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EVALUATION OF THE ANTIPYRETIC ACTIVITY OF PRATAPA MARTTANDA RASA IN BREWER'S YEAST-INDUCED PYREXIA IN WISTAR RATS: AN EXPERIMENTAL STUDY

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ABSTRACT

Background

Fever is a common clinical manifestation associated with infectious and inflammatory disorders and represents an important protective response of the host against pathogenic invasion. Although synthetic antipyretic drugs effectively reduce elevated body temperature, their prolonged administration may lead to gastrointestinal, hepatic, renal, and cardiovascular adverse effects. Ayurveda describes numerous formulations for the management of ***Jwara (fever)****, among which* ***Pratapa Marttanda Rasa****, a classical herbo-mineral formulation described in Bhaisajya Ratnavali, is traditionally indicated for different types of fever. However, experimental evidence supporting its antipyretic efficacy remains limited.*

Aim

To evaluate the antipyretic activity of Pratapa Marttanda Rasa in Brewer's yeast-induced pyrexia in Wistar rats.

Materials and Methods

Twenty-four healthy Wistar rats of either sex weighing 150–300 g were randomly divided into four groups (n = 6). Fever was induced by subcutaneous administration of 20% Brewer's yeast suspension. Group I served as normal control, Group II received paracetamol (100 mg/kg), Group III received Pratapa Marttanda Rasa at 10 mg/kg, and Group IV received Pratapa Marttanda Rasa at 20 mg/kg orally. Rectal temperatures were recorded before yeast administration, after induction of pyrexia, and at hourly intervals following treatment. Data were expressed as Mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD post hoc test.

Results

No statistically significant difference was observed in baseline temperatures among the experimental groups, confirming homogeneity before treatment. Brewer's yeast produced significant pyrexia in all treated groups. Administration of Pratapa Marttanda Rasa produced a dose-dependent reduction in rectal temperature. The high-dose group exhibited an antipyretic response comparable to paracetamol from the fourth hour onward, whereas the low-dose group demonstrated moderate but significant activity. One-way ANOVA revealed highly significant differences among groups ($p < 0.0001$) at successive observation periods.

Conclusion

Pratapa Marttanda Rasa possesses significant dose-dependent antipyretic activity against Brewer's yeast-induced pyrexia in Wistar rats. The higher dose demonstrated efficacy comparable to the standard drug paracetamol, supporting the traditional Ayurvedic use of this formulation in the management of Jwara.

KEYWORDS*: Ayurveda, Pratapa Marttanda Rasa, Jwara, Antipyretic activity, Brewer's yeast, Wistar rats, Rasashastra, Experimental pharmacology*

1. INTRODUCTION

Fever, clinically defined as an elevation of body temperature above the normal physiological range, is one of the most frequent manifestations encountered in infectious, inflammatory, autoimmune, and neoplastic disorders. It develops due to the action of endogenous pyrogens, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and prostaglandin E_2 (PGE_2), which elevate the hypothalamic thermoregulatory set point. Although fever is considered a protective physiological response that enhances host immune defence, persistent or high-grade fever may lead to dehydration, metabolic disturbances, increased oxygen consumption, neurological complications, and significant patient discomfort. Consequently, effective management of fever remains an important therapeutic objective in both conventional and traditional systems of medicine.

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Currently available antipyretic agents such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) act primarily through inhibition of cyclooxygenase enzymes and suppression of prostaglandin synthesis. While these medications are clinically effective, prolonged or excessive use has been associated with hepatotoxicity, nephrotoxicity, gastrointestinal irritation, cardiovascular complications, and hypersensitivity reactions. These limitations have stimulated increasing interest in the development of safer and evidence-based herbal or herbo-mineral alternatives.

Ayurveda considers **Jwara** to be one of the most important disease entities. Classical Ayurvedic texts describe Jwara as a systemic disorder affecting both body and mind and regard it as a disease capable of influencing all physiological functions. According to Ayurvedic principles, disturbance of **Agni**, vitiation of **Doshas**, accumulation of **Ama**, and impairment of **Rasa Dhatu** play major roles in the pathogenesis of Jwara. Management therefore aims not only to reduce elevated body temperature but also to restore digestive fire, eliminate metabolic toxins, normalize doshic balance, and improve tissue metabolism.

Among the numerous formulations described in Rasashastra, **Pratapa Marttanda Rasa** is a classical herbo-mineral preparation indicated in the treatment of various types of fever. The formulation contains ingredients possessing Deepana, Pachana, Jwarahara, and Rasayana properties. Classical Ayurvedic literature attributes rapid therapeutic action to such formulations due to their unique pharmaceutical processing, enhanced bioavailability, and synergistic interactions among ingredients. Modern pharmacological studies on individual constituents have also demonstrated anti-inflammatory, immunomodulatory, antioxidant, antimicrobial, and antipyretic properties that may collectively contribute to its therapeutic efficacy.

Despite its extensive traditional use, systematic scientific evaluation of Pratapa Marttanda Rasa remains limited. Experimental validation using standardized pharmacological models is therefore essential to establish evidence supporting its traditional claims and to facilitate integration into evidence-based clinical practice.

The Brewer's yeast-induced pyrexia model is a widely accepted experimental method for evaluating antipyretic activity. Brewer's yeast stimulates the production of endogenous pyrogens, resulting in prostaglandin-mediated elevation of hypothalamic temperature similar to the mechanism observed in infectious fever in humans. Consequently, this model provides a reliable experimental platform for assessing potential antipyretic agents.

Therefore, the present study was undertaken to evaluate the antipyretic activity of Pratapa Marttanda Rasa in Brewer's yeast-induced pyrexia in Wistar rats using paracetamol as the standard reference drug. The findings of this investigation are expected to provide scientific evidence supporting the classical Ayurvedic indications of Pratapa Marttanda Rasa and contribute toward its evidence-based therapeutic application.

2. MATERIALS AND METHODS

2.1 Study Design

The present investigation was designed as an **in vivo experimental pharmacological study** to evaluate the antipyretic activity of the classical Ayurvedic herbo-mineral formulation **Pratapa Marttanda Rasa** using the Brewer's yeast-induced pyrexia model in Wistar rats. The study was conducted under controlled laboratory conditions following standard experimental pharmacology protocols.

