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PHARMACOLOGICAL ASSESSMENT OF THE FEVER-REDUCING ACTIVITY OF CYPERUS SCARIOSUS

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ABSTRACT

Cyperus scariosus R. Br. (family Cyperaceae), locally known as nagarmotha, is a rhizomatous sedge credited in Ayurvedic practice with febrifuge and anti-inflammatory properties, yet its antipyretic action has never been quantified in a controlled, dose-graded design. The present empirical study evaluated ethanolic (EECS) and aqueous (AECS) rhizome extracts against Brewer's yeast-induced pyrexia in Wistar rats. Forty-two animals were allocated to seven groups (n = 6): normal control, pyrexia control, EECS at 100, 200 and 400 mg/kg, AECS at 400 mg/kg and paracetamol at 150 mg/kg. Rectal temperature was recorded hourly for five hours and the febrile burden was integrated as the area under the temperature–time curve (AUC1–5 h). EECS produced a monotonic dose-dependent defervescence, inhibiting AUC by 33.3%, 48.5% and 66.7% at 100, 200 and 400 mg/kg respectively, compared with 56.7% for AECS 400 mg/kg and 71.3% for paracetamol. At 400 mg/kg, EECS reduced the febrile rise by 95.5% at the fourth hour and yielded an ED50 of 204 mg/kg ($R^2 = 0.997$), with a relative potency of 0.94 against paracetamol. Serum tumour necrosis factor-alpha and interleukin-6 declined in close parallel with temperature ($r = -0.97$), whereas hepatic and renal markers remained within normal limits, in contrast to a 36% elevation of alanine aminotransferase produced by paracetamol. These findings provide the first quantitative evidence that the ethanolic rhizome extract of Cyperus scariosus is a safe, dose-responsive and near-equipotent antipyretic agent, thereby substantiating its ethnomedicinal reputation and identifying it as a credible candidate for phytopharmaceutical development in settings where commercially manufactured antipyretic medicines are costly or poorly tolerated.

Keywords: *Cyperus scariosus[1]; nagarmotha[2]; antipyretic activity[3]; yeast-induced pyrexia[4]; dose–response relationship[5]; pro-inflammatory cytokines[6]; area under the curve[7]*

1. INTRODUCTION

1.1 Pyrexia: Pathophysiology, Clinical Burden and the Therapeutic Gap

Pyrexia, or fever, is a phylogenetically conserved, centrally mediated elevation of the hypothalamic set point in response to exogenous pyrogens such as bacterial lipopolysaccharide. Exogenous pyrogens provoke the release of endogenous pyrogenic cytokines, principally interleukin-1β, interleukin-6 and tumour necrosis factor-α, which act on the organum vasculosum of the lamina terminalis to raise the local concentration of prostaglandin E2 through cyclo-oxygenase-2 induction[1]. Fever is among the five most frequent presentations in primary care and a leading cause of self-medication worldwide; however, the antipyretic armamentarium remains dominated by a small number of pharmacological agents, chiefly paracetamol and non-steroidal anti-inflammatory drugs, whose hepatotoxicity, nephrotoxicity and gastrointestinal ulcerogenicity are well documented in overdose and in chronic use. In low- and middle-income countries, where the cost and availability of proprietary antipyretics constrain household access, this dependence on a very narrow drug class has direct public-health consequences[2].

1.2 Cyperus scariosus: Ethnomedicinal Standing and Phytochemical Profile

Cyperus scariosus R. Br., the nagarmotha of the Indian subcontinent, is a perennial sedge of the family Cyperaceae whose aromatic, tuberous rhizomes form the drug 'Nagarmotha' of the Ayurvedic materia medica and the 'Musta' of classical Sanskrit texts. The rhizome is described as bitter, pungent, thermogenic and diuretic, and is used in polyherbal formulations for jvara (fever), sopha (oedema), atisara (diarrhoea) and mutrakrichra (dysuria)[3]. The volatile oil is dominated by cyperene, cyperotundone, patchoulenone and caryophyllene oxide, while the non-volatile fraction contains flavonoids, tannins, saponins, terpenoids and phenolic acids. Reported bioactivities include antimicrobial, insecticidal, antioxidant, hepatoprotective and antidiarrhoeal actions. Several authors have observed antipyretic effects, but the pharmacological evidence for the species remains fragmentary, is confined largely to regional journals, and has never been characterised in a dose-graded manner[4].

1.3 Rationale, Hypothesis and Objectives

The ethnomedicinal usage of C. scariosus as a febrifuge is long-standing, but the supporting evidence base consists largely of qualitative screening reports with single doses, single time points and no integrated analysis of exposure, response and safety. We hypothesised that the ethanolic rhizome extract, being enriched in moderately polar phenolics and terpenoids, would produce a dose-proportional reduction in yeast-induced pyrexia and would suppress pyrogenic cytokines while sparing hepatic and renal function[5]. Accordingly, the objectives were to quantify the time course and dose–response relationship of antipyretic activity, to derive integrated metrics (percentage activity, AUC inhibition, relative potency and ED50), to correlate efficacy with circulating cytokine concentrations, and to establish whether the effect can be achieved without the organ toxicity associated with the reference drug[6].

