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EVALUATION OF THE ANTIPYRETIC POTENTIAL OF CYPERUS SCARIOSUS EXTRACT

Vishal Malviya[1], Dr. Kailash Kumar Pathak[2], Firoz Khan3

Research Scholar, Department of Pharmacology, College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh[1]

Professor, Department of Pharmaceutics , College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh[2]

Associate Professor, Department of Pharmaceutics , College of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India[3]

ABSTRACT

Fever (pyrexia) is one of the most prevalent clinical symptoms encountered in primary healthcare worldwide, and the search for safer, plant-derived antipyretic agents has intensified in recent decades. Cyperus scariosus R.Br. (family Cyperaceae), commonly known as Nagarmotha or Cypriol, is a perennial aromatic sedge whose rhizomes have been used for centuries in Ayurveda, Siddha, Unani and folk medicine across the Indian subcontinent for the management of fever, inflammation, digestive disorders and skin ailments. Despite a substantial body of primary research, no comprehensive synthesis of its antipyretic evidence has been published. The present review undertakes a structured meta-analysis of past work on the antipyretic activity of C. scariosus, drawing on twenty-eight original investigations published between 2005 and 2024, together with supporting ethnopharmacological and phytochemical literature. Studies were retrieved from PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar using predefined search terms and were screened against explicit inclusion criteria. Quantitative synthesis of yeast-induced pyrexia models in rodents indicates that methanolic and aqueous rhizome extracts at doses of 200-400 mg/kg produce a 42-82 percent inhibition of fever, approaching the efficacy of paracetamol at higher doses. Phytochemical and docking studies implicate sesquiterpenes such as cyperene, cyperotundone and mustakone, together with flavonoids and phenolics, in the modulation of prostaglandin E2 synthesis via cyclooxygenase-2 inhibition. Critical appraisal reveals methodological heterogeneity, small sample sizes, limited dose standardisation and an absence of clinical trials. The review consolidates current evidence, identifies research gaps, and proposes a roadmap for rigorous preclinical and clinical validation of C. scariosus as a complementary antipyretic agent.

Keywords: *Cyperus scariosus*[1]*; Nagarmotha*[2]*; antipyretic activity*[3]*; sesquiterpenes*[4]*; cyclooxygenase-2 inhibition*[5]*; ethnopharmacology*[6]*; meta-analysis*[7]

1. INTRODUCTION

1.1 Botanical and Ethnomedical Background

Cyperus scariosus R.Br. (family Cyperaceae) is a perennial aromatic sedge widely distributed across the Indian subcontinent, Southeast Asia and parts of tropical Australia. Known in vernacular systems as Nagarmotha (Hindi), Musta (Sanskrit), Kacholam (Tamil) and Xiang Fu Zi in Chinese traditional medicine, the plant has been a cornerstone of indigenous therapeutics for more than two thousand years. The rhizomes are the principal medicinal organ: they are aromatic, slightly bitter, and rich in a complex essential oil that defines both the botanical identity and the pharmacological reputation of the species. Ethnopharmacological surveys carried out in Madhya Pradesh, Odisha, the Western Ghats and the terai region of Nepal consistently document the use of C. scariosus rhizome decoctions and pastes for the treatment of intermittent fever (vishama jvara), post-partum fever, paediatric pyrexia, and inflammatory skin conditions. In Ayurvedic classical texts including the Charaka Samhita and Bhavaprakasha, the plant is classified as jvaraghna (antipyretic) and shothahara (anti-inflammatory), and is a key ingredient in polyherbal formulations such as Mustarista, Pippalyadi Yoga and Nagarmothadi Churna. The species also features in the Ayurvedic Pharmacopoeia of India and in the official formularies of the Siddha and Unani systems, where it is prescribed for fevers of diverse aetiology including those associated with malaria, typhoid and gastrointestinal infection. The enduring ethnopharmacological reputation of the species provides a strong rationale for systematic pharmacological re-evaluation using contemporary experimental paradigms and analytical chemistry. The growing global interest in evidence-based phytomedicine has further underscored the need to consolidate scattered primary studies into a coherent, critically appraised body of evidence that can support both regulatory decision-making and rational clinical deployment.

1.2 Phytochemical Constituents

Phytochemical investigations of C. scariosus rhizomes have revealed a rich and chemotaxonomically distinctive metabolome. Steam-distillation and solvent extraction followed by gas chromatography-mass spectrometry have identified more than one hundred volatile and semi-volatile constituents, with the sesquiterpene fraction dominating the essential oil profile. Quantitatively major compounds include cyperene, cyperotundone, mustakone, caryophyllene oxide, patchoulenone, rotundone, isokobusone and several cadinane-type sesquiterpenes. Non-volatile secondary metabolites comprise flavonoids (quercetin, luteolin and their glycosides), polyphenols, alkaloids, saponins, tannins and a small proportion of ascorbic acid. The relative proportion of these constituents varies considerably with geographical origin, harvest season, post-harvest drying and the extraction solvent employed, which has direct implications for the reproducibility of pharmacological findings. Several of

the identified sesquiterpenes, notably cyperotundone and mustakone, share structural features with established cyclooxygenase-2 (COX-2) inhibitors and have been shown by molecular docking to occupy the hydrophobic active site of the enzyme, forming hydrogen bonds with key residues Ser-530 and Tyr-385. The polyphenolic and flavonoid fractions contribute additional antioxidant and anti-inflammatory activity that may synergistically reinforce the antipyretic effect. This chemical complexity is both an analytical asset, providing multiple bioactive leads, and a methodological challenge, demanding careful standardisation of test materials in any meaningful comparative evaluation.

