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Original Article

Evaluation of Anti-Inflammatory Activity of *Tinospora sinensis* Aqueous Extract Using the Formalin-Induced Rat Paw Edema Model

Kinjal P. Patel*, Navneet Rajput, Simran Dimri, Rahul Trivedi, Rajesh A. Maheshwari

Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Vadodara, Gujarat, INDIA.

ABSTRACT

Background: *Tinospora sinensis* (Lour.) Merr., belonging to the family *Menispermaceae*, is traditionally acclaimed for its use in managing fever, inflammation, and metabolic disorders. Despite its ethnomedicinal reputation, scientific validation of its anti-inflammatory efficacy remains limited. The present study aimed to evaluate the anti-inflammatory potential of the Aqueous Extract of *T. sinensis* (TSAE) using the formalin-induced rat paw edema model. **Materials and Methods:** Acute inflammation was induced by subplantar injection of 1% formalin (0.1 mL) in the right hind paw of wistar rats. Animals were divided into five groups (n=6): normal control, disease control, *T. sinensis* 150 mg/kg, *T. sinensis* 300 mg/kg, and standard (diclofenac sodium 10 mg/kg). Paw volume was recorded at predetermined intervals using a plethysmometer. Hematological parameters (RBC, WBC) and inflammatory biomarkers (TNF-α, CRP) were assessed using standard protocols and ELISA kits. Statistical significance was analyzed by one-way ANOVA followed by Bonferroni's *post hoc* test. **Results:** The disease control group exhibited a significant increase in paw volume, WBC count, and pro-inflammatory cytokine levels, confirming induction of inflammation. Treatment with *T. sinensis* extract significantly reduced paw edema in a dose-dependent manner, with the 300 mg/kg dose showing marked inhibition comparable to diclofenac sodium (p<0.05). The extract also restored RBC counts and significantly decreased serum TNF-α and CRP concentrations, indicating systemic anti-inflammatory and immunomodulatory actions. **Conclusion:** The aqueous extract of Tinospora sinensis demonstrates potent anti-inflammatory activity through suppression of cytokine-mediated responses and stabilization of hematological parameters. The findings provide pharmacological evidence supporting its traditional therapeutic use and highlight its potential as a safe and effective plant-based anti-inflammatory agent.

Keywords: CRP, Cytokines, Diclofenac sodium, Inflammation, Paw edema, Phytotherapy, *Tinospora sinensis*, TNF-α.

Correspondence:
Dr. Kinjal P. Patel
Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Vadodara-391760, Gujarat, INDIA.
Email: kinjalpatel54@gmail.com

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INTRODUCTION

Inflammation is a critical component of the innate immune response, serving as a defensive reaction to injury, infection, or irritation. It is characterized by a cascade of cellular and molecular events including vasodilation, increased vascular permeability, and leukocyte infiltration, