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CARICA PAPAYA AS A SOURCE OF NATURAL MEDICINE AND ITS UTILIZATION IN SELECTED PHARMACEUTICAL APPLICATIONS

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ABSTRACT

This paper aims at reviewing *Carica papaya* as potential natural medicinal source. Several studies on methods used in extracting *Carica papaya* materials from different parts of the plant were highlighted. Extracts from different parts of *Carica papaya* plant have shown protective effects against many diseases such as intestinal worms infection and different types of wounds. Extracts also showed positive effects when used as antiparasitic, antiseptic, antiparasitic, antimicrobial, antiinflammatory, antihyperlipidemic, antihypertensive and antidiabetic. For instance, treating rats with extract prepared from *Carica papaya* leaves resulted in significant effects on wound healing. However, when rats supplemented with diet mixed with extract from the leaves of the plant it protected them against gastric damage. Moreover, extracts of both ripe and unripe fruit have proven antiulcer when examined in laboratory animals. However, studies on the effects of the types of the extracts on treatments of laboratory animals in selected pharmaceutical applications were also summarized. As a conclusion, *Carica papaya* is one of the most effective sources of natural medicine and widely used in pharmacological applications. It is used to treat several diseases such as tumors, nervous pain, asthma and wounds.

Keywords: *Carica papaya*, laboratory animals, pharmaceutical applications, wound healing

INTRODUCTION

Carica papaya is known with many other common names such as papaya, papaw, pawpaw, chichpu, mamao and melon tree [1]. It may cultivate for its young leaves, shoots and fruits which are cooked as a vegetable or for its ripe fruit which is well known as a popular beverage [2]. Earlier, it was reported that papaya had positive effect against bacterial infections [3]. It was found that treatment of wound with *Carica papaya* improved efficiency of phagocytic cells that destroy bacteria [4]. *In vitro* studies conducted on extracts from skin, flesh, and seeds of both ripe and unripe *Carica papaya* gave antibacterial activities against various microorganisms including *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Enterobacter cloacae*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Shigella Flexner* [5]. Papain which is the main enzyme found in *Carica papaya* is recognized as effective natural medicine in controlling both edema and inflammation associated with surgical operations [6]. It also produced therapeutic effects in patients with inflammatory disorders of intestine, liver and eye [7]. It was suggested that some diseases which have inflammatory conditions such as arthritis, rheumatism, asthma and wound healing can be treated using extracts from leaves of *Carica papaya* [8]. An aqueous extract of *Carica papaya* was also examined for its effect on growth of various tumor cell lines and on human lymphocytes and have shown positive significant results [9]. The results also showed significant growth inhibitory activity of *Carica papaya* extract on tumor cell lines [9].

Chemical properties of Carica papaya

Several chemical materials are reported in different parts of *Carica papaya*. Copious amounts of Latex are found in the leaves, stems and fruits [10]. The latex was chemically investigated and found that it was rich in chymopapain and papain and the later is also known as vegetable pepsin [2]. Other constituents which include omega endopeptidase and a mixture of cysteine endopeptidases such as papaya endopeptidase II and papaya endopeptidase IV were also reported [11]. *Carica papaya* was also investigated for its chemical properties and the results revealed the presence of proteins without known functions, linamarase, protease inhibitors and chinitases [12]. Young leaves and unripe fruit of *Carica papaya* contain carpaine which known as an alkaloid [2]. The leaves of *Carica papaya* contain glycoside carposide and the seeds contain myrosinase, caricin and sinigrin glycosides [1]. It was reported that when myrosin is combined with caricin, a mustard-like odor is produced [13]. The seeds and the pulp of *Carica papaya* contain

benzyl glucosinolate which can be hydrolyzed by myrosinase to produce benzyl isothiocyanate [14]. A preliminary phytochemical analysis of *Carica papaya* leaves revealed the presence of tannins, flavonoids, saponins, alkaloids, anthraquinones, cardiac glycosides, steroids, reducing sugars, cardenolides and phenolics compounds [8]. The utilizations of different parts of *Carica papaya* in some folk medicine are presented in Table 1.

