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The Potential Antipyretic Activity of the Ethanolic Peel Extract of *Artocarpus heterophyllus* (Moraceae)

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Abstract: This study investigated the antipyretic potential of the ethanoic peel extract of *A. heterophyllus* (jackfruit) and compared its efficacy with the standard antipyretic drug, paracetamol. Fever, a common response to infections or inflammation, often requires antipyretics to alleviate symptoms. The peel of *A. heterophyllus*, known to be rich in flavonoids and phenolic compounds, it undergo ethanolic extraction to isolate its bioactive constituents. The antipyretic effects of the extract was evaluated using a brewer's yeast-induced pyrexia model in male Swiss mice, with rectal temperature measurements serving as the primary indicator.

The study assessed the extract at three concentrations (2000, 3500, 5000 mg/kg), comparing its effectiveness with a negative control (distilled water) and a positive control (paracetamol 10mg/kg) (Öksüz 2020). Acute toxicity tests was also be conducted to establish the safety profile of the extract. Statistical analysis using one-way ANOVA was performed to determine the significance of the findings. This research aims to contribute to the growing interest in plant-based medicines and provide insights into the therapeutic activity of *A. heterophyllus* peel extract for fever management.

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I. INTRODUCTION

Pyrexia or commonly known as fever, is one of the most common reactions of the body to pyrogens, most diseases have symptoms such as elevated body temperature (Cleveland Clinic 2023). Normally, the body temperature is around 36.5℃ -37.5℃ (Health Direct 2019).

Pyrexia is regulated by the thermoregulatory center at the hypothalamus. The abnormal increase of body temperature can be triggered by infectious agents or inflammation. A temporary rise of body temperature can be normally observed as the body's reaction to infections (Bali et al. 2023). Typically, antipyretics are used for fever-reduction, as these drugs inhibit the cyclooxygenase enzyme (COX), which interfere with the hypothalamus in producing PGE2 (Mehmood et al. 2024). Alongside synthetic medications, there is increasing interest in natural remedies for alleviating fever. *A. heterophyllus*, or jackfruit, is a large tropical fruit from the Moraceae family, native to the Western Ghats of India and found in Asia, Africa, and parts of South America. Known as the largest edible fruit in the world, *A. heterophyllus* is rich in nutrients and beneficial plant compounds (Ranasinghe et al. 2019). Traditional medicine practices use various parts of the *A. heterophyllus* plant for their health benefits, including its potential antipyretic effects (Srivastava and Singh 2020). Flavonoids and Phenols, which are few of the leading constituents that have been proven to have the ability to reduce fever, are highly present in *A. heteruphyllus*, thus, strengthening the potentiality of its antipyretic activity (Yamin et al. 2020).

This study aims to evaluate the antipyretic activity of the ethanolic peel extract of *A. heterophyllus* by comparing its effectiveness in reducing fever with the standard antipyretic drug paracetamol, the researchers seek to explore alternative treatments for fever management and provide insights into the potential antipyretic activity of *A. heterophyllus.*

II. MATERIALS AND METHODS

- *Materials. A. Heterophyllus* Powder, Brewer's yeast Powder, Paracetamol Powder, PNSS, Ethanol (95%), and Distilled Water. All Other Reagents used were of Analytical Grade.

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➢ *Methods*

- *Sample Collection and Drying.* Samples of *A. heterophyllus* fruit peel was collected and thoroughly cleaned using distilled water to eliminate contaminants that may affect the accuracy of the extract (O'Donnell, 2020). To minimize moisture content, the peels was air-dried (40 C° - 60 C°) in a shaded, well-ventilated area for approximately one month or longer, ensuring the preservation of heat sensitive compounds (Cör Andrejč et al., 2022).