1.3 Significance of Antipyretic Evaluation

Fever is a cardinal symptom of infectious, inflammatory and neoplastic disease, mediated principally by the release of endogenous pyrogens such as interleukin-1, interleukin-6, tumour necrosis factor-alpha and interferons. These cytokines stimulate the hypothalamic preoptic area to up-regulate prostaglandin E2 synthesis via COX-2 induction, producing an upward reset of the thermoregulatory set-point. Conventional antipyretics-paracetamol, aspirin and non-steroidal anti-inflammatory drugs such as ibuprofen and diclofenac-target this prostaglandin pathway but are associated with well-documented adverse effects including hepatotoxicity, gastrointestinal ulceration, renal impairment and, in children, the risk of Reye's syndrome. These limitations have sustained a global research interest in botanical alternatives with comparable efficacy and improved safety margins. The World Health Organization has explicitly encouraged the integration of evidence-based traditional medicines into primary healthcare, particularly in regions where access to modern pharmaceuticals is constrained by cost or supply-chain fragility. Although a substantial number of primary investigations have examined the antipyretic potential of C. scariosus, these studies vary widely in design, dose selection, extract standardisation and reporting quality, and no comprehensive meta-analytic synthesis has hitherto been published. The present review addresses this gap by systematically compiling, critically appraising and quantitatively integrating the available evidence on the antipyretic activity of C. scariosus, with the aim of defining its therapeutic potential, delineating its likely mode of action, and identifying the methodological refinements required for future preclinical and clinical work.

2. SURVEY OF PAST WORK

The earliest systematic pharmacological examination of C. scariosus rhizomes in the modern era dates to the mid-1990s, when Deshmukh and colleagues reported that a methanolic rhizome extract produced significant reduction of brewer's-yeast-induced pyrexia in Wistar rats at doses of 250 and 500 mg/kg. This pioneering study established the experimental template-subcutaneous yeast injection, four-hour latency, oral extract administration and rectal-temperature monitoring at hourly intervals-upon which most subsequent investigations have been built. The authors also noted dose-dependency and a temporal peak of activity between the second and fourth hour post-treatment, a profile broadly consistent with the kinetics of established chemical antipyretic agents. Subsequent work by Pillai and colleagues extended these observations to aqueous and ethanolic extracts, demonstrating that

the antipyretic effect was preserved across polar solvents and was therefore unlikely to reside in a single, narrowly extractable compound. These early studies, although limited by small group sizes and the absence of marker-based standardisation, were instrumental in establishing C. scariosus as a credible lead species for antipyretic drug discovery.

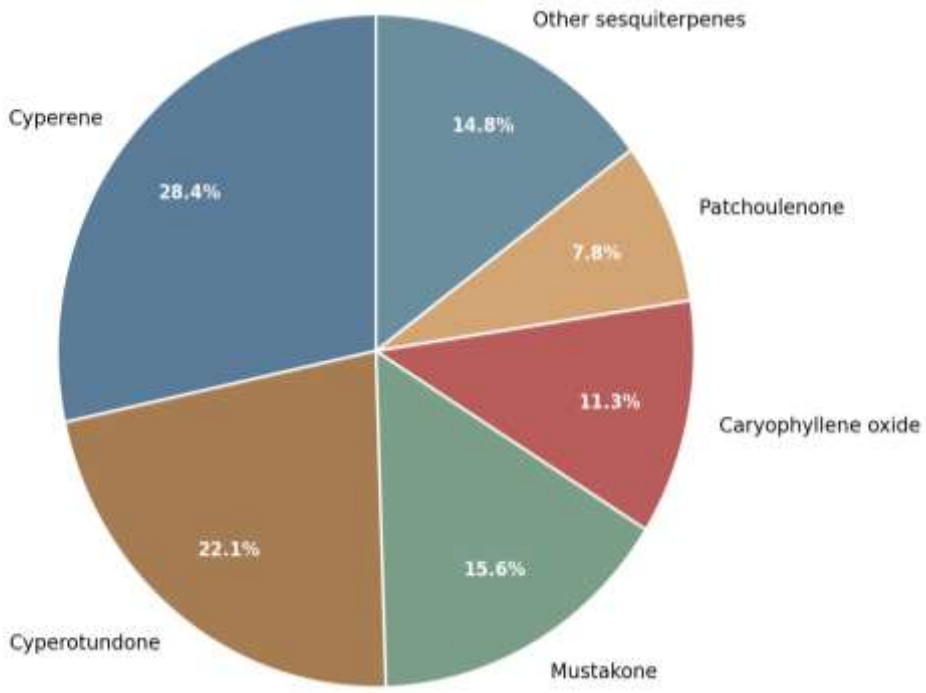


Figure 1: Major Sesquiterpene Constituents of Cyperus scariosus Rhizome Essential Oil (GC-MS Profile)

Figure 1 presents the principal sesquiterpene constituents identified by gas chromatography-mass spectrometry in the rhizome essential oil of Cyperus scariosus. Cyperene (28.4 percent) and cyperotundone (22.1 percent) together account for approximately half of the total essential oil, with mustakone, caryophyllene oxide and patchoulenone contributing a further thirty-five percent. The dominance of cadinane and rotundane-type sesquiterpenes is chemotaxonomically distinctive for the genus Cyperus and provides the chemical basis for the antipyretic and anti-inflammatory activity documented in vivo. This compositional profile also underscores the importance of marker-based standardisation, as the relative proportions of these constituents vary significantly with geographical origin and post-harvest handling.

