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An *in-vivo* study to assess the antipyretic activity of an ayurvedic herbo- mineral formulation *Sannipata Bhairava Rasa*

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Fever, or pyrexia, is a physiological response triggered by infectious and non-infectious stimuli, primarily mediated by prostaglandin E2 (PGE2) in the brain. Ayurveda describes fever (*Jwara*) as a systemic disturbance which effects the body, mind, and sensory organs. Although several Ayurvedic formulations are traditionally recognized for their antipyretic potential, their clinical relevance has diminished due to lack of scientific validation. Addressing this gap, our study was aimed at evaluating the antipyretic activity of *Sannipata Bhairava Rasa*, a herbo-mineral formulation from *Bhaishajya Ratnavali* (*Jwaradhikara*). This study represents the first scientific investigation on this formulation. *Sannipata Bhairava Rasa* was prepared following classical guidelines. The study was conducted in two phases: acute toxicity study and antipyretic evaluation. Acute toxicity was assessed in six Wistar albino rats as per OECD Guideline 423. Antipyretic activity was tested using Brewer's yeast-induced pyrexia in Wistar albino rats divided into five groups (n=6), maintained under standard laboratory conditions. The control group received no treatment, while the standard group received Paracetamol (150 mg/kg). Test groups received *Sannipata Bhairava Rasa* at 100 mg/kg, 200 mg/kg, and 400 mg/kg. Statistical analysis was performed using R-ANOVA and post hoc Bonferroni tests. Acute toxicity assessment demonstrated that a single 2000 mg/kg dose of *Sannipata Bhairava Rasa* was non-toxic. The test groups exhibited dose-dependent antipyretic effects, with the highest efficacy observed at 400 mg/kg. These findings suggest that *Sannipata Bhairava Rasa* exhibits significant antipyretic activity in Wistar albino rats, with maximum efficacy at 400 mg/kg, supporting its potential therapeutic application.

Keywords: Acute toxicity, Antipyretic activity, *Jwara*, Pyrexia, *Sannipata Bhairava Rasa*

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Fever is one of the most frequently observed conditions in medical practice. It occurs either as a primary disease or as a secondary sign of other conditions. In Ayurveda, *Jwara* denotes fever, but its scope extends beyond the modern concept of elevated body temperature. It is primarily defined as a pathological state afflicting both body and mind, characterized by *Santāpa* (elevated body heat), accompanied by chills, discomfort, and a pervasive sense of distress[1]. Rather than appearing as a disease in itself, most of the time it appears as a symptom of an underlying illness. Many antipyretic formulations are mentioned in ayurvedic classics. Many of these formulations might have excellent therapeutic efficacy but due to the lack of scientific documentation regarding their function, significance, and effectiveness, most of these formulations are gradually getting out of practice. *Sannipata Bhairava Rasa* is one such formulation with excellent combination of herbal and mineral drugs having *Jwarahara* (antipyretic) property as per classical Ayurvedic texts. The formulation consists of *Shudha Hingula* (*Cinnabar*), *Shudha Gandhaka (Sulphur)*, *Shudha Vatsanabha* (*Aconitum chasmanthum*), *Shudha Dhaturabeeja* (*seeds of Datura metel*), and *Shudha Tankana* (*Borax*), which are triturated with *Jambeera Swarasa* (fresh lime juice) to form 125 mg pills. No research activities or *in-vitro/in-vivo* studies have been conducted on this formulation so far. However individual toxicity study of some of the ingredients in this formulation were done previously. As per previous research works it was found that *Shodhita Vatsanabha* have no acute toxicity when administered at a dose of 300 mg/kg[2], and *Shodhita Tankana* by oral route with doses upto 1.8 mg/kg did not produce any signs of toxicity/death in rats, suggesting a LD50 above 1.8 mg/kg[3].

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The current study on the antipyretic activity of *Sannipata Bhairava Rasa* represents a dedicated effort to evaluate the safety and efficacy of this formulation.

