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ANTIPYRETIC AND PHYTOCHEMICAL EVALUATION OF *ZEPHYRANTHES CANDIDA* HERB

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ABSTRACT

Zephyranthes candida Herb. (Amaryllidaceae), commonly known as the rain lily, has garnered attention in ethnopharmacology for its traditional use in managing fever, convulsions, and epilepsy in Indian and South American folk medicine. This study provides a comprehensive evaluation of its antipyretic activity and phytochemical profile, incorporating recent advancements in phytochemical analysis and in vivo modeling. The methanolic flower extract was assessed for antipyretic effects using the yeast-induced pyrexia model in Wistar rats (n=36), at doses of 100, 200, and 400 mg/kg body weight, benchmarked against paracetamol (100 mg/kg). Results demonstrated significant dose-dependent temperature reduction, with the 200 mg/kg dose achieving 92.30% inhibition at 3 hours ($p < 0.001$ vs. control), surpassing the standard (78.57%). Phytochemical screening identified key bioactive compounds, including flavonoids (45.2 mg QE/g), phenolics (28.6 mg GAE/g), and alkaloids (3.8% w/w), corroborated by HPLC-MS revealing quercetin (8.2 µg/mg) and lycorine analogs. Antioxidant assays (DPPH IC50 = 142.3 µg/mL; FRAP = 1.8 mmol Fe^{2+}/g) suggest anti-inflammatory synergy via ROS scavenging and COX-2 inhibition. Acute toxicity (OECD 423) confirmed safety (LD50 >2000 mg/kg). Two tables illustrate dose-responses and phytochemical yields. Present study on Amaryllidaceae bioactivity, highlighting lycorine's role in PGE2 modulation and Z. candida's potential as a non-toxic antipyretic amid rising synthetic drug resistance. Limitations include single-model validation; future research recommends molecular docking and multi-herb synergies for clinical translation.

KEYWORDS: *Zephyranthes candida*, antipyretic activity, yeast-induced pyrexia, phytochemical screening, Amaryllidaceae alkaloids, flavonoids, oxidative stress, ethnopharmacology.

INTRODUCTION

Fever (pyrexia) is a regulated physiological response to infection or inflammation, mediated by hypothalamic PGE2 synthesis, but persistent hyperthermia (>39°C) risks dehydration, seizures, and organ failure. Globally, fever contributes to 5 million deaths annually, particularly in low-resource settings reliant on traditional remedies.[1-4] Synthetic antipyretics like paracetamol and ibuprofen, while effective (70–90% inhibition), are marred by hepatotoxicity (ALT elevation >3x in 1–2% users) and gastric ulceration (15% chronic users). This has revitalized interest in plant-based alternatives, especially from Ayurveda and Siddha traditions, where >80% of India's population uses herbal medicine for primary care.[5-9]

Zephyranthes candida Herb. (Amaryllidaceae), a bulbous perennial native to subtropical Americas but naturalized in India, is traditionally employed for fever, tetanus, and infantile convulsions in Uttar Pradesh and West Bengal folklore. Its white flowers, blooming post-rain, symbolize renewal, aligning with its purported "cooling" effects.[9-12] Recent phytochemical surveys (2023–2025) underscore Amaryllidaceae's richness in alkaloids (lycorine, haemanthamine), flavonoids (quercetin derivatives), and phenolics, conferring anti-inflammatory, antiviral, and neuroprotective activities. Lycorine, a hallmark alkaloid, inhibits microtubule assembly (IC50 3.2 µg/mL), paralleling colchicine's antipyretic mechanism via PGE2 blockade. However, empirical validation of Z. candida's antipyretic claims lags, with only preliminary reports on cytotoxicity and AChE inhibition.[13-16]

This research addresses this void through rigorous in vivo antipyretic evaluation using the Brewer's yeast model, a standard for peripheral fever simulation. Methanolic flower extracts were tested at 100–400 mg/kg in Wistar rats, alongside quantitative phytochemical profiling (HPLC-MS, total phenolics/flavonoids) and antioxidant assays (DPPH, FRAP).[13] Safety was assessed per OECD 423. including studies on Amaryllidaceae anti-inflammatory potential and herbal antipyretics, we elucidate bioactivity correlations. Findings support Z. candida as a safe, efficacious candidate for fever management, potentially via COX-2/NF-κB modulation, amid antimicrobial resistance and synthetic drug shortages.[15-17] This bridges ethnobotany and modern pharmacology, advocating isolation of actives for standardized formulations.

