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Research Paper

Mechanistic and Pharmacological Evaluation of *Cassia rhombifolia* Fruit Extract in Murine Models of Pain, Fever, and Acute Inflammation

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Abstract
This work investigated the pharmacological profile and dose-response behavior of an ethanol extract prepared from *Cassia rhombifolia* fruits (EECR) in mouse models of nociception, pyrexia, and short-term inflammatory reactions. Swiss albino mice were given EECR by mouth at 100, 200, or 300 mg/kg. Thermal pain thresholds were evaluated using the hot plate and tail-flick paradigms. Yeast-induced hyperthermia was employed to assess antipyretic activity, and λ-carrageenan-evoked paw swelling served as an index of acute inflammation. Serum cyclooxygenase-2 (COX-2), prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) were assessed by enzyme-linked immunosorbent assay (ELISA). EECR significantly increased reaction latencies in both nociceptive paradigms and reduced fever and paw edema in a clear dose-related fashion ($p < 0.01$). At 300 mg/kg, the extract inhibited the tail-flick response by 83.27%, lowered hyperthermia by 68.42%, and diminished paw swelling by 64.25%. These functional benefits were accompanied by a marked suppression of pro-inflammatory mediators, and the EECR dose showed a pronounced negative relationship with cytokine levels ($r = -0.98$; $p < 0.05$). Across behavioral and biochemical outcomes, correlation coefficients and determination indices (R^2) supported pronounced, almost linear dose-response patterns. Overall, the data indicate that EECR exerts potent pain-relieving, fever-lowering, and inflammation-attenuating effects in animal models and warrant further studies to isolate active principles, clarify molecular mechanisms, and evaluate its translational relevance.

Keywords
Cassia rhombifolia, Ethanol Extract, Dose-Response Relationship, Analgesic Activity, Antipyretic Activity, Anti-Inflammatory Activity

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1. INTRODUCTION

Cassia rhombifolia Roxb. (Fabaceae) has long been used in tropical and subtropical regions of Asia to manage febrile states, painful conditions, and inflammatory disorders, yet its pharmacological profile remains poorly characterized in the scientific literature. The genus *Cassia* (frequently treated taxonomically within *Senna*) is ethnomedicinally important. It is known to accumulate a wide range of secondary metabolites, including anthraquinones, flavonoids, phenolic acids, terpenoids, saponins, and alkaloids, which underpin diverse biological activities (Khurm et al., 2020). Recent phytochemical investigations of *Cassia* species such as *C. angustifolia*, *C. alata*, *C. timoriensis*, and related taxa have consistently demonstrated abundant flavonoids, polyphenols, terpenoids, and saponins in leaves, flowers, and pods (Ahmadi et al., 2024; Saptarini et al., 2024). These chemical classes are widely recognized for their antioxidant, membrane-stabilizing, and immunomodulatory properties and provide a rational phytochemical basis for exploring *C. rhombifolia* as a potential multi-target therapeutic resource (Al-Khayri et al., 2022; El Oirdi, 2024; Berillo et al., 2022).

In parallel, there is growing pharmacological evidence that several *Cassia* species exert analgesic, antipyretic, and anti-inflammatory effects. Extracts of *C. fistula* pods and fruit pulp have shown anti-inflammatory and antioxidant activities *in vivo* and *in vitro* (Zubairi et al., 2025), while *C. alata* has demonstrated broad bioactivities, including antimicrobial, antioxidant, and anti-inflammatory actions that are consistent with its rich content of flavonoids, terpenoids, and saponins (Oladeji et al., 2020; Michelle et al., 2024). Similarly, flower extracts of *C. timoriensis* exhibit antioxidant and anti-inflammatory effects and contain tannins, flavonoids, saponins, terpenoids, and steroids (Alhawarri et al., 2021). Consistently, a comprehensive network pharmacology and molecular docking study on *C. fistula* has elucidated multiple anti-inflammatory targets and signaling pathways for this species (Sayed et al., 2025), and a recent review on *C. alata* has summarized its bioactive constituents and demonstrated robust antioxidant and anti-

inflammatory activities across *in silico*, *in vitro*, and *in vivo* models (Michelle et al., 2024). Furthermore, comparative work on *Senna alata* and *S. occidentalis* has confirmed high levels of phenolics and flavonoids together with notable antioxidant and enzyme-inhibitory activities (Yagi et al., 2024). Collectively, these converging lines of evidence strengthen the scientific rationale for investigating underexplored members of the genus such as *C. rhombifolia*. Despite this favorable phytochemical and pharmacological background, the evidence base for *C. rhombifolia* itself remains relatively limited. Comprehensive ethnopharmacological and phytochemical overviews of the genus *Cassia* and of *C. fistula* in particular highlight extensive traditional use of these species for fever, pain, and inflammatory disorders and document a broad spectrum of bioactive constituents and anti-inflammatory activities (Khurm et al., 2020; Ghosh et al., 2023). Within this genus-level context, ethnobotanical reports and local traditional knowledge also describe the fruits and aerial parts of *C. rhombifolia* as remedies for febrile and painful inflammatory ailments, and a recent in vivo study has demonstrated hepatoprotective effects of its ethanol extract against carbon tetrachloride-induced liver injury in mice (Tran et al., 2024). However, beyond this hepatoprotective evaluation, there is still a lack of systematic in vivo studies on the analgesic, antipyretic, and anti-inflammatory activities of *C. rhombifolia* fruits. In particular, no previous work has comprehensively examined graded dose–response relationships for *C. rhombifolia* fruit extract across nociceptive, pyretic, and acute inflammatory endpoints, nor quantified mechanistic biomarkers such as cyclooxygenase-2 (COX-2), prostaglandin E_2 (PGE_2), and key pro-inflammatory cytokines [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in this context. This knowledge gap hampers accurate assessment of both efficacy and safety margins and limits the translational development of *C. rhombifolia*-derived preparations.

