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Study Protocol

Double-Blind Randomized Controlled Trial Evaluating the Antipyretic Efficacy of *Panchatikta Kashaya* Rectal Suppository in Children Aged 1–5 Years: Study Protocol

[1]Anjali V Jayan, [2*]Reena K

ABSTRACT:

Background: Fever is a frequent pediatric presentation and, though physiologically protective, may cause adverse outcomes if inadequately treated. Conventional antipyretics are limited by tolerability and challenges in oral administration in young children. Ayurveda describes fever as *Jwara,* arising from impaired *Agni* (digestive fire), *Ama* (metabolic toxin) accumulation, and *Dosha* (humor) imbalance, for which *Tikta-rasa* (bitter taste) predominant formulations are indicated in early stages. *Panchatikta Kashaya*, described in *Chakradatta Jwara Cikitsa*, possesses antipyretic potential but has poor palatability. Rectal delivery, as *Gudavarti* (rectal suppository), offers improved absorption and compliance. This double-blind randomized controlled trial evaluates the antipyretic efficacy of *Panchatikta Kashaya Gudavarti* in children aged 1-5 years with mild to moderate fever, compared with *Amrutottaram Kashaya Gudavarti.* **Objective:** To compare and assess the antipyretic efficacy of a single administration of *Panchatikta Kashaya Gudavarti* with *Amrutottaram Kashaya Gudavarti* (rectal suppositories) in children aged 1-5 years. **Methods:** The ongoing study is a prospective, double-blind, randomized controlled, superiority, single-center, efficacy trial of a total 50 participants diagnosed with *Jwara* (Fever). The trial group will receive single administration of *Panchatikta Kashaya Gudavarti,* rectal suppository of 2 grams, and the antipyretic effect will be assessed 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post-administration based on the reduction in temperature. Control group participants will similarly receive *Amrutottaram Kashaya Gudavarti* of 2 grams, and will be assessed for reduction in temperature in the same way. The primary outcome is the reduction in temperature and other features of fever on GRASP fever chart and graded clinical parameters of *Jwara.* The secondary outcome measure is to note the comparative efficacy of *Panchatikta Kashaya Gudavarti* with *Amrutottaram Kashaya Gudavarti.* **Conclusion:** The study is expected to demonstrate the safety and efficacy of the Ayurvedic intervention *Panchatikta Kashaya Gudavarti* (rectal suppository) in reducing mild to moderate fever.

KEYWORDS: *Amrutottaram Kashaya Gudavarti,* GRASP Fever chart, *Jwara Santapa, Panchatikta Kashaya Gudavarti*, Rectal suppository, Study Protocol.

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Corresponding Author Email: drreenakulkarni@gmail.com

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1. INTRODUCTION

Fever or pyrexia is a common and distressing symptom in pediatric practice, accounting for nearly 70% of outpatient visits. [1] Defined as an elevation in core body temperature due to a rise in the hypothalamic set point, it often indicates an immune response to infection or inflammation. [2] Globally, acute febrile illness affects approximately 20- 30% of children under five years of age, and in India, this age group comprises around 9.7% of the total population. [3] Despite being a physiological defense mechanism, persistent or untreated fever can lead to complications, including dehydration, febrile seizures, and in extreme cases, hyperpyrexia and organ damage. [4] Management typically includes the use of antipyretics, which, although effective, sometimes can result in adverse effects, poor palatability, and limited applicability in children with vomiting, swallowing difficulties, or intolerance to oral medications. [5]

Ayurveda, with its holistic and individualized approach, recognizes fever under the term *Jwara,* which is described as *Rogadhipati* (the king of diseases), due to its ability to affect the body (*deha*), sense organs (*indriya*), and mind (*manas*). [6] *Jwara* (Fever) arises due to the disturbance of *Agni* (digestive fire) and vitiation of *Dosha* (humor), often triggered by improper dietary habits and the accumulation of *Ama* (metabolic toxins), which leads to blockage of the bodily channels and manifests as systemic heat, restlessness, and discomfort. [7]