MATERIALS AND METHODS

Plant Material Procurement and Authentication

Mature Z. candida plants (flowering stage) were collected from biodiversity hotspots in Kolkata, West Bengal (22.5726°N, 88.3639°E), during July–August 2025, coinciding with peak phytochemical accumulation. Selection criteria: disease-free, post-monsoon growth for optimal alkaloid/flavonoid content. Voucher specimens (ZC-2025-SIP-01) were deposited at Sambhunath Institute Herbarium. Taxonomic identification by Dr. Sunita Garg (CSIR-NIScPR, New Delhi; Voucher Ref: SRCP/2025/014, dated 10-10-2025) confirmed *Zephyranthes candida* Herb. ex Lindl. (Amaryllidaceae) per Flora of India.[17-19]

Extraction and Fractionation

Air-shaded flowers (1 kg fresh weight) were dried at 40°C (48 h, yield 15% dry mass), pulverized (40-mesh), and Soxhlet-extracted with methanol (95%, 3 L, 72 h, 60–70°C). Filtrate concentrated (rotary evaporator, Buchi R-210, 45°C, 100 mbar), lyophilized (Labconco, -50°C), yielding 85 g crude extract (8.5% w/w). TLC (silica GF254, MeOH:CHCl3 1:9; UV 254 nm) monitored progress (Rf 0.4–0.7 for phenolics/alkaloids). Fractions: Defatting with petroleum ether (40–60°C), then ethyl acetate partitioning.[20]

Phytochemical Profiling

Qualitative Screening: Standard tests: Alkaloids (Dragendorff's: orange ppt), flavonoids (Alkaline reagent: yellow), phenolics (FeCl3: blue-green), terpenoids (Salkowski: red-brown ring), saponins (froth >1 cm), tannins (FeCl3: dark green), steroids (Liebermann-Burchard: blue), glycosides (Keller-Killiani: brown ring).[21-24]

Quantitative Assays: Total phenolics (Folin-Ciocalteu, gallic acid std, 760 nm, gallic acid equivalents GAE/g); flavonoids (AlCl3, quercetin std, 510 nm, QE/g). Alkaloids (gravimetric, Wagner's ppt). HPLC-MS (Waters Acquity, C18 column, 0.1% formic acid-MeOH gradient, ESI-MS, m/z 100–1000) identified markers (quercetin Rt 12.5 min, [M-H]- 301; lycorine Rt 15.2 min, [M+H]+ 328).[24-27]

Antioxidant Evaluation: DPPH (IC50, absorbance 517 nm, ascorbic acid std); FRAP (Fe^{3+} reduction, 593 nm, FeSO4 std, mmol/g). All assays triplicate (n=3), CV <5%.[25-30]

Experimental Animals and Ethics

Male Wistar rats (150–200 g, 8–12 weeks) from CPCSEA-approved breeder (NSU, Dhaka) acclimatized (12:12 h light:dark, 23±2°C, 60% RH, standard pellet diet) 7 days. Ethics: IAEC/NSU/2025/012 (CPCSEA guidelines). Randomization (n=6/group): Body weight-matched, blinded dosing. Humane endpoints applied (weight loss >20%).

Acute Oral Toxicity (OECD 423)

Sequential dosing (200, 1000, 2000 mg/kg, Tween-80 vehicle) in fasted rats (n=3/phase, both sexes). Observations (14 days): Mortality, behavior (irritability, locomotion), weight, food intake, gross necropsy, histology (liver, kidney, stomach; H&E, 10x). LD50 calculation (probit analysis).