The pathophysiology of pain, fever, and acute inflammation is tightly coupled to enhanced prostaglandin synthesis via COX-2, overproduction of pro-inflammatory cytokines, and redox-sensitive signaling driven by reactive oxygen and nitrogen species (ROS/RNS) (Chavda et al., 2024; Mittal et al., 2014). Disruption of ROS homeostasis activates transcription factors such as nuclear factor κB (NF-κB) and promotes the expression of COX-2, TNF-α, IL-1β, and IL-6, thereby sustaining nociceptive sensitization, pyrexia, and edema (Yu et al., 2024; Rauf et al., 2023). Conversely, nuclear factor erythroid-2-related factor 2 (Nrf2) coordinates the expression of antioxidant and cytoprotective enzymes, and its activation can dampen NF-κB-dependent inflammatory cascades (Kim and Jeon, 2022; Pant et al., 2024). Numerous plant-derived polyphenols and flavonoids are now recognized as Nrf2 agonists and concurrent inhibitors of NF-κB and related pathways, leading to reduced ROS burden, lower COX-2/PGE_2 output, and decreased cytokine production (Della Vedova et al., 2025; Li et al., 2022; Sara et al., 2025). Building on this mechanistic framework, the substantial polyphenol and flavonoid content previously observed in the ethanol extract of *C. rhombifolia* fruits (EECR) suggests that it may exert combined antioxidant and immunomodulatory effects that translate into functional analgesic, antipyretic, and anti-inflammatory outcomes.

From a clinical perspective, pain and inflammatory disorders represent a major global health burden and frequently co-occur with chronic noncommunicable diseases in which oxidative stress and low-grade inflammation play central roles (Nhung and Quoc, 2023; Nediani et al., 2024). Although nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional antipyretics remain the mainstay of pharmacotherapy, their long-term or inappropriate use is often constrained by gastrointestinal, renal, and cardiovascular adverse events (Salis and Sainsbury, 2024; Abdullah et al., 2024). These limitations have intensified interest in phytochemical-based interventions with multitarget pharmacology and potentially more favorable safety profiles, particularly polyphenol-rich extracts that can simultaneously modulate oxidative stress, inflammatory signaling, and nociceptive processing (Al AlSheikh et al., 2020; El Oirdi, 2024; Ahmed et al., 2024; Sun et al., 2024). Within this broader search space, *C. rhombifolia* represents an attractive yet underexplored candidate.

Therefore, assessing the effects of *C. rhombifolia* fruit ethanol extract on both functional and biochemical readouts in validated murine models of nociception, fever, and acute inflammation can provide mechanistic insight into its potential therapeutic value. In particular, simultaneous measurement of COX-2, PGE_2, and circulating TNF-α, IL-1β, and IL-6 levels allows evaluation of whether any observed pharmacological benefits are accompanied by coherent modulation of key inflammatory pathways. The present study was designed to (i) evaluate the analgesic, antipyretic, and anti-inflammatory activities of an ethanol extract of *C. rhombifolia* fruits (EECR) in mouse models, and (ii) characterize dose–response relationships between EECR and both functional outcomes (reaction latencies and indices in hot-plate and tail-flick tests, rectal temperature and fever reduction, paw edema and its inhibition), and mechanistic biomarkers (COX-2, PGE_2, TNF-α, IL-1β, and IL-6). We hypothesized that EECR would exert dose-dependent protective effects against nociceptive, pyretic, and inflammatory challenges through convergent antioxidant and immunomodulatory mechanisms involving Nrf2–Keap1/NF-κB signaling and downstream suppression of COX-2/PGE_2 and pro-inflammatory cytokines.

2. EXPERIMENTAL SECTION

2.1 Chemicals and Instruments

All reagents, tramadol, paracetamol, indomethacin, λ-carrageenan, and Brewer's yeast, were analytical grade and used as received. Cytokines were quantified with commercial ELISA kits (Absolute Biotech, USA). Core equipment included a rotary evaporator (Büchi, Switzerland), UV-Vis spectrophotometer (Shimadzu, Japan), microplate reader (Bio-Rad, USA), digital caliper (Mitutoyo, Japan), and a calibrated clinical thermometer (Omron, Japan).

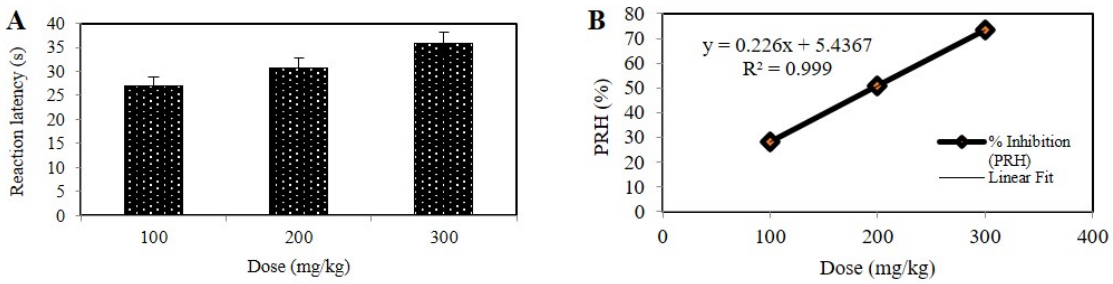

Figure 1. Hot-Plate Test: EECR Increases Reaction Latency Dose-Dependently. (A) RLH. (B) PRH vs Dose

