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Research Article

The potential Seribu kuman leaves (*Rhinacantus nasutus* (L.) Kurz) as anti-inflammatory in lowering volume of edema and interleukin-6 levels post carrageenan on Wistar rats

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ABSTRACT

Inflammation is the body's physiological response to various stimuli such as infections and tissue injuries. One of the medicinal plants with potential anti-inflammatory properties is Seribu Kuman leaves (*Rhinacanthus nasutus* (L.) Kurz), which contains active compounds such as naphthoquinone, flavonoids, alkaloids, phenolics and saponins. This study aimed to evaluate the anti-inflammatory effect of the ethanol extract of Seribu kuman in carrageenan-induced Wistar rats and its effect on interleukin-6 (IL-6) levels, an inflammatory marker. In this study, an experimental method with a true experimental and a posttest control group design is used. The test animals consisted of 30 Wistar strain rats divided into five groups: control group (only received carrageenan). positive control (received sodium diclofenac 50 mg/kg BW), and treatment groups with the ethanol extract of *R. nasutus* at a dose of 100 mg/kg BW, 300 mg/kg BW, and 500 mg/kg BW. All rats were injected with 1% carrageenan. Edema measurements were performed every 30 to 240 min using a plethysmometer, while IL-6 levels were measured using an ELISA reader at 24, 48 and 72 h. *R. nasutus* ethanol extract at a dose of 500 mg/kg BW showed a significant anti-inflammatory effect, reducing edema in carrageenan-induced rat legs. The results are nearly the same as those of sodium diclofenac. The One-Way ANOVA statistical test showed a significant difference between the treatment and positive control groups ($p<0.05$). In addition, IL-6 levels decreased significantly after the administration of the ethanol extract of *R. nasutus* leaves. With a dose of 500 mg/kg BW at the 48th hour as the most effective dose in lowering IL-6 ($p<0.05$). *R. nasutus* leaves ethanol extract has a significant anti-inflammatory effect on carrageenan-induced edema in Wistar strain rats. and can also significantly reduce IL-6 levels. Therefore, *R. nasutus* extract demonstrates potential as a natural anti-inflammatory agent, warranting development into ointment-based medicinal preparations.

Keywords: Anti-inflammatory, *Rhinacanthus nasutus* (L.) Kurz., carrageenan, strain Wistar rat, edema induction, interleukin-6

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INTRODUCTION

Inflammation is the defence response of the body to injury or tissue damage. This process serves to destroy or weaken destructive agents, limit their spread, and repair damaged tissues (Kaur *et al.*, 2020; Abdul Khaleq *et al.*, 2018). Inflammation is divided into acute and chronic inflammation. Acute inflammation occurs rapidly and involves the vascular and immune systems, as well as inflammatory cells. Uncontrolled inflammation can progress to chronic inflammation and contribute to various degenerative diseases (Susilo *et al.*, 2022). Symptoms of inflammation include redness, heat, swelling, pain, and impaired function in the affected area (Chen *et al.*, 2017). Inflammation can be triggered by a variety of factors, such as pathogens, damaged cells, toxic substances, and radiation. This inflammatory response is mediated by a variety of molecules, including pro-inflammatory mediators such as IL-1, TNF-α, INF-γ, IL-6, IL-12, and IL-18, as well as anti-inflammatory mediators such as IL-4, IL-10, IL-13, and IFN-α (Chen *et al.*, 2017).

Interleukin-6 (IL6) is a pro-inflammatory cytokine that plays a role in inflammation. IL-6 is produced by various cell types, including macrophages, T cells, endothelial cells, and smooth muscle cells. These cytokines act as warning signals to the body against infection or tissue damage. Elevated levels of IL-6 are commonly associated with chronic inflammatory conditions and are regulated by a network of signaling molecules, among which cytokines play a pivotal role. Interleukin-6 (IL-6) is a major pro-inflammatory cytokine that drives the acute-phase response. IL-6 is produced by a variety of cell types, including macrophages, T cells, endothelial cells, and smooth muscle cells (Chen *et al.*, 2017). These cytokines serve as warning signals to the body against infection or tissue damage. High levels of IL-6 in the body are often associated with chronic inflammatory conditions and can serve as an indicator of inflammation level. Because of its role in inflammation, IL-6 is a primary target for anti-inflammatory research (Kaur *et al.*, 2020; Aldaham *et al.*, 2015).

