Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i7.6990

THE ANTI-INFLAMMATORY POTENTIAL OF CARICA PAPAYA LINN. LEAVES: AN IN VIVO STUDY

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ABSTRACT

This study explores the anti-inflammatory activities of Carica papaya Linn. leaves. The research involved in vivo experimentation using rats as the animal model. The anti-inflammatory effect of papaya leaves was demonstrated through carrageenan-induced paw edema, a widely recognized method. Four different oral doses (100 mg/kg, 200 mg/kg, 300 mg/kg, and 400 mg/kg) were tested. Comparative analysis was conducted among the experimental, control, and reference groups. Statistical analysis using ANOVA and t-test ($p<0.05$) confirmed the anti-inflammatory properties of the leaves. All doses exhibited significant anti-inflammatory effects, with 300 mg/kg and 400 mg/kg doses showing particularly marked effects, displaying percent inhibition of paw edema comparable to or exceeding that of the reference drug, indomethacin. This method revealed that the anti-inflammatory activity of aqueous Carica papaya leaf extract is dose-dependent, with effects increasing over time. The results support the potential of aqueous papaya leaf extract for treating acute inflammatory diseases.

KEYWORDS: Inflammatory Diseases, Carica papaya, Anti-Inflammatory, Plant Extract, Therapeutic Dose, Oral Drug, Carrageenan Paw Edema, Pharmacological Activities, Rats.

1 INTRODUCTION

Inflammation is the body's protective response against foreign particle invasion or tissue injury that promotes healing of the tissue. US National Library of Medicine defines inflammation as "the body's immune system's response to stimulus". (Du, Bhatia, Tang, Zhang, & Steiner, 2015) The word 'Inflammation' is derived from Latin word 'Inflammare' meaning 'to burn'. Inflammation is a significant mechanism of body as it creates an alerting system, alarming the immune system of possible invasion of inflammatory substances or any tissue injury of external or internal origin. (Oronsky, Caroen, & Reid, 2022)

Inflammation can be subdivided into two categories:

a) Acute Inflammation: It is the type of inflammation that occurs spontaneously and disappears after some time. Examples include mild fever, small wound injury etc.

b) Chronic Inflammation: When the inflammatory reactions persists for long period of time they are termed as chronic inflammation. This occurs due to various causes like neurodegenerative disorders, autoimmune diseases, cardiovascular problems, mutagenic maladies etc. (Karim et al., 2019)

Carica papaya Linn. is the botanical name of the Papaya tree which is also commonly known as Papaya. Carica papaya belongs to the family Caricaceae, which is constituting of 34 species. Caricaceae family is further distributed into 6 genera, of which papaya belongs to genus Carica. (Alara, Abdurahman, & Alara, 2020) It is a tropical plant (Adel, Elnaggar, Al-Sayed, & Rabeh, 2021) commonly found and cultivated in various parts of the world. Its native origin was first suggested to be discovered in Central America.

Owing to the diverse nutritional and medicinal benefits of different parts of papaya tree that have been known to mankind for centuries, and its easy availability, people have been using it for the treatment of different ailments, along with its common utilization as a popular food and meat-tenderizing agent. (Abhishek et al., 2020; Deshpande et al., 2021) The leaves and flowers of the plant are cooked as spinach and soup. (Alara et al., 2020; Nagarathna et al., 2021; Sharma, Bachheti, Sharma, Bachheti, & Husen, 2020)

During certain clinical studies (Ahmad et al., 2011; Siddique, Sundus, & Ibrahim, 2014) and six different randomized clinical trials safety of oral treatment with papaya leaves extract has been recognized for adults as well as pediatric volunteers, for adult dose of as much as 500 mg while children aged more than a year were tested with formulation doses of 275 mg and further. (Sabir, Suciangto, Rahmani, Lestari, & Mubin, 2023)

Herbal medicines can be solely used as well as can also be used along with the modern medicines as a combined therapy to achieve maximum effective outcome, so as to take advantage from the rapid recovery rate of synthetic medicines and surpassing their undesirable side effects by the use of relatively safer and effective herbal drugs. (Abdulkhaleq et al., 2018)

2 MATERIALS AND METHOD

2.1 Animal Models

Wistar albino rats were used. Rattus norvegicus commonly known as Wistar rat is an outbred specie of albino rats originally breed at Wistar institute for laboratory biomedical research purpose and now widely outbred, supplied and used as common animal research model. (Clause, 1993; Palm, 1975)
The animals were provided by the Animal House of the Department of Pharmacology, located in the Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi.

