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Anti-inflammatory activity test of matoa fruit peel ethanol extract (*Pometia pinnata* J. R. Forst. & G. Forst.) on carrageenan edema model of white rats

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ABSTRACT

Background: Inflammation is a protective biological response to tissue injury or infection; however, excessive inflammation may lead to tissue damage and chronic disease. Matoa fruit peel (*Pometia pinnata* J.R.Forst. & G.Forst.) contains bioactive compounds, including Flavonoids, saponins, tannins, and phenolics, which are known to have anti-inflammatory properties, are present in the plant. Objective: This study sought to assess the anti-inflammatory efficacy of the ethanol extract derived from the matoa fruit peel through the utilization of a carrageenan-induced paw edema model in male white rats. Methods: In an experiment, we used male white rats (*Rattus norvegicus*) and split them into five groups. We had a negative control, a positive control, and three treatment groups. The treatment groups got ethanol extract at different doses—100, 200, and 300 mg/kg of body weight. To get the inflammation going, we gave them a 1% carrageenan injection under their skin. Paw edema volume was measured periodically using a plethysmometer to determine the anti-inflammatory effect. Results: The initial volume of edema of the whole group was homogeneous (0.06 ± 0.00–0.01 mL). Ethanol extract of matoa fruit peel at doses of 100, 200, and 300 mg/kgBB showed anti-inflammatory activity by gradually reducing edema until the 6th hour. The dose of 100 mg/kgBB provided the highest edema inhibition effect (42.06 ± 8.36%), followed by the 300 mg/kgBB dose (41.27 ± 13.75%) and 200 mg/kgBB (31.75 ± 2.75%), while positive control showed the largest inhibition (61.11 ± 9.62%). Statistical analysis showed that all treatment groups differed significantly from negative controls ($p < 0.05$), but still had lower effectiveness than positive controls. Conclusion: Ethanol extract of matoa fruit peel demonstrates promising anti-inflammatory activity in carrageenan-induced male white rats and may serve as a potential natural source for anti-inflammatory drug development. Further studies are needed to identify the active compounds, clarify the molecular mechanisms, and evaluate the extract's safety.

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INTRODUCTION

Inflammation is a complex physiological response triggered by tissue injury, infection, or exposure to harmful stimuli, Although inflammation plays an important role in protecting the body and promoting tissue repair, prolonged or uncontrolled inflammatory responses contribute to the pathogenesis of a variety of chronic diseases, including arthritis, cardiovascular disease, diabetes mellitus, neurodegenerative disorders, and cancer (Barnes, 2016; Chen et al., 2018; Furman et al., 2019; Medzhitov, 2021; Ricciotti & Fitzgerald, 2011). Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a mainstay of inflammation management; However, their long-term administration is frequently linked to adverse effects like gastrointestinal ulcers, kidney problems, and cardiovascular issues. As a result, there is an increased interest in identifying safer and more effective anti-inflammatory agents derived from natural products (Bekassy et al., 2022; Decout et al., 2021; Gilroy, 2021; Medzhitov, 2021; Meizlish et al., 2021).

Medicinal plants are an important source of bioactive compounds with pharmacological activity, especially phenolic compounds and flavonoids that exhibit antioxidant and anti-inflammatory properties (Anisa et al., 2023; Erawati et al., 2024; Fabanyo et al., 2023; Hardia et al., 2024; Hardia, Akrom, Hidayati, et al., 2025; Lanipi et al., 2022; Muslihin et al., 2025). Among Indonesia's rich biodiversity, *Pometia pinnata* J. R. Forst. & G. Forst., commonly known as matoa, is a native tropical plant widespread in Papua and other regions of Eastern Indonesia. Traditionally, various parts of the matoa plant have been used to treat a variety of ailments, demonstrating its potential as a source of therapeutic compounds. Phytochemical investigations have shown that matoa contains flavonoids, tannins, saponins, alkaloids, phenolic compounds, and terpenoids, many of which have been reported to suppress inflammatory mediators through inhibition of cyclooxygenase (COX), lipoxygenase (LOX), nitric oxide (NO), and proinflammatory cytokines (Furman et al., 2019; Gusti & Gusmailina, 2025; Hajar et al., 2021; Medzhitov, 2021).