Materials and Methods

Selection and authentication of the raw drugs

The required raw drugs were collected from authorised local vendor in Taliparamba, Kannur. The mineral substances *Hingula* (cinnabar), *Gandhaka* (sulphur), and *Tankana* (borax) were identified and authenticated by the Department of *Rasashastra and Bhaishajya Kalpana*, while the herbal drugs *Dhatura* (seeds of *Datura metel*) and *Vatsanabha* (tuber of *Aconitum chasmanthum*) were identified based on their morphological characteristics by the Department of *Dravyaguna*, Government Ayurveda College, Kannur.

Preparation of Sannipata Bhairava Rasa[4]

To ensure the quality of this formulation, each ingredient was subjected to *Shodhana* (purification). *Shodhana* of *Hingula* (Cinnabar) was done by trituration in *Ardraka Swarasa* (ginger juice) 7 times[5].*Gandhaka* (Sulphur) was purified using cow's ghee and milk as per the classical texts[6]. *Shodhana* of *Vatsanabha* (tuber of *Aconitum chasmanthum*) was done by the method of *Atapasthapana* in *Gomutra* (keeping in cow's urine) for 7 days[7]. Then it was washed with hot water and the outer layer was removed. *Shodhana* of *Tankana* (Borax) was done by *Bharjana* the method in which it is fried in iron kadai till it bloomed and the crackling sound disappeared[8]. *Dhaturabeeja* (*seeds of Datura metel*) was purified by *Swedana* in *Dola Yantra* for one *Yama* (3 h) with cow milk as the medium[9]. Later, it was washed with warm water.

The purified raw drugs were powdered separately and passed through a No. 85 sieve (180 µm aperture) to ensure uniform particle size. The powdered materials were taken in the following proportion: *Shudha Hingula* (27 g), *Shudha Gandhaka* (12 g), *Shudha Vatsanabha* (12 g), *Shudha Dhatura* (19 g), *Shudha Tankana* 6.5 g). All the powdered materials were mixed thoroughly and was taken in a grinding stone and sufficient quantity of *Nimbu Swarasa* (lemon juice) was poured till the powder gets completely immersed. It was triturated until pill rolling consistency was obtained. Pills weighing 125 mg were rolled out of it and dried in shade.

Experimental study

The study was carried out at Animal House, S A Raja Pharmacy College, Vadakkangulam, Tirunelveli. Wistar strain albino rats weighing between 150-200 g, were selected from Animal house, S A Raja Pharmacy College, Tirunelveli. The rats were maintained under strict laboratory conditions. The temperature in the experimental room was around 24ºC (+3º). Humidity was maintained between 40-70%. Lighting was natural, the sequence being 12 h dark/light cycle. The rats were individually housed in well-ventilated polypropylene cages with paddy husk bedding for 7 days prior to dosing to allow them to acclimatize to the laboratory environment. Animals were provided standard food pellets and purified water *ad libtum*.

Acute oral toxicity study

The acute toxicity study was conducted following the guidelines set by the Committee for Control and Supervision of Experiments on Animals (CCSEA) and the Organization for Economic Co-Operation and Development (OECD) 423.

Young, healthy adult female Wistar Albino rats, weighing between 150-200 g, were allocated into two groups, with 3 animals in each group. As the drug is insoluble in water, 0.5% Carboxy methyl cellulose (CMC) was taken as the vehicle. The CMC was calculated for rat dose of 5 mL/kg body weight. Animals in control group were administered with carboxymethyl cellulose 5 mL/kg (by mixing 0.5 g of Carboxy methyl cellulose in 100 mL of distilled water) and animals in trial group were administered with test drug 2000 mL/kg.

After dosing, the animals were closely observed for mortality and abnormal clinical signs. They were checked at least once during the first 30 min, periodically throughout the first 24 h-with special attention during the first 4 h-and daily for the following 14 days.

Histopathological studies

On 14th day both control and trial groups animals are sacrificed to know the significant target organ toxicity. After overnight fasting, the rats were euthanized under Xylazine + Ketamine (16 + 100 mg/kg I.M.) and subjected to gross pathological examination.