2.2 Study Site

The experimental work was carried out in the Central Animal House Facility of Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India. All experimental procedures were performed under standardized environmental conditions and in accordance with institutional laboratory practices.

2.3 Ethical Approval

The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

2.4 Experimental Animals

Twenty-four healthy adult Wistar albino rats of either sex, weighing between **150 and 300 g** and approximately **three months of age**, were selected for the study. The animals were procured from a CPCSEA-registered breeding facility and acclimatized for one week before experimentation.

The rats were housed in polypropylene cages with clean paddy husk bedding under controlled environmental conditions:

- Temperature: **22 ± 2°C**
- Relative humidity: **50–60%**
- Light–dark cycle: **12 h/12 h**
- Standard pellet diet and purified drinking water were provided ad libitum.

The bedding material was replaced daily, and cages were cleaned regularly to maintain hygienic conditions.

2.5 Inclusion and Exclusion Criteria

Inclusion Criteria

- Healthy Wistar rats
- Body weight between 150–300 g
- Rectal temperature within the normal physiological range
- Active and disease-free animals

Exclusion Criteria

- Animals showing signs of illness
- Pregnant females
- Animals exhibiting abnormal behaviour
- Animals with rectal temperature outside the normal range

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2.6 Test Drug

The investigational drug was **Pratapa Marttanda Rasa**, a classical Ayurvedic herbo-mineral formulation prepared according to the method described in **Bhaisajya Ratnavali**.

The formulation consisted of purified ingredients processed according to classical Rasashastra procedures before pharmaceutical preparation.

Sl. No.	Ingredient	Quantity
1	Śodhita Vatsanabha	40 g
2	Śodhita Hingula	80 g
3	Śodhita Jayapala	120 g
4	Śodhita Tankana	160 g
5	Jala (Water)	Quantity Sufficient (Q.S.)

2.7 Standard Drug

Paracetamol was used as the standard antipyretic drug because of its well-established efficacy against experimentally induced pyrexia.

Dose: **100 mg/kg body weight orally**

2.8 Vehicle

Pratapa Marttanda Rasa tablets were finely powdered and suspended in distilled water immediately before administration to ensure uniform dosing.

2.9 Acute Oral Toxicity Study

Prior to pharmacological evaluation, an acute oral toxicity study was carried out according to **OECD Guideline 420 (Fixed Dose Procedure)**.

The powdered formulation suspended in distilled water was administered orally using the staircase method at sequential doses of:

- 500 mg/kg
- 2000 mg/kg
- 5000 mg/kg

Animals were continuously observed during the first four hours after administration and thereafter periodically for fourteen days for the appearance of mortality or signs of toxicity including:

- behavioural changes
- locomotor abnormalities
- salivation
- tremors
- convulsions
- respiratory distress
- feeding behaviour
- body weight changes

No mortality or treatment-related toxic manifestations were observed even at **5000 mg/kg**, indicating a wide safety margin of the formulation.

Accordingly, the therapeutic experimental doses were selected based on one-tenth of the maximum non-toxic dose and body surface area conversion.

2.10 Dose Calculation

The human therapeutic dose of Pratapa Marttanda Rasa described in **Bhaisajya Ratnavali** is **one Ratti (125 mg/day)**.

The rat equivalent dose was calculated using the body surface area conversion method proposed by **Paget and Barnes**.

Human dose = 125 mg/60 kg = 2.08 mg/kg

Animal dose = Human dose × (Human Km/Rat Km) = 2.08 × (37/6) = 12.84 mg/kg

For convenience and experimental standardization, two doses were selected:

- Low dose: **10 mg/kg**
- High dose: **20 mg/kg**

These doses were administered orally using an intragastric feeding tube.

2.11 Experimental Grouping

Twenty-four rats were randomly allocated into four groups comprising six animals in each group.

Group	Treatment	Dose
Group I	Normal Control	Saline
Group II	Standard	Paracetamol 100 mg/kg
Group III	Test Low Dose	PMR 10 mg/kg
Group IV	Test High Dose	PMR 20 mg/kg

Randomization was performed before initiation of the study to minimize selection bias.

2.12 Induction of Pyrexia

Experimental fever was induced using **Brewer's yeast**, one of the most widely accepted models for antipyretic screening.

A **20% suspension of Brewer's yeast in normal saline** was freshly prepared.

Each animal received **10 mL/kg body weight**

through **subcutaneous injection** into the loose skin of the nape of the neck.

Following injection:

- food was withheld for 18 hours
- water was allowed ad libitum

Rectal temperature was measured after 18 hours.

Animals demonstrating an increase of at least **1°C above basal temperature** were included in the study.

2.13 Drug Administration

Following confirmation of pyrexia,

the respective treatments were administered orally using an intragastric feeding tube.

Group I received saline.

Group II received paracetamol.

Group III received Pratapa Marttanda Rasa (10 mg/kg).

Group IV received Pratapa Marttanda Rasa (20 mg/kg).

2.14 Measurement of Rectal Temperature

Rectal temperature was recorded using a calibrated digital thermometer.

The thermometer probe was gently inserted approximately **2 cm into the rectum** until a stable reading was obtained.

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Temperature was recorded at

- Baseline
- 18 hours after yeast administration (0 hour)
- 1 hour
- 2 hours
- 3 hours
- 4 hours
- 5 hours
- 6 hours

after drug administration.
All observations were recorded in degrees Celsius.

2.15 Outcome Measures

Primary Outcome

Reduction in rectal temperature following administration of Pratapa Marttanda Rasa.

Secondary Outcome

Comparison of antipyretic efficacy between:

- Standard drug
- Low-dose PMR
- High-dose PMR

2.16 Statistical Analysis

Data were expressed as **Mean ± Standard Deviation (SD).**

Normality of the data was assessed prior to analysis.

Comparisons among experimental groups were performed using **one-way analysis of variance (One-way ANOVA).**

When a statistically significant difference was detected, **Tukey's Honestly Significant Difference (HSD) post hoc test** was applied for multiple pairwise comparisons.
Statistical significance was considered at **$p < 0.05$.**

2.17 ARRIVE Guideline Compliance

The study was designed and reported according to the **ARRIVE 2.0 (Animal Research: Reporting of In Vivo Experiments)** guidelines to ensure transparency, reproducibility, and scientific rigor.