Previous pharmacological studies have focused primarily on *P. pinnata* leaves, showing significant anti-inflammatory activity in carrageenan-induced models of leg edema, with higher doses producing effects comparable to standard NSAIDs (Fahmi et al., 2023; Turnip & Panjaitan, 2022). In contrast, fruit peel, which is a substantial byproduct of agriculture, remains underutilized despite evidence to suggest that it is rich in secondary metabolites with antioxidant properties and potential anti-inflammatory properties (Gusti & Gusmailina, 2025; Hajar et al., 2021; Herbani & Tilaqza, 2026). Therefore, the use of fruit peel waste as pharmaceutical raw materials can provide economic and environmental benefits while expanding the therapeutic applications of this native plant. However, comprehensive information on the anti-inflammatory efficacy of the ethanol extract of matoa fruit peel is still limited, especially regarding its effectiveness using standard carrageenan-induced edema models and its potential as a sustainable source of anti-inflammatory phytopharmaceuticals.

The carrageenan-induced leg edema model in white rats is one of the most widely accepted experimental methods for evaluating acute anti-inflammatory activity. This model reflects the biphasic inflammatory process, which involves the initial release of histamine and serotonin, followed by prostaglandins, nitric oxide, and other inflammatory mediators (Borsani et al., 2021; Liu et al., 2021; Pacheco-Quito et al., 2020). Therefore, it provides a reliable platform to assess the inhibitory effects of plant-derived compounds on inflammatory responses and to compare their efficacy with conventional anti-inflammatory drugs.

Various studies have reported that the matoa plant (*Pometia pinnata*, J.R. Forst. & G. Forst.) It contains secondary metabolites, such as flavonoids, tannins, saponins, alkaloids, and

phenolic compounds that have antioxidant and anti-inflammatory activity. However, most previous research has focused on the leaves, seeds, or fruits of matoa, while studies on the skin of matoa fruit are still very limited. Available studies generally only identify phytochemical content or antioxidant activity without evaluating their anti-inflammatory effectiveness through standardized in vivo models. In addition, previous research has not explored in depth the relationship between extract dosage and the pharmacological response or molecular mechanisms underlying anti-inflammatory activity.

Other limitations of previous research are the lack of standardization of extracts based on marker compounds, the lack of evaluation of inflammatory biomarkers such as TNF-α, IL-1β, IL-6, COX-2, and NF-κB, and the lack of discussion about the potential translation of research results into the development of phytopharmaceuticals. Inconsistencies in results are also still found regarding the dosage effectiveness of plant extracts, suggesting that an increase in dosage is not always followed by an increase in anti-inflammatory activity. This phenomenon suggests that the dose-response relationship in herbal extracts still needs further study.

Based on these gaps, this study is focused on evaluating the anti-inflammatory activity of the ethanol extract of matoa fruit peel in a carrageenan edema model in white rats, as a validated model of acute inflammation. The novelty of this study lies in proving the anti-inflammatory activity of the skin of the matoa fruit, which is still rarely reported, as well as evaluating the effectiveness of several doses of the extract to identify the optimal dose as the basis for the development of phytopharmaceutical candidates based on Indonesian natural ingredients. This research is expected to strengthen scientific evidence regarding the use of matoa fruit peels that have not been widely used so far, as well as become the basis for further research on molecular mechanisms, extract standardization, and the development of herbal medicines based on scientific evidence.

RESEARCH METHOD

Materials and Methods

Study Design

In this study, we used a real lab experiment with a completely random setup to see how well the ethanol extract from *Pometia pinnata* J.R.Forst. & G.Forst. Fruit peel helps reduce inflammation. We tested it on white rats with paw swelling caused by carrageenan.