Table 1. Phytochemical Constituents Identified and Quantified in the Ethanol Extract of *Cassia rhombifolia* Fruits (EECR)

Phytochemical	Presence in EECR	Content
Flavonoids	+	40.89 ± 1.37 mg QE/g
Terpenoids	+	66.95 ± 1.76 mg TAE/g
Polyphenols	+	69.98 ± 1.49 mg GAE/g
Alkaloids	+	4.28 ± 0.21 mg AE/g
Saponins	+	NT
Steroids	+	NT
Tannin	+	NT
Cardiac glycosides	–	–

Note: Phytochemicals in EECR are indicated as (+) present, (–) absent, and (NT) not tested (qualitative: +/–; quantitative: NT).

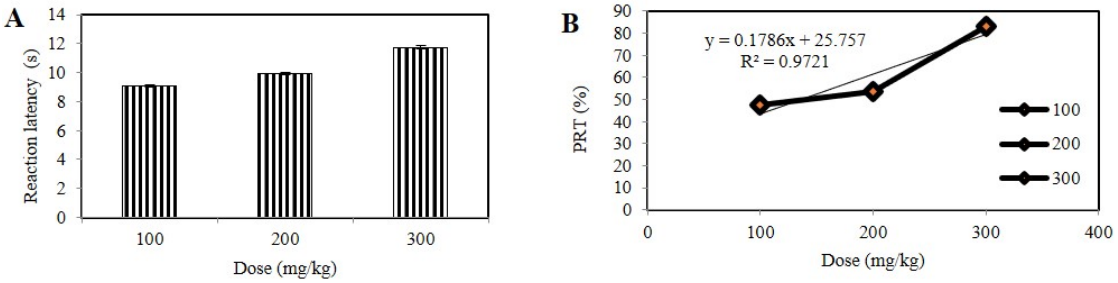

Figure 2. Tail-Flick Test: EECR Increases Reaction Latency and Pain-Inhibition Dose-Dependently. (A) RLT. (B) PRT vs Dose

2.2 Plant Material and Extraction

Mature fruits of *Cassia rhombifolia* from Cu Chi (Vietnam) were botanically authenticated, dried, milled, and macerated in 70% ethanol. The pooled filtrates were concentrated under reduced pressure and stored at 4 °C (yield ≈ 82%). Qualitative screening and spectrophotometric assays were performed for major classes (polyphenols, flavonoids, alkaloids, terpenoids) using validated procedures (Tran and Tran, 2021).

2.3 Animals and Ethical Approval

Male Swiss albino mice (28 ± 2 g) were acclimatized under controlled temperature-humidity and a 12 h light/dark cycle with ad libitum access to standard chow and filtered water. All procedures conformed to institutional and international ethical guidelines and were approved by the local ethics committee.

2.4 Experimental Design

Mice were randomized into control, positive-control, and EECR groups (100, 200, and 300 mg/kg). Treatments were delivered orally at doses appropriate to each assay; group sizes and observation windows followed the requirements of the corresponding test.

2.5 Pharmacological Assessments

Analgesic properties of EECR were investigated using both the hot-plate and tail-flick paradigms, in which reaction latencies were recorded at predefined time points and subsequently converted to percentage change or inhibition indices. Antipyretic efficacy was examined in the Brewer's yeast-induced pyrexia model by monitoring endpoint rectal temperature, in parallel with determination of serum COX-2 and PGE_2 concentrations by ELISA (Nhung and Quoc, 2024a). Anti-inflammatory

Table 2. Correlation Between Oral Doses of *Cassia rhombifolia* Fruit Ethanol Extract and Analgesic Responses in the Hot Plate Test in Mice

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
RLH (s)	100	27.06 ± 1.87	0.9994	0.9484	0.0216	↑↑
	200	30.72 ± 2.13	0.9951	0.9461	0.0139	↑↑
	300	35.85 ± 2.23	0.9138	0.9559	0.0241	↑↑
PRH (%)	100	28.03 ± 1.02	0.9927	0.9949	0.0098	↑↑
	200	50.63 ± 3.55	0.9889	0.9916	0.0056	↑↑
	300	73.22 ± 4.08	0.9915	0.9967	0.0073	↑↑

Reaction latency in seconds (s) of hot plate test (RLH); Percentage increase in reaction time (%) of hot plate test (PRH). ↑↑: Strong positive correlation.

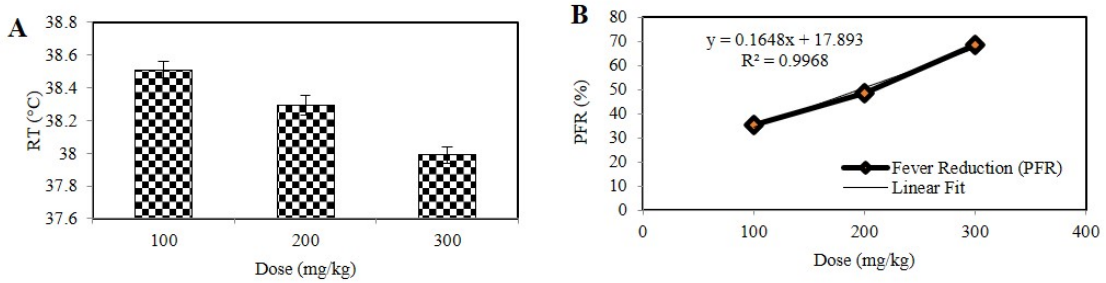

Figure 3. Yeast-Induced Pyrexia: EECR Reduces Rectal Temperature and Fever Dose-Dependently. (A) RT. (B) PFR vs Dose