Table 1: Utilization of different parts of *Carica papaya* in some folk medicine applications

Part of <i>Carica papaya</i> used	Application purpose
Ripe fruit juice and flesh	To treat tumors, indurations of the skin, warts, cancers, corns, rheumatism and alkalinizing the urine [1]
Roots extract	To treat syphilis, tumors of the uterus, hemorrhoids, yaws and to remove urine concretions [14]
Unripe fruit extract	To treat diuretic or mild laxative and to stimulate lactation [1]
Seeds paste	Used as anthelmintic, stimulation of menstruation or abortion [1]
Leaves extract	Used as poultice to treat elephantoid growths, nervous pains and smoked for asthma relief and burn wound healing [14]

Selected studies on pharmaceutical application of *Carica papaya* on laboratory animals

The effects of *Carica papaya* on laboratory animals have been reported as remarkable antifertility natural medicine [8,16]. Abortifacient properties were earlier reported in female rats [17]. However, a decrease in count and sperm motility was seen in rabbits [18] and male rats [19]. Treating rats with papaya extract in a dose of 200 mg/kg/day for periods of 1 and 8 weeks revealed pronounced hypertrophy in sperm characteristics and its ultra structure. Rats treated with a lower dose of 50 mg/kg showed mild hypertrophy and hyperplasia effects in the mentioned characteristics. However, gradual degeneration of the Sertoli cells, Leydig cells germinal epithelium and germ cells were also reported [19]. Tubules of epididymis of rats treated with the dose of 200 mg/kg of *Carica papaya* extract was eliminated indicating

degeneration of sperm cells in the lumina. These results suggest that the male rats reproductive functions was influenced due to the effect and interaction of *Carica papaya* extract [20]. These findings were strongly supported by other studies in which rats were given oral doses of 50, 100, 250, and 500 mg/kg methanolic extract of *Carica papaya* seeds for 28- and 90-day periods [16]. It was found that in the rats treated with doses of 50, 100 mg/kg of the extract the density of the sperm decreased whereas in the rats treated with the dose of 500 mg/kg levels for the same period, the interval total sperm motility was inhibited. Similar findings were reported in dose-dependent study in which suppression of aqueous *Carica papaya* seed extract on sperm motility in mice was investigated and revealed that with high dosages of the extract, decreases in both sperm count and viability were observed [21]. The researchers [21] also noticed that complete normalcy in mice was restored in a period of 45 days. However, the safety of the extract was evidenced after 360 days by observing unaltered health status such as hematology, clinical chemistry and increase in both body and organs weights [21].

Extract of *Carica papaya* leaves was investigated for anti-inflammatory activity in several animals models included carrageenan induced paw oedema rats, cotton pellet granuloma rats and formaldehyde induced arthritis rats [8]. The experimental models of rats received doses of 25-200 mg/kg (orally) of *Carica papaya* extracts while the rats in control group treated with saline and the reference rats group received 5 mg/kg of indomethacin. The results revealed that the extracts of *Carica papaya* significantly ($p < 0.05$) caused reduction in the amount of granuloma in the investigated animal models which became noticeable from the 4th day to the 10th day of the investigation.

The biological activity of the dried leaves which are used traditionally for treatment of inflammatory condition was investigated in few studies [8]. In the early 1980s, chymopapain derived from *Carica papaya* was approved in both types of patients who had not responded to conservative therapy and those with documented herniated lumbar intervertebral discs using intradiscal injection [22]. Chymopapain was also used earlier to aid in recovery and healing of surgical wounds [23]. Papain showed the ability of dissolving dead tissue without damaging living cells [2]. It was also reported that a formulation containing 8.3×10^5 mg papain, 100 mg of urea and 1000 mg of an ointment was effective in treating derided necrotic tissue and liquefy slough in a variety of both short- and long-term lesions ulcers [24]. When gauze was soaked in milk of unripe fruit or milk that comes from the trunk of *Carica papaya* and applied 3 times daily on ulcer at home treatment it gave positive good results [25].

