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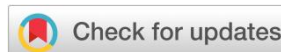
Journal of Drug Delivery and Therapeutics

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Research Article

Evaluation of Anti-Inflammatory Property of *Muntingia calabura* Using Carrageenan-Induced Rat Paw Edema Model

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Article Info:



Article History:

Received 25 July 2026
Reviewed 30 Aug 2026
Accepted 24 Sep 2026
Published 15 Oct 2026

Cite this article as:

Kambi A, Sanjeeva PS, Menon SV, Suhas YS, Jahan N, Evaluation of Anti-Inflammatory Property of *Muntingia calabura* Using Carrageenan-Induced Rat Paw Edema Model, Journal of Drug Delivery and Therapeutics. 2026; 16(10):52-59 DOI: <https://doi.org/10.22270/jddt.v16i10.8019>

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Abstract

Inflammation is a fundamental physiological process, crucial for the body's defence mechanisms, but when uncontrolled, it can contribute to various pathological conditions such as arthritis. The treatment for inflammation is usually done with NSAIDs. However, these drugs inhibit various short-term and long-term side effects such as indigestion, stomach ulcers, kidney and liver problems. So, there is a need for an alternative which have fewer and no side effects along with efficacy. *Muntingia calabura* is a multi-therapeutic plant having effective anti-inflammatory properties. This investigation focuses on determining the efficacy of *Muntingia calabura*, for mitigating acute inflammation. Ethanolic extracts of *M. calabura* leaves were prepared and administered to both male and female Wistar rats in three different concentrations and acute inflammation was induced by injecting 1% carrageenan in the hind paw of the Wistar rats after 30 minutes of administering the extract orally. Paw volume was measured at 1, 2, 3 and 4-hour intervals. Results indicated that all the doses of extract produced a significant reduction in paw edema compared to the positive group. The percentage of inhibition was dose-dependent and the peak inhibition was observed on the 3rd hour. In conclusion, *M. calabura* exhibits promising potential as a natural anti-inflammatory agent.

Keywords: anti-inflammation, carrageenan-induced rat paw edema, *Muntingia calabura*, phytochemicals

INTRODUCTION

Over the last few years, there has been a growing interest in exploring plant-based products for their potential therapeutic benefits. Medicinal plants are now considered as important sources for treating various types of diseases¹. This renewed focus on natural remedies is largely driven by the limitations and side effects associated with many synthetic drugs. Researchers and healthcare professionals are turning their attention to various medicinal plants, aiming to discover and validate their medicinal properties.²

One such plant that has garnered attention is *Muntingia calabura*, commonly known as the Jamaican cherry.³ This small tropical tree, native to Central and South America but now found in tropical regions worldwide, has a long history of use in traditional medicine. It has multi-therapeutic properties and is studied for its antioxidant⁴, anti-inflammatory⁵, anti-microbial,⁶ anti-diabetic⁷, and anti-ulcer⁸ properties. Different parts of the plant, including the leaves, bark, and fruit, are

reputed for their diverse therapeutic properties. There are many studies that discuss the high phenolic content in *M. calabura*^{9,10,11,12,13} which have various properties, among which anti-inflammatory property is one of the most prominent one^{14,15}. Despite its therapeutic properties, this plant has not been widely studied. Therefore, the information available is effectively less and the therapeutic properties are still being discovered. The primary emphasis of this study is the anti-inflammatory effect of the leaves of the *Muntingia calabura* plant. Inflammation is a fundamental physiological process, crucial for the body's defence mechanisms against harmful stimuli such as pathogens, damaged cells, or toxic compounds.¹⁶ Inflammation is important not only for host defence but also because of its role in several diseases.¹⁷ It is a common symptom of many diseases like cancer¹⁸, cardiovascular diseases¹⁹, and other life-threatening disorders. Recently inflammation has also been seen in hypertension due to reactive oxygen species (ROS) released from exposure to angiotensin II.²⁰ The complex process of inflammation

involves several different mediator molecules like histamine (β -Imidazolyethylamine), leukotrienes, prostaglandins, kinins, and many other molecules.^{21,22}

There are various kinds of secondary metabolites present in different parts of the plants, among them the major metabolites found are alkaloids, terpenoids, phenols, flavonoids, saponins. Secondary metabolites such as flavonoids are a really good anti-oxidising agent which decreases the level of ROS which in-turn decreases cytotoxicity and inflammation.²³ This study was done to determine the anti-inflammatory effects of the ethanolic leaf extract from *M.calabura* (ELME) using carrageenan-induced paw edema on wistar albino rats. The study also showed the efficacy of ELME compared to the standard control (*diclofenac*) in acute inflammation conditions. A well-known method used for studying acute inflammation is the carrageenan-induced rat paw edema model. Any drug can be curative or toxic depending on the dosage of the drug, hence an attempt was also made to determine the toxicity of ELME in-vitro using cell lines, as well as in-vivo.