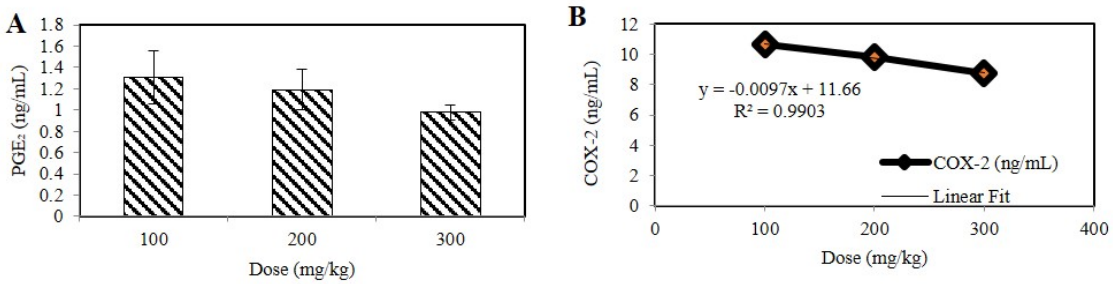

Figure 4. EECR Decreases Serum PGE_2 and COX-2 levels. (A) PGE_2. (B) COX-2 vs Dose

effects were assessed in λ-carrageenan-induced paw edema, where paw thickness was measured repeatedly with a digital caliper over a 4 h period, and serum TNF-α, IL-1β, and IL-6 levels were quantified using commercial ELISA kits. For each bioassay, we followed established procedures with minor adjustments in dosing schedule and sampling times to match the present experimental design (Nhung, 2025).

2.6 Statistical Analysis

All quantitative results are expressed as mean ± SD. Before group comparisons, distributional assumptions (normality and homogeneity of variance) were checked using the Shapiro-Wilk and Levene tests. When these criteria were satisfied, one-way ANOVA followed by Tukey's multiple comparison test was applied; otherwise, the Kruskal-Wallis test with Dunn's post hoc procedure was used. Associations between dose and pharmacological outcomes were examined with Pearson or Spearman correlation coefficients, depending on data characteristics. A p-value < 0.05 was considered statistically significant. All statistical analyses and graphing were carried out in GraphPad Prism (version 9.0) and R software (version 4.2.0).

3. RESULT AND DISCUSSIONS

The EECR produced robust and dose-dependent antinociceptive, antipyretic, and anti-inflammatory effects, as evidenced by prolonged hot-plate and tail-flick latencies, reduced yeast-induced hyperthermia, and attenuation of λ-carrageenan-evoked paw edema. These functional improvements were accompanied by marked and graded reductions in circulating COX-2, PGE_2, TNF-α, IL-1β, and IL-6 levels, indicating coherent modulation of key inflammatory pathways. The strongest effects were observed at 300 mg/kg, and the high correlation co-

Table 3. Correlation Between EECR Dose and Analgesic Responses in the Tail-Flick Test

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
RLT (s)	100	9.07 ± 0.09	0.9434	0.9713	0.0158	↑↑
	200	9.94 ± 0.07	0.9846	0.9827	0.0262	↑↑
	300	11.76 ± 0.11	0.9962	0.9946	0.0243	↑↑
PRT (%)	100	47.56 ± 1.80	0.9663	0.9829	0.0154	↑↑
	200	53.57 ± 2.30	0.9794	0.9902	0.0178	↑↑
	300	83.27 ± 3.20	0.9939	0.9795	0.0297	↑↑

Reaction latency in seconds (s) of the tail-flick test (RLT); Percentage of pain inhibition (%) of the tail-flick test (PRT). ↑↑: Strong positive correlation

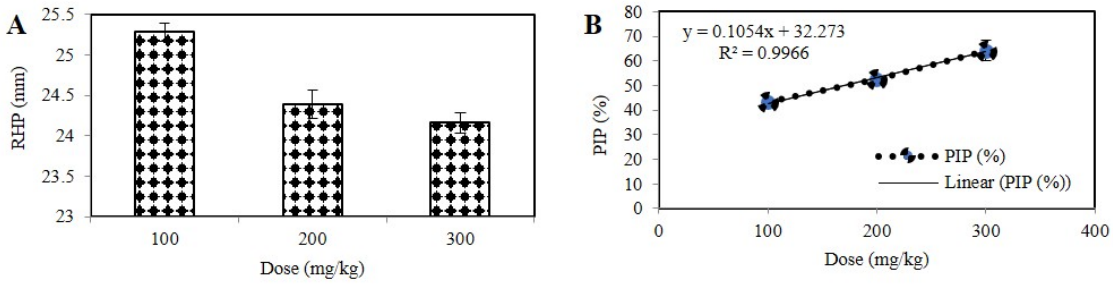

Figure 5. Carrageenan Paw Edema: EECR Reduces Paw Thickness and Inhibits Edema Dose-Dependently. (A) RHP. (B) PIP vs Dose

efficients and determination indices (r, R^2 = 0.94-0.99) across multiple endpoints suggest a predictable dose-response relationship. These findings are consistent with the multi-target actions reported for other polyphenol-rich Cassia extracts and provide a mechanistic framework for the more detailed discussion of EECR's analgesic, antipyretic, and anti-edematous activities below.