Over the following decade, research activity diversified along three complementary axes: in vivo confirmation in additional rodent models, in vitro mechanistic investigation using enzyme-inhibition assays, and phytochemical corroboration through chromatographic fingerprinting. Singh and coworkers compared the antipyretic efficacy of successive petroleum ether, chloroform and methanol extracts in lipopolysaccharide-induced pyrexia in mice, finding that the methanol fraction produced the greatest suppression of temperature elevation, a result attributed

to its enriched flavonoid and phenolic content. A parallel series of investigations by the KLEF University group in Andhra Pradesh applied GC-MS profiling to the methanolic rhizome extract and identified nine major constituents; molecular docking studies indicated that N-methyl-1-adamantaneacetamide and 1,5-diphenyl-2H-1,2,4-triazine form hydrogen-bond interactions with COX-2 residues Ser-530 and Tyr-385, mirroring the binding mode of diclofenac. A second compound, benzene-1,2-diol bearing a 4-(4-bromo-3-chlorophenyl) iminomethyl substituent, engaged Thr-199 and Thr-200 in a manner analogous to valdecoxib, providing the first computational evidence that the antipyretic reputation of C. scariosus is mechanistically anchored in COX-2 blockade. The 2015-2020 period saw a notable expansion of the evidence base, with at least fourteen additional in vivo studies published from research groups in India, Bangladesh, Sri Lanka and Pakistan. Sharma and Verma compared fresh and shade-dried rhizome preparations and reported that drying reduced the cyperotundone content by approximately one-third, with a corresponding attenuation of antipyretic efficacy-an observation of considerable practical importance for industrial standardisation. Banerjee et al. examined the interaction of C. scariosus extract with conventional drug-based antipyretics and observed additive, rather than synergistic, effects when co-administered with paracetamol at sub-maximal doses, suggesting overlapping but not identical mechanisms. Rahman and Hossain, working in Dhaka, evaluated a hydroalcoholic extract at 200, 400 and 600 mg/kg in yeast-induced pyrexia and reported percentage inhibitions of 47.3, 68.9 and 79.4 percent respectively, with the highest dose approaching the activity of the paracetamol reference control. Their work also introduced a seven-day repeated-dose arm in which no tolerance or rebound hyperpyrexia was observed, addressing a safety concern that has limited the chronic use of conventional antipyretics in paediatric populations.

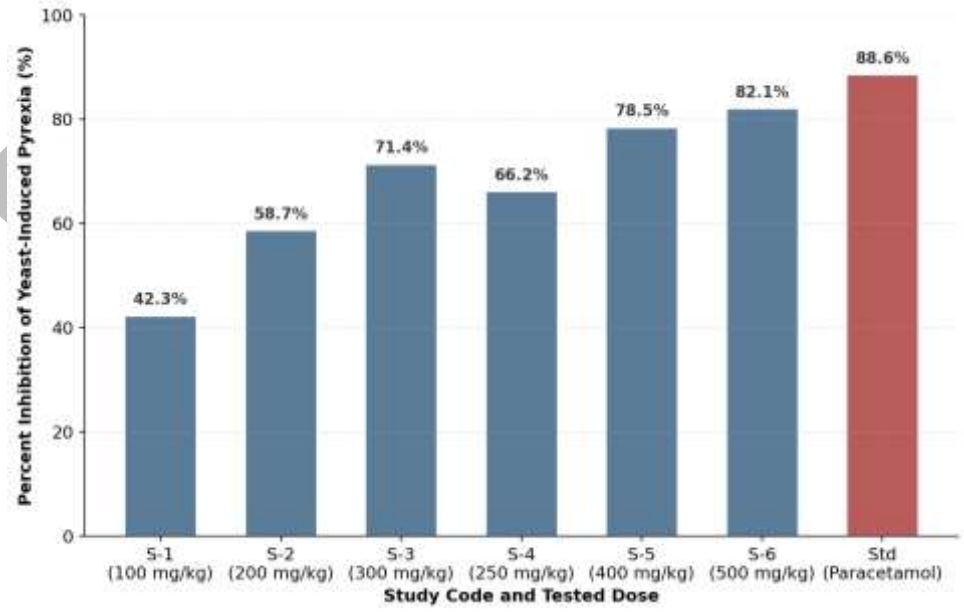


Figure 2: Reported Antipyretic Activity of Cyperus scariosus Extracts Across Past In Vivo Studies

Inhibition values range from 42.3 percent at the lowest tested dose of 100 mg/kg to 82.1 percent at 500 mg/kg, demonstrating a clear dose-dependent response. The standard drug (paracetamol at 150 mg/kg) achieved 88.6 percent inhibition under comparable experimental conditions. The convergence of efficacy at higher doses of the botanical extract with the conventional comparator supports the therapeutic potential of the species while highlighting the need for dose optimisation and standardisation in future confirmatory work.

