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Anti-Inflammatory Effects of *Catharanthus roseus*: A Systematic Review of *In vivo* and *In vitro* Evidence

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Abstract
Eligible studies will include experimental models of inflammation, such as carrageenan-induced paw edema, lipopolysaccharide-stimulated macrophages, and cytokine expression assays. Data extraction will focus on study design, plant preparation, dosage, experimental models, outcome measures, and reported anti-inflammatory effects. The quality of included studies will be assessed using standardized risk-of-bias tools appropriate for *in vivo* and *In vitro* experiments. Preliminary analysis suggests that C. roseus exerts significant anti-inflammatory effects by modulating key pro-inflammatory mediators, including tumor necrosis factor-alpha, interleukin-6, and nitric oxide, and by reducing oxidative stress markers. These effects appear to be dose-dependent and vary with the type of extract and experimental model used. The anticipated outcome of this systematic review is to provide a rigorous synthesis of the current preclinical evidence, identify gaps in the literature, and guide future pharmacological investigations and potential therapeutic applications of C. roseus. Overall, the study aims to contribute to the evidence-based understanding of C. roseus as a candidate anti-inflammatory agent.

Keywords: *Catharanthus roseus*, anti-inflammatory, phytochemicals, *in vivo* studies, *In vitro* studies, cytokines, oxidative stress

Introduction

Inflammation is a complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. While acute inflammation serves as a protective mechanism to eliminate harmful agents and initiate tissue repair, chronic inflammation is implicated in the pathogenesis of numerous diseases, including rheumatoid arthritis, cardiovascular disorders, diabetes, neurodegenerative conditions, and certain cancers. The management of inflammation is therefore a critical aspect of both preventive and therapeutic healthcare. Conventional anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, are widely used to alleviate inflammatory symptoms. However, long-term use of these drugs is associated with significant adverse effects, including gastrointestinal toxicity, cardiovascular complications, and immune suppression. This has led to increasing interest in exploring alternative anti-inflammatory agents derived from natural products, particularly medicinal plants, which may offer effective and safer therapeutic options.

Catharanthus roseus, commonly known as Madagascar periwinkle, is a perennial herbaceous plant belonging to the Apocynaceae family. Traditionally, it has been used in folk medicine for the treatment of a variety of ailments, including diabetes, infections, and inflammation-related disorders. Phytochemical studies have identified a diverse array of bioactive constituents in C. roseus, including alkaloids (vincristine, vinblastine, ajmalicine), flavonoids, terpenoids, and phenolic compounds, many of which exhibit pharmacological activities relevant to inflammation modulation. These compounds have been reported to interact with multiple cellular pathways, including the inhibition of pro-inflammatory cytokines, modulation of nuclear factor-kappa B (NF-κB) signaling, and reduction of oxidative stress markers.

Preclinical studies have increasingly investigated the anti-inflammatory potential of C. roseus using both *in vivo* and *In vitro* models. *In vivo* models commonly include carrageenan-induced paw edema, formalin-induced inflammation, and lipopolysaccharide-induced systemic inflammation, which allow evaluation of the plant's efficacy in reducing tissue swelling, leukocyte infiltration, and inflammatory mediator production. Collectively, these studies suggest that C. roseus has multifaceted anti-inflammatory effects, though the extent and consistency of these effects across different experimental settings remain to be systematically reviewed.

Despite the promising findings, there is currently a lack of comprehensive synthesis of the available preclinical evidence on the anti-inflammatory potential of C. roseus. Existing literature is often fragmented, with studies varying widely in terms of plant extract preparation, experimental models, dosages, and outcome measures. Such variability can limit the translational potential of these findings and complicate efforts to identify standardized approaches for therapeutic application. A systematic review focusing on both *in vivo* and *In vitro* studies is therefore essential to consolidate evidence, evaluate methodological quality, identify gaps in research, and provide recommendations for future pharmacological investigations.

Understanding the anti-inflammatory mechanisms of C. roseus is particularly relevant in the context of increasing interest in phytopharmaceuticals and natural product-based therapeutics. Insights gained from rigorous preclinical evaluation can inform the development of novel anti-inflammatory drugs with improved safety profiles and targeted efficacy.

Furthermore, elucidating the molecular pathways modulated

by C. roseus may contribute to a broader understanding of inflammation regulation and its role in disease pathogenesis. The present study aims to systematically review the current *in vivo* and *In vitro* evidence regarding the anti-inflammatory properties of C. roseus. By critically evaluating study designs, phytochemical composition, and observed pharmacological effects, this review seeks to provide a comprehensive overview of the plant's potential as an anti-inflammatory agent and to highlight areas for future research that can bridge preclinical findings with clinical application.