Classical texts emphasize the use of *Tikta-rasa* (bitter taste) predominant formulations in the management of *Taruna Jwara* (mild fever) to restore *Agni* (digestive fire), digest *Ama* (metabolic toxins), and pacify *Pitta* and *Kapha Doshas*. *Panchatikta Kashaya*, described in *Chakradatta Jwara Chikitsa*, contains *Guduchi (Tinospora cordifolia* (Wild.) Miers), *Kantakari (Solanum xanthocarpum* Schrad & Wendl), *Kiratatikta (Swertia chirata* Buch-Ham), *Shunti (Zingiber officinale* Roscoe) and *Pushkaramula (Inula racemose* Hook.f), which are traditionally indicated for their *Jwaraghna* (antipyretic), *Dipana* (carminative), and anti-inflammatory properties. Experimental and pharmacological studies have demonstrated antipyretic and immunomodulatory effects of its individual components. However, the bitterness of *Kashaya* (medicated decoction) limits pediatric compliance.

Rectal administration offers an effective alternative route, enabling rapid absorption and improved compliance while bypassing first-pass metabolism. Although a preliminary experimental study suggests promising antipyretic activity of *Panchatikta Kashaya Gudavarti*, robust clinical evidence in children is limited. In fact, antipyretic efficacy trials on *Jwarahara Gudavarti* are only very few. One study on *Amrutottaram Kashaya Gudavarti* was done with paracetamol suppository as a control reported good antipyretic effect and reported no side effects. [8] Yet another study on efficacy of *Jwarahara Mahakashyaya Gudavarti* on *Jwara santapa* (mild to moderate fever) was done with *Amrutottaram Kashaya Gudavarti* as control in children. [9] In both these studies, *Amrutottaram Kashaya Gudavarti* was safe and results were encouraging. Moreover, it is the only *Gudavarti* used in 2 clinical studies and an experimental study with proven antipyretic efficacy thus, prompting us to select it as a control drug. Additionally, randomized controlled trials involving comparison of various *Jwarahara Gudavarti* is not available. Furthermore, controlled clinical researches over *Gudavarti on Jwara santapa* (mild to moderate fever) in children is less researched. Moreover, such studies can yield in establishing the safety and efficacy of *Ayurveda* formulations on fever using the alternative route in children who are otherwise reluctant to take these bitter medicines orally. Thus, this double blind randomized controlled trial was planned to establish the relative efficacy and safety of *Panchatikta Kashaya Gudavarti* in comparison with *Amrutottaram Kashaya Gudavarti* on the reduction of temperature in children aged 1-5 years with mild to moderate fever.

Hypothesis:

Null Hypothesis (Ho): *Panchatikta Kashaya Gudavarti,* rectal suppository*,* is as efficacious as *Amrutottaram Kashaya Gudavarti,* rectal suppository, in the management of *Jwara Santapa* (mild to moderate fever*)* in children of 1-5 years age group.

Alternate Hypothesis

H1: *Panchatikta Kashaya Guda varti,* rectal suppository is more efficacious as *Amrutottaram Kashaya Gudavarti,* rectal suppository in the management of *Jwara Santapa* (mild to moderate fever) in children of 1-5 years age group.

H2: *Panchatikta Kashaya guda varti,* rectal suppository, is less efficacious than *Amrutottaram Kashaya Gudavarti*, rectal suppository in the management of *Jwara Santapa* (mild to moderate fever) in children aged 1-5 years age group.

Objectives:

Primary Objective:

To compare and assess the antipyretic efficacy of a single administration of *Panchatikta Kashaya Gudavarti* with *Amrutottaram Kashaya Gudavarti* (rectal suppositories) in children aged 1–5 years with *Jvara Santapa* (mild to moderate fever), by evaluating the reduction in axillary temperature and improvement in clinical features of *Jwara* (fever), as assessed using the GRASP Fever Chart and graded clinical parameters over a period of 3 hours.

