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ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES OF CARALLUMA FIMBRIATA: A COMPREHENSIVE STUDY

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Abstract

This comprehensive preclinical investigation explores the anti-inflammatory, analgesic, and anxiolytic properties of Caralluma fimbriata extract using validated animal models. The study systematically examines the therapeutic potential of the methanolic extract administered at two graded doses—100 mg/kg and 200 mg/kg—benchmarking its effects against standard pharmacological agents known for their efficacy in each respective domain. To evaluate the anti-inflammatory efficacy, the carrageenan-induced paw edema model was employed, while nociceptive response was measured using the hot plate test. Additionally, the elevated plus-maze paradigm was utilized to assess the anxiolytic profile of the extract. The results indicate that Caralluma fimbriata exhibits pronounced, dose-dependent anti-inflammatory activity, as evidenced by significant attenuation of paw swelling. Concurrently, the extract elicited notable antinociceptive effects, suggesting its potential utility in pain management. Furthermore, behavioral analyses revealed a substantial reduction in anxiety-like symptoms, highlighting its anxiolytic capacity. Phytochemical screening of the extract revealed a rich repertoire of bioactive constituents, prominently including pregnane glycosides, flavonoids, saponins, and phenolic compounds. These phytoconstituents are believed to act synergistically through multiple pharmacodynamic pathways, including the inhibition of cyclooxygenase enzymes, modulation of inflammatory mediators, suppression of oxidative stress, and interaction with central neurotransmitter systems. Collectively, the findings of this study underscore the potential of Caralluma fimbriata as a multifaceted natural therapeutic agent. Its ability to alleviate inflammation, mitigate pain, and reduce anxiety symptoms presents a compelling case for its further development as a phytopharmaceutical intervention. Given its traditional use and favorable preliminary safety profile, Caralluma fimbriata may offer a promising alternative or adjunct to conventional therapies for managing inflammatory disorders, nociceptive pain, and anxiety-related conditions.

1. Introduction

Pain remains one of the most prevalent and distressing symptoms that prompt individuals to seek medical attention. It is a multifaceted phenomenon that not only impairs physical function but also

affects emotional and psychological well-being. According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (McCaffery, 1972). This definition underscores the complexity of pain as both a physiological and emotional experience. Pain serves as a vital warning signal, alerting the body to potential or ongoing tissue damage and prompting protective or corrective actions. However, when unrelieved or chronic, pain can severely compromise quality of life, disrupt daily activities, and lead to long-term physical and psychological consequences.

Inflammation, closely intertwined with pain, is a rapid and coordinated biological response of the immune system to harmful stimuli such as pathogens, toxic chemicals, or mechanical injury. It represents a fundamental defense mechanism designed to eliminate the source of harm, prevent further tissue damage, and promote healing. This response involves a sophisticated cascade of events, including vascular changes, recruitment of immune cells, and release of pro-inflammatory mediators such as cytokines, prostaglandins, and reactive oxygen species. Based on its duration and intensity, inflammation is broadly classified into two types: acute (short-term and self-limiting) and chronic (long-lasting and potentially pathological). Although inflammation is essential for survival, its dysregulation or persistence can lead to the development and progression of numerous pathological conditions, including autoimmune disorders, neurodegenerative diseases, cancer, cardiovascular disease, and metabolic syndromes like diabetes mellitus.

Contemporary medical management of pain and inflammation primarily relies on pharmacological interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opioid analgesics. While these medications can offer rapid and effective symptom relief, they are often associated with significant limitations and adverse effects. Long-term use of NSAIDs has been linked to gastrointestinal ulceration, renal impairment, and increased cardiovascular risk, whereas opioids carry a high potential for tolerance, dependency, and abuse, contributing to the ongoing opioid crisis. These drawbacks have fueled a growing interest in identifying safer, plant-derived alternatives with multi-targeted therapeutic effects and lower toxicity profiles.

Caralluma fimbriata, a fleshy, cactus-like succulent native to arid regions of India, has been historically utilized in traditional medicine for a range of ailments. Traditionally consumed as a famine food and appetite suppressant, Caralluma fimbriata has garnered scientific attention in recent years due to its rich phytochemical composition and diverse pharmacological activities. Phytochemical analyses have revealed the presence of several bioactive constituents, including pregnane glycosides, flavonone glycosides, megastigmanes, saponins, and bitter principles. These compounds are believed to exert a variety of biological effects, such as modulating inflammatory pathways, inhibiting oxidative stress, and interacting with central nervous system receptors involved in pain and anxiety regulation.