The research study was approved by the Advanced Studies & Research Board (ASRB) of University of Karachi. All the animals used were in healthy condition and were retained in clean cages. The rats used had weights ranging between 180-200g. The animals were supplied with food and water ad libitum.

2.2 Plant Extract Preparation

The extract of Carica papaya Linn. leaves was prepared in aqueous medium. Leaves of papaya were cleaned and finely grounded in mortar and pestle. 400g of leaves were macerated with 2L of water. The mixture obtained was evaporated, dried and filtered. The aqueous papaya leaves extract was then stored in refrigerator for use.

2.3 Carrageenan Induced Paw Edema

Carrageenan induced paw edema method (Morris, 2003) is employed as initially stated by (Winter, Risley, & Nuss, 1962) and used to evaluate anti-inflammatory property of Carica papaya leaves by (Owoyele, Adebukola, Funmilayo, & Soladoye, 2008). Carrageenan solution was prepared to create inflammation in paw of the animal model. The animals were distributed in six groups with each group comprising a set of five rats. Group I, II, III, IV were experimental groups that were administered the plant extract in doses 100 mg/kg, 200 mg/kg, 300 mg/kg, and 400 mg/kg respectively. Group V was reference group which was given anti-inflammatory drug, Indomethacin, of brand name 'Indocin' manufactured by Siza International (Pvt.) Limited. Group VI was control group and received 0.1 ml of 0.9% normal saline. The doses tested were 100 mg/kg, 200 mg/kg, 300 mg/kg, and 400 mg/kg which were tested against control group and compared with the reference group drug indomethacin. Based on the marketed strength of indomethacin which is also the once oral adult dose i.e. 25mg for 75kg, the indomethacin was used at a dose of 0.3 mg/kg.

Table 1 Dosing Chart of Groups

Groups	Drug	Dose	Route	No. of animals
Group I	Carica papaya Leaf Extract	100 mg/kg	Oral	5
Group II	Carica papaya Leaf Extract	200 mg/kg	Oral	5
Group III	Carica papaya Leaf Extract	300 mg/kg	Oral	5
Group IV	Carica papaya Leaf Extract	400 mg/kg	Oral	5
Group V	Indomethacin	0.3 mg/kg	Oral	5
Group VI	Normal Saline 0.9%	0.1 ml	Oral	5

All doses were induced orally using 1 ml feeding tube having marked divisions of 100 units. After half an hour of introduction of doses, 0.1 ml of 1% freshly formulated carrageenan was inoculated in the sub plantar region of the right hind paw of rats via syringe. Measurement of rat paw sizes were performed with Vernier calipers having the least count of 0.05 millimeters (mm). The original rat paw sizes were measured and referred to as 0hr. After inserting carrageenan solution, paw dimensions were taken at hourly time intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr and were referred accordingly.
The edema was calculated by formula: $Edema = C_t - C_0$
The percentage inhibition of paw edema was calculated by formula (Olajide et al., 2000; Owoyele et al., 2008):

$$\%Inhibition = \frac{(C_t - C_0)\ \text{control} - (C_t - C_0)\text{treated} * 100}{(\ C_t - C_0)\text{control}}$$

Where,
C_t = paw size at time t after injecting carrageenan
C_0 = paw size at time 0 before injecting carrageenan
(C_t -C_0) control = paw size at respective time of control group
(C_t -C_0) treated = paw size at respective time of treated group

2.4 Statistical Analysis

Statistical analysis has been performed using statistical software of IBM (International Business Machines Corporation.) known as SPSS (Statistical Package for Social Sciences).

Data analysis was performed utilizing statistical measures; Mean, Standard Deviation (S.D.). One-way Analysis of Variance (ANOVA) was applied with multiple comparisons post-hoc test using Tukey HSD test. Statistical significance was find out with 95% confidence interval and p-values ≤ 0.05 were considered to be significant. The data values were also verified with independent sample t-test.

Percentage Inhibition calculations were performed and graphs were made using both MS Excel version 2016 and SPSS Statistics version 21.0.