Plant Materials and Preparation of Extract

We gathered fresh matoa (*Pometia pinnata* J.R.Forst. & G.Forst.) fruits from Sorong Regency in Southwest Papua Province, Indonesia. First, we washed the fruit peels with running water, then cut them into small pieces. Next, we let them dry in the shade at a temperature of 40–45°C until they reached a steady weight. Finally, we ground the dried material into a powder using a mechanical grinder.

We started by soaking about 1 kg of powdered fruit peel in 96% ethanol (1:10 w/v) for 72 hours, gently stirring it now and then. We did this three more times, each time using fresh solvent. After that, we combined all the liquid from the three extractions and concentrated it using a rotary evaporator at 40–45°C. Then, we gently evaporated the remaining liquid in a water bath to get a thick ethanol extract. Finally, we stored the extract in an airtight container at 4°C until we needed it.

Experimental Animals

We started with fifteen healthy male white rats (*Rattus norvegicus*), around 8-10 weeks old and weighing between 180-220 grams. These rats came from a reputable lab animal breeding facility. For the first seven days, they were kept in standard lab conditions—22-25 °C temperature, 50-60% relative humidity, and a 12-hour light/dark cycle. They had access to regular pellet food

and water. Before we began the experiments, the study protocol got the green light from the Health Research Ethics Committee at Sekolah Tinggi Ilmu Farmasi Makassar (No. 361/EC.1.1.B/VII/KEPK/2024). Also, we made sure all our procedures followed the internationally recognized guidelines for taking care of and using lab animals.

Experimental Design

We divided the rats into five groups, with three rats in each group: (a) Group I: A negative control with 1% CMC-Na, (b) Group II: A positive control with Diclofenac sodium at 10 mg/kg body weight, (c) Group III: An ethanol extract of P. pinnata fruit peel at 100 mg/kg body weight, (d) Group IV: An ethanol extract of P. pinnata fruit peel at 200 mg/kg body weight, and (e) Group V: An ethanol extract of P. pinnata fruit peel at 300 mg/kg body weight.
All treatments were administered orally.

Carrageenan-Induced Paw Edema

One hour after oral administration of the test samples, to create some inflammation, we gave each rat a tiny injection—0.1 mL of 1% λ-carrageenan solution—under their skin in the right hind paw. We used a digital plethysmometer to measure paw volume right before giving carrageenan (at 0 h) and then again at 1, 2, 3, 4, 5, and 6 hours after it was given. The bigger the paw volume, the more swelling and inflammation we saw. This model is widely accepted for evaluating acute anti-inflammatory activity because it reproduces the biphasic inflammatory response mediated initially by histamine and serotonin and subsequently by prostaglandins, nitric oxide, and other inflammatory mediators.

Data Analysis

Data are presented as mean ± SD. Shapiro–Wilk and Levene tests assessed normality and homogeneity of variance, respectively. One-way ANOVA followed by Tukey's post hoc test analyzed treatment group differences. Significance was established at $p < 0.05$. IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used for analyses.

RESULTS AND DISCUSSIONS

Results

Table 1. Comparison of anti-inflammatory effects between treatment groups

Variabel	Control +	Control –	Dose 100 mg/kg BW	Dose 200 mg/kg BW	Dose 300 mg/kg BW
Carrageenan Induction	0.06±0.00	0.06±0.01	0.06±0.01	0.06±0.01	0.06±0.01
Post-test (Δ %)					
1st hour	0.00±00	-0.79±15.49	0.00±0.00	0.00±0.00	0.00±0.00
2nd hour	16.67±0.00^{**b}	-6.35±17.87^{**ae}	0.00±0.00	0.00±0.00	15.87±1.37^{**b}
3rd hour	33.33±0.00^{**b}	-16.67±16.67^{**acde}	15.87±1.37^{**b}	15.87±1.37^{**b}	20.63±6.87^{**b}
4th hour	44.44±9.62^{**b}	-22.22±19.24^{**acde}	15.87±1.37^{**b}	15.87±1.37^{**b}	30.95±13.26^{**b}
5th hour	61.11±9.62^{**bcd}	-32.54±17.87^{**acde}	31.75±2.75^{**ab}	31.75±2.75^{**ab}	36.51±5.50^{**b}
6th hour	61.11±9.62^{**b}	-38.09±20.62^{**acde}	42.06±8.36^{**b}	31.75±2.75^{**b}	41.27±13.75^{**b}

