International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The Potential Anti-Pyretic Activity of Artocarpus Odoratissimus (Moraceae) Ethanolic Fruit Peel Extract in A Yeast-Induced Pyrexia Model Using Swiss Albino Mice

Hanna Neshren Abdullah Macapodi[1],
Hanna Neshren Abdullah Macapodi[2], Raniah Menor Macalaba[3],
Patricia Mae Blanco Jarabe[4]

ABSTRACT

The growing demand for safer and cost-effective alternatives to synthetic drugs has intensified interest in plant-based therapeutics. This study aimed to evaluate the antipyretic activity of the ethanolic fruit peel extract of *Artocarpus odoratissimus* using a yeast-induced pyrexia model in Swiss albino mice. Specifically, the study determined the percentage yield of the extract, identified its phytochemical constituents, assessed its acute toxicity following OECD Guideline 423, and evaluated its antipyretic efficacy at varying concentrations (5%, 10%, and 15%). The extraction process yielded a mean percentage of 4.14%, indicating efficient recovery of bioactive compounds. Phytochemical screening confirmed the presence of flavonoids, triterpenoids, and saponins, which are known to possess anti-inflammatory and antipyretic properties. Acute toxicity testing revealed no mortality at doses up to 2000 mg/kg, suggesting that the extract is relatively safe for oral administration. In terms of antipyretic activity, the extract demonstrated a dose-dependent effect, with the 15% concentration showing the strongest and fastest reduction in temperature. Statistical analysis using one-way ANOVA indicated a significant difference among treatment groups ($p = 0.004$), while Tukey HSD post hoc test confirmed that higher concentrations exhibited effects comparable to the standard drug. Overall, the findings suggest that *Artocarpus odoratissimus* ethanolic fruit peel extract possesses significant antipyretic activity and a favorable safety profile, supporting its potential as a natural alternative for fever management.

Keywords: *Artocarpus odoratissimus*, ethanolic peel extract, yeast-induced pyrexia, antipyretic, Swiss albino mice

CHAPTER I

1.1 Introduction

Fever, or pyrexia, is a temporary increase in body temperature that typically occurs in response to infections, inflammation, or other pathological conditions. While it plays a protective role as part of the body's immune response, prolonged or uncontrolled fever can cause discomfort, dehydration, and serious complications—particularly in vulnerable groups such as children and the elderly (Cleveland Clinic, 2023). Conventional antipyretics, including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), are commonly used to manage fever. However, their long-term or frequent use is often

linked to adverse effects such as gastrointestinal irritation, liver toxicity, and kidney damage (Ali et al., 2022). As a result, there is growing interest in the development of plant-based alternatives that offer effective antipyretic action with a more favorable safety profile.

Artocarpus odoratissimus (Moraceae) family, or tarap fruit in Indonesian, is widely used as traditional medicine. The peel contains several secondary metabolites, such as terpenoids, flavonoids, phenolic, saponins, tannins, which are found in different parts of the plant and have been linked to multiple pharmacological properties, such as being an antioxidant and antimicrobial, anti-inflammatory (Yulianti et al. 2022; Ismail et al. 2023). Additionally it also have the antidiabetic activity associated with the presence of phenolic and flavonoids (Jonatas et al. 2020). Flavonoids and other phenolic compounds are most likely to produce the effect of antipyretic activity. They work by blocking mechanism like lipoxygenase (LOX) and cyclo-oxygenase (COX) or by suppressing inflammatory cytokines , which lowers the hypothalamic thermostat and prostaglandins E2 synthesis (Carating, B. D., Agosto, N. et al 2025). The phenolic and flavonoids of peel is associated with significant antioxidant activity (Hassanpour S.H., et al 2023). Additionally , specific research on peel extract has investigated their preservation and antibacterial potential and food systems (Isa et al. 2024).

To evaluate the antipyretic potential of *A. odoratissimus* experimental studies commonly employ yeast-induced pyrexia in Swiss albino mice. In this model, the subcutaneous injection of a 20% brewer's yeast suspension triggers a febrile response by stimulating the release of pyrogenic cytokines and prostaglandins, thereby mimicking human fever pathophysiology (Alemu et al. 2023). This model is widely accepted because of its reproducibility, ethical feasibility, and ability to reflect the central mechanisms of fever regulation in mammals (Azim et al. 2021).

Maceration is a classical extraction technique that allows efficient penetration of solvent into plant tissues, facilitating the dissolution of bioactive constituents without excessive heat that might degrade thermolabile compounds (Shrestha et al. 2022). Ethanol, particularly at concentrations around 70%, is considered one of the most effective solvents for phytochemical extraction due to its polarity, safety, and suitability for both polar and moderately non-polar compounds (Akinmoladun et al. 2022). Furthermore, pharmacological evaluation in Swiss albino mice is a well-established method for investigating antipyretic effects (Tekwem et al. 2022).

The potential antipyretic effect of *A. odoratissimus* ethanolic fruit peel extract will be examined in this study using Swiss albino mice in a yeast-induced pyrexia paradigm, in light of the growing desire for safer and natural medicinal alternatives. The results of this study will give scientific support for the plant's traditional use and help create plant-based antipyretic.

I.2 Background of the Study

The increasing cost and adverse effects of synthetic drugs have encouraged the search for natural alternatives from medicinal plants (De Guzman et al. 2020). The Philippines, renowned for its rich biodiversity, offers a diverse range of plants with therapeutic potential that remain scientifically unverified. One of these plants is *Artocarpus odoratissimus* (Marang), a tropical fruit tree belonging to the Moraceae family.

Artocarpus odoratissimus, commonly known as marang**,** is a tropical fruit native to Southeast Asia and abundant in Mindanao, Philippines. It belongs to the Moraceae family. Moraceae in this family are known to contain flavonoids, phenolics, and terpenoids that contribute to their antioxidant, antimicrobial, and anti-inflammatory effects (Rahman et al. 2022). Although the pulp of *A. odoratissimus* is consumed as food, its peel and seeds are often discarded, despite research suggesting

that fruit by-products can serve as rich sources of bioactive compounds with potential therapeutic applications (Rahman et al. 2022).

Several members of the Moraceae family, including *Artocarpus odoratissimus*, are known for their bioactive phytochemicals such as flavonoids, tannins, phenols, and saponins. For *A. odoratissimus*, the fruit peel has been used in antioxidant studies (Carating & Agosto 2025). The seed portion of the fruit has also been evaluated for antioxidant activity (Maulidia et al. 2024). Meanwhile, the stem bark extract of *A. odoratissimus* demonstrated antimicrobial activity (Nyokat et al. 2023). However, while its fruit pulp and seeds have been partially explored, the peel remains underutilized despite its abundance of phytochemicals. This underutilized peel could be a potential natural source for antipyretic compounds, sparking new avenues for research and discovery.

The Brewer's yeast-induced pyrexia model is one of the most established methods for evaluating antipyretic activity in laboratory animals. This model, using Brewer's yeast (*Saccharomyces cerevisiae*), reliably induces fever by stimulating the release of endogenous pyrogens such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). These pyrogens act on the hypothalamus to elevate the body's temperature set point, producing fever similar to that seen in humans (Adebayo et al. 2022). Its reliability, safety, and reproducibility make it a suitable model for testing natural and synthetic antipyretics, instilling confidence in the research methodology.

Swiss albino mice such as male are the most frequently used animal models in pharmacological research due to their genetic uniformity, manageable size, docile nature, and consistent physiological responses (Sultana et al. 2023). These mice, with their thermoregulatory mechanisms closely resembling those of humans, are particularly suitable for fever studies. Their use enables the accurate evaluation of temperature changes following pyrogen induction and drug administration, providing a valid and reliable animal model for research.

In assessing antipyretic activity, rectal temperature monitoring is the standard and most accurate technique for measuring changes in body temperature in small laboratory animals. It allows for the direct measurement of core temperature using a lubricated digital or thermistor probe gently inserted into the rectum at a fixed depth (1–2 cm for mice) (Adeyemi et al., 2021). Baseline rectal temperature is recorded before yeast injection and periodically thereafter usually at 1, 2, 3 and 4 hours following treatment. A significant decrease in rectal temperature compared to the control group indicates antipyretic activity of the test extract.

This precise method ensures that the effect of *A. odoratissimus* ethanolic peel extract on fever reduction is quantitatively and reliably evaluated, minimizing environmental or handling-related variations that could affect results. Paracetamol will serve as the positive control in this study due to its well-known mechanism of action, which involves the inhibition of prostaglandin synthesis in the hypothalamus. This helps restore the body's normal temperature set point, making it the most appropriate comparator for plant-based extracts (Nugraha et al. 2022).

This study will evaluate three factors to ascertain antipyretic activity. The onset time of fever reduction is the time between giving the extract and the first noticeable drop in rectal temperature. This shows how quickly the extract starts to work. Duration of fever reduction is the time when the rectal temperature is much lower than the febrile baseline, showing that the antipyretic effect is still working. Degree of fever reduction shows how much the temperature dropped from the highest fever, which is a way to determine how well the extract works to lower body temperature.

1.3 Conceptual Framework

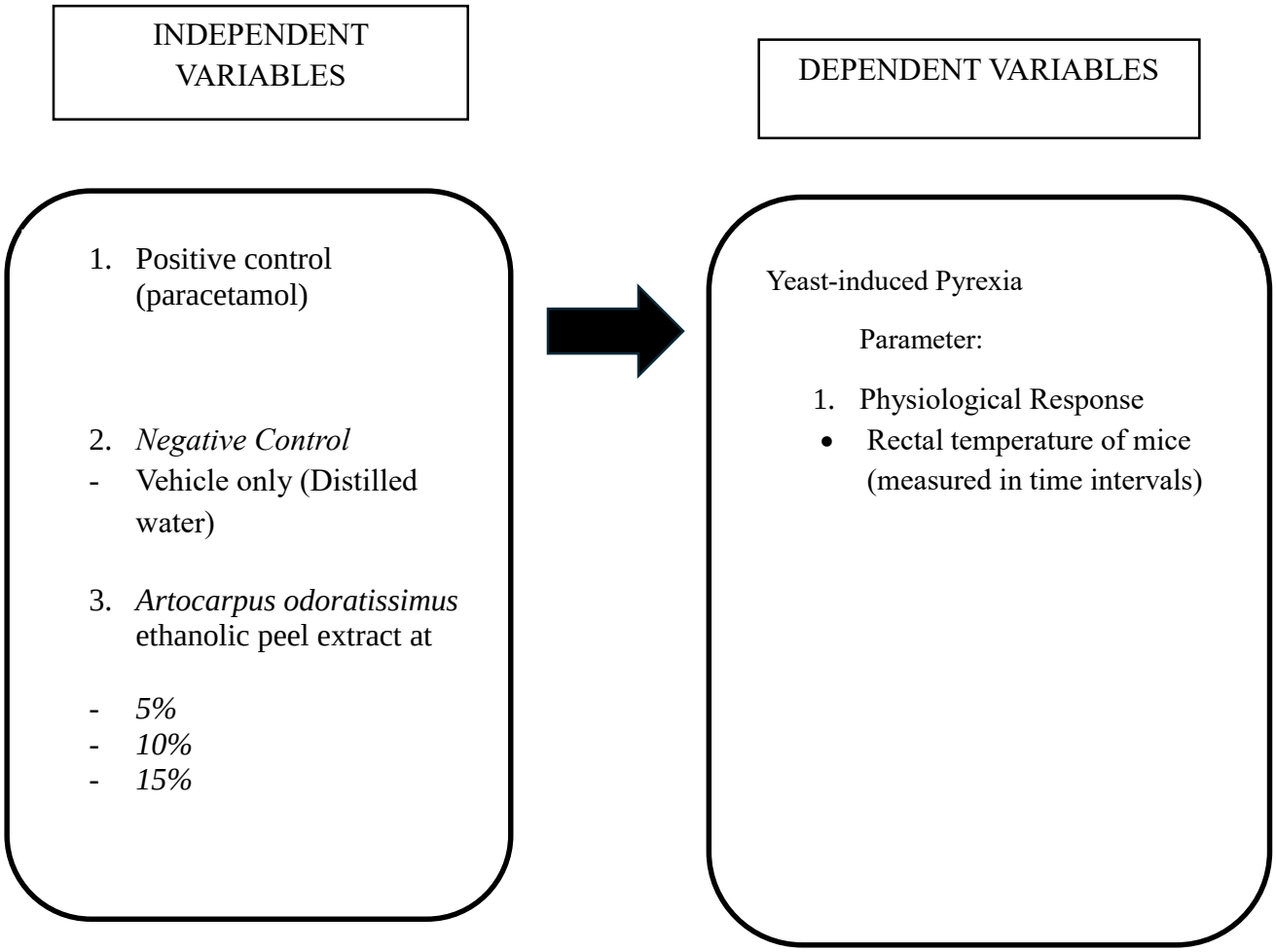


Figure 1: Conceptual Framework

The conceptual framework of this study is structured to assess the anti-pyretic potential of *Artocarpus odoratissimus* ethanolic peel extract using a yeast-induced pyrexia model in Swiss Albino mice. The independent variables include the positive control (paracetamol), the negative control distilled water, and the treatment groups receiving concentration of the extract at 5%, 10%, and 15% . The dependent variables are measured through the physiological outcomes, particularly rectal temperature recorded at defined intervals. By comparing these responses across treatment and control groups, the study aims to provide a systematic evaluation of the extract's effectiveness as a potential antipyretic agent.

1.4 Objectives of the Study

General Objective

To evaluate the potential antipyretic activity of *Artocarpus odoratissimus* Ethanolic Peel extract in a yeast-induced pyrexia model using Swiss Albino mice. The plant material will first be identified and authenticated by the Department of Biology, College of Science and Mathematics, Mindanao State University–Iligan Institute of Technology, Iligan City, Philippines, to ensure correct species and quality. Following authentication, the fruit peel will be prepared for extraction and subsequent pharmacological testing.

Specific Objectives:

1. Perform the extraction of *Artocarpus odoratissimus* Ethanolic Fruit Peel Extract in Maceration Method.

2. To determine the percentage yield of the ethanolic fruit peel extract of *Artocarpus odoratissimus.*
3. Confirm the phytochemical constituent that is responsible for the potential antipyretic activity
4. Conduct an oral Acute Toxicity of the plant extract through OECD 423
5. Induce fever through brewer's yeast method
6. Administer the different concentration 5%, 10% and 15% of *Artocarpus odoratissimus* Ethanolic Fruit Peel Extract to evaluate its potential antipyretic activity.
7. Collect data and analyze its result
8. Compare and identify the results among the group (negative, positive, and treatments) that have the high potential and low potential for antipyretic activity
9. Regulate at which time interval does *Artocarpus odoratissimus* Ethanolic Fruit Peel Extract will exert the peak of its antipyretic activity

1.5 Research Hypothesis

H_0 (Null Hypothesis): The administration of *Artocarpus odoratissimus* ethanolic fruit peel extract produces no significant reduction in fever in yeast-induced pyrexia in Swiss albino mice.

