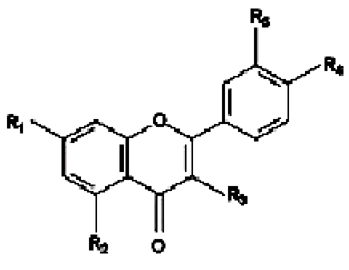

Fig. 6. Structure of kaempferol and Quercetin[5]

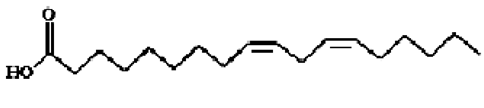

Fig. 7. Structure of linoleic acid (9, 12-octadecadienoic acid)

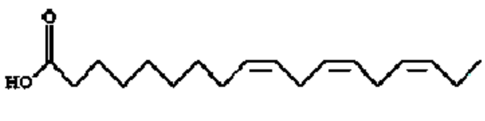

Fig. 8. Structure of linolenic acid (9, 12, 15-octadecatrienoic acid)

and platelet count in a mouse model infected with dengue virus. During the dengue viral infection, a crushed leaf extract was found to improve the body immunity[1].

Antioxidant effect

The leaf contains flavonoids (quercetin), phenols, tannins[26] and vitamins as the source of natural anti-oxidants. It has a potent hydroxy radical scavenging activity as found in some in-vitro conditions. It reduced acrylamide induced oxidative stress in stomach, liver, and kidney in an in-vivo animal model[27]. In an in-vitro assay, it scavenged1,1-diphenylehydrazyl (DPPH), 2,2-azinobis-(3-ethyle benzothiazoline-6-sulfonate) (ABTS), nitric oxide, superoxide, and lipid peroxide in rat brain and liver[28]. It inhibited nitric oxide and TNF-α production in in-vitro conditions[29]. It reduced alcohol-induced acute gastric damage and blood oxidative stress in *Sprague-Dawley* rats[30].

Hepatoprotective effect

The fresh leaves of the plant are traditionally used to cure liver associated problems. The leaf extracts help regularize liver enzyme during cirrhosis, hepatitis, and jaundice conditions. Carbon tetrachloride-induced liver damage was rectified by the aqueous extracts of *C. papaya* leave in in-vivo animal models[31]. The freeze-dried leaf extracts considerably protected hepatic cells from oxidative injury caused by *tert*-butyl hydroperoxide in in-vitro conditions. This chemical induced free radicals were scavenged by the anti-oxidants, phenolic and flavonoids, which are present in the leaves[32].

Anti-inflammatory effects

The leaves also act as analgesic. It can reduce carrageenan induced paw oedema, cotton pellets induced granuloma, and formaldehyde induced arthritis in in-vivo models[33]. It could reduce *Salmonella typhi* infection induced inflammation in albino rats[34].

Hypoglycemic effect

The extracts showed a significant hypoglycemic effect in in-vivo rat animal models[35], where diabetes was induced by streptozotocin[36].

Anti-sickling effect

The methanolic extracts of the leaves protected the membranes and reduced the sick cell formation under in-vitro conditions[37].

Anti-gout effect

Xanthine oxidase enzyme is primarily involved in gout. The dry leaf extracts are the source of xanthine oxidase inhibitors, which can act as an anti-gout agent[38].

Toxicity

The leaf extracts showed no pathological differentiation forms in the tissues and there were no contrary effects on the major functional organs like liver, kidney, and bone marrow by its aqueous extracts in in-vivo animal models.Thus the leaf extracts were found to be safe.

CONCLUSION

Carica papaya L. leaves contain chemicals that are multi-functional and of a great medicinal importance. Several in-vitro and in-vivo studies have approved its therapeutic efficacy and attainable mechanisms against newly emerging infectious diseases. However, further research is required for the development of potential anti-viral drugs from this leaf. The immunity development mechanisms during dengue viral infections have confirmed the anti-viral efficacy of *Carica papaya* L. leaves. The further exploration of dengue viral control mechanism is required and it may lead to the development of several anti-viral therapies. The toxicity level of pawpaw leaves is less and it doesnot hinder the medicinal beneficial effect. Therefore, the ethanomedicinal usage of these leaves is much safer than any other synthetic drugs.

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