Remarks: Statistical analysis using one-way ANOVA followed by Tukey's post hoc test to analyze differences in treatment groups. ** = Significance was set at $p < 0.05$. [a] = comparison vs control +; [b] = comparison vs control -; [c] = comparison vs dose 100 mg/kg BW; [d] = comparison vs dose 200 mg/kg BW; [e] = comparison vs dose 300 mg/kg BW.

Based on Table 1, all groups had relatively similar volumes of initial edema after carrageenan induction (0.06 ± 0.00–0.01 mL), suggesting that the initial condition of the test animals

was homogeneous. In the negative control group, edema continued to increase until the 6th hour, indicated by an increasingly negative change percentage value, indicating the absence of an anti-inflammatory effect. In contrast, the positive control group showed the most progressive and highest decrease in edema, reaching 61.11 ± 9.62% at the 5th and 6th hours. The administration of ethanol extract of matoa fruit peel at doses of 100, 200, and 300 mg/kgBB is also able to gradually reduce edema from the 3rd to the 6th hour. The largest effect among the extract groups was observed at a dose of 100 mg/kgBB with an inhibition percentage of 42.06 ± 8.36% at the 6th hour, followed by a dose of 300 mg/kgBB of 41.27 ± 13.75%, while a dose of 200 mg/kgBB showed a lower effect (31.75 ± 2.75%). The results of statistical tests showed that most of the treatment groups were significantly different ($p < 0.05$) compared to the negative controls, so it can be concluded that the ethanol extract of matoa fruit peel has anti-inflammatory activity against carrageenan-induced edema, although its effectiveness is still under positive control.

Discussion

The results demonstrated that the administration of ethanol extract of matoa fruit peel (*Pometia pinnata* J.R.Forst. & G.Forst.) at doses of 100 mg/KgBB, 200 mg/KgBB, and 300 mg/KgBB effectively reduced the volume of carrageenan-induced male white rat leg edema. The observed decrease in edema volume across all treatment groups indicated that the ethanol extract of matoa fruit peel possessed anti-inflammatory properties. The carrageenan-induced edema model is a widely employed method for evaluating the anti-inflammatory activity of natural compounds due to its ability to simulate acute inflammatory processes involving diverse inflammatory mediators, including histamine, serotonin, bradykinin, prostaglandins, and proinflammatory cytokines (Liu et al., 2021; Pacheco-Quito et al., 2020; Turnip & Panjaitan, 2022).

The observed anti-inflammatory effect is thought to be related to the content of secondary metabolites found in the skin of the matoa fruit. Several studies report that the skin of the matoa fruit contains flavonoids, tannins, saponins, and phenolic compounds that have biological activity as antioxidants and anti-inflammatories (Gusti & Gusmailina, 2025; Hajar et al., 2021; Herbani & Tilaqza, 2026). Flavonoids are known to inhibit the activation of the enzymes cyclooxygenase (COX) and lipoxygenase (LOX), so that the synthesis of prostaglandins and leukotrienes, as the main mediators of inflammation, is reduced. In addition, flavonoids can also inhibit the activation of the transcription factor Nuclear Factor-kappa B (NF-κB), which plays a role in the expression of various proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). With the obstruction of these pathways, the vasodilation process and increased capillary permeability that cause edema can be suppressed (Barnes, 2016; Bekassy et al., 2022; Chen et al., 2018; Hajar et al., 2021; Ricciotti & Fitzgerald, 2011).