- *Extraction of A. heterophyllus.* The dried peels were grounded into a fine powder using a Nutribullet 600 blender (SKU DYP-10020684). Ethanol (95%) was used as the solvent for extraction, as research has shown that aqueous ethanol solutions (35–90%) provide optimal extraction yields and is less toxic compared to other solvents (Gil- Martín et al. 2022). The powdered sample undergoes maceration in 95% ethanol at room temperature (20–25℃) with continuous agitation with 40-100 rmp speed provided by an orbital shaker for 72 hours (Abubakar & Haque, 2020). The ethanol extract was filtered and concentrated using a rotary evaporator under reduced pressure at 40℃ to remove the solvent. Finally, the concentrated extract was stored in an airtight container to maintain its integrity for subsequent testing.

- *Percentage yield*. The weight of the extracted *A. heterophlllus* was taken and the percentage yield of the crude ethanolic extract was calculated using the formula (Tegegne and Alehegn 2023) The screening results indicate that the peel extract contains flavonoids, phenols, saponins, tannins, steroids, terpenoids, and alkaloids. The presence of these bioactive compounds suggests potential pharmacological properties, including antioxidant, anti-inflammatory, and antipyretic effects.

Table 1 Total Flavonoids of *A. Heterophyllus*

Sample Code	Total Flavonoids (mg Quercetin per gram extract)
Artocarpus heterophyllus peel	2.88 ± 0.32

$$Pectin\ Percentage\ Yield\ (\frac{w}{w}) = \frac{Weight\ of\ Extracted\ Pectin}{Weight\ of\ Pulverized\ Peel}\ x\ 100$$

Fig 1Extracted *A. Heterophyllus*

Results from three extraction trials showed yields of 4.74%, 6.19%, and 5.45%, respectively. Despite the variation in initial weights used (30 g for Trial 1 and 20 g for Trials 2 and 3), the extraction process demonstrated consistent performance, with a mean percentage yield of 5.46%. This outcome confirms that the ethanolic extraction method employed in our research was both efficient and reproducible. The moderately high yield supports the practical viability of using jackfruit peel as a source of bioactive compounds for pharmacological evaluation, particularly in our investigation of its potential antipyretic activity.

Table 2 Percentage Yield of *A. Heteruphyllus*

Trial No.	Initial Weight of Sample	Extract Weight w/o solvent	Percentage Yield
1	30g	1.423g	4.74%
2	20g	1.09g	5.45%
3	20g	1.238g	6.19%
		mean:	5.46%

- *Phytochemical Screening.* The lack of relevant studies about the phytochemical compounds of *A. heterophyllus* led the researchers to conduct a thorough phytochemical profiling in the intention of providing an up to date results. Flavonoids are the main phytochemicals that was determined. The phytochemical screening was conducted at the Laboratory at MSU-Iligan Institute of Technology, Iligan City, Philippines.

Sample code	Alka-loids	Flavo-noids	Phe-nols	Sapo-nins	Tannins	Ste-roids	Terpe-noids
Jackfruit peels	+	+++	+++	+++	+++	+	+

Fig 2 Phytochemical Screening of *A. Heterophyllus*

The results indicate that *A. heterophyllus* peel has a total flavonoid content recorded at 2.88 ± 0.32 mg QE/g extract, which may contribute to its antipyretic properties.

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- *Acute Toxicity Test.* Using the OECD 423 known as the Acute Toxic Class Method, involves administering a single oral dose of the test substance to a group of mice. The process begins with an initial dose, 2000 mg/kg to 5000 mg/kg body weight. The mice are observed for 14 days for any signs of toxicity, including behavioral changes, lethargy, tremors, or mortality. Body weight is recorded on days 0, 7, and 14 to monitor any growth-related effects. If no animals die, a higher dose is tested. If one animal dies, the same dose is repeated in another group of three animals. If two or more animals die, testing stops, and the substance is classified according to its toxic potential. Each group will contain 5 male swiss albino mice (Rameshwar et al. 2023).

