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## Healing Potential of *Carica Papaya* Leaf

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### ABSTRACT

*Carica papaya* Linn., (Family: Caricaceae) is a very well known plant which is found in various parts of India. The main aim of this study is to assay the wound healing activity of ethanolic extract of *C. papaya* leaf by using healthy rats of both sex and almost same age. Three types of models namely excision wound, incision wound and burn wounds which was created on dorsal part of saved rats using a metal rod heated to 80-85<sup>0</sup> C and exposed for 20 seconds. The effects of ethanolic extract of *C. papaya* leaf on wound healing were observed by the rate of wound closure, period of epithelialisation and finally wound breaking strength. Povidone iodine ointment (5% w/w) is used as reference for excision and incision wounds models. During this study, it is observed that animals treated with *C. papaya* ethanolic extract, shows wound healing at a faster rate by comparing with animals treated with povidone iodine ointment. Similarly in burn wound healing study Silver-sulfadiazine used as reference drug for activity comparison and the efficacy of treatment was evaluated based on reduction of burn wound area. The ethanolic extract treated animals showed significant reduction in the burn wound area when compared with control groups. The result of the present study offers pharmacological evidence on the folklore use of *C. papaya* leaves for healing wounds including burns.

**Keywords:** *Carica papaya*, Wound healing activity, Excision wound, Incision wound, Povidone ointment.

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## INTRODUCTION

Nature always played a significant role in the treatment of various diseases for the last few decades. Now a day's chemical constituents from various plants are very important tool for drug development in spite of tremendous development of combinatorial chemistry. Synthetic drugs, if used for a prolonged period of time, produce some side effects which can overcome by using herbal drugs and its dosage form. Traditional medicaments which are obtained from various plants play an important role in curing disease for human existence on this planet<sup>1,2</sup>

Wound healing is the process by which skin injury can be recovered which is essential for the restoration of disturbed functional status of the skin<sup>3</sup>. Various medicinal plants have been used from time to time for treatments of human for cuts, wounds and burns and obtained satisfactory result. In Ayurveda and Siddha systems of medicines some very common plants have been extensively reported for their wound healing potential<sup>4</sup>.

*Carica papaya* Linn., (Family: Caricaceae) is commonly and erroneously referred to as a "tree", the plant is growing fastly at the rate of 6 to 10 ft for the first year and reaching 20 or 30 ft in height, having a hollow green or deep purple stem becoming 12 to 16 in or more thick at the base and roughened by leaf scars. From the upper part of the stem, the leaves are emerged in a spiral on nearly horizontal petioles which are 1 to 3 ½ ft long, hollow, succulent, green or sometimes dark purple. The blade is deeply divided into 5 to 9 main segments which are irregularly subdivided, varies from 1 to 2 ft (30-60 cm) in width and has prominent yellowish ribs and veins. Both the stem and leaves contain copious white milky latex. In traditional medicine, various parts of *C. papaya* were including leaves, barks, roots, latex, fruit, flowers and seeds having a wide range of reputed medicinal application. In Jamaica, the ripe fruit is used as topical ulcer dressings for promoting desloughing, granulation, healing, and reducing odour in chronic skin ulcers<sup>[5]</sup>. The leaves are used for colic, fever, beriberi, abortion, asthma in India and cancer in Australia<sup>[6]</sup>. The green fruit is used for contraceptive purposes by traditional healers in Pakistan, India and Sri Lanka as well as various human and veterinary diseases in Nigeria such as malaria, hypertension, diabetes mellitus, jaundice, intestinal Helminthiasis<sup>7</sup>.

As per the folklore information the tribal people apply the juice of leaves over severe open wounds and claim for its promising effectiveness towards healing of wounds, so the present study to regenerate and reconstruct the disrupted anatomical continuity and functional status of the skin and to investigate the medicinal use of *C. papaya* as wound healing promoter that had been cited in folkloric literature.

## MATERIALS AND METHODS

### Plant material

The plant leaves were collected from rural area of Visakhapatnam district of Andhra Pradesh and authenticated. The leaves were washed, shade dried and pulverized to coarse powder. The powdered leaves (500 g) was defatted with petroleum ether (40 - 60<sup>0</sup> C) for 72 h and then extracted with ethanol for 48 hours by using Soxhlet apparatus. After complete extraction, the solvent is allowed to remove to make the extract dry. Preliminary phytochemical screening of the extract has done by standard methods<sup>[8]</sup> to know the nature of phytoconstituents present in it.