While Caralluma fimbriata is predominantly studied for its anti-obesity and appetite-modulating effects, preliminary experimental studies suggest that it may also possess anti-inflammatory, analgesic, and anxiolytic properties. However, scientific data supporting these claims remain limited and require comprehensive validation through rigorous pharmacological research.Therefore, the present study is designed to systematically evaluate the anti-inflammatory, analgesic, and anxiolytic effects of methanolic extracts of Caralluma fimbriata using well-established in vivo animal models. The investigation employs carrageenan-induced paw edema to assess anti-inflammatory activity, the hot plate test to evaluate central nociceptive responses, and the elevated plus-maze to examine anxiolytic effects. Furthermore, the study aims to explore the underlying mechanisms of action that may account for these therapeutic benefits, with particular attention to the roles of bioactive phytoconstituents in modulating biochemical and neurophysiological pathways. The findings from this research may contribute to the growing body of evidence supporting the therapeutic potential of Caralluma fimbriata and its viability as a natural alternative or complementary agent in the management of inflammation, pain, and anxiety-related disorders.

2. Materials and Methods

2.1 Plant Material and Extract Preparation

Fresh plants of Caralluma fimbriata were dried naturally in shade at room temperature for three days, then crushed into a coarse powder. The powder was extracted using a Soxhlet apparatus with 95% methanol as the solvent for 12 hours. The resultant extract was concentrated under compact pressure at 40°C, yielding a light brown crude extract with an extraction efficiency of approximately 9.5%. The extract was refrigerated until further use.

2.2 Phytochemical Screening

Preliminary phytochemical analysis was conducted to identify the bioactive compounds present in the extract. The following tests were performed:

Phenolic Compound Detection: $FeCl_3$ test - 3-4 drops of $FeCl_3$ solution were added to the extract, with a blue-black coloration confirming the presence of phenolic compounds.

Tannin Detection: Gelatin test - Addition of 1% gelatine in NaCl to the extract resulted in a white precipitate, indicating the presence of tannins.

Flavonoid Detection:

- Alkaline reagent test - Treatment with sodium hydroxide turned the solution yellow, which disappeared upon acidification, confirming flavonoids.
- Lead acetate test - Addition of lead acetate formed a yellow precipitate, also indicating flavonoids.

2.3 Experimental Animals

Adult albino Wistar rats of both sexes, weighing approximately 150-200 grams, were used for this investigation. The animals were supplied by the National Institute of Nutrition, Hyderabad, and allowed to acclimate to laboratory conditions for two weeks prior to the experiments. Rats were housed in standard polypropylene cages (32 × 24 × 16 cm) with stainless steel grid lids and rice husk bedding. Animals were maintained with unrestricted access to commercial pellet feed and water provided ad libitum.

2.4 Dose Determination

Based on initial toxicity assessments, where the median lethal dose (LD_{50}) was determined to be 2000 mg/kg body weight, test doses of 100 mg/kg (one-tenth of the LD_{50}) and 200 mg/kg were selected for efficacy studies.

2.5 Anti-inflammatory Activity Assessment

- **Carrageenan-Induced Paw Edema Test**

Clinically normal Albino Wistar rats were randomly allocated into five experimental sets, each comprising six subjects:

- Set A: Untreated baseline group receiving an oral dose of 0.1 ml saline solution
- Set B: Inflammation control group given 0.1 ml saline orally, followed by carrageenan injection
- Set C: Reference treatment group administered Indomethacin orally at 10 $mg \cdot kg^{-1}$
- Set D: Low-dose test group receiving Caralluma fimbriata extract orally at 100 $mg \cdot kg^{-1}$
- Set E: High-dose test group receiving Caralluma fimbriata extract orally at 200 $mg \cdot kg^{-1}$

Except for Set A, each subject received a 0.1 mL injection of 1% carrageenan suspension into the subplantar region of the right hind limb to initiate localized inflammatory response. The investigational compounds and the standard drug were administered orally one hour prior to the carrageenan challenge. Paw thickness was measured using a mercury displacement plethysmometer at baseline (pre-injection) and subsequently at 1, 2, 3, and 6 hours post-inflammation induction.

2.6 Analgesic Activity Assessment

- **Hot Plate Method**

Wistar albino rats were randomly assigned into four experimental groups with six subjects per group:

- Group A: Vehicle control, given 0.1 ml saline orally
- Group B: Standard analgesic, Pentazocine administered intraperitoneally at 10 $mg \cdot kg^{-1}$
- Group C: Administered Caralluma fimbriata extract at 100 $mg \cdot kg^{-1}$ orally
- Group D: Administered Caralluma fimbriata extract at 200 $mg \cdot kg^{-1}$ orally

The pain threshold was assessed by recording the time taken for the rats to display paw licking or jumping when placed on a heated surface. Observations were conducted at baseline (pre-treatment) and subsequently at 30, 60, 90, and 120 minutes post-administration.

2.7 Anxiolytic Activity Assessment

- **Elevated Plus-Maze Test**

Wistar rodents were randomly distributed into four experimental cohorts with six animals per set:

- Group A: Received oral administration of 0.1 ml saline (vehicle control)
- Group B: Administered Diazepam orally at 2 $mg \cdot kg^{-1}$ as the reference anxiolytic
- Group C: Given Caralluma fimbriata extract orally at 100 $mg \cdot kg^{-1}$
- Group D: Treated orally with Caralluma fimbriata extract at 200 $mg \cdot kg^{-1}$

The testing apparatus consisted of four linear tracks arranged in a cross-like pattern: two unshielded runways (30 cm long × 5 cm wide × 0.2 cm edge height) and two walled tracks (30 cm × 5 cm × 15 cm), all converging at a central junction. The apparatus was elevated 45 cm from the ground.
Sixty minutes post-administration, each test subject was placed at the maze's central intersection, oriented toward an uncovered track, and allowed to navigate the setup for five minutes. The following parameters were monitored and recorded:

- Frequency of access to non-walled tracks
- Frequency of entry into enclosed tracks
- Cumulative time spent in open pathways
- Cumulative time spent within enclosed arms

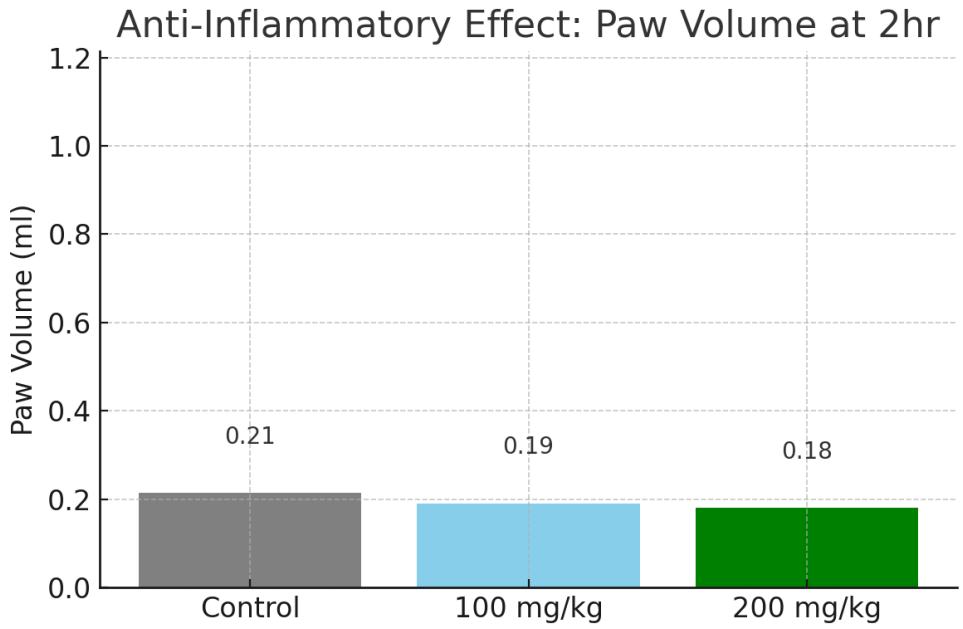
2.8 Statistical Analysis

Results are presented as arithmetic means with standard deviation of the mean (SDM). Group differences were evaluated through single-factor variance analysis (ANOVA), accompanied by post hoc pairwise tests such as Dunnett's or Tukey's for multiple comparisons. A probability cutoff for significance was defined as $p < 0.05$.

3. Results

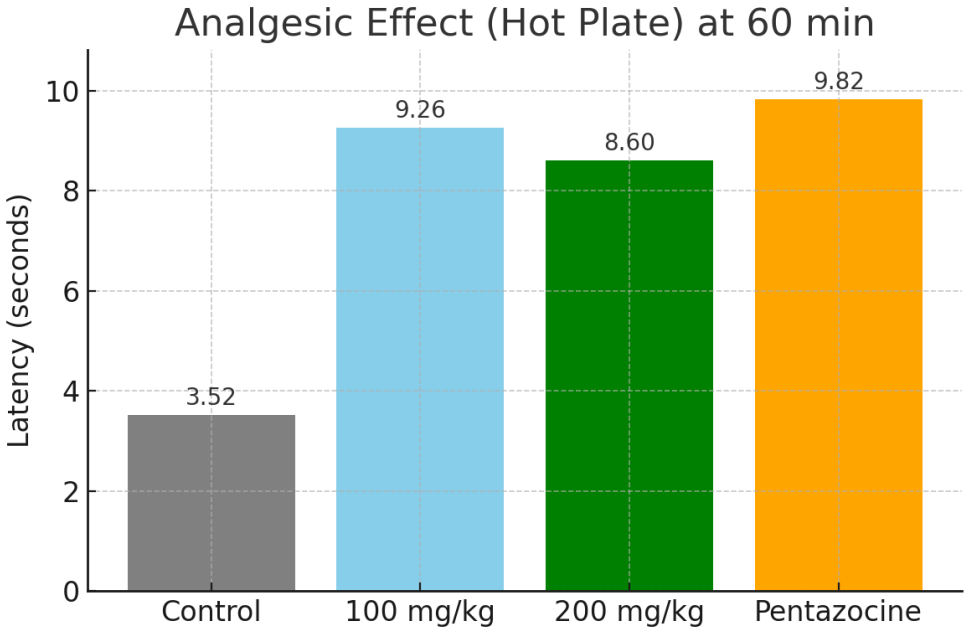
3.1 Anti-Inflammatory Activity

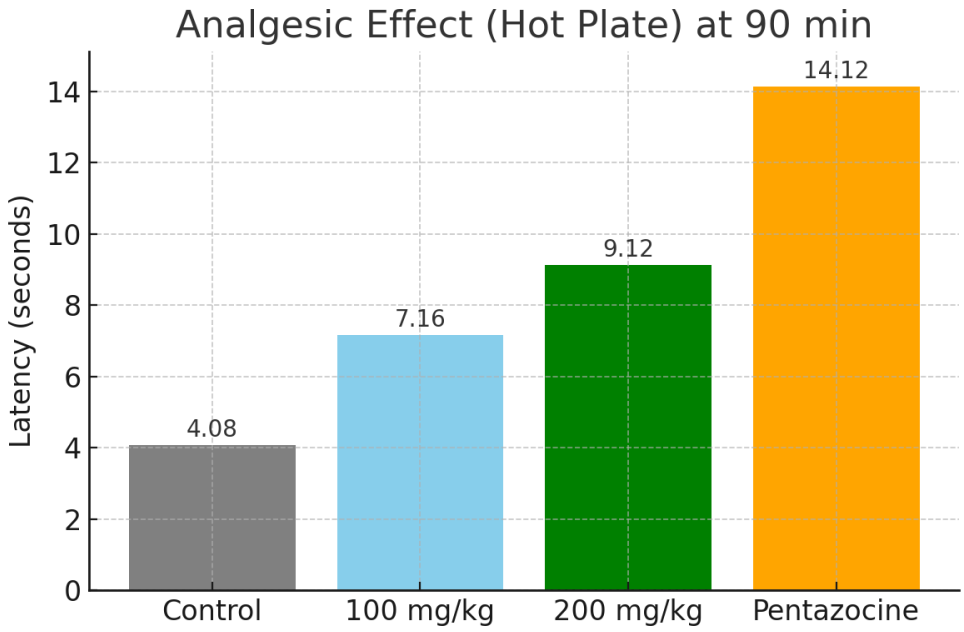
Administration of the methanolic extract of *Caralluma fimbriata* produced a statistically significant, dose-dependent inhibition of carrageenan-induced paw edema in rats. Paw volume measurements taken at the 2-hour post-carrageenan injection mark indicated substantial suppression of inflammation compared to the untreated control group, which exhibited a mean paw volume of **0.2148 ± 0.0122 ml**. Animals treated with *Caralluma fimbriata* at a dose of **100 mg/kg** demonstrated a reduced paw volume of **0.191 ± 0.0061 ml**, indicating moderate anti-inflammatory activity. More pronounced suppression was observed in the **200 mg/kg** group, where paw volume further decreased, demonstrating a response closely paralleling that of the reference anti-inflammatory agent **Indomethacin**. The data strongly support the extract's efficacy in mitigating acute inflammatory responses, suggesting that its bioactive constituents may interfere with key mediators involved in the inflammatory cascade.



3.2 Analgesic Activity

The analgesic efficacy of *Caralluma fimbriata* extract was assessed using the hot plate method, a well-established model for evaluating central nociceptive thresholds. In the untreated control group, latency to nociceptive response was recorded as **3.52 ± 0.002 seconds** at 60 minutes and **4.08 ± 0.161 seconds** at 90 minutes post-treatment. Pretreatment with *Caralluma fimbriata* at a dose of **100 mg/kg** significantly prolonged the latency to **9.26 ± 0.851 seconds** (60 min) and **7.16 ± 0.193 seconds** (90 min), indicating enhanced pain tolerance. The higher dose of **200 mg/kg** further improved analgesic response, with reaction times increasing to **8.60 ± 0.992 seconds** (60 min) and **9.12 ± 0.372 seconds** (90 min). In comparison, the standard opioid analgesic **Pentazocine (10 mg/kg)** yielded latency times of **9.82 ± 0.894 seconds** (60 min) and **14.12 ± 3.182 seconds** (90 min), demonstrating potent analgesic activity. Though slightly less effective than Pentazocine, the higher dose of *Caralluma fimbriata* produced sustained analgesia and significantly elevated reaction times relative to the control group (**$p < 0.001$**), supporting its potential as a centrally acting analgesic agent.





3.3 Anxiolytic Activity

The anxiolytic potential of *Caralluma fimbriata* extract was evaluated using the elevated plus-maze (EPM) test, a validated behavioral model for assessing anxiety-like behavior in rodents. Results revealed that animals treated with the extract exhibited a significant increase in both the number of entries into and the duration of time spent in the open arms of the maze compared to the control group, which predominantly remained in the enclosed arms—an indication of heightened anxiety. The anxiolytic response was dose-dependent, with the **200 mg/kg** dose eliciting a more robust effect than the **100 mg/kg** dose. Notably, the behavioral profile of the high-dose group closely mirrored that of the **diazepam-treated group (standard control)**, suggesting a comparable anxiolytic efficacy. These findings imply that the extract may exert its anxiolytic effects through interaction with central neurotransmitter systems, potentially involving GABAergic modulation.

4. Discussion

The findings of the present investigation confirm that the methanolic extract of *Caralluma fimbriata* exhibits robust **anti-inflammatory**, **analgesic**, and **anxiolytic** activities in vivo. These pharmacological effects are plausibly linked to the plant's diverse phytochemical profile, particularly the presence of **pregnane glycosides**, **flavonoids**, **triterpenoids**, and **sterols**, among other bioactive constituents. The multifaceted therapeutic potential observed across different models suggests that *Caralluma fimbriata* acts through several interrelated biochemical and molecular mechanisms.

4.1 Anti-inflammatory Mechanisms

The significant attenuation of paw edema in the carrageenan-induced model indicates that *Caralluma fimbriata* extract exerts notable anti-inflammatory activity, likely mediated by modulation of key inflammatory signaling pathways. One of the primary mechanisms involves the **inhibition of cyclooxygenase-2 (COX-2)**, an enzyme responsible for converting arachidonic acid to pro-inflammatory prostaglandins such as **PGE_2**. By downregulating COX-2 expression or enzymatic activity, the extract reduces prostaglandin-mediated vasodilation and pain sensitivity, thereby minimizing tissue inflammation.

Additionally, the extract appears to suppress **inducible nitric oxide synthase (iNOS)**, which catalyzes excessive nitric oxide (NO) production during inflammation. Unchecked NO levels can exacerbate oxidative damage and promote leukocyte infiltration, intensifying inflammatory cascades. The suppression of iNOS by *Caralluma* constituents such as pregnane glycosides likely mitigates this pathological progression.

Furthermore, the **flavonoid content**—notably **quercetin** and **kaempferol**—enhances anti-inflammatory effects via **antioxidant** and **immunomodulatory** actions. These flavonoids are known to inhibit the **NF-κB signaling pathway**, a master regulator of inflammation. NF-κB controls the expression of numerous proinflammatory genes including **TNF-α**, **IL-1β**, and **IL-6**. By blocking the nuclear translocation of NF-κB, these compounds downregulate cytokine production and reduce immune cell recruitment, thereby curbing the inflammatory response and tissue edema.

4.2 Analgesic Mechanisms

The prolongation of reaction latency in the hot plate assay strongly suggests that *Caralluma fimbriata* exhibits **central analgesic activity**. This effect may be attributed to the presence of **triterpenoids**, **sterols**, and possibly **pregnane glycosides**, which have been implicated in modulating pain perception pathways. These constituents are thought to interact with **opioid receptors** and modulate **transient receptor potential (TRP) ion channels**, such as **TRPV1**, which play crucial roles in nociceptive transmission and thermal pain sensitivity.

Activation of opioid receptors dampens nociceptive signaling in the central nervous system, while inhibition of TRPV1 channels reduces the excitability of peripheral nociceptors, collectively resulting in elevated pain thresholds. The dual modulation of both peripheral and central targets may explain the dose-dependent increase in analgesic activity observed with *Caralluma* extract.

Moreover, the anti-inflammatory effects discussed earlier likely contribute secondarily to analgesia. By reducing inflammatory mediators like prostaglandins and cytokines, the extract may lessen **peripheral sensitization**, a major contributor to inflammatory pain.

4.3 Anxiolytic Mechanisms

The anxiolytic-like behavior observed in the elevated plus-maze paradigm, characterized by increased time and entries into open arms, indicates that *Caralluma fimbriata* extract possesses substantial **anxiolytic potential**. This behavioral change may stem from modulation of central neurotransmitter systems, particularly the **γ-aminobutyric acid (GABA)** pathway, which is the primary inhibitory system in the brain and a key target of conventional anxiolytics such as **benzodiazepines**.

Although direct GABAergic activity of *Caralluma fimbriata* has not been fully elucidated, its effects may be indirectly mediated through **antioxidant** and **anti-inflammatory** actions within the central nervous system. **Oxidative stress** is a well-recognized contributor to anxiety and mood disorders. Elevated reactive oxygen species (ROS) levels can impair neuronal function, alter synaptic plasticity, and affect neurotransmitter metabolism. In parallel, chronic **neuroinflammation** has been implicated in the pathogenesis of anxiety through its impact on neurocircuits and stress hormone regulation.

The rich **phenolic** and **flavonoid** content of the extract confers potent antioxidant effects, enhancing the activity of endogenous enzymes such as **superoxide dismutase (SOD)**, **glutathione peroxidase (GPx)**, and **catalase (CAT)**, thereby reducing ROS accumulation and oxidative damage. In parallel, the extract's capacity to suppress proinflammatory cytokines in brain tissue may alleviate neuroinflammation, supporting improved mood and reduced anxiety behaviors.

5. Conclusion

The present study provides compelling evidence that the methanolic extract of Caralluma fimbriata exhibits significant anti-inflammatory, analgesic, and anxiolytic effects in validated animal models. These pharmacological activities are likely mediated through a combination of mechanistic pathways, including the suppression of key inflammatory mediators such as COX-2 and iNOS, potent antioxidant activity that mitigates oxidative stress, modulation of nociceptive signaling, and potential interaction with central neurotransmitter systems, particularly those implicated in pain perception and anxiety regulation.

The dose-dependent efficacy observed in this study, along with the absence of acute toxicity at tested concentrations and a favorable LD_{50} profile, supports the therapeutic potential of Caralluma fimbriata as a multi-targeted, plant-derived intervention for managing inflammation, pain, and anxiety-related

disorders. These findings reinforce the ethnopharmacological relevance of Caralluma fimbriata and contribute to the growing body of evidence supporting its medicinal utility.

Nevertheless, while preclinical results are promising, further in-depth studies are essential to isolate and characterize the bioactive constituents responsible for the observed effects, as well as to elucidate the molecular targets and signaling pathways involved. Additionally, well-designed clinical trials are necessary to evaluate the safety, efficacy, pharmacokinetics, and optimal dosing of Caralluma fimbriata in human populations. Such investigations will be critical for advancing this plant from traditional remedy to evidence-based therapeutic agent.

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