Carica papaya seeds were approved and confirm in some studies for their effective anthelmintic properties against nematodes found in animals [26]. Methanolic and aqueous extracts of both unripe and ripe fruits of *Carica papaya* were examined in experimental rat models [27]. The results showed that the methanolic extract demonstrated remarkable reduction in ulcer index and gave better protection against both indomethacin induced ulcers and gastric ulcers.

Comparison studies on the effects of doses of a mixture of 20 mg/kg of unripe fruit *Carica papaya* extract and 200 mcg per 100 g antihypertensive hydralazine intravenously were carried out on two

groups of rats [28]. The investigators found that both treatments produced salt - hypertensive and depression in the value of arterial pressure in the rats. The arterial pressure was reduced by 28% in the hydralazine rat groups compared to the hypertensive ones [28]. The study concluded that the unripe fruit of *Carica papaya* may contains antihypertensive agents which caused alpha-adrenoceptor activity in the experimental rats [28].

Diuretic activity was demonstrated in Sprague -Dawley adult male rats orally using root extracts of *Carica papaya* at a dose of 10 mg/kg. Significant ($P < 0.01$) increase in urine output value was reported at a dose of 10 mg/kg of hydrochlorothiazide which was similar to rats receiving *Carica papaya* at the dose of 10 mg/kg [29]. The fruit of *Carica papaya* was investigated in Sprague-Dawley rats using a high-fat diet compared with injection of triton WR1339 methods using hyperlipidemia induced rats [30]. The results displayed potential effects of the fruits as an antihyperlipidemic in the rats. It was found that fresh juice of *Carica papaya* reduced triglycerides and serum cholesterol within the first 24 hours in rats and similarly, methanolic and aqueous extracts of *Carica papaya* reduced the levels markedly after 7 days of the repeated oral treatment compared with the control rats [30]. However, the potential of antioxidant activity of *Carica papaya* juice in a dose of 100 - 400 mg/kg/day was determined in a comparison to alpha-tocopherol using Wistar rats [31]. The study revealed that the investigated alpha-tocopherol and the *Carica papaya* juice gave the same effect of the antioxidative stress potential.

Aqueous extract of *Carica papaya* seeds at doses of 100 - 400 mg/kg/day was investigated for its effects on hypolipidemic, cardioprotective parameters in normal male Wistar rats for 30 days [32]. Three groups of rats were orally administered either with extract of *Carica papaya* seed at doses of 100, 200, and 400 mg/kg/day of the extract or 0.1 mg/kg/day of glibenclamide or 10 ml/kg/day of distilled water (control) for a period of 30 days. The results showed that *Carica papaya* extract significantly ($p < 0.05$) lowered the total cholesterol, serum triglyceride, fasting blood glucose and significantly ($p < 0.05$) reduced the density of lipoprotein cholesterol in a dose dependent manner compared to the untreated control rats. A single oral dose at 2,000 mg/kg or 5,000 mg/kg of methanolic and aqueous extracts of whole unripe extract of *Carica papaya* seeds were tested for their toxic effects in rats and they did not elicit signs of toxicity in the treated animals [27]. This study was in a good agreement with the previous investigated study [16]. It was also found that rats orally administrated with methanolic extract of *Carica papaya* seeds daily for long term affected sperm parameters of the rats such as motility, viability and count [33]. Recently, extract of *Carica papaya* leaves was investigated for its toxicity [34]. In the study, Sprague Dawley rats received fixed doses of 5, 50, 300 and 2000 mg/kg of the extract and observed for 14 days. The given doses even at the higher level (2000 mg/kg) did not produce mortality or significant changes in body weight or food and water consumption. The investigated rats did not showed signs of toxicity and no deaths were observed. In addition, normal relative weights of the internal organs were observed. However, significant increases in hemoglobin (HGB), hematocrit (HCT), red blood cell (RBC) and total protein were recorded indicating dehydration. Table 2 shows selected methods used in *Carica papaya* extraction and utilizations of the extracts in different pharmaceutical and medical applications.