In the ongoing effort to search for more effective and safe anti-inflammatory agents, research into natural ingredients continues to advance. One plant that has been recognised for its anti-inflammatory potential is the *R. nasutus* (L.) Kurs. This plant belongs to the Acanthaceae family, is widespread in tropical regions, including Southeast Asia, India, and China (Boonyaketgoson *et al.,* 2018). In Indonesia, it is known as “manukan” or “Seribu kuman” leaves. Various parts of this plant, including the roots, stems, and leaves, have been used in traditional medicine to treat a range of ailments, such as hepatitis, diabetes, hypertension and skin disorders like psoriasis, eczema, and herpes (Siriwatanametanon *et al.*, 2010). In addition, *R. nasustus* leaves extract is also known to serve as an antidote to snakebites (Brimson *et al.*, 2020; Bukke *et al.*, 2011).

R. nasutus contains a variety of bioactive compounds, including flavonoids, alkaloids, phenolics, benzenoids, anthraquinones, coumarins, naphthoquinones, saponins, and tannins (Bukke *et al.*, 2011). Rhinacanthin (Figure 1), a naphthoquinone derivative, exhibits anti-inflammatory activity by inhibiting the expression of the iNOS and COX-2 genes and suppressing the release of LPS-induced nitric oxide (NO), PGE2, and TNF-α in RAW 264.7 cells. (Brimson *et al.*, 2020; Boueroy *et al.*, 2018). Moreover, compounds from the naphthoquinone class have been reported to exhibit cytotoxic activity against KB cell cultures (Wu *et al.*, 1988; Boonyaketgoson *et al.*, 2018). The flavonoids in *R. nasutus* are known to inhibit capillary permeability, reduce lysosomal enzyme secretion, and block the cyclooxygenase (COX-2) and lipoxygenase pathways, thereby reducing the production of prostaglandins and leukotrienes, which act as inflammatory mediators. Therefore, this plant has the potential to serve as a natural anti-inflammatory agent (Al-Khayri *et al.*, 2022).

Our previous report on the antibacterial properties of *R. nasutus* ethanolic extract against *Staphylococcus aureus* (Fitriyasti *et al.*, 2024) supported the study by Puttarak *et al.* (2010). The leave extracts rich in rhinacanthin showed antibacterial properties against *S. mutans*, with MIC (Minimum inhibitory concentration) and MBC (Minimum

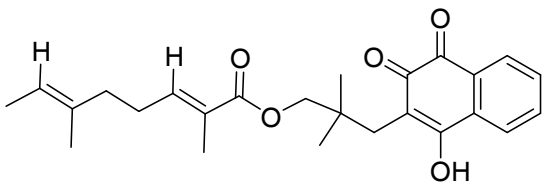

Figure 1: Structure of Rhinacanthin-C

Bactericidal Concentration) of 4 mg/mL, and potent bacteriostatic activity against *S. epidermidis*, *P. acnes*, and *S. aureus*, with MIC values ranging between 8 and 16 mg/mL. The ethanolic extract of *R. nasutus* leaves also exhibited *in vitro* antibacterial activity against human pathogens. In addition to its antibacterial and antifungal properties, the ethanol extract of *R. nasutus* leaves has also been reported to exhibit strong antioxidant and α-glucosidase inhibitory activities by Irawan *et al.* (2022 and 2021). Hence, this study aims to evaluate the anti-inflammatory potential of ethanol extract of *R. nasutus* in reducing post-carrageenan edema volume and IL-6 levels in Wistar rats.

In this study, Carrageenan is used as an agent to induce inflammation; it is neutral and causes only edema without damaging tissue. Carrageenan is well tolerated and is commonly used in animal models to evaluate the effectiveness of anti-inflammatory agents. The method for inducing edema involves administering 1% carrageenan sub-plantar on the hind foot of Wistar rats, which triggers an inflammatory response through leukocyte migration, particularly neutrophils, and vascular changes marked by increased capillary permeability (Sukmawati *et al.*, 2015). The results provide scientific information regarding the effectiveness of the ethanol extract of *R. nasustus* as a potential natural anti-inflammatory agent for the development of future inflammation therapies.

