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Antipyretic Effects of Ethanolic Leaf Extract of Villebrunea Rubescens: An in Vivo Study

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ABSTRACT

Villebrunea rubescens, locally referred to as “jilat leaves,” is a wild plant traditionally employed by indigenous communities in Yapen Islands Regency, Papua, for managing wounds and contusions. Phytochemical analyses have revealed the presence of secondary metabolites, particularly flavonoids, which are hypothesized to contribute to its antipyretic properties. This study investigated the antipyretic efficacy of ethanol extract from V. rubescens leaves and determined the most effective dosage. Utilizing a Completely Randomized Design, 25 male mice (Mus musculus) were allocated into five groups: a positive control (paracetamol), a negative control (0.5% Na-CMC), and three treatment groups receiving 50, 100, and 150 mg/kg body weight of the extract, respectively. Rectal temperatures were recorded over 180 minutes post-treatment. Statistical analysis using one-way ANOVA followed by Duncan’s multiple range test indicated that the extract significantly reduced fever in a dose-dependent manner, with 150 mg/kg demonstrating the greatest efficacy, comparable to paracetamol. These findings suggest that V. rubescens leaf extract holds promise as a natural antipyretic agent, with 150 mg/kg identified as the optimal dose.

KEYWORDS: Antipyretic, Extract, In Vivo, Leaf.

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I. INTRODUCTION

Indonesia possesses vast biodiversity, particularly in its array of medicinal plants, which serve as invaluable resources for traditional healthcare practices. Herbal medicine remains deeply ingrained in the cultural heritage of many Indonesian communities, with therapeutic applications passed down through generations. Various plant components—such as roots, bark, leaves, fruits, and seeds—continue to be utilized as primary ingredients in natural remedies.[1]

Fever is common physiological response to infection, and numerous herbal remedies have been explored for their antipyretic properties due to their perceived safety profile when compared to synthetic pharmaceuticals.[2] Plant-derived secondary metabolites, including flavonoids, alkaloids, terpenoids, and steroids, are recognized for their diverse pharmacological actions.[3-4]

Papua, a region known for its rich flora, is home to many medicinal plants traditionally used by local populations. Among them, Villebrunea rubescens, or "jilat leaves," from the Urticaceae family, is widely utilized by indigenous people in the Yapen Islands Regency. Traditionally, the leaves have been applied for treating bruises, eye inflammation, headaches, chickenpox, and urinary tract infections. Prior research has indicated that V. rubescens exhibits cytotoxic activity (LC_{50} = 17.98 ppm) and contains numerous bioactive compounds such as flavonoids, alkaloids, chalcones, isoflavones, fatty acids, and triterpenoids.[5] Despite its reported traditional use in fever reduction, the antipyretic potential of V. rubescens has yet to be validated through scientific investigation. Thus, further studies are warranted to explore its potential as a plant-based antipyretic remedy, particularly for the benefit of local communities in Papua.[6]

Fever results from an elevation in body temperature, typically triggered by the release of endogenous pyrogens from immune cells in response to microbial infection. Although it is a natural defense mechanism, fever can cause

various symptoms such as flushed skin, increased respiratory rate, chills, dehydration, and reduced appetite.[7] Paracetamol, a widely used antipyretic and analgesic, serves as a reference standard in antipyretic studies. Experimental models often employ Mus musculus (mice) due to their manageable size, ease of care, and physiological compatibility with pharmacological research.[8] In such studies, fever is typically induced using pyrogens like peptone, which reliably elicit febrile responses in laboratory animals.[9]

II. MATERIAL AND METHODS

A. Instruments and Materials

The tools employed in this study included glass beakers, an analytical balance, measuring cylinders, 1 mL injection syringes, test tubes, oral gavage devices, droppers, blender, vacuum rotary evaporator, water bath, porcelain crucibles, mortars, digital thermometers and standard animal cages.

The materials used comprised 96% ethanol, peptone, 0.5% sodium carboxymethyl cellulose (Na-CMC), 500 mg paracetamol tablets, 2N hydrochloric acid (HCl), Dragendorff and Mayer reagents, magnesium powder, distilled water, ferric chloride ($FeCl_3$) solution, Sodium hydroxide (NaOH), chloroform ($CHCl_3$) and aquadest.

B. Sample Collection

Fresh leaves of V. rubescens were collected from Kampung Rambai, Yapen Islands Regency, Papua Province. Samples were selected randomly based on healthy morphology. Approximately 1 kg of leaves was harvested and processed immediately to preserve phytochemical integrity.