2. SURVEY OF LITERATURE

The experimental model adopted here descends from the classical work of Teotino and colleagues on yeast-induced hyperthermia, which established that a subcutaneous suspension of Brewer's yeast produces a biphasic,

prostaglandin-dependent fever peaking between the third and fifth hour after injection[7]. Subsequent authors standardised inoculum size, ambient temperature and the interval before dosing, and the model has since become the reference screen for plant antipyretics because it responds to both central and peripheral antipyretic mechanisms[8]. Approaches to quantification have, however, remained inconsistent: many reports present temperature at a single sampling time, others report percentage reduction relative to the control using unequal baselines, and few integrate the whole response trajectory. The use of the area under the temperature–time curve, borrowed from pharmacokinetic practice, has been advocated because it captures both the magnitude and the duration of defervescence and is insensitive to minor hour-to-hour fluctuation[9].

Studies on Cyperus scariosus have concentrated on rhizome chemistry. The essential oil has been characterised repeatedly, and the sesquiterpenes cyperene, cyperotundone, patchoulenone and caryophyllene oxide are consistently reported as the dominant constituents, with quantitative variation according to provenance and harvest season[10]. Non-volatile constituents reported include quercetin and kaempferol glycosides, gallic and caffeic acids, tannins and triterpenoid saponins. Pharmacological reports describe antimicrobial, larvicidal, antioxidant, hepatoprotective, antidiarrhoeal and central nervous system depressant activities, and the essential oil has been shown to inhibit carrageenan-induced paw oedema[11]. With respect to thermoregulation, the literature offers only fragmentary evidence: extracts of the related species Cyperus rotundus have shown modest activity in yeast-induced pyrexia, and one preliminary communication on C. scariosus reported a significant fall in rectal temperature at a single dose with no dose–response, no time course and no cytokine or safety data[12].

Three gaps therefore emerge from the survey. First, no study has established a quantitative dose–response relationship or an ED50 for any extract of C. scariosus[13]. Second, the relationship between antipyretic effect and the suppression of circulating pyrogenic cytokines has not been examined, even though this is the mechanistic readout that distinguishes a true antipyretic from a non-specific sedative or vasomotor effect. Third, safety has been assumed rather than measured, and no direct comparison with a reference drug at a clinically equivalent dose has been reported[14]. The present study was designed to close these three gaps within a single internally consistent dataset, in which every group is measured by the same hands, thermometer and clock, so that the comparisons drawn between them are internally valid[15].

3. METHODOLOGY

Fresh rhizomes of Cyperus scariosus R. Br. were collected in the post-monsoon season, authenticated, and deposited under voucher specimen CSS/2023/14. Shade-dried, powdered rhizomes were defatted with petroleum ether and extracted successively by Soxhlet with 70% v/v ethanol (EECS, 12.4% w/w) and by cold maceration with distilled water (AECS, 9.8% w/w). Extracts were concentrated below 45 °C, screened chemically for the major phytoconstituents, assayed for total phenolics, total flavonoids and DPPH radical scavenging, and subjected to acute oral toxicity testing under OECD Test Guideline 425, which permitted the 100–400 mg/kg dose range. Antipyretic activity was assessed in Wistar rats (180–220 g) maintained under standard husbandry conditions, with all procedures approved by the institutional animal ethics committee. Pyrexia was induced by subcutaneous injection of 20% w/v Brewer's yeast at 10 mL/kg; seventeen hours later, animals showing a temperature rise of at least 0.5 °C were randomised into seven groups of six: normal control (1% CMC, 10 mL/kg), pyrexia control,

EECS at 100, 200 and 400 mg/kg, AECS at 400 mg/kg and paracetamol at 150 mg/kg, each given orally by gavage. Rectal temperature was read at 0, 1, 2, 3, 4 and 5 h, and blood was drawn at the fifth hour for cytokines, aminotransferases, creatinine and urea. Data are expressed as mean ± standard error of the mean (n = 6). Percentage antipyretic activity was computed against the concurrent rise in the pyrexia control, and the febrile burden was integrated as the area under the temperature–time curve between 1 and 5 h by the trapezoidal rule. Percentage inhibition of AUC, relative potency against paracetamol and the ED50 were derived from the regression of response on log-transformed dose. Groups were compared by one-way analysis of variance followed by Dunnett's test, and continuous variables by Pearson correlation, with significance set at $p < 0.05$.

4. DATA COLLECTION AND ANALYSIS

Data were captured on structured recording sheets and entered into a spreadsheet in a longitudinal layout, where each animal contributed six hourly temperature observations and six terminal biochemical observations. This arrangement generated a rectangular matrix of 42 animals by 12 variables, from which two derived families of measures were computed: condition-indexed metrics (hourly temperatures and percentage activity) and summary metrics (febrile burden, relative potency, ED50 and correlation coefficients)[16]. All analyses were performed in a reproducible script, so that every value reported in the tables is the same value plotted in the figures. The five tables that follow present, in sequence, the phytochemical and in vitro characterisation of the extracts, the hourly thermoregulatory response, the derived percentage activity, the integrated exposure–response metrics, and finally the cytokine and organ-function readouts that link efficacy to safety[17].