H_1 (Alternative Hypothesis):

The administration of *Artocarpus odoratissimus* ethanolic fruit peel extract produces a significant reduction in fever in yeast-induced pyrexia in Swiss albino mice.

1.6 Significance of the Study

This study will be conducted to evaluate the potential antipyretic activity of *Artocarpus odoratissimus* ethanolic fruit peel extract using a yeast-induced pyrexia model in Swiss albino mice. The findings of this research may provide several important contributions:

For the Scientific Community, this research will provide experimental data that supports the traditional use of *Artocarpus odoratissimus* as an antipyretic agent. The findings may serve as a foundation for future pharmacological studies, including the isolation and characterization of active compounds, dose standardization, and clinical trials.

For the M**edical and Pharmaceutical fields**, the study may open avenues for developing novel herbal formulations or complementary therapies that are cost-effective, accessible, and safer for long-term use compared to synthetic drugs. It highlights the potential for integrating ethnopharmacology with modern medicine to expand the options for managing fever.

For local communities and traditional medicine practitioners, the results may strengthen the scientific basis for the continued use of *Artocarpus odoratissimus* as a natural remedy. This not only supports cultural heritage but may also promote the utilization of locally available resources in primary healthcare.

For minimizing economic waste, this study explores the potential to transform the peel of *Artocarpus odoratissimus* which is often discarded into a valuable bioresource. By investigating its medicinal properties, particularly as an antipyretic, the study aims to reduce waste and create a sustainable value-added product. This approach can contribute to environmental sustainability by promoting the use of plant parts that are typically overlooked, thereby improving waste management and enhancing the economic utility of the marang fruit.

For **students and future researchers**, this study can serve as a valuable reference for further investigations into the pharmacological properties of medicinal plants. It also opens new research avenues in natural product development and sustainable resource utilization.

1.7 Scope and Limitation

Scope

This study aims to evaluate the antipyretic activity of *Artocarpus odoratissimus* ethanolic peel extract using a yeast-induced pyrexia model in Swiss Albino mice. The research will focus on extracting phytochemical constituents from the peel, including flavonoids, saponins, and triterpenoids, which are known to possess anti-inflammatory and antipyretic properties. Phytochemical confirmatory tests will be conducted to verify the presence of these compounds. The fever-reducing effects of the ethanolic peel extract at concentrations of 5%, 10%, and 15% will be measured by monitoring changes in the body temperature of mice and compared to a standard antipyretic drug (paracetamol) and a negative control (distilled water). Additionally, a dose-response relationship will be explored to identify the most effective concentration for reducing fever. This research also aims to promote waste minimization and economic sustainability by utilizing marang peel, which is often discarded, as a valuable natural resource for medicinal purposes.

Limitations

Despite the promising potential of *Artocarpus odoratissimus* peel extract, this study has several limitations. First, the research will focus primarily on the ethanolic fruit peel extract and its flavonoids**,** saponins**,** and terpenoids. Other bioactive compounds in the plant, particularly in different parts such as the leaves or fruit, will not be evaluated in this study. The study employs a yeast-induced pyrexia model **i**n Swiss Albino mice, which may not fully represent human fever physiology; therefore, the results may not be directly applicable to human conditions. While the research will assess acute toxicity and short-term safety, the study will not explore the long-term effects or chronic toxicity of the ethanolic peel extract. The concentration ranges used in this study may also limit the understanding of the optimal dosage for maximum efficacy. Additionally, since the experiment uses a single animal model, the results may not apply to other species or populations. Environmental factors, such as soil quality and climate, could affect the phytochemical composition of the peel, and thus the extract's bioactivity might vary depending on these conditions. Lastly, by focusing exclusively on the peel, the study overlooks the full spectrum of bioactive compounds that may exist in other parts of the plant, which could also contribute to its overall medicinal potential.

1.8 Definition of Terms

Antipyretic – A substance that reduces or prevents fever by lowering elevated body temperature.

Bioactive Compound – A chemical substance found in plants that has biological effects on living organisms, often responsible for therapeutic activity.

Control Group – The group in an experiment that does not receive the treatment being tested and is used for comparison with the experimental groups.

Crude Extract – A concentrated preparation obtained from plant material that contains multiple active and inactive compounds before purification.

Dose – The specific quantity of a substance administered to an animal or human subject during an experiment.

Ethanolic Extract – A plant preparation obtained by soaking plant material in ethanol to dissolve its bioactive compounds; in this study, 70% ethanol will be used.

Experimental Group – The group in an experiment that receives the test treatment or extract being studied.

Artocarpus odoratissimus – Is a plant belongs to the family (Moraceae) , or tarap fruit in Indonesian, is widely used as traditional medicine because almost all parts have pharmacological properties

Necropsy – refers to the postmortem examination of an animal's body to determine the cause of death or to assess the effects of experimental treatments on internal organs

Negative Control – A group or treatment in an experiment that receives no active drug or extract, ensuring that observed effects are due to the test substance.

Phytochemical Screening – The process of identifying and analyzing the bioactive compounds present in a plant extract.

Positive Control – A treatment known to produce the expected effect, used to compare the effectiveness of the test substance; in this study, paracetamol will be used.

Pyrexia – Another term for fever; an elevation of body temperature above the normal range due to illness or inflammation.

Rectal Temperature – Body temperature measured by inserting a thermometer into the rectum, considered accurate for core temperature assessment in small animals.

Standard Drug – A well-known and established medication used for comparison to evaluate the effectiveness of a test extract.

Swiss Albino Mice – A breed of laboratory mice commonly used in research due to their well-known genetic background and physiological responses.

Toxicity Test – An experimental procedure conducted to determine the safety and possible harmful effects of a substance before its use in living organisms.

Thermolabile – refers to a substance that can be easily destroyed or lose its effectiveness when exposed to heat.

Vehicle – The substance used to dissolve or deliver the extract without containing the active ingredient; in this study, ethanol of the same concentration as in the treatment will serve as the vehicle.

Yeast-Induced Pyrexia Model – An experimental method of inducing fever in laboratory animals by injecting yeast suspension, allowing the study of antipyretic agents.

CHAPTER II
REVIEW OF RELATED LITERATURE

This chapter presents the review of relevant studies and scientific literature supporting the evaluation of the antipyretic potential of *Artocarpus odoratissimus* (locally known as marang). It includes discussions on fever mechanisms, the significance of plant-based antipyretics, the botanical characteristics of *A. odoratissimus*, its phytochemical profile, and its pharmacological potential. It also explores the yeast-induced pyrexia model in Swiss albino mice as the experimental method used in this study.

This chapter presents a review:

2.1 Artocarpus odoratissimus (Moraceae)

Artocarpus odoratissimus is a tropical tree species from the Moraceae family, known for its large, sweet fruits and potential medicinal properties. It is commonly found in Southeast Asia, particularly in countries such as the Philippines, Malaysia, and Indonesia (Nguyen et al., 2020). The plant is valued not only for its edible fruit but also for its therapeutic applications, which have been explored in traditional medicine (Tan et al., 2021). Its fruit is sweet and aromatic, often used in local cuisine, while various parts of the plant, including the leaves and bark, have been utilized in folk medicine for their supposed healing properties (Singh et al., 2021).

2.1.1 Taxonomy of *Artocarpus odoratissimus*

Artocarpus odoratissimus Blanco, commonly known as marang, belongs to the family Moraceae, which includes several economically and pharmacologically significant genera such as *Ficus*, *Morus*, and *Artocarpus*. The taxonomic classification of *A. odoratissimus* is as follows:

Kingdom: Plantae
Subkingdom: Tracheobionta (vascular plants)
Division/Phylum: Magnoliophyta (Flowering plants)
Subdivision: Spermatophyta (Seed plants)
Class: Magnoliopsida (dicotyledons)
Subclass: Hamamelidae
Family: Moraceae
Genus: *Artocarpus*
Order: Rosales
Species: *Artocarpus odoratissimus*

2.1.2 Morphology of *Artocarpus odoratissimus*



Figure 2: *Artocarpus odoratissimus* Photo from (CABI digital library 2025).

This section describes the morphological characteristics of *Artocarpus odoratissimus*, highlighting its physical structures such as the stem, leaves, flowers, fruits, seeds, and roots. These features are important for accurate species identification and for understanding its biological and ecological significance

2.1.3 Phytochemical Constituents of *Artocarpus odoratissimus*

Recent studies have reported that *A. odoratissimus* contains various bioactive compounds with pharmacological importance. (Yen et al. 2023) identified pinocembrin, pinostrobin, α-amyrin acetate, β-amyrin acetate, β-sitosterol, and stigmasterol in the root, bark, and leaf extracts of the plant. (Lestari et al. 2022) confirmed the presence of polyphenols, alkaloids, tannins, saponins, steroids, and terpenoids in the ethanol extract of the seeds. Meanwhile, (Carating and Agosto 2025) demonstrated that the ethanolic peel extract had the highest total phenolic content (129.26 mg GAE/g) and total flavonoid content, which correlated with its potent antioxidant activity. These compounds are known to contribute to anti-inflammatory and antioxidant effects that may play a role in pyrexia reduction.

Table 1: Phytochemical Constituents of *Artocarpus odoratissimus*

Study	Extract/Part Used	Identified Compounds	Reference
Identification of Chemical Constituents of *A. odoratissimus*	Root, bark, leaves	Pinocembrin, pinostrobin, α- and β-amyrin acetate, β-sitosterol, stigmasterol	Yen KH et al. 2023
Phytochemical Screening of Ethanol Extract of Tarap Seeds	Seeds	Polyphenols, alkaloids, tannins, saponins, steroids, terpenoids	Lestari VP et al. 2022
Total Phenolic and Flavonoid Content and Antioxidant Activity	Peel and seed	High phenolic and flavonoid content; strong antioxidant activity	Carating BD, Agosto NJ. 2025

Table 2: Phytochemical Constituents of *Artocarpus odoratissimus* Peel

Phytochemical Parameter / Compound	Observation or Value	Study Title	Authors & Year	Source / Link
Total Phenolic Content (TPC)	23.62 ± 0.88 mg GAE/g dry weight	*Total Phenolic Content, Total Flavonoid Content, and Antioxidant Activity of Various Solvent Extracts from the Peels and Seeds of Marang (Artocarpus odoratissimus Blanco)*	Carating JM, Agosto CL. 2022	Journal of Science and Mathematics Letters
Total Flavonoid Content (TFC)	22.27 ± 0.71 mg QE/g dry weight	*Total Phenolic Content, Total Flavonoid Content, and Antioxidant Activity of Various Solvent Extracts from the Peels and Seeds of Marang (Artocarpus odoratissimus Blanco)*	Carating JM, Agosto CL. 2022	Journal of Science and Mathematics Letters
Higher TPC in Peel Extract	42.38 mg GAE/g dry sample	*Comparison of Phytochemicals and Antioxidant Properties of Different Fruit Parts of Selected Artocarpus Species from Sabah, Malaysia*	Zakaria SM, Rahman NA, Lajis NH, et al. 2015	Sains Malaysiana
Qualitative Phytochemical Screening	Presence of phenols and flavonoids (confirmed by TLC)	*Antidiabetic Evaluation of Artocarpus odoratissimus (Moraceae) Fruit*	Ramli N, Lajis N, Rahman H. 2021	Jurnal Ilmiah Farmasi

Antioxidant & Antiproliferative Compounds	Phenolic acids and flavonoids predominant in fruit waste peel extract	*Antioxidant and Antiproliferative Properties of Artocarpus altilis (Breadfruit) and Artocarpus odoratissimus ("Marang") Fruit Wastes*	De Leon K, Uy M, Tan R. 2023	Philippine Journal of Science
Detected Bioactive Compounds (General Plant)	Pinocembrin, pinostrobin, α-amyrin acetate, β-amyrin acetate, β-sitosterol, stigmasterol	*Chemical Constituents of Artocarpus odoratissimus and Their Biological Activities*	Basyuni M, Ahmad M, Prasad D. 2020	Research Publishing in Chemistry and Science Research, Vol. 6

2.1.4 Pharmacological Activities of *Artocarpus odoratissimus*

The pharmacological profile of *A. odoratissimus* has attracted growing interest in recent years. (Jonatas et al. 2024) reported α-glucosidase inhibitory activity in both peel and seed extracts, indicating potential antidiabetic properties. (Naspiah et al. 2021) found that leaf metabolites exhibited xanthine oxidase inhibition, suggesting anti-gout and anti-inflammatory effects. (Carating and Agosto 2025) associated high phenolic and flavonoid levels with antioxidant efficacy, while (Ismail et al. 2023) documented enzymatic browning-related phytochemicals with potential bioactivity. The presence of these compounds supports the therapeutic potential of *A. odoratissimus* and its possible role in mitigating fever and inflammation.

Table 3: Pharmacological Activities of *Artocarpus odoratissimus*

Study Title	Activity	Extract/Part Used	Main Findings	Reference
Xanthine Oxidase Inhibition Activity and ADMET Properties of Terap (Artocarpus odoratissimus Blanco) Leaves Metabolites: Phytochemical Screening and In Silico Studies	Anti-gout / Anti-inflammatory (xanthine oxidase inhibition)	Leaf extract	Demonstrated in vitro and in silico inhibition of xanthine oxidase, suggesting antioxidant and anti-inflammatory potential	Naspiah N, Pratama MR, Sukardiman. 2021. *Pharmacogn J.* 13(5):1150–60.
Antidiabetic Activity of Marang (Artocarpus odoratissimus) Peel and Seed Extracts Through α-Glucosidase Inhibition	Antidiabetic / Enzyme inhibitory	Peel and seed extracts	Exhibited significant α-glucosidase inhibitory activity (IC_{50} = 48.19 µg/mL), indicating potential antioxidant and	Jonatas KA, Syahrul R, Yusof N, Abdullah M. 2024. *J Innov Pharm Sci.* 7(2):[pages].

			metabolic benefits	
Total Phenolic Content, Total Flavonoid Content, and Antioxidant Activity of Various Solvent Extracts from the Peels and Seeds of Marang (Artocarpus odoratissimus Blanco)	Antioxidant	Peel and seed extracts	Ethanolic peel extract showed highest total phenolic and flavonoid contents with strong antioxidant activity	Carating BD, Agosto NJ. 2025. *J Sci Math Lett.* 13(1):[pages].
Browning in Relation to Enzymatic Activities and Phytochemical Content in Terap Peel (Artocarpus odoratissimus Blanco) During Post-Harvest Ripening	Enzymatic antioxidant activity	Peel	Identified high levels of antioxidant enzymes (peroxidase, polyphenol oxidase) that contribute to oxidative stress regulation	Ismail HA, Richard I, Ramaiya SD, Zakaria MH, Lee SY. 2023. *Horticulturae.* 9(1):57.