C. Simplisia Preparation

Collected leaves were cleaned, cut into small pieces, and dired under indirect sunlight to reduce moisture content. The dried material was milled using a blender and sieved to produce fine powder suitable for extraction.

D. Extraction Procedure

The powdered plant material was subjected to maceration with 96% ethanol at a ratio of 1:4 (w/v). The initial soaking lasted three hours with intermittent stirring, followed by three days of static maceration. The extract was filtered and concentrated using a rotary evaporator at 40°C. Final solvent removal was conducted in a water bath at 60°C, yielding a viscous ethanol extract.

E. Ethanol Residue Test

To ensure the absence of residual ethanol, one drop of the extract was placed on a spot plate, followed by two drops of concentrated H_2SO_4 and one drop of potassium dichromate ($K_2Cr_2O_7$). A bluish-green color would indicate residual ethanol. The absence of color change confirmed ethanol-free extract.[10]

F. Phytochemical Screening Results

Alkaloids: Detection involved dissolving 5 mL of extract in 2N HCl and adding either Dragendorff's or Mayer's reagent. Positive results were indicated by orange (Dragendorff) or white-yellow (Mayer) precipitates.

- Flavonoids: Indicated by an orange-red coloration upon addition of magnesium and concentrated HCl.
- Saponins: Foam formation (≥1 cm height for ≥7 minutes) after shaking with warm water and adding HCl signified the presence of saponins.
- Tannins: A greenish-black color appeared upon mixing the extract with 5% $FeCl_3$ solution.
- Quinonenes: A dark yellow to red coloration upon addition of NaOH indicated quinones.

G. Experimental Animals

A total of 25 healthy male mice, aged 2–4 months, weighing between 20 – 30 grams, were used. The health of the animals was verified during a pre-study acclimatization period, ensuring that weight variation did not exceed 10%.

H. Experimental Design

The study adopted a Completely Randomized Design (CRD), allocating the mice into five groups: a negative control (0.5% Na-CMC), a positive control (paracetamol), and three test groups treated with ethanol extract of V. rubescens leaves at doses of 50, 100, and 150 mg/kg body weight (BW). Group sizes were determined based on Federer's formula:

$$(t-1)\,(n-1) \geq 15 \qquad (1)$$

Solving this yielded a minimum requirement of five animals per group.

I. Animals Acclimatization

The animals were housed in plastic cages with rice husk bedding and mesh covers. A 7-day acclimatization period preceded the experiment. Ethical clearance for animal testing was obtained from the appropriate institutional ethics committee.[11]

J. Preparation of Test Solutions

- 0.5% Na-CMC Suspension: Prepared by swelling 0.5 g Na-CMC in 10 mL of hot water, triturating, and diluting to 100 mL with distilled water.
- Extract Suspension: The extract was weighed to achieve target doses and dissolved in 0.5% Na-CMC.
- Peptone Solution: A 10% peptone solution was prepared (10 g in 100 mL water) and administered subcutaneously at 1% of body weight (e.g., 0.2 mL for a 20 g mouse).
- Paracetamol Suspension: Ground paracetamol tablets (87.75 mg) were dissolved in 0.5% Na-CMC to yield a 10 mL suspension following dose conversion guidelines.

K. Antipyretic Activity Assessment

Baseline rectal temperature was recorded for all mice using a digital thermometer inserted 0.5–1 cm rectally. Fever was induced via subcutaneous injection of 10% peptone solution. One-hour post-induction, temperatures were rechecked, and mice exhibiting <0.6°C increase were excluded. Treatments were then administered based on group allocation, and

temperatures were measured at 30-minute intervals for 180 minutes.[12]

L. Data Analysis

- AUC calculated via trapezoidal method
- Antipyretic effect (%) =

$$\frac{(T_0 - T_n)}{(T_0 - T_{initial})} \times 100 \quad (2)$$

where:

- T_o = Temperature after fever induction
- T_n = Temperature at each interval

$T_{initial}$ = Pre-induction temperature

III. RESULTS AND DISCUSSION

A. Preparations of Simplisia

Approximately 1 kg of Villebrunea rubescens leaves were collected, thoroughly cleaned, and air-dried to reduce moisture content. The drying process was carried out under direct sunlight for three consecutive days. After drying, the leaves were ground into a fine powder and passed through a sieve to obtain uniform particle size. This procedure resulted in 401 g of powdered simplisia.