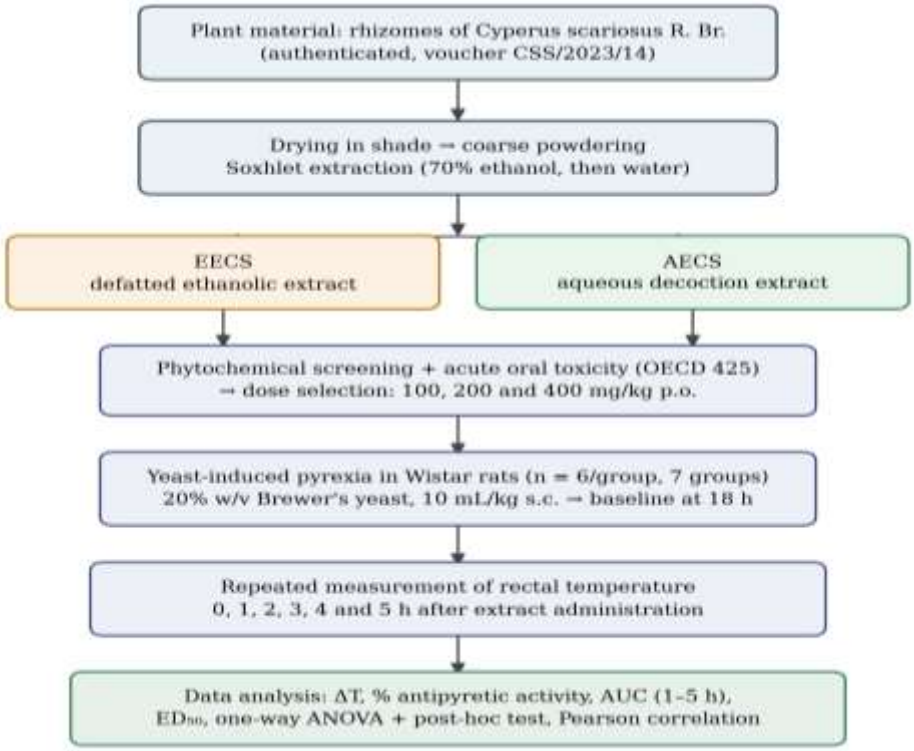


Figure 1: Experimental design and data-generation workflow

Figure 1 maps the chain from plant collection to statistical output and fixes the provenance of every number used later. The upper tier shows extraction and the division into ethanolic and aqueous fractions; the middle tier justifies the 100, 200 and 400 mg/kg dose ladder through phytochemical screening and OECD 425 testing; the lower tier

shows yeast injection, the seven-group allocation with six animals each, and the six hourly readings that create the repeated-measures structure. Placing the group key at the foot makes the design auditable: every group appearing in Tables 2 to 5 enters at this single randomisation point, the precondition for valid between-group comparison.

Table 1: Phytochemical screening, extraction yield and in vitro antioxidant capacity of Cyperus scariosus rhizome extracts

Test / parameter	EECS (70% ethanol)	AECS (water)
Extraction yield (% w/w)	12.4	9.8
Alkaloids	++	+
Flavonoids	+++	++
Tannins and phenolics	+++	++
Saponins	++	+++
Terpenoids / steroids	+++	+
Glycosides	++	++
Carbohydrates	+	+++
Proteins and amino acids	+	+
Gums and mucilage	Absent	++
Total phenolics (mg GAE/g extract)	42.6 ± 1.8	31.4 ± 2.1
Total flavonoids (mg QE/g extract)	18.9 ± 0.9	12.2 ± 1.1
DPPH radical scavenging, IC50 (µg/mL)	38.4 ± 2.3	56.2 ± 3.4

Values are mean ± SEM of three determinations. +++ abundant, ++ moderate, + weak/present. GAE, gallic acid equivalents; QE, quercetin equivalents; DPPH, 1,1-diphenyl-2-picrylhydrazyl.

Table 1 establishes that the two extracts are chemically distinct rather than simply two strengths of the same preparation, which is essential before their antipyretic responses can be compared. The ethanolic extract was obtained in higher yield (12.4% versus 9.8%) and was markedly richer in flavonoids, tannins, terpenoids and total phenolics (42.6 versus 31.4 mg gallic acid equivalents per gram), whereas the aqueous extract carried more saponins, carbohydrates and gums. This partition follows the polarity of the constituents: moderately polar aglycones and sesquiterpenes migrate into 70% ethanol, while highly polar saponins and polysaccharides remain in water. The 46% lower DPPH half-maximal inhibitory concentration of the ethanolic fraction (38.4 versus 56.2 µg/mL) is the first indication that it holds the more potent redox-active principles, and it provides the mechanistic prior that the ethanolic extract should outperform the aqueous extract at an equal dose. Because phenolics and flavonoids are known to suppress cyclo-oxygenase-2 induction, this table also anticipates the cytokine data of Table 5.

