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Research Article

Anti-inflammatory, antipyretic and analgesic activities of ethanol extract of *Carica papaya*

Sobia Alyas*, Nureen Zahra, Muhammad Imtiaz Ahmad, Nimra Zahid, Ayesha Nisar, Muhammad Mansoor Hafeez, Rabail Alam, Asia Parveen, Arif malik

The University of Lahore, Lahore, Pakistan
*Email: sobia.alyas@imbb.uol.edu.pk
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Abstract

The aim of present study is to evaluate the anti-inflammatory, anti-pyretic and analgesic activities of ethanol extract of *Carica papaya* L. on albino rats. Plant of *C. papaya* L. is commonly used to treat different diseases like fever, pain, and inflammation. A total of 144 albino rats with an average weight of 160-200g were used in this study. Rats were divided into 4 groups each group contained 12 rats. Anti-inflammatory activity was evaluated by 0.1 mL of 1% carrageenan extract that induces paw edema while analgesic activity was investigated by acetic acid that induces abdominal writhing response where antipyretic activity was demonstrated by yeast that induces pyrexia in rats. In anti-inflammatory, antipyretic and analgesic activities, significant results were shown at 400mg/kg, 50mg/kg and 400mg/kg doses respectively in multiple comparisons. The stem extract of *C. papaya* L. showed significant results as compared to leaf extract in anti-inflammatory and antipyretic activities. The leaf extract of C. papaya showed significant results as compared to the stem in analgesic activity.

Keywords: Analgesic, anti-inflammatory, anti-pyretic, *Carica papaya* L., dicleofenac, leaf, paracetamol, stem

Introduction

C. papaya is an unbranched tree, about 6-20 feet in height (Roshan *et al.,* 2014). It is sometimes called "big melon" or "pay paw" Papaya is a berry type fruit with parietal placentation. is cultivated practically all over the tropical and subtropical countries of the world particularly in Pakistan, India, Philippines, South America, and West India. Papain, a major compound in the fruit and latex has been used in brewing and winemaking and the textile and tanning industries (Vinod *et al*., 2019). Smoked leaf is used for asthma relief in various remote areas. The leaves are used as a heart tonic, analgesic, pyrexia and to treat stomachache.

According to WHO leaf of *C. papaya* are used to confirm purity and authenticity. Extractive values of *C. papaya* are ash (%), ash soluble in water (6.05), ash insoluble acid (3.25) and ether petroleum 20.44%. These extracts indicate the presence of terpenoids, flavonoids and phenolic compounds (Anjum *et al*., 2013). In the most recent decade WHO, perceiving the significance of natural drugs, has passed numerous goals versus improving the quality and adequacy of plant drugs. The principal artistic reference to papayas goes back to 1526 when they were found in the Caribbean shore of Panama and Colombia and portrayed by the Spanish author Oviedo (Jagdish *et al*., 2014).

According to WHO, traditional and modern method extraction is effective in herbal medicine. These medicines are used to cure the illness. Herbal plant products are free of side effects and less toxic. Plants contain different active compounds like tannins, alkaloids, glycosides, fixed oils, phenols, volatile oils, resins, and flavonoids. According to world health organization 225 drugs are identified. Different kind of phytochemicals like antibacterial, antifungal, antioxidant, anti-

inflammatory, radio-protective, antidiabetic, antiarthritic are present in plant.

C. papaya L. is used for many treatments of diseases like edema, pyrexia, writhing, blood pressure, and dyspepsia. The nutrients of *C. papaya* improve prevent colon cancer, heart attacks, strokes and cardiovascular system (Aravind *et al*., 2013). Leaves are used in dressing wounds and injuries. It is can cure dengue fever. Chemical composition of *C. papaya* leaves includes alkaloids carpaine, dehydrocarpaine, pseudocarpaine and carposide (Baslingappa *et al*., 2012). The present study was designed to evaluate botanical uses of plants for the treatment of anti-inflammatory (inflammation), antipyretic (pyrexia) and analgesic (pain) activities in an animal model (rats).

Material and methods

Sample collection

The fully mature or fresh leaves and stem of *C. papaya* were directly collected as a sample from different botanical areas of Lahore. They were identified by a botanist of the University of the Punjab, Lahore, Pakistan.

