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Research Article

Anti-inflammatory activities of ethanolic extract of *Carica papaya* leaves

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Abstract. The anti-inflammatory activity of an ethanolic extract of *Carica papaya* leaves was investigated in rats using carrageenan induced paw oedema, cotton pellet granuloma and formaldehyde induced arthritis models. Experimental animals received 25–200 mg/Kg (orally) of the extracts or saline (control group) and the reference group received 5 mg/Kg of indomethacin. The ulcerogenic activity of the extract was also investigated. The results show that the extracts significantly ($p < 0.05$) reduced paw oedema in the carrageenan test. Likewise the extract produced significant reduction in the amount of granuloma formed from 0.58 ±0.07 to 0.22 ±0.03 g. In the formaldehyde arthritis model, the extracts significantly reduced the persistent oedema from the 4th day to the 10th day of the investigation. The extracts also produced slight mucosal irritation at high doses. The study establishes the anti-inflammatory activity of *Carica papaya* leaves.

Keywords: Anti-inflammatory; Arthritis; *Carica papaya*; Extracts; Gastric mucosa; Oedema; Rats; Ulcer

Introduction

Pawpaw (*Carica papaya* L.) is the most economically important fruit in the Caricaceae family (Oliver-Bever, 1986). It is an erect fast growing and usually un branched tree or shrub. Although it is native to Central America, it has been transported to many parts of the tropics (Samson, 1986). The ripe fruit of the pawpaw plant is commonly consumed as food in different parts of the world. However, the unripe fruit is used as mild laxative, for diuresis, as galactogogue and as an abortifacient agent (Gill, 1992). Many parts of the plant are employed in the treatment of several ailments; for example the seed is used for expelling worms, and the seed and the roots are also used as abortifacient agent**.** The leaves (especially fallen ones) are used variously for the treatment of fever, pyrexia, diabetes, gonorrhoea, syphilis, inflammation and as dressing for foul wounds (Gill, 1992). Some of the scientifically validated uses of *C. papaya* include the abortifacient activity of the seeds (Oderinde et al., 2002), the effects of the seeds on germinal epithelium of the seminiferous tubules (Uche-Nwachi et al., 2001), the fruit juice for lowering blood pressure (Eno et al., 2000), the wound healing effects of the leaves (Starley et al., 1999; Mikhal'chik et al., 2004), and several other studies.

The fallen dry leaves along with leaves of *Azaridacta indica*, *Cymbopogon citratus*, *Psidium guava* and stem bark of *Alstonia boonei* are boiled together, cooled and drunk for the treatment of inflammatory (arthritis and rheumatism) and feverish conditions (Gill, 1992). Usually about 0.5L of the decoction is consumed thrice daily during treatment. The poultice of the leaves is applied on elephantoid growths (i.e. large swollen parts of the body). Many reports have also shown that the leaves of *C. papaya* contain many bioactive agents which may be responsible for the biological activity of the plant. Such agents include carpaine, nicotinic acid, etc. (Duke, 1984; Gill, 1992). The biological effect of the latex of the plant which is rich in papain has been studied extensively (Madrigal et al., 1980; Brocklehurst et al., 1985; Morton, 1987; Gill, 1992.). However there are only few reports on the investigation into the biological activity of the dried leaves extract which is the form in which the plant is used traditionally for the treatment of inflammatory conditions.

The present study was undertaken based on the observation in our local community that the leaves of *C. papaya* are used for the treatment of inflammatory conditions such as asthma, rheumatism or arthritis and wound healing. The relative lack of information on the anti-inflammatory activity of dried leaves extract of the plant also contributed to the desire to undertake this study.

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Materials and Methods

Plant material and preparation of extract

The leaves of *Carica papaya* used for this study were collected from Carica garden in Ilorin metropolis, Nigeria. Identification of the plant was subsequently carried out at the Forestry Research Institute of Nigeria (FRIN, Ibadan) by T.K. Odewo where a voucher specimen (FHI 106933) was deposited. The harvested leaves of *C. papaya* were air dried after which they were reduced to powdered form using mortar and pestle. 400 g of the powdered sample was extracted by cold maceration using 2L of ethanol. The macerated mixture was filtered and evaporated in a carefully regulated water bath (maintained at 50 °C) to yield 27.2 g of a dark green semi solid extract. The extract was stored in a refrigerator at 4 °C and prepared for oral administration using tween 80 (2.5 %) and normal saline during pharmacological studies.