3.1 Phytochemical Characterization of EECR

Phytochemical screening of the fruit extract revealed a complex secondary-metabolite profile characterized by the presence of flavonoids, terpenoids, alkaloids, sterols/saponins, and a high content of polyphenols, whereas cardiac glycosides were not detected (Table 1). Quantitatively, polyphenols represented the predominant class (69.98 ± 1.49 mg GAE/g), followed closely by terpenoids (66.95 ± 1.76 mg/g), with moderate levels of flavonoids (40.89 ± 1.37 mg/g) and a comparatively low alkaloid content (4.28 ± 0.21 mg/g). This profile is broadly consistent with reports on other Cassia species, in which polyphenols, flavonoids, and terpenoids constitute the major bioactive constituents and underpin a wide range of pharmacological activities (Al-Khayri et al., 2022; El Oirdi, 2024; Mantiniotou et al., 2025). The absence of cardiac glycosides is also noteworthy, as it suggests a lower likelihood of glycoside-related cardiotoxicity and supports the safety of the extract within the tested dose range.

The predominance of phenolic and flavonoid constituents in EECR has important functional implications. Numerous polyphenols and flavonoids are recognized as potent activators of the Nrf2–Keap1 pathway, leading to upregulation of endogenous antioxidant defenses such as SOD, CAT, GPx/GR, GSH, and TAC and concomitant suppression of lipid peroxidation markers including MDA and H_2O_2 (Al-Khayri et al., 2022; Ahmed et al., 2024; Sun et al., 2024). By restoring redox homeostasis, these compounds indirectly attenuate NF-κB activation and downregulate the transcription of key pro-inflammatory genes encoding COX-2, TNF-α, IL-1β, and IL-6. In parallel, the abundant terpenoid and sterol/saponin fractions are known to stabilize cellular membranes and interfere with TLR4–MyD88-dependent signaling, which further limits prostaglandin synthesis and edema formation (El Oirdi, 2024; Nurlaili et al., 2023). Several flavonoids and alkaloids present in Cassia species have also been reported to modulate nociceptive processing through opioidergic pathways, NO–cGMP–K^+ channel signaling, and other ion-channel-related mechanisms, thereby prolonging reaction latency in thermal pain models (Mantiniotou et al., 2025).

Taken together, the quantitative predominance of polyphenols and terpenoids, in combination with appreciable levels of flavonoids and saponins, provides a coherent phytochemical basis for the multi-target pharmacological profile observed in this study. The same classes of compounds have been implicated in hepatoprotective, antioxidant, and anti-inflammatory effects in related plant systems, and their collective presence in EECR offers a plausible biochemical explanation for the pronounced reductions in COX-2, PGE_2, TNF-α, IL-1β, and IL-6, as well as for the dose-dependent improvements in antinociceptive, antipyretic, and anti-edematous outcomes documented in the

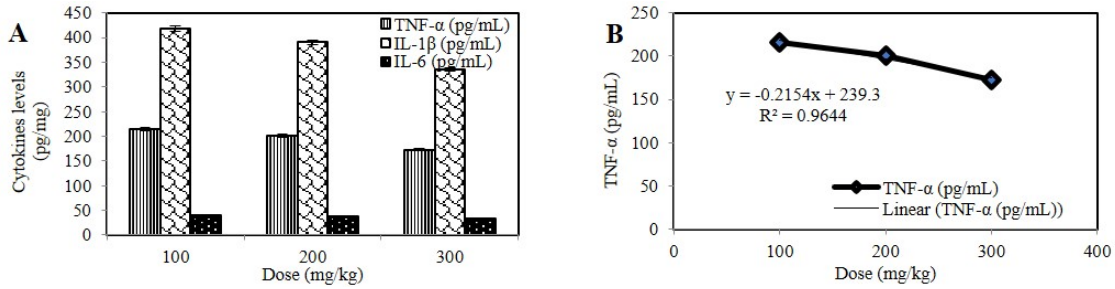

Figure 6. Carrageenan Paw Edema: EECR Reduces Paw Thickness and Inhibits Edema Dose-Dependently. (A) RHP. (B) PIP vs Dose

Table 4. Correlation Between EECR Dose and Antipyretic Responses in the Yeast-Induced Pyrexia Model

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
RT (°C)	100	38.51 ± 0.05	0.9772	-0.9885	0.0187	↓↓
	200	38.29 ± 0.06	0.9894	-0.9943	0.0165	↓↓
	300	37.99 ± 0.05	0.9921	-0.9799	0.0224	↓↓
PFR (%)	100	35.47 ± 1.35	0.9658	0.9821	0.0214	↑↑
	200	48.64 ± 2.18	0.9784	0.9923	0.0207	↑↑
	300	68.42 ± 3.26	0.9895	0.9898	0.0158	↑↑

RT: Rectal temperature (°C) during the antipyretic test; PFR: Percentage fever reduction (%) in the antipyretic test. ↑↑: Strong positive correlation; ↓↓: Strong negative correlation

subsequent sections (Ahmed et al., 2024; Nurlaili et al., 2023; Sun et al., 2024).