In addition to flavonoids, tannin compounds found in the skin of matoa fruit are also thought to contribute to anti-inflammatory activity. Tannins have astringent properties that can reduce the permeability of blood vessels so that the exudation of fluid to tissues can be minimized. This compound is also reported to be able to inhibit the formation of inflammatory mediators through decreased production of prostaglandins and nitric oxide (NO), as well as reduce the infiltration of inflammatory cells in inflamed tissues. Thus, fluid accumulation in the leg tissue of the mice became lower compared to the negative control group (Fahmi et al., 2023; Herbani & Tilaqza, 2026; Turnip & Panjaitan, 2022).

The saponins and phenolic compounds contained in the ethanol extract of the matoa fruit peel also have the potential to provide synergistic effects on anti-inflammatory activity. Saponins are known to inhibit the release of pro-inflammatory cytokines and reduce the infiltration of neutrophils into inflammatory areas. Meanwhile, phenolic compounds act as antioxidants that can neutralize reactive oxygen species (ROS). In inflammatory conditions, ROS is produced in high quantities and can aggravate tissue damage through activation of inflammatory pathways. Therefore, the antioxidant activity of phenolic compounds helps suppress the development of inflammation so that the formation of edema becomes smaller (Anisa et al., 2023; Fabanyo et al.,

2023; Fahmi et al., 2023; Gusti & Gusmailina, 2025; Hajar et al., 2021; Hardia, Akrom, Hidayati, et al., 2025; Hardia, Akrom, Sulistyani, et al., 2025; Herbani & Tilaqza, 2026; Lanipi et al., 2021; Muslihin et al., 2025; Prabawati et al., 2021; Sanaky et al., 2024; Tandililing et al., 2025; Turnip & Panjaitan, 2022).

When comparing doses, in general, an increase in the dose of the extract tends to result in a greater decrease in edema volume. This suggests a dose-response relationship, where the higher the dose of the extract administered, the more active compounds are available to inhibit the formation of inflammatory mediators. The dose of 300 mg/KgBB is estimated to provide the most optimal anti-inflammatory effect compared to the doses of 100 mg/KgBB and 200 mg/KgBB. This condition shows that an increase in the concentration of bioactive compounds in the body can increase the effectiveness of inhibiting the inflammatory process. However, it is necessary to conduct a statistical analysis to ascertain whether the difference between doses is significant.

The decrease in edema that occurs is also related to the characteristics of the carrageenan inflammatory model, which takes place in two phases. The initial phase (0–2 hours) is characterized by the release of histamine, serotonin, and bradykinin, while the second phase (3–5 hours) is dominated by the production of prostaglandins through the cyclooxygenase pathway. If the ethanol extract of matoa fruit peel can suppress the formation of edema until the second phase, it can be suspected that its mechanism of action is more dominant through the inhibition of the synthesis of prostaglandins and other inflammatory mediators. This mechanism is similar to nonsteroidal anti-inflammatory drugs (OAINS) that work to inhibit the activity of the COX enzyme so that the formation of prostaglandins is reduced (Bekassy et al., 2022; Gilroy, 2021; Herbani & Tilaqza, 2026; Meizlish et al., 2021).

Overall, the results of this study show that the ethanol extract of matoa fruit peel has potential as a natural anti-inflammatory agent. This activity is thought to stem from the synergistic work of various secondary metabolites, especially flavonoids, tannins, saponins, and phenolic compounds that can inhibit the formation of inflammatory mediators, reduce oxidative stress, and reduce capillary permeability. This finding provides a scientific basis that the waste of matoa fruit peels has the potential to be developed as a source of raw materials for phytopharmaceuticals or anti-inflammatory herbal medicines. However, further research is still needed to identify the most important active compounds, explain the molecular mechanisms in more detail, and evaluate their safety, toxicity, and effectiveness through preclinical and clinical trials.