3. RESULTS

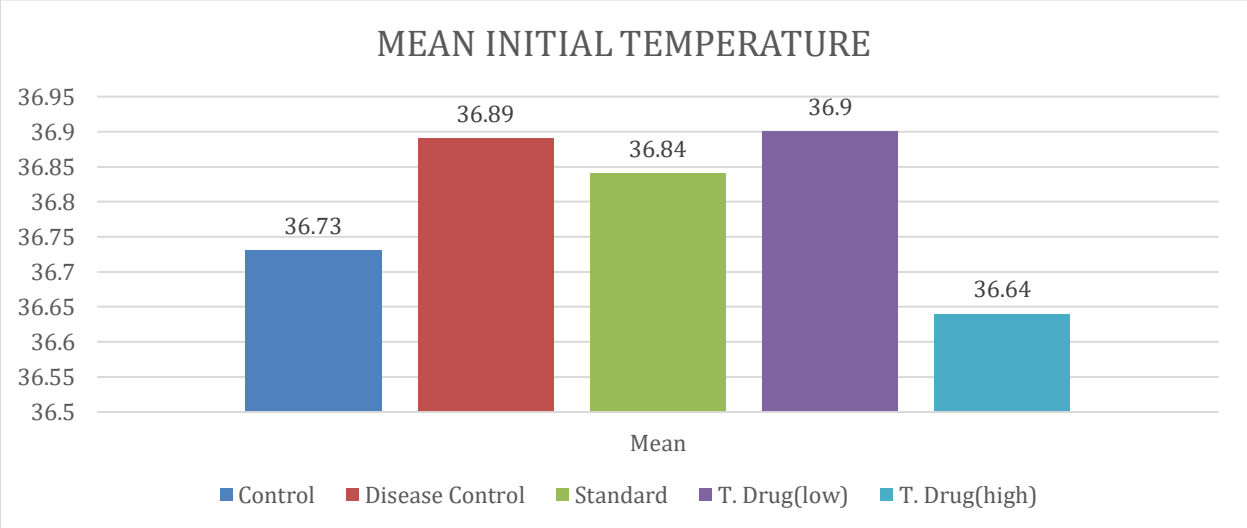
3.1 Acute Oral Toxicity Study

Acute oral toxicity assessment of **Pratapa Marttanda Rasa** was carried out according to OECD Guideline 420. Oral administration of the formulation at doses of **500, 2000, and 5000 mg/kg body weight** did not produce mortality or any observable signs of toxicity during the observation period. No abnormalities in behaviour, locomotor activity, food intake, water consumption, or physical appearance were observed. Therefore, the formulation was considered safe under the experimental conditions, and doses of **10 mg/kg** and **20 mg/kg** were selected for pharmacological evaluation.

3.2 Effect on Baseline Rectal Temperature

Before induction of pyrexia, the mean rectal temperatures of all experimental groups were comparable. One-way ANOVA demonstrated **no statistically significant difference** among the groups ($F = 1.37$, $p > 0.05$), confirming successful randomization and homogeneity of the animals before treatment.

Table 1. Baseline Rectal Temperature of Experimental Groups



Group	Mean ± SD (°C)
Normal Control	36.73 ± 0.25
Disease Control	36.89 ± 0.20
Standard (Paracetamol)	36.84 ± 0.31
PMR 10 mg/kg	36.90 ± 0.25
PMR 20 mg/kg	36.89 ± 0.20

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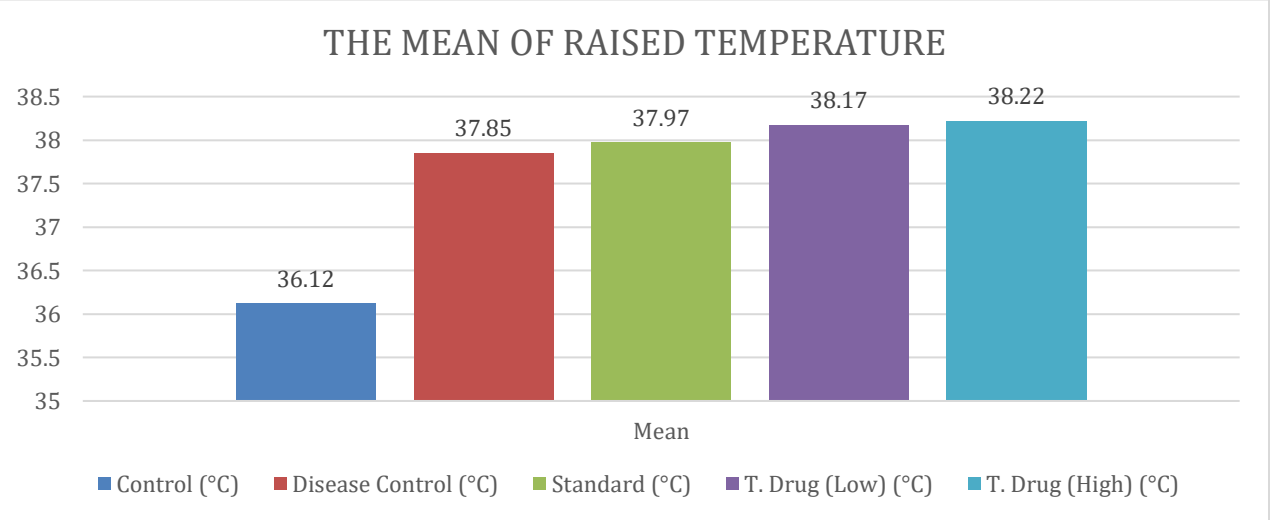
ANOVA: F = 1.37; p > 0.05 (Not Significant)
The absence of statistically significant differences confirmed that all groups had similar physiological body temperatures prior to induction of fever.

3.3 Induction of Experimental Pyrexia

Eighteen hours after subcutaneous administration of Brewer's yeast, all experimental groups except the normal control developed significant pyrexia. The disease control, standard, and treatment groups exhibited comparable elevations in rectal temperature, indicating successful induction of fever.