Animals

Male Wistar rats weighing 200–250 g were used for the study. The animals were bred and housed in the Animal house of the Faculty of Basic Medical Sciences, University of Ilorin. Animals were kept in clean and standard cages with good ventilation. They were also provided with mouse cubes (Bendel feeds) and water *ad libitum* prior to the commencement of anti-inflammatory studies.

Anti-inflammatory studies

Carrageenan induced paw oedema

Pedal inflammation was produced in rats according to the method described by Winter et al. (1962). Four groups (comprising of five animals each) of rats were treated orally with 25, 50, 100 and 200 mg/Kg of *C. papaya* while the control and reference groups received saline (orally) and indomethacin (5 mg/Kg, orally) respectively. One hour after the administration of extract, indomethacin or saline, 0.1 ml of 1 % carrageenan was injected into the left hind paw of each animal under the sub plantar aponeurosis.

Measurement of paw size was carried out as described previously (Owoyele et al., 2005) by wrapping a piece of cotton thread round the paw and measuring the circumference with a metre rule. Paw sizes were measured immediately before and 1–5 hrs after carrageenan injection. Oedema inhibitory activity was calculated according to the following formula (Olajide et al., 2000; Owoyele et al., 2005).

$$\text{Percentage inhibition} = \frac{(C_t - C_o)\text{Control} - (C_t - C_o)\text{treated}}{(C_t - C_o)\text{Control}} \times 100$$

Where C_t = paw circumference at time t, C_o = paw circumference before carrageenan injection and $C_t - C_o$ = Oedema

Cotton pellet granuloma in rats

This study was carried out as described by Ismail et al. (1997). A sterilized cotton pellet weighing 30 mg was implanted subcutaneously into the groin region of rats after which four groups were treated (once daily) with 25, 50, 100 or 200 mg/Kg of the extract for seven consecutive days. Animals in the control and reference groups received saline and indomethacin (5 mg/Kg) respectively. The animals were sacrificed on the 8th day with an over dose of ether. Thereafter, the pellets surrounded by granuloma tissue were dissected out carefully and oven dried at 60 °C to a constant weight. The mean weight of the granuloma tissue formed around each pellet was obtained and the percentage inhibition was determined.

Formaldehyde induced arthritis

This study was carried out as previously described (Owoyele et al., 2005). The animals were divided into six groups as in the carrageenan and cotton pellet models. Each of the left paws of the animals was injected with 0.1 ml of 4 % formaldehyde on the first and third day of the experiment. The extracts (25–200 mg/Kg), saline or indomethacin were administered orally to the animals once daily for 10 consecutive days starting from the first day of formaldehyde injection. The daily changes in the paw sizes were measured using cotton thread and metre rule as in carrageenan model. Changes in paw sizes of the extracts administered groups were compared with that of the control group.

Ulcerogenic studies

This study was carried out by modifying the methods used by Singh et al. (1997) and Goel et al. (1986). Animals were administered the extracts (50–800 mg/Kg), saline or indomethacin once daily for three consecutive days. Animals were fasted for 24 h before the administration of the first and last doses of the drug, extracts or saline. The animals were sacrificed with an over dose of ether 12 h after the last dose of extracts, indomethacin or saline and their abdominal cavity was dissected. The stomachs were removed, slit open through the greater curvature, washed with normal saline and viewed under a hand held lens (x10) for the presence of mucosal irritation. Ulceration was scored according to the arbitrary scale used by Singh et al. (1997), where 0 = no lesion, 0.5 = hyperaemia, 1 = one or two slight lesions, 3 = very severe lesions, 4 = mucosa full of lesions. Ulcer index was calculated as mean ulcer scores (Tan et al., 1996).