METHODOLOGY

In-Vitro Studies

1.Sample collection

Muntingia calabura is one of the most widely growing trees, hence it was easy to find and identify it. The leaves were picked up by hand, and stored in a clean polythene bag and were used for the experimentation on the same day. While collecting the leaves, mature leaves were preferred as they would contain more secondary metabolites. Two trees were identified and were used as the primary source of leaves for experiment. The leaves were collected from the trees located in Kannada Bhavan, JC Road, Bangalore, Karnataka. The location of the trees are - <https://goo.gl/maps/4KtA3R9SmzhCQtXq6> 12°57'47.3"N 77°35'05.5"E and <https://goo.gl/maps/egUUZ4TAVP1qMWZe7> 12°57'43.2"N 77°35'08.0"E. The studied plant was sent for specimen identification to Herbarium and the plant was identified by Dr. Noorunnisa Begum, Curator, Foundation for revitalisation of local health traditions, Yelahanka, Bangalore-560064, Karnataka, India and the voucher specimen number is FRLHT Acc. No. 6107. The plant identified was Muntingia calabura L. (Botanical name) belonging to family Muntingiaceae.

2.Extract preparation

The leaves were washed and dipped in a small amount of warm ethanol to remove the excess chlorophyll for about 15 minutes. This was then grinded in ethanol using a mortar and pestle. It was then centrifuged to get the supernatant. A rotary evaporator was then used to concentrate the extracted material. The concentrated sample was stored and dissolved in appropriate solvents as per the required concentration.

3.Sample preparation for HPLC analysis

Extract preparation for HPLC analysis: 25g of the leaves of *M.calabura* was taken and contaminants were removed by washing as well as the chlorophyll present using the same method as above. The grinded leaves in ethanol were centrifuged and the supernatant was taken. A silica column was made in a syringe, in which the tip of the syringe was incorporated with activated charcoal. The extract was allowed to flow through the silica-coated syringe. This step was repeated and elute was collected each time to get the pure extract.

HPLC analysis: The analysis was made on the C-18 column (symmetry, 4.6 mm×250 mm) in isocratic mode. The mobile phase used was acetonitrile and water in the ratio of 7:3 with the RP-HPLC C-18 column at a flow rate of 1 mL/min. The standard gallic acid of concentration 0.4mg/mL and sample (0.1 mL) were dissolved in the mobile phase, 20 μ L was injected and the elution was monitored at 254 nm (modified methodology).²⁴

Cytotoxicity analysis by WST-8 assay

WST-8 assay (cell counting kit-8 assay) is a colorimetric assay used to determine viable cell numbers and can be used for cytotoxicity assays. The cell lineage used in this assay was the THP1-human monocyte leukemia cell line and the cell culture media utilized was Roswell Park Memorial Institute (RPMI1640) supplemented with 10% Foetal Bovine Serum (FBS).

The cells were aspirated into a 5ml centrifuge tube and centrifuged at 300G to collect the cells in the pellet. Using RPMI medium containing 10% FBS, the cell count was adjusted so that about 10,000 cells are present in 50 μ L of suspension. Then 50 μ L of the cell suspension was added to each well of a microtiter plate and the plate was incubated at 37°C and 5% CO₂ atmosphere for 24 h. After 24 h, 50 μ L of different test concentrations (2X) of the ethanolic leaf extract was added to the corresponding wells. The plate was then incubated for 24h under the same conditions. The plate was removed from the incubator after 24h and 10 μ L WST-8 reagent was added to each and was incubated at 37°C and 5% CO₂ atmosphere for 3 h. The absorbance was measured at 450 nm using a microplate reader. The percentage growth inhibition was then calculated.^{25,26}

In-Vivo Studies

1.Experimental Animals and Ethical Approval

Male and female Wistar albino rats weighing around 100-200 g were used for experimenting, procured from Vaarunya Biolabs Private Limited, Kumbalgodu, Ind. Area, Bengaluru, Karnataka, India. The rats were kept in the animal house of National Institute of Unani Medicine, Kottigepalya, Magadi Main Rd, Bengaluru, Karnataka, where they are acclimatized for 7 days. They were housed in polypropylene cages with three rats per cage and were maintained at standard conditions according to the guidelines of OECD²⁷. Approval for the use of the animals was obtained from the Animal in Research Ethical group of National Institute of Unani Medicine, with approval number: IAEC/06/22/IA/06.