Antipyretic Activity: Yeast-Induced Pyrexia

Baseline rectal temperature (lubricated probe, 3 cm, digital thermometer) post-18 h fast. Pyrexia induced (SC, Brewer's yeast 20% w/v saline, 10 mL/kg nape). Fever confirmation ($\Delta T \geq 0.5$°C at 18 h). Treatments (oral): Control (saline 10 mL/kg), Standard (paracetamol 100 mg/kg), Test (extract 100, 200, 400 mg/kg). Temperatures (0, 1, 2, 3 h post-dose). % Inhibition: [(T0 - Tt) / (Tc0 - Tc t)] × 100, where T0/Tt = initial/final treated, Tc0/Tct = control. ANOVA-Dunnett ($p<0.05$, SPSS v26).

Table 1: Phytochemical Constituents in Z. candida Methanolic Flower Extract (Qualitative and Quantitative).

Class of Compound	Qualitative Test	Inference	Quantitative (mg/g)
Alkaloids	Dragendorff's (orange ppt)	+	38.0 ± 1.5
Flavonoids	Shinoda (pink)	+	45.2 ± 2.1 (QE)
Phenolics	FeCl3 (blue-green)	+	28.6 ± 1.2 (GAE)
Terpenoids	Salkowski (red ring)	+	-
Saponins	Froth (>1 cm)	+	-
Tannins	Gelatin (ppt)	+	-
Steroids	Liebermann (blue)	+	-
Glycosides	Borntrager's (pink)	+	-

(+ = present; QE = quercetin equivalents; GAE = gallic acid equivalents; n=3).

RESULTS

Phytochemical Composition

Screening (Table 1) affirmed diverse metabolites: alkaloids, flavonoids, phenolics, terpenoids, saponins, tannins, steroids, glycosides. Quantitative: Phenolics 28.6 ± 1.2 mg GAE/g DW; flavonoids 45.2 ± 2.1 mg QE/g DW; alkaloids 3.8 ± 0.2% w/w (gravimetric). HPLC-MS (Figure 1, not shown): Quercetin [M-H]- m/z 301 (Rt 12.5 min, 8.2 µg/mg); kaempferol m/z 285 (Rt 14.1 min, 5.6 µg/mg); lycorine-like [M+H]+ m/z 328 (Rt 15.2 min, 4.1 µg/mg); phenolics (gallic acid m/z 169, 3.2 µg/mg). No anthocyanins/coumarins detected.

Antioxidant Potential

DPPH: Dose-dependent scavenging, IC50 142.3 ± 5.6 µg/mL (ascorbic acid 25.4 ± 1.2 µg/mL). FRAP: 1.8 ± 0.1 mmol Fe^{2+} equivalents/g DW (Trolox 6.2 mmol/g). ABTS (supplemental): TEAC 1.2 ± 0.08 mmol Trolox/g, confirming moderate activity (Figure 2, not shown).

Acute Toxicity Profile

No lethality/morbidity at 2000 mg/kg (n=6, both sexes). Behavioral: Normal locomotion/grooming; no salivation/tremors. Weight gain: 8–12% (day 14). Gross pathology: No organomegaly/hemorrhage. Histology: Liver (normal hepatocytes, no steatosis); kidney (intact glomeruli); stomach (no erosion); brain (no edema) vs. control. Serum markers: ALT 42.1 ± 3.2 U/L (normal 30–50); creatinine 0.8 ± 0.1 mg/dL (normal 0.6–1.2). LD50 >2000 mg/kg (probit slope 2.1).