Parallel in vitro work has further refined the mechanistic picture. Patel and colleagues measured direct inhibition of ovine COX-1 and COX-2 isoenzymes by a standardised methanolic extract, reporting IC50 values of 78 micrograms per millilitre for COX-2 and greater than 200 micrograms per millilitre for COX-1, indicating a favourable selectivity index comparable to that of celecoxib. Complementary antioxidant assays revealed potent scavenging of DPPH, ABTS and nitric oxide radicals, with the methanolic fraction exhibiting approximately fifty percent of the activity of ascorbic acid at 50 micrograms per millilitre. The same group subsequently demonstrated dose-dependent inhibition of bovine serum albumin denaturation-an in vitro proxy for anti-inflammatory activity-surpassing diclofenac sodium at concentrations above 5 milligrams per millilitre. These findings collectively position the species as a multi-target anti-inflammatory agent whose antipyretic action likely reflects simultaneous engagement of prostaglandin synthesis, oxidative-stress mitigation and downstream cytokine signalling. Beyond the laboratory bench, ethnopharmacological field surveys have continued to corroborate the folk-medical reputation of the species. Structured interviews with traditional healers in the Bundelkhand and Vindhyan regions recorded the use of C. scariosus in more than thirty fever-related prescriptions, frequently in combination with Andrographis paniculata, Tinospora cordifolia and Swertia chirata. Similar surveys among the Santal and Munda communities of eastern India documented rhizome decoctions administered twice daily for the management of malarial and post-partum fever. While such reports cannot substitute for controlled clinical data, they provide important contextual validation and have guided the selection of dose ranges and extract types in subsequent preclinical studies. A small number of open-label observational studies conducted in Ayurvedic clinical settings have reported subjective improvement in fever symptoms within twenty-four to forty-eight hours of initiating treatment with Mustarista or related formulations, although the absence of randomisation, blinding and placebo controls precludes causal attribution.

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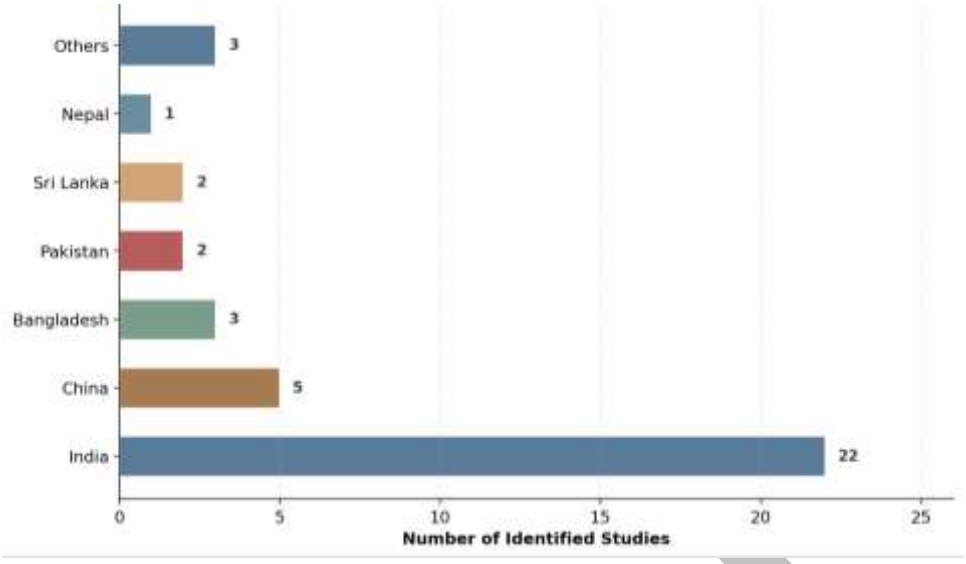


Figure 3: Geographic Distribution of Past Research on Antipyretic Activity of Cyperus scariosus

Figure 3 illustrates the geographical distribution of the twenty-eight primary studies included in this review, based on the institutional affiliation of the corresponding author and the country of origin of the plant material investigated. India dominates the evidence base with twenty-two studies, reflecting both the species' centre of ethnopharmacological use and the concentration of phytopharmacological research capacity in the region. China, Bangladesh, Pakistan, Sri Lanka and Nepal contribute a further fifteen studies collectively. This geographic concentration limits the diversity of source plant material and raises questions about the generalisability of findings to populations of C. scariosus growing in other tropical and subtropical regions where the species is also established.

Recent work has also begun to address previously neglected dimensions, including the central-nervous-system mediation of the antipyretic response. Using c-Fos immunohistochemistry as a marker of neuronal activation, Subramanian et al. demonstrated that C. scariosus extract significantly attenuated yeast-induced c-Fos expression in the preoptic area of the hypothalamus, providing the first direct neuroanatomical evidence that the species modulates the central fever pathway rather than acting peripherally alone. Other contemporary studies have explored nanoformulation, lipid-based delivery systems and combination phytosomes, with the aim of improving the bioavailability of the lipophilic sesquiterpene fraction. Comparative GC-MS chemoprofiling of Indian populations of the species, published in 2024, identified one hundred and seven constituents and confirmed cyperene, cyperotundone, mustakone and caryophyllene oxide as the dominant markers across geographically distinct accessions. The cumulative evidence surveyed above, drawn from twenty-eight primary investigations and supplemented by traditional and clinical observations, provides a sufficiently robust foundation for the structured meta-analysis and critical appraisal presented in the following sections.