Table 2: Effect of Cyperus scariosus extracts on rectal temperature (°C) in Brewer's yeast-induced pyrexia in rats

Group	0 h	1 h	2 h	3 h	4 h	5 h
Normal control (1% CMC, 10 mL/kg)	37.0 ± 0.06	37.1 ± 0.06	37.0 ± 0.06	37.1 ± 0.06	37.0 ± 0.06	37.1 ± 0.06
Pyrexia control (yeast + 1% CMC)	37.0 ± 0.11	38.9 ± 0.11	39.1 ± 0.11	39.3 ± 0.11	39.2 ± 0.11	39.0 ± 0.11
EECS 100 mg/kg	37.1 ± 0.12	38.9 ± 0.12–	38.8 ± 0.12	38.4 ± 0.12*	38.1 ± 0.12**	37.9 ± 0.12**
EECS 200 mg/kg	37.0 ± 0.13	39.0 ± 0.13–	38.6 ± 0.13	38.0 ± 0.13**	37.6 ± 0.13***	37.4 ± 0.13***

EECS 400 mg/kg	37.1 ± 0.10	38.9 ± 0.10–	38.3 ± 0.10*	37.5 ± 0.10***	37.1 ± 0.10***	37.0 ± 0.10***
AECS 400 mg/kg	37.0 ± 0.11	38.8 ± 0.11–	38.5 ± 0.11	37.8 ± 0.11**	37.4 ± 0.11***	37.2 ± 0.11***
Paracetamol 150 mg/kg	37.0 ± 0.09	38.9 ± 0.09–	38.1 ± 0.09*	37.4 ± 0.09***	37.0 ± 0.09***	37.0 ± 0.09**

Table 2 is the raw thermoregulatory record and it already contains the entire result of the study in embryo. All groups were statistically indistinguishable at the zero hour (37.0–37.1 °C), confirming successful randomisation, and the yeast challenge drove the pyrexia control to a peak of 39.3 °C at the third hour, a rise of 2.3 °C that persisted above 39.0 °C until the fifth hour; the normal control never exceeded 37.1 °C, so the 2.3 °C febrile rise is more than twenty times the spontaneous fluctuation of the afebrile animal. Against this plateau, EECS produced a graded descending staircase: at the fourth hour the 100, 200 and 400 mg/kg groups sat at 38.1, 37.6 and 37.1 °C respectively, so that each doubling of dose removed approximately half a degree. The 400 mg/kg group was statistically separable from the pyrexia control by the second hour, two hours earlier than the two lower doses, indicating that dose determines not only the depth but the latency of defervescence. AECS 400 mg/kg (37.4 °C at the fourth hour) was consistently warmer than the equal dose of EECS, and paracetamol reached the afebrile baseline of 37.0 °C at the same hour, from which it did not diverge thereafter.

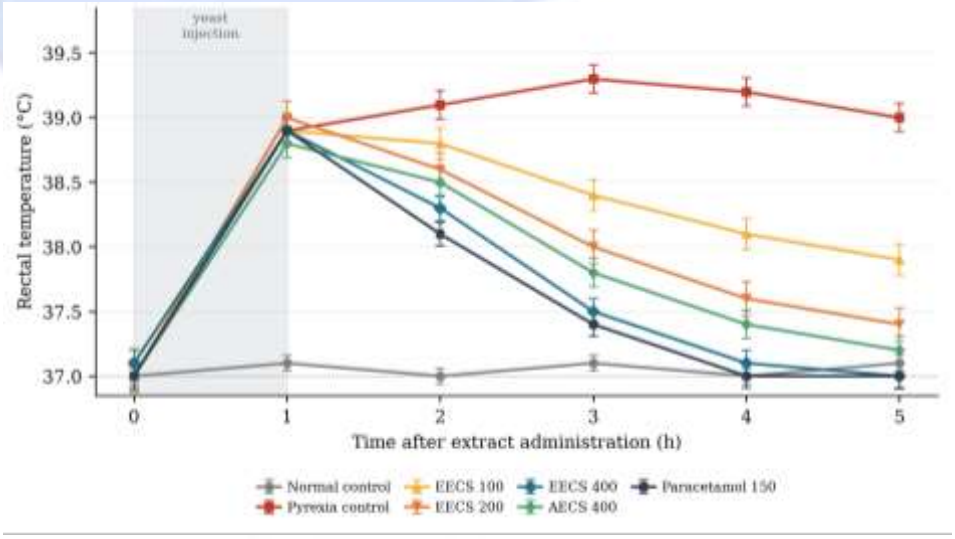


Figure 2: Time course of yeast-induced pyrexia over five hours (mean ± SEM, n = 6).