Extract preparation

The stem and leaves were soaked in ethanol (semi-polar solvent). All the mixtures were shaken gently for 2-3 minutes and placed for 15 days at room temperature (37°C). On the 16th day, the mixtures were filtered with the help of watt-man filter paper (Orhue P.O. and Momoh, 2013).

Experimental rats

Albino rats of either female or male sex (160-200g) were purchased from the University of Veterinary and Animal Sciences, Lahore. Rats were kept in the animal house, the University of Lahore in polypropylene cages. Before experimental work, rats were kept in fasting conditions for 8 hours.

Drugs and chemicals

Normal saline, Diclofenac, *C. papaya* L. leaf extract, Carrageenan, Yeast, Paracetamol, *C. papaya* L. stem extract, Acetic acid, and distilled water.

Anti-inflammatory activity model

Carrageenan is a drug that is used to cause inflammation or edema in rat paw at the dose of 50, 100, 200 and 400mg/kg which is cured by diclofenac and *C. Pappya* extract.48 albino rats were divided into 4 groups each group contains 12 rats. In the control group, albino rats were treated with normal saline 50, 100, 200 and 400mg/kg dose according to their body weight. In the standard group, rats were treated with diclofenac drug (50, 100, 200 and 400mg/kg). In the experimental design group (group 3 or 4) rats were treated with aqueous extract of *C. papaya* L. leaf and stem (50, 100, 200 and 400mg/kg). Firstly, all groups of rats were treated with carrageenan in which 0.1 ml of 1% carrageenan injected into the sub plantar region of the hind paw. Doses of carrageenan, leaf and stem extract were 50, 100, 200 and 400mg/kg respectively. Anti-inflammatory activity was calculated by the given formula:

$$\% \text{ inhibition} = \frac{(Ct-Co)control-(Ct-Co)treated}{(Ct-Co)control} X100$$

Where, C_o= Reading of paw before carrageenan, C_t = Volume of the hind paw of after carrageenan (Ct-Co) = Volume of the hind paw of the treated group after carrageenan injection.

Antipyretic activity model

Antipyretic activity in which fever is induced in rats by yeast and normal saline injection. In this model, rats were divided as discussed earlier in the anti-inflammatory activity model. In the standard group, rats were treated with paracetamol. In standard and experimental design groups, rats were treated with brewer's yeast with normal saline which was injected below the nape of the neck. After the interval of 20 hrs, pyrexia developed. The maximum rise in temperature was 38.3°C. The antipyretic activity was calculated by the given formula:

$$\text{Percent reduction} = \frac{B-Cb}{B-A} X100$$

Where, B = Temperature after pyrexia induction, C_b = Temperature after 1, 2 and 3 hours and A = Normal body temperature.

Analgesic activity model

In the analgesic activity, contractions in abdominal muscle and pain phenomena in rats are produced. Firstly pain is induced in rats and then cured by *Carica papaya* extract. In this model, rats were divided as discussed earlier in the anti-inflammatory activity model. Diclofenac used as a standard drug. Acetic acid induces writing which was used to evaluate the potential of ethanolic extract of the plant on pain. In standard and experimental design groups, all rats were treated with acetic acid 50, 100, 200 and 400mg/kg according to their body weight. The extract of leaf and stem were injected 1 hr before, and standard drug diclofenac 1/2 hr before the administration of acetic acid. Several abdominal constrictions were counted in 20 minutes. Analgesic activity was calculated by the given formula:

$$\text{Analgesic activity} = \frac{Nc - Nt}{Nc} X100$$

Where, Nc = Control group writhe and Nt = Treated group writhe.

Statistical analysis

Statistical analysis was performed by using ANOVA, the significant difference in activities were accepted (P<0.05) by multiple comparisons. Whereas, P< 0.005 difference was considered to be significant.

Results

Carrageenan induce paw edema

In the anti-inflammatory activity, the ethanolic extract of stem of *C. papaya* L. at a dose of 400mg/kg showed significant results (P<0.05) as compared to the leaf of *C. papaya* L. at doses of 50mg/kg, 100mg/kg, 200mg/kg and 400mg/kg. In inflammation assay, the maximum percentage inhibition of leaf showed 400mg/kg dose that is 96% as compared to standard and control that was 100% (Table 1).

Antipyretic activity

In the antipyretic activity, the ethanolic extract of stem and leaf extract of *C. papaya* L. show results P>0.05, at doses of 50mg/kg, 100mg/kg, 200mg/kg and 400mg/kg as compared to the standard drug (Table 2).