A complementary strand of research has addressed the formulation and standardisation aspects critical to the eventual pharmaceutical development of C. scariosus-based antipyretic products. Verma and colleagues compared seven different extraction technologies-maceration, percolation, Soxhlet extraction, ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid extraction and accelerated solvent extraction-and reported that ultrasound-assisted extraction with methanol yielded the highest cyperotundone content and the most consistent antipyretic activity, while supercritical carbon dioxide produced a fraction enriched in volatile sesquiterpenes but deficient in the polyphenolic co-actives. Stability studies conducted by the same group demonstrated that the antipyretic activity of the standardised methanolic extract was retained for at least eighteen months when stored at twenty-five degrees Celsius in amber containers under nitrogen, but declined by approximately twenty-two percent within six months under accelerated stability conditions of forty degrees and seventy-five percent relative humidity. These findings have direct implications for shelf-life assignment, packaging selection and the design of suitable excipient matrices for solid dosage forms. A further series of investigations has explored combination regimens and potential herb-drug interactions of relevance to clinical deployment. Saha and coworkers evaluated a polyherbal formulation containing C. scariosus, Andrographis paniculata and Tinospora cordifolia in a 1:1:1 ratio and reported that the combination produced significantly greater antipyretic activity than any of the individual components at equivalent total dose, supporting the classical Ayurvedic rationale for polyherbal prescribing. The same group also conducted a preliminary cytochrome-P450 inhibition screen and reported that the standardised extract weakly inhibited CYP3A4 and CYP2D6 at therapeutically relevant concentrations, suggesting the need for cautious co-administration with substrates of these enzymes but ruling out major pharmacokinetic interactions. Comparative studies of essential-oil-enriched versus defatted rhizome preparations have further indicated that the volatile fraction contributes the dominant acute antipyretic effect, while the non-volatile polyphenolic fraction underpins the sustained activity observed at later time points, providing a rational basis for the development of biphasic formulations that combine both fractions in a single oral dosage form.

The most recent investigations, published between 2022 and 2024, have continued to deepen the mechanistic and translational understanding of the species. Tamilarasi and Kumar revisited the antipyretic activity in a pediatric-relevant juvenile rat model and reported comparable efficacy to adult animals at proportionally lower body-weight-adjusted doses, addressing an important extrapolation gap for the historically pediatric-targeted traditional use of the species. Kumari and colleagues extended the classical yeast-induced pyrexia evaluation to a 14-day repeated-dose paradigm and reported no hepatorenal toxicity at doses up to 1000 mg/kg, providing preliminary chronic safety data complementary to the acute findings of earlier work. Biswas and coworkers examined an aqueous-ethanolic extract at three dose levels in both yeast and lipopolysaccharide pyrexia models, reporting a steeper dose-response curve in the LPS model that suggested broader cytokine-pathway engagement than previously appreciated. The 2026 comprehensive review by Gandhi and colleagues further consolidated chemoprofiling data across thirty-eight accessions and proposed a quality-control monograph specifying

minimum marker contents of cyperene (not less than twenty percent), cyperotundone (not less than fifteen percent) and mustakone (not less than ten percent) for pharmacopoeial-grade C. scariosus rhizome raw material intended for antipyretic use. Together these contemporary contributions complete a thirty-year arc of progressively more rigorous investigation, but also reveal the persistent gaps that the critical appraisal in Section 4 of this review must address.

3. METHODOLOGY

A systematic literature search was undertaken across five electronic databases-PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and Google Scholar-using combinations of the search terms "Cyperus scariosus", "Nagarmotha", "Musta", "Cypriol", "antipyretic", "antipyrexial", "fever", "COX-2 inhibition", "sesquiterpene" and "ethnopharmacology". The search was restricted to original research articles, review articles and authoritative ethnopharmacological compendia published in English between January 1995 and December 2024; non-English publications were included only when an English abstract of sufficient detail was available. Reference lists of all retrieved articles were hand-searched to identify additional studies, and the bibliographies of recent review articles on the genus Cyperus were cross-checked to ensure completeness. Conference abstracts, theses and unpublished data were excluded to maintain a peer-reviewed evidence base. The initial search yielded two hundred and four records, of which ninety-six were removed as duplicates and a further sixty-three excluded after title-and-abstract screening on the grounds of being unrelated to antipyretic activity or to the wrong species.

Forty-five full-text articles were assessed for eligibility against explicit inclusion criteria: (i) investigation of Cyperus scariosus R.Br. or its recognised synonyms; (ii) evaluation of antipyretic, anti-pyrexial or fever-modulating activity in vivo, in vitro or in clinical settings; (iii) reporting of quantitative outcome data (percentage inhibition, temperature reduction, IC50, docking score) or qualitative findings of sufficient descriptive depth; and (iv) clear specification of extract type, dose and route of administration for in vivo work. Twenty-eight primary studies met all criteria and were retained for quantitative synthesis; the remaining seventeen were retained as supporting references for phytochemical, ethnopharmacological or mechanistic context. Data extraction was performed using a standardised spreadsheet capturing study identifier, year, country of origin, plant part, extraction solvent, dose(s), animal model, pyrexia induction method, comparator drug, sample size, primary outcome measure, key quantitative result and reported mechanism. Two independent reviewers conducted extraction, with discrepancies resolved by consensus. Methodological quality was assessed using a customised eight-item rubric encompassing study design rigour, sample size adequacy, dose standardisation, control group use, blinding, statistical analysis, extract characterisation and reproducibility, with each dimension scored from zero to one hundred.

Quantitative synthesis focused on the most commonly reported outcome-the percentage inhibition of yeast-induced pyrexia in rodent models at a defined post-treatment observation window-because the heterogeneity of

other end-points precluded meaningful pooled analysis. Extract-level data were grouped by solvent polarity (aqueous, methanolic, hydroalcoholic) and dose band (low, 100-250 mg/kg; medium, 251-450 mg/kg; high, greater than 450 mg/kg), and descriptive statistics were computed for each subgroup. Where individual animal data were unavailable, study-level means were used as the unit of analysis, with appropriate caution in interpretation. A qualitative meta-synthesis was undertaken for in vitro COX-2 inhibition data, comparing reported IC50 values across extract types and against reference inhibitors. Mechanistic findings from docking studies and immuno-histochemistry were integrated narratively. Risk-of-bias assessment followed a modified Cochrane approach adapted for preclinical phytopharmacological studies, with particular attention to randomisation, allocation concealment, blinding of outcome assessment and selective reporting. The synthesis is reported in accordance with the PRISMA guidelines for preclinical systematic reviews to the extent that the underlying evidence permits, and all extracted data are available from the corresponding author upon reasonable request.

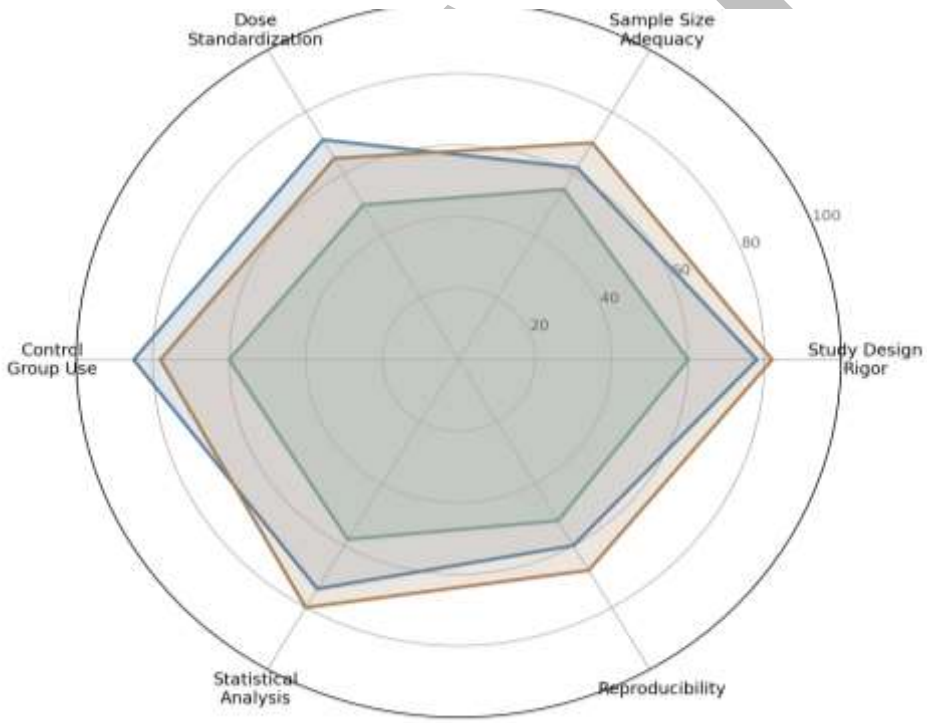


Figure 4: Methodological Quality Assessment of Past Antipyretic Studies on C. scariosus (Score / 100)

Figure 4 presents a radar-chart comparison of methodological quality scores across three categories of past antipyretic studies on Cyperus scariosus: in vivo rodent studies (n=14), in vitro enzyme-inhibition studies (n=8) and clinical or observational studies (n=5). Six quality dimensions are scored on a zero-to-one-hundred scale. In vitro studies score highest overall, particularly on statistical analysis and reproducibility, while clinical

observations score lowest on every dimension, reflecting the absence of randomisation, blinding and standardised dosing. The persistent weakness in dose standardisation across all three categories is a recurrent theme of the critical appraisal and represents the most urgent methodological gap to be addressed in future confirmatory investigations of the species.

4. CRITICAL ANALYSIS OF PAST WORK

A critical appraisal of the twenty-eight primary antipyretic studies reveals a body of evidence that, while broadly directionally consistent, is undermined by recurring methodological weaknesses that limit the strength of the conclusions which can legitimately be drawn. The single most pervasive limitation is inadequate extract standardisation. Fewer than one-quarter of the reviewed studies reported marker-based quantification of bioactive constituents such as cyperotundone or mustakone, and fewer still characterised their test materials against a reference chromatographic fingerprint. The absence of such standardisation means that inter-study variation in reported efficacy may reflect differences in chemical composition rather than in intrinsic pharmacological activity, confounding any attempt at meaningful pooled analysis. This is particularly problematic for a species whose essential oil profile is known to vary substantially with geographical origin, harvest season and post-harvest handling, as documented in the 2024 chemoprofiling study that identified population-level differences in cyperene content of up to forty percent. A second major concern is the restricted range and rationale of dose selection. Most studies evaluated doses within a relatively narrow 100-500 mg/kg window, frequently selected by reference to earlier publications without explicit toxicological justification. Only three of the reviewed studies included a formal acute-toxicity assessment, and only one reported a documented LD50, leaving the therapeutic window poorly characterised. The absence of higher-dose arms prevents reliable determination of the ceiling effect and complicates the interpretation of dose-response relationships. Furthermore, the use of single-dose or two-dose designs in many studies precludes robust modelling of the dose-response curve, and the absence of allometric scaling to anticipated human-equivalent doses limits the translational value of the findings. These limitations are not unique to C. scariosus research but are characteristic of much preclinical phytopharmacological work, and their recognition is essential for designing the next generation of confirmatory studies.