Phytochemical analysis

Preliminary phytochemical analysis of the extract was performed using the method described by Trease and Evans (1989) and other authors as follows:

Alkaloids: 1.0 ml of 1 % v/v HCl was added to 3.0 ml of the extract of the plant in a test tube. The mixture was heated for 20 minutes, cooled and filtered. The filtrate was then used for the following tests:
- 2 drops of Mayer's reagent was added to 1.0 ml of the extract. A creamy precipitate indicated the presence of alkaloids in the extract.
- 2 drops of Wagner's reagent was added to 1.0 ml of the extract. A reddish brown precipitate indicated the presence of alkaloids (Harborne, 1973).

Tannins: 1.0 ml of freshly prepared 10 % w/v ethanolic KOH was added to 1.0 ml of the extract. A dirty white precipitate indicates the presence of tannins (Odebiyi and Sofowora, 1978).

Anthraquinone: 3.0 ml of the extract was shaken with 10.0 ml of benzene, the mixture was filtered and 5.0 ml of 10 % v/v NH_3 solution was added to the filtrate. The presence of a pink, red or violet colour in the ammoniacal (lower) phase indicated the presence of free hydroxyl anthraquinones (Trease and Evans, 1989).

Saponins: (Frothing Test) – 2.0 ml of the extract in test tubes were vigorously shaken with water for 2 minutes and warmed. Frothing which persisted on warming indicated the presence of saponins (Wall et al., 1954).

Cardenolides: 1.0 ml of the extract was added to 2.0 ml of glacial acetic acid containing one drop of 5 % w/v $FeCl_3$ solution. This was followed by 2.0 ml of concentrated H_2SO_4. A brown ring at the interface indicated the presence of a deoxy sugar characteristic of Cardenolides (Trease and Evans, 1989).

Phenolics: 2 drops of 5 % w/v $FeCl_3$ was added to 1.0 ml of each of the plant extract. A greenish precipitate indicated the presence of Phenolics (Awe and Sodipo, 2001).

Cardiac glycosides: (Salkowski Test) – 1.0 ml of the extract was added to 2.0 ml of Chloroform and H_2SO_4 was carefully added. A reddish-brown colour at the interface indicated the presence of aglycone portion of cardiac glycoside (Sofowora, 1993).

Flavonoids: 1.0 ml of 10 % w/v NaOH was added to 3.0 ml of the extract. A yellow colouration indicated the presence of flavonoids (Awe and Sodipo, 2001).

Steroids: 5 drops of concentrated H_2SO_4 were added to 1.0 ml of the extract. Red colouration indicated the presence of steroid (Trease and Evans, 1989).

Reducing Sugars: Two drops of Fehling's A and B solution were added to 0.5 g of the extract. Deep blue or black colouration indicates the presence of reducing sugars (Awe and Sodipo, 2001).

Table 1. Effects of the ethanolic extract of *Carica papaya* leaves on carrageenan induced paw oedema in rats

Group	Dose (mg/kg) orally	Paw size (mm)[a]		Inhibition (%)	
		3h	5h	3h	5h
Control	–	8.2 ± 0.8	9.6 ± 0.6	–	–
C. papaya	25	5.2 ± 0.4*	2.2 ± 0.4***	36.6	77.1
C. papaya	50	3.2 ± 0.4*[b,c]	1.6 ± 0.4***	61.0	83.3
C. papaya	100	2.8 ± 0.3**[b,c]	1.4 ± 0.5***	65.9	85.4
C. papaya	200	2.6 ± 0.5***[b,c]	0.6 ± 0.3***[b,c]	68.3	93.8
Indomethacin	5	5.8 ± 0.6*	1.8 ± 0.4***	29.3	81.3

[a] Each value is the mean ± S.E.M. for 5 rats
* P <0.05; **P <0.01; *** P <0.001 compared with control;
[b] p <0. 05 compared with 25 mg/Kg;
[c] p <0. 05 compared with Indomethacin; Student's t-test

Statistical analysis

In this study values are expressed as mean ± standard error of the mean (SEM). Statistical significance was determined using the Student's t-test. Values with p <0.05 compared with the control group were considered as being significantly different.

