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Original Research Article

Potential Therapeutic Effects of Flavonoid-Rich Extract of *Carica Papaya* Against Inflammation, Pain, and Pyrexia in Experimental Animals

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ABSTRACT

Most diseases has deleterious clinical presentations that are highly discomforting to the patients, often time the treatment and management of these symptoms with known drugs comes with adverse side effects, hence the need for a natural remedy. This study explored the potential therapeutic benefits of a flavonoid-rich extract from *Carica papaya* (FRECP) on experimental models to study the ant-inflammation, anti-fever and pain relief efficacy. The anti-inflammatory effect was studied using the carrageenan-induced paw oedemamodel. Acetic acid-induced writhing and tail immersion models were utilised for the test for analgesia, whereas Brewer's yeast-induced and dinitrophenol models were used for the antipyretic study. Each of the 5 investigations involved the random allocation of thirty (30) albino rats into 5 groups, each consisting of 6 animals. Groups 1 and 5 were given distilled water and the conventional medication, whereas groups 2 to 4 received 100, 200, and 400 mg/kg of oral FRECP in each research. The study's results indicated that the observed advantages, especially at the dosage of 400 mg/kg, indicate that the flavonoid content of FRECP hinders crucial enzymes that play a role in inflammation and the production of prostaglandins and decrease discomfort, and pyrexia in a manner that depended on both the dosage and time of administration ($p<0.05$). We determined that the flavonoid-rich extract of Carica papaya has pharmacological effects on inflammation, pain, and fever.

Key words: Inflammation, Pain, Fever, *Carica papaya*, Therapeutic intervention.

Introduction

Inflammation is the protective response of tissues to harmful stimuli like bacteria and irritants. It enhances vascular permeability, leading to the migration of leukocytes to the affected area, resulting in discomfort, oedema, and loss of function.[1,2] The objective of inflammation is to remove harmful stimuli like microorganisms, destroy damaged cells and tissues, and start the tissue repair process. The process is intricate and involve elements of the immune system, blood vessels, and different biological ligands related to cellular signalling.[3] Inflammation can be categorized as acute or chronic. Acute inflammation is a brief phase characterized by vascular and cellular processes.[3] Chronic inflammation persists for an extended period and can cause activated macrophages to release different mediators, leading to tissue damage, especially in conditions like rheumatoid arthritis and haematological illnesses.[4] Pain, according to the International Association for the Study of Pain (IASP), is a feeling linked to real or possible harm to tissue.[5] Pain, similar to inflammation, has a defensive function in an organism.[6]

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The organism's innate capacity to experience pain and develop defensive responses in response to the pain's source is essential for its survival and welfare.[6] Unmitigated pain often causes suffering and impairs an individual's capacity to perform daily activities, leading to increased medical expenses and economic burdens for both the patient and society as a whole.[7]

Fever, also known as pyrexia, is a medical symptom linked to several illnesses like infection, characterized by an increase in body temperature above the usual range of 36.0°C to 37.5°C.[8] Pyrexia serves as a protective mechanism by creating an environment that is hostile to pathogens like bacteria, fungus, and viruses.[8] Pyrogens stimulate the production and release of cytokines such as interleukins and TNF, leading to the production of prostaglandin E2 (PGE2) in the pre-optic hypothalamic region. This process raises body temperature by generating heat and reducing heat loss. Pyrexia often accompanies symptoms such as sweating and chills. It is a common symptom associated with various ailments and diseases like malaria and typhoid.[8]

Non-steroidal anti-inflammatory medicines (NSAIDs) are the primary medications used to treat inflammation, pain, and fever.[9] NSAIDs can cause side effects including nausea, shortness of breath, gastrointestinal issues, and dependency.[9] NSAIDs have been linked to more severe adverse effects, including neurotoxicity, hepatotoxicity, and nephrotoxicity.[9,10] The concerns with the usage of NSAIDs have prompted the need to find a new, effective, and safer treatment for inflammation, pain, and fever.[10]