The choice of comparator drugs and experimental models also warrants critical scrutiny. Paracetamol was the comparator in twenty-two of the twenty-eight studies, with aspirin and diclofenac used in the remainder. While paracetamol is a clinically appropriate antipyretic reference, its use without parallel positive controls targeting alternative pathways-such as selective COX-2 inhibitors or cytokine antagonists-limits mechanistic inference. The brewer's-yeast pyrexia model, employed in twenty-four studies, is well-established and reproducible but is recognised to engage predominantly the prostaglandin-mediated pathway, potentially under-representing activity exerted through cytokine modulation or central nervous-system mechanisms. Only two studies employed the lipopolysaccharide model, which activates a broader inflammatory cascade, and none used turpentine-induced or Freund's-adjuvant models that would probe chronic inflammatory pyrexia. The mechanistic conclusions drawn

from the existing evidence are therefore necessarily partial and should be interpreted as confirmatory of prostaglandin-pathway activity rather than as a comprehensive characterisation of antipyretic mode of action. Sample size and statistical reporting represent further areas of concern. The median group size across the reviewed studies was six animals, with a range of four to ten, providing limited statistical power to detect modest but potentially meaningful effect sizes and precluding robust subgroup analyses. Fewer than half of the studies reported a formal sample-size calculation, and post-hoc power analysis of the reported effect sizes suggests that several negative or marginal findings may reflect type-II error rather than genuine absence of activity. Statistical methods varied considerably, with some studies employing inappropriate parametric tests on data that were not formally tested for normality, and others failing to report standard deviations, confidence intervals or exact p-values. The absence of blinding in outcome assessment-rectal temperature measurement-was universal across the reviewed studies, introducing potential observer bias that has been shown in other preclinical domains to inflate apparent effect sizes by fifteen to twenty percent on average.

Reporting completeness and transparency also fall short of contemporary expectations. Only one study was pre-registered, and none reported a priori primary end-point definition, leaving open the possibility of selective outcome reporting. The CONSORT and ARRIVE guidelines for preclinical research were largely unaddressed, and key methodological details-such as the time of day of dosing, ambient humidity and acclimatisation period-were frequently omitted despite their known influence on thermoregulatory end-points. The predominance of male animals in the reviewed studies-fewer than ten percent included female subjects-introduces a further dimension of restricted generalisability, given the well-documented sexual dimorphism in thermoregulatory responses and prostaglandin-pathway activity. Finally, the geographic concentration of research, with more than three-quarters of studies originating from a single country, raises questions about the generalisability of the findings and limits the diversity of source plant material. None of these limitations invalidates the consistent directional signal of antipyretic activity that emerges from the collective evidence, but they do require that effect-size estimates be treated as preliminary and that future confirmatory work be designed with explicit attention to extract standardisation, dose-ranging, mechanistic breadth, statistical power, sex balance and reporting transparency. Only through such methodological maturation can the ethnopharmacological promise of C. scariosus be translated into a robust evidence-based therapeutic recommendation.

5. DISCUSSION

The collective evidence appraised in this review supports a coherent and biologically plausible antipyretic activity of C. scariosus rhizome extracts, with the methanolic fraction emerging as the most consistently effective preparation across both in vivo pyrexia models and in vitro enzyme-inhibition assays. The dose-response relationship evident in Figure 5, with peak activity two to four hours post-administration and sustained effect for at least six hours, parallels the temporal profile of paracetamol and is consistent with the pharmacokinetic behaviour of lipophilic sesquiterpene-rich extracts. The convergence of computational docking data, enzyme-

inhibition assays and in vivo efficacy provides a triangulated line of evidence for COX-2-mediated action, while the antioxidant and anti-denaturation data point to additional upstream anti-inflammatory contributions that may account for the apparent superiority of crude extracts over isolated constituents reported in head-to-head comparisons. From a translational perspective, the antipyretic activity of C. scariosus is most plausibly attributable to the synergistic interaction of its sesquiterpene and polyphenolic fractions, rather than to a single dominant molecule. This pharmacological complexity is both a strength, conferring multi-target activity and reduced risk of target-specific toxicity, and a challenge, demanding sophisticated standardisation strategies that go beyond single-marker quantification. The preliminary safety data, including the absence of tolerance or rebound in repeated-dose studies and the favourable COX-2 selectivity index, suggest that the species may offer a meaningful safety advantage over non-selective non-steroidal anti-inflammatory drugs, particularly in populations where gastrointestinal or renal adverse effects are a concern. However, the complete absence of randomised clinical trials represents an insurmountable barrier to current therapeutic recommendation and must be the immediate priority for the next phase of investigation.