One-way ANOVA revealed a highly significant difference among the groups (F = 111.22, p < 0.0001). However, Tukey's HSD analysis showed no significant differences among the disease control, standard, and treatment groups, whereas all pyrexic groups differed significantly from the normal control.

Table 2. Rectal Temperature After Yeast-Induced Pyrexia (0 Hour)



Group	Mean ± SD (°C)
Normal Control	36.12 ± 0.13
Disease Control	37.85 ± 0.05
Standard	37.97 ± 0.17
PMR 10 mg/kg	38.17 ± 0.24
PMR 20 mg/kg	38.22 ± 0.39

ANOVA: F = 111.22; p < 0.0001
These findings confirmed successful induction of pyrexia prior to treatment.

3.4 Antipyretic Effect at the First Hour

One hour after drug administration, paracetamol produced the greatest reduction in rectal temperature (0.30°C), followed by PMR 20 mg/kg (0.26°C) and PMR 10 mg/kg (0.21°C). In contrast, the disease control group showed no reduction in temperature

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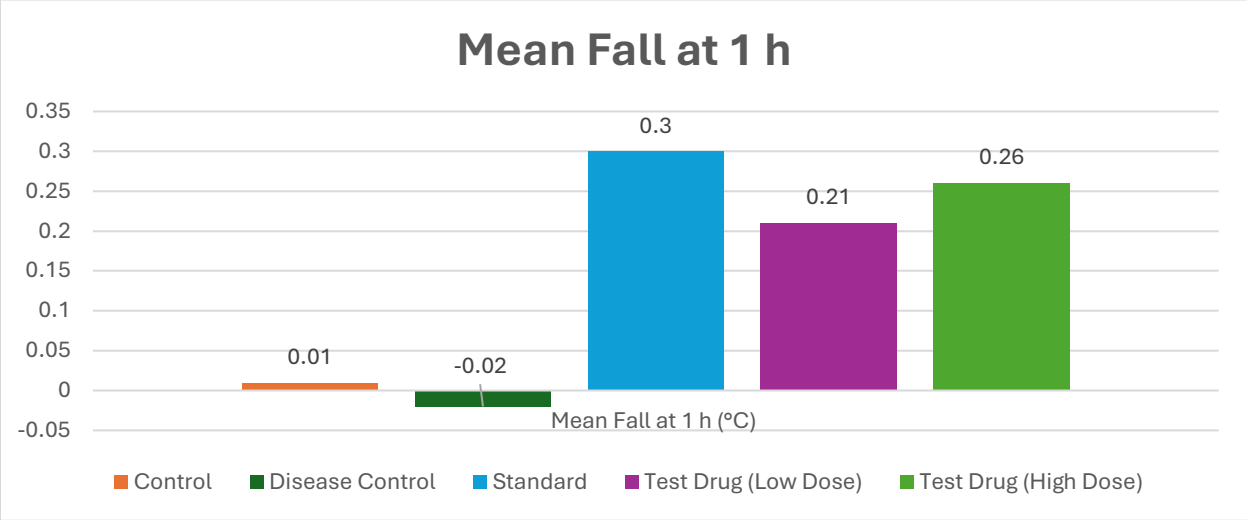
Table 3. Mean Reduction in Rectal Temperature at 1 Hour



Group	Mean Fall (°C)
Normal Control	0.01
Disease Control	–0.02
Standard	0.30
PMR 10 mg/kg	0.21
PMR 20 mg/kg	0.26

One-way ANOVA demonstrated a statistically significant difference among groups ($F = 16.29$, $p < 0.0001$).

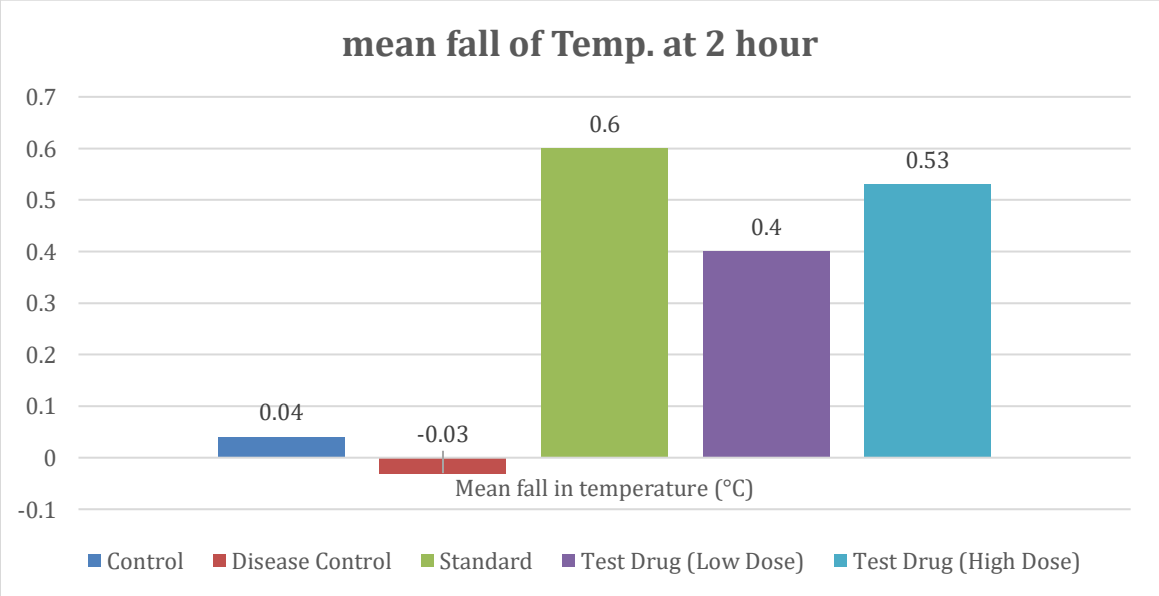
Tukey's HSD test revealed no significant differences between the standard drug and either dose of PMR, whereas both PMR-treated groups showed highly significant reductions compared with the disease control group.