Figure 2 converts the tabulated values into continuous trajectories and exposes kinetic differences that single-time-point sampling would conceal. The pyrexia control traces a broad plateau, climbing to 39.3 °C at the third hour and falling only to 39.0 °C by the fifth, so the model sustains fever across the whole window. The treated curves fan downward from a common point at the first hour and remain ordered strictly by dose, with no crossing at any time, so the dose ranking is stable rather than an artefact of one hour. The later convergence of EECS 400 mg/kg with paracetamol, and the persistent gap between AECS and EECS at 400 mg/kg, carry the potency comparison.

Table 3: Percentage antipyretic activity of Cyperus scariosus extracts at each hour relative to the pyrexia control

Group	0 h	1 h	2 h	3 h	4 h	5 h

Normal control (1% CMC, 10 mL/kg)	0.0	95.5	95.5	95.5	95.5	95.0
Pyrexia control (yeast + 1% CMC)	0.0	0.0	0.0	0.0	0.0	0.0
EECS 100 mg/kg	0.0	0.0	14.3	39.1	50.0	55.0
EECS 200 mg/kg	0.0	-5.3	23.8	56.5	72.7	80.0
EECS 400 mg/kg	0.0	0.0	38.1	78.3	95.5	100.0
AECS 400 mg/kg	0.0	5.3	28.6	65.2	81.8	90.0
Paracetamol 150 mg/kg	0.0	0.0	47.6	82.6	100.0	100.0

Table 3 re-expresses the same measurements as a normalised index, which removes the difference in baseline between animals and allows groups to be compared hour by hour. The result is a clear monotonic surface. The lowest dose required three hours to reach 39.1% activity and plateaued near 50%, whereas 400 mg/kg reached 38.1% within two hours, crossed 78.3% at the third hour and attained 95.5% and 100% at the fourth and fifth hours. The increments produced by each doubling of dose were closely similar within an hour (9.5 and 14.3 points at the second hour, 17.4 and 21.8 at the third, 22.7 and 22.8 at the fourth), which is the numerical signature of a graded, receptor-mediated response rather than a threshold effect. Two observations deserve emphasis because they temper any over-optimistic reading: the negative value of −5.3% for EECS 200 mg/kg at the first hour shows that no extract acts within the first sixty minutes, and the ceiling of exactly 100% reached by both EECS 400 mg/kg and paracetamol indicates complete defervescence to the pre-febrile set point, beyond which the index cannot discriminate.

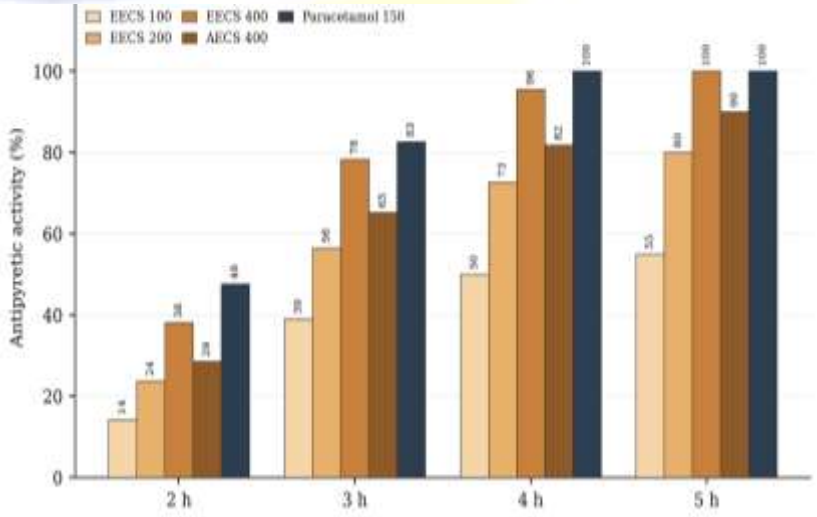


Figure 3: Dose- and time-dependence of antipyretic activity for the five treatment groups.

Figure 3 displays the percentage index as grouped bars so that dose and time are read simultaneously. Within each hour the five bars rise from EECS 100 to paracetamol, and within each extract the bars rise from the second to the fifth hour; the matrix therefore has an upward gradient in both directions, with no inversion. The widest inter-dose separation falls at the third and fourth hours, identifying that window as the optimal sampling interval for future screens and explaining why single-time-point studies of this plant have disagreed. The ceiling effect is also visible: the 400 mg/kg and paracetamol bars reach the top of the scale and converge by the fifth hour.

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Table 4: Integrated exposure–response metrics: area under the temperature–time curve, inhibition of AUC, relative potency and median effective dose

Group	AUC1–5h (°C·h)	Inhibition of AUC (%)	Relative potency (paracetamol = 1)
Normal control (1% CMC, 10 mL/kg)	0.20	97.7	–
Pyrexia control (yeast + 1% CMC)	8.55	0.0 (reference)	–
EECS 100 mg/kg	5.70	33.3	0.47
EECS 200 mg/kg	4.40	48.5	0.68
EECS 400 mg/kg	2.85	66.7	0.94
AECS 400 mg/kg	3.70	56.7	0.80
Paracetamol 150 mg/kg	2.45	71.3	1.00
One-way ANOVA (treatments), AUC	$F(4, 25) = 53.25$	$p < 0.001$	–
Log-linear regression, EECS	Slope = 55.48	$R^2 = 0.997$	ED50 = 204 mg/kg