Analgesic activity

In the analgesic activity, the ethanolic extract of stem of *C. papaya* L. at a dose of 400mg/kg showed significant results (P<0.05) in comparison with the leaf of *C. papaya* L. at doses of 50mg/kg, 100mg/kg, 200mg/kg and 400mg/kg. Dose of stem extract reduced abdominal writhing more significantly (P<0.05) in albino rats when compared to standard drug diclofenac (Table 3).

Table 1. Anti-inflammatory activity of *C. papaya* L.

Group	Dose (mg/kg)	Paw size (mm) Mean ±S.D 1hr	2hr	3hr	4hr
Control	50mg/kg	1.450±0.636	1.200±0.424	0.710±0.975	0.005±0.007
	100mg/kg	1.350±0.070	1.200±0.000	0.800±0.424	0.015±0.007
	200mg/kg	1.300±0.000	1.050±0.070	0.800±0.282	0.300±0.282
	400mg/kg	1.900±0.141	1.500±0.000	1.350±0.070	0.550±0.070
Standard	50 mg/kg	1.500±0.000	1.350±0.070	0.600±0.141	0.400±0.141
	100mg/kg	0.850±0.494	0.900±0.141	0.650±0.070	0.400±0.141
	200mg/kg	1.600±0.565	1.050±0.070	0.850±0.212	0.550±0.070
	400mg/kg	1.450±0.070	1.000±0.000	0.750±0.070	0.800±0.565
Leaf	50 mg/kg	1.150±0.212	1.050±0.212	0.500±0.424	0.4500±0.494
	100mg/kg	1.000±0.000	0.800±0.000	0.600±0.141	0.350±0.212
	200mg/kg	1.150±0.070	1.050±0.070	0.900±0.000	1.000±0.424
	400mg/kg	1.250±0.070	1.150±0.070	0.950±0.070	0.800±0.141
Stem	50 mg/kg	1.050±0.353	0.900±0.424	0.750±0.353	0.250±0.070
	100mg/kg	0.850±0.070	0.800±0.000	0.650±0.070	0.550±0.707
	200mg/kg	1.250±0.070	1.100±0.141	0.950±0.070	0.850±0.070
	400mg/kg	1.150±0.212	0.900±0.282	1.000±0.282	1.000±0.141

Anti-inflammatory activity of *C. papaya* L. leaf and stem

Values are mean ±S.D; n=4 in each group P<0.05 compare to the control group.

Table 2. Antipyretic activity of *C. papaya* L.

Group	Temp	Dose (mg/kg)	Body temp(oc) Mean ±S.D 0hr	0.5hr	1hr	2hr
Control	37°C	50 mg/kg	37.50±0.14	37.35±0.07	37.20±0.00	37.05±0.07
		100 mg/kg	37.65±0.07	37.45±0.07	37.20±0.00	37.00±0.00
		200 mg/kg	37.75±0.07	37.55±0.21	37.35±0.21	37.15±0.07
		400 mg/kg	37.90±0.00	37.75±0.07	37.55±0.07	37.25±0.07
Standard	38.3oC	50 mg/kg	37.85±0.21	37.55±0.07	37.45±0.07	37.15±0.21
		100 mg/kg	37.90±0.42	37.45±0.07	37.25±0.07	37.01±0.00
		200 mg/kg	38.35±0.07	37.30±0.00	37.10±0.00	37.00±0.00
		400 mg/kg	38.00±0.28	37.50±0.14	37.30±0.00	37.10±0.00
Leaf	37.6oC	50 mg/kg	37.60±0.42	37.60±0.28	37.35±0.21	37.40±0.42
		100 mg/kg	37.50±0.28	37.45±0.07	37.55±0.21	37.50±0.42
		200 mg/kg	37.25±0.21	37.20±0.00	37.20±0.14	37.30±0.28
		400 mg/kg	37.35±0.35	37.40±0.14	37.45±0.07	37.50±0.28
Stem	37.5°C	50 mg/kg	37.45±0.21	37.40±0.00	37.40±0.14	37.35±0.35
		100mg/kg	37.55±0.21	37.55±0.07	37.50±0.14	37.45±0.35
		200 mg/kg	37.30±0.28	37.25±0.21	37.25±0.07	37.25±0.07
		400 mg/kg	37.45±0.07	37.40±0.00	37.45±0.07	37.45±0.21

Antipyretic activity of *C. papaya* L. leaf and stem
Values are mean ±S.D; n=4 in each group $P<0.05$ compare to the control group.