Secondary Objective:

I. To assess the comparative efficacy of *Panchatikta Kashaya Gudavarti* with *Amrutottaram Kashaya Gudavarti* in reducing the *Jwara santapa* (mild to moderate fever).

II. To study the qualitative parameters of *Panchatikta Kashaya Gudavarti* as per the Ayurveda Pharmacopoeia of India.

2. METHODS

Trial design: Prospective double blind randomized controlled, clinical, superiority, single center, efficacy trial with two study groups, with the trial involving children of 1-5 years diagnosed with mild to moderate fever. Participants in two groups will simultaneously receive Rectal suppository and will be analyzed for an endpoint of 3 hours for reduction in temperature.

Participant Timeline

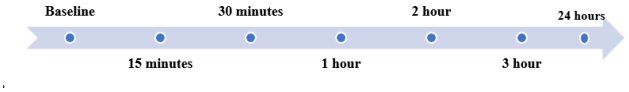

Figure 1: Participant Timeline

Study setting: Outpatient and Inpatient Department of Sri Dharmasthala Manjunatheshwara Institute of Ayurveda and Hospital (SDMIAH), Bangalore, Karnataka, India

Study duration: The total duration of the clinical study will be 3 hours and the primary outcome (reduction in body temperature) will be assessed over a period of 3hours post intervention for every 15mintues, 30 minutes, 1 hour, 2 hours, and 3 hours and those who respond to the therapy for 3 hours will be followed up for next 24 hours for monitoring recurrence of fever safety and any adverse events. .

Eligibility criteria

ICD - 11 - “MG26”

NAMC Code - “EC-3”

Participants must provide written informed consent before starting any trial.

Inclusion criteria:

1. Children of either gender aged between 1- 5 years.
2. Children presenting with pyrexia of 99.1°F- 102. °F(mild-moderate) were included.
3. Children whose parents or legal guardians provide written informed consent/assent for the trial.

Exclusion criteria:

1. Children presenting with high-grade fever (> 102.2°F).
2. Children who are known case of high-grade fever with an infective origin.
3. Children diagnosed with chronic systemic illness presenting with fever.

4. Children who are known cases of febrile seizures.
5. Children with chronic fever.

Interventions and Comparator:

The study medications for both the intervention and control arms will be procured from a GMP-certified pharmacy (Gloris Biomed Research Centre Private Limited, Chennai), adhering to standard manufacturing guidelines. All raw materials and finished formulations will undergo appropriate quality control testing and standardization in accordance with the Ayurvedic Pharmacopoeia of India, including organoleptic, physicochemical, and phytochemical evaluation to ensure safety, quality, and batch-to-batch consistency. The prepared *Gudavarti* (rectal suppositories) will be individually packed in aluminum foil wrap to maintain stability, prevent contamination, and ensure aseptic conditions. The formulations will be stored at a temperature below 10°C under controlled conditions to preserve their integrity, potency, and safety throughout the study period and will be labeled with the manufacturer's details, batch number, and other relevant specifications. The final preparations will undergo validation for uniformity of weight, consistency, hardness, disintegration time, and pH to ensure suitability for rectal administration. Standard operating procedures will be followed throughout the processes of preparation, packaging, storage, and administration of the suppositories. The trial drug, *Panchatikta Kashaya Gudavarti*, contains *Guduchi (Tinospora cordifolia* (Wild.) Miers*, Kantakari (Solanum xanthocarpum* Schrad & Wendl*), Kiratatikta (Swertia chirata* Buch-Ham*), Shunti (Zingiber officinale* Roscoe) and *Pushkaramula (Inula racemose* Hook.f) prepared as per the classical reference of *Chakradatta Jwara Chikitsa. The* control drug, *Amrutottaram Kashaya Gudavarti*, contains *Guduchi (Tinospora cordifolia* (Wild.) Miers, *Haritaki* (*Terminalia chebula* Retz) and *Shunti* (*Zingiber officinale* Roxb).The *Kashaya* (decoction) for both the trial and control drug will be prepared according to classical guidelines, concentrated, and processed into a solid suppository form

Dose and frequency: Participants in both groups will receive *Gudavarti* (rectal suppository) of 2 g administered via the rectal route under direct supervision. No repeat dosing will be performed during the study period. The intervention group will receive *Panchatikta Kashaya Gudavarti*, while the control group will be administered *Amrutottaram Kashaya Gudavarti*.