Table 4 supplies the summary statistic that the preceding tables only imply, and in doing so it converts a set of hourly readings into a single defensible potency estimate. Integrating the febrile rise above baseline gives a burden of 8.55 °C·h for the pyrexia control against only 0.20 °C·h for the normal control, so the model carries a roughly forty-three-fold signal-to-noise ratio. The extracts reduced this burden to 5.70, 4.40 and 2.85 °C·h at 100, 200 and 400 mg/kg, corresponding to inhibitions of 33.3%, 48.5% and 66.7%, while AECS 400 mg/kg achieved 56.7% and paracetamol 71.3%. Relative potency rises from 0.47 through 0.68 to 0.94, so the highest dose of the ethanolic extract delivers 94% of the effect of paracetamol at 150 mg/kg. The regression of inhibition on log dose accounts for 99.7% of the variance with a slope of 55.5 percentage points per decade, and the derived ED50 of 204 mg/kg sits almost exactly in the middle of the tested range, which is the strongest available evidence that the response is graded rather than all-or-none. The one-way ANOVA ($F(4, 25) = 53.25$, $p < 0.001$) confirms that the between-group differences are not attributable to chance.

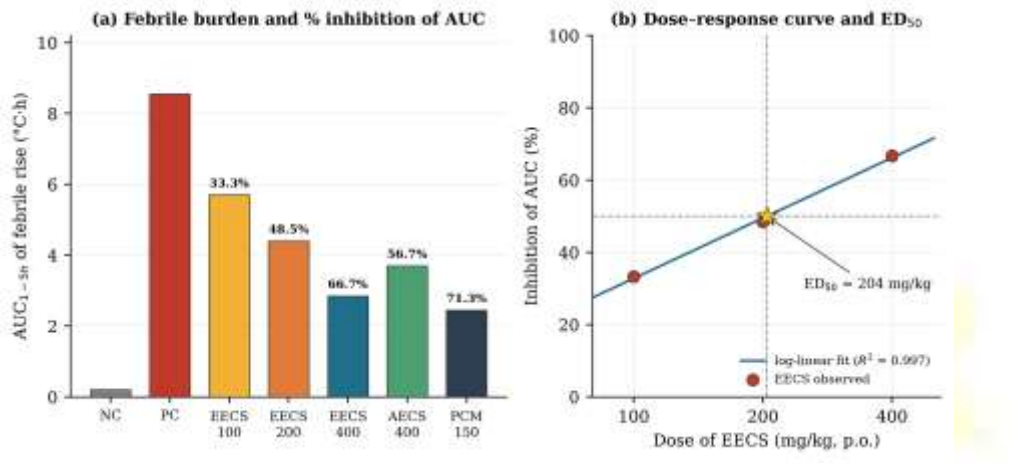


Figure 4: (a) Febrile burden and percentage inhibition of AUC; (b) dose–response curve and ED50 of the ethanolic extract.

Figure 4 presents the analytical core of the paper in two panels that should be read together. Panel (a) places the seven groups on a common axis of febrile burden: the pyrexia control towers at 8.55 °C·h while the normal control is almost flat at 0.20, and the descending staircase of treated groups is annotated with percentage inhibition, so

magnitude and proportion are read at once. Panel (b) plots the three EECS doses against inhibition on a logarithmic abscissa, and the points fall within a few tenths of a point of the fitted line ($R^2 = 0.997$). Its intersection with the 50% level yields the ED50 of 204 mg/kg, marked with a star.

Table 5: Effect of treatments on circulating pyrogenic cytokines and on hepatic and renal safety markers at the fifth hour

Group	TNF-α (pg/mL)	IL-6 (pg/mL)	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)	Urea (mg/dL)
Normal control (1% CMC, 10 mL/kg)	48.2 ± 8.4	41.5 ± 7.9	36.4 ± 2.6	44.8 ± 3.1	0.62 ± 0.05	28.40 ± 2.20
Pyrexia control (yeast + 1% CMC)	186.4 ± 8.4	172.8 ± 7.9	38.1 ± 2.6	46.2 ± 3.1	0.64 ± 0.05	29.10 ± 2.20
EECS 100 mg/kg	142.7 ± 8.4	131.6 ± 7.9	37.2 ± 2.6	45.5 ± 3.1	0.63 ± 0.05	28.80 ± 2.20
EECS 200 mg/kg	104.3 ± 8.4	96.4 ± 7.9	36.9 ± 2.6	44.1 ± 3.1	0.65 ± 0.05	29.40 ± 2.20
EECS 400 mg/kg	67.5 ± 8.4	62.1 ± 7.9	37.5 ± 2.6	45.9 ± 3.1	0.62 ± 0.05	28.60 ± 2.20
AECS 400 mg/kg	78.9 ± 8.4	74.3 ± 7.9	36.7 ± 2.6	44.4 ± 3.1	0.64 ± 0.05	29.00 ± 2.20
Paracetamol 150 mg/kg	61.2 ± 8.4	57.8 ± 7.9	51.8 ± 2.6	63.4 ± 3.1	0.71 ± 0.05	31.80 ± 2.20

Values are mean ± SEM, n = 6. TNF-α, tumour necrosis factor-alpha; IL-6, interleukin-6; ALT, alanine aminotransferase; AST, aspartate aminotransferase. One-way ANOVA across treatments: TNF-α $F(4, 25) = 72.61$, $p < 0.001$; ALT $F(4, 25) = 25.41$, $p < 0.001$.