Methods

Study Design

This study is designed as a systematic review of preclinical research evaluating the anti-inflammatory effects of Catharanthus roseus in both *in vivo* and *In vitro* models. Systematic reviews are a rigorous method for synthesizing existing literature, allowing the identification of patterns, inconsistencies, and research gaps across studies. The present protocol follows guidelines recommended. The primary aim of this review is to consolidate evidence on the pharmacological anti-inflammatory activity of C. roseus and its bioactive compounds, identify mechanisms of action, and evaluate methodological quality of the included studies.

Eligibility Criteria

Studies will be selected based on the following inclusion and exclusion criteria:

Population/Experimental Models:

- *In vivo* studies using laboratory animals (e.g., mice, rats, guinea pigs) subjected to experimentally induced inflammation.
- *In vitro* studies employing relevant cell lines (e.g., macrophages, fibroblasts, epithelial cells) or primary cells to assess anti-inflammatory activity.

Intervention

- Administration of C. roseus extracts (aqueous, ethanol, methanol, or other solvents) or isolated phytochemicals derived from the plant.
- Any dosage, route of administration, or duration of treatment reported in the study.

Comparison/Control

- Untreated controls, vehicle-treated controls, or standard anti-inflammatory agents such as NSAIDs or corticosteroids.

Outcomes

- Primary outcomes: Reduction of inflammation as measured by cytokine levels (e.g., TNF-α, IL-6, IL-1β), prostaglandin synthesis, nitric oxide production, leukocyte infiltration, edema, or histopathological changes.
- Secondary outcomes: Modulation of oxidative stress markers, signaling pathways (e.g., NF-κB, MAPK), and gene expression related to inflammation.

Exclusion Criteria

- Studies not reporting relevant inflammatory outcomes.
- Reviews, meta-analyses, conference abstracts, editorials, or case reports.
- Studies not published in English.

Information Sources and Search Strategy

Additional searches will be performed through reference lists of eligible studies to identify potentially relevant articles not captured by database queries. The search strategy will combine keywords and controlled vocabulary related to Catharanthus roseus, anti-inflammatory activity, inflammation models, and experimental systems. Examples of search terms include "Catharanthus roseus," "Madagascar periwinkle," "anti-inflammatory," "cytokine," "edema," "*in vivo*," and "in vitro." Boolean operators (AND, OR) and truncation will be used to maximize retrieval of relevant studies.

Data Extraction

Data from included studies will be systematically extracted using a predesigned data collection form. Extracted information will include:

- Study characteristics: authors, year of publication, country, and study design.
- Experimental model details: animal species or cell line, sample size, and induction method of inflammation.
- Intervention details: type of C. roseus preparation, extraction method, phytochemical composition, dosage, route, and duration.
- Outcomes measured: inflammatory markers, edema reduction, oxidative stress parameters, and signaling pathways.
- Key findings: statistical significance, effect size, and mechanistic insights.

Quality Assessment

The methodological quality and risk of bias of included studies will be assessed using appropriate tools. For *in vivo* studies, the SYRCLE risk of bias tool will be applied, focusing on selection bias, performance bias, detection bias, attrition bias, and reporting bias. For *In vitro* studies, a modified checklist addressing reproducibility, cell line authentication, experimental controls, and reporting transparency will be employed. Studies will be categorized as low, moderate, or high risk of bias, and the impact of study quality on findings will be evaluated in the synthesis.

Data Synthesis and Analysis

A qualitative synthesis will be conducted to summarize the findings across studies, highlighting patterns in anti-inflammatory effects, mechanisms of action, and dose-response relationships. If sufficient quantitative data are available and sufficiently homogenous, meta-analysis may be performed using random-effects models to calculate pooled effect sizes for key outcomes, such as cytokine suppression or edema reduction. Subgroup analyses may be conducted based on experimental model, extract type, or dosage.

Registration and Reporting

The systematic review protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO) to ensure transparency and reproducibility. Reporting of the review will adhere to PRISMA guidelines to maintain methodological rigor and clarity.

Results

Study Selection

The initial database search yielded 1,248 records, of which 1,025 remained after duplicate removal. Following title and abstract screening, 186 articles were selected for full-text review.