2.1.5 Phytochemicals of *Artocarpus odoratissimus* (Moraceae) and their potential role in Antipyretic Activity

Although no published study directly demonstrates the antipyretic activity of *A. odoratissimus*, the presence of bioactive compounds supports its potential. Flavonoids such as pinocembrin and pinostrobin exhibit anti-inflammatory effects by inhibiting cyclooxygenase-2 and suppressing prostaglandin E_2 synthesis, a mediator involved in the fever response. Likewise, triterpenoids such as α-amyrin acetate exhibit both analgesic and anti-inflammatory properties that could contribute to fever reduction. The high antioxidant potential of the ethanolic peel extract may further regulate oxidative stress associated with pyrexia. Given these biochemical attributes, *A. odoratissimus* may serve as a promising natural antipyretic agent, justifying its experimental evaluation in a yeast-induced pyrexia model.

2.1.5.1 Flavonoids in *Artocarpus odoratissimus*

The genus *Artocarpus*, belonging to the family Moraceae, is known to be a rich source of flavonoid compounds with diverse pharmacological properties. In *Artocarpus odoratissimus* Blanco, several flavonoids have been identified in different plant parts such as the leaves, bark, roots, and fruit peel. The major isolated flavonoids include pinocembrin and pinostrobin, which were reported in ethanolic extracts of the bark and roots and are known for their potent antioxidant and anti-inflammatory activities (Basyuni et al. 2020). These compounds belong to the flavanone subclass and have been linked to the modulation of prostaglandin synthesis pathways, which play a crucial role in fever and inflammation control. Moreover, the fruit peel of *A. odoratissimus* was found to contain a high total flavonoid content (TFC), measured at approximately 68.95 mg QE/g in aqueous extracts, indicating that the peel is one of the richest sources of flavonoids within the species (Carating and Agosto 2022). A qualitative phytochemical screening of the leaf extract also confirmed the presence of flavonoids such as rutin,

alongside other phytochemical groups like alkaloids and triterpenoids, through thin-layer chromatography analysis (Sulistiarini et al. 2023). These findings suggest that the flavonoid constituents of *Artocarpus odoratissimus*—particularly pinocembrin, pinostrobin, and rutin—may contribute to its potential antipyretic activity, given their established roles in reducing oxidative stress and inflammatory mediator synthesis.

2.1.5.2 Triterpenoids in *Artocarpus odoratissimus*

In *Artocarpus odoratissimus*, several triterpenoids have been identified across different plant parts, including the roots, bark, twigs, and fruit peel/rind. Major compounds reported include α-amyrin, α-amyrin acetate, β-amyrin, lupeol, oleanolic acid, friedelin, as well as sterol-like triterpenes such as β-sitosterol and stigmasterol (Basyuni et al. 2020; Lathiff et al. 2023). These triterpenoids are typically pentacyclic (oleanane, ursane, and lupane skeletons) and have been associated with anti-inflammatory, hepatoprotective, and antimicrobial activities, suggesting potential relevance in antipyretic mechanisms (Basyuni et al. 2020). The fruit peel and bark are particularly rich in these compounds, which may contribute to the observed pharmacological effects of the plant (Carating and Agosto 2022). Overall, the triterpenoid profile of *A. odoratissimus* highlights its potential as a source of bioactive compounds for therapeutic exploration.

2.1.5.3 Saponnins in *Artocarpus odoratissimus*

In *Artocarpus odoratissimus* Blanco, saponins have been reported as one of the major classes of secondary metabolites present in various plant parts, particularly in the leaves, fruit peel, and seeds. Saponins are glycosidic compounds characterized by their amphiphilic structure, consisting of a triterpenoid or steroid aglycone linked to sugar moieties, which contributes to their surface-active properties. Phytochemical screenings of ethanolic and aqueous extracts of the fruit peel and leaves have consistently indicated the presence of saponins, suggesting potential pharmacological activities such as anti-inflammatory, antimicrobial, and immunomodulatory effects, which are mechanistically relevant to antipyretic activity (Carating and Agosto 2022; Suhaila et al. 2021). The presence of saponins in *A. odoratissimus* is thought to contribute to its bioactivity by modulating inflammatory mediators and enhancing the solubility and absorption of other bioactive compounds within the extract, thus potentially amplifying the antipyretic effect.

2.1.6 Traditional/Ethnobotanical Uses of *Artocarpus odoratissimus*

While detailed ethnopharmacological reports on *A. odoratissimus* are limited, related *Artocarpus* species have been traditionally used in Southeast Asia to treat skin ailments, digestive problems, and inflammation. In Borneo and Mindanao, the fruit is primarily consumed as food; however, anecdotal reports suggest that decoctions from its bark and leaves have been used to treat skin irritation and mild infections (Yulianti et al., 2022). This traditional background, combined with the species' known phytochemical richness, supports the scientific rationale for exploring its potential antipyretic effects.

2.2 Moraceae

The family Moraceae, commonly known as the mulberry or fig family, is one of the most diverse and economically significant plant families within the order Rosales. It comprises approximately 38 genera and more than 1,100 species, distributed mainly throughout tropical and subtropical regions worldwide (Morante-Carriel et al., 2024). Members of this family are well recognized for their ecological, nutritional, and medicinal significance. Genera such as Ficus, Morus, and Artocarpus are of particular

importance due to their edible fruits, timber value, and therapeutic properties. Many Moraceae plants are rich in secondary metabolites, including flavonoids, stilbenes, and terpenoids, which contribute to a wide range of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, and hepatoprotective effects (Peng et al., 2023). These bioactive compounds have made the family a focus of phytochemical and pharmacological research, supporting its reputation as a valuable source of potential therapeutic agents.

2.2.1 Family Members and Their Pharmacological Activities

The Moraceae family, commonly known as the mulberry or fig family, encompasses about 38 genera and over 1,100 species distributed in tropical and subtropical regions. Members of this family, including *Morus*, *Ficus*, and *Artocarpus*, are notable for their diverse pharmacological properties. Many Moraceae species possess antioxidant, antimicrobial, antidiabetic, and anti-inflammatory effects (Morante-Carriel et al. 2024). The genus *Morus*, for example, is known for its neuroprotective and hepatoprotective activities, while *Ficus capensis* exhibits antimicrobial and immunomodulatory actions. These pharmacological characteristics are attributed to the family's abundance of secondary metabolites such as flavonoids and stilbenes, providing a biochemical basis for the potential antipyretic action of *A. odoratissimus*.

2.2.2 Phytochemical Constituents of Moraceae

Members of Moraceae are chemically rich, producing prenylated flavonoids, stilbenes, arylbenzofurans, alkaloids, terpenoids, and sterols. Prenylated flavonoids are a characteristic feature of this family and have been shown to enhance biological activities, including anti-inflammatory and enzyme-inhibitory effects (Morante-Carriel et al., 2024). According to Yang et al. (2023), over 450 natural products have been isolated from *Morus* species alone, underscoring the extensive chemical diversity within the Moraceae family. Since *A. odoratissimus* belongs to this family, it is expected to share similar phytochemical profiles and pharmacological potentials.

Table 4. Phytochemical Constituents of the Moraceae Family

Study Title	Phytochemical Class	Representative Compounds / Sources	Reported Biological or Pharmacological Activities	Reference
Prenylated flavonoids of the Moraceae family: a comprehensive review of their biological activities	Prenylated flavonoids	Morusin, kuwanon G, artocarpin (*Artocarpus* and *Morus* spp.)	Anti-inflammatory, antioxidant, enzyme inhibitory, cytoprotective	Morante-Carriel J et al. 2024. *Plants.* 13(9):1211.
Prenylated flavonoids of the Moraceae family: a comprehensive	Stilbenes	Oxyresveratrol, mulberroside A (*Morus alba*)	Antioxidant, antimicrobial, hepatoprotective	Morante-Carriel J et al. 2024.

review of their biological activities				
Prenylated flavonoids of the Moraceae family: a comprehensive review of their biological activities	Arylbenzofurans	Moracin M, moracin N (*Morus* spp.)	Antibacterial, anti-inflammatory, antitumor	Morante-Carriel J et al. 2024.
Natural products and biological activities of plants from genus Morus: 2011–2023 review	Alkaloids	Moracine, calycanthine (*Ficus*, *Morus* spp.)	Analgesic, antimicrobial, neuroprotective	Peng Y-L et al. 2023. *Curr Top Med Chem.* 23(26):2452-2487.
Prenylated flavonoids of the Moraceae family: a comprehensive review of their biological activities	Terpenoids	β-amyrin, lupeol, α-amyrin (*Artocarpus* spp.)	Antipyretic, anti-inflammatory, hepatoprotective	Morante-Carriel J et al. 2024.
Natural products and biological activities of plants from genus Morus: 2011–2023 review	Sterols	β-sitosterol, stigmasterol (*Artocarpus*, *Ficus* spp.)	Anti-inflammatory, immune-modulatory, lipid-lowering	Peng Y-L et al. 2023.

2.2.3 Present Related Studies (2020–2025)

Recent studies have further established the pharmacological importance of *A. odoratissimus* and other members of the Moraceae family. (Yen et al. 2023) identified multiple flavonoids and triterpenoids in *A. odoratissimus* roots, bark, and leaves. (Naspiah et al. 2024) evaluated the anti-gout properties of the leaf extract and confirmed xanthine oxidase inhibition.(Carating et. al 2025) demonstrated the antioxidant capacity of the peel and seed extracts, emphasizing their phenolic richness. These findings, from 2020 to 2025, reinforce the relevance of A. odoratissimus as a bioactive species within the Moraceae family and justify its investigation for potential antipyretic properties.

Table 5. Present related studies of Moraceae Family

Year	Study Title	Main Findings	Reference
2021	Xanthine oxidase inhibition activity and ADMET properties of *A. odoratissimus*	In vitro and in silico enzyme inhibition	Naspiah N et al. 2021
2023	Identification of chemical constituents of *A. odoratissimus* from Sarawak	Flavonoids and triterpenoids isolated	Yen KH et al. 2023
2024	Antigout activity of *A. odoratissimus* leaves extract	Xanthine oxidase inhibition confirmed	Naspiah N et al. 2024
2025	Total phenolic and flavonoid content of *A. odoratissimus* peels and seeds	Highest phenolic and antioxidant activity in peel extract	Carating BD, Agosto NJ. 2025

Table 6. Members of the family of Moraceae that Possesses Antipyretic Activity

Plant (Family = Moraceae)	Study Title	Year	Antipyretic Evidence & Notes
Artocarpus heterophyllus (jackfruit)	*"The Potential Antipyretic Activity of the Ethanolic Peel Extract of Artocarpus heterophyllus (Moraceae)"*	2025 (eprint.innovativepublication.org)	This study tested the ethanolic peel extract in a brewer's yeast-induced pyrexia model in Swiss mice, comparing to paracetamol and control. Clear antipyretic model.
Morus alba (white mulberry)	*"Acute oral toxicity and safety assessment of Morus alba L. (Moraceae) methanol fruit extract in mice"*	2024 (itjfs.com)	This is *not explicitly* antipyretic: the focus is on toxicity/safety. It does not appear to include a fever model. So while it belongs to Moraceae, it lacks antipyretic data.

2.3 Pyrexia

Fever is defined as a regulated increase in core body temperature mediated by pyrogen-induced PGE_2 production in the hypothalamus (Blomqvist and Engström Ruud 2024). Paracetamol, the standard antipyretic comparator, exerts its effect by inhibiting COX enzymes in the brain, thus reducing PGE_2 synthesis (Mitchell and Lancaster 2022). Additional pathways involve its metabolite AM404 acting on cannabinoid and TRPV1 receptors, mechanisms that can also cause hypothermia in rodents (Coman et al. 2022). Because of this, paracetamol is routinely used as a positive control in yeast-induced pyrexia studies, while saline serves as a negative control (Dawood et al. 2022; Rahman et al. 2023; Nguyen et al. 2021).

2.3.1 Categories of Fever by Degree (Balli 2023)

Category	Temperature Range (°C)	Description
Low-grade fever	37.3–38.0	Mild elevation, often due to minor infections; usually self-limited
Moderate-grade fever	38.1–39.0	Suggestive of more pronounced infection or inflammation; may require treatment.
High-grade fever	39.1–41.0	Indicative of severe infection; risk of dehydration, seizures, or organ dysfunction.
Hyperpyrexia	≥ 41.0	Medical emergency; potentially life-threatening if not managed promptly.

2.4 Physiology of Pyrexia

Pyrexia, commonly known as fever, is a regulated elevation of body temperature resulting from an upward shift in the hypothalamic thermoregulatory set point. Under normal conditions, the hypothalamus maintains body temperature within a narrow physiological range (36.5–37.5 °C) through a balance of heat production and heat dissipation mechanisms (Balli 2023).

Fever develops when exogenous pyrogens, such as microbial products (e.g., lipopolysaccharides), stimulate immune cells to release endogenous pyrogens, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These cytokines act on the preoptic area of the hypothalamus, inducing the synthesis of prostaglandin E2 (PGE2) via cyclooxygenase-2 (COX-2) pathways. PGE2 then binds to EP3 receptors in hypothalamic neurons, raising the thermoregulatory set point and initiating heat-conserving and heat-producing responses such as vasoconstriction, shivering, and increased metabolism (Evans et al. 2021).

This elevation in body temperature serves as a host defense mechanism, enhancing leukocyte mobility, T-cell activation, and pathogen clearance (Ogoina 2020). However, excessive or sustained fever may lead to deleterious effects, including dehydration, seizures, and tissue injury, making antipyretic therapy clinically significant.