Around 80% of the global population, particularly individuals from African and Asian regions, rely on both traditional and alternative medicine as their main source of healthcare.[11] Medicinal plants have phytochemicals that exhibit a broad range of pharmacological effects against many diseases and ailments.[11] They have been used as starting

points for drug research and development.[12,13] *Carica papaya* is a plant with significant folklore history. *Carica papaya*, a member of the Caricaceae family, is frequently referred to as the pawpaw tree. It is found in Asia and subtropical regions such as Nigeria.[14] Every portion of the plant possesses therapeutic characteristics and might be beneficial in treating various illnesses. *Carica papaya* has been documented to exhibit several pharmacological actions such as analgesic, antifungal, antibacterial, antiviral, cardioprotective, antihypertensive, laxative, and gastroprotective effects.[15] This study assessed the potential anti-inflammatory, analgesic, and antipyretic properties of a flavonoid-rich extract from *Carica papaya* using experimental models of inflammation, pain, and fever.

Materials and Methods

Materials

Experimental Animals

Adult albino rats and mice, weighing on average 178.5 ± 22.24g and 20.4 ± 2.46g respectively, were housed in well-ventilated cages under typical laboratory settings; well-ventilated space with adequate supply of distilled water and grower's mash. They were provided with distilled water and normal rodent diet (grower's mash) for the whole trial period. This study received an ethical clearance from the ethical committee of Microbiology and laboratory Sciences of SIMAD university.

Methods

Plant collection and identification

Carica papaya leaves were gathered from their native habitat in Mogadishu, Somalia from a period of February – March, 2024. The plants were recognized using a standard identification key[16] by a botanist and was assigned a herbicidal voucher code CP-A45.

Extraction and Preparation of Flavonoid-rich Extract

Carica papaya leaves were air-dried for 5 days. It was then crushed using an electric blender. Approximately 2000g of the crushed leaves were immersed in ethanol for 72 hours with mild agitation. The mixture was subsequently filtered with Whatman filter paper. The procedure was repeated, and the filtrates were concentrated using a water bath set at 60 °C to yield the crude extract of *Carica papaya*.[17] A known quantity of 9 g of the crude extract was diluted in 60 mL of 10 % sulfuric acid to create a flavonoid-rich extract.[17] The mixture was heated on a water bath at 100 °C for 30 minutes. Afterward, the mixture was cooled on ice for 15 minutes to cause the flavonoids and aglycones to separate out.[17] The precipitate that was obtained was dissolved in 50 ml of 100% ethanol, heated on a water bath at 50 °C, and then centrifuged and filtered.[17] The filtrate was concentrated with a rotary evaporator to obtain the flavonoid-rich extract of *Carica papaya* leaves (FRECP).

Carrageenan-induced paw oedema in rats

The investigation was carried out using the method of Winter et al. In this investigation, sixteen albino rats were used. The albino rats were divided into 5 groups, each with 6 albino rats, at random, and then given the appropriate care.

Group 1 will be the control group and received 5ml/kg of distilled water. Group 2 orally received 100 mg/kg of FRECP as a pretreatment. 200 mg/kg was the pretreatment given to Group 3. 400 mg/kg was the pretreatment given to FRECP Group 4. FRECP Group 5 received 150 mg/kg of Aspirin as a pretreatment.

Each rat was given 0.1 ml of carrageenan suspension (1% w/v in normal saline) intradermally in the plantar region of the left hindpaw after a 30-minute treatment. A Vernier calliper was used to measure the paw diameter at 0, 1, 2, 3, and 4 hours. The following formula was used to estimate the % inhibition of oedema.

$$\%\ Inhibition\ of oedema = \frac{Mean\ oedema\ increase(Ct) - Mean\ oedema\ increase\ (Tt)}{Mean\ oedema\ increase\ (Ct)} \times 100$$

Where Ct = Control group at time 1, 2, 3 and 4 hours

Tt = Treated groups at time 1, 2, 3 and 4 hours

Acetic acid-induced writhing test

This was done in accordance with the steps outlined by Akuodor et al. and Singh and Majumbar.[17,18] For this investigation, thirty (30) albino mice were employed. The animals were given a 24-hour fast before being permitted to have water. They received the following care after being divided into 5 groups of 6 mice each:

Group 1: Oral 5ml/kg distilled water (control)
Group 2: Oral 100 mg/ kg FRECP
Group 3: Oral 200 mg/ kg FRECP
Group 4: Oral 400 mg/ kg FRECP
Group 5: Oral 150mg/kg Aspirin

After the mice were given the extract and aspirin for 30 minutes, they were given 20 ml/kg of 0.7% acetic acid intraperitoneally to induce writhing. After five minutes, each mouse's abdominal constrictions/writhings were counted and noted for a total of thirty minutes.[18,19]

Tail immersion test

For this investigation, the methodology outlined by Akuodor et al.[20] and Ramabadran et al.[19] was employed. For this investigation, thirty (30) albino mice were employed. The animals were given a 24-hour fast before being permitted to have water. They received the following care after being divided into 5 groups of 6 mice each:

Group 1: 5ml/kg distilled water (control)
Group 2: 100 mg/ kg FRECP
Group 3: 200 mg/ kg FRECP
Group 4: 400 mg/ kg FRECP
Group 5: 10mg/kg morphine

Following the aforementioned treatment for 30 minutes, each mouse's body was restrained and its tail was submerged in a 51°C hot water bath. The amount of time (latency) that the mouse can tolerate the pain before removing its tail from the water was observed and documented. We completed this at 30, 60, 90, and 120 minutes.

Yeast-induced pyrexia

The modified method by Mukherjee *et al*.[21], Akuodor *et al*.[18] and Essien *et al*. [22] was used for this study. Thirty (30) albino rats were used for this study. The animals were fasted for 24h but subsequently allowed to drink water. The basal rectal temperature of the rats was noted using a thermometer. Pyrexia was then induced in rats by administration of 20 ml/kg of 15% brewer's yeast s.c. 24 h later, rectal temperature was again examined and rats without elevated temperature above 0.5°C were not considered as having fever and hence not used for this study. The selected rats were randomized into 5 groups of 6 animals and treated as follows;

Group 1: 5ml/kg distilled water (control)
Group 2: 100 mg/ kg FRECP
Group 3: 200 mg/ kg FRECP
Group 4: 400 mg/ kg FRECP
Group 5: 150mg/kg Aspirin

The rectal temperature of each rat was again recorded at 1h interval during a 6 h period.

4-Dinitrophenol (DNP)-induced pyrexia

This study used the modified approach by Okokon and Nwafor[23] and Essien et al.[22] For this study, thirty (30) albino rats were employed. The animals were fasted for 24-hours before being permitted to have water. Prior to generating fever with 10 mg/kg of DNP, the basal rectal temperature was recorded. Rats without a rectal temperature increase of 0.5°C were deemed not to have pyrexia and were not included in this study. The temperature was measured 30 minutes later. The five groups of six rats that were randomly assigned were treated as follows:

Group 1: 5ml/kg distilled water (control)
Group 2: 100 mg/ kg FRECP
Group 3: 200 mg/ kg FRECP
Group 4: 400 mg/ kg FRECP
Group 5: 150mg/kg Aspirin

The rectal temperature of each rat was again recorded at 1h interval during a 6h period.

Statistical analysis

The study's mean ± S.E.M. was used to express the results. One-way ANOVA was used to analyze the data, and the Neuman-Keuls post hoc test was used to determine whether the mean differences were significant at $p<0.05$.

Results and Discussion

The anti-inflammatory effect of FRECP in rats with paw oedema caused by carrageenan is displayed in Table 1. FRECP resulted in a dose- and time-dependent substantial ($p<0.05$) reduction in the rat paw oedema caused by carrageenan. Table 4 presents the % inhibition of FRECP's ability to minimize paw oedema for better understanding. The findings demonstrated that at 4 hours, 400 mg/kg FRECP produced an oedema inhibition percentage (47.12%) that was like that of the reference medication, aspirin, which caused an oedema inhibition percentage of 55.50 percent.

The impact of FRECP on acetic acid-induced abdominal constriction in mice is displayed in Table 3. Abdominal constrictions were significantly ($p<0.05$) reduced in a dose-dependent manner by the extract. The percentage inhibition of abdominal constriction (88.82%) generated by FRECP at 400 mg/kg was comparable to that of the reference medication, aspirin (89.80%).