3.5 Antipyretic Effect at the Second Hour

A progressive reduction in body temperature was observed in all treatment groups at the second hour.

The standard drug produced a mean reduction of **0.60°C**, whereas PMR produced reductions of **0.40°C** and **0.53°C** at low and high doses, respectively.

Table 4. Mean Reduction in Rectal Temperature at 2 Hours



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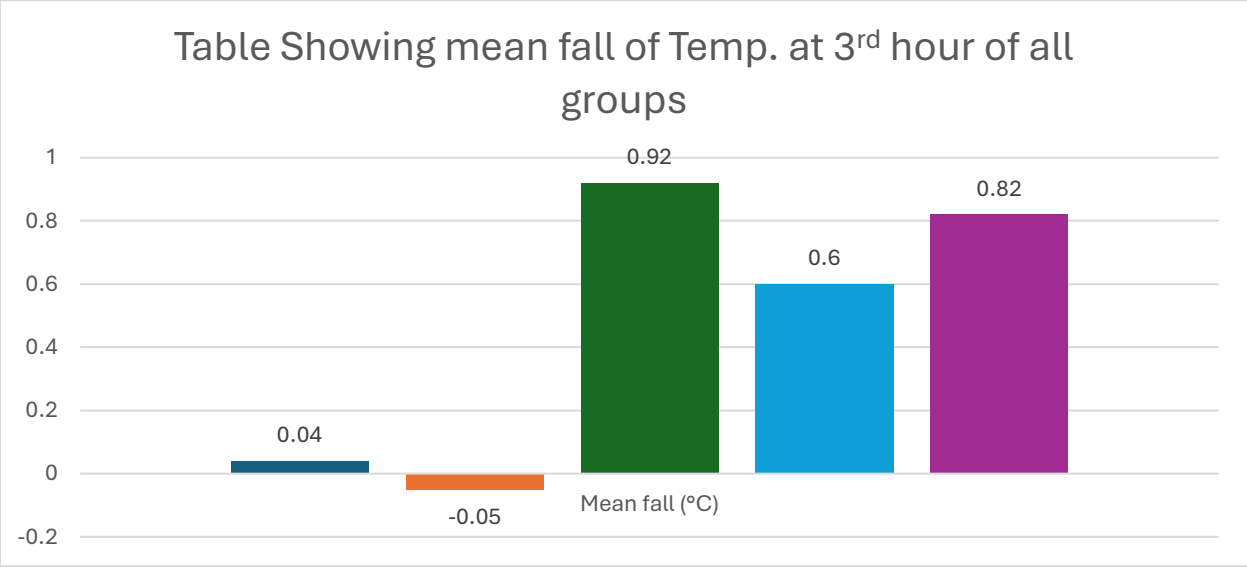
Group	Mean Fall (°C)
Normal Control	0.04
Disease Control	–0.03
Standard	0.60
PMR 10 mg/kg	0.40
PMR 20 mg/kg	0.53

One-way ANOVA indicated highly significant differences among the groups ($F = 132.39$, $p < 0.0001$).
Pairwise comparison demonstrated that both doses of PMR significantly reduced fever compared with the disease control group. No statistically significant difference was observed between the standard drug and the high-dose PMR group.

3.6 Antipyretic Effect at the Third Hour

The antipyretic response continued to increase during the third hour.
Mean reductions in rectal temperature were:



Group	Mean Fall (°C)
Normal Control	0.04
Disease Control	–0.05
Standard	0.92
PMR 10 mg/kg	0.60
PMR 20 mg/kg	0.82

One-way ANOVA showed highly significant differences among groups ($F = 61.22$, $p < 0.0001$).
The high-dose PMR group exhibited a significantly greater antipyretic effect than the low-dose group and approached the efficacy of paracetamol.

3.7 Antipyretic Effect at the Fourth Hour

At four hours, a marked reduction in rectal temperature was observed in both PMR-treated groups.

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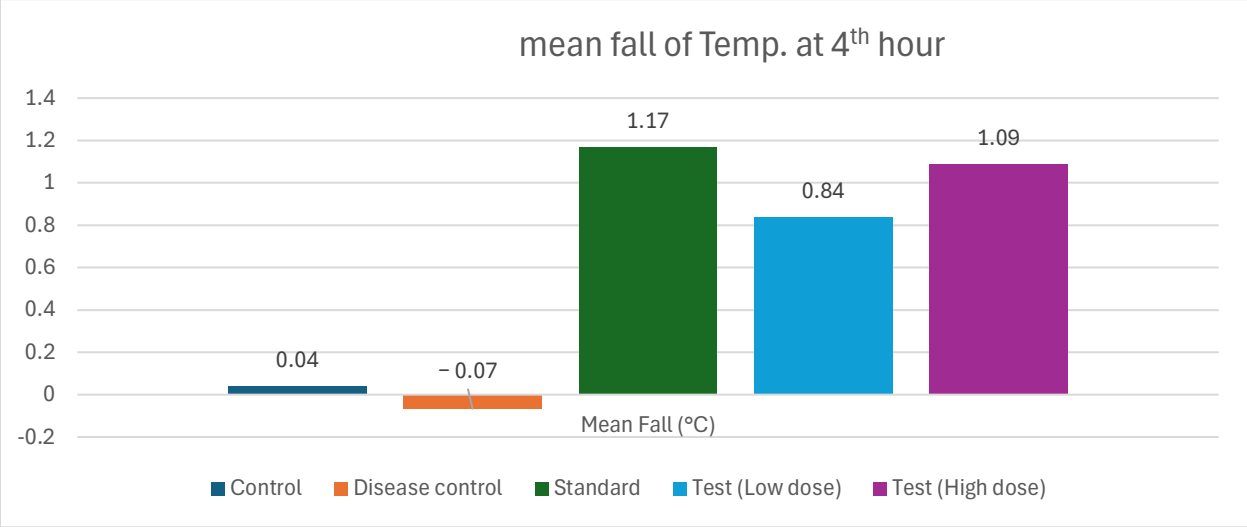
Table 6. Mean Reduction in Rectal Temperature at 4 Hours