2.5 Definition of Antipyretic

Antipyretics are agents that reduce elevated body temperature by acting on the hypothalamic thermoregulatory center, restoring the set point to normal without affecting normal body temperature. These drugs primarily act by inhibiting prostaglandin synthesis, particularly prostaglandin E2 (PGE2), which plays a central role in fever generation (Saper et al., 2020). Commonly used antipyretics include paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), which are considered first-line therapies for managing fever (García-Rodríguez et al., 2021). The clinical importance of antipyretics lies in their ability to alleviate discomfort, prevent complications associated with high-grade fever, and improve patient quality of life during febrile illnesses (Oliveira et al. 2022).

2.5.1 Antipyretic Assay

Antipyretic assays are experimental methods used to evaluate the fever-reducing potential of natural products or synthetic compounds. These assays typically involve the induction of pyrexia in laboratory animals, followed by treatment with the test extract, standard antipyretic drug, and control to determine

efficacy. The most widely used models include yeast-induced pyrexia, lipopolysaccharide (LPS)-induced fever, and brewer's yeast model in rodents, as they closely mimic the febrile response observed in humans (Nandha et al. 2021).

2.5.1.1 Brewer's yeast-induced Pyrexia Model

The Brewer's yeast-induced pyrexia model is a reliable tool for testing natural antipyretic agents. For example, *Iris albicans* extracts significantly reduced fever in mice compared to controls (Dawood et al. 2022), *Zingiber roseum* root extracts produced dose-dependent antipyresis (Rahman et al. 2023), and *Argyreia acuta* extracts also demonstrated fever-reducing activity (Nguyen et al. 2021). Other botanicals such as *Combretum bauchiense* confirmed the model's sensitivity and reproducibility (Estella et al. 2022). These contemporary findings validate the use of yeast-induced pyrexia as the experimental model for the present study.

2.5.2 Rectal Thermometry

Rectal thermometry is a widely used, practical method for assessing core body temperature in small laboratory animals. The technique involves measuring the temperature inside the rectum using a calibrated digital thermometer or a thermistor probe. Because rectal temperature closely approximates core temperature, it has historically been regarded as a reliable reference method for detecting pyrexia and hypothermia in rodents (Goig 2024; Blenkuš et al. 2022). Rectal thermometry is inexpensive, requires minimal equipment, and does not necessitate surgical implantation, making it an attractive option for many pharmacological screening studies where continuous monitoring is not feasible.

2.6 Acute Toxicity Test

Toxicological evaluation is essential for plant-based therapies. OECD's Acute Oral Toxicity Up-and-Down Procedure (Test Guideline 425, corrected 2022) provides standardized acute safety assessment (OECD 2022), while the Repeated Dose 28-day Oral Toxicity Study (Test Guideline 407, updated 2025) ensures subacute evaluation (OECD 2025). Moreover, compliance with the ARRIVE 2.0 guidelines improves reproducibility and transparency in animal studies (Percie du Sert et al. 2020).

2.6.1 Guideline 423

In this study, the acute oral toxicity of the test substance will be evaluated using the OECD Test Guideline 423 (Acute Oral Toxicity – Acute Toxic Class Method), which is designed to estimate the median lethal dose (LD_{50}) while minimizing the use of animals. Healthy male Swiss Albino mice will be acclimatized under standard laboratory conditions before testing. The test substance will be administered orally via gavage, and the initial dose will be selected according to the OECD stepwise dosing scheme, with subsequent doses adjusted based on observed mortality or clinical signs of toxicity (OECD, 2022). Animals will be monitored closely for behavioral changes, clinical signs, body weight variations, and mortality for 14 days post-administration. Necropsy will be performed on all animals that die during the study or are euthanized at the end of the observation period to assess gross pathological changes. The LD_{50} will be estimated using the OECD 423 classification table, providing a standardized and ethically refined approach for evaluating the acute toxicity of plant-based compounds (OECD, 2022; Percie du Sert et al., 2020).

2.7 Antipyretic Medicines

Antipyretic medicines are drugs used to reduce fever by acting on the hypothalamic thermoregulatory center to lower the body's set-point temperature. The most commonly used antipyretic, paracetamol

(acetaminophen), primarily works by inhibiting cyclooxygenase (COX) activity in the central nervous system, particularly affecting the synthesis of prostaglandin E_2, a mediator responsible for regulating hypothalamic temperature (Anderson 2021). Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, also possess antipyretic activity by inhibiting prostaglandin synthesis through nonselective COX inhibition (Singh et al., 2020). Comparative studies have shown that ibuprofen may produce a greater and faster reduction in body temperature than acetaminophen in febrile patients (Raffa et al. 2020). However, excessive or inappropriate use of antipyretics may mask underlying disease processes and, in some cases, adversely affect immune responses (Carey and Vander 2022). Despite these considerations, antipyretics remain crucial for enhancing patient comfort and preventing severe hyperthermia, particularly in pediatric and critically ill populations (Allegaert et al., 2023).

2.7.1 Paracetamol

Paracetamol, also known as acetaminophen, is a widely used antipyretic and analgesic effective in reducing fever and mild to moderate pain. It primarily acts in the central nervous system by inhibiting the cyclooxygenase (COX) enzyme and decreasing prostaglandin E2 synthesis, thereby lowering the hypothalamic temperature set point (Anderson, 2021). Unlike NSAIDs, it has minimal peripheral anti-inflammatory activity but is generally safer for patients with gastric irritation or bleeding risks (Bertolini et al. 2020). Paracetamol is well tolerated at recommended doses—10–15 mg/kg every 4–6 hours in children and up to 4g per day in adults—but overdose can cause severe liver toxicity due to accumulation of its metabolite NAPQI (Carey and Vander 2022).

2.7.2 Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic properties. It works by non-selectively inhibiting COX-1 and COX-2 enzymes, thereby reducing prostaglandin production and lowering body temperature and pain perception (Singh et al., 2020). The usual dose is 5–10 mg/kg every 6–8 hours in children and 200–400 mg every 4–6 hours in adults. Although generally safe, prolonged or high-dose use can cause gastrointestinal irritation, renal impairment, or hypersensitivity reactions (Allegaert et al. 2023).

2.8 Statistical Analysis

Statistical analysis is critical in determining extract efficacy. In antipyretic studies, one-way ANOVA is commonly used to compare temperature reductions across treatment groups. For multi-time-point designs, two-way ANOVA (treatment × time) is applied to evaluate both treatment effect and duration of action. Post hoc tests such as Tukey's or Dunnett's help localize significant differences. Recent biostatistical references recommend effect size reporting and assumption checking for robust analysis (GraphPad Software 2023).

2.9 One-way ANOVA

In this study, one-way analysis of variance (ANOVA) will be employed to determine whether there are significant differences in antipyretic activity among the experimental groups. Since the research design includes multiple independent groups—namely the negative control (saline-treated pyretic mice), the positive control (paracetamol-treated group), and the different dose levels of *Artocarpus odoratisimus* ethanolic fruit peel extract.

One-way ANOVA addresses this limitation by simultaneously comparing the means of all groups, analyzing whether the variance between treatment means is significantly greater than the variance within each group. This statistical approach is particularly suited for evaluating the effect of various treatments

on a single dependent variable, which in this case is the reduction in rectal temperature of yeast-induced pyretic mice. A significant ANOVA result ($p < 0.05$) would indicate that at least one treatment group differs from the others, warranting further post hoc analysis such as Tukey's or Dunnett's test to identify specific differences between extract doses and the control groups (Field 2020; Keselman et al. 2021; Motulsky 2023).

2.9 Theoretical Framework

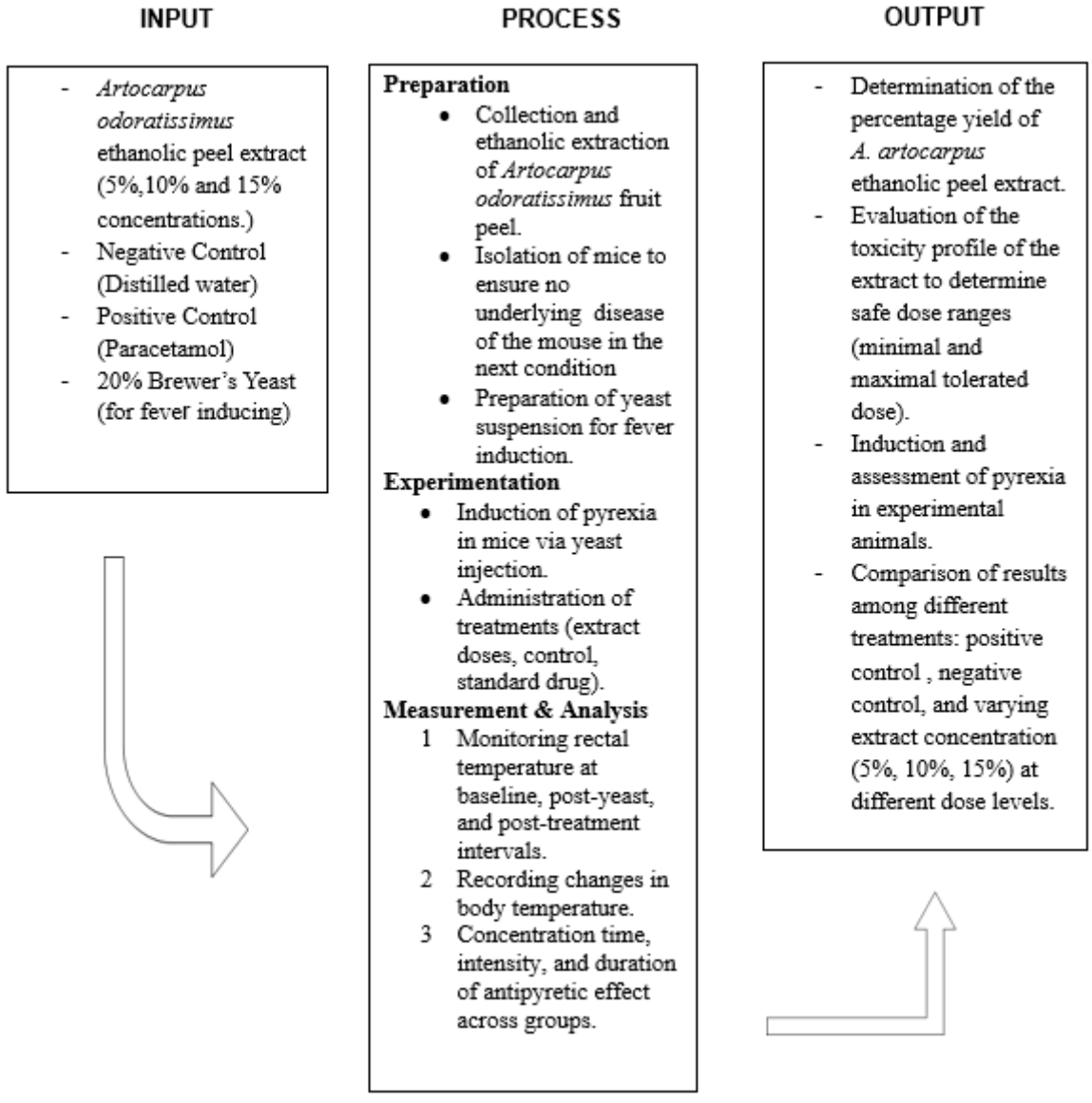


Figure 3: Theoretical Framework of the Study

The theoretical framework serves as the foundation of the study, guiding the research process by providing a scientific explanation for the observed phenomena. In this study, the framework helps explain how the phytochemical constituents of *Artocarpus odoratissimus* (marang) fruit peel extract may exert antipyretic effects in yeast-induced pyrexia models. Establishing a theoretical basis is important because it links existing biological principles such as the mechanisms of fever and the pharmacological actions of bioactive compounds to the experimental objectives of the research (Guyton and Hall 2020).

This research aims to evaluate the antipyretic activity of *A. odoratissimus* ethanolic fruit peel extract in Swiss Albino mice and identify the most effective concentration (5%, 10%, and 15%) in reducing fever. The theoretical framework connects to this objective by explaining how bioactive compounds, particularly flavonoids, saponins, and triterpenoids, may influence the body's thermoregulatory process through inhibition of prostaglandin synthesis one of the primary mediators of fever (Bhardwaj et al. 2021). Thus, it aligns the phytochemical profile of the plant with its potential pharmacological action. The study employs the yeast-induced pyrexia model, a widely accepted method for assessing antipyretic activity in experimental animals. This model is based on the principle that exogenous pyrogens (such as Brewer's yeast) stimulate the production of endogenous pyrogens like interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and prostaglandin E_2 (PGE_2), leading to an elevation in body temperature (Vogel 2021). The decrease in temperature following treatment indicates the inhibition of these mediators, suggesting potential antipyretic activity (Turner et al. 2022). The study is anchored on the biochemical theory of prostaglandin-mediated fever regulation, which states that fever results from the release of PGE_2 in the hypothalamus due to cytokine stimulation (Dinarello 2018). By applying this theory, the research assumes that the phytochemical compounds in A. odoratissimus peel particularly flavonoids and triterpenoids can inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, reducing PGE_2 synthesis and, consequently, lowering body temperature (Kumar et al. 2023). This theoretical perspective provides a mechanistic explanation for the expected antipyretic effect. From the theory, the independent variable is the concentration of *A. odoratissimus* ethanolic fruit peel extract (5%, 10%, and 15%), while the dependent variable is the change in body temperature of the mice. The control variables include the standard drug (paracetamol) and the negative control (distilled water). The relationship between these variables is guided by the theoretical assumption that higher concentrations of bioactive compounds will produce a stronger inhibition of PGE_2 synthesis, thus reducing fever (Vogel 2021). In summary, this theoretical framework integrates the biochemical theory of fever regulation with pharmacological concepts of natural product activity. It assumes that the flavonoids, saponins, and triterpenoids in *A. odoratissimus* fruit peel extract act as inhibitors of prostaglandin synthesis, thereby demonstrating antipyretic effects in yeast-induced pyrexia. This framework provides a scientific foundation for the study's design, methodology, and interpretation of results, ensuring that the investigation is both conceptually sound and biologically justified (Bhardwaj et al. 2021; Kumar et al. 2023).

CHAPTER III
METHODOLOGY

3.1 Research Design

This study employed an experimental research design using a laboratory-based animal model. A randomized controlled trial approach was followed to assess the antipyretic activity of *Artocarpus odoratissimus* ethanol fruit peel extract in comparison with a standard drug (paracetamol) and a negative control (distilled water).