3RESULT

The mean and standard deviations of paw sizes of each group of carrageenan induced rats at each time point is logged in **Table 2**. In **Fig. 1** mean paw sizes of all treatment groups were compared, it shows that mean paw sizes decline gradually with group III and IV showing the greatest reduction in paw sizes. **Fig. 2** represents the efficacy of papaya leaves extract doses and reference drugs where it can be seen that paw sizes of all groups decrease as the time passes with mean paw size exhibiting marked reduction at 6hr inferring reduction of swelling.
The details of results of percentage inhibition of experimental and standard drug are documented in **Table 3.** The **Fig. 3** illustrates that at 6hr percent inhibition of group III, IV and V were in quite similar proportions. **Fig. 4** shows that in all groups of carrageenan induced rats, edema is inhibited with the passage of time and the paw size almost returns to the original size after 6hr.

The observed edema is illustrated in **Fig. 5** which validates the drop in paw edema of carrageenan induced rats with groups III, IV and V showing noticeable reduction and group IV manifesting decrease even more than the reference group V.

The observations of all groups of carrageenan induced rats were analyzed statistically by applying one way ANOVA, Tukey HSD post hoc testing and the results were found to be significantly different at $p<0.05$. The observations were additionally testified from independent sample t test which displayed results of experimental groups to be noteworthy different than control groups at level of significance 0.05 i.e. confidence interval of 95%.

Table 2 Mean ± S.D. of paw sizes of carrageenan-induced rats

Groups	Size of Rat Paw (mm)*						
	0hr	1hr	2hr	3hr	4hr	5hr	6hr
Group I	3.30±0.07	5.65±0.12	5.10±0.09	4.65±0.11	4.50±0.12	4.45±0.07	4.29±0.18
Group II	3.25±0.07	4.60±0.07	4.43±0.10	4.40±0.07	4.20±0.07	4.04±0.04	3.79±0.09
Group III	3.20±0.11	5.60±0.07	5.10±0.07	4.65±0.09	4.06±0.06	3.45±0.07	3.40±0.07
Group IV	3.15±0.07	5.25±0.11	4.79±0.09	4.00±0.23	3.70±0.07	3.50±0.07	3.25±0.07
Group V	3.25±0.07	5.06±0.06	4.70±0.07	4.30±0.07	3.96±0.12	3.60±0.07	3.36±0.07
Group VI	3.35±0.20	5.50±0.15	5.75±0.09	5.90±0.09	6.10±0.07	6.40±0.07	6.65±0.07

*Each value is the mean ± S.D. for 5 rats

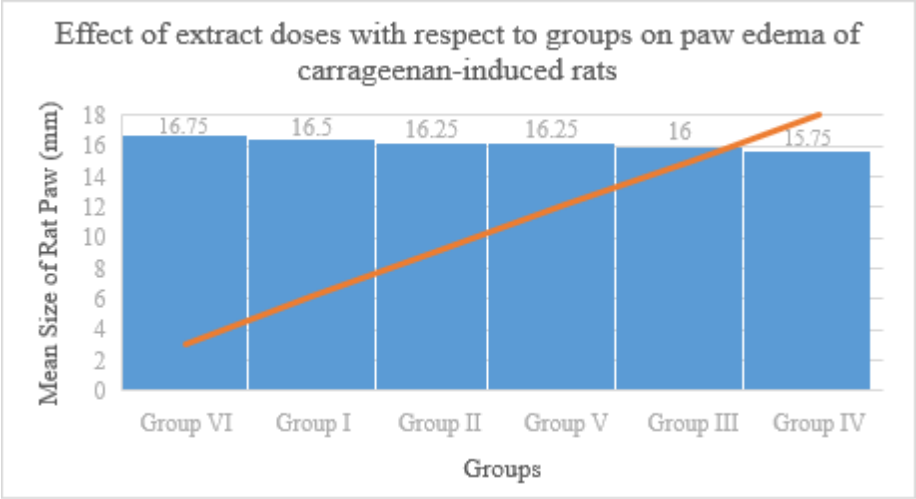

Fig. 1 Effect of extract doses with respect to groups on paw edema of carrageenan-induced rats