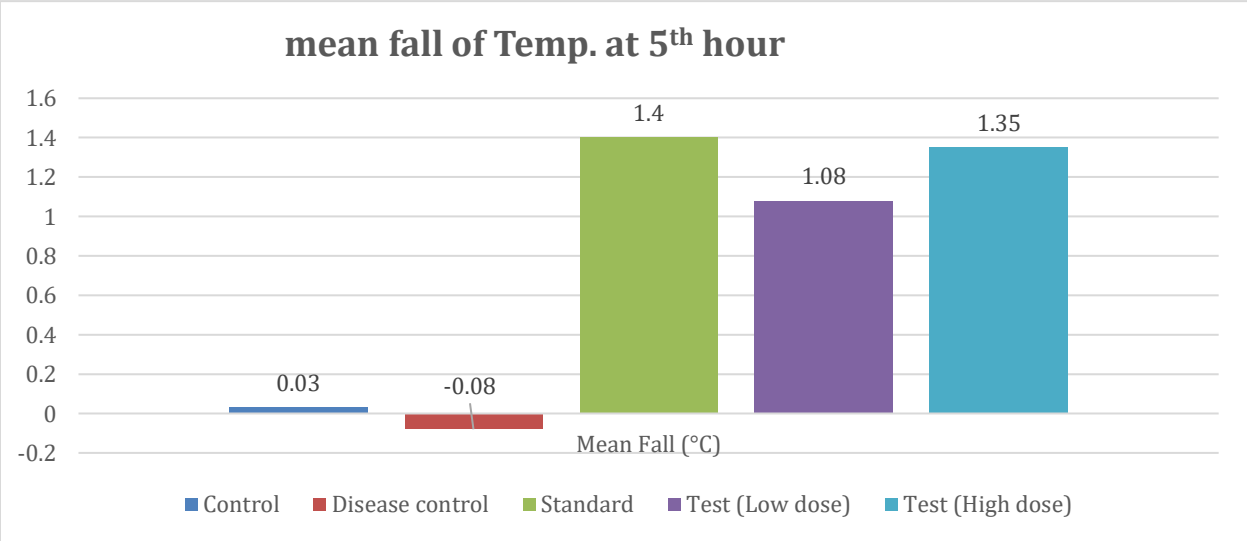


Group	Mean Fall (°C)
Normal Control	0.04
Disease Control	–0.07
Standard	1.17
PMR 10 mg/kg	0.84
PMR 20 mg/kg	1.09

One-way ANOVA demonstrated a highly significant treatment effect ($F = 62.07$, $p < 0.0001$).
Tukey's HSD test showed no statistically significant difference between the standard drug and the high-dose PMR group ($p > 0.05$), indicating comparable antipyretic efficacy.

3.8 Antipyretic Effect at the Fifth Hour

Further reduction in body temperature was observed at the fifth hour.



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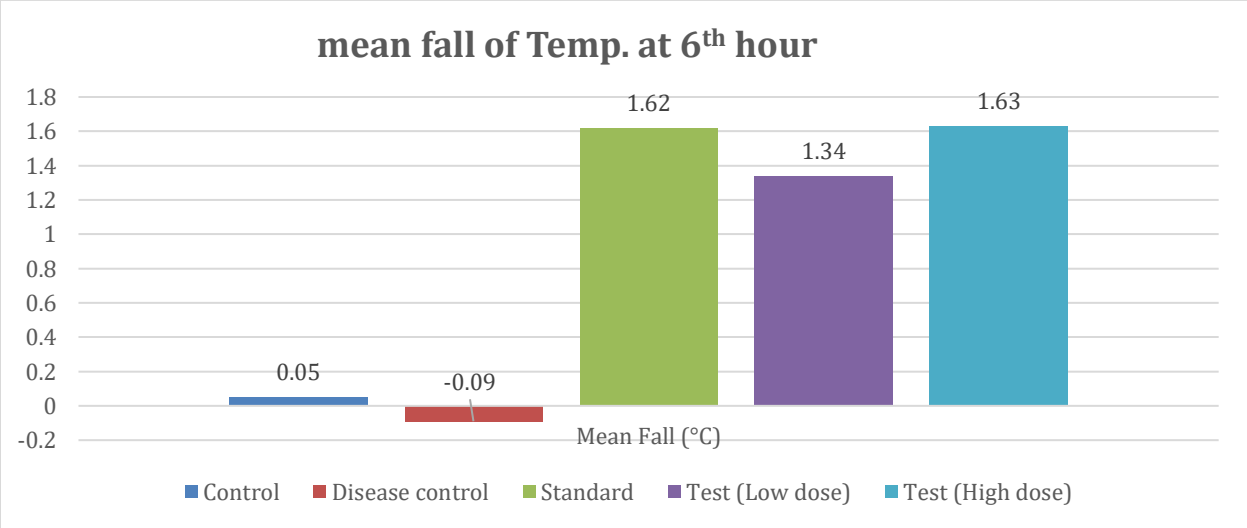
Group	Mean Fall (°C)
Normal Control	0.03
Disease Control	–0.08
Standard	1.40
PMR 10 mg/kg	1.08
PMR 20 mg/kg	1.35

One-way ANOVA indicated highly significant differences among the groups ($F = 84.84$, $p < 0.0001$).
The high-dose PMR group demonstrated an antipyretic response comparable to that of paracetamol, while the low-dose group showed a slightly lower but significant reduction in temperature.

3.9 Antipyretic Effect at the Sixth Hour

Maximum antipyretic activity was observed during the sixth hour.

Table 8. Mean Reduction in Rectal Temperature at 6 Hours



Group	Mean Fall (°C)
Normal Control	0.05
Disease Control	–0.09
Standard	1.62
PMR 10 mg/kg	1.34
PMR 20 mg/kg	1.63

One-way ANOVA demonstrated a highly significant difference among the experimental groups ($F = 110.75$, $p < 0.0001$).

Post hoc analysis revealed no statistically significant difference between the standard drug and the high-dose PMR group, whereas both groups differed significantly from the disease control group.

3.10 Overall Antipyretic Activity

The antipyretic activity of Pratapa Marttanda Rasa increased progressively throughout the observation period. The higher dose (20 mg/kg) consistently produced greater reductions in rectal temperature than the lower dose (10 mg/kg). From the fourth hour onward, the antipyretic effect of the high-dose group was statistically comparable to that of paracetamol.