B. Ethanolic Extraction

The powdered simplisia was subjected to maceration using 96% ethanol, a solvent widely recognized for its polarity and efficacy in extracting a broad spectrum of phytochemicals.[13] Following filtration, the extract was concentrated using a rotary evaporator at 50°C, followed by further evaporation in a water bath at 60°C to remove any residual solvent. The resulting viscous extract weighed 39.677 g, corresponding to a yield of 9.89%.

This yield is consistent with the threshold established in the second edition of the Indonesian Herbal Pharmacopoeia (2017)[14], which prescribes a minimum of 9.2% for the thick extract of Moringa oleifera leaves. Given that both V. rubescens and M. oleifera belong to the same taxonomic division and class, the comparison offers a valid reference point. Factors such as extraction temperature, duration, solvent efficiency, and sample-to-solvent ratio likely influenced the observed yield.[15] The yield percentage is summarized in the Table 1.

Table 1: Yield of Ethanol Extract of V. rubescens Leaves

Sample	Sample Color	Sample Mass (g)	Extract Mass (g)	Yield (%)
V. rubescens leaves	Dark green (powder) Dark greenish-black (extract)	401	39.677	9.89

C. Ethanol Residue Test

The absence of residual ethanol in the extract was confirmed using a spot test with concentrated sulfuric acid (H_2SO_4) and potassium dichromate ($K_2Cr_2O_7$). The lack of a greenish-blue color change indicated that the extract was free from ethanol residues.[16] The results are summarized in Table 2.

Table 2: Ethanol Residue Analysis

Test Performed	Observation Result	Conclusion
Extract + H_2SO_4 (conc.) + $K_2Cr_2O_7$	No greenish-blue color formation	Ethanol-free extract

D. Phytochemical Screening Results

The phytochemical screening results of the ethanolic extract of Jilat leaves are presented in the Table 3.

Table 3: Qualitative Phytochemical Screening of Ethanol Extract

Phytochemical	Result	Description
Alkaloid	Mayer: No color change or precipitate	Mayer: (-)
	Dragendorff: Orange color formed	Dragendorff: (+)
Flavonoid	Orange-brownish color formed	(+)
Saponin	Foam formed up to 1.8 cm for ± 5 minutes	(+)
Tannin	Dark green color formed	(+)
Quinone	No color change observed	(-)

Note: (+) : indictaes presence

(-) : indicates absence of compound

The extract was found to contain several secondary metabolites, including alkaloids, flavonoids, saponins, and tannins. Alkaloids were identified by the formation of an orange precipitate upon the addition of Dragendorff's reagent, while Mayer's reagent produced no observable color change. This result suggests a positive alkaloid reaction due to ligand substitution between the alkaloid and the reagent. Alkaloids are nitrogen-containing compounds that are typically insoluble in water but soluble in semi-polar solvents. They are known for their diverse pharmacological activities, including antipyretic effects.[17]

Flavonoids were also detected, indicating the presence of polar compounds soluble in ethanol. These compounds are well-documented for their antipyretic activity through the inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis.[18-19] Saponins were confirmed by the formation of persistent froth when the extract was shaken with water, a result of their amphipathic nature. These glycosides possess surfactant properties and

are known for various biological effects, including membrane interaction and immune modulation.[20-21] Tannins were detected as well, classified as polyphenolic compounds and potential analgesic or antipyretic effects—particularly due to their corilagin and geraniin subgroups.[22–24]

E. Antipyretic Activity Test Results

The antipyretic potential of the ethanolic extract of V. rubescens (Jilat) leaves was evaluated using a peptone-induced pyrexia model in male mice. Fever was induced by subcutaneous injection of 10% peptone solution, a protein source known to trigger febrile responses through systemic protein imbalance and the release of endogenous pyrogens.[25-26] Following fever induction, mice with a body temperature increase of ≥ 0.6°C from baseline were considered successfully induced and randomly assigned into five groups (n = x/group): a positive control group receiving paracetamol, a negative control group receiving 0.5% sodium carboxymethyl cellulose (CMC-Na), and three treatment groups receiving the ethanol extract of V. rubescens at doses of 50, 100, and 150 mg/kg body weight. Body weights were recorded prior to treatment, and each mouse was marked and grouped randomly. Rectal temperatures were measured using a digital thermometer at baseline, immediately before treatment, and at 30-minute intervals for 3 hours post-treatment to assess the antipyretic effect. The average temperature readings for each group are presented in Table 4.