2. Acute toxicity studies

The acute toxicity studies of the ethanolic extract of *Muntingia calabura* were done in the Wistar rats according to the suggested methods in the IAEC guidelines. For this study, female rats were used because of their increased sensitivity than the male rats. They were grouped into four, 300mg/kg body weight (first two groups) and 2000mg/kg bw (last two groups) of the ELME. The first two groups were administered 300mg/kg bw and were observed attentively for the first hour and further monitoring was made every 3hr for 24 hr. If there was an absence of death the experiment was taken to the second phase. In this phase, the remaining two groups of rats were administered with 2000mg/kg bw of the ethanolic extract of the plant material. Signs of any toxicity were observed keenly for 24 hr, daily thereafter, for a total of 21 days for general behavioural and body weight changes, food intake, hazardous symptoms, and mortality were observed. A lower dose will be selected if mortality occurs in two out

of the three rats. But if fatality is observed in only one rat the same dose will be repeated.^{27,28,29}

3. Carrageenan-induced rat paw edema

Carrageenan- induced rat paw edema model was used to evaluate the anti-inflammatory properties of the ethanolic extract of *M. calabura*. Rats were categorized into 5 groups (n=5) group, such that the first group was the positive control group, group 2 was the standard control, and groups 3-5 were the test group of different extract concentrations as shown in table 1. The ethanolic extracts were administered orally using a gastric feeding tube and carrageenan was injected as an inflammatory agent in the right paw of Wistar albino rats. Each animal was observed after dosing every 30 min in the first 5 hours after giving the dose, and daily for 48 hours. The behavioural changes were monitored per the OECD guidelines.²⁹

Where pVc indicates the paw volume of the positive control group, pVt is the paw volume of the test groups.

Table 1: Grouping and dosage of the animals for anti-inflammatory studies.

S. No.	Groups	No. of Animals (males+females)	Route of administration	Dosage	Frequency	Duration
01	Positive control (carragenan)	3+3	Oral		Single dose	1 Day
02	Standard (diclofenac)	3+3	Oral	10mg/kgbw	Single dose	1 Day
03	Lower dose of test drug	3+3	Oral	100mg/kgbw	Single dose	1 Day
04	Intermediate dose of test drug	3+3	Oral	200mg/kgbw	Single dose	1 Day
05	High dose of test drug	3+3	Oral	400mg/kgbw	Single dose	1 Day

The percentage of inhibition was calculated using the formula

$$\text{Percentage inhibition of edema} = \left(\frac{\text{PVc} - \text{PVt}}{\text{PVc}} \right) 100$$

RESULTS

1. HPLC analysis

The HPLC analysis of the ELME showed a prominent peak in the retention time of 2.480 min, which was slightly similar to the retention time of the standard gallic acid as shown in table 2.

Table 2: showing the retention time and area of the HPLC graph

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	2.480	7139.601	231.245	100.0	100.0	0.39
	Total	7139.601	231.245	100.0	100.0	

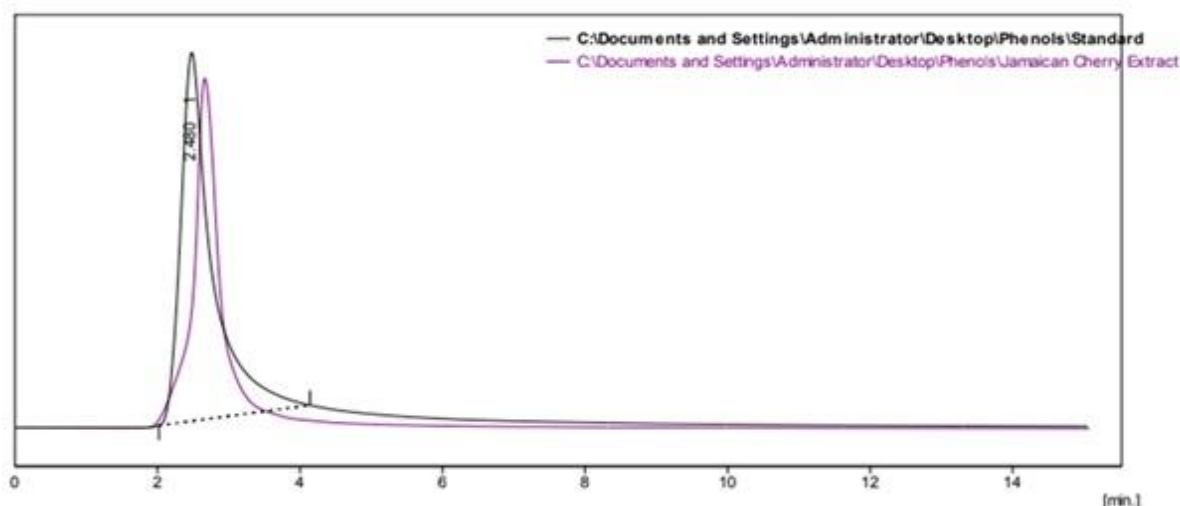


Figure 1: showing the peak obtained in the HPLC

2. Cytotoxicity analysis by WST-8 assay

WST-8 assay done using the ELME showed no toxicity to the live cells. The below graph shows the percentage of viable cells when treated with varying concentrations of the extract compared with the untreated one. The number of viable cells is very near to 100% even at high concentrations of the extract, indicating that no cells have undergone death and the extract is non-toxic as shown in figure 2 and 3.