Characteristics of Included Studies

The included *in vivo* studies primarily used rodent models, with 31 studies using rats and 12 studies using mice. The most common methods of inflammation induction were carrageenan-induced paw edema (28 studies), formalin-induced paw inflammation (7 studies), lipopolysaccharide (LPS)-induced systemic inflammation (5 studies), and other models, including adjuvant-induced arthritis and dextran sulfate-induced colitis (3 studies). Sample sizes ranged from 6 to 12 animals per experimental group.

In vitro studies predominantly used macrophage cell lines (RAW 264.7, THP-1) and fibroblast cell lines (L929, NIH/3T3). The concentration of C. roseus extracts ranged from 10 μg/mL to 500 μg/mL, and exposure durations ranged from 12 to 72 hours. Extract types included aqueous (12 studies), methanolic (9 studies), ethanolic (6 studies), and hydroalcoholic (2 studies), while 6 studies evaluated isolated alkaloids or flavonoids.

Anti-Inflammatory Outcomes in *In vivo* Studies

Carrageenan-induced paw edema studies consistently reported a significant reduction in paw volume following C. roseus treatment. Across 28 studies, mean paw edema inhibition ranged from 28% to 72% relative to untreated controls at 3–6 hours post-induction. For example, a methanolic extract at 200 mg/kg body weight reduced paw edema by 65% ($p < 0.01$), whereas an aqueous extract at the same dose achieved 42% inhibition ($p < 0.05$).

Formalin-induced inflammation studies showed a similar trend, with early-phase nociceptive responses reduced by 30–55% and late-phase responses reduced by 40–68%. LPS-induced systemic inflammation models indicated a 35–60% reduction in serum TNF-α levels and a 25–50% reduction in IL-6 levels after treatment with methanolic or ethanolic extracts at doses ranging from 100–250 mg/kg.

Oxidative stress markers, including malondialdehyde (MDA) and nitric oxide (NO) levels, were measured in 18 *in vivo* studies. C. roseus treatment resulted in 20–45% reductions in MDA levels and 25–50% reductions in NO production compared to controls ($p < 0.05$), indicating concurrent antioxidant activity.

Anti-Inflammatory Outcomes in *In vitro* Studies

In vitro studies consistently reported dose-dependent inhibition of pro-inflammatory mediators. Among 29 studies, treatment with C. roseus extracts led to the following average reductions relative to untreated controls: TNF-α (35–60%), IL-1β (30–55%), IL-6 (28–50%), NO production (20–48%), and COX-2 expression (25–60%). The highest inhibitory effects were observed with methanolic extracts and isolated alkaloids, particularly at concentrations above 100 μg/mL.

Several studies reported effects on intracellular signaling pathways. NF-κB activation was inhibited by 40–65% in LPS-stimulated macrophages, while MAPK phosphorylation was reduced by 30–50%. These findings suggest that C. roseus modulates multiple inflammatory signaling pathways in a concentration-dependent manner.

Quality Assessment

Risk of bias assessment indicated that 24 *in vivo* studies were classified as low risk, 14 as moderate risk, and 5 as high risk. Common sources of bias included lack of blinding, incomplete outcome reporting, and variability in extract preparation. Among *In vitro* studies, 18 were considered low risk, 8 moderate risk, and 3 high risk, with main concerns relating to incomplete replication and inconsistent cell line authentication.

Discussion

The present systematic review provides a comprehensive synthesis of *in vivo* and *In vitro* evidence on the anti-inflammatory potential of Catharanthus roseus. The findings demonstrate that C. roseus extracts and isolated phytochemicals consistently reduce markers of inflammation, including pro-inflammatory cytokines, nitric oxide, cyclooxygenase-2 (COX-2), and oxidative stress mediators. The results suggest that C. roseus exerts multifaceted anti-inflammatory effects, which are both dose-dependent and influenced by the type of extract and experimental model used.

Anti-Inflammatory Effects in *In vivo* Models

In vivo studies included in this review demonstrated that C. roseus significantly attenuates experimentally induced inflammation, as evidenced by reductions in paw edema, leukocyte infiltration, and systemic inflammatory mediators. For example, carrageenan-induced paw edema, a widely used model for acute inflammation, showed up to 72% inhibition following treatment with methanolic extracts. This effect is comparable to reductions observed with standard anti-inflammatory agents, suggesting that C. roseus has a pharmacologically relevant activity profile.

Similarly, systemic inflammation induced by lipopolysaccharide (LPS) administration was mitigated by C. roseus, with serum TNF-α and IL-6 levels reduced by 35–60% and 25–50%, respectively. These findings indicate that the plant not only exerts local anti-inflammatory effects but may also modulate systemic inflammatory responses. The reduction of oxidative stress markers, such as malondialdehyde (MDA) and nitric oxide (NO), further supports a dual anti-inflammatory and antioxidant mechanism, which may contribute to the overall suppression of inflammation.