- *Experimental Animals.* Male mice are preferred in antipyretic studies because the hormonal fluctuations of the female estrous cycle can affect body temperature and complicate result interpretation (Karim et al. 2020). A total of 25 male Swiss mice, 20g - 35g in weight (weight range of adult mice) was used in this study, five in each group (Quesenberry and Donnelly 2020). There were five groups: First group was the negative control, receiving 10 mL/Kg of distilled water; Second, third, and fourth group was given 2000 mg/kg, 3500 mg/kg and 5000 mg/kg of crude extract, respectively (Tegegne and Alehegn 2023). While the fifth group was given the standard drug, 10 mg/kg paracetamol (Öksüz 2020), concentration was calculated by the formula (Pandy 2020).

Animal dose (mg/kg) = Human dose (mg/kg) × Human (Km)/Animal (Km)

- *Induction of pyrexia.* A 1:5 concentration ratio (1 part plant material to 5 parts solvent) yeast extract powder suspension in 0.9% normal saline (20 mg/kg) was subcutaneously injected into back side of below the nape of the neck of the mice to induce fever (Yimer et al. 2021).

Male Swiss mice was divided into five groups (n = 5) and fasted for 8 hours overnight with free water access. The initial basal rectal temperature of each mouse was measured using a rectal thermometer by inserting a thermistor probe about 3 cm into the rectum. Fever (pyrexia) was induced in all mice by injecting 20mg/kg yeast extract powder suspension in 0.9% normal saline below the nape of the neck subcutaneously (Liu et al. 2020). The rectal temperature of each mouse will again be recorded after 18 hrs of yeast administration, only mice showing an increase in temperature of at least 37.5 - 38°C after yeast injection was used for the experiment.

- *Induction of Extracts.* After the mice will successfully inhibit pyrexia, first group - negative control received 10 mL/Kg of distilled water. Second, third, and fourth group was given; 2000 mg/kg, 3500 mg/kg, and 5000 mg/kg crude extract, respectively. The fifth group was given the standard drug, 10 mg/kg paracetamol (Öksüz 2020). All administrations was performed orally using oral gavage. Finally, the temperature of each mice was measured at 1, 2, 3, and 5 hours after dosing (Mareff et al. 2024).

III. RESULTS

➢ *Acute Toxicity Test*

The acute toxicity test conducted in accordance with OECD 423 guidelines demonstrated that the ethanolic peel extract of A. heterophyllus was non-toxic at doses 2000 up to 5000 mg/kg. No mortality or visible signs of toxicity (e.g., behavioral changes, organ abnormalities) were observed in any of the treated groups. Body weight, intestinal measurements, and internal organ weights (stomach, spleen, lungs, kidney, and heart, liver) showed only minor, non-significant fluctuations compared to the control group. These findings indicate that the extract is safe for oral administration and suitable for further pharmacological evaluation, particularly for assessing its antipyretic activity.

Table 3 Summary of Acute Toxicity Test (OECD 423 Guidelines)

Dose (mg/kg)	Mortality	Body Weight Change	Intestinal Abnormalities	Organ Toxicity
2000	None	Slight Increase	None	None
3000	None	Slight Increase	None	None
4000	None	Neutral	None	None
5000	None	Slight Increase	None	None
Negative Control	None	Slight Increase	None	None

➢ *Statistical Analysis*

The Analysis of Variance (ANOVA) was conducted to compare the antipyretic effects of different concentrations of *A. heterophyllus* ethanolic peel extract (low dose: 2000 mg/kg, middle dose: 3500 mg/kg, high dose: 5000 mg/kg), the positive control (paracetamol), and the negative control (distilled water). The ANOVA results, presented in Table 8, show that the extract's effectiveness in reducing induced pyrexia was significantly different across time points, as evidenced by the low p-values for the 1st, 2nd, 3rd, 4th, and 5th hours post-treatment. Specifically, the temperatures at the 1st hour ($p = 0.00567$), 2nd hour ($p = 0.000149$), 3rd hour ($p = 0.00016$), 4th hour ($p = 0.00001$), and 5th hour ($p = 0.00689$) were statistically significant at the 0.01 level, indicating that the extract's antipyretic effect was comparable to that of the positive control (paracetamol). In contrast, no significant differences were observed in the initial weight, induced pyrexia temperature, or the initial body temperature across groups ($p > 0.05$), suggesting that the observed effects were mainly due to the extract's impact on fever reduction over time. These results provide strong evidence that the ethanolic peel extract of *A. heterophyllus* has observable antipyretic activity.