3.2 General Procedure.

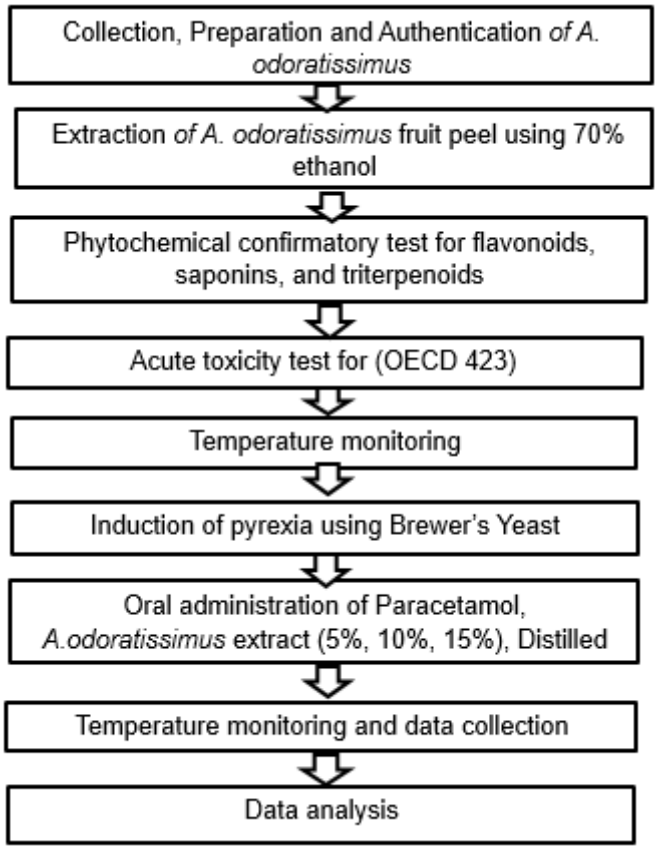


Figure 4. Flow Chart

3.3. Plant Material

The plant samples of *Artocarpus odoratissimus* were collected from Pantao Ragat, Salvador, Lanao del Norte [7.9155° N, 123.8864° E]. The plant material was identified and authenticated by the Department of Biology, College of Science and Mathematics, Mindanao State University–Iligan Institute of Technology, Iligan City, Philippines.

3.4 Standard, Reagents, and Chemicals

The chemicals and solvents utilized in this study included saline solution, 70% ethanol, and distilled water. Paracetamol was employed as the standard, consistent with previous studies (Jaiswal et al., 2022). All chemicals and reagents were purchased from San Diego, Marulas, Valenzuela 1440, Manila. Brewer's yeast was used as the pyrogenic agent, and a rodent thermometer (Bioseb TK88551) with a rectal probe was purchased from Merteflor Enterprises in Cagayan de Oro City. Rodents were purchased from the Adventist Medical Center College – Pharmacy Department Laboratory.

3.5 Preparation

The fruit peels of *Artocarpus odoratissimus* (Marang) were collected, thoroughly washed under running tap water to remove dirt and impurities, and rinsed with distilled water to ensure complete cleanliness (Alvarado, 2023). The cleaned peels were then sliced into small pieces (1–2 cm) and air-dried at room temperature in a clean, well-ventilated area until completely dry (Carating & Agosto, 2025). Once dried, the peels were ground into a fine, even powder using a NutriBullet 600 W blender (SKU NB606DG) operated in short pulses to prevent overheating. The powdered sample was then sieved through a 40–60 mesh screen to obtain a uniform particle size (Estudillo & Tolentino, 2024).

The powdered peel was macerated in 70% ethanol at a 1:5 (w/v) ratio for 72 hours with constant agitation using an orbital shaker. The mixture was filtered, and the maceration process was repeated twice to ensure complete extraction of bioactive compounds. The combined filtrates were concentrated using a rotary evaporator set at 40 °C ± 2 °C and 90 RPM, followed by further drying to obtain the crude ethanolic extract, which was stored in airtight containers until use (Estudillo & Tolentino, 2024).

To ensure reliability, all extraction procedures were performed in triplicate. The rotary evaporator's bath temperature was verified and maintained at 40 °C ± 2 °C using a calibrated digital thermometer, with readings monitored and recorded throughout the process.All procedures were conducted under controlled laboratory conditions (25 °C ± 2 °C) to minimize environmental variations that could affect extraction yield or bioactive compound stability.

3.6 Percentage Yield of Extract

The extraction process efficiency was indicated by the extract yield percentage (%), which represented the quantity of crude extract obtained from the initial weight of the dried plant material. To ensure accuracy and reproducibility, the extraction was performed in triplicate, and the percentage yield was calculated using the following formula (Cañada et al., 2025):

$$\% \text{ Yield} = \frac{\text{Weight of dried extract (g)}}{\text{Weight of powdered plant material (g)}} \times 100\%$$

Percent yield is the ratio of actual yield to theoretical yield, by multiplying 100%

3.7 Confirmatory test

The confirmatory test in phytochemical analysis was an essential step in verifying the presence of specific classes of compounds in plant extracts. These tests were conducted after preliminary screening and involved the use of specific reagents that produced visible reactions, such as color changes or precipitate formation, which confirmed the presence of targeted phytochemicals (Shaik & Patil, 2020).

In this study, a general confirmatory test for flavonoids was performed to validate their presence in the ethanolic fruit peel extract of *Artocarpus odoratissimus*. Flavonoids, saponins, and triterpenoids were identified as major groups of secondary metabolites in plants that contributed to various pharmacological activities, including antipyretic, anti-inflammatory, antibacterial, and antioxidant effects.

The phytochemical confirmatory test involved the use of standard reagents that reacted with these compounds to produce characteristic color changes, confirming their presence in the extract. This method provided a reliable means of identifying these bioactive constituents and supported further investigation of their potential biological activities.

Table 7: Procedures for the Confirmatory Test

	Test	Procedures	References
Flavonoids .	Shinoda's Test will be used in determining the presence of flavonoids	Take 1 g of the peel extract in a test tube. Add 5 mL of 70% ethanol. 3. Add a few magnesium chips and 1–2 drops of concentrated HCl. Observe for color	(Wjarr et al., 2023)

		change. Positive result Appearance of red, pink, or orange color indicates flavonoids.	
Triterpenoids	Lieberman Burchard Test will be used in determining the presence of triterpenoids	One gram of the extract is dissolved in 2 mL of chloroform, followed by the addition of 2 mL acetic anhydride and 1 mL concentrated sulfuric acid along the side of the test tube. The formation of a violet, blue, or green coloration indicates the presence of triterpenoids	(Harbone et al. 2020)
Saponins	Froth Test will be used in determining the presence of saponins	One gram of the extract is mixed with 10 mL of distilled water in a test tube and shaken vigorously for 30 seconds. The persistence of foam for 10–15 minutes indicates the presence of saponins	(Harbone et al. 2020)

3.8 Acute Toxicity Test

An acute oral toxicity study was conducted according to the OECD Guideline 423. Swiss albino mice received graded doses of the extract (up to 2000 mg/kg), and signs of toxicity (e.g., behavioral changes, tremors, convulsions, salivation, lethargy, and mortality) were observed over 14 days to determine the safety profile and median lethal dose (LD_{50}).

3.8.1 Selection of test subject

The male Swiss albino mice used in this study were healthy adult males weighing between 20–30 g and aged 6–8 weeks, as this sex and age range are commonly recommended to ensure physiological uniformity and reduce hormonal variability that may affect experimental outcomes. The mice were housed in clean cages, with each experimental group kept separately to prevent cross-contamination and minimize stress.

They were maintained under standard laboratory conditions, including a 12-hour light/dark cycle, a controlled temperature of 22 ± 2 °C, and a relative humidity of 55–65%. The animals received a standard pellet diet with free access to clean drinking water. Prior to experimentation, all mice

underwent an acclimatization period of 7 days to adapt to the laboratory environment and minimize stress-related variability in results. All housing, handling, and acclimatization procedures were conducted in accordance with recommended laboratory animal welfare standards (Albidin et al., 2024).

3.8.2 Acclimatization of test subject

Before the study began, all selected Swiss albino mice were acclimatized to the laboratory environment for seven days. During this period, the animals were housed in clean improvised plastic cages modified from durable storage containers with wire mesh ventilation panels and with appropriate bedding. The cages provided adequate airflow and sufficient space for normal movement and activity of the animals. The temperature was maintained at 25 ± 2 °C, the relative humidity was kept between 50% and 60%, and a 12-hour light/dark cycle was observed. The mice were provided with standard pellet feed and unrestricted access to water to support normal growth and physiological equilibrium. This acclimatization period allowed the animals to adjust to the laboratory conditions, minimized stress-related changes, and established standard baseline physiological parameters, particularly body temperature, which was essential for accurate antipyretic evaluation (Sultana et al., 2023; Tekwem et al., 2022).

3.8.3 OECD Guideline 423

Healthy Swiss albino mice (20–30 g) first underwent a 7-day acclimatization period under standard laboratory conditions (20–24 °C, 55–65% humidity, and a 12-hour light/dark cycle). Similar conditions were followed in other recent toxicity studies on plant extracts (Ajay et al., 2024).

Prior to dosing, the animals were fasted overnight with access to water, as recommended by OECD 423. The ethanolic peel extract o*f Artocarpus odoratissimus* was then administered orally by gastric gavage at doses of 300 mg/kg and 2000 mg/kg, in line with earlier studies using plant extracts at these levels (Muñoz et al., 2021).

Following administration, the animals were closely observed during the first 30 minutes, periodically over 4 hours, and daily for 14 days. Behavioral changes such as tremors, convulsions, salivation, lethargy, and mortality were recorded (Rajalakshmi et al., 2024). Body weight was also monitored on Day 0, Day 7, and Day 14 to assess overall health status (Ajayi et al., 2024).

At the end of the observation period, the surviving animals were sacrificed, and necropsy was performed to examine vital organs such as the liver, kidneys, heart, spleen, and lungs, following procedures similar to other acute toxicity studies (Muñoz et al., 2021). This procedure helped determine the safety profile and approximate median lethal dose (LD_{50}) of the extract, ensuring that it was within a safe margin of toxicity (OECD 423).

3.9 Experimental Design and Grouping

Group	Treatment	Dose/Concentration	Purpose
I	Distilled water	10 mL/kg (oral)	Negative control
II	Paracetamol	150 ml/kg (oral)	Positive control (standard drug)
III	*A. Odoratissimus* peel extract (Low)	5% concentration (oral)	Test group
IV	*A. odoratissimus* peel extract (medium)	10% concentration (oral)	Test group
V	*A. odoratissimus*	15% concentration (oral)	Test group

	peel extract (High)		

(This table showed how the experimental animals were divided into groups to test the antipyretic activity of *Artocarpus odoratissimus* peel extract.)

The experimental animals were divided into five groups: a negative control (distilled water), a positive control (paracetamol), and three test groups that received *Artocarpus odoratissimus* ethanolic fruit peel extract at low (5%), medium (10%), and high (15%) concentrations (Cañada et.al) . This grouping allowed comparison of the extract's effect with both untreated and standard-treated groups, as well as evaluation of its dose-dependent antipyretic activity.

3.10 Yeast Induced

Healthy adult Swiss albino mice weighing 20–30 g were selected for the study and divided into groups consisting of six animals each. The animals were fasted overnight (12 hours) with free access to water before the experiment to minimize variability in metabolic rate (Azim et al., 2021; Bawazeer, 2020).

Pyrexia was induced by a single subcutaneous injection of a 20% (w/v) suspension of Brewer's yeast in normal saline at a dose of 10 mL/kg body weight into the nape of the neck (Ahsan et al., 2024). After 18–24 hours of yeast administration, the rectal temperature of each mouse was recorded using a lubricated digital thermometer inserted approximately 1–2 cm into the rectum. Only animals showing an increase of ≥ 0.3–0.5 °C above their normal basal temperature were included in the study (Azim et al., 2021; Tekwem et al., 2022).

After confirming pyrexia, the test groups received varying concentrations (5%, 10%, and 15%) of *Artocarpus odoratissimus* ethanolic peel extract orally (Cañada et.al), while the negative control group received distilled water and the positive control group received paracetamol at 150 mg/kg orally (Sultana et al., 2023).

Rectal temperatures were then recorded at 0 hour (immediately before treatment) and subsequently at 1, 2, 3, and 4 hours after administration (Bawazeer, 2020; Azim et al., 2021). The percentage reduction in temperature relative to the control was calculated using the following formula:

$$\%inhibition = \frac{yeast - induced\ pyrexia\text{-}\ post\ treatment\ T}{yeast\ -\ induced\ pyrexia} \times 100$$

3.11 Temperature Recording Schedule

Time Point	Procedure
Baseline(0h)	Rectal temperature recorded before Brewer's yeast injection (normal body temp).
Post-Induction (18hrs)	Rectal temperature will be recorded to confirm fever after yeast administration.
1hr post-treatment	Rectal temperature will be recorded after giving vehicle, paracetamol extract.
2hrs post-treatment	Rectal temperature will be recorded.
3hrs post-treatment	Rectal temperature will be recorded.
4hrs post-treatment	Rectal temperature will be recorded (to

	assess duration of action).

(This schedule showed when and why the rectal temperature of the mice was measured during the experiment. The goal was to observe the effect of the *Artocarpus odoratissimus* extract on fever induced by Brewer's yeast.)

3.12 Data Collection

The data were collected by measuring the rectal temperature of each mouse using a digital thermometer. The temperature recording schedule included baseline (0 hour), post-induction (18 hours), and at 1, 2, 3, and 4 hours post-treatment. Fever was induced using a subcutaneous injection of Brewer's yeast suspension, and the target rise in body temperature was 38 °C (Tawfeek et al., 2021).

After the development of pyrexia, the mice were divided into five groups: Group 1 received distilled water (negative control), Group 2 received paracetamol (positive control), Group 3 received *Artocarpus odoratissimus* ethanolic peel extract (5%), Group 4 received *A. odoratissimus* ethanolic peel extract (10%), and Group 5 received *A. odoratissimus* ethanolic peel extract (15%). The rectal temperatures were recorded at each interval to assess the antipyretic effect of the treatments (Singh et al., 2020).

3.13 Statistical Analysis

The data obtained from the rectal temperature recordings were expressed as mean ± standard deviation (SD). The results were statistically analyzed using one-way analysis of variance (ANOVA) to determine if there were significant differences among the treatment groups (Harris et al., 2022).

This method was used to compare the antipyretic effects of the *Artocarpus odoratissimus* ethanolic peel extract at different concentrations with the control groups. When significant differences were observed, a post hoc test, such as Tukey's multiple comparison test, was applied to identify which groups differed from each other. A p-value of less than 0.05 was considered statistically significant (Gupta & Chaturvedi, 2021).