Antipyretic activity

30 healthy male Wistar rats, with body weights ranging from 150 to 200 g, were divided into five groups, each consisting of 6 rats. The initial rectal temperature of all the rats was recorded using a digital thermometer. Pyrexia was induced by administering a subcutaneous injection of 10 mL/kg of a 20% suspension of Brewer's yeast. The injection site was

gently massaged to ensure the suspension spread beneath the skin. Immediately after the yeast administration, food was withheld for 18 h post-challenge. Rectal temperatures were recorded every hour for 18 h. Only animals that exhibited at least a 1°C rise in body temperature were included in the experiment. Since all the animals experienced a rise in body temperature, they were selected for the study. The test drug and standard drug were administered orally using an intragastric tube. Rectal temperatures were recorded again at ½, 1, 2 and 3 h after dosing.

Standard drug: Paracetamol (150 mg / kg body weight)

Test drug: *Sannipata Bhairava Rasa*

No mortality was observed with the test drug at dose of 2000 mg/kg.

Therefore, calculating the effective dose using the formula, effective dose = $1/10^{th}$ of the $LD50^{10}$.

Effective dose, X = 2000 mg/kg/ 10 = 200 mg/kg bd wt.

Low dose = X/2 = 200 mg/kg/2 = 100 mg/kg bd wt.

High dose = 2X = 2 x 200 mg/kg = 400 mg/kg bd wt.

The grouping of rats and dose administration for the antipyretic study are shown in Table 1.

Statistical evaluation

The result is presented as mean ± standard deviation. Statistical analysis was performed using the Repeated Measures Analysis of Variance (R-ANOVA) test and post hoc Bonferroni test.

Results

Acute toxicity study

In accordance with the OECD 423 guidelines for acute toxicity studies, no mortality or signs of toxicity were observed in the animals treated with *Sannipata Bhairava Rasa* at an oral dose of 2000 mg/kg. There were no indications of writhing, tremors, seizure, or hind limb paralysis. Respiratory activity, urinary output and response to sensory stimuli was normal. Additionally, the rats showed no abnormalities in their skin, fur, eyes, mucous membranes, or overall behaviour.

Table 1 — Grouping of Rats for antipyretic study

Groups	Administration
Control	CMC (oral) + Yeast (subcutaneously)
Standard	Paracetamol 150 mg/kg (oral) + Yeast (subcutaneously)
Sannipata Bhairava Rasa	100 mg/kg+ CMC (oral) + Yeast (subcutaneously)
	200 mg/kg+CMC (oral)+ Yeast (subcutaneously)
	400 mg/kg+CMC (oral)+ Yeast (subcutaneously)

Histopathology results

Liver-liver shows normal hepatocytes. There is no evidence of necrosis or micro vesicular steatosis, sinusoidal haemorrhages and dilatations.

Kidney- kidney shows normal tubules.

Heart -Section from the myocardium shows normal myocardial fibres and myocytes. There is no evidence of inflammation or necrosis, nuclear fatty infiltration, oedema, inflammatory cells. Normal fragmentation of muscle fibres is seen when compared with the control treated rat.

Representative histopathology images of the liver, kidney, and heart are shown in Figure 1.

Antipyretic activity

Subcutaneous yeast injection resulted in an increase in the rectal temperature of rats 18 h post-administration. Oral administration of *Sannipata Bhairava Rasa* at 200 mg/kg and 400 mg/kg significantly reduced temperature after 2 h of treatment compared to the control group. The 400 mg/kg dose exhibited antipyretic activity comparable to the standard drug, paracetamol (150 mg/kg) (Table 2 & Fig. 2).