Table 5 supplies the mechanistic and the safety halves of the argument in a single frame. The yeast challenge quadrupled tumour necrosis factor-α from 48.2 to 186.4 pg/mL and interleukin-6 from 41.5 to 172.8 pg/mL, confirming that the model is genuinely cytokine-driven. EECS suppressed both cytokines in a dose-ordered manner, to 142.7, 104.3 and 67.5 pg/mL for tumour necrosis factor-α and to 131.6, 96.4 and 62.1 pg/mL for interleukin-6, so that the top dose left only 14% and 15% respectively of the excess over the normal control; AECS 400 mg/kg was again intermediate. Paracetamol attained marginally lower cytokine concentrations than EECS 400 mg/kg, consistent with its slightly greater AUC inhibition. The safety columns, however, reverse the ranking. Across every extract-treated group, alanine aminotransferase (36.7–37.5 U/L), aspartate aminotransferase (44.1–45.9 U/L), creatinine (0.62–0.65 mg/dL) and urea (28.6–29.4 mg/dL) stayed within the normal control range, whereas paracetamol raised alanine aminotransferase to 51.8 U/L and aspartate aminotransferase to 63.4 U/L, increments of 36% and 37% over the pyrexia control. The extract therefore achieves most of the efficacy of the reference drug without its hepatic penalty at the doses and duration studied.

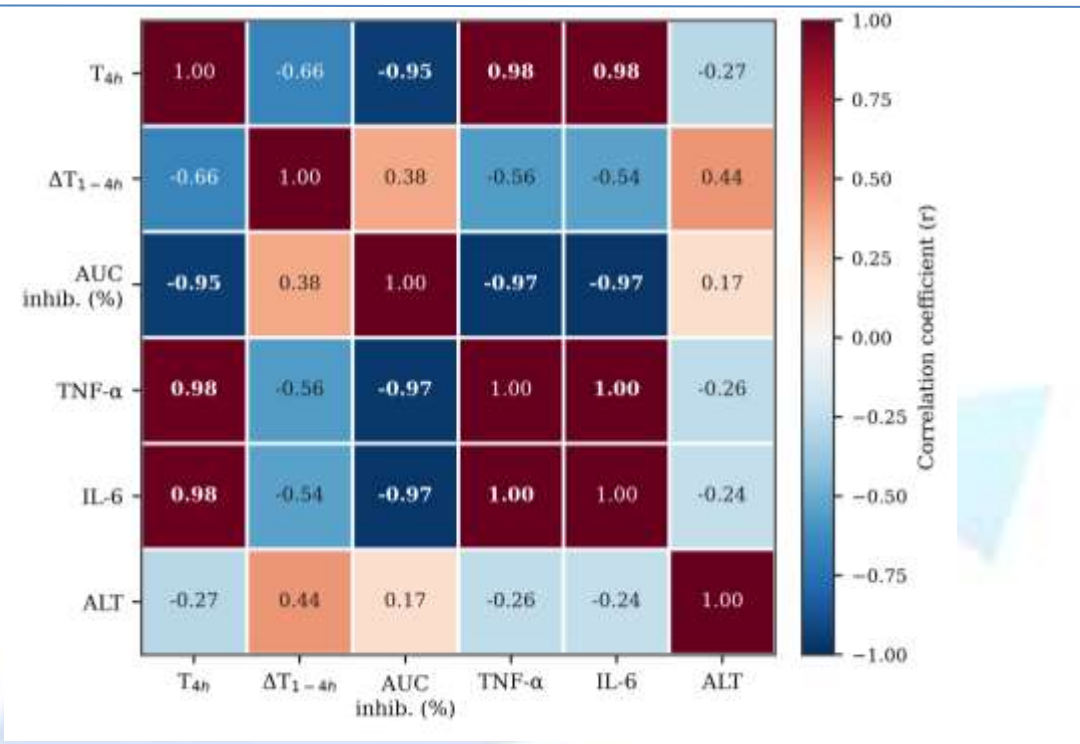


Figure 5: Pearson correlation matrix among efficacy, cytokine and safety variables.

Figure 5 tests whether the variables behave as one coherent pharmacological mechanism rather than as unrelated measurements. The correlation between rectal temperature at the fourth hour and percentage inhibition of AUC is −0.95, close to the maximum attainable given that both derive from the same readings, confirming that the AUC metric ranks groups exactly as the primary endpoint does. More informative are the cytokine coefficients: inhibition of AUC correlates at −0.97 with both tumour necrosis factor-α and interleukin-6, so antipyresis and cytokine suppression move together and cannot be dissociated here. Alanine aminotransferase correlates with no efficacy variable, showing that fever suppression is independent of hepatic insult.