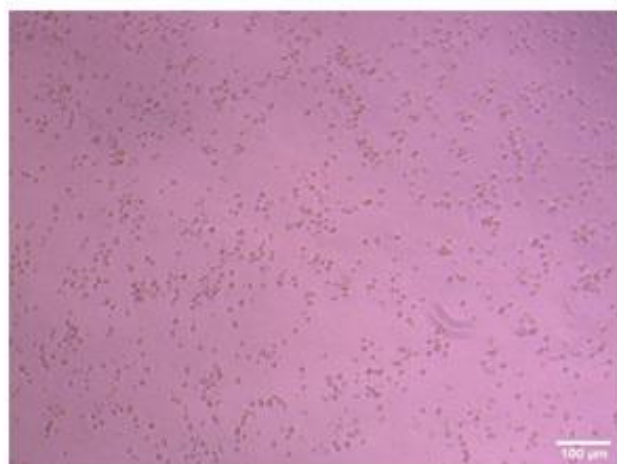


Figure 2: showing viable cells after treating with ethanolic extract

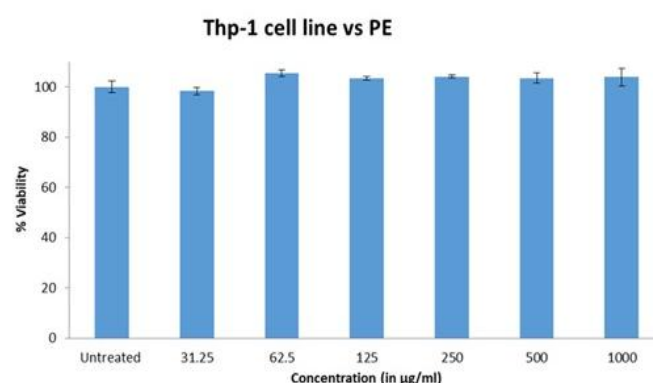


Figure 3: Graph showing the percentage viability of the cells after treating with different concentrations of extract.

In-Vivo Studies

1. Acute oral toxicity of the plant extract

The study showed that, even at the maximum dose of 2000mg/kg body weight, there were no signs of lethality and death as shown in table 3. However, some rats in higher concentration manifested diarrhoea in the first hour of the dosing, and it subsided after 4-5 hours. Behavioural and physical changes of the rats were observed for the first 4 hours continuously for any toxicity signs. As shown in table 4, no particular signs of toxicity were observed.

Table 3: Acute oral toxicity of Jamaican cherry ethanolic leave extract in rats

Group number	Dosage (mg/kg of body weight)	Number of rats died
1	300mg/kg	0/3
2	300mg/kg	0/3
3	2000mg/kg	0/3
4	2000mg/kg	0/3

Table 4: Behavioural and physical changes observed in the rats

Observation	0 th min.	30 min	1 hour	2 hour	4 hour
Change in skin colour	-	-	-	-	-
Eye colour change	-	-	-	-	-
Food intake	Fasting	Fasting	Fasting	Normal	Normal
General physique	Normal	Normal	Normal	Normal	Normal
Diarrhoea	-	-	-	-	-
Breathing difficulty	-	-	-	-	-
Sedation	-	-	-	-	-
Tremor	-	-	-	-	-
Lethargy	-	-	-	-	-
Coma	-	-	-	-	-
Death	-	-	-	-	-

2. Evaluation of anti-inflammatory effects of the herbal extract

Various secondary metabolites derived from natural sources have been identified as pharmacologically active molecules responsible for many biological actions. In the first group, which was positive control, carrageenan was subcutaneously injected into the hind paw of the rat and no treatment was given. The inflammation was seen to be increased over time. The paw volume reached its maximum in the 4th hour. The paw was observed to have swelling, redness, and heightened temperature which indicated inflammation. The rat exhibited discomfort and pain in the hind paw as a result of edema.

In the standard control, diclofenac, which is an NSAID, showed a declined paw edema. As compared to the positive control, in the first hour itself reduction of inflammation was shown by diclofenac. The herbal extract was compared with the standard drug, the edema was suppressed irrespective of the dosage used. The percentage of inhibition increased based on the concentration of the extract used. The figures below emphasized the comparison between the edema in all the groups. The percentage inhibition was at its peak on the 3rd hour for all the dosages used. From the current study, we were able to get a higher edema inhibition even in the lowest dosage (100mg/kg bw) as shown in table 5. As the dosage increased, the efficacy also seemed to have increased.

Table 5: Percentage inhibition observed in rats treated with ELME and control

Treatment Group	Dosage	1hr		2hr		3hr		4hr	
		Male	Female	Male	Female	Male	Female	Male	Female
Positive Control	2%	-	-	-	-	-	-	-	-
Standard Control	10mg/kg	-	-	-	7.02%	7.53%	14.8%	8.12%	16.67%
Low Dosage	100mg/kg	15.6%	15.43%	24.37%	22.81%	27.96%	28.57%	25.49%	24.56%
Intermediate Dosage	200mg/kg	18.35%	36.11%	26.61%	17.54%	28.49%	39.84%	24.49%	14.04%
High Dosage	400mg/kg	37.16%	36.11%	42.44%	40.35%	45.16%	43.54%	26.61%	19.30%

DISCUSSION

The exploration of plants as sources of anti-inflammatory agents has attained significant attention in the previous decades. The main reason for this was because of its fewer side effects compared to the conventional drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) are the standard drugs used for inflammatory reactions. But these drugs on prolonged usage can cause kidney problems, gastro-intestinal and heart issues.³⁰ Nowadays, plants with therapeutic properties like antioxidant, anti-inflammatory have been widely studied and the demand for more effective alternatives continues to grow. The medicinal properties of the plants are interlinked with the phenolic compounds or the secondary metabolites present in them. Phenolic compounds, like flavonoids, terpenoids, phenolic acids, tannins, etc. play crucial roles in mitigating inflammation through various mechanisms.

Carrageenan induction is a mechanism used to trigger acute inflammation, which can induce the release of prostaglandins, histamine, and serotonin. Carrageenan-induced rat paw edema is a commonly used experimental model for examining acute inflammation and evaluating the effectiveness of anti-inflammatory drugs.³¹ When carrageenan is injected into the rat paw, it triggers a well-characterized inflammatory response that progresses through two phases. The first phase which is observed in the first hour, is characterised by the release of histamine, serotonin, bradykinin, and to a small degree of prostaglandins produced by cyclooxygenase enzyme (COX). As a result of these inflammatory mediators, initial swelling will begin, as well as an increased vascular permeability is also observed. The second phase, which is also known as the delayed phase, happens after 1 h. This phase is dominated by the neutrophil infiltration and the release of pro-inflammatory mediators such as prostaglandins, particularly prostaglandin E₂ (PGE₂), and cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor-alpha (TNF- α).³² These inflammatory mediators will amplify the inflammatory response.

Carrageenan-induced paw edema occurs in two phases (early and late phase), the early phase begins after the administration of the irritant and lasts for an hour. It is characterized by the release of serotonin, histamine, and bradykinins. Nonsteroidal anti-inflammatory drugs for example indomethacin or aspirin do not inhibit this phase. The late phase occurs from the second to the fourth hour after the administration of the irritant and is ascribed to the release of prostaglandins, oxygen-derived free radicals, lysosome enzymes and proteases. Most drugs show their anti-inflammatory response at this phase. Moreover, carrageenan-induced edema test is a standard experimental model for assessing the anti-inflammatory activities of natural products as well as synthetic chemical compounds. From the results obtained in the anti-inflammatory study of the ELME, the extracts showed dose-dependent inhibition of paw edema. The most reduction in the paw volume was seen in the third hour. From the acute toxicity studies, it was

shown that the extract possesses no toxic effect in the in vitro animal cell culture as well as in the rats.

The herbal extract's ability to reduce paw edema in both phases of the carrageenan-induced edema in mice suggests the involvement of the herbal extracts active principles in inhibiting the release or action of the early and late phase mediators of inflammation thereby suppressing edema. The phenolic compounds found in the leaf extract can inhibit inflammation in many different ways. It may exert its anti-inflammatory effects by modulating the production and activity of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukins (IL-1 β , IL-6), and interferon-gamma (IFN- γ).³³ The cyclooxygenase (COX) and lipoxygenase (LOX) pathways are crucial in the biosynthesis of pro-inflammatory mediators such as prostaglandins and leukotrienes.^{34,35} The phenolic compounds present in the plant extract can inhibit these enzymes, leading to decreased production of inflammatory mediators. In one of the study by Misra et al.³⁶ due to the presence of the phenolic compounds it was known to increase the immunity in rats. *M.calabura* leaves were found to have an efficient antioxidant activity.³⁷ The antioxidants present in plants can scavenge the reactive free radicals produced by the macrophages and neutrophils and can reduce the inflammation caused by them, preventing further damage. More studies have to be done, in order to have a proper understanding of the mechanism followed by the phenolic compounds in *M.calabura* plant.