Discussion

The present study was undertaken to evaluate the acute toxicity and antipyretic activity of the Ayurvedic herbo-mineral formulation *Sannipāta Bhairava Rasa*. In the acute toxicity assessment, the formulation did not produce any signs of toxicity or mortality even at a limit dose of 2000 mg/kg. Histopathological evaluation of vital organs including the liver, kidney, and heart revealed no abnormalities, indicating the safety of the formulation at therapeutic and high doses. These findings indicate that *Sannipāta Bhairava Rasa*, when

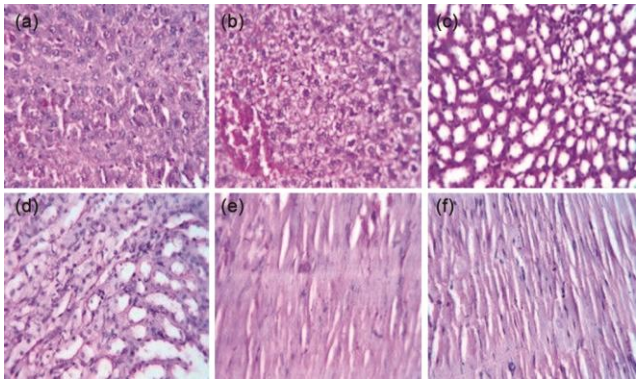

Fig. 1 — Histopathology Images, (a) Liver (control) (b) Liver (test) (c) Kidney (control) (d) Kidney (test) (e) Heart (control) (f) Heart (test)

prepared with ingredients subjected to appropriate *Shodhana* (purification) processes, exhibits biological compatibility and does not produce toxicity.

Fever begins when exogenous pyrogens such as microbial components stimulate immune cells to release endogenous cytokines like IL-1, IL-6, and TNF-α.[11]. These cytokines act on the hypothalamus, leading to COX-2-mediated production of prostaglandin E_2 (PGE_2), which resets the body's thermoregulatory set point, thereby inducing fever[12]. In this study, the antipyretic efficacy of the formulation was evaluated using the well-established Brewer's yeast-induced pyrexia model in rats, which mimics the prostaglandin-mediated fever pathway.

According to Ayurvedic principles, *Jwara* (fever) is considered a manifestation of systemic imbalance caused by vitiation of *Tridoṣhas* (Vāta, Pitta, and Kapha), often resulting from *Mithya Āhāra-Vihāra* (improper diet and lifestyle). The resulting *Mandagni* (weak digestive fire) leads to the formation of *Āma* (toxins), which blocks the *Srotas* (body's subtle channels), impairs sweating, and generates *Santāpa* (systemic heat)[13]. Effective management of *Jwara*, therefore, includes the use of *Dīpana* (digestive stimulants), *Pācana* (digestive correctives), and *Srotoshodhana* (channel-purifying agents) therapies.

Sannipata Bhairava Rasa contains potent ingredients like *Shuddha Hingula*, *Shuddha Gandhaka*, *Shuddha Tankana*, *Shuddha Vatsanabha*, and *Shudha Dhatura*, all processed through classical *Shodhana* methods to ensure safety and enhance efficacy. *Shuddha Hingula* and *Shuddha Vatsanabha* are noted for their *Jvarāghna* (antipyretic) properties[14,15]. *Hingula*, *Gandhaka*, and *Vatsanabha* possess *Dīpana* (digestive stimulant) and *Pācana* (digestive corrective) actions, aiding *Amapācana* (digestion of ama) and restoring digestive fire for systemic detoxification[15-17]. Their *Uṣṇa* (hot) and *Tīkṣṇa* (sharp) qualities help remove obstructions. *Vatsanabha* and *Dhatura*, as *Viṣa Dravyas*, exhibit