Administration protocol: The suppository will be administered per rectally under aseptic precautions by the principal investigator or trained medical personnel. The child will be placed in the left lateral position, and the *Gudavarti* will be gently inserted into the rectum using a gloved hand. Post administration the participant will be observed for retention, expulsion, or any immediate discomfort. Following this, the participant will be monitored for clinical response in terms of reduction in axillary temperature and graded clinical features of *jwara*(fever), at predefined time intervals of 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours. Additionally, a follow-up period of 24 hours will be undertaken to monitor recurrence of fever safety and any adverse event for those participants who respond to the therapy for 3 hours.

Table 1: Intervention and comparator

Sl. No	Age	Dose of control/ trial drug	Route of administration	Time of administration	Assessment
1.	1-5 years	2g	Rectal	Single Administration	Every 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours post administration

Discontinuation/modification criteria: Participants will be monitored for duration of 3 hours for clinical improvement, compliance, and any adverse reaction. In case of any persistent elevation of temperature even after 1 hour, and

any identifiable complications if any, then subjects may be withdrawn from the trial, and the use of rescue medication will be permitted, that is, standard paracetamol suppository (based on per kg body weight). However, the same will be documented in the appropriate Column in the Case Record Form (CRF).

Adherence monitoring and retention plan: Participant adherence will be ensured through direct supervision of drug administration. The *Gudavart*i (rectal suppository) will be administered as a single dose in an outpatient (OPD) or inpatient setting by the principal investigator, ensuring complete compliance and aseptic measures at the time of intervention. Adherence will be further assessed by monitoring the immediate post-administration period for any issues such as expulsion, incomplete retention. Any deviations from the protocol will be systematically recorded and reported. As the intervention involves a single, directly observed administration, only participants whose parents or legal guardians provide informed consent will be enrolled in the study. Parents/caregivers will be instructed to observe the child for fever-related symptoms following administration and to promptly communicate any concerns, changes, or adverse events through telecommunication or digital platforms. Continuous support will be provided to clarify doubts and enhance retention.

Concomitant care

All coexisting illnesses and medications being taken by the participants during the time of recruitment will be noted in the Case Report Form (CRF). Participants will be strictly instructed to avoid self-medication or administration of any additional drugs throughout the study period. If participants experience any symptoms, complaints, or unusual health conditions during the trial, they will be advised to consult the investigating physician for appropriate evaluation and management. Medications that is essential or part of ongoing long-term treatment, provided they do not interfere with the study intervention, will be permitted to continue. However, the administration of any other medications throughout the study period will be strictly restricted. In cases where treatment is required for concurrent ailments, the investigating physician may prescribe the necessary medications, and all such prescriptions will be properly documented in the CRF.

Outcomes: The outcome of reduction in temperature will be compared before and after intervention in every 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours.

Primary outcome measure: Mean Reduction in body temperature from baseline to a 3-hour period, assessed every 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post-intervention, documented on the GRASP Fever Chart.[10] for parameters such as heart rate, respiratory rate, temperature capillary refill time, and traffic light categorisation and graded clinical features of *Jwara* (fever)

Secondary outcome measures: Reduction in graded clinical features of *Jwara*(fever).

Table 2: gives a comprehensive plan of study.