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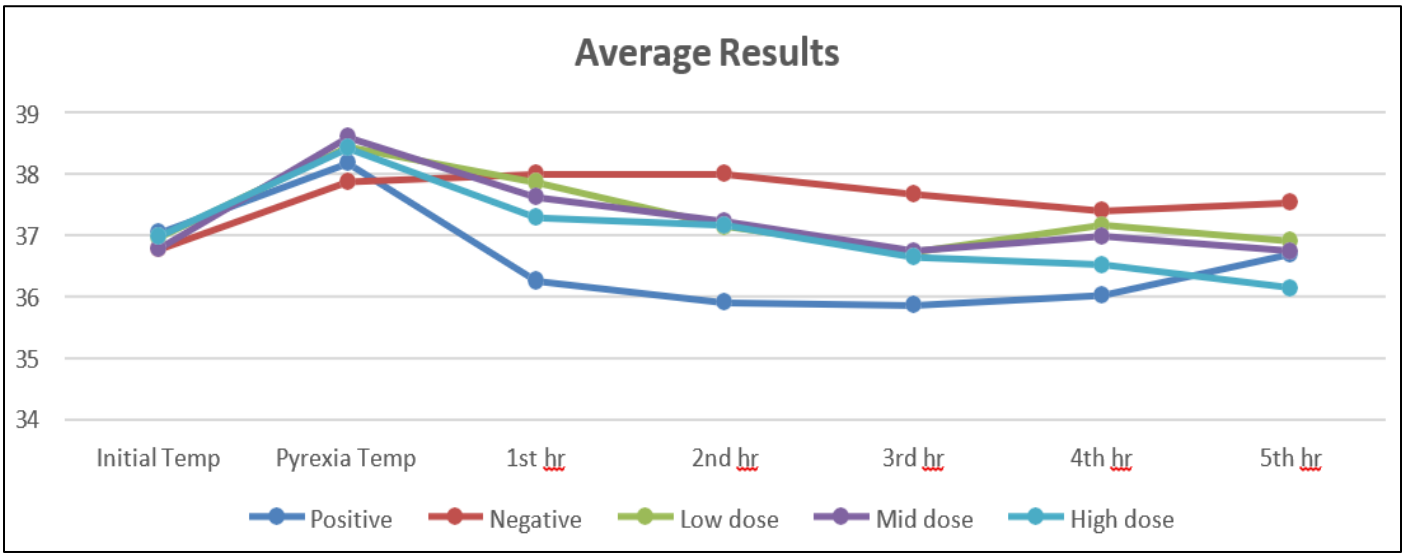

Fig 3 Average Results of all Concentrations in Temperature Monitoring

Table 4 ANOVA Result of Comparing Different Concentrations (Low, Middle, High Dose), Positive Control (Paracetamol) and Negative Control (Distilled Water)

ANOVA Result	f-value	p-value	Significance
Weight	1.4341	0.259	Not signifanct
Initial Temperature	0.409	0.799	Not signifanct
Induced Pyrexia Temp.	0.9815	0.4398	Not signifanct
1st hr temp	5.036	0.00567**	significant
2nd hr temp	6.584	0.000149**	significant
3rd hr temp	9.7138	0.00016**	significant
4th hr temp	10.8746	0.00001**	significant
5th hr temp	4.8215	0.00689**	significant

A post-hoc test following ANOVA was conducted to further analyze the significant differences in temperature reduction among the groups at the 1st hour after treatment. The results revealed that paracetamol (positive control) significantly reduced fever compared to distilled water (negative control) and to the middle (3500 mg/kg) and high dose (5000 mg/kg) extract groups. However, no significant difference was observed between paracetamol and the low dose (2000 mg/kg) extract group. The high dose extract showed a significant temperature reduction compared to the negative control, while no significant differences were found among the extract-treated groups themselves. These findings indicate that while all extract doses had some antipyretic effect, only the high dose approached the efficacy of paracetamol in reducing fever.