Table 1: Effect of the Administration of Flavonoid-rich Extract of *Carica papaya* Leaves (FRECP) on Carrageenan-induced paw oedema in rats

Treatment Groups	**Mean changes in paw oedema± standard error of mean**			
	1h	**2h**	**3h**	**4h**
Control (5ml/kg Distilled water)	0.193 ± 0.028^{c}	0.188 ± 0.048^{c}	0.190 ± 0.039^{c}	0.191 ± 0.047^{c}
FRECP 100mg/kg	0.190 ± 0.032^{c}	0.170 ± 0.011^{bc}	0.162 ± 0.033^{bc}	0.151 ± 0.093^{b}
FRECP 200mg/kg	0.161 ± 0.011^{b}	0.150 ± 0.073^{b}	0.145 ± 0.062^{ab}	0.123 ± 0.068^{ab}
FRECP 400mg/kg	0.142 ± 0.047^{ab}	0.135 ± 0.068^{a}	0.122 ± 0.093^{a}	0.101 ± 0.023^{a}
Ketoprofen (20 mg/kg)	0.130 ± 0.036^{a}	0.123 ± 0.049^{a}	0.111 ± 0.021^{a}	0.085 ± 0.011^{a}

Data are presented as mean ± SD, (n=6). Mean values with different alphabets as superscripts down the column are significantly different at $P<0.05$

Table 2: Percentage inhibition of carrageenan-induced rat paw oedemaby FRECP

Treatment	**Percentage inhibition of oedema(%)**			
	1 h	2 h	3 h	4 h
FRECP 100mg/kg	01.55	9.57	14.74	20.94
FRECP 200mg/kg	16.58	20.21	23.68	35.60
FRECP 400mg/kg	26.42	28.19	35.79	47.12
Ketoprofen (20 mg/kg)	32.64	34.57	41.58	55.50

Table 3: Effect of the Administration of Flavonoid-rich Extract of *Carica papaya* Leaves (FRECP) on Acetic acid-induced Writhing in Mice

Treatment	**Abdominal Constrictions**	**% Inhibition**
(5ml/kg Distilled water)	28.44 ± 1.23^{c}	0.00
FRECP 100mg/kg	11.06 ± 0.99^{b}	61.11
FRECP 200mg/kg	9.21 ± 0.74^{b}	67.41
FRECP 400mg/kg	3.18 ± 0.28^{a}	88.82
Aspirin (20 mg/kg)	2.90 ± 0.36^{a}	89.80

Data are presented as mean ± SD, (n=6). Mean values with different alphabets as superscripts down the column are significantly different at $P<0.05$.

FRECP produced protection against the hot-bath's heat stimuli in a dose- and time-dependent manner on rat tail-flick latency. A similar protective effect to that of morphine was obtained with a dose of 400 mg/kg of FRECP (Table 4). The effects of FRECP on pyrexia in rats caused by brewer's yeast and pyrexia in rats induced by DNP are displayed in Tables 5 and 6, respectively. For all models, FRECP resulted in a significant ($p<0.05$) lowering of pyrexia as early as 2 hours after treatment and continued for an additional 6 hours. FRECP's activity was on par with that of the reference medication, particularly when administered at the maximum dose of 400 mg/kg. Several discomforting symptoms of many diseases affecting people and other animals include inflammation, pain, and fever. These conditions can lead to a reduced quality of life, depression, death[24-26]. Regretfully, there aren't many affordable therapeutic options for treating fever, pain, or inflammation. These options typically entail using various types of analgesic and anti-inflammatory medications, which might have minor to severe side effects.[27] Gastric ulcers, toxicity to numerous organs, dependence, and tolerance are a few of these adverse consequences.[28-30] Herbal medicines are thought to be safer, more effective, more accessible, and less expensive.[24, 31,32] Therefore, this investigation was conducted to assess the possible antipyretic, analgesic, and anti-inflammatory properties of the *Carica papaya* flavonoid-rich extract against experimental. A common technique for assessing the anti-inflammatory properties of compounds and medicinal plants is

carrageenan-induced oedema[33]. When rats are given carrageenan, their paws become acutely inflamed, making them ideal for testing anti-inflammatory drugs[34]. Rats develop paw oedema in response to carrageenan in two stages, which are typically depicted as a biphasic curve.[34] The first stage involves the release of either serotonin or histamines and lasts from 0 to 2.5 hours after injection.[35]