CONCLUSION

Phenolic compounds present in the plants offer significant therapeutic properties like anti-inflammation, antioxidant, anti-diabetic, anti-aging etc. Incorporation of these medicinal-valued plants into diet and therapeutic applications provides novel opportunities for managing chronic health conditions. Our study revealed the potential value of the leaves of *M.calabura* as a potent anti-inflammatory agent. However, many other studies have to be done in order to properly understand the molecular mechanisms involved and to develop the plant as an effective medicine against inflammatory diseases. The histopathological and molecular identification of biochemical cues can explore the anti-inflammatory application of this medicinal plant in novel drug discovery in the future. Further refining and purification of the extract can lead us to the exact molecules responsible for the anti-inflammatory activity and can further help in designing of anti-inflammatory drugs.

Acknowledgement: We acknowledge the funding provided by School of Sciences, Jain (Deemed-to-be) University, Bangalore, Karnataka under the seed money project scheme (Ref: JU/MRP/SOS/19/2022)

Abbreviations

ELME: Ethanolic leaf extract from *M. calabura*

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

IAEC: Institutional Animal Ethics Committee

CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals

WST-8: Water-Soluble Tetrazolium Salt

Data Availability Statement: The data underlying this article are available in the article and in its online supplementary material.

REFERENCES

1. Ukwubile CA, Ikpefan EO, Dibal MY, Umeano VA, Menkiti DN, Kaosi CC, Paul S, Famurewa AC, Nettoy H, Yerima TS. Pharmacognostic profiles, Evaluation of analgesic, anti-inflammatory and anticonvulsant activities of *Newbouldia laevis* (P. Beauv.) Seem. ex Bureau leaf and root extracts in Wistar rats, *Journal of Ethnopharmacology*, 2023; <https://doi.org/10.1016/j.jep.2023.116632> PMID:37211190
2. Shumaila Tasneem, Bin Liu, Bin Li, M. Iqbal Choudhary, Wei Wang, Molecular pharmacology of inflammation, Medicinal plants as anti-inflammatory agents, *Pharmacological Research*, 2019; 139:126-140 <https://doi.org/10.1016/j.phrs.2018.11.001> PMID:30395947
3. Mahmood ND, Nasir NLM, Rofiee MS, Tohid SFM, Ching SM, The LK, Salleh MZ, Zakaria ZA, Muntingia calabura: A review of its traditional uses, chemical properties, and pharmacological observations, *Journal of Pharmaceutical Biology*, 2024; 52: <https://doi.org/10.3109/13880209.2014.908397> PMID:25068675
4. Gustavo AP, Henrique SA, Damila RM, Marcos NE, Glaucia MP, Carbohydrates, volatile and phenolic compounds composition, and antioxidant activity of calabura (*Muntingia calabura* L.) fruit, *Food Research International*, 2018; 108: 264-273 <https://doi.org/10.1016/j.foodres.2018.03.046> PMID:29735056
5. Preethi K, Premasudha P, Keerthana K, Anti-inflammatory activity of *Muntingia calabura* fruits, *Pharmacognosy Journal*, 2012; 4:51-56 <https://doi.org/10.5530/pj.2012.30.10>
6. Adila S, Ramasamy K, Ahmat N, Zainul A, Zakaria M, Izwan M, Yusof, Isolation and identification of antibacterial and cytotoxic compounds from the leaves of *Muntingia calabura* L, *Journal of Ethnopharmacology*, 2013; 146:198-204. DOI: 10.1016/j.jep.2012.12.032 <https://doi.org/10.1016/j.jep.2012.12.032> PMID:23276785
7. Aligita W, Susilawati E, Sukmawati I K, Holidayanti L, Riswanti J, Antidiabetic activities of *Muntingia calabura* L. leaves water extract in Type 2 diabetes mellitus animal models. *Indonesia Biomedical Journal*, 2016; 10:165-70. Doi: <https://doi.org/10.18585/inabj.v10i2.405>
8. Zainul Amiruddin Zakaria, Tavamani Balan, Velan Suppaiah, Syahida Ahmad, Fadzureena Jamaludin, Mechanism(s) of action involved in the gastroprotective activity of *Muntingia calabura*, *Journal of Ethnopharmacology*, 1:1184-1193.
9. Diana Pacheco Seixas, Fernanda Helena Palermo, Tatiane Maria Rodrigues, Leaf and stem anatomical traits of *Muntingia calabura* L. (*Muntingiaceae*) emphasizing the production sites of bioactive compounds, *Flora*, 2021; 78:151802, <https://doi.org/10.1016/j.flora.2021.151802>