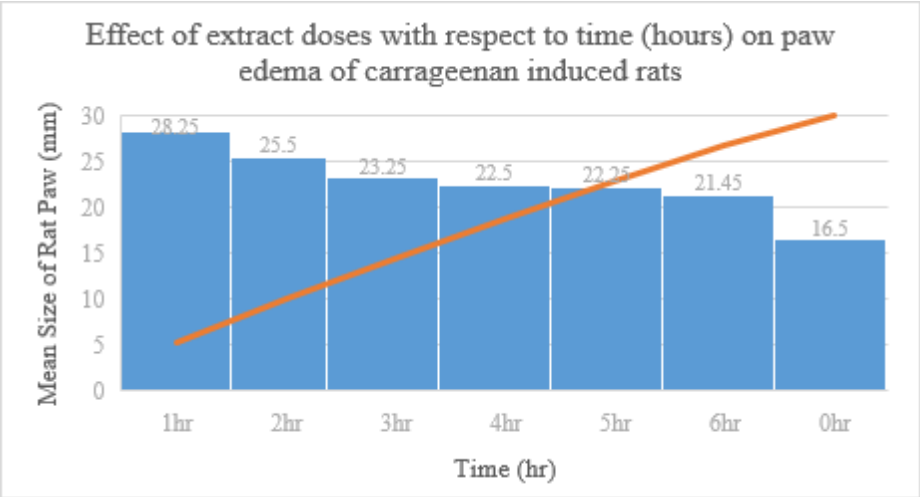

Fig. 2 Effect of extract doses with respect to time (hours) on paw edema of carrageenan-induced rats

Table 3 Percent (%) Inhibition of edema in paw of carrageenan-induced rats

Groups	0hr	1hr	2hr	3hr	4hr	5hr	6hr
Group I	-	-12.28%	33.47%	58.27%	67.80%	73.78%	80.64%
Group II	-	47.48%	62.12%	75.15%	76.21%	83.64%	90.67%
Group III	-	-13.65%	29.78%	55.18%	79.18%	95.58%	96.90%
Group IV	-	6.76%	43.07%	77.40%	87.86%	93.72%	98.51%
Group V	-	22.54%	50.61%	69.99%	83.23%	93.54%	98.31%
Group VI	-	-	-	-	-	-	-

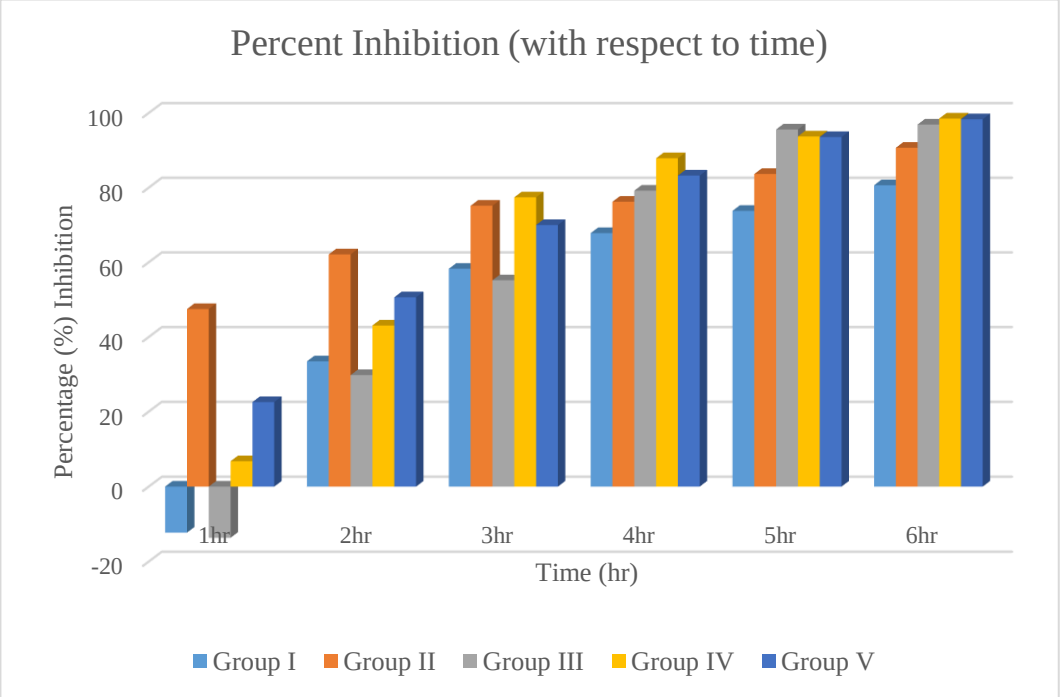

Fig. 3 Percent (%) Inhibition of edema with respect to hourly time intervals in paw of carrageenan-induced rats