Study event	Baseline	15 minutes	30 minutes	1 hour	2 hours	3 hours	24 hours
Baseline assessment of vitals- -temperature, HR, RR, GRASP FEVER CHART	✔						
Informed consent	✔						
Recruitment	✔						
Demographic profile	✔						
Intervention (3hrs)	✔						

Follow-up 24hrs		✔	✔	✔	✔	✔	✔
Assessment by clinical evaluation, GRASP FEVER CHART, i.e., Temperature, HR, RR, Capillary refill time, traffic light status. Objective parameters	✔	✔	✔	✔	✔	✔	
Drug compliance	✔	✔	✔	✔	✔	✔	✔
Rescue medication (If required)				✔			
Assessment of adverse events		✔	✔	✔	✔	✔	✔

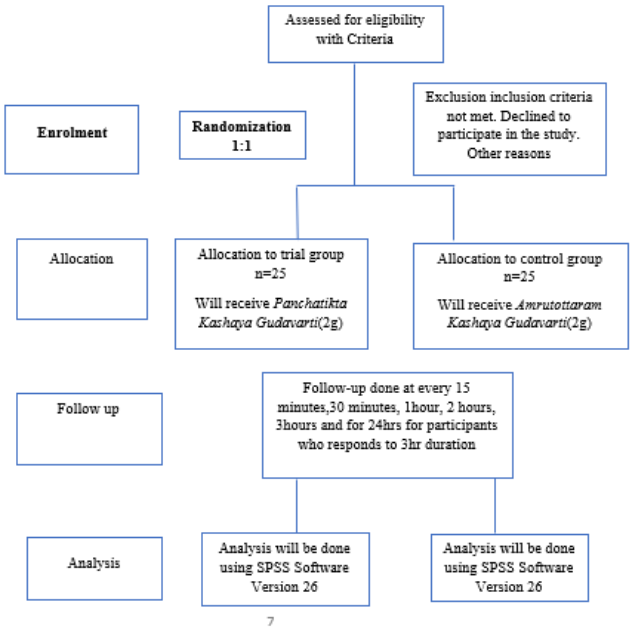

Figure 02: Participant Flow Diagram

Sample size:

The sample size is determined using a standard formula.

The sample size in this trial is calculated based on the "Standard deviation" of the previous clinical study.

N = 2(SD)2 x (Z(1-α) +Zβ)2 / d2

Zα=1.96 for 95% confidence level

Standard deviation = 0.6 from the prior study

Zβ = 0.84 corresponding to 80% power,

Effect size d= 0.5

N = 2 x (0.6)2 x (1.96 + 0.84)2 / (0.5)2

= 2 x 0.36x 7.84 / 0.25

= 22.5

Thus, the minimum required sample size was 23 participants per group, which was rounded up to 25 participants in each group to account for feasibility and ensure adequate power.

Therefore, sample size (N)

N = 25 (in each group)

To document the magnitude of the clinical effect between the two-intervention effect size will be calculated and interpreted as small (0.2), moderate (0.5), and large (0.8). This analysis will be applied to parametric outcome variables to assess the comparative efficacy of the intervention.

Taking into account the feasibility of conducting the study, 25 eligible subjects will be allocated to each group, making the sample size a total of 50 participants.

Unblinding: In case of medical emergency or serious adverse events, unblinding will be carried out by the Supervisor. The allocation code will be securely maintained and accessed only when necessary. The reason and timing of unblinding will be documented.

Recruitment Strategy: Eligible subjects will be screened and recruited from the Outpatient and Inpatient Departments of *Kaumarabhritya* at SDMIAH. Children aged 1- 5 years who satisfy the predefined eligibility criteria will be identified by the investigator. A screening log will be maintained to document the total number of children assessed for eligibility, those included, and those excluded, along with reasons for exclusion. Before enrolment, the parents or legal guardians will receive a Comprehensive account of the study procedures, and participation will be voluntary with written

informed consent/assent. Caregivers will have the right to refuse participation at any stage without affecting the standard care provided. Reasons for refusal, if voluntarily disclosed, will be recorded. Children whose parents or guardians are willing to comply with the study protocol and remain under observation for the required 3-hour period will be included. Participants who withdraw or are lost during the study period will be documented, and reasons for dropout will be recorded. Recruitment will continue until the desired 50 participants is attained.