10. Zakaria ZA, Sulaiman MR, Jais, AMM, Somchit, MN, Jayaraman KV, Balakhrisnan G, Abdullah FC, The antinociceptive activity of *Muntingia calabura* aqueous extract and the involvement of l-arginine/nitric oxide/cyclic guanosine monophosphate pathway in its observed activity in mice, *Fundamental and Clinical Pharmacology*, 2006; 20: 365-372 <https://doi.org/10.1111/j.1472-8206.2006.00412.x> PMID:16867020
11. Zainul Amiruddin Zakaria, Safarul Mustapha, Mohd. Roslan Sulaiman, Abdul Manan Mat Jais, Muhammad Nazrul Somchit, Fatimah Corazon Abdullah, The Antinociceptive Action of Aqueous Extract from *Muntingia calabura* Leaves: The Role of Opioid Receptors, *Medical Principle Practice*, 2007; 16:130-136 <https://doi.org/10.1159/000098366> PMID:17303949
12. Zainul Amiruddin Zakaria, Tavamani Balan, Velan Suppaiah, Syahida Ahmad, Fadzureena Jamaludin, Mechanism(s) of action involved in the gastroprotective activity of *Muntingia calabura*, *Journal of Ethnopharmacology*, 2014; 1:1184-1193 <https://doi.org/10.1016/j.jep.2013.12.045> PMID:24380736
13. Zakaria ZA, Mahmood ND, Omar MH, Taher M, Basir R, Methanol extract of *Muntingia calabura* leaves attenuates CCl₄-induced liver injury: possible synergistic action of flavonoids and volatile bioactive compounds on endogenous defence system. *Pharmaceutical Biology*, 2019; 57: 335-344. <https://doi.org/10.1080/13880209.2019.1606836> PMID:31068038 PMCID:PMC6508049
14. Kathirvel Preethi, Paramasivam Premasudha, Kittusamy Keerthana, Anti-inflammatory Activity of *Muntingia calabura* Fruits, *Pharmacognosy Journal*, 2012; 4:51-56, <https://doi.org/10.5530/pj.2012.30.10>
15. Sani MH, Zakaria ZA, Balan, T, Teh LK, Salleh, MZ, Antinociceptive Activity of Methanol Extract of *Muntingia calabura* Leaves and the Mechanisms of Action Involved. Evidence-based complementary and alternative medicine, 2012; 890361. <https://doi.org/10.1155/2012/890361> PMID:22611437 PMCID:PMC3351243
16. Yesli K, Turpin G, Jamtsho T, Wangchuk P. Indigenous Uses, Phytochemical Analysis, and Anti-Inflammatory Properties of Australian Tropical Medicinal Plants. *Molecules*, 2022; 27:3849. <https://doi.org/10.3390/molecules27123849> PMID:35744969 PMCID:PMC9231311
17. Mansouri MT, Hemmati AA, Naghizadeh B, Mard S A, Rezaie A, Ghorbanzadeh B, A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. *Indian journal of pharmacology*, 2015; 47:292-298. <https://doi.org/10.4103/0253-7613.157127> PMID:26069367 PMCID:PMC4450555
18. Zinger A, Cho WC, Ben-Yehuda A, Cancer and Aging - the Inflammatory Connection. *Aging Disease*, 2017; 8:611-627. <https://doi.org/10.14336/AD.2016.1230> PMID:28966805 PMCID:PMC5614325
19. Sun Y, Rawish E, Nording HM, Langer HF, Inflammation in Metabolic and Cardiovascular Disorders-Role of Oxidative Stress. *Life*, 2021; 11:672. <https://doi.org/10.3390/life11070672> PMID:34357044 PMCID:PMC8308054
20. Agita A, Alsagaff MT, Inflammation, Immunity, and Hypertension. *Acta medica Indonesiana*, 2017; 49:158-165.
21. Abdulkhaleq LA, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MN M, The crucial roles of inflammatory mediators in inflammation: A review. *Veterinary world*, 2018; 11:627, 10.14202/vetworld.2018.627-635 <https://doi.org/10.14202/vetworld.2018.627-635> PMID:29915501 PMCID:PMC5993766
22. White M. (1999). Mediators of inflammation and the inflammatory process. *The Journal of allergy and clinical immunology*, 103:S378-S381. [https://doi.org/10.1016/S0091-6749\(99\)70215-0](https://doi.org/10.1016/S0091-6749(99)70215-0) PMID:10069896
23. Abdallah HM, Esmat A, Antioxidant and anti-inflammatory activities of the major phenolics from *Zygophyllum simplex* L. *Journal of ethnopharmacology*, 2017; 205: 51-56. <https://doi.org/10.1016/j.jep.2017.04.022> PMID:28465252
24. Steinmann D, Ganzera M, Recent advances on HPLC/MS in medicinal plant analysis. *Journal of Pharmacy and Biomedical Analysis*, 2011, 55:744-757 <https://doi.org/10.1016/j.jpba.2010.11.015> PMID:21131153
25. Kamiloglu S, Sari G, Ozdal, T, Capanoglu E, Guidelines for cell viability assays. *Food Frontiers*, 2020; 1: 332-349 <https://doi.org/10.1002/fft2.44> PMCID:PMC10440554
26. Präbst K, Engelhardt H, Ringgeler S, Hübner H, Basic colorimetric proliferation assays: MTT, WST, and resazurin. *Cell viability assays: methods and protocols*, 2017; 1-17. https://doi.org/10.1007/978-1-4939-6960-9_1 PMID:28470513