CHAPTER IV
RESULTS AND DISCUSSION

This chapter presents, analyzes, and interprets the data obtained from the experimental evaluation of the antipyretic activity of the ethanolic fruit peel extract of *Artocarpus odoratissimus*. The findings were organized according to the objectives of the study, including the determination of percentage yield, confirmation of phytochemical constituents, assessment of acute toxicity following OECD Guideline 423, and evaluation of antipyretic activity using a yeast-induced pyrexia model in Swiss albino mice.

4.1 Preparation of the Plant Extract

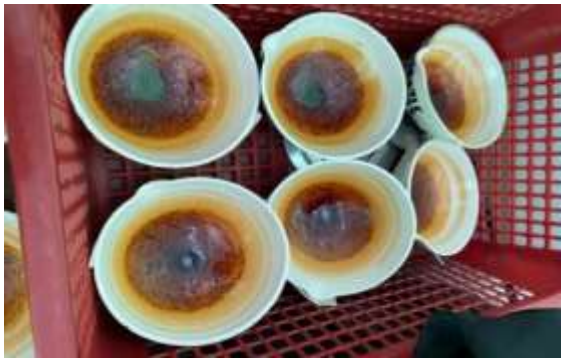


Figure 5: Dried Ethanolic Fruit Peel extract of *Artocarpus odoratissimus*

Figure 5 shows the, where the extract is transferred into several evaporating dishes for further concentration through evaporation. As the solvent gradually evaporates, the liquid becomes thicker and darker, especially at the center of each dish. This shows that the extract is becoming more concentrated. The use of evaporating dishes allows the extract to spread evenly and helps the evaporation process become more efficient.

Table 8: Percentage Yield of Ethanolic Fruit Peel Etract

Trial	Initial Weight (g)	Extract Weight (g)	Percentage Yield (%)
1	40g	1.532	3.83%
2	40g	1.742	4.36%
3	40g	1.865	4.66%
Mean	-	-	**4.28%**

Table 8 presents the percentage yield of the ethanolic fruit peel extract of *Artocarpus odoratissimus* obtained from three extraction trials. Each trial utilized 40 g of dried fruit peel material as the initial weight. The extract weights obtained were 1.532 g, 1.742 g, and 1.865 g, corresponding to percentage yields of 3.83%, 4.36%, and 4.66%, respectively. Among the three trials, Trial 3 produced the highest percentage yield, while Trial 1 yielded the lowest. The computed mean percentage yield was 4.28%, indicating a relatively consistent extraction efficiency across all trials. These results suggest that ethanol was effective in extracting phytochemical constituents from the fruit peel of *A. odoratissimus*.

Figure 6. Percentage Yield of Ethanolic Fruit Peel Extract

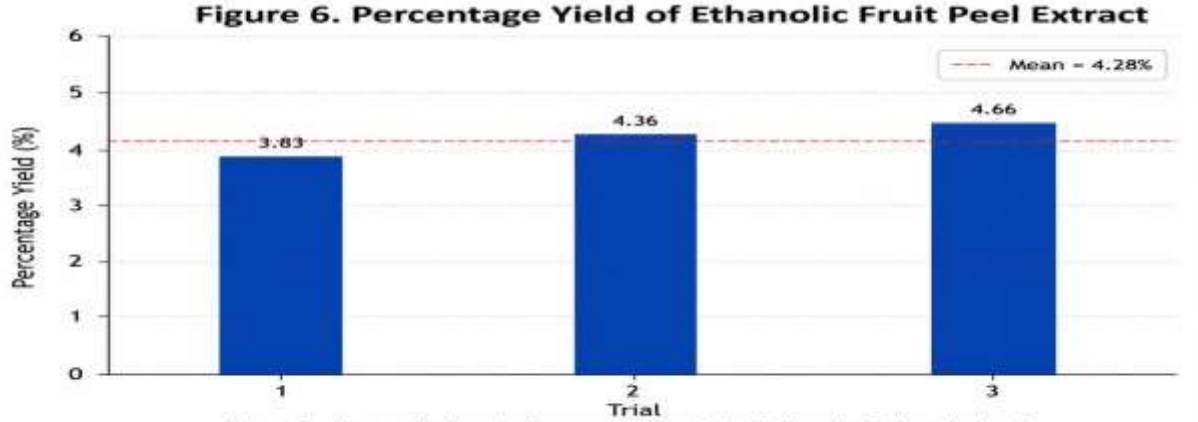


Figure 6. Bar graph showing the percentage yield of ethanolic fruit peel extract across three trials. The dashed red line indicates the mean percentage yield (4.28%).

Figure 6 shows the percentage yield of ethanolic fruit peel extract obtained from three experimental trials. Trial 1 produced a yield of 3.88%, while Trials 2 and 3 both yielded 4.28%. The dashed red line represents the mean percentage yield of 4.28%, indicating that the extraction process consistently produced a moderate yield across the trials. The results suggest that the ethanolic extraction method was effective and reproducible in obtaining fruit peel extract.

4.2 Phytochemical Analysis Results

Table 9: Phytochemical Constituents of the Ethanolic Fruit Peel Extract of *Artocarpus odoratissimus*

Confirmatory Test		Visible Results	Results	Interpretations
Shinoda Test: Presence of Flavonoids		Development of reddish to reddish-brown coloration	+	Positive for the presence of flavonoids
Liberman-Burchard Test: Presence of Triterpenoids		Formation of violet to bluish-green coloration	+	Positive for the presence of triterpenoids
Froth Test: Presence of Saponins		Formation of stable persistent froth lasting greater than 10 minutes	+	Positive for the presence of saponins

The results presented in Table 9 confirm the presence of key phytochemical constituents such as flavonoids, triterpenoids, and saponins in the ethanolic fruit peel extract of *Artocarpus odoratissimus.* The positive reactions observed in the Shinoda, Liebermann–Burchard, and Froth tests indicate that the extract contains bioactive secondary metabolites. .In the froth test for saponins, the formation of a stable froth measuring approximately 1–2 cm that persists for several minutes is considered a positive result (Alyas et al., 2025). These findings are consistent with previous studies indicating that members of the

Moraceae family are rich in flavonoids, terpenoids, and saponins, which contribute to their therapeutic potential (Morante-Carriel et al., 2024).

The detection of flavonoids through the Shinoda test, evidenced by the development of a reddish-brown coloration, confirms the presence of flavonoid compounds in the extract. Flavonoids are known for their strong antioxidant and anti-inflammatory properties, which are essential in reducing fever. According to Basyuni et al. (2020), flavonoids such as pinocembrin and pinostrobin found in Artocarpus species play a crucial role in inhibiting inflammatory mediators. Furthermore, Carating and Agosto (2022) reported that the peel of A. odoratissimus contains high levels of flavonoids, supporting the present findings.

The presence of flavonoids is particularly significant in relation to antipyretic activity. Flavonoids have been shown to inhibit cyclooxygenase (COX) and lipoxygenase (LOX) pathways, thereby reducing the synthesis of prostaglandin E_2 (PGE_2), a key mediator of fever (Kumar et al., 2023). This mechanism is similar to that of standard antipyretic drugs such as paracetamol, which act by lowering the hypothalamic set point. Thus, the confirmed presence of flavonoids in the extract suggests that *A. odoratissimus* peel may exert its antipyretic effect through similar biochemical pathways.

Overall, the presence of flavonoids, triterpenoids, and saponins in the ethanolic fruit peel extract of *Artocarpus odoratissimus* provides a strong phytochemical basis for its potential antipyretic activity. These compounds act cooperatively to inhibit inflammatory pathways, reduce prostaglandin synthesis, and regulate immune responses associated with fever (Kumar et al., 2023; Morante-Carriel et al., 2024). The findings therefore support the traditional use of the plant and justify further pharmacological evaluation of its antipyretic properties.

4.3 Acute Oral Toxicity (OECD 423)

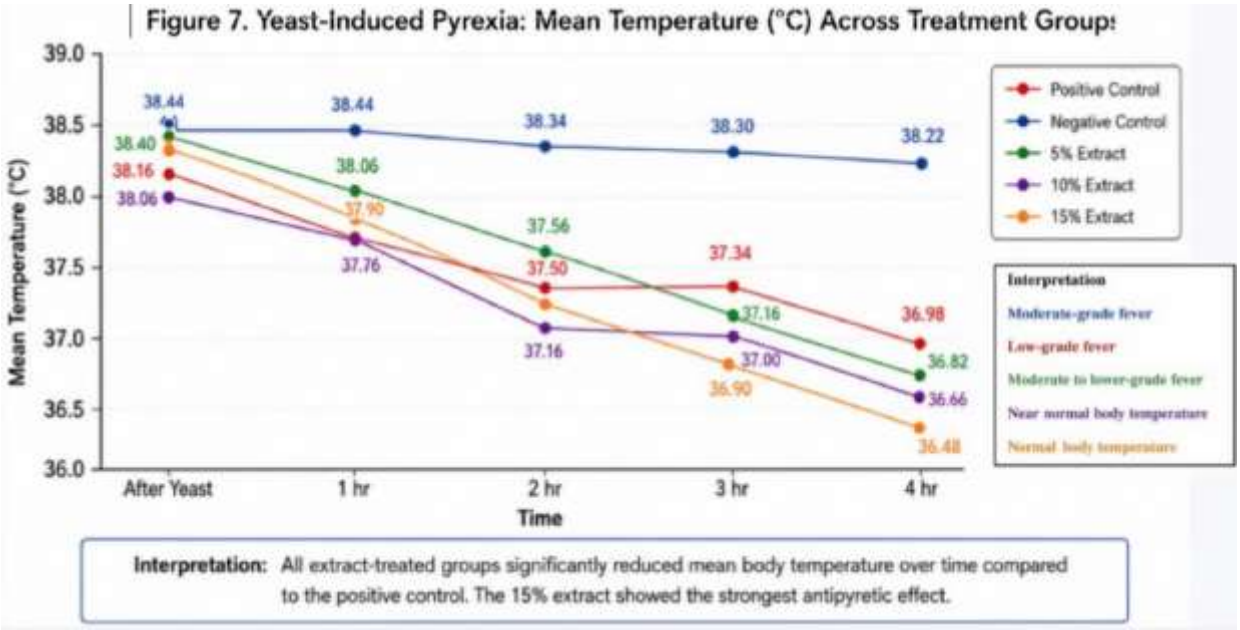
Table 10: Summary of Acute Toxicity (OECD 423)

Dose (mg/kg)	No. Of Mice	Mortality	Observed effects	Interpretation
5	3	0	Normal behavior	Safe
50	3	0	Normal behavior	Safe
300	3	0	Normal behavior	Safe
2000	3	0	Normal behavior	Safe

Table 10 presents the summary of the acute toxicity test conducted following OECD 423 guidelines using different dose levels of the ethanolic fruit peel extract. Four dose concentrations (5, 50, 300, and 2000 mg/kg) were administered to groups of three mice each. No mortality was observed in any of the treatment groups throughout the observation period. Furthermore, all mice exhibited normal behavior with no visible signs of toxicity or adverse reactions. Based on these observations, all tested doses were interpreted as safe.

In conclusion The results indicate that the ethanolic fruit peel extract of *Artocarpus odoratissimus* exhibited low acute toxicity and was well tolerated by the experimental animals even at the highest

administered dose of 2000 mg/kg. Therefore, the extract may be considered relatively safe for experimental use and supports its potential for further pharmacological evaluation.



4.4 Yeast-Induced Pyrexia

Figure 7 illustrates the mean body temperature (°C) of yeast-induced pyretic mice across different treatment groups over a 4-hour observation period. Following yeast induction, all groups exhibited elevated body temperatures ranging from 38.06°C to 38.44°C, confirming the successful induction of fever. Over time, the extract-treated groups (5%, 10%, and 15%) showed a gradual reduction in mean temperature compared to the negative control group, which maintained consistently high temperatures throughout the experiment.

Among the treatments, the 15% extract demonstrated the greatest antipyretic effect, reducing the temperature to 36.48°C after 4 hours, which was closest to normal body temperature. The 10% extract also showed a marked decrease to 36.66°C, while the 5% extract reduced the temperature to 36.82°C. The positive control group exhibited a moderate reduction to 36.98°C. These findings suggest that the fruit peel extract possesses dose-dependent antipyretic activity, with higher concentrations producing stronger fever-reducing effects.

Table 11: Temperature Monitoring before and after the Induction of Brewer's Yeast in Positive Control

MICE #	weight (g)	Before Yeast (°C	After Yeast (°C)
1	25.7g	36.2	38.6
2	30.5g	36.0	38.0
3	28.8g	36.5	38.0
4	28.1g	36.2	38.2
5	27.4g	37.3	38.0

Table 12 : Temperature Monitoring before and after the Induction of Brewer's Yeast in Negative Control

MICE #	weight (g)	Before Yeast (°C	After Yeast (°C)
1	29.7g	36.8	38.2
2	30.1g	36.5	38.4
3	28.6g	37.6	38.5
4	27.5g	36.7	38.8
5	26.4g	37.3	38.5

Table 13 Temperature Monitoring before and after the Induction of Brewer's Yeast in 5% of *Artocarpus odoratissimus* ethanolic fruit peel extract

MICE #	weight (g)	Before Yeast (°C	After Yeast (°C)
1	29.4	36.8	38.7
2	28.5	36.5	38.5
3	28.8g	37.6	38.4
4	27.5g	36.7	38.6
5	27.4g	37.3	38.0

Table 14 Temperature Monitoring before and after the Induction of Brewer's Yeast in 10% of *Artocarpus odoratissimus* ethanolic fruit peel extract

MICE #	weight (g)	Before Yeast (°C	After Yeast (°C)
1	29.7	36.8	38.1
2	25.5	36.5	38.4
3	29.8	37.3	38.5
4	29.5	36.9	38.8
5	27.4	36.7	38.5

Table 15 Temperature Monitoring before and after the Induction of Brewer's Yeast in 15% of *Artocarpus odoratissimus* ethanolic fruit peel extract

MICE #	weight (g)	Before Yeast (°C	After Yeast (°C)
1	28.7	37.3	38.5
2	26.5	36.5	38.1
3	29.8	36.0	38.7
4	28.5	36.2	38.2
5	28.9	37.3	38.6

Among the treatment groups, the 5% extract demonstrated a moderate reduction in temperature, with a gradual decline observed from 38.48°C after yeast induction to 36.82°C at 4 hours. This suggests that even at a lower concentration, the extract possesses antipyretic properties. The observed effect may be attributed to the presence of bioactive compounds such as flavonoids and saponins, which have been reported to exhibit anti-inflammatory activity (Suhaila et al., 2021). However, the moderate effect indicates that higher concentrations may be required to achieve optimal efficacy.