Randomization: Simple random sampling 1:1 allocation

Sequence generation: Medical faculty in the department who is not involved in the study will produce a computer-generated random sequence and assign participants to either group.

Allocation and concealment: Study subjects will be randomly assigned using a computer-generated random sequence and will be allotted using a sequentially numbered opaque sealed envelope (SNOSE) prepared by an independent medical faculty in the department who is not involved in participant recruitment or assessment. The envelopes will be opened in front of the supervisor before the start of the intervention.

Blinding: The study will be double blind. The trial drug and control drug will be procured from a GMP-certified manufacturing unit and packaged in identical, opaque aluminium foil sachets to ensure uniformity in appearance, texture, and presentation. Each intervention will be labelled with a unique code (A or B) generated and maintained by an independent third party who is not involved in participant enrolment, intervention administration, or outcome assessment. The allocation sequence and corresponding codes will be securely stored and concealed until completion of data analysis. Both participants and the primary investigator will remain blinded to treatment allocation throughout the study duration. Unblinding will be strictly limited to situations of medical necessity, where knowledge of the allocated intervention is essential for participant safety

Methods

The proposed study will be a double blind, interventional, prospective, superiority, randomized controlled clinical trial.

Data collection method:

Data shall be gathered on a specially designed “Case Report Form” (CRF), and the assessment tools. The CRF will be designed based on relevant clinical and diagnostic parameters and will undergo content validation by subject experts. Participants who fulfil the inclusion criteria and diagnostic criteria will be interacted to collect the demographic data, previous medical conditions and will be screened and monitored with the clinical data following administration of the suppository, will be marked using the GRASP FEVER CHART which was developed and practised at UK by PRIMIS at the University of Nottingham in collaboration with Health Innovation Network (HIN). [10] Collection of data and consent will be done solely by the Principal Investigator and data will be collected by direct interrogation with the parents/participants using the standardised CRF to ensure consistency and uniformity in data collection.

Data management

The data will be digitised into a secure electronic database, and access will be restricted to authorised study persons only. The study will be conducted in accordance with standard research and ethical guidelines, including Good Clinical Practice (GCP) and applicable institutional protocols. The evaluation of the collected data will be obtained using SPSS software version 26 to ensure effective data backup. All subjects will receive a unique ID to avoid double data entry. Investigators will review the data for completeness, consistency, and accuracy, and any discrepancies will be cross-verified with source documents. All the personal details of the participants will be kept confidential throughout the study. The study will be conducted independently by the

investigators. The manufacturer of the study medications will have no role in study design, data collection, data analysis, interpretation of results, or manuscript preparation, thereby ensuring scientific integrity and avoidance of bias.

Statistical methods:

Primary Analysis: The collected observations will be compiled using MS Office Excel and subsequently analyzed with IBM SPSS software (Version 26). Participants will be categorized into Intention-to-Treat (ITT) and Per-Protocol (PP) groups for analytical purposes, and Safety-related outcomes will be evaluated using data from the ITT population, whereas the PP population will be considered for assessing the effectiveness of the intervention. Missing data will be handled using appropriate imputation methods such as last observation carried forward (LOCF). Missing data more than 10% will be regarded as dropouts and omitted from the final statistical evaluation. The Per-Protocol PP population will include only those participants who complete the study without major protocol deviations and will be used for assessing treatment effectiveness.