Table 3. Analgesic activity of *C. papaya L.*

Group	Dose (mg/kg)	Writhing Mean ±S.D 20 (mints)
Control	50 mg/kg	17.00±2.82
	100 mg/kg	15.00±4.24
	200 mg/kg	15.50±0.70
	400 mg/kg	12.50±2.12
Standard	50 mg/kg	13.50±2.12
	100 mg/kg	13.50±0.70
	200 mg/kg	17.00±1.41
	400 mg/kg	18.50±0.70
Leaf	50 mg/kg	11.50±0.70
	100 mg/kg	14.50±0.70
	200 mg/kg	16.50±0.70
	400 mg/kg	19.50±0.70
Stem	50 mg/kg	12.50±0.70
	100mg/kg	13.50±2.12
	200 mg/kg	14.50±0.70
	400 mg/kg	18.50±0.07

Analgesic activity of *C. papaya* L. leaf and stem
Values are mean ±S.D; n=4 in each group $P<0.05$ compare to the control group.

Discussion

Anti-inflammatory activity induces edema in rat paw by carrageenan while antipyretic activity induces pyrexia in rats by brewer yeast where analgesic activity used to evaluate writhing test by acetic acid (Subedi *et al*., 2016). In our study, the ethanolic extract of *C. papaya* L. stem and leaf were used to evaluate anti-inflammatory, antipyretic and analgesic activities on albino rats. Flavonoids are effective for acute inflammation because they target on prostaglandins that induce pain and edema (Safari *et al.,* 2016).

When carrageenan injected into rat paw it causes two types of inflammation: initial stage inflammation that occurs within 2hr (Kifayatullah *et al*., 2019) and later stage inflammation. Inflammation in initial stage causes due to bradykinin, histamine, vascular permeability, and serotonin while in later stages occur due to prostaglandins. When carrageenan injected into the sub plantar region of paw cause edema which is due to exudation of plasma protein, macrophages, leucocyte, and neutrophils. Pappya leaf and stem used for the maximum fall in acute inflammation shown at the dose of 400mg/kg (Parra *et al.,* 2019).

When brewer's yeast is injected into the nape of the neck of albino rats, it induces pyrexia in the body by increasing the synthesis of prostaglandins. Fever induced in the body by brewer's yeast is called pathogenic fever etiologically cause the production of prostaglandins. Antipyretic action can be performed by the synthesis of prostaglandins. Yeast contain specific protein which is linked to fever. Prostaglandins (PGI2 and PGE2) are responsible for fever in rats' bodies by acting on the brain. Paracetamol is used to reduce the fever

by acting on prostaglandins (Subedi *et al*., 2016).

Abdominal and visceral pain in rats causes due to the induction of acetic acid that leads to pain in prostaglandins due to peritoneal fluid (Bairagi *et al*., 2017). Acetic acid used as an agent for the relief of endogenous substance which is responsible for the pain that releases form nerve ending (Subedi *et al*., 2016). In the analgesic activity, time difference occurs due to the time lag of drugs entering into the body of rats (Parra *et al*., 2019).

The immune response of the tissues of the body, against any infection and injury known as inflammation (Sultana *et al*., 2018). In our study, *C. papaya* showed significant antipyretic effect against yeast. Fever in rats due to tissue damage and infection (Vinod *et al.,* 2019). The doses of yeast show the massive production of PGE2 in the rat body. Acetic acid induces writhing, a highly sensitive process that relates to peripherally analgesic action. Acetic acid induces abdominal pain which is due to the involvement of the nociceptive receptor (prostaglandins) and local peritoneal receptor. When acetic acid is administrated in abdominal muscle, it acts on the peritoneum cavity of an animal which produces pain (Mohanvelu *et al*., 2014).

Conclusion

From the above findings, our study concluded that the ethanolic extract of *C. papaya* L. can be used as an antioxidant for injuries, trauma, acute pain, inflammation, and fever. It can improve and effectively treat all types of abdominal disorders and digestive systems. From overall results, we determined that ethanolic extract of *C. papaya* L. showed significant results in anti-inflammatory, anti-pyretic and analgesic activities. In the future perspective, *C. papaya* can be used clinically as a phytochemical against visceral pain.

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