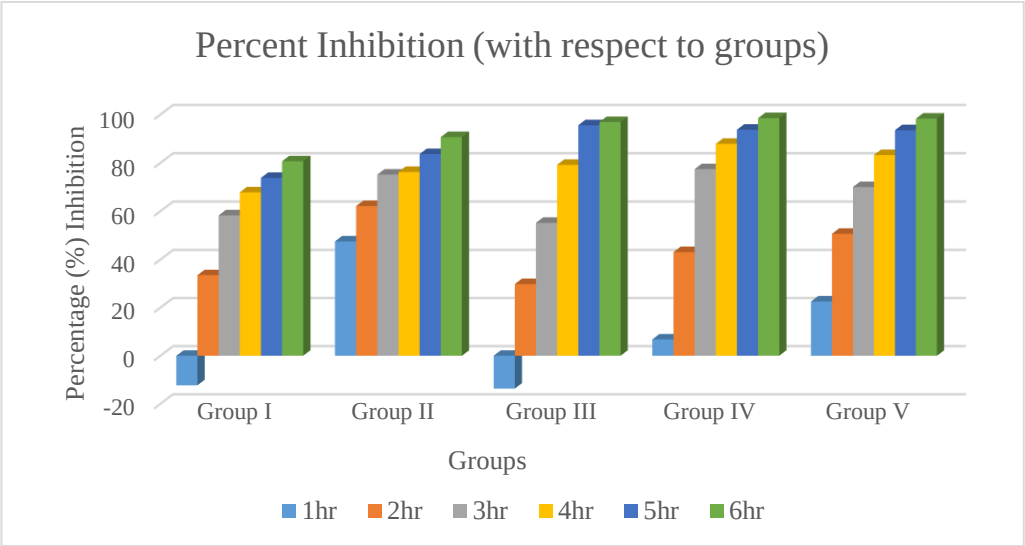

Fig. 4 Percent (%) Inhibition of edema with respect to dosing groups in paw of carrageenan-induced rats

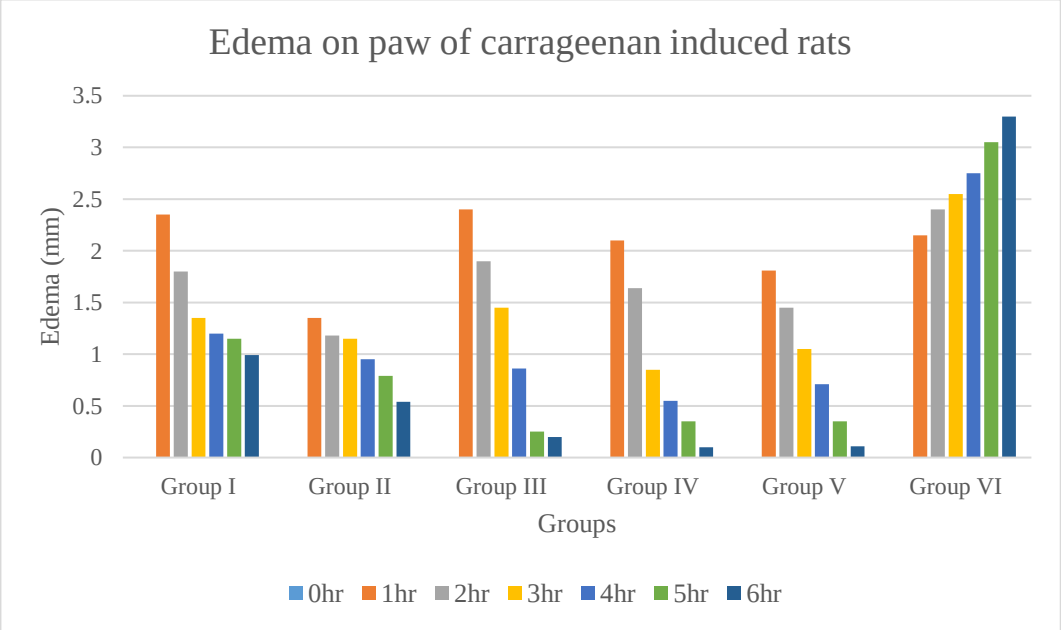

Fig. 5 Hourly intensity of edema in dosing groups of carrageenan-induced rats

4DISCUSSION

In the present world consumption of processed products along with several other factors have given risen to different physiological disorders among which inflammatory diseases are of noteworthy importance due to their large prevalence in human population.