MATERIALS AND METHODS

This study was conducted at the biomedical laboratory of the Faculty of Medicine, Baiturrahmah University and the pharmacology laboratory of the Faculty of Pharmacy, Andalas University. The carrageenan-induced edema model of inflammation in Wistar strain rats (*Rattus norvegicus*) aged 2 to 3 months was used to evaluate anti-inflammatory activity. The anti-inflammatory properties are observed through the decrease in edema and the reduction of interleukin-6 levels after treatment.

Laboratory animals

30 Wistar strain rats (*R. norvegicus*), weighing 180-200 grams, were divided into five groups: Group I: control (only injected carrageenan 1%) and CMC-Na 0.5%; Group II: carrageenan 1% and administered Diclofenac 5 mg/kg BW; Group III, IV, V: carragenaan 1% and treatment of *R. nasustus* ethanol extract (100, 300, 500 mg/kg BW) groups.

Preparation of ethanol extract

R. nasutus (L.) Kurz) leaves were collected from Lubuk Minturun village in West Sumatera. It is authenticated and registered in the national herbarium at the ANDA Herbarium under registration number ANDA00015732. They were dried in the shade at 40 °C and ground to a fine powder. Seven hundred grams of fine powder was extracted by maceration using ethanol (3 x 2 L) for 24 hours. The macerate was evaporated using an evaporator to obtain a concentrated extract.

Preparation of coloidal CMC-Na 0.5% solution

CMC (carboxymethyl cellulose) was weighed at 0.5 grams and slowly sprinkled into a mortar containing 100 mL of hot water. After expansion, CMC is allowed to stand for 1 hour, then stirred until a colloidal solution forms.

Preparation of 1% carrageenan suspension

One gram of carrageenan powder was placed in a 100 mL beaker and then mixed with 0.9% NaCl until the mark was reached. It was then left to sit for 1 hour to achieve good viscosity.

Carrageenan-induced hind paw edema

Wistar strain rats (*R. norvegicus*) aged 2 to 3 months, weighing 200 to 300 grams were used. The rats were shifted to the animal house of the Faculty of Pharmacy, Andalas University, 10 days earlier. Animals were kept on a 12-h light/12-h dark cycle at 25 ± 2 °C. Rats were fasted for 24 h before the experiment and deprived of water only during the experiment. Edema measurements were carried out every 30 to 240 mins using a plethysmometer.

The decrease in interleukin levels after carrageenan induction

After the mice were induced with carrageenan, the levels of interleukin-6 were also measured. Interleukin-6 (IL-6) levels were measured using an ELISA reader (Brimson EZ Read 400) at 24, 48, and 72 h.

This research is an experimental study using a Pretest-Posttest Control Group design and proper experimental

procedures. The samples in this study were rats that met the inclusion criteria and had no exclusion criteria. In the edema volume study, parametric tests were used. Meanwhile, interleukin-6 levels were measured using the Rat IL-6 ELISA Kit, and quantification was performed using an ELISA reader (Figure 2).

Data analysis for both studies was conducted using a One-Way ANOVA. Data from each variable were processed and analysed using IBM SPSS Statistics version 25.0.

RESULTS

Carrageenan-induced hind paw edema

Table 1 shows the average reduction of edema from 10 to 240 minutes. The lowest decrease was shown in group 3 test animals (receiving 500 mg of *R. nasutus* extract). The average decrease in edema was 0.91 ± 0.08. This value was similar to that of the positive control, given sodium diclofenac 5 mg/BW (Table 1).