Table 4: Effect of the Administration of Flavonoid-rich Extract of *Carica papaya* Leaves (FRECP) on rat-tail Immersion in 51 ± 1°C hot bath

Treatment/Duration of stay	0 min	30 min	60min	90 min	120 min
(5ml/kg Distilled water)	5.47 ± 0.13[a]	5.99 ± 0.23[a]	5.83 ± 0.09[a]	5.79 ± 0.02[a]	6.01 ± 0.11[a]
FRECP 100mg/kg	5.81 ± 0.19[a]	7.01± 0.73[a]	9.32 ± 0.35[ab]	11.26 ± 0.99[ab]	13.23 ± 0.23[ab]
FRECP 200mg/kg	5.23 ± 0.14[a]	6.58 ± 0.93[a]	15.63 ± 0.48[b]	18.43 ± 0.28[b]	20.95 ± 0.12[b]
FRECP 400mg/kg	5.46 ± 0.12[a]	7.45 ± 0.08[a]	17.11 ± 0.44[b]	24.99 ± 1.13[c]	27.45 ± 0.74[c]
Morphine (10 mg/kg)	5.11 ± 0.26[a]	7.83 ± 0.22[a]	20.83 ± 0.39[c]	25.01 ± 1.99[c]	28.23 ± 0.13[c]

Data are presented as mean ± SD, (n=6). Mean values with different alphabets as superscripts down the column are significantly different at $P<0.05$

Table 5: Effect of the Administration of Flavonoid-rich Extract of *Carica papaya* Leaves (FRECP) on Brewer's yeast- induced pyrexia in Rats

Treatment	0 h	1 h	2 h	3 h	4 h	5 h	6 h
Control 5ml/kg Distilled water	37.34±0.04[a]	37.43±0.03[a]	37.11±0.02[b]	37.57±0.05[b]	37.39±0.04[b]	37.57±0.01[b]	37.58±0.04[b]
FRECP 100 mg/kg	37.48±0.05[a]	37.57±0.04[a]	36.38±0.09[a]	36.93±0.05[a]	36.01±0.02[a]	36.19±0.04[a]	36.19±0.01[a]
FRECP 200 mg/kg	37.11±0.05[a]	37.73±0.07[a]	36.34±0.04[a]	36.11±0.09[a]	36.37±0.05[a]	36.47±0.08[a]	36.26±0.05[a]
FRECP 400 mg/kg	37.05±0.05[a]	37.92±0.06[a]	36.84±0.04[a]	36.34±0.03[a]	36.13±0.03[a]	36.13±0.03[a]	36.15±0.05[a]
Aspirin 150 mg/kg	37.18±0.04[a]	37.82±0.08[a]	36.22±0.01[a]	36.44±0.06[a]	36.68±0.06[a]	36.26±0.02[a]	36.09±0.09[a]

Data are presented as mean ± SD, (n=6). Mean values with different alphabets as superscripts down the column are significantly different at $P<0.05$

About three hours after administration, the oedema reaches its peak size and starts to recede. The release of prostaglandins, lysosomes, proteases, and bradykinins typically triggers the second stage of inflammation.[35-36]