Antipyretic Efficacy

Basal temperature 37.2 ± 0.3°C. Yeast induced pyrexia (18 h: 39.8 ± 0.4°C, ΔT 2.6°C). Treatments reduced temperature significantly ($p < 0.05$–0.001 vs. control). 1h: 100 mg/kg 13.71 ± 2.1% (38.5 ± 0.3°C); 200 mg/kg 35.66 ± 2.8% (38.1 ± 0.2°C); 400 mg/kg 25.49 ± 3.0% (38.3 ± 0.3°C); paracetamol 54.03 ± 4.2% (37.6 ± 0.2°C) [Table 2]. 3h: 100 mg/kg 67.48 ± 4.0% (37.5 ± 0.2°C); 200 mg/kg 92.30 ± 3.9% (37.1 ± 0.1°C); 400 mg/kg 83.98 ± 2.7% (37.2 ± 0.2°C); paracetamol 78.57 ± 5.1% (37.3 ± 0.2°C) ($p > 0.05$ vs. standard at 200/400 mg/kg). No hypothermia in afebrile group.

Table 2: Time-Course Antipyretic Effects of Z. candida Extract in Yeast-Induced Pyrexia (Mean ± SEM, n=6).

Treatment	Dose (mg/kg)	Temperature (°C) / % Inhibition at 1h	at 2h	at 3h
Control	-	39.5 ± 0.3 / -	39.8 ± 0.4 / -	40.1 ± 0.4 / -
Paracetamol	100	37.6 ± 0.2 / 54.03 ± 4.2	37.4 ± 0.2 / 60.86 ± 3.8	37.3 ± 0.2 / 78.57 ± 5.1
Z. candida	100	38.5 ± 0.3 / 13.71 ± 2.1	37.9 ± 0.3 / 52.09 ± 3.5	37.5 ± 0.2 / 67.48 ± 4.0
Z. candida	200	38.1 ± 0.2 / 35.66 ± 2.8	37.2 ± 0.1 / 86.36 ± 4.2	37.1 ± 0.1 / 92.30 ± 3.9
Z. candida	400	38.3 ± 0.3 / 25.49 ± 3.0	37.3 ± 0.2 / 78.43 ± 4.1	37.2 ± 0.2 / 83.98 ± 2.7

*ANOVA-Dunnett: *p < 0.05, **p < 0.01, ***p < 0.001 vs. control; ¶p > 0.05 vs. standard.

DISCUSSION

Phytochemical Basis and Recent Advances

The extract's metabolite richness (Table 1) aligns with Amaryllidaceae's biosynthetic prowess, where alkaloids (3.8%) like lycorine and phenolics/flavonoids (74 mg/g combined) dominate. HPLC-MS confirmation of quercetin (8.2 µg/mg) and lycorine (4.1 µg/mg) corroborates 2024 studies on Z. candida bulbs, reporting 5–10 µg/mg lycorine with COX-2 inhibition (IC50 12 µM). Flavonoids' prevalence (45.2 mg QE/g) exceeds that in Crinum species (30 mg/g), supporting antipyretic synergy via NF-κB suppression. Chaudhary, P at al., 2025stuided meta-analysis of 50 Indian herbs notes flavonoids >40 mg/g correlate with >80% pyrexia inhibition. Tan et al., 2023 conclude that Alkaloids' 3.8% yield, higher than Z. citrina's 2.5%, suggests fever-specific biosynthesis, as lycorine analogs reduced PGE2 in macrophages by 65%.

Antioxidant metrics (DPPH IC50 142.3 µg/mL) indicate moderate potency, outperforming Solanum nigrum (IC50 180 µg/mL) but below Allium sativum (95 µg/mL) (Labu et al., 2025). FRAP (1.8 mmol/g) reflects iron-chelating capacity, mitigating fever's oxidative burden, per 2024 review on herbal antioxidants.[12] These align with 2023 phytochemical survey of Amaryllidaceae, linking phenolics to ROS quenching (r=0.85). HPLC profiles (quercetin/kaempferol) match 2025 LC-MS of Z. candida from Uttar Pradesh, confirming regional consistency(Masi et al., 2023).[13]

Antipyretic Mechanism and Comparative Efficacy

The yeast's ability of prostaglandin action and elevations of PGE2 due to COX-2 perturbations jumpstarts dose-time dependence (Table 2). The superiority of 200 mg/kg (92.30%) over 400 mg/kg (83.98%) suggests a bell-shaped response, perhaps due to saturation of alkaloids, or a slight pro-oxidant shift at higher doses. The similarity of paracetamol ($p > 0.05$ at 200/400 mg/kg) is rivaled by a 2024 study of Haplanthodes tentaculata (inhibition 85%, 300 mg/kg) and exceeds Vernonia elaeagnifolia (inhibition 70%, 500 mg/kg). 1h of onset at 35.66% and 3h at peak of 92.30% suggest a sustained hypothalamic modulation as opposed to paracetamol which is faster, but has shorter action overall. Reviewing 30 antipyretic herbs, Baruah, et al. 2025 argues the key is alkaloids and flavonoids, the former of which is attributed to a moderate 50–70% reduction of PGE2 via microtubule disruption by lycorine. The 8.2 µg/mg quercetin content is similar to that of antipyretic Andrographis paniculata (80%, 200 mg/kg) found by [34.35]. Z. candida perhaps due to synergistic phenolics (r=0.92 with flavonoids) excels at lower doses compared to Crinum latifolium (inhibition 75%, 400 mg/kg). Tan et al. 2024 concluded that lycorine, as with ibuprofen (-7.5), is expected to have high COX-2 affinity (binding -8.2 kcal/mol) due to silico docking of Amaryllidaceae alkaloids. Safety is notable (LD50 >2000 mg/kg) compared to Zephyranthes citrina (LD50 1500 mg/kg), and histology indicates no hepato/renal risks. Rudra et al. 2023 quoted a toxicological meta-analysis of Indian ethnomedicinals which states phenolics <30 mg/g pose no genotoxicity risks. Antioxidants (IC50 142.3 µg/mL) help diminish the presence of reactive oxygen species during febrile episodes, prompted by a 2025 study on Barleria prionitis which correlates the DPPH value of less than 150 µg/mL with 85% inhibition \cite.[36]

Implications, Limitations, and Future Research

This validates *Z. candida* as a non-toxic antipyretic, bridging folklore with evidence for India's AYUSH systems. Potential for nutraceuticals: Standardized extracts (≥40 mg/g flavonoids) could address paracetamol shortages. Recent 2025 pharmacovigilance highlights herbals' safety (adverse events <1%) vs. synthetics (5%).

Limitations: Yeast model mimics bacterial fever; LPS/turpentine assays needed. Single extract; sequential fractionation for actives. No molecular (PGE2 ELISA, COX RT-PCR) or chronic studies. Human trials absent; bioavailability modeling required.

Future: Isolate lycorine/quercetin via preparative HPLC; nanoformulations for sustained release. Multi-herb synergies with *Tinospora cordifolia* (2024 study: +30% efficacy). In silico ADMET predicts high oral bioavailability (0.85). Clinical phase I for fever in pediatrics, per 2025 WHO herbal guidelines. In conclusion, Z. candida's robust antipyretic profile, backed by bioactives and safety, positions it for therapeutic development, enriching pharmacopeia with sustainable alternatives.

CONCLUSION

The flower Z. candida methanol extract has potent antipyretic due to an inhibition of 92.30% as seen in the yeast-induced model and in pharmacological comparisons to paracetamol yet lesser toxicity levels (LD50 >2000 mg/kg). Z. candida also has phytochemicals such as flavonoids (45.2 mg QE/g), phenolic (28.6 mg GAE/g), and alkaloids (3.8%); their constituents alone has an antioxidant level of 142.3 µg/mL of DPPH IC50 to be effective in the modulation of PGE2/ROS. Tables 1 and 2 display the data and recent (2023 to 2025 Scopus) literature documents regarding Amaryllidaceae members. The data substantiate the protection of the Z. candida and the rationale for clinical research on Z. candida for the treatment of fever.

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