Figure 2: Research flowchart

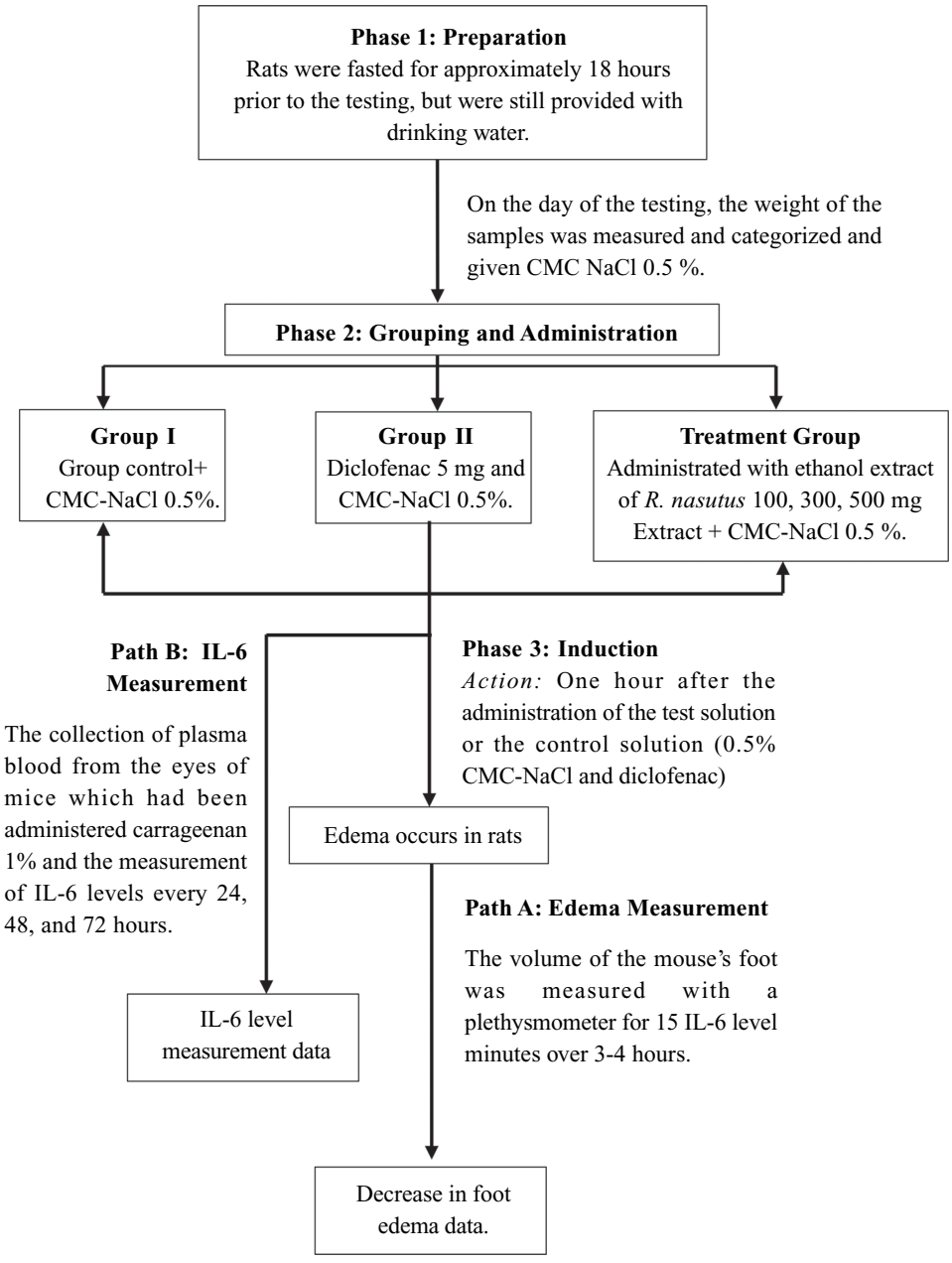

Table 1: Average reduction of paw edema in wistar strain rats induced by carrageenan after administration of ethanol extract of *R. nasutus* from 30 to 240 min

Group	Decrease in foot edema (mm)
Carrageenan (positive control group)	0.36±0.04[a]
Diclofenac Sodium Group 5 mg	0.17±0.02[b]
Group 1. Extract 100 mg	0.30±0.05[a]
Group 2. Extract 300 mg	0.23±0.04[a]
Group 3. Extract 500 mg	0.19±0.08[b]

a) insignificant difference; b) significant difference

The results of the Kruskal-Wallis test showed that, at 30 mins, further testing could not be conducted because the decrease in oedema was similar to that of the positive control across all research groups (Table 2). Meanwhile, the Kruskal-Wallis test was performed at 60, 90, 120, and 150 minutes, and a significance value (sig)>0.05 was obtained. The findings indicated that H1 is rejected; as such, it is proven that there is no activity of ethanol extract from Manukan leaves (*R. nasutus*) compared to the positive control. In contrast, at 180, 210, and 240 minutes, a significance value (sig) of <0.05 was obtained. As a result, H1 is accepted; the ethanol extract from *R. nasutus* leaves has been shown to exhibit anti-inflammatory activity in male Wistar rats.