Results

Anti-inflammatory studies

The results of the carrageenan oedema test show that there was a significant (p <0.05) and dose dependent reduction of the paw size from 8.2 ± 0.8 (control group) to 2.6 ± 0.5mm (200 mg/Kg group) after 3 h of extract administration (Table 1). Likewise the extract (25-200 mg/Kg) produced significant (p <0.05) reduction of paw sizes compared with indomethacin (Table 1).

In the granuloma test the extract at the dose range 25–200 mg/Kg significantly (p <0.05) reduced the amount of granuloma formed. The highest dose (200 mg/Kg) reduced the weight of granuloma from 0.58 ± 0.07 (control group) to 0.20 ± 0.03 g (Table 2).

The results obtained from the formaldehyde induced arthritis show that the extract at the dose range of 25–200 mg/Kg significantly (p <0.05) reduced the level of inflammation in the arthritic rats. The trend of the activity of the extract closely resembles that of indomethacin (Fig. 1).

Ulcerogenic studies

The results of the ulcerogenic study are shown in Table 3. The results show that the extract produced significant gastric mucosal irritation only at high doses (i. e. ≥200 mg/Kg). However, only the 800 mg/Kg of the extract produced comparable ulcerogenic effect with a standard ulcerogenic dose of indomethacin (20 mg/Kg).

Phytochemical analysis

Preliminary phytochemical analysis of the extract revealed the presence of alkaloids, flavonoids, saponins, tannins, cardiac glycosides, anthraquinones, reducing sugars, steroids, phenolics and cardenolides.

Discussion and conclusion

In the present study, the anti-inflammatory activity of the ethanol extract of *C. papaya* has been established using the carrageenan-induced paw oedema, cotton pellet granuloma and formaldehyde-induced arthritis models. These methods are used to evaluate inflammation at acute, subchronic and chronic stages respectively. The carrageenan paw oedema test was used in this study based on its several advantages which include the ability to detect orally acting anti-inflammatory agents especially in the acute phase. In fact, it has been reported that the carrageenan test was very useful in the discovery of the anti-inflammatory activity of indomethacin (Di Rosa, 1972). Furthermore, the carrageenan oedema model has two distinct phases (Vinegar et al., 1969; Olajide et al., 2000; Hosseinzadeh and Younesi, 2002; Gupta et al., 2003; Parvataneni et al., 2005). The first phase starts immediately after carrageenan injection and lasts for about two and half hours while the second phase starts after the first phase and ends at about six hours after carrageenan injection (Di Rosa, 1972; Willis and Cornelson, 1973). Serotonin, histamine and kinins have been strongly linked with the inflammatory process in the early phase (Crunkhon and Meacock,

Table 2. Effects of the ethanolic extract of *Carica papaya* leaves on Cotton pellet- induced granuloma in rats

Group	Dose (mg/kg) orally	Increase in weight of pellet (g)[a]	Inhibition (%)
Control	–	0.58 ± 0.07	–
C. papaya	25	0.22 ± 0.04**	62.1
C. papaya	50	0.22 ± 0.04**	62.1
C. papaya	100	0.20 ± 0.04**	65.5
C. papaya	200	0.19 ± 0.03***	65.5
Indomethacin	5	0.17 ± 0.02***	70.7

[a] Each value is the mean ± S.E.M. for 5 rats
* P <0.05; **P <0.01; *** P <0.001 compared with control; Student's t-test