Table 4: Mean Rectal Temperature (°C) of Mice

Mean Temperature (°C) ± SD								
Group	**T (Initial)**	**T_0 (Fever)**	**T_{30}**	**T_{60}**	**T_{90}**	**T_{120}**	**T_{150}**	**T_{180}**
Positive Control	36.18 ± 0.20	37.10 ± 0.15	36.90 ± 0.15	36.68 ± 0.10	36.48 ± 0.13	36.28 ± 0.10	36.06 ± 0.08	35.82 ± 0.08
Negative Control	36.22 ± 0.28	37.16 ± 0.20	37.32 ± 0.22	37.44 ± 0.24	37.52 ± 0.22	37.56 ± 0.19	37.60 ± 0.21	37.68 ± 0.21
EEJL 50 mg/KgBW	36.16 ± 0.28	37.10 ± 0.15	37.08 ± 0.19	37.00 ± 0.15	36.82 ± 0.19	36.64 ± 0.16	36.50 ± 0.14	36.34 ± 0.11
EEJL 100 mg/KgBW	36.18 ± 0.25	37.18 ± 0.31	37.08 ± 0.31	36.92 ± 0.29	36.78 ± 0.31	36.66 ± 0.32	36.48 ± 0.30	36.34 ± 0.31
EEJL 150 mg/KgBW	36.10 ± 0.22	37.00 ± 0.21	36.84 ± 0.20	36.68 ± 0.20	36.48 ± 0.20	36.30 ± 0.23	36.12 ± 0.17	35.96 ± 0.15

Note:
T = Baseline temperature
T_o = Post-induction fever temperature
T_{30}-T_{180} = Temperature measured every 30 minutes
EEJL = Ethanolic Extract of Jilat Leaves
mg/KgBW = Milligrams per kilogram of body weight

Table 4 presents the changes in mean rectal temperature across all treatment groups. An elevated rectal temperature reflects a successful febrile response, while a subsequent reduction after treatment indicates potential antipyretic activity. The administration of the ethanol extract of Villebrunea rubescens leaves at doses of 50, 100, and 150 mg/kg, as well as the positive control (paracetamol suspension), resulted in a notable reduction in body temperature compared to the negative control group (0.5% Na-CMC).

In contrast, the negative control group exhibited no significant reduction in rectal temperature throughout the 180-minute observation period. This is consistent with the pharmacological profile of sodium carboxymethyl cellulose, which lacks antipyretic properties and functions primarily as a vehicle to prevent dehydration during febrile conditions.[27] Notably, temperature reductions in both the paracetamol and extract-treated groups were not linear. These fluctuations may be influenced by factors such as stress induced by repeated handling during temperature measurement, inter-individual variations in drug absorption and pharmacodynamic response, or environmental conditions including ambient room temperature during the testing period.

The rectal temperature data collected from each group were used to calculate the Area Under the Curve (AUC) and the percentage of antipyretic activity.[28] The mean AUC values and corresponding antipyretic efficacy percentages for each treatment group are summarized in Table 5.

Table 5: AUC of Rectal Temperature

Group	AUC (°C x min)
Positive Control	109.43
Negative Control	112.43
EEJL 50 mg/KgBW	93.33
EEJL 100 mg/KgBW	110.34
EEJL 150 mg/KgBW	109.45

The AUC was calculated for each treatment group to quantify the overall antipyretic effect. The trapezoidal rule was employed, wherein two consecutive rectal temperature values were averaged and multiplied by the time interval between them. The AUC values were subsequently used to determine the percentage of antipyretic activity of the V. rubescens ethanolic extract relative to the positive control (paracetamol). The results are summarized in Table 6.

Table 6: Antipyretic Activity of Ethanol Extract

Group	Antipyretic Effect (%)
Positive Control	79.35%
EEJL 50 mg/KgBW	39.54%
EEJL 100 mg/KgBW	47.00%
EEJL 150 mg/KgBW	67.04%

The highest antipyretic activity was observed in the positive control group receiving paracetamol, consistent with its (COX) enzymes in the hypothalamic thermoregulatory center, thereby reducing prostaglandin synthesis and lowering body temperature.[29] Among the extract-treated groups, the 150 mg/kg BW dose exhibited the greatest antipyretic effect, suggesting a dose-dependent response.