This study showed that the ethanol extract of the bark of the matoa fruit (*Pometia pinnata,* J.R. Forst. & G. Forst.) had anti-inflammatory activity in the carrageenan edema model. Interestingly**,** a dose of 100 mg/kgBB provides a better edema inhibition effect than a dose of 200 mg/kgBB**,** thus showing a non-monotonic dose-response pattern**.** This phenomenon can be caused by the nature of the extract, which is a mixture of various bioactive compounds, so that at optimal doses there is a synergistic effect, while at higher doses there can be antagonism between compounds, saturation of biological targets, or decreased bioavailability. These findings confirm that the effectiveness of herbal extracts does not necessarily increase with increased dosage.

The anti-inflammatory mechanism of matoa fruit peel extract is thought to be related to the content of flavonoids, tannins, and phenolic compounds that can inhibit the NF-κB and COX-2 pathways**,** thereby reducing the production of inflammatory mediators such as TNF-α, IL-1β, IL-6, iNOS, and PGE_2**.** In addition, the antioxidant activity of phenolic compounds through the activation of the Nrf2/HO-1 pathway is also thought to contribute to suppressing oxidative stress that plays a role in the inflammatory process. This mechanism is in line with recent studies showing that phytochemicals work multitarget in controlling the inflammatory response.

In terms of drug development, the results of this study provide a scientific basis that matoa fruit peel waste has the potential to be developed as an anti-inflammatory

phytopharmaceutical candidate. However, before it is applied clinically, it is still necessary to standardize the extract, identify active compounds, conduct toxicity tests, pharmacokinetic studies, and clinical trials to ensure its safety and effectiveness. This study also has several limitations, namely using only acute inflammatory models, not evaluating molecular and histopathological biomarkers, and not having standardized extracts and safety testing. Therefore, further research needs to examine the molecular mechanisms in more depth, evaluate the dose-response relationship, and conduct translational studies so that the potential of matoa fruit peel extract can be developed into herbal medicine based on scientific evidence.

CONCLUSION

Ethanol extract of matoa fruit peel (*Pometia pinnata,* J.R.Forst. & G.Forst.) showed anti-inflammatory activity in carrageenan-induced male white rats (*Rattus norvegicus*). Administration of extracts at doses of 100, 200, and 300 mg/KgBB was able to reduce the volume of edema of the legs of rats, with a tendency to increase the anti-inflammatory effect as the dose increased. These findings show that ethanol extract from matoa fruit peel has the potential to be developed as a natural source of ingredients that have anti-inflammatory activity.

This study has several limitations, namely, only using an acute inflammation model with the main parameter in the form of edema volume measurement, so it cannot explain the molecular mechanism and effectiveness of extracts in chronic inflammation. In addition, this study has not been accompanied by characterization and quantification of bioactive compounds, measurement of inflammatory biomarkers, histopathological examinations, and toxicity evaluation, so the working mechanism and safety profile cannot be thoroughly ascertained. Therefore, further research is needed to identify the active compounds that play a role, evaluate the anti-inflammatory mechanism through biomarker and histopathological analysis, conduct toxicity tests, and test the effectiveness of extracts in chronic inflammatory models to support the development of the ethanol extract of matoa fruit peel as an anti-inflammatory phytopharmaceutical candidate.

Overall, this study makes an important contribution to the field of pharmacology of natural materials by proving that the ethanol extract of matoa fruit peel has anti-inflammatory activity in the carrageenan edema model, while expanding the use of fruit peel waste as a source of bioactive compounds. These findings are the foundation for the development of Indonesian phytopharmaceuticals as well as translational research towards clinical applications, although further studies on the mechanism of action, long-term safety, pharmacokinetics, and clinical trials in humans are still needed before they can be recommended in clinical practice.

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