3.2 Pharmacological evaluation of EECR

3.2.1 Analgesic Activity

In both nociceptive test systems, EECR produced clear and dose-related elevations in pain thresholds, reflected by increases in reaction latencies (RLH, RLT) and corresponding improvements in percentage indices (PRH, PRT) compared with the control group (Tables 2 and 3; Figures 1 and 2). At 300 mg/kg, EECR yielded the greatest prolongation of hot-plate and tail-flick latencies, with marked increases in PRH and PRT, indicating a strong antinociceptive effect in both supraspinally and spinally mediated thermal pain models. The graded pattern across the three doses suggests a consistent dose-response relationship for the analgesic action of EECR. When placed in the context of the broader literature, the magnitude of the analgesic effects observed with EECR, particularly at 300 mg/kg (e.g., PRT exceeding 80%), is comparable to or greater than that reported for other polyphenol-rich plant extracts tested in similar nociceptive paradigms. Ethanolic extracts of *Indigofera argentea* have been shown to significantly increase hot-plate and tail-immersion latencies and to reduce acetic acid-induced writhing in rodents, alongside anti-inflammatory and antipyretic effects, supporting a triad of activities similar to those observed for EECR (Javed et al., 2020). Likewise, a recent study on Salacia lehmbachii root ethanol extract demonstrated dose-dependent increases in tail-immersion reaction time and robust inhibition of chemically induced writhing, effects that were again accompanied by anti-inflammatory and antipyretic actions in rats and mice (Akuodor et al., 2021). Furthermore, aqueous or hydroethanolic extracts of *Cassia fistula* have been reported to elevate pain thresholds in the tail-flick test and modulate acute pain in mice, thereby corroborating the analgesic potential of Cassia species enriched in phenolics and flavonoids. Taken together, these reports indicate that the analgesic profile of EECR is consistent with, and in some aspects comparable to, other polyphenol-rich extracts employed in thermal nociception models.

Mechanistically, the antinociceptive effect of EECR is compatible with both peripheral and central modes of action. Peripherally, the observed dose-dependent reductions in COX-2 and PGE_2 levels would be expected to lessen prostaglandin-driven sensitization of primary afferent nociceptors, thereby raising the threshold for thermal pain. In parallel, the decreases in TNF-α, IL-1β, and IL-6 likely attenuate NF-κB-mediated pronociceptive signaling and the cytokine-driven component of hyperalgesia (Raichurkar and Reddy, 2020; Nhung and Quoc, 2024b; Sic et al., 2024). Concurrent rebalancing of redox status, characterized by increases in SOD, CAT, and GPx activities and reductions in MDA and H_2O_2, would also be expected to diminish ROS-induced activation of TRP channels and other nociceptive ion channels, further contributing to prolonged latencies (Esh et al., 2021; Mehmood et al., 2024). Central mechanisms may also be involved. Several polyphenol- and flavonoid-rich extracts have been shown to exert antinociceptive effects via modulation of opioid receptors, the NO-cGMP-K^+ channel pathway, and descending monoaminergic systems.

Table 5. Correlation Between EECR Dose and Levels of COX-2 and PGE_2 in the Yeast-Induced Pyrexia Model

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
COX-2 (ng/mL)	100	10.64 ± 0.25	0.9752	-0.9813	0.0164	↓↓
	200	9.84 ± 0.19	0.9955	-0.9927	0.0202	↓↓
	300	8.71 ± 0.07	0.9896	-0.9754	0.0143	↓↓
PGE_2 (ng/mL)	100	1.31 ± 0.07	0.9816	-0.9874	0.0155	↓↓
	200	1.19 ± 0.08	0.9943	-0.9786	0.0168	↓↓
	300	0.98 ± 0.06	0.9899	-0.9992	0.0206	↓↓

COX-2: Cyclooxygenase-2; PGE_2: Prostaglandin E_2. Concentrations were expressed in ng/mL.
↓↓: Strong negative correlation

Table 6. Correlation Between EECR Dose and Anti-Inflammatory Responses in the Carrageenan-Induced Paw Edema Model

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
RHP (mm)	100	25.28 ± 0.11	0.9835	-0.9927	0.0213	↓↓
	200	24.39 ± 0.17	0.9921	-0.9884	0.0172	↓↓
	300	24.16 ± 0.13	0.9972	-0.9931	0.0157	↓↓
PIP (%)	100	43.17 ± 1.80	0.9817	0.9881	0.0185	↑↑
	200	52.64 ± 2.25	0.9915	0.9902	0.0146	↑↑
	300	64.25 ± 2.78	0.9936	0.9958	0.0123	↑↑

RHP: Right hind paw thickness (mm); PIP: Percentage inhibition of paw edema (%).
↑↑: Strong positive correlation; ↓↓: Strong negative correlation

For example, a recent study demonstrated that the bark extract of Ximenia americana and its major phenolic constituent caffeic acid produce significant increases in hot-plate latency and formalin test antinociception through interference with opioid and NO-cGMP signaling (Pessoa et al., 2024). Although these specific pathways were not directly tested here, the magnitude and time course of the EECR-induced increases in RLH, RLT, PRH, and PRT, together with cytokine and COX-2/PGE_2 suppression, strongly suggest that EECR acts in a multi-target manner at both peripheral and central levels, in line with other phenolic- and flavonoid-rich phytoextracts (Nhung and Quoc, 2024b; Pakale et al., 2024).