Table 2: Selected Extraction Procedures and Utilization Purposes of *Carica papaya* Extracts in Pharmaceutical and Medical Applications

Extraction procedure	Purpose of utilization
The dry leaves were prepared to a fine texture form using grinder. 50 g of the powder were placed into 1000 mL flask. Water was added on hotplate for 3 h. After being left to cool mixture was filtered with filter paper, the filtrate was rotor evaporated to remove the water. The Aqueous extract was then freeze dried to produce powder.	Wound healing [35]
The leaves were air dried and reduced to powder form using pestle and mortar. 400 g of the prepared powder was extracted with 2L ethanol using cold maceration method. The mixture was then filtered and evaporated at 50°C in water bath to obtain 27.2 g of semi solid extract. The extract was stored at 4°C and prepared later for oral administration.	Anti-inflammatory [8]
Unripe fruits of <i>Carica papaya</i> were cleaned with distilled water and the outer green thin layers were peeled and discarded. The underlying epicarp (200 g) was blended with 50 mL of distilled water to a fine texture form using a blender. The mixture was then filtered using a fine muslin cloth followed by rotor evaporation to remove water. Then the filtrate was oven-dried at 40°C and the obtained extract was used in the study.	Diabetic wound healing [36]

Selected studies on pharmaceutical application of *Carica papaya* on wound healing

Carica papaya fruit is well recognized with the ability of healing wound but until recently no systematic clinical investigations have been carried out. A study investigated the efficiency of *Carica papaya* on burn wound induced in Swiss albino mice was carried out [4]. It was concluded that concentrations of 1% and 2.5% dried *Carica papaya* formulated in carbogel were both effective in treating burn wound. A significant increase in the percentage of wound contraction was observed from day 12 in the mice group treated with the 2.5% *Carica papaya* and from day 20 in those treated with the 1% *Carica papaya* as well as the standard treatment group (group treated with silver sulfadiazine/chlorhexidine cream). It was also found that epithelization time was shorter in the 2.5% *Carica papaya* – treated group compared with the others [4]. This finding supports promising results from previous study [6] in which burn wounds were either treated with papaya gel or remain without treatment (control). It was observed that in the treated group, the wounds became much less inflamed and healed quicker and healing progress of the wound became noticeable on day 8 and 12. Moreover, the wound area was became half in the size in the treated group compared with the untreated group.

Aqueous extracts of unripe versus ripe of *Carica papaya* fruits were studied to compare their effects on wound healing in rats [36]. The extracts in a dose of 100 mg/kg were applied to excision and dead space wound models using streptozotocin-induced diabetic rats observed for 10 day. The treatments exhibited 77% reduction in wound area compared with controls (59%). This finding agreed with the previously investigated study [37]. The unripe fruit extract-treated wounds were found to heal faster which induced complete healing in shorter period (13 days) than that required by ripe papaya (17 days). Fermented papaya extract was investigated for its effect on wound healing orally [38]. The prepared samples were given via oral supplementation on wound healing in adult obese diabetic mice model and provided the first evidence that this preparation may specifically influence the response of wound site macrophages and the subsequent angiogenic response [38].

Aqueous extract of *Carica papaya* leaves in concentrations of 5 and 10% mixed with vaseline was evaluated for its effect on wound healing using male Sprague Dawley rats for a period of 48 h [34]. The rats (6 animals per group) were wounded in the posterior neck area. Blank vaseline was used for the control group in this treatment. The results showed that wound treated with the extract of *Carica papaya* leaves significantly ($p < 0.05$) caused acceleration in wound healing process. In another investigation a rate of burn wounds healing treated using extract of *Carica papaya* and silver sulfadiazine cream (SSD) were compared [39]. Partial and full thickness (2 cm x 2 cm) burn wounds were induced on the dorsal part of anaesthetized rats using heated metal plates. The rats were treated daily with silver sulfadiazine cream (SSD) in a concentration of 1% and or 500 mg of *Carica papaya*. The experiments were lasted for 34 days when the burn wound of all rats were healed completely. A digital camera was used to take photographs of the burn wounds daily to monitor their healing. It was observed that there was no significant difference in the healing time of *Carica papaya*-treated group compared to the SSD treated group [39].

CONCLUSION

This review paper presents *Carica papaya* as an important and promising natural medicinal plant which could be utilized in several pharmaceutical and medical applications because of its effectiveness, availability and safety.

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