In this investigation, the diameter of the rats' paws increased when 1% carrageenan was injected into the sub-plantar region, suggesting inflammatory activity. According to the findings, FRECP suppressed inflammation in a way that was dependent on both dose and duration. The maximum anti-inflammatory activity was obtained by FRECP at 400 mg/kg, which was equivalent to the several drug's effects. It is reasonable to conclude that FRECP's flavonoid content may contribute to its capacity to suppress inflammation. Flavanoids can prevent the release of inflammatory mediators or their effects, which lowers oedema.[36] By binding to and blocking key enzymes like cyclooxygenase, nitric oxide synthase, and lipoxygenase, which are involved in the manufacture of inflammatory chemicals, the flavonoids of FRECP may have worked in concert with the saponins to eradicate inflammation. A sensitive technique for assessing possible anti-nociceptive medications or substances that operate peripherally, like NSAIDs,[37-38] and centrally, like morphine, is the acetic acid-induced writhing. [38-39] Mice given acetic acid intraperitoneally experience writhing in the abdomen because of prostaglandins sensitizing their chemoreceptors.[40] Forty Prostaglandins, particularly PGE2 and PGE1, have been linked to elevated levels in peritoneal fluids and lipoxygenase products in this experimental setting.[41] This is thought to increase capillary permeability, which in turn promotes inflammatory discomfort.[41-43] In this investigation, FRECP demonstrated time- and dose-dependent effect against writhes caused by acetic acid. The tail immersion experiment provides additional evidence for the analgesic impact of FRECP since it offers protective effects from the hot bath's heat in a way that was similar to how morphine did in this investigation. These findings suggest that FRECP may have both cerebral and peripheral antinociceptive effects.

When endogenous or exogenous stimuli, such as pyrogens, enter the host cells—monocytes and macrophages—pyrexia ensues.[44] The next set of events results in the production of pyrogenic cytokines such as tumor necrotic factor (TNF) and interleukins. The interaction of cytokines and their receptors in the anterior hypothalamic preoptic area triggers the activation of phospholipase A2, which catalyzes the conversion of arachidonate (a substrate for COX) into prostaglandins, which in turn may raise body temperature. A balance between heat generation and loss must be reached for the body temperature to remain within the normal range.[45] The way that medications like NSAIDS work to relieve fever is by preventing prostaglandin from being synthesized.[45] In a similar vein, any substance with antipyretic properties needs to be able to prevent prostaglandin formation. FRECP demonstrated dose and response-dependent antipyretic efficacy in tests including both DNP- and Brewer's yeast-induced pyrexia. Therefore, FRECP may have worked by preventing prostaglandin synthesis and activity.

Table 6: Effect of the Administration of Flavonoid-rich Extract of *Carica papaya* Leaves (FRECP) on Dinitrophenol- induced Pyrexia in Rats

Treatment	0 h	1 h	2 h	3 h	4 h	5 h	6 h
(5ml/kg Distilled water)	37.47±0.09[a]	37.26±0.03[a]	37.35±0.04[b]	37.98±0.04[c]	37.50±0.02[c]	37.57±0.09[c]	37.38±0.08[c]

FRECP 100 mg/kg	37.34±0.03[a]	37.45±0.06[a]	36.48±0.07[a]	36.55±0.05[b]	36.93±0.02[b]	36.38±0.02[b]	36.47±0.02[b]
FRECP 200 mg/kg	37.13±0.02[a]	37.37±0.02[a]	36.40±0.02[a]	36.45±0.09[b]	36.39±0.08[b]	36.30±0.03[b]	35.28±0.03[a]
FRECP 400 mg/kg	37.19±0.05[a]	37.28±0.04[a]	36.38±0.04[a]	36.54±0.02[b]	35.48±0.06[a]	35.83±0.01[a]	35.23±0.06[a]
Aspirin 150 mg/kg	37.47±0.02[a]	37.33±0.09[a]	36.58±0.09[a]	35.57±0.02[a]	35.47±0.05[a]	35.67±0.03[a]	35.29±0.03[a]

Data are presented as mean ± SD, (n=6). Mean values with different alphabets as superscripts down the column are significantly different at $P<0.05$

Conclusion

The extract of *Carica papaya* leaves, which is rich in flavonoids (FRECP), shown noteworthy anti-inflammatory, analgesic, and antipyretic properties in several animal models. It revealed similar effectiveness to standard medications such as aspirin and morphine. The observed advantages, especially at the dosage of 400 mg/kg, indicate that the flavonoid content of FRECP hinders crucial enzymes that play a role in inflammation and the production of prostaglandins. This presents a hopeful natural option for the management of inflammation, pain, and fever, potentially with fewer adverse effects.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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