3.2.2 Antipyretic Activity

In the Brewer's yeast-induced fever model, EECR produced a significant and dose-dependent reduction in terminal rectal temperature, with the highest dose (300 mg/kg) showing the greatest decrease and the highest percentage pyrexia reduction (Table 4; Figure 3). The temporal profile of the antipyretic effect, becoming apparent within the first few hours after dosing and persisting over the observation period, suggests that EECR effectively counteracts the pyrogenic influence of yeast. These findings place EECR within the range commonly classified as moderate to strong antipyretic activity when compared with plant extracts evaluated in comparable models. Several plant-derived extracts with similar phytochemical profiles have shown comparable antipyretic efficacy. The ethanol root bark extract of Salacia lehmbachii significantly reduced Brewer's yeast-induced and d-amphetamine-induced pyrexia in rodents in a dose-dependent fashion, with effects approaching those of paracetamol at higher doses (Akuodor et al., 2021). Other polyphenol-rich extracts have also demonstrated significant temperature reductions in yeast-induced pyrexia, including formulations of *Ceiba pentandra* and *Ipomoea pes-caprae*, as well as methanolic plant extracts tested across multiple dose levels in mice (Silue et al., 2025). Comparable to these preparations, EECR produced a clear, graded reduction in rectal temperature and a substantial PFR at 300 mg/kg, supporting its categorization as a promising antipyretic agent. The mechanistic interpretation of these findings is closely aligned with the biochemical data. Yeast-induced fever arises from increased production of endogenous pyrogens (TNF-α, IL-1β, IL-6) that stimulate COX-2 expression and PGE_2 synthesis in brain endothelial cells and the preoptic hypothalamus, thereby elevating the thermoregulatory set-point (Akuodor et al., 2021). In the present study, EECR not only lowered rectal temperature but also significantly reduced circulating COX-2 and PGE_2 (Table 5; Figure 4), along with TNF-α, IL-1β, and IL-6 (Table 7), in a dose-dependent manner. This pattern strongly suggests that EECR interrupts the cytokine-COX-2-PGE_2 axis that underlies yeast-induced pyrexia.

Moreover, restoration of redox homeostasis (increased SOD, CAT, and GPx; decreased MDA and H_2O_2) is expected to limit redox-sensitive NF-κB activation and, consequently, reduce transcription of COX-2 and pro-inflammatory cytokines (Esh et al., 2021; Hasani et al., 2025; Mehmood et al., 2024). In combination, these changes are compatible with a dual peripheral-central mode of antipyretic action, whereby EECR attenuates systemic cytokine release and COX-2/PGE_2 production and, at the same time, dampens prostaglandin signal-

Table 7. Correlation Between EECR Dose and Pro-Inflammatory Cytokine Levels in the Carrageenan-Induced Inflammation Model

Parameters	Dose (mg/kg)	Mean ± SD	R^2	r	p-value	Correlation
TNF-α (pg/mL)	100	215.38 ± 3.28	0.9816	-0.9814	0.0173	↓↓
	200	201.01 ± 3.16	0.9936	-0.9881	0.0154	↓↓
	300	172.31 ± 2.23	0.9907	-0.9958	0.0128	↓↓
IL-1β (pg/mL)	100	418.51 ± 5.47	0.9874	-0.9853	0.0186	↓↓
	200	390.61 ± 4.58	0.9899	-0.9934	0.0162	↓↓
	300	334.81 ± 3.42	0.9961	-0.9981	0.0117	↓↓
IL-6 (pg/mL)	100	41.07 ± 0.79	0.9841	-0.9996	0.0194	↓↓
	200	38.33 ± 0.35	0.9905	-0.9879	0.0149	↓↓
	300	32.86 ± 0.43	0.9987	-0.9942	0.0132	↓↓

TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6. Concentrations were expressed in pg/mL. ↓↓: Strong negative correlation

ing at the level of the hypothalamic thermoregulatory centers. Similar integrated mechanisms have been proposed for other phenolic-rich extracts that combine antioxidant, anti-inflammatory, and antipyretic effects in yeast-based models (Yimer et al., 2021).

3.2.3 Anti-Inflammatory Activity

EECR also showed marked anti-inflammatory effects in the λ-carrageenan-induced paw edema model. Paw thickness (RHP) was significantly reduced in a dose-dependent manner at successive time points, and the corresponding percentage inhibition of paw edema (PIP) increased with rising doses (Table 6; Figure 5). At 300 mg/kg, EECR achieved substantial inhibition of edema during both the early (1-2 h) and late (3-4 h) phases, although the reference drug indomethacin retained somewhat greater efficacy. This pattern indicates a strong but not maximal anti-edematous effect, consistent with an active, multi-target anti-inflammatory profile.

The carrageenan-induced paw edema model is a well-established tool for assessing acute inflammation and features a biphasic response: an early phase driven mainly by histamine and serotonin, followed by a late phase dominated by prostaglandins and pro-inflammatory cytokines (Widyarini et al., 2023). The ability of EECR to significantly inhibit edema in the late phase parallels findings from other polyphenol-rich plant extracts. For instance, aqueous leaf extracts of Lepisanthes alata, which possess high total phenolic content, significantly reduced carrageenan-induced paw edema and lowered TNF-α and IL-1β levels in paw tissues, while also improving SOD activity and reducing oxidative stress markers (Nhung, 2025). Similarly, butanol extracts of Pleurospermum candollei and polyphenol-rich grape pomace fractions have been reported to attenuate carrageenan-induced paw swelling and decrease inflammatory and oxidative biomarkers in a dose-dependent manner (Fatima et al., 2025). The dose-dependent anti-edematous effect of EECR, together with its systemic modulation of inflammatory mediators, therefore aligns well with these established models and strengthens the case for EECR as an effective acute anti-inflammatory agent.