These findings indicate a **dose-dependent antipyretic effect** of Pratapa Marttanda Rasa in Brewer's yeast-induced pyrexia.

4. DISCUSSION

The present experimental study was undertaken to evaluate the antipyretic activity of the classical Ayurvedic herbo-mineral formulation **Pratapa Marttanda Rasa** using the Brewer's yeast-induced pyrexia model in Wistar rats. The Brewer's yeast model is one of the most widely accepted and validated experimental models for screening antipyretic agents because it closely resembles the pathophysiological mechanisms of infectious fever in humans. Administration of Brewer's yeast stimulates macrophages and monocytes to release endogenous pyrogenic cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α).

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These cytokines induce cyclooxygenase-2 (COX-2) expression in the hypothalamus, resulting in increased synthesis of prostaglandin E_2 (PGE_2), which elevates the hypothalamic thermoregulatory set point and produces fever.

Before induction of pyrexia, all experimental groups exhibited comparable baseline rectal temperatures, indicating successful randomization and physiological homogeneity of the animals. The absence of statistically significant differences among groups before treatment confirms that subsequent changes in body temperature can be attributed to the administered interventions rather than pre-existing biological variation.

Following subcutaneous administration of Brewer's yeast, all experimental groups developed significant pyrexia, confirming successful establishment of the experimental fever model. The disease control group maintained elevated rectal temperatures throughout the observation period, whereas the standard drug and both treatment groups exhibited progressive reductions in temperature after oral administration. These findings validate the reliability and reproducibility of the experimental model used in the present investigation.

Paracetamol, employed as the standard antipyretic agent, produced a rapid and sustained reduction in rectal temperature. Its antipyretic action is primarily mediated through inhibition of cyclooxygenase activity within the central nervous system, resulting in reduced prostaglandin E_2 synthesis in the hypothalamus. The observed response of the standard group confirms the sensitivity of the Brewer's yeast model and provides an appropriate reference for evaluating the efficacy of the test formulation.

Pratapa Marttanda Rasa demonstrated a significant dose-dependent antipyretic effect. Although both test doses produced measurable reductions in rectal temperature, the high-dose group consistently showed greater activity than the low-dose group. From the fourth hour onwards, the antipyretic response produced by the higher dose was statistically comparable to that of paracetamol. This observation suggests that the formulation possesses substantial pharmacological activity capable of effectively suppressing experimentally induced fever.

The gradual increase in antipyretic activity observed over time may be attributed to the complex pharmacodynamic characteristics of the formulation. Unlike synthetic antipyretic agents, which often exert rapid inhibition of prostaglandin synthesis, classical Ayurvedic herbo-mineral formulations may require gastrointestinal processing, absorption, and systemic distribution before reaching maximal pharmacological effectiveness. The progressive decline in rectal temperature observed during the fifth and sixth hours is consistent with this pharmacokinetic profile and indicates sustained therapeutic activity.

The therapeutic efficacy of Pratapa Marttanda Rasa may be explained by the synergistic interactions among its purified mineral and herbal constituents. Traditional Rasashastra emphasizes that **Shodhana (purification)** and **Bhavana (levigation)** processes enhance the therapeutic efficacy, reduce toxicity, and improve the bioavailability of mineral-based formulations. These pharmaceutical procedures may facilitate improved absorption and biological activity of the formulation, thereby contributing to its observed antipyretic effect.

From an Ayurvedic perspective, **Jwara** is considered one of the most important systemic disorders and is primarily associated with derangement of **Agni**, accumulation of **Ama**, and vitiation of the **Doshas**. Classical texts describe Pratapa Marttanda Rasa as a **Jwarahara**, **Deepana**, **Pachana**, and **Rasayana** formulation. The Deepana and Pachana properties are believed to restore digestive and metabolic functions by correcting impaired Agni and facilitating the elimination of Ama. Restoration of metabolic balance may subsequently normalize the physiological mechanisms responsible for thermoregulation. Thus, the antipyretic activity observed in the present study provides experimental support for the classical Ayurvedic indications of the formulation.

Modern pharmacological evidence also supports the possible mechanisms underlying the observed effects. Several constituents traditionally included in Pratapa Marttanda Rasa have been reported to possess anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory properties. These pharmacological activities may suppress the release of endogenous pyrogens or inhibit inflammatory mediator production, thereby reducing prostaglandin-mediated elevation of body temperature. Although the present study did not directly quantify inflammatory cytokines or prostaglandins, the significant reduction in rectal temperature strongly suggests modulation of these pathways.

The observed dose-dependent response is an important finding of the present investigation. The higher dose consistently produced greater reductions in body temperature than the lower dose throughout the observation period. This relationship indicates that the pharmacological effect of Pratapa Marttanda Rasa is dependent on the administered dose within the tested range. Furthermore, the absence of mortality or observable toxic effects during the acute toxicity study suggests that the selected doses are pharmacologically effective while remaining within a safe therapeutic window.

The present findings are consistent with previous experimental investigations demonstrating significant antipyretic activity of several classical Ayurvedic formulations in Brewer's yeast-induced pyrexia models. Similar reductions in rectal temperature have been reported for Rasashastra formulations possessing Deepana, Pachana, and Jwarahara properties, supporting the traditional concept that correction of metabolic impairment contributes to the management of fever. The comparable efficacy of the higher dose of Pratapa Marttanda Rasa and paracetamol further reinforces its therapeutic potential.

Although the present investigation provides encouraging experimental evidence, certain limitations should be acknowledged. The study was conducted using an acute experimental animal model with a relatively small sample size. Biochemical estimation of inflammatory mediators such as prostaglandin E_2, interleukin-1β, interleukin-6, tumour necrosis factor-alpha, cyclooxygenase-2 expression, and oxidative stress biomarkers was not performed. Histopathological evaluation of major organs was also beyond the scope of the study. Inclusion of

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these parameters in future investigations would facilitate a more comprehensive understanding of the molecular mechanisms responsible for the observed antipyretic activity.