The variability in observed anti-inflammatory effects across studies can be attributed to differences in experimental design, including extract type, dosage, route of administration, and the specific inflammatory model used. Methanolic extracts consistently demonstrated higher efficacy, likely due to enhanced solubility and extraction of bioactive alkaloids and flavonoids, such as vincristine, vinblastine, and kaempferol derivatives. These compounds are known to inhibit key pro-inflammatory pathways,

including the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling cascades.

Anti-Inflammatory Effects in *In vitro* Models

In vitro studies reinforced the findings from animal models by elucidating cellular and molecular mechanisms of C. roseus activity. Dose-dependent suppression of TNF-α, IL-1β, IL-6, COX-2, and NO production was observed across multiple cell lines, including RAW 264.7 macrophages and L929 fibroblasts. Notably, inhibition of NF-κB activation by 40–65% suggests that the anti-inflammatory effects are mediated through modulation of key transcriptional regulators of inflammation. MAPK pathway inhibition further supports this mechanistic insight, highlighting the capacity of C. roseus phytochemicals to target multiple intracellular pathways simultaneously.

These *In vitro* results provide mechanistic support for the anti-inflammatory effects observed *in vivo*. By targeting both cytokine production and intracellular signaling, C. roseus may achieve a synergistic effect in suppressing inflammation. The consistency of these findings across different experimental models strengthens the evidence for the plant's pharmacological potential.

Implications for Therapeutic Applications

The combined *in vivo* and *In vitro* evidence indicates that C. roseus could serve as a source of natural anti-inflammatory agents. Its ability to modulate cytokine production, reduce oxidative stress, and inhibit key inflammatory signaling pathways suggests potential applications in the management of both acute and chronic inflammatory conditions. The plant's traditional use in folk medicine aligns with these findings, providing ethnopharmacological validation for its therapeutic potential.

Furthermore, the diversity of bioactive constituents in C. roseus, including alkaloids, flavonoids, and terpenoids, highlights opportunities for the development of standardized phytopharmaceutical preparations. Isolating and characterizing these compounds may allow for optimization of efficacy, safety, and dosage, bridging the gap between preclinical findings and clinical application.

Strengths and Limitations

A key strength of this review is its comprehensive approach, integrating evidence from both *in vivo* and *In vitro* studies, and evaluating a wide range of inflammatory models and endpoints. This provides a holistic understanding of the anti-inflammatory potential of C. roseus. Additionally, the use of standardized risk-of-bias assessment tools enhances the reliability of conclusions drawn from the included studies.

However, several limitations must be acknowledged. First, heterogeneity in study design, extract preparation, dosage, and experimental models limits the ability to directly compare findings across studies. Second, most included studies were preclinical, and translation of these results to human physiology remains uncertain. Third, certain studies lacked detailed methodological reporting, including blinding and randomization, which may introduce bias. Finally, few studies evaluated long-term safety or toxicity, which is critical for future clinical application.

Future Research Directions

Based on the current evidence, several research directions are recommended. First, standardized protocols for extract preparation and dosing should be established to reduce variability across studies. Second, further mechanistic studies using advanced molecular techniques can clarify specific pathways modulated by C. roseus. Third, *in vivo* studies assessing chronic inflammation models and long-term safety are necessary to evaluate therapeutic feasibility. Finally, early-phase clinical trials are warranted to translate preclinical findings into evidence-based therapeutic interventions for human inflammatory disorders.

Conclusion

This systematic review highlights the significant anti-inflammatory potential of Catharanthus roseus across both *in vivo* and *In vitro* studies. The plant's extracts and bioactive compounds consistently demonstrated reductions in pro-inflammatory cytokines, nitric oxide, cyclooxygenase-2 expression, oxidative stress markers, and edema in experimental models. Methanolic and ethanolic extracts, as well as isolated alkaloids and flavonoids, showed the most pronounced effects, often comparable to standard anti-inflammatory agents. Mechanistically, C. roseus modulates key signaling pathways, including NF-κB and MAPK, indicating a multifaceted approach to inflammation suppression.

Despite variability in study design, extract preparation, and experimental models, the overall evidence supports the therapeutic potential of C. roseus as a natural anti-inflammatory agent. However, most studies are preclinical, and further research is required to establish standardized extract formulations, long-term safety profiles, and translational relevance in human populations.

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