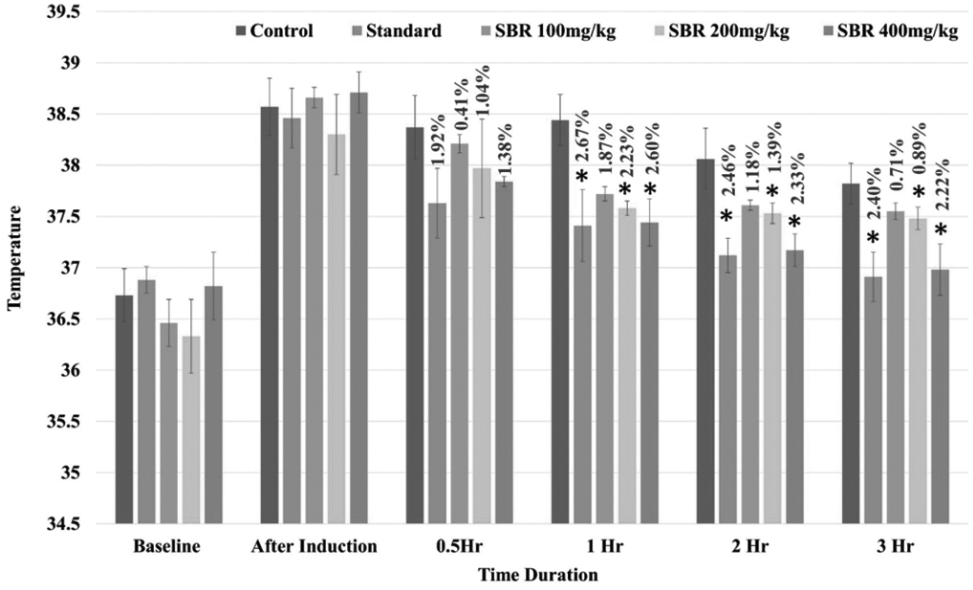

Fig. 2 — Antipyretic activity of *Sannipata Bhairava Rasa*. Data represent Mean + SD, n=6.*p < 0.05 vs control; based on repeated measures ANOVA followed by Bonferroni post hoc test. % = percentage fall in temperature from post-induction

Table 2 — Antipyretic activity of *Sannipata Bhairava Rasa*

Group	Dose (mg/kg)	Baseline (°C)	After induction (°C)	After treatment (°C)			
				30 min	1 h	2 h	3 h
Control	–	36.73±0.26	38.57±0.28	38.37±0.31	38.44±0.25	38.06±0.30	37.82±0.20
Standard (Paracetamol)	150	36.88±0.13	38.46±0.29	37.63±0.34*	37.41±0.35*	37.12±0.17*	36.91±0.24*
Sannipāta Bhairava Rasa	100	36.46±0.23	38.66±0.10	38.21±0.09	37.72±0.07	37.61±0.05	37.55±0.08
	200	36.33±0.36	38.30±0.39	37.97±0.48*	37.58±0.07*	37.53±0.10*	37.48±0.11*
	400	36.82±0.33	38.71±0.20	37.84±0.05*	37.44±0.23*	37.17±0.16*	36.98±0.25*

(Values are Mean ± SD; n = 6) *p < 0.05 vs control; based on repeated measures ANOVA followed by Bonferroni post hoc test.

Vyavāyī (fast-spreading), *Vikāśī* (expanding), *Aśukārī* (quick-acting), and *Sūkṣma* (subtle) qualities, enabling deep tissue penetration and channel clearance to relieve *Swedavarodha*[18] (inhibition of sweating). *Vatsanabha's Sweda-janana* (diaphoretic) action induces sweating, reducing *Santāpa* (heat/discomfort) in fever[15]. Additionally, its *Yogavāhī* (catalytic) nature enhances the effectiveness of the other ingredients in the formulation[15].

Modern pharmacological findings further validate the classical rationale. *Vatsanabha* (*Aconitum chasmanthum*) contains highly toxic diester diterpenoid alkaloids especially aconitine, along with other compounds such as indaconitine, chasmaconitine, chasmanthinine, chasmanine, and homochasmaconitine[19]. However, classical *Shodhana* (detoxification) with cow's urine has been shown to significantly reduce this toxicity. High-performance liquid chromatography (HPLC) studies confirm a notable decrease in aconitine content after purification, while thin-layer chromatography (TLC) findings indicate the conversion of toxic diester alkaloids into relatively safer monoester derivatives such as benzoylaconine and veratroyl pseudoaconine[2]. The converted alkaloids continue to exhibit analgesic and anti-inflammatory actions, supporting their contribution to fever control[20].

Datura species contain toxic tropane alkaloids—atropine, hyoscyamine, and scopolamine-with strong anticholinergic effects. Purification through *Dola Yantra Swedana* in cow's milk for about three hours reduces hyoscyamine by 70-90% and almost eliminates scopolamine, as confirmed by HPLC and GC-MS, ensuring safety while maintaining therapeutic value[21].