Adjustment analysis will be performed, where necessary, to control for potential confounding variables such as baseline temperature and age using appropriate statistical methods

The "Shapiro–Wilk test" will be used for checking the normality of the dataset before the statistical testing, and if the data demonstrate normal distribution, parametric statistical tests will be utilised; otherwise, appropriate non-parametric tests will be employed. **Descriptive Statistics:** Demographic data and other relevant descriptive information will be analysed with descriptive statistics expressed in Frequency (f), Percentage (%) and Range. Categorical and Ranked data will be expressed in Median and Percentages. Mean and Standard deviation will be used to express the continuous data.

Inferential Statistics: Appropriate Parametric and Non-Parametric statistical tests will be applied to analyze the clinical study results and draw conclusions.

Level of significance: $P<0.05$

Non-parametric test: The subjective data within the group would be analyzed using the Wilcoxon signed-rank test to obtain the difference in treatment before and after. Between the trial and control group, the "Mann-Whitney U test" will be employed. For comparisons of multiple data sets of more than 2 within the same group, "Friedman's test" for non-parametric data would be used.

Parametric test: The objective data, between the groups, would be analyzed using the unpaired t-test, and within the group will be assessed using the paired t-test to assess the change before and after treatment. Repeated observations are measured through the ANOVA test.

Effect size: The Magnitude of the effect size would be calculated with "Cohen's D formula", and the values will be interpreted as small (0.2), moderate (0.5), and large (0.8). This analysis will be applied to parametric outcome variables to assess the comparative efficacy of the interventions.

Data and trial monitoring

The Primary Researcher and the Supervisor will oversee the overall conduct of the trial, ensuring proper participant recruitment, compliance with the treatment regimen, follow-up of participants, and accurate documentation of any side effects. The Data Monitoring Committee, which includes designated members of the Institutional Research Committee and the Departmental Research Committee, who are not directly involved in the conduct of the study, will be responsible for periodic monitoring and auditing. The Data Monitoring Committee will function independently of the investigators and will not have any role in study execution, thereby ensuring unbiased oversight. As the duration of the research is short, subgroup and interim analysis will not be undertaken. However, participant safety will be continuously

monitored throughout the study period and all adverse events will be recorded and managed as per standard clinical practice and Institutional ethics guidelines. Auditing the progress pertaining to the research and the quality of the collected data will be reviewed in every 6 months interval and reported to the Institutional Research and Data Monitoring Committee. Any protocol modifications or occurrence of adverse events will be promptly communicated to the IEC.

Adverse events management and safety measures:

Before participant enrolment, any history of known or suspected allergies will be obtained. Serious adverse effects are unlikely; however, any untoward reactions observed during the intervention period will be documented using the ADR (Ayush Suraksha) reporting form. These reactions will be categorised as mild, moderate, or severe based on their clinical manifestations, and appropriate management will be provided accordingly. Upon occurrence of any severe adverse reaction, the participant will be withdrawn from the study and given necessary medical treatment. Such incidents will be reported to the institutional Pharmacovigilance unit within 24 hours and will also be included in the final study report.

Ancillary Care: If participants present with any concurrent illness during the study, they will be given medical care without compromising or altering the trial protocol. Upon completion of the study, participants will be provided with necessary medical advice. No monetary compensation will be provided to participants for participation in the study. However, in the event of any study-related adverse event or injury, appropriate medical care will be provided as per institutional and ethical guidelines.

Protocol amendments – During the course of research, if any factors are found to affect the safety and scientific quality of research, the same will be informed to the Institutional ethical committee within 24 hours, and if required, amendments will be made to ensure that research remains ethically valid and in compliance with guidelines.

Informed consent and Ethical issues

On JULY 16, 2025, the "Institutional Ethics Committee" of Sri Dharmasthala Manjunatheshwara Institute of Ayurveda and Hospital (SDMIAH), Bengaluru, granted ethical approval of the trial (SDMIAH/IEC/16/2025). The trial was prospectively registered with the Clinical Trials Registry of India (CTRI/2026/01/102385) on 29/01/2026 prior to enrolment of the first participant. This study will be carried out following the ethical principles set forth in the Declaration of Helsinki, and written informed assent/consent will be obtained from the participants/ parents by the principal investigator. Participation in the trial will be voluntary, and participants may withdraw at any stage without any impact on their ongoing treatment. Investigators responsible for assessing participants and documenting findings will operate independently. Any adverse events occurring during the study will be managed, and appropriate post-trial treatment will be provided if necessary.