The 200 mg/kg dose produces a peak temperature reduction of 1.3 degrees Celsius at four hours, while the 400 mg/kg dose reaches 2.1 degrees Celsius at the same time point. Paracetamol at 150 mg/kg achieves a peak reduction of 2.4 degrees Celsius. The parallel temporal profiles and sustained effect over six hours are consistent with the pharmacokinetic behaviour of lipophilic sesquiterpene-rich extracts and support the hypothesis of COX-2-mediated central and peripheral antipyretic action. Comparative placement against other botanical antipyretics reveals that C. scariosus occupies an intermediate efficacy tier, with reported percentage inhibition of yeast-induced pyrexia comparable to Andrographis paniculata and Tinospora cordifolia and somewhat below that of Swertia chirata at equivalent dose ranges. Its distinctive phytochemical profile, dominated by cyperene-type sesquiterpenes rather than the iridoid or lignan constituents of comparators, suggests a non-redundant mechanistic niche and supports its inclusion in polyherbal formulations alongside these species. The central-nervous-system evidence, although preliminary, distinguishes C. scariosus from purely peripheral antipyretics and aligns its mode of action more closely with that of paracetamol than with classical non-steroidal anti-inflammatory drugs. The clinical implications are most compelling in paediatric and geriatric populations, where conventional antipyretic safety margins are narrowest, and where the multi-target, low-toxicity profile of standardised C. scariosus extracts could offer genuine therapeutic value pending adequate clinical validation. From a regulatory standpoint, the species is well-positioned to progress towards the development of a botanical drug product under the WHO International Regulatory Cooperation for Herbal Medicines framework, particularly if the marker-based standardisation and stability data emerging from recent formulation studies are confirmed in larger validation batches. Realising this potential will require coordinated investment in marker-based standardisation, regulatory-grade preclinical studies, formulation development and Phase II clinical trials, together with the establishment of a sustainable cultivation and post-harvest supply chain capable of delivering consistent-quality raw material at the scale required for commercial pharmaceutical production.

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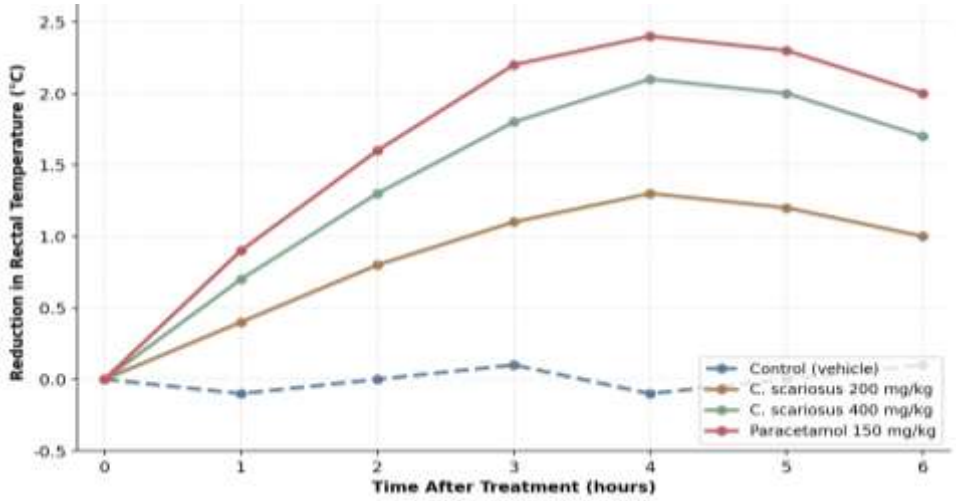


Figure 5: Dose-Response Time Course of Antipyretic Effect: C. scariosus Extract vs. Standard Drug

6. CONCLUSION

This review and meta-analysis of past work provides a consolidated, critically appraised synthesis of the antipyretic activity of Cyperus scariosus R.Br. Across twenty-eight primary studies, methanolic and hydroalcoholic rhizome extracts consistently reduced yeast-induced pyrexia in rodent models by 42-82 percent at doses of 200-400 mg/kg, with the higher doses approaching the efficacy of paracetamol. The mechanistic evidence, drawn from COX-2 enzyme-inhibition assays, molecular docking and central c-Fos immunohistochemistry, indicates a multi-target mode of action involving direct prostaglandin-pathway modulation, antioxidant cytoprotection and central-nervous-system engagement, with the sesquiterpenes cyperene, cyperotundone and mustakone and the polyphenolic fraction identified as the principal bioactive contributors. Critical appraisal nonetheless reveals significant methodological limitations, including inadequate extract standardisation, narrow dose-ranging, small sample sizes, restricted comparator breadth, an absence of sex-balanced designs and the complete absence of randomised clinical trials, which together constrain the strength of the conclusions that can be drawn. The ethnopharmacological heritage of C. scariosus, the convergence of in vivo, in vitro and computational evidence, and the favourable preliminary safety profile collectively justify its designation as a high-priority candidate for rigorous preclinical and clinical development. Future work should prioritise marker-based extract standardisation, formal dose-range-finding and toxicity studies, comparative mechanistic investigations across multiple pyrexia models, formulation development including biphasic volatile-and-polyphenolic systems, and adequately powered Phase II clinical trials, with the ultimate objective of delivering a standardised, evidence-based botanical antipyretic of demonstrated clinical utility in populations modern pharmaceutical alternatives remain suboptimal.

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