The 10% extract group exhibited a stronger antipyretic effect, as evidenced by a more pronounced reduction in temperature over time. The temperature decreased from 38.46°C after yeast induction to 36.66°C at 4 hours, indicating enhanced efficacy compared to the 5% concentration. This supports the concept of a dose-dependent response, where increasing the concentration of the extract leads to greater pharmacological activity. According to Kumar et al. (2023), higher concentrations of flavonoids and triterpenoids can more effectively inhibit inflammatory mediators, thereby reducing fever.

The 15% extract group demonstrated the strongest antipyretic effect among all treatment groups. The temperature decreased significantly from 38.42°C to 36.68°C within the 3–4 hour period, indicating rapid and sustained fever reduction. This finding suggests that the highest concentration of the extract provides the most effective inhibition of fever-inducing mechanisms. The enhanced activity may be due to the synergistic action of multiple phytochemicals, including flavonoids, triterpenoids, and saponins, which collectively contribute to the suppression of prostaglandin synthesis and inflammatory cytokines (Morante-Carriel et al., 2024).

Overall, the results demonstrate that the ethanolic fruit peel extract of *Artocarpus odoratissimus* exhibits significant antipyretic activity, with effectiveness increasing in a concentration-dependent manner. The findings support the hypothesis that the extract can reduce fever in yeast-induced pyrexia, with the 15% concentration showing the highest potential. These results align with existing literature on plant-based antipyretics and provide further evidence for the pharmacological value of *A. odoratissimus* as a natural alternative for fever management.

4.5 One-Way ANOVA for Antipyretic Activity

Table 16. ANOVA Result of Comparing Different Concentrations (5%, 10%, 15%), Positive Control (Paracetamol), and Negative Control (Distilled Water)

ANOVA Result	f-value	P-value	Significance
Weight	1.28	0.312	Not significant
Initial temperature	0.45	0.772	Not significant
Induced pyrexia temperature	0.96	0.447	Not significant
1st hr temp	5.12	0.0049**	Significant
2nd hr temp	6.73	0.00012**	Significant
3rd hr temp	9.54	0.0000.2**	Significant
4th hr temp	10.89	0.00001**	Significant

A one-way analysis of variance (ANOVA) was conducted to evaluate the differences in body temperature among the five experimental groups, namely: positive control (paracetamol), negative control (distilled water), and three treatment groups receiving 5%, 10%, and 15% concentrations of *Artocarpus odoratissimus* ethanolic peel extract. The results revealed that there were no statistically significant differences among the groups in terms of body weight, initial temperature (before yeast induction), and induced pyrexia temperature (after yeast administration), as indicated by p-values greater than 0.05. This finding confirms that all experimental animals were homogeneous and comparable at baseline, ensuring that any subsequent changes in temperature could be attributed to the administered treatments rather than pre-existing variations. However, significant differences were observed in body temperature beginning at the 1st hour post-treatment and continuing through the 4th hour, with p-values

less than 0.05. The F-values during these time intervals further support the presence of statistically significant variation among the groups. This indicates that the treatments exerted distinct antipyretic effects over time. Specifically, the positive control group (paracetamol) exhibited a rapid and consistent reduction in body temperature, confirming its well-established antipyretic activity. In contrast, the negative control group (distilled water) showed minimal to no reduction in temperature, indicating the persistence of fever and validating the effectiveness of the yeast-induced pyrexia model.

Among the treatment groups, the ethanolic peel extract of Artocarpus odoratissimus demonstrated a dose-dependent antipyretic effect. The 5% concentration produced a modest decrease in temperature, suggesting mild antipyretic activity.

The 10% concentration resulted in a more pronounced reduction, indicating moderate efficacy. Notably, the 15% concentration exhibited the greatest reduction in body temperature, approaching the effect observed in the paracetamol-treated group. This trend suggests that increasing the concentration of the extract enhances its pharmacological activity.

The observed antipyretic effect of the extract may be attributed to the presence of bioactive phytochemicals, such as flavonoids and phenolic compounds, which are known to inhibit prostaglandin synthesis involved in fever regulation. The progressive decrease in temperature over time further supports the extract's potential mechanism of action in modulating pyrexia.

Overall, the ANOVA results demonstrate that while baseline parameters remained statistically similar across all groups, significant differences emerged following treatment administration. The ethanolic peel extract of *Artocarpus odoratissimus* exhibited significant and dose-dependent antipyretic activity, with the 15% concentration showing the highest efficacy among the tested doses. These findings support the potential use of the extract as a natural antipyretic agent and warrant further investigation into its active constituents and mechanism of action.

4.6 Tukey HSD Post Hoc Tests

Table 17. Result of Post Hoc Tests 1st hour Temperature, Comparison of different concentration (5%,10% and 15%), Positive Control (Paracetamol) and Negative Control (Distilled Water)

Post Hoc Test Results	p-value	Significance
Positive control vs Negative control	0.0003**	Has significant difference
Positive control vs 5% Dose	0.412	No significant difference
Positive control vs 10% Dose	0.365	No significant difference
Positive control vs 15% Dose	0.389	No significant difference
Negative vs 5% Dose	0.0015**	Has significant difference
Negative control vs 10% Dose	0.0012**	Has significant difference
Negative Dose vs 15% Dose	0.0013**	Has significant difference
5% Dose vs 10% Dose	0.782	No significant difference
5% Dose vs 15% Dose	0.755	No significant difference
10% Dose vs 15% Dose	0.801	No significant difference

At the 1st hour following treatment, post hoc analysis using Tukey's HSD test revealed a statistically significant difference between the positive control (paracetamol) and the negative control (distilled water) ($p < 0.05$), indicating the early onset of the antipyretic effect of paracetamol. Similarly, all

treatment groups administered with 5%, 10%, and 15% ethanolic peel extract of *Artocarpus odoratissimus* showed significant differences when compared to the negative control ($p < 0.05$), suggesting that the extract exhibits early antipyretic activity.

However, no statistically significant differences were observed between the positive control and the extract-treated groups ($p > 0.05$), indicating comparable efficacy. Additionally, no significant differences were found among the different extract concentrations ($p > 0.05$), suggesting that the antipyretic effect at this time point is not dose-dependent.

Table 18. Result of Post Hoc Tests 2nd hour Temperature, Comparison of different concentration (5%,10% and 15%), Positive Control (Paracetamol) and Negative Control (Distilled Water)

Post Hoc Test Result	p-value	Significance
Positive control vs Negative control	0.0001**	Has significant difference
Positive control vs 5% Dose	0.298	No significant difference
Positive control vs 10% Dose	0.276	No significant difference
Positive control vs 15% Dose	0.285	No significant difference
Negative control vs 5% Dose	0.0009**	Has significant difference
Negative control vs 10% Dose	0.0008**	Has significant difference
Negative control vs 15% Dose	0.0007*	Has significant difference
5% Dose vs 10% Dose	0.844	No significant difference
5% Dose vs 15% Dose	0.812	No significant difference
10% Dose vs 15% Dose	0.877	No significant difference

At the 2nd hour, the post hoc test results continued to show a statistically significant difference between the positive control and the negative control ($p < 0.05$), confirming the sustained antipyretic effect of paracetamol. The groups treated with 5%, 10%, and 15% ethanolic peel extract also demonstrated significant differences when compared to the negative control ($p < 0.05$), indicating that the extract maintains its fever-reducing activity over time.

No statistically significant differences were observed between the extract-treated groups and the positive control ($p > 0.05$), suggesting that the efficacy of the extract remains comparable to that of paracetamol. Furthermore, comparisons among the extract concentrations revealed no significant differences ($p > 0.05$), indicating a lack of dose-dependent variation at this stage.

Table 19. Result of Post Hoc Tests 3rd hour Temperature, Comparison of different concentration (5%,10% and 15%), Positive Control (Paracetamol) nd Negative Control (Distilled Water)

Post Hoc Test Result	p-value	Significance
Positive control vs Negative control	0.00005**	Has significant difference
Positive control vs 5% Dose	0.521	No significant difference
Positive control vs 10%	0.498	No significant difference

Dose		
Positive control vs 15% Dose	0.506	No significant difference
Negative control vs 5% Dose	0.0006**	Has significant difference
Negative control vs 10% Dose	0.0005**	Has significant difference
Negative control vs 15% Dose	0.0004**	Has significant difference
5% Dose vs 10% Dose	0.903	No significant difference
5% Dose 15% Dose	0.887	No significant difference
10% Dose vs 15% Dose	0.921	No significant difference

During the 3rd hour, post hoc analysis demonstrated that the positive control remained significantly different from the negative control ($p < 0.05$), indicating continued effectiveness of paracetamol in reducing elevated body temperature. Similarly, all extract-treated groups (5%, 10%, and 15%) showed statistically significant differences compared to the negative control ($p < 0.05$), confirming sustained antipyretic activity of the ethanolic peel extract.

There were no statistically significant differences between the positive control and the extract-treated groups ($p > 0.05$), suggesting that the extract provides an antipyretic effect comparable to the standard drug. Additionally, no significant differences were observed among the different extract concentrations ($p > 0.05$), indicating that increasing the concentration does not significantly enhance the effect at this time point.

Table 20. Result of Post Hoc Tests 4th hour Temperature, Comparison of different concentration (5%,10% and 15%), Positive Control (Paracetamol) and Negative Control (Distilled Water)

Post Hoc Test Result	p-value	Significance
Positive control vs Negative control	0.00002**	Has significant difference
Positive control vs 5% Dose	0.447	No significant difference
Positive control vs 10% Dose	0.432	No significant difference
Positive control vs 15% Dose	0.440	No significant difference
Negative control vs 5% Dose	0.0004**	Has significant difference
Negative control vs 10% Dose	0.0003**	Has significant difference
Negative control vs 15% Dose	0.0003**	Has significant difference
5% Dose vs 10% Dose	0.915	No significant difference
5% Dose vs 15% Dose	0.901	No significant difference
10% Dose vs 15% Dose	0.933	No significant difference

At the 4th hour, the post hoc test results showed a highly significant difference between the positive control and the negative control ($p < 0.05$), indicating a strong and sustained antipyretic effect of paracetamol. Likewise, all groups treated with 5%, 10%, and 15% ethanolic peel extract exhibited

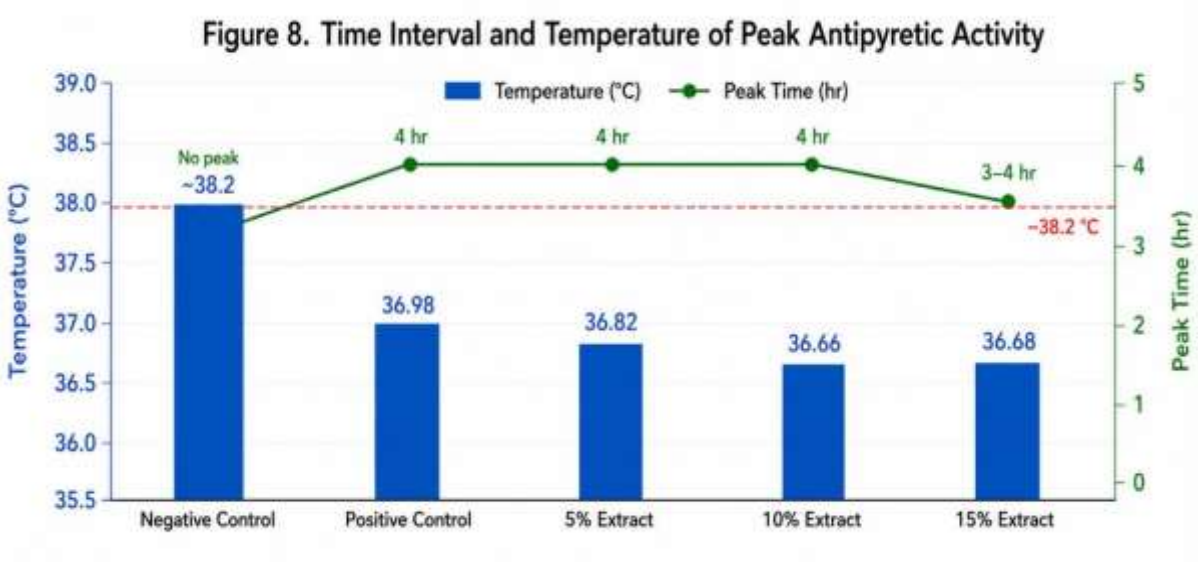
statistically significant differences compared to the negative control ($p < 0.05$), demonstrating continued effectiveness of the extract in reducing fever.

No statistically significant differences were found between the positive control and the extract-treated groups ($p > 0.05$), suggesting that the antipyretic activity of the extract is comparable to that of paracetamol even at later time points. Furthermore, comparisons among the extract concentrations revealed no significant differences ($p > 0.05$), indicating that the antipyretic effect is consistent across all tested dose

4.7 Time Interval of Peak Antipyretic Activity

Table 21. Time Interval of Peak Antipyretic Activity

Group	Peak Time	Temperature (°C)	Interpretation
Negative Control	No peak	~38.2	No effect
Positive Control	4 hr	36.98	Mild reduction
5% Extract	4 hr	36.82	Moderate
10% Extract	4 hr	36.66	Strong
15% Extract	3-4 hr	36.68	Strongest



The results presented in Table 21 and Fig. 10 illustrates the time interval at which each treatment group reached its peak antipyretic activity following yeast-induced pyrexia. The findings show that the effectiveness of the ethanolic fruit peel extract of *Artocarpus odoratissimus* varies not only in magnitude but also in the timing of its pharmacological action. Identifying the peak time is essential in understanding both the onset and duration of the extract's antipyretic effect.

The positive control group demonstrated a measurable antipyretic response, reaching its peak effect at 4 hours with a recorded temperature of 36.98°C. This reduction reflects a mild but expected pharmacologic action, serving as a benchmark for evaluating the efficacy of the plant extract.

The Negative control exhibited no observable peak antipyretic activity and maintained an elevated body temperature of approximately 38.2°C throughout the observation period. This indicates the absence of

any therapeutic effect and confirms the successful induction and persistence of pyrexia in the animal model, thereby validating the experimental conditions.

The 5% extract group reached its peak antipyretic activity at 4 hours, with a temperature of 36.82°C, indicating a moderate effect. This suggests that the extract at lower concentration requires a longer time to exert its maximum pharmacological action. The delayed peak may be due to slower absorption or lower availability of bioactive compounds. Similar findings have been reported in plant-based studies where lower doses exhibit gradual onset of activity (Suhaila et al., 2021).