27. OECD. OECD Guideline for Testing of Chemicals, Repeated Dose 28-day Oral Toxicity in Rodents, Test No. 407; OECD: Paris, France, 2008
28. Morris CJ, Carrageenan-induced paw edema in the rat and mouse. *Methods in Molecular Biology*, 2003; 225:115-121. <https://doi.org/10.1385/1-59259-374-7:115> PMID:12769480
29. OECD. OECD Guidelines for Testing of Chemicals: Acute Oral Toxicity-Acute Toxic Class Method. Test No. 423, Adopted 22nd March 1996, and Revised Method Adopted 17th December 2001; OECD: Paris, France, 2001.
30. Harirforoosh S, Asghar W, Jamali F, Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques*, 2013; 16: 821-847. <https://doi.org/10.18433/J3VW2F> PMID:24393558
31. Chauhan P, Singh S, Gupta Y, Kumar U, Evaluation of toxicity studies and anti-inflammatory activity of *Terminalia Bellerica* in carrageenan-induced paw edema in experimental rats. *Journal of Natural Science, Biology and Medicine*, 2017; 9(2). https://doi.org/10.4103/jnsbm.JNSBM_159_17
32. Ou Zhaoping Jing, Zhao Lijuan, Zhu Lin Huang, Yurong Ma, Chaoyang Ma, Chenxi Luo et al. Anti-inflammatory effect and potential mechanism of betulinic acid on λ -carrageenan-induced paw edema in mice, *Biomedicine & Pharmacotherapy*, 2019; 118: 109347. <https://doi.org/10.1016/j.biopha.2019.109347> PMID:31545273
33. Abd-Allah AAM, El-Deen NAMN, Mohamed WAM, Naguib FM, Mast cells and pro-inflammatory cytokines roles in assessment of grape seeds extract anti-inflammatory activity in rat model of carrageenan-induced paw edema. *Iran Journal of Basic Medicine Science*, 2018; 21:97-107.
34. Braca A, Dal Piaz F, Marzocco S, Autore G, Vassallo A, De Tommasi N, Triterpene derivatives as inhibitors of protein involved in the inflammatory process: molecules interfering with phospholipase A2, cyclooxygenase, and lipoxygenase. *Current drug targets*, 2011; 12:302-321. <https://doi.org/10.2174/138945011794815284> PMID:20955150
35. Lappa EL, Zangueu CB, Nguemfo EL, Wanche JJK, Sonfack CS, Fongang ALM et al. Anti-inflammatory activity and metabolites profiling of aqueous stem bark extract of *Ficus vogelii* (Moraceae) in rats. *Phytomedicine plus*, 2011; 2:100348. <https://doi.org/10.1016/j.phyplu.2022.100348>
36. Mishra A, Sharma AK, Kumar S, Saxena AK and Pandey AK. *Bauhinia Variegata* Leaf Extracts Exhibit Considerable Antibacterial, Antioxidant, and Anticancer Activities. *Biomedical Research International*, 2013; 2013: 915-922 <https://doi.org/10.1155/2013/915436> PMID:24093108 PMCID:PMC3777169
37. Sinaga SP, Lumbangaol DA, Iksen RFR, Gurning K, Determination of phenolic, flavonoid content, antioxidant and antibacterial activities of seri (*Muntingia calabura* L.) leaves ethanol extract from North Sumatera, Indonesia. *Rasayan Journal of Chemistry*, 2022; 15: 1534-1538 <https://doi.org/10.31788/RJC.2022.1526730>