### Animals

Adult Wistar rats (150–250 g) of either sex were maintained in the animal house at GITAM institute of pharmacy, GITAM University, Visakhapatnam, Andra pradesh under standard environmental condition of temperature (25<sup>0</sup>C) and light/dark cycles (12/12h). All experimental protocols were approved by the Institutional Animal Ethics committee of GITAM Institute of Pharmacy, Visakhapatnam, Andhra Pradesh, India (Regd. No.1287/ac/09/CPCSEA and protocol No: IAEC/GIP-1287/B Pharm/IP/SM-ASSP/07/2012-13). Experiments were performed according to the guide for the care and use of laboratory animals.

### Excision wound model

The excision wound model was used to study the wound healing activity of the test sample. Animals were anesthetized prior to and during creation of the wounds, with 1 ml of intravenous ketamine hydrochloride (10 mg/kg). The rats were inflicted with excision wounds as described by Morton *et. al.*, 1972<sup>9</sup> and Kamath *et. al.*, 2003<sup>10</sup> An impression was made on the dorsal thoracic region 1 cm away from vertebral column and 5 cm away from ear on the anaesthetized rat. The dorsal fur of the animals was shaved with an electric clipper and the anticipated area of the wound to be created was outlined on the back of the animals with methylene blue using a circular stainless steel stencil. A full thickness of the excision wound of circular area of 500 mm<sup>2</sup> and 2 mm depth was created along the markings using toothed forceps, scalpel and pointed scissors. Haemostasis was achieved by blotting the wound with cotton swab soaked in normal saline and the entire wound was left open under aseptic conditions. The control group animals (Group I) were treated with the vehicle (Simple ointment I. P.), the positive control (Group II) was applied with Povidone iodine (5% w/w). Test group of animals were treated with ethanolic extract of *C. papaya* leaves at a concentration of 10% w/w in simple ointment I. P. in a similar manner.

The wound closure rate was assessed by treating the wound on days 5, 10 and 15 post wounding days using transparent paper and a permanent marker. By using graph paper the recorded areas were measured. The percentage wound healing was calculated by comparing the size of original wound. Development in wound area calculated is the indication of wound contraction <sup>11</sup>.

### **Incision wound model**

The rats were anaesthetized before creation of the wounds, with 1 ml of intravenous ketamine hydrochloride (10mg/kg). By using an electronic clipper, the dorsal fur of the animals was shaved. A 6 cm long longitudinal paravertibral incision was made through the skin and cutaneous tissue on the back as described by Mondal *et. al.*, 2013 <sup>12</sup>. After the incision, the parted skin was sutured 1 cm apart using a surgical thread and curved needle. The wounds were left undressed. Topical application of the extract has done to the wound once a day. The sutures were removed on 8<sup>th</sup> post wound day and continued the application of the extract. The wound breaking strength was measured on the 10<sup>th</sup> day evening after the last application <sup>13</sup>.

### **Evaluation of burn wound healing activity**

Burn wounds were created on dorsal part of saved rats using a metal rod (1.5 cm diameter) heated to 80-85<sup>o</sup> C and exposed for 20 sec <sup>14</sup>. After 24 h dead tissues were excised using sterile surgical blade. Control group was dressed with simple ointment base, while positive control (Group II) was treated with silver sulfadiazine (1% w/w) and the test group (Group III) was dressed with 10% w/w EECPL in simple ointment I. P. in a similar manner.

### **Statistical analysis**

For the determination of significant difference, the obtained data were subjected to one way of analysis of variance (ANOVA). By using Dunnett's t-test, the inter group significance was analyzed. A p-value <0.05 was considered to be significant. All the values were expressed as Mean  $\pm$  SEM.

## **RESULTS AND DISCUSSION**

In this study the therapeutic effect was assessed on the reduction of wound diameter area. The findings of wound area measurement demonstrated, that the treated rats with ethanolic extract from *Carica papaya* leaf (EECPL). Preliminary phytochemical tests revealed presence of alkaloids, sterols, flavonoids, tannins, saponins, phenol and phenolic compounds in the ethanolic extracts of *C. papaya* leaf.