Data normality was assessed and confirmed, indicating a normal distribution. Subsequently, Levene's test was conducted to evaluate the homogeneity of variances among the treatment groups. Homogeneity is confirmed when the significance value (Sig.) exceeds 0.05, suggesting equal variances across groups.[30] The test produced a significance value of 0.187, indicating no significant variance differences between groups. Following confirmation of data normality and homogeneity, a One-Way ANOVA test was performed to compare the five treatment groups. The analysis yielded a significance value of 0.000 ($p < 0.05$), indicating statistically significant differences among the treatment groups.

The analysis was further extended using Duncan's multiple range test to identify specific groups that exhibited significant differences in their mean values. The results showed that all doses of Jilat leaves ethanol extract did not differ significantly from the positive control, but did show significant differences compared to the negative control. These findings suggest that the antipyretics effect of the extract is comparable to that of the standard drug (paracetamol). When compared with previous studies, such as antipyretics test of Urtica dioica (L.) leaf extract in albino mice by VZ et al. (2016), it was found that doses of 50, 100, and 150 mg/kg BW produced significant antipyretics effects. In that study, the 100 mg/kg BW dose exhibited the established pharmacological mechanism. Paracetamol acts centrally by inhibiting cyclooxygenase

highest efficacy in reducing rectal temperature compared to both the positive control and other doses.

A similar study was conducted on the ethanol extract of Indian nettle (Acalypha indica Linn), which involved a positive control group (aspirin), a negative control group (0.5% Na-CMC), and three extract doses (70, 140 and 280 mg/kg BW). The extract significantly reduced rectal temperature, with the 280 mg/kg BW dose producing an effect comparable to the positive control.[31] Interestingly, all three plants evaluated in these studies-V. rubescens, Urtica dioica (L.), and Acalypha indica Linn- belong to the Urticaceae family and demonstrate similar antipyretic activities. Among the Jilat extract-treated groups, the 150 mg/kg BW dose exhibited the highest antipyretic percentage, indicating optimal effectiveness at this dose.

The antipyretic activity of Jilat leaves is presumed to be closely related to their phytochemical constituents, particularly flavonoids, which were identified through phytochemical screening. Flavonoids possess chemical structures resembling those of paracetamol, notably the presence of benzene rings and phenolic groups. This structural similarity is believed to contributed to their antipyretic properties.[32] Flavonoids have been reported to exhibit analgesic, anti-inflammatory, and antipyretic properties, as demonstrated in previous studies.[33-34] The proposed mechanism by which flavonoids exert antipyretics effect involves the inhibition of pyrogenic activity associated with receptors in the anterior preoptic nucleus of the hypothalamus. Consequently, the elevation of

prostaglandins via the cyclooxygenase pathway can be suppressed, thereby mitigating the febrile response.[35]

In addition to flavonoids, the ethanol extract of jilat leaves also contains alkaloids and tannins, both of which may contribute to its antipyretic mechanism. Alkaloids are known to inhibit cyclooxygenase (COX) enzymes responsible for prostaglandin production, a key mediator in fever. Tannins, on the other hand, contain compounds such as corilagin and geraniin, which are known to suppress cytokine release, the primary mediators of the febrile response.[36] An illustration of antipyretic mediator interactions within the hypothalamus is provided in the figure 1.[37]

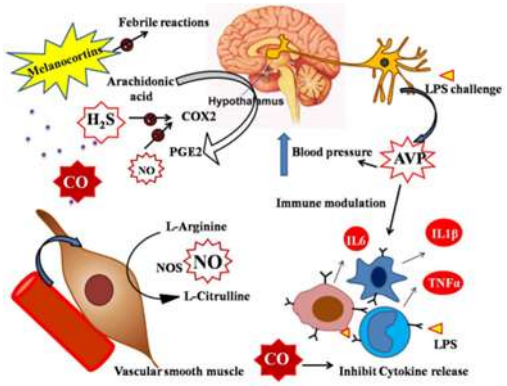

Figure 1. Interaction of Antipyretic mediators in hypothalamus

CONCLUSION

The ethanol extract of V. rubescens leaves exhibits significant antipyretic activity in male mice, as evidenced by a notable reduction in body temperature. Statistical analysis using one-way ANOVA revealed significant differences among the treatment group, and Duncan's post hoc test indicated no significant difference between the positive control (paracetamol) and the three doses of the extract. Among the doses tested, the 150 mg/kg body weight dose exhibited the highest antipyretic efficacy based on the percentage of antipyretic activity.

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