Table 2: Results of ethanol extract activity of (*R. nasutus*) as an anti-inflammatory in male wistar rats

Times	Sig	Description
30 minutes	-	-
60 minutes	0.912	Not significant
90 minutes	0.317	Not significant
120 minutes	0.310	Not significant
150 minutes	0.559	Not significant
180 minutes	0.009	Significant
210 minutes	0.001	Significant
240 minutes	0.000	Significant

The results of interleukin-6 levels in the Wistar strain post carrageenan induction are shown in Table 3 and Figure 3. The lowest average interleukin-6 level was observed in the comparative control group, at 3.9385 ± 0.4787, followed by treatment group 3, with a value of 4.4304 ± 1.3830 at the second 48-hour observation. The Post Hoc test evaluates significant differences among two or more group means after a significant overall difference has been found. The Post Hoc Test showed a significant difference in the positive control at 48 hours for the 500 mg extract dose, with a Sig value of 0.021 (<0.05) (Table 4).

DISCUSSION

The results of the IL-6 level measurement (Table 3 and Figure 3) show that the ethanol extract of *R. nasustus* leaves not only works at the local level (reducing edema) but also affects systemic inflammatory responses. At 500 mg/kg BW,

Table 3: Interleukin-6 levels in wistar strain post carrageenan induction

Observation times (h)	Control +	Diclofenac Sodium (CC)	P1	P2	P3
24	6.0836 ±	5.0127 ±	4.4717 ±	3.5320 ±	6.0836 ±
Measurement 1	1.0822	0.4787	0.7372	0.9106	1.3830
Measurement 2	4.1837 ±	4.5543 ±	3.8162 ±	3.2485 ±	5.5211 ±
	1.0822	0.4787	0.7372	0.9106	1.3830
48	3.1271 ±	5.0127 ±	5.8657 ±	5.3506 ±	8.0551 ±
Measurement 1	1.0822	0.4787	0.7372	0.9106	1.3830
Measurement 2	4.3069 ±	3.9385 ±	4.6787 ±	5.3931 ±	4.4304 ±
	1.0822	0.4787	0.7372	0.9106	1.3830
72	3.1271 ±	4.3069 ±	3.9385 ±	4.7619 ±	5.4304 ±
Measurement 1	1.0822	0.4787	0.7372	0.9106	1.3830
Measurement 2	4.1837 ±	3.9793 ±	4.8036 ±	4.1837 ±	4.8453 ±
	1.0822	0.4787	0.7372	0.9106	1.3830

CC: Compare control (Diclofenac Sodium 5 mg). P1: Treatment (Extract 100 mg), P2: Treatment (Extract 300 mg), P3: Treatment (Extract 500 mg).