Plants as a whole are rich in phytochemicals. Papaya is a plant of significance prominence in the developing world being source of different flavonoids and other bioactive constituents. It has various anti-oxidant components especially ascorbic acid (Vitamin C) which attributes for its pharmacological importance including its potent anti-inflammatory action. (Abdullah et al., 2011)

There is still a research gap and insufficiency of proof as a great extent of parts, constituents, and pharmaceutical activities of Carica papaya plant are undiscovered yet. Consequently, an effort has been made to uncover some area of this scope by providing documented evidence. Based on the ethno-medicinal claim of the anti-inflammatory action of papaya leaves, and the ancient use of papaya as an antagonist of inflammatory progressions, the contemporary work is planned to verify the

pharmacological action of papaya leaves against inflammation, and to explore up to what level the leaves of papaya tree are effective in reducing and reversing the inflammation.

Using Carica papaya Linn. is profitable as papaya is economical and easily accessible. Utilization of leaves will be supportive, in consuming the whole plant apart from fruit, avoiding wastage of other parts, and because of the abundance of leaves, promoting easy cost-effective availability and thus utility. Recognized methods have been implicit and subsequent slight variations been created too so as to judge the potency of papaya leaves with the disparity of dosage sizes, as well as with testing for greater time duration so as to establish standard evidence for its aptitude of inflammation inhibition.

Various methods and models exist for in vivo testing of anti-inflammatory molecules and compounds that utilize substances that are well-known irritants or mediators that are produced inside human body during inflammatory processes (Patil et al., 2019). From the different available methods, carrageenan induced paw edema method is applied here. The testing method is used to assess anti-inflammatory action of papaya leaves for greater time duration and with increased doses. It was witnessed that the potency of Carica papaya leaves increased in dose dependent manner and efficacy of doses were perceived to be directly proportional to time.

The paw edema produced is due to the inflammatory response occurring due to the exudation of various leukocytes and other pro-inflammatory cells and mediators migrating towards the affected area.

Carrageenan paw edema has been considered the most suitable inflammatory model for assessment of acute inflammation suppressing activity of drugs. (Morris, 2003; Owoyele et al., 2008) The application of carrageenan paw edema method has additionally been acknowledged because of its successful usage during drug development stages of indomethacin, a first choice therapeutic agent for arthritis (Di Rosa, Giroud, & Willoughby, 1971); which is why indomethacin is generally used as reference drug for judging oral anti-inflammatory compounds during such studies. (Owoyele et al., 2008)

Carrageenan in rats is known to work in three phases. First phase causes nociception and is considered to be because of vasodilation produced due to vasoactive amines 5HT, histamine. Second phase appears to be kinins mediated mainly contributed by vasoactive peptides, bradykinins. Whereas third phase triggers swelling which is believed to be due to the stimulation of cyclooxygenase pathway and subsequent involvement of prostaglandins. (Di Rosa et al., 1971; Morris, 2003)

Similarly it can be predicted, the elevating percent inhibition readings shown by papaya extract here in carrageenan induced model at greater time points may also manifest that Carica papaya leaves extract may instigate its inflammation alleviating reaction by adjusting the release of prostaglandins.

Non clinical animal studies and clinical trials have been conducted utilizing papaya leaf extract and the results proved them safe to be administered because of the absence of any major toxicological effect. (Ugbogu et al., 2023)

Inflammation that initiates against any kind of tissue damage involves a complex cascade of; infiltration of various leukocytes causing production of inflammatory cytokines, prostaglandins, leukotrienes; which is followed with the movement of keratinocytes, fibroblasts etc. inducing angiogenesis and tissue rebuilding; and is henceforth accomplished with the formation of type III collagen that is transformed to type I collagen promoting tissue remodeling and tissue strength. Papaya leaves extract have been found to be effective in cases of inflammation and wound injuries as they aid tissue healing simultaneously by increasing the release of protective inflammatory mediators, suppressing harmful and extensive effects of inflammation by regulating the release of vasoactive peptides, cytokines, leukotrienes and other chemicals, along with augmenting the growth of collagen fibers assembly facilitating in the recovery of the destructive tissue. Apart from asserting an advantageous intervention in the mechanism of inflammation, tissue proliferation and remodeling, papaya leaves are considered to exert their benign influence due to the presence of its bioactive chemical composition including carpaine, choline, quercetin, kaempferol and other bioactive flavonoids. (Soib et al., 2020)