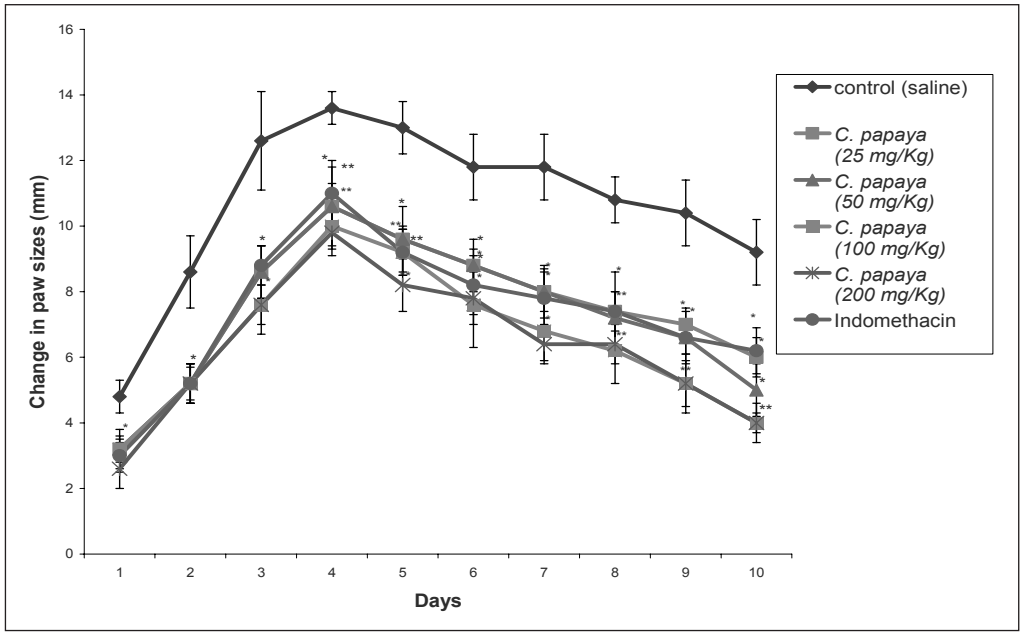

Fig. 1. Effect of ethanolic extract of *Carica papaya* leaves on formaldehyde induced arthritis in rats. Each value is the mean ± S.E.M. of 5 rats. *** P <0.001 compared with control; Student's t-test.

Table 3. Effects of the ethanolic extract of *Carica papaya* leaves on gastric mucosa

Group	Dose	Incidence of ulcer (%)	Ulcer score[a]
Control (saline)	–	0	0.0 ± 0
C. papaya	50 mg/Kg	0	0.0 ± 0[e]
C. papaya	100 mg/Kg	0	0.0 ± 0[e]
C. papaya	200 mg/Kg	20	0.3 ± 0.10***[b,e]
C. papaya	400 mg/Kg	60	1.2 ± 0.2***[c,e]
C. papaya	800 mg/Kg	100	1.8 ± 0.22***[d]
Indomethacin	20 mg/Kg	100	2.0 ± 0.20***

[a] Each value is the mean ± S.E.M. for 5 rats.
* P <0.05; **P <0.01; *** P <0.001 compared with control. [b] P <0.05 vs 50 and 100 mg/Kg, [c] P <0.05 vs 50, 100 and 200 mg/Kg, [d] P <0.05 vs 50, 100, 200 and 400 mg/Kg, [e] p<0. 05 compared with Indomethacin; Student's t-test.

1971) while prostaglandins are mainly involved in the second phase of the oedema (Vinegar et al., 1969). Although these two phases have been identified, it is generally accepted that carrageenan functions maximally after 3 h of its administration. Therefore, the result of the carrageenan test shows that the ethanol extract of *C. papaya* can inhibit prostaglandins mediated inflammation since the extract produced marked reduction in the carrageenan induced oedema after 3 and 5 h of carrageenan injection (Table 1.).

The formaldehyde test is also a commonly used model for the evaluation of arthritis (Saxena et al., 1984; Singh et al., 1997; Hosseinzadeh and Younesi, 2002). In this model the animal experiences inflammatory pain both in the limbs and joints. The results obtained from this test show that the extract can inhibit arthritis. The trend of the anti arthritic activity of the extract closely resembles that of the standard reference drug (indomethacin). Likewise this trend resembles those obtained from other previous studies on some medicinal plants (Owoyele et al., 2005; Singh et al., 1997; Hosseinzadeh and Younesi, 2002.)

According to Parvataneni et al. (2005) cotton pellet granuloma is the most suitable method for studying the efficacy of drugs against proliferative phase of inflammation. The dry weight of the pellets correlates well with the amount of granulomatous tissue (Swingle and Shideman, 1972). The extract of *C. papaya* produced significant inhibition of granulomatous tissue formation. This indicates that the extract can inhibit sub chronic inflammation in which various types of cellular migration are (e. g. fibroblast) involved (Olajide et al., 2003).