Mechanistically, the simultaneous lowering of COX-2 and PGE_2 observed in EECR-treated animals (Table 5; Figure 4) would be expected to blunt the prostaglandin-dependent late phase of carrageenan inflammation, during which COX-2-derived prostanoids drive vasodilatation, vascular permeability, and pain. In parallel, the reductions in TNF-α, IL-1β, and IL-6 (Table 7; Figure 6) indicate attenuation of upstream NF-κB signaling, which plays a central role in the induction and maintenance of acute inflammatory responses, including leukocyte recruitment and exudate formation (Barbosa et al., 2024; Pant et al., 2024; Yang and Lee, 2025). The normalization of redox balance, lower MDA and H_2O_2 together with higher SOD, CAT, and GPx activities, would further limit ROS-mediated activation of NF-κB and other redox-sensitive pathways, thereby breaking the self-amplifying loop between oxidative stress and inflammation (Ahmed et al., 2024; Nurlaili et al., 2023; Sun et al., 2024; Veeramani et al., 2022). Collectively, these effects on the TLR4-NF-κB-COX-2/PGE_2 and cytokine axes provide a coherent mechanistic explanation for the anti-edematous profile of EECR in the carrageenan model. They also mirror the mechanistic patterns described for other phenolic-rich extracts, such as Lepisanthes alata and Pleurospermum candollei, that exhibit combined antioxidant and anti-inflammatory actions through coordinated suppression of COX-2, PGE_2, and pro-inflammatory cytokines while enhancing endogenous antioxidant defenses (Fatima et al., 2025).

3.3 Dose-Response Correlation

Overall, the magnitude of the pharmacological effects increased progressively with EECR dose across nociceptive, antipyretic, and anti-inflammatory endpoints, yielding high correlation and determination coefficients ($|r/\rho|$ and R^2) as summarized in Table 8. The almost linear dose–response relationships (R^2 = 0.94–0.99) observed for multiple functional outcomes (RLH/RLT, PRH/PRT, RT/PFR, RHP/PIP) and biochemi-

Table 8. Summary of Dose-Response Correlations Between EECR and Pharmacological Parameters

Parameter	Correlation Type	R^2	r	p-value
Tail-flick test (RLT, PRT)	↑↑	0.94-0.99	0.97-0.99	< 0.03
Hot plate test (RLH, PRH)	↑↑	0.95-0.99	0.97-0.99	< 0.02
Pyrexia (RT, PFR)	↑↑	0.96-0.99	0.97-0.99	< 0.01
COX-2 / PGE_2 levels	↓↓	0.97-0.99	-0.99-0.97	< 0.02
Paw edema (RHP, PIP)	↑↑	0.98-0.99	0.99-1.00	< 0.03
	↓↓	0.98-0.99	-1.00-0.99	< 0.03
Cytokines (TNF-α, IL-1β, IL-6)	↓↓	0.98-0.99	-0.98-1.00	< 0.01

Positive (↑↑) or negative (↓↓) trends reflect the directionality of correlation. R^2 indicates linear regression strength; r denotes Pearson's or Spearman's correlation coefficient. All correlations were statistically significant ($p < 0.05$)

cal markers (COX-2, PGE_2, TNF-α, IL-1β, IL-6) suggest a predictable pharmacological profile of EECR within the 100–300 mg/kg range (Mittal et al., 2014; Tran and Tran, 2024). From a practical standpoint, such near-linear patterns are advantageous because they facilitate the selection and adjustment of doses in subsequent preclinical experiments and provide an initial framework for defining an efficacy window, as has been emphasized for other polyphenol-rich extracts and multi-component botanical preparations.

From a mechanistic perspective, higher doses of EECR are likely to deliver increased exposure to its abundant polyphenols and flavonoids, thereby promoting stronger activation of the Nrf2–Keap1 pathway and greater augmentation of endogenous antioxidant systems (SOD, CAT, GPx/GR, GSH, TAC). Enhanced antioxidant capacity lowers MDA and H_2O_2 levels and constrains redox-sensitive NF-κB activation, leading to reduced transcription of pro-inflammatory mediators (COX-2, TNF-α, IL-1β, IL-6) and decreased PGE_2 generation. Similar dose-related improvements in oxidative and inflammatory parameters have been reported for other phenolic-rich extracts, where incremental increases in polyphenol intake translated into proportionate reductions in oxidative stress and systemic cytokine production *in vivo* (Rudrapal et al., 2022). In this context, the parallel shifts observed here between EECR dose, suppression of COX-2/PGE_2 and cytokines, and improvements in nociceptive, pyretic, and edema indices support the view that modulation of Nrf2–NF-κB–COX-2/cytokine signaling is a central mechanism linking the biochemical and functional effects of EECR (Tran et al., 2023; Mittal et al., 2014; Yang and Lee, 2025).

The almost linear dose-response curves without an obvious plateau in the 100-300 mg/kg range imply that the maximal effect of EECR has not yet been reached within the tested doses. On one hand, this suggests that further increases in dose might yield additional therapeutic benefit; on the other hand, it underscores the need to delineate the upper limit of efficacy and safety. In line with current recommendations for the development of complex phytopharmaceuticals, careful exploration of higher doses combined with subchronic and chronic toxicity testing will be required to define the true therapeutic window and to balance efficacy against potential adverse effects.

4. CONCLUSIONS

In conclusion, the present work demonstrates that the ethanol extract of *Cassia rhombifolia* fruits elicits pronounced effects in murine models of nociception, fever, and acute inflammation, and that these actions vary systematically with dose across the different outcome measures. Oral EECR enhanced nociceptive reaction latencies, lowered rectal temperature in yeast-induced fever, attenuated carrageenan-evoked paw edema, and reduced circulating concentrations of key pro-inflammatory cytokines, indicating concurrent analgesic, antipyretic, and anti-inflammatory activities *in vivo*. These results substantiate the ethnomedicinal use of *C. rhombifolia* for inflammatory ailments and provide a mechanistic and quantitative basis for considering this species as a promising multi-target phytotherapeutic candidate.

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