An ulcerogenic study identified minor gastric mucosal irritation with higher doses of papaya leaf extract (Owoyele et al., 2008). Although no perceptible side effect was observed during our study

which is in correspondence to other papaya leaves anti-inflammatory studies (Alyas et al., 2020), more research studies applying histological and physiological examination need to be conducted for evaluating greater doses of the extract.

Attributing to the benevolent uses of papaya as a whole plant, constituents from its different parts can be used for therapeutic uses by manufacturing them as either dietary supplements or pharmacological drug products. However both physiological and pharmacological doses will vary in either cases as dietary nutritional supplements are based on their nutritional value, however pharmacological medicines are for the purpose of treating ailments. (Liu, 2004)

Carica papaya leaves being packed with an enriched supply of vitamins, alkaloids, flavonoids, phenolic acids, coumarins appeared to be the basis of its incredible anti-inflammatory properties. As certain studies have also exposed the presence of many useful phytochemicals in papaya leaves including Vitamin C, Carpaine, Kaempferol, Palmitic Amide, p-Coumaric Acid, Choline etc. These compounds are well accredited for their beneficial properties of Reactive Oxygen Species (ROS) scavenging, anti-inflammatory and wound healing, subsequently making the papaya leaves ideal in the use of suppression of multiple acute as well as progressive persisting inflammatory disorders. (Soib et al., 2020; Ugbogu et al., 2023)

It is recommended to use the papaya leaf extract as a whole than extracting the specific flavonoids and constituents seemed to be responsible for imparting its inflammatory action, since the ratio and proportions formed by Nature are rather more advantageous due the reason of being associated with negligible adverse effects, maximum safety and efficacy.

However since the plant metabolites have a complex structure, the major bioactive flavonoids and phenolic acids of papaya leaves can also be isolated separately for their utilization in the manufacturing of drug products because the plant-based secondary metabolites are generally considered safer and efficacious, likewise they also pave the way for the development of novel compounds to augment the available treatment options since currently available therapies haven't been fruitful in eradication of inflammatory maladies. Promoting the use of herbal drugs can also avoid the NSAIDs side effects exclusively linked with the long term use.

Some studies acclaimed that papaya leaves constituents might work in similar manner as that of COX-2 inhibitors at small doses via inhibition of pathological COX-2 enzyme (Owoyele et al., 2008) and not affecting the physiological COX-1 enzyme (Vane & Botting, 1998); but others have also quoted that both COX enzymes seems to have physiological and pathological role (Abdulkhaleq et al., 2018). This may also reject the hypothesis of different actions of COX 1 &2 enzymes supported by the fact that several newly approved selective COX-2 inhibitors have been expelled because of the severe side effects. Meanwhile many researches have cited the anti-inflammatory effect of papaya leaves is owing to a cascade of mechanisms, including depletion from free oxygen radicals to, involving action on certain T lymphocytes as well as affecting release of pro-inflammatory mediators and also enhancing the mechanisms involved in tissue proliferation and regeneration (Owoyele et al., 2008; Soib et al., 2020). This justifies the outstanding role of papaya leaves in decreasing inflammation with almost no evident side effects.

5 CONCLUSION

The results of the testing method 'Carrageenan induced rat paw edema', applied to confirm the anti-inflammatory activity of the leaves of Carica papaya Linn., were found to be satisfactory.

The present work however is distinguishably positive as it proves the anti-inflammatory activity of aqueous-based papaya leaves extract as well as affirms that the doses of papaya leaf extract work in a dose-dependent manner displaying direct proportionality with the increase of dose as well as time; i.e. better and more enhanced anti-inflammatory action of the papaya leaf extract will be produced with the increase of dose of extract, and more effective results will be obtained with the span of time. The above research work embarks that Carica papaya leaf extract can suitably be used to prepare oral herbal anti-inflammatory drug at commercial scale owing to its similar efficacy as that of industrially available synthetic anti-inflammatory drugs.

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