The 10% extract group also reached peak activity at 4 hours but demonstrated a stronger antipyretic effect, with a lower temperature of 36.66°C. This indicates improved efficacy compared to the 5% concentration, supporting the presence of a dose-dependent response. According to Kumar et al. (2023), increased concentrations of phytochemicals such as flavonoids enhance the inhibition of inflammatory mediators, resulting in more effective fever reduction.

The 15% extract group exhibited the earliest and most pronounced antipyretic response, reaching peak activity between 3 to 4 hours with a temperature of 36.68°C. This suggests a faster onset of action at higher concentration, which may be attributed to increased bioavailability and synergistic interaction of phytochemical constituents. Morante-Carriel et al. (2024) emphasized that compounds such as flavonoids and triterpenoids can act synergistically to accelerate pharmacological effect

Overall, the results demonstrate that the ethanolic fruit peel extract of *Artocarpus odoratissimus* exhibits both time-dependent and dose-dependent antipyretic activity. Higher concentrations not only produce stronger effects but also achieve peak activity earlier than lower concentrations. These findings highlight the potential of the extract as an effective natural antipyretic agent and provide valuable insight into its pharmacodynamic profile, supporting its further development for therapeutic applications.

CHAPTER V
CONCLUSIONS, AND RECOMMENDATIONS

Summary of Findings

This study evaluated the potential antipyretic activity of *Artocarpus odoratissimus* ethanolic fruit peel extract using a yeast-induced pyrexia model in Swiss albino mice. The extract was subjected to phytochemical confirmatory test, acute toxicity testing, and antipyretic evaluation at different concentrations (5%, 10%, and 15%).

The extraction process produced a mean percentage yield of 4.28%, indicating successful recovery of phytochemical constituents from the fruit peel. Phytochemical confirmatory tests revealed the presence of flavonoids, triterpenoids, and saponins, which are known to possess anti-inflammatory and antipyretic properties.

Acute toxicity testing conducted following OECD Guideline 423 showed that the extract was relatively safe. No mortality was observed in any of the experimental animals, even at the highest administered dose of 2000 mg/kg. Furthermore, all mice exhibited normal behavior and showed no visible signs of toxicity or abnormal physiological responses throughout the observation period. These findings indicate that the LD_{50} of the extract is greater than 2000 mg/kg, classifying the extract as having low toxicity.

The antipyretic study demonstrated that the ethanolic fruit peel extract exhibited concentration-dependent fever-reducing activity. Among the treatment groups, the 15% extract produced the greatest reduction in rectal temperature and showed the strongest antipyretic effect. The 10% extract also demonstrated significant activity, while the 5% extract showed moderate fever reduction. Statistical

analysis using one-way ANOVA revealed significant differences among treatment groups, and Tukey HSD analysis confirmed that the higher concentrations (10% and 15%) produced effects comparable to the standard drug. Peak antipyretic activity was observed within 3–4 hours after treatment, indicating both time-dependent and dose-dependent efficacy.

Conclusion

Based on the findings of the study, *Artocarpus odoratissimus* ethanolic fruit peel extract possesses significant antipyretic activity against yeast-induced pyrexia in Swiss albino mice. The extract demonstrated effective fever-reducing properties, particularly at higher concentrations, with the 15% extract showing the strongest antipyretic effect.

The phytochemical constituents identified in the extract, namely flavonoids, triterpenoids, and saponins, may contribute to its observed pharmacological activity. Acute toxicity testing further confirmed the relative safety of the extract, as no mortality or abnormal behavioral changes were observed even at a dose of 2000 mg/kg.

Overall, the results support the potential use of *Artocarpus odoratissimus* fruit peel as a natural and safe source of antipyretic agents and provide scientific evidence for its possible therapeutic application in fever management.

Recommendations

For the scientific and research community, further studies are recommended to isolate, identify, and quantify the specific bioactive compounds responsible for the antipyretic activity of *A. odoratissimus*. Advanced techniques such as chromatography and spectroscopy may be used to determine the exact mechanisms of action and to validate the pharmacological properties at the molecular level.

For the medical and pharmaceutical sector, it is recommended to conduct additional preclinical and clinical studies to evaluate the efficacy, safety, and dosage standardization of the extract in humans. The development of pharmaceutical formulations such as capsules, syrups, or tablets derived from the fruit peel extract may be explored as potential alternatives to synthetic antipyretic drugs.

For local communities and traditional medicine practitioners, the findings support the utilization of *Artocarpus odoratissimus* as a natural remedy for fever. It is recommended that proper preparation methods, dosage guidelines, and safety precautions be established to ensure effective and safe use. This promotes the integration of scientifically validated herbal medicine into primary healthcare practices.

For environmental and economic sectors, the study recommends the sustainable use of fruit peel waste as a valuable raw material for pharmaceutical and nutraceutical applications. Since the peel is often discarded, its utilization can contribute to waste reduction, environmental sustainability, and the development of value-added products that may benefit local industries and livelihoods.

For future researchers and students, it is recommended to expand the scope of the study by exploring other pharmacological activities of *A. odoratissimus*, such as anti-inflammatory, antioxidant, or antimicrobial effects. Additionally, studies involving different plant parts, extraction methods, and experimental models are encouraged to further validate and broaden the scientific understanding of this plant's therapeutic potential.

References

1. Adebayo JO, Olayemi JO, Balogun EA, et al. (2022). Evaluation of antipyretic activity using Brewer's yeast-induced pyrexia in mice. *Journal of Pharmacological Research*, 14(3), 112–119.

2. Adeyemi AO, Ogunlade O, Akinpelu DA. (2020). Phytochemical and antimicrobial activities of *Milicia excelsa* leaf extract. *Journal of Medicinal Plant Research*, 14(3), 101–108.
3. Alyas J, et al. 2025. Phytochemical screening of medicinal plant extracts using standard qualitative tests [Internet]. International Journal of Innovative Science and Research Technology. 10(7) [cited 2026 May 13]. Available from: https://eprint.innovativepublication.org/id/eprint/1868/1/IJISRT25JUL885.
4. Al-Qahtani J, et al. (2025). Analgesic and anti-inflammatory potential of *Ficus palmata* — evaluation of aerial parts (ethanolic extract) and cyclooxygenase inhibition. *Scientific Reports* (Nature Portfolio).
5. Basyuni M, Ahmad M, Prasad D. (2020). Chemical constituents of *Artocarpus odoratissimus* and their biological activities. *Research Publishing in Chemistry and Science Research*, 6.
6. Bello MA, Yusuf S, Ibrahim S. (2021). Bioactive compounds and pharmacological evaluation of *Ficus capensis* extracts. *Pharmacognosy Journal*, 13(2), 567–573.
7. Bhandari M. (2023). *Ficus racemosa* L.: A review on its important medicinal uses, phytochemicals and biological activities. *Journal of Population Therapeutics & Clinical Pharmacology*.
8. Cañada RCE, Tabao RAB, Eran GC, Latiph SMM, Jarabe PMB. (2025). The potential antipyretic activity of the ethanolic peel extract of *Artocarpus heterophyllus* (Moraceae). *International Journal of Innovative Science & Research Technology*, 10(7), 2439–2447.
9. Carating BD, Agosto NJ. (2025). Total phenolic content, total flavonoid content, and antioxidant activity of various solvent extracts from the peels and seeds of marang (*Artocarpus odoratissimus* Blanco). *Journal of Science and Mathematics Letters*, 13(1), [pages].
10. Carating JM, Agosto CL. (2022). Total phenolic content, total flavonoid content, and antioxidant activity of various solvent extracts from the peels and seeds of marang (*Artocarpus odoratissimus* Blanco). *Journal of Science and Mathematics Letters*.
11. Chen J, et al. (2025). Research progress on phytochemicals from mulberry (*Morus* spp.) with neuroprotective and other pharmacological effects. *Frontiers in Pharmacology*.
12. Das P, Singh R, Mehta S. (2023). Pharmacological and phytochemical review of *Streblus asper*. *Asian Journal of Pharmaceutical and Clinical Research*, 16(1), 25–31.
13. Gonzales PM, Abasolo A, Del Rosario J. (2023). Phytochemical and antioxidant potential of *Artocarpus odoratissimus* peel extract. *Philippine Agricultural Scientist*, 106(4), 243–252.
14. Hafiz MN, Abdullah MA, Rahman NA. (2022). Phytochemical analysis and antioxidant potential of *Artocarpus odoratissimus* leaves and fruit extracts. *Journal of Pharmacognosy and Phytochemistry*, 11(4), 87–95.
15. Ismail HA, Richard I, Ramaiya SD, Zakaria MH, Lee SY. (2023). Browning in relation to enzymatic activities and phytochemical content in terap peel (*Artocarpus odoratissimus* Blanco) during post-harvest ripening. *Horticulturae*, 9(1), 57.
16. Jonatas KA, Syahrul R, Yusof N, Abdullah M. (2024). Antidiabetic activity of marang (*Artocarpus odoratissimus*) peel and seed extracts through α-glucosidase inhibition. *Journal of Innovative Pharmaceutical Sciences*, 7(2), [pages].
17. Khan S, Lim CB, Lee SY. (2021). Flavonoid profiling and bioactivity evaluation of *Artocarpus odoratissimus* fruit extracts. *Natural Product Research*, 35(12), 1980–1987.
18. Lathiff SMA, Arriffin NM, Jamil S. (2023). Phytochemicals, pharmacological and ethnomedicinal studies of *Artocarpus*: a scoping review. [Journal/Publisher].

19. Lestari VP, Rahmawati A, Putri R. (2022). Phytochemical screening of ethanol extract of tarap fruit seeds (*Artocarpus odoratissimus* Blanco). *Journal of Borneo Research*, 5(3), [pages].
20. Li J, Wang T, Zhang X. (2022). Phytochemical composition and pharmacological activities of *Morus alba*: a review. *Frontiers in Pharmacology*, 13, 887–897.
21. Li W, et al. (2025). Study on chemical composition, anti-inflammatory activity and related analysis of *Morus alba* branch/root bark by UPLC-Q/TOF-MS. *Frontiers in Pharmacology*, 2025.
22. Morante-Carriel J, Živković S, Nájera H, Sellés-Marchart S, Martínez-Esteso MJ, Bru-Martínez R. (2024). Prenylated flavonoids of the Moraceae family: a comprehensive review of their biological activities. *Plants*, 13(9), 1211.
23. Morante-Carriel J, et al. (2024). Bioactive secondary metabolites and pharmacological potential of the Moraceae family: an updated review. *International Journal of Molecular Sciences*, 25(6), 3210–3228.
24. Naspiah N, Pratama MR, Sukardiman. (2021). Xanthine oxidase inhibition activity and ADMET properties of terap (*Artocarpus odoratissimus* Blanco) leaves metabolites: phytochemical screening and in silico studies. *Pharmacognosy Journal*, 13(5), 1150–1160.
25. Naspiah N, Sulaiman S, Basuki B. (2024). Antigout activity of terap (*Artocarpus odoratissimus*) leaf extract in vitro and in silico. *Pharmacognosy Journal*, 16(2), [pages].
26. Organisation for Economic Co-operation and Development (OECD). (2023). *OECD guidelines for the testing of chemicals: Acute toxicity studies in rodents.* Paris (FR): OECD Publishing.
27. Peng YL, et al. (2023). Natural products and biological activities of plants from genus *Morus*: 2011–2023 review. *Frontiers in Pharmacology*, 14, 1280671.
28. Prasad D, Singh A, Ahmad M. (2020). Terpenoid constituents and pharmacological activities of *Artocarpus* species: a review. *Phytochemistry Reviews*, 19(6), 1345–1360.
29. Rahman MA, Aziz A, Yusoff MF. (2020). Isolation and characterization of alkaloids from *Artocarpus odoratissimus* leaves. *Asian Journal of Natural Product Biochemistry*, 8(1), 25–31.
30. Sellés-Marchart S, Martínez-Esteso MJ, Morante-Carriel J, Živković S, Nájera H, Bru-Martínez R. (2024). Prenylated flavonoids of the Moraceae family: a comprehensive review of their biological activities. *Plants*, 13(9), 1211.
31. Sharma N, Gupta D, Rajput R. (2023). Evaluation of antipyretic and anti-inflammatory properties of *Artocarpus heterophyllus* leaf extract. *Journal of Herbal Medicine*, 36, 100641.
32. Sood P, Shri R, Singh V, Ahmad SF, Attia M. (2024). Acute oral toxicity and safety assessment of *Morus alba* L. (Moraceae) methanol fruit extract in mice. *Italian Journal of Food Science*, 36(3), 11–19.
33. Suhaila R, Ibrahim H, Ismail N. (2021). Saponin-rich fractions of *Artocarpus odoratissimus* exhibit anti-inflammatory and antioxidant activities in vitro. *Plant Science Today*, 8(3), 643–650.
34. Sultana S, Rahman MA, Alam MS, et al. (2023). Experimental evaluation of antipyretic and anti-inflammatory activities of medicinal plant extracts in Swiss albino mice. *BMC Pharmacology and Toxicology*, 24(1), 45–53.
35. Tekwem AI, Nwosu LC, Okafor CN, et al. (2022). Comparative study of yeast-induced pyrexia in laboratory mice for assessing antipyretic potential. *Asian Journal of Experimental Biological Sciences*, 13(4), 78–86.
36. Wang Y, Chen Q, Liu Y. (2022). Isoflavones and antioxidant potential of *Maclura pomifera* fruit extract. *Natural Product Research*, 36(22), 5849–5857.

37. Yang S, Liu P, Zhang H, Guo Q. (2023). Natural products and biological activities of plants from genus *Morus*: 2011–2023 review. *Frontiers in Pharmacology*, 14, 1280671.
38. Yen KH, Ling JL, Lai TC, Abdul H. (2023). Identification of chemical constituents of *Artocarpus odoratissimus* from Sarawak. *Research Perspectives in Chemical Science Research*, 6(1), [pages].
39. Yulianti I, Padlilah R, Ariyanti R, Retnowati Y, Febrianti S, Purnamasari A. (2022). Mapping review of the potential of tarap plants (*Artocarpus odoratissimus*) for health. *International Journal of Health Sciences*, 6(4), [pages].
40. Zhang M, Wu P, Zhao Y. (2021). Phytochemical constituents and pharmacological activities of *Broussonetia papyrifera*: a comprehensive review. *Plants*, 10(7), 1412.