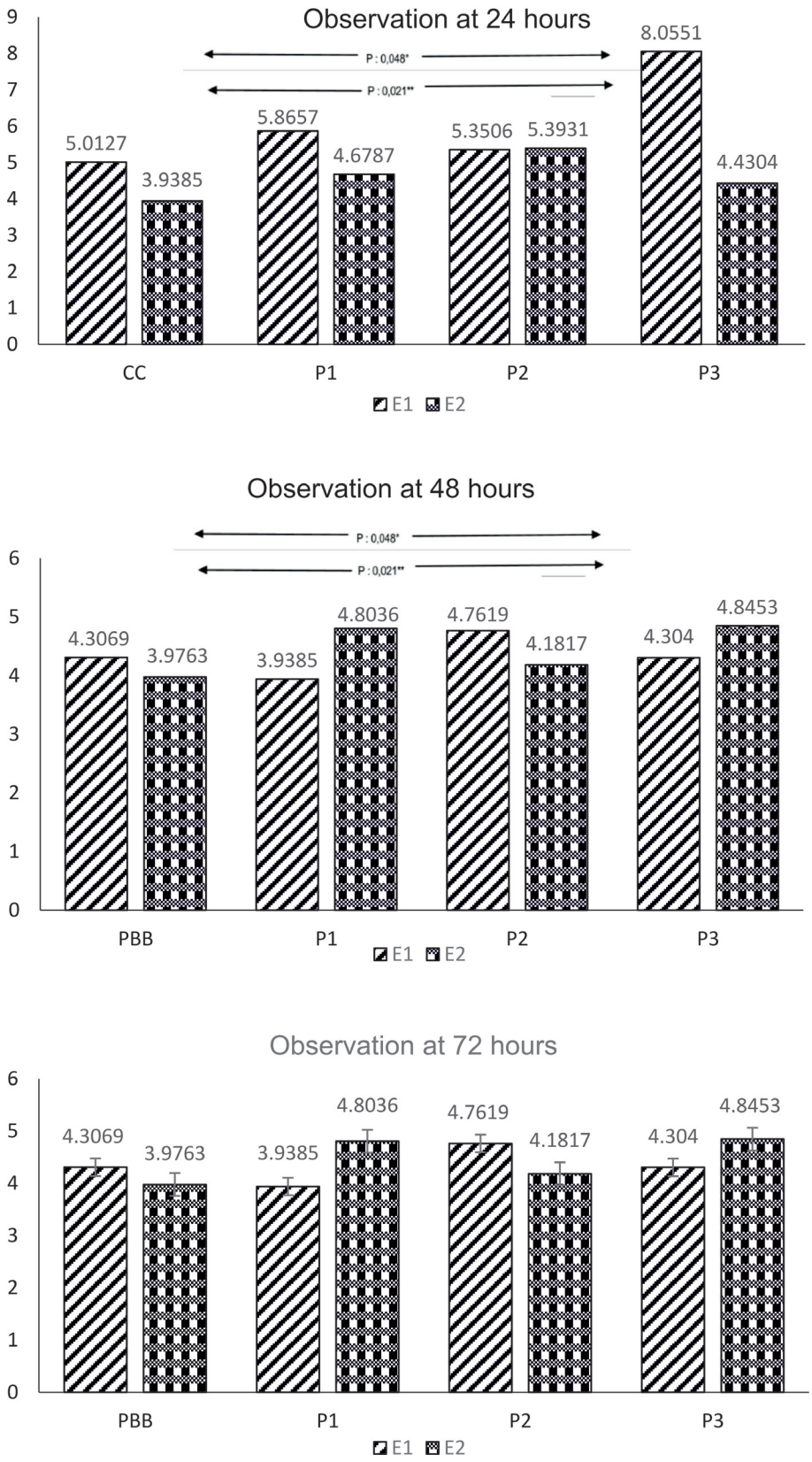

Figure 3: Differences in interleukin-6 levels in wistar strain rats after carrageenan induction were observed at 24, 48 and 72 hours.

CC: Compare control (Diclofenac Sodium). P: Treatment (100, 300 and 500 mg/BW), E1 and E2: Examination. * Anova Test Result, ** Post Hoc Result.

Table 4: Post hoc test at concentrations measurement of interleukin-6 levels

(I) Concentration	(J) Concentration	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Lower Bound
Positive control	CC	-0.7228833	.5330610	.752	-2.344238	.898472
	P1	-0.8512167	.5330610	.607	-2.472572	.770138
	P2	-0.6671167	.5330610	.808	-2.288472	.954238
	P3	-1.8164667*	.5330610	.021	-3.437822	-.195112
CC	Positive control	0.7228833	.5330610	.752	-.898472	2.344238
	P1	-0.1283333	.5330610	1.000	-1.749688	1.493022
	P2	0.0557667	.5330610	1.000	-1.565588	1.677122
	P3	-1.0935833	.5330610	.339	-2.714938	.527772
P1	Positive control	0.8512167	.5330610	.607	-.770138	2.472572
	CC	0.1283333	.5330610	1.000	-1.493022	1.749688
	P2	0 .1841000	.5330610	.999	-1.437255	1.805455
	P3	.9652500	.5330610	.474	-2.586605	.656105
P2	Positive control	.6671167	.5330610	.808	-.954238	2.288472
	CC	-.0557667	.5330610	1.000	-1.677122	1.565588
	P1	-.1841000	.5330610	.999	-1.805455	1.437255
	P3	-1.1493500	.5330610	.287	-2.770705	.472005
P3	Positive control	1.8164667*	.5330610	.021	.195112	3.437822
	CC	1.0935833	.5330610	.339	-.527772	2.714938