The studies on excision wound healing model showed that the ethanolic extract from *C. papaya* leaf (EECPL) demonstrated significant healing potency compared to control. However, 10% w/w

ethanolic extracts of *C. papaya* exhibited higher potency than the reference drug 5% w/w Povidone iodine ointment. The crude extract achieved 98.96% and reference drug achieved 97.23% wound contraction on 15<sup>th</sup> day. The epithelialization period was also reduced in the treated groups (16.04±0.61) when compared with control group (29.86±3.81), the period of epithelialization was 16.63±2.02 in case of standard drug, as evidenced from Table 1. Similarly in incision wound model is summarized in Table 2. EECPL treated animals showed increase in breaking strength (401.82±6.91) when compared with both control (108.26±8.28) and standard group (385.03±4.91). Whereas the efficacy of ethanolic extracts of *C. papaya* leaf based on reduction of burn wound area. The EECPL treated animals showed significant reduction (p<0.01) in the burn wound area when compared with control groups. In burn wound healing study Silver-sulfadiazine used as reference drug for activity comparison which possess 94.83±1.88 percentage wound closure on 20th day of the study whereas the ethanolic extract from *C. papaya* leaf (EECPL) achieved 91.66±4.03 percentage wound closure when compare with the control group, similarly the animals treated with EECPL (group III) and silver sulfadiazine (group II) showed faster epithelialization than control group respectively (Table 5). Similarly in group I (control group) in study period, there was not any sign of hair growth on the burn region but in group II and III the hair growth gradually started from day 17.

**Table 1: Effect of ethanol extract from *Carica papaya* leaf on percentage wound closure (Excision wound model)**

Group	Treatment	Percentage (%) wound closure.			Period of epithelialization (No. of days)
		5 <sup>th</sup> days	10 <sup>th</sup> days	15 <sup>th</sup> days	
I	Control	2.66±0.08	10.55±1.08	46.7±1.87	29.86±3.81
II	Povidone iodine (5% w/w)	12.75±0.96**	59.36±3.16**	97.23±1.62**	16.63±0.09**
III	EECPL (10% w/w)	36.2±0.86**	86.73±4.23**	98.96±2.07**	16.04±0.61**

Values are expressed as mean ± S.E. (n = 6). All columns are significant using ANOVA.\* P<0.05, \*\* P<0.01 when compared to control; Dunnet's t-test.

**Table 2: Effect of ethanol extract from *Carica papaya* leaf on wound breaking strength (Incision wound model)**

Group	Treatment	Breaking strength (g)
I	Control	108.26±8.28
II	Povidone iodine(5% w/w)	385.03±4.91**
III	EECPL(10% w/w)	401.82±6.91**

Values are expressed as mean  $\pm$  S.E. (n = 6). All columns are significant using ANOVA. \* P<0.05, \*\* P<0.01 when compared to control; Dunnet's t-test.

**Table 3: Effect of the treatments on burn wound healing.**

Group	Treatment	Percentage (%) wound closure.				Period of epithelialization (No. of days)
		4 <sup>th</sup> days	8 <sup>th</sup> days	16 <sup>th</sup> days	20 <sup>th</sup> days	
I	Control	4.16 $\pm$ 0.47	11.83 $\pm$ 1.24	41.16 $\pm$ 1.47	49.83 $\pm$ 2.15	30.33 $\pm$ 2.23
II	Silver Sulfadiazine (1% w/w)	12.33 $\pm$ 1.16**	28.66 $\pm$ 1.38**	84.5 $\pm$ 2.48**	94.83 $\pm$ 1.88**	21.63 $\pm$ 1.81**
III	EECPL (10% w/w)	10.06 $\pm$ 1.03**	24.07 $\pm$ 2.15**	78.03 $\pm$ 1.08**	91.66 $\pm$ 4.03*	22.09 $\pm$ 2.88**

Values are expressed as mean  $\pm$  S.E. (n = 6). All columns are significant using ANOVA. \*

P<0.05, \*\* P<0.01 when compared to control; Dunnet's t-test

Wound healing is a process by which a damaged tissue is restored as closely as possible to its normal state and wound contraction is the process of shrinkage of area of the wound. It depends upon the reparative abilities of the tissue, type and extent of the damage and general state of the health of the tissue. By obtaining the results of the present study, it can be concluded that animals treated with ethanolic extracts of *Carica papaya* leaf showed faster rate of epithelialization in excision wound model. The wound healing effects of the EECPL may be attributed to the presence of phytoconstituents like alkaloids, tannins and flavonoids in the extracts which are known to promote the wound healing process mainly due to their antimicrobial property. Flavonoids, terpenoids and tannins are also known to promote the wound-healing process mainly due to their astringent and antimicrobial property, which seems to be responsible for wound contraction and increased rate of epithelialization<sup>15</sup>.

## CONCLUSION

So, the wound healing property of *Carica papaya* ethanolic extract may be attributed for the presence of phytoconstituents it contain, which may be their individual or additive effect that promotes the process of wound healing. At this stage, which phytoconstituents is responsible for wound healing activity, is difficult to say, but further phytochemical studies are required to isolate the active compound(s) responsible for pharmacological activities. The result of the present study offers pharmacological evidence on the folklore use of *Carica papaya* L., leaves for healing wounds including burns.

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