In the ulcerogenic study, the lower doses (≤100 mg/Kg) produced no significant ulceration of the gastric mucosa. However the result indicates that only the extract dose of 800 mg/Kg can produce gastric effect that is similar to a standard ulcerogenic dose of indomethacin. The design of the ulcerogenic test and the result obtained closely resemble that of other authors (Goel et al., 1986; Singh et al., 1994; Olajide et al., 1998; Pandit et al., 2000; Goulart et al., 2005). Although a higher dose of indomethacin was used in this study compared with those of the anti-inflammatory studies, nevertheless the dose of indomethacin used for the ulcerogenic test was in accordance with standard practices since a lower dose of indomethacin may not have produced gastric irritation during the short days of administration as is the case in this study. The general observation from the ulcerogenic study show that lower doses of the extract may not be acting via the mechanism of action of non steroidal anti-inflammatory drugs (NSAIDs) because of the apparent inability of the extract (≤200 mg/Kg) to produce gastric irritation. NSAIDs have various degrees of anti-inflammatory and ulcerogenic activities. Further studies are required before the mechanism of action of the extract or its active

constituent can be identified. This is because some NSAIDs (e. g. Celecoxib and rofecoxib) are selective inhibitors of cyclooxygenase 2 (COX 2) and they produce anti-inflammatory effect without gastric mucosal irritation (Steinmeyer, 2000). Thus the extract at lower doses might be manifesting its anti-inflammatory activity like the COX selective inhibitors. On the other hand since the extract contain active constituents such as flavonoids, alkaloids and tannins it may be possible that the extract is acting via a different mechanism. For instance some flavonoids may act via NSAID mechanism and some may act by scavenging reactive oxygen species, etc (Nafeeza et al., 2002; Graziani et al., 2005 Zayachkivska et al, 2005).

Phytochemical analysis also shows that the extract contains saponins, cardiac glycosides, anthraquinones and reducing sugars in addition to flavonoids, alkaloids and tannins that were mentioned earlier. These findings agree with the report of previous authors which showed that the leaves (especially dried ones) contain alkaloids (including carpain and pseudocarpain) flavonols, glycosides, tannins, saponins and phenolics (Tang, 1979; Duke, 1984; Gill, 1992). Other constituents reported by Gill (1992) includes nicotinic acid and tocopherol. *Carica papaya* leaves also contain benzyglucosinolate (MacLeod and Pieris, 1983). Alkaloids, flavonoids, saponins, tannins and glycosides have all been associated with various degrees of anti-inflammatory activities (Gene et al., 1994; Wang et al., 1994; Olaleye et al., 2002; Hosseinzadeh and Younesi, 2002). Therefore the anti-inflammatory effects observed in this study may be due to the activity of one or a combination of some of the identified constituents. The latex of the fresh aerial part of the plant, the fruit and not the dried leaves (used in this study) are rich in papain- a protein that have been linked with several biological activity of the plant. The methods used for the identification of phytochemical constituents are preliminary in nature therefore further studies are required to identify the presence of other constituents and the relative concentration of each constituents in the leaves.

The method used in this study for obtaining the extract was similar to the method commonly used by local medical practitioners except that we proceeded further to prepare solid extract and administered the extract in quantifiable dosages (25- 200 mg/Kg). The local medical practitioners prescribe the liquid decoction in wine cups and it is slightly difficult to quantify the effective dosages administered since many practitioners will not quantify the weight of dried leaves used. Thus in arriving at the dosages used in this study we followed the common pattern of dosages used in anti-inflammatory studies especially on crude extracts (Singh et al., 1997; Olajide et al., 2000; Gupta et al., 2003; Owolabi and Omagbai, 2007). However, we assume that the 25 mg/Kg may be close to the quantity prescribed daily by the local medical practitioners.

In conclusion, this study has established the anti-inflammatory activity of the ethanolic extract of *C. papaya.* Further basic and clinical studies are required in order to identify the exact active ingredient, determine the precise mechanism of action and to examine the toxicity of the extract.

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