In addition, *Citrus limon* (lemon juice) used in the *Bhāvana* (trituration) process is rich in vitamin C and flavonoids like hesperidin and eriocitrin, which exert antioxidant and immune-regulating effects, thereby assisting in the control of inflammatory fever responses[22-24]. *Zingiber officinale* (ginger juice) used in the *Shodhana* of *Hingula* contributes gingerols and shogaols known to inhibit prostaglandin synthesis, further enhancing antipyretic potential[25,26].

The results of the experimental study, analysed using repeated measures ANOVA and Bonferroni post hoc tests, revealed a dose-dependent antipyretic effect of *Sannipāta Bhairava Rasa*. While the 100 mg/kg dose showed a mild reduction in rectal temperature, the 200 mg/kg and 400 mg/kg doses demonstrated statistically significant effects ($p<0.05$). Particularly, the 400 mg/kg dose produced a temperature-lowering response comparable to that of standard paracetamol ($p<0.05$), indicating promising therapeutic action. The control group exhibited only a slight and statistically insignificant decrease in temperature, whereas paracetamol and the test formulation groups showed rapid and sustained antipyretic responses across all time points. These outcomes confirm that the formulation not only possesses antipyretic activity but does so in a manner that is both effective and predictable across a range of doses.

Comparative evaluation with other classical herbomineral formulations like *Mrityunjaya Rasa* and *Suryaprabha Gulika* further supports these findings; prior research has shown that *Mrityunjaya Rasa* produced significant antipyretic effects ($p<0.001$) within 30-60 min of administration, while *Suryaprabha Gulika* exhibited antipyretic activity comparable to the standard drug in brewer's yeast-induced pyrexia in Wistar rats[27,28]. Similar to *Sannipāta Bhairava Rasa*, both *Mrityunjaya Rasa* and *Suryaprabha Gulika* contain core ingredients such as *Shuddha Hingula* (*or shudha Parada*), *Shuddha Gandhaka*, and *Shuddha Vatsanabha*, with shared components like *Trikatu* (*Piper nigrum, Piper longum, Zingiber officinale*) in *Suryaprabha Gulika* and *Mrityunjaya Rasa*, and lemon juice used for *Bhavana* (trituration) in both *Sannipata Bhairava Rasa* and *Suryaprabha Gulika.* However, the current study distinguishes itself by incorporating a detailed histopathological safety assessment, early time-point measurements (at 30 min, 1-,2, and 3 h post-dose) and broader dose–response design (100, 200, and 400 mg/kg). While the findings are promising, they are based on an animal model and lack long-term toxicity evaluation, warranting further clinical studies.

The formulation's pharmacological profile is consistent with both Ayurvedic principles and modern fever mechanisms, supporting its therapeutic relevance. These results suggest that, when prepared with properly purified ingredients, *Sannipāta Bhairava Rasa* may serve as a safe and effective complementary option for fever management. Further studies can be done to assess its efficacy in diseases such as Dengue, Malaria, Typhoid which usually presents with fever. Also, the formulation can be evaluated for antibacterial or antiviral activity as well.

Conclusion

Sannipāta Bhairava Rasa was well-tolerated, with no signs of toxicity or adverse effects observed

during the experimental period. The double therapeutic dose elicited the most significant antipyretic response, demonstrating efficacy comparable with the standard drug.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

Author Contributions

R.P.P. and S.V.K conceived and designed the study. The experimental methodology was developed by V.T. and S.S. Data collection was done by RPP. Data analysis was carried out by V.T. The initial draft of the manuscript was prepared by R.P.P., with critical review and editing provided by V.T. and S.V.K. All authors reviewed and approved the final version of the manuscript.

Ethics Approval

The study was approved by the Institutional Animal Ethics Committee (IAEC) of S A Raja Pharmacy College, Vadakkangulam, Tirunelveli, approval no. RPC/AH/IAEC/P-854/2023 and the study was conducted according to Committee for Control and Supervision of Experiments on Animals (CCSEA) guidelines.

Data Availability

Relevant data will be provided by the corresponding author upon reasonable request.

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