Additional consent will be obtained for the Acquisition and utilisation of data and biological specimens in ancillary studies, if applicable: Not applicable

Declaration of interests: No competing interests

Trial status: Open for participant enrolment.

Dissemination: Upon completion of the clinical study, it will be published in an open-access indexed journal. An organized awareness program may be conducted if the study results are found to be effective.

3. DISCUSSION

Fever is among the most frequent clinical presentations in children and constitutes a significant proportion of paediatric healthcare visits. Conventional antipyretic agents are effective; however, their use in young children is often limited by poor palatability, gastrointestinal intolerance, difficulty in oral administration, and concerns related to repeated dosing. *Panchatikta Kashaya*, described in *Chakradatta Jwara Chikitsa*, possesses established *Jwaraghna* (antipyretic),

Deepana (carminative), and *Pachana* (digestive) properties, supported by experimental evidence demonstrating antipyretic and anti-inflammatory actions of its ingredients. Despite its therapeutic potential, the intense bitterness of *Panchatikta Kashaya* limits oral acceptability in children. This study seeks to harmonize traditional Ayurveda knowledge with current pediatric clinical practice by evaluating *Panchatikta Kashaya* in a child-friendly *Gudavarti* (Rectal suppository) formulation. By addressing the practical limitations of oral administration while preserving the therapeutic integrity of the formulation, the intervention aims to enhance compliance, ensure effective drug delivery, and maintain safety in young children. The participant flow through different stages of the study, including recruitment, allocation, and analysis, is illustrated in Figure 2. The schedule of enrolment, intervention, and outcome assessment at predefined time intervals is detailed in Table 1, ensuring a structured and systematic approach to data collection. The outcomes of this research are anticipated to provide structured clinical evidence supporting the rational use of Rectal *Ayurvedic* formulations in *Jwara* (Fever) management. On evaluating risk of bias analysis as per Cochrane Risk of Bias Tool (RoB 2 for RCT), [11] the end analysis was interpreted to have a low risk of bias, indicating less chance of systematic errors. However, the relatively small sample size and short duration of follow-up (3 hours) may limit the generalizability of the findings. Additionally, the study is conducted in a single center, which may restrict external validity. Despite these limitations, the study is expected to provide preliminary clinical evidence supporting the use of rectal Ayurvedic formulations in pediatric fever management and contribute towards the development of standardized child-friendly dosage forms.

Abbreviations:

ICD: International Classification of Diseases

NAMC: National Ayurveda Morbidity Codes

g:Gram

Kg: kilogram

GMP: Good Manufacturing Practice

CRF: Case Report Form

IRC: Institutional Research Committee

IEC: Institutional Ethics Committee

CTRI: Clinical Trials Registry of India

SNOSE: Sequentially numbered opaque sealed envelope

HIN: Health Innovation Network

GCP: Good Clinical Practice

UK: United Kingdom

ITT: Intention-to-Treat

PP: Per-Protocol

LOCF: last observation carried forward

Authors Details:

[1]2nd Year Post Graduate Scholar, Department of Kaumarabhritya, Shri Dharmasthala Manjunatheshwara Institute of Ayurveda and Hospital, Bengaluru.

[2*]Professor & HOD, Department of Kaumarabhritya, Shri Dharmasthala Manjunatheshwara Institute of Ayurveda and Hospital, Bengaluru.

Authors Contribution:

Conceptualization and clinical management: RK, AVJ

Data collection and Literature search: AVJ, RK

Writing- Original draft: AVJ, RK

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Declaration of Generative AI

The authors declare this manuscript was written without the use of generative artificial intelligence tools. All the content, including text

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