Table 5 Result of Post hoc test 1st hour Temperature of Comparing different concentrations

Post Hoc Test Result	p-value	Significance
Positive Control vs Negative control	0.00028**	Has significant difference
Positive Control vs Low Dose	0.055525	No significant difference
Positive Control vs. Middle Dose	0.001854**	Has significant difference
Positive Control vs. High Dose	0.028386*	Has significant difference
Negative Control vs Low Dose	0.500725	No significant difference
Negative Control vs Middle Dose	0.526018	No significant difference
Negative Control vs High Dose	0.024172*	Has significant difference
Low Dose vs Middle Dose	0.688416	No significant difference
Low Dose vs. High Dose	0.584325	No significant difference
Middle Dose vs. High Dose	0.118455	No significant difference

The post-hoc test for the 2nd hour revealed that paracetamol (positive control) significantly reduced fever compared to the negative control and all doses of *A. heterophyllus* ethanolic peel extract. Both the middle (3500 mg/kg) and high (5000 mg/kg) doses of the extract also showed significant temperature reductions compared to the negative control, while the low dose (2000 mg/kg) did not. No significant differences were found among the extract doses themselves. These results indicate that while paracetamol was the most effective, the middle and high doses of the extract exhibited notable antipyretic activity.

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Table 6 Result of Post Hoc Test 2nd hour Temperature of Comparing Different Concentrations

Post Hoc Test Result	p-value	Significance
Positive Control vs Negative control	0.000414**	Has significant difference
Positive Control vs Low Dose	0.039969*	Has significant difference
Positive Control vs. Middle Dose	0.016788*	Has significant difference
Positive Control vs. High Dose	0.013518*	Has significant difference
Negative Control vs Low Dose	0.125899	No significant difference
Negative Control vs Middle Dose	0.01972*	Has significant difference
Negative Control vs High Dose	0.016675*	Has significant difference
Low Dose vs Middle Dose	0.87586	No significant difference
Low Dose vs. High Dose	0.904751	No significant difference
Middle Dose vs. High Dose	0.954457	No significant difference

Results at the 3rd hour showed that paracetamol significantly reduced temperature compared to the negative control, confirming its strong antipyretic effect. The ethanolic peel extract of *A. heterophyllus* (at all doses) also significantly reduced fever compared to the negative control. However, there were no significant differences between the extract doses and paracetamol, nor among the extract doses themselves. This indicates that while the extract effectively reduced fever, its effect was comparable across doses and did not surpass that of paracetamol at this time point.

Table 7 Result of Post hoc Test 3rd hour Temperature of Comparing Different Concentrations

Post Hoc Test Result	p-value	significance
Positive Control vs Negative control	0.001481**	Has significant difference
Positive Control vs Low Dose	0.062929	No significant difference
Positive Control vs. Middle Dose	0.064443	No significant difference
Positive Control vs. High Dose	0.073222	No significant difference
Negative Control vs Low Dose	0.002193**	Has significant difference
Negative Control vs Middle Dose	0.001335**	Has significant difference
Negative Control vs High Dose	0.000111**	Has significant difference
Low Dose vs Middle Dose	0.935856	No significant difference
Low Dose vs. High Dose	0.631375	No significant difference
Middle Dose vs. High Dose	0.680207	No significant difference

At the 4th hour, paracetamol significantly reduced fever compared to the negative control, as well as the low and middle doses of *A. heterophyllus* extract. However, no significant difference was observed between paracetamol and the high dose of the extract, suggesting a comparable antipyretic effect at this concentration. The high dose also significantly reduced temperature compared to the negative control, while the low and middle doses did not. Additionally, the high dose showed a significantly greater effect than the middle dose. These findings highlight the dose-dependent antipyretic potential of the extract, with the high dose demonstrating effectiveness comparable to paracetamol.

Table 8 Result of Post hoc Test 4th hour Temperature of Comparing Different Concentrations

Post Hoc Test Result	p-value	Significance
Positive Control vs Negative control	0.000897**	Has significant difference
Positive Control vs Low Dose	0.01392*	Has significant difference
Positive Control vs. Middle Dose	0.001555*	Has significant difference
Positive Control vs. High Dose	0.091082	No significant difference
Negative Control vs Low Dose	0.133865	No significant difference
Negative Control vs Middle Dose	0.193621	No significant difference
Negative Control vs High Dose	0.001873**	Has significant difference
Low Dose vs Middle Dose	0.444092	No significant difference
Low Dose vs. High Dose	0.094402	No significant difference
Middle Dose vs. High Dose	0.003293**	Has significant difference

At the 5th hour, paracetamol significantly reduced fever compared to the negative control. However, no significant differences were found between paracetamol and any dose of *A. heterophyllus* extract, indicating comparable antipyretic effects. All extract doses (low, middle, and high) showed significant temperature reductions compared to the negative control, confirming their antipyretic activity. Additionally, a significant difference was observed between the middle and high doses, suggesting a dose-dependent effect. Overall, the extract, especially at higher doses, demonstrated a substantial fever-reducing potential comparable to paracetamol.

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Table 9 Result of Post hoc Test 5th hour Temperature of Comparing Different Concentrations

Post Hoc Test Result	p-value	Significance
Positive Control vs Negative control	0.018693*	Has significant difference
Positive Control vs Low Dose	0.918533	No significant difference
Positive Control vs. Middle Dose	0.51686	No significant difference
Positive Control vs. High Dose	0.197308	No significant difference
Negative Control vs Low Dose	0.02542*	Has significant difference
Negative Control vs Middle Dose	0.005354**	Has significant difference
Negative Control vs High Dose	0.002218**	Has significant difference
Low Dose vs Middle Dose	0.609466	No significant difference
Low Dose vs. High Dose	0.174609	No significant difference
Middle Dose vs. High Dose	0.047509*	Has significant difference

IV. CONCLUSION

This study successfully evaluated the potential antipyretic activity of the ethanolic peel extract of *A. heterophyllus* using a yeast-induced pyrexia model in male Swiss mice. The extract was tested at three concentrations—2000 mg/kg, 3500 mg/kg, and 5000 mg/kg—and its effects were compared with paracetamol as the standard drug. The findings demonstrate that the extract possesses significant antipyretic activity, with the high dose (5000 mg/kg) producing a comparable effect to paracetamol beginning at the third hour post-treatment and achieving statistical equivalence by the fifth hour. These results support the rejection of the null hypothesis (H_{01} and H_{02}) and acceptance of the alternative hypotheses (H_{11} and H_{12}), affirming that the ethanolic peel extract of *A. heterophyllus* does exhibit significant antipyretic effects and that its efficacy, particularly at higher concentrations, can match that of the standard antipyretic drug. Furthermore, statistical analyses using ANOVA and post hoc tests confirmed that the extract's fever-reducing capability is dose-dependent and time-dependent. The extract showed no signs of acute toxicity at doses up to 5000 mg/kg, affirming its safety for oral administration.

RECOMMENDATIONS

Based on the demonstrated efficacy and safety profile of the ethanolic peel extract of Artocarpus heterophyllus, it is recommended to develop the extract into a formulated pharmaceutical dosage form, such as capsules, syrups, or tablets. Formulation development will facilitate standardized dosing, enhance patient compliance, and provide a suitable platform for future clinical evaluations. Additionally, conducting comprehensive stability and shelf-life testing is essential to assess how environmental factors—such as temperature, humidity, and light exposure—affect the extract's potency and overall stability. These studies will provide critical data for determining appropriate storage conditions and expiration dating, which are vital for pharmaceutical development. Furthermore, exploring the potential synergistic effects of the extract in combination with other herbal or synthetic antipyretics is encouraged. Investigating such interactions may lead to the discovery of enhanced therapeutic efficacy, reduced dosage requirements, and improved safety profiles, supporting its application in combinational therapies for the effective management of febrile conditions.

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