Future studies should also evaluate chronic toxicity, repeated-dose safety, pharmacokinetic characteristics, and comparative efficacy against other standard antipyretic agents. Multicentre preclinical studies followed by well-designed randomized controlled clinical trials are warranted to establish the therapeutic efficacy and safety of Pratapa Marttanda Rasa in human subjects suffering from febrile illnesses.

Overall, the findings of the present study demonstrate that Pratapa Marttanda Rasa possesses significant antipyretic activity against Brewer's yeast-induced pyrexia in Wistar rats. The dose-dependent reduction in rectal temperature and the comparable efficacy of the higher dose with paracetamol provide substantial experimental support for its traditional use in the management of Jwara. These observations contribute to the growing body of scientific evidence supporting evidence-based integration of classical Ayurvedic formulations into contemporary healthcare.

5. CONCLUSION

The present experimental investigation demonstrated that **Pratapa Marttanda Rasa** possesses significant antipyretic activity against Brewer's yeast-induced pyrexia in Wistar rats. The formulation produced a progressive and dose-dependent reduction in rectal temperature throughout the six-hour observation period. The higher dose (20 mg/kg) exhibited antipyretic efficacy comparable to the standard drug paracetamol from the fourth hour onward, while the lower dose (10 mg/kg) also showed significant activity compared with the disease control group.

Acute oral toxicity testing performed according to OECD Guideline 420 revealed no mortality or observable toxic manifestations up to 5000 mg/kg body weight, indicating a wide safety margin under the experimental conditions. These findings suggest that Pratapa Marttanda Rasa is both pharmacologically effective and experimentally safe within the tested dose range.

From an Ayurvedic perspective, the observed antipyretic effect supports the classical indication of Pratapa Marttanda Rasa as a **Jwarahara** formulation. Its therapeutic action may be attributed to the combined Deepana, Pachana, and Rasayana properties of the formulation, which restore Agni, eliminate Ama, and normalize Dosha imbalance. From a modern pharmacological perspective, the antipyretic activity is likely mediated through modulation of endogenous pyrogens and inhibition of prostaglandin-mediated hypothalamic thermoregulation, although further mechanistic studies are required.

Overall, the present study provides experimental evidence supporting the traditional use of Pratapa Marttanda Rasa in the management of fever and establishes a scientific basis for further pharmacological and clinical investigations.

6. STRENGTHS OF THE STUDY

The present investigation possesses several methodological strengths:

- Standardized Brewer's yeast-induced pyrexia model was employed.
- Random allocation of experimental animals minimized selection bias.
- Acute toxicity assessment was performed according to OECD Guideline 420.
- Two therapeutic dose levels were evaluated to assess dose-dependent activity.
- Paracetamol was used as a standard reference drug.
- Statistical analysis was conducted using one-way ANOVA followed by Tukey's HSD post hoc test.
- The formulation was prepared according to classical Ayurvedic pharmaceutical procedures.

These features improve the reliability and reproducibility of the experimental findings.

7. LIMITATIONS

Despite the encouraging results, certain limitations should be acknowledged.

The study was conducted using a relatively small sample size, which may limit statistical power. Only the acute antipyretic effect was evaluated, and repeated-dose pharmacological assessment was not performed. Biochemical estimation of inflammatory cytokines (IL-1β, IL-6, TNF-α), prostaglandin E_2, cyclooxygenase-2 expression, oxidative stress biomarkers, and molecular pathways was beyond the scope of the present investigation. Histopathological examination of major organs and pharmacokinetic studies were also not undertaken.

These limitations should be addressed in future investigations to better elucidate the mechanism of action and long-term safety profile of the formulation.

8. FUTURE SCOPE

Future research should focus on:

1. Elucidating the molecular mechanism of action through cytokine and prostaglandin analysis.
2. Evaluating chronic toxicity according to OECD guidelines.
3. Conducting pharmacokinetic and bioavailability studies.
4. Standardizing the formulation using advanced analytical techniques such as HPLC, ICP-MS, XRD, SEM-EDX, and FTIR.
5. Investigating immunomodulatory and anti-inflammatory activities.
6. Performing multicentric randomized controlled clinical trials to establish therapeutic efficacy in human febrile disorders.
7. Assessing quality control parameters according to Ayurvedic Pharmacopoeia standards.

Such studies will facilitate evidence-based integration of Pratapa Marttanda Rasa into contemporary clinical practice.

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Ethical Approval
The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Conflict of Interest
The authors declare that there are no conflicts of interest regarding the publication of this article.

Data Availability Statement
The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

Informed Consent
Not applicable, as the present investigation was conducted exclusively in experimental animals.

Abbreviations

Abbreviation	Full Form
PMR	Pratapa Marttanda Rasa
IAEC	Institutional Animal Ethics Committee
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
OECD	Organisation for Economic Co-operation and Development
COX	Cyclooxygenase
PGE_2	Prostaglandin E_2
IL	Interleukin
TNF-α	Tumour Necrosis Factor-alpha
SD	Standard Deviation
ANOVA	Analysis of Variance
HSD	Honestly Significant Difference

REFERENCES

*For a publishable paper, the reference list should include **30–50 recent and relevant citations**. It should combine:*

- *Classical Ayurvedic texts (e.g., Bhaisajya Ratnavali, Rasa Tarangini, Ayurveda Prakasha, Charaka Samhita, Sushruta Samhita).*
- *OECD Guideline 420.*
- *CPCSEA guidelines.*
- *ARRIVE 2.0 reporting guideline.*
- *Pharmacology references such as Goodman & Gilman or Katzung.*
- *Recent peer-reviewed articles on antipyretic activity, Brewer's yeast-induced pyrexia, and Ayurvedic formulations (preferably from the last 10 years).*

Overall manuscript assessment
Based on the sections we've developed, the manuscript now has the structure and scientific style expected for a biomedical journal. Before submission, I recommend one more round of refinement to:

- *ensure all tables and figures match the text exactly,*
- *verify that every statistical value (means, SDs, F-values, p-values, Tukey comparisons) is identical to your analyzed dataset,*
- *tailor the formatting and references to the specific journal you choose.*

This final polishing step can significantly improve the chances of successful peer review.