CC: Compare control (Diclofenac Sodium). P1: Treatment (100 mg/BW), P2: Treatment (300 mg/BW), P3: Treatment (500 mg/BW), *significant difference

IL-6 levels decreased significantly at 48 hours post-administration of the extract. This indicates that the bioactive compounds in the extract can inhibit IL-6 production, a key cytokine in acute and chronic inflammatory responses. The decrease in IL-6 is consistent with an anti-inflammatory mechanism that suppresses NF-κB pathway activation, which is known to regulate pro-inflammatory cytokine production.

The mechanism of action of this extract is related to its active compound content, particularly flavonoids and naphthoquinone. Flavonoids have been shown to inhibit enzyme cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), which play a role in the synthesis of inflammatory mediators such as prostaglandins and leukotrienes. Additionally, flavonoids can inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-1α, thereby helping reduce inflammation. Naphthoquinone compounds in *R. nasutus* have been shown to inhibit the inflammatory pathway by suppressing the expression of iNOS and COX-2, thereby reducing the production of NO and PGE2, two main inflammatory mediators (Sirippong *et al.*, 2006; Suksawat *et al.*, 2023).

These findings are supported by Thongrakard *et al.* (2010). The ethanol extract of *R. nasutus* leaves can inhibit leukocyte infiltration into the inflammatory area, thereby reducing inflammation progression. The reduction in leukocyte migration observed in this study may be related to flavonoids' inhibition of inflammatory cell adhesion and chemotaxis to the site of inflammation, thereby reducing leukocyte infiltration, particularly neutrophils, which release proteolytic enzymes and reactive oxygen species (ROS) (Thongrakard *et al.*, 2010).

In addition, the antioxidant properties of flavonoids help suppress oxidative stress, which often contributes to chronic inflammation. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity. Flavonoids found in the *R. nasutus* leaves act as ROS scavengers, helping protect tissues from further damage caused by prolonged inflammation (Dias *et at.,* 2021).

Statistical testing using the One-Way ANOVA showed a significant difference between the treatment group and the positive control ($p < 0.05$), particularly at the highest dose (500 mg/kg BW). Post Hoc test results indicated that the 500 mg/kg BW dose had a significant effect compared to the positive control at the 48th hour ($p=0.021$). These results support the hypothesis that the ethanol extract of Seribu Kuman leaves has a noticeable anti-inflammatory effect.

Based on previous research, the anti-inflammatory effects of *R. nasutus* have also been associated with its ability to inhibit inflammatory pathways involving nitric oxide (NO), PGE2, and COX-2. (Boueroy *et al.*, 2018; Al-Khayri *et al.*, 2022). *In vitro* studies have shown that rhinacanthin, the active compound in this plant, inhibits the expression of inflammatory genes, supporting the hypothesis that this extract has anti-inflammatory mechanisms (Boueroy *et al.*, 2018). Furthermore, the combination of flavonoids and saponins in this extract is known to accelerate wound healing by stimulating collagen production and epidermal growth factor signalling.

CONCLUSION

The research concludes that the ethanol extract of leaves of *R. nasutus* has significant potential as a natural therapeutic agent for the treatment of both acute and chronic inflammation. Further studies are necessary to optimise the dosage, more thoroughly evaluate the underlying mechanisms, and test its effectiveness in other inflammatory models before its application in human clinical therapy. Additionally. formulations in the form of pharmaceutical preparations, such as gels or ointments, based on *R. nasustus* leaves extract could serve as an alternative development for more practical clinical applications.

Conflict of interest

The authors declared no conflict of interest.

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