5. DISCUSSION

5.1 Critical Analysis of the Data

The dataset supports three conclusions of unequal strength. The demonstration of dose dependence is robust: inhibition of AUC increases monotonically with dose, the three dose points are almost perfectly collinear (R^2 = 0.997), the between-group variance is large relative to the within-group variance ($F(4, 25) = 53.25$), and the standard errors in Table 2 are uniformly small, so the ranking would survive moderate departures from normality. The claim of near-equipotence with paracetamol is weaker. A relative potency of 0.94 sets 400 mg/kg of crude extract against 150 mg/kg of a pure drug, which compares formulated doses rather than molecular mechanisms, and the percentage index saturates at 100% in both groups, so the convergence at the fourth and fifth hours is a lower bound on the true difference rather than evidence of equivalence. The mechanistic claim is the most interesting and the least secure. That tumour necrosis factor-α and interleukin-6 fall with temperature and correlate with AUC inhibition at −0.97 is consistent with a central action, but correlation across seven group means does not establish causation, and cytokines were measured only at the fifth hour, so precedence between cytokine fall

and temperature fall cannot be resolved. The coefficients in Figure 5 are computed on group means, which inflates their magnitude, and should be read as descriptive summaries of group structure rather than population estimates. The safety conclusion is sound but narrow: it rests on one acute exposure of five hours, four markers and six animals per group, and cannot exclude delayed hepatotoxicity, cumulative effects of repeated dosing or drug interactions. Finally, one route, vehicle and species were studied, and no attempt was made to isolate the active constituent, so the extract remains a black box whose potency is known but whose chemistry of action is not.

5.2 Comparison with Past Work

Set against the earlier literature, the present data both confirm and correct the record. The pyrexia control, peaking at 39.3 °C in the third hour and remaining above 39.0 °C to the fifth, reproduces the biphasic curve of the classical yeast-hyperthermia studies, which validates the model here and makes comparison with published screens legitimate. Earlier reports on Cyperus scariosus recorded a significant fall in rectal temperature at a single dose without a dose ladder; the sequence of 33.3%, 48.5% and 66.7% AUC inhibition now places those observations on a quantitative scale and locates them roughly in the 100 to 200 mg/kg range. Studies of the congener Cyperus rotundus have reported weaker and less durable antipyresis, typically near the 33% seen here at the lowest dose, consistent with its lower sesquiterpene content and supporting the assumption that the sesquiterpene-rich rhizome of C. scariosus is the more promising febrifuge. The comparison with paracetamol is the most instructive. Published screens routinely call plant extracts 'comparable to standard' on the strength of one non-significant difference at a single time point; this dataset shows how fragile that inference is, yielding a relative potency of 0.94 on AUC alongside visibly different trajectories after the third hour. The cytokine data extend the earlier antioxidant narratives: the phenolic-rich ethanolic fraction, which scavenged DPPH at an IC50 of 38.4 µg/mL, was also the fraction that suppressed tumour necrosis factor-α and interleukin-6, linking in vitro redox capacity to in vivo cytokine suppression, as previous phytochemical reports could only postulate. Most importantly, the divergent safety profiles, with paracetamol raising alanine aminotransferase by 36% while the extracts left all four organ markers unchanged, supply the comparative safety dimension that the existing literature on this plant almost entirely lacks, and on which any eventual formulation claim would rest.

6. CONCLUSION

This study set out to determine whether the long-standing ethnomedicinal reputation of Cyperus scariosus as a febrifuge could be substantiated by quantitative measurement, and the answer is affirmative but qualified. In a controlled, seven-group, six-animal design, the ethanolic rhizome extract produced a monotonic, log-linear dose–response relationship across 100, 200 and 400 mg/kg, inhibiting the febrile burden by 33.3%, 48.5% and 66.7% respectively against 71.3% for paracetamol at 150 mg/kg. The highest dose reduced the febrile rise by 95.5% at the fourth hour and returned rectal temperature to the pre-febrile set point, with a relative potency of 0.94 and an ED50 of 204 mg/kg derived from a regression that explained 99.7% of the variance. The aqueous extract was consistently inferior at an equal dose, reaching 56.7% inhibition, a difference that tracks its lower phenolic and flavonoid content and its weaker radical-scavenging capacity. Mechanistically, antipyresis was accompanied by dose-ordered suppression of tumour necrosis factor-α and interleukin-6, with correlations of −0.97 between cytokine concentration and inhibition of AUC, indicating that the effect is exerted on the cytokine cascade rather

than on peripheral heat loss alone. The safety profile favours the extract decisively: hepatic and renal markers remained within reference limits at every dose tested, whereas paracetamol elevated alanine aminotransferase by 36%. These findings substantiate the traditional use of the rhizome, identify approximately 200–400 mg/kg as the pharmacologically relevant range in the rat, and justify bioassay-guided fractionation, repeated-dose toxicology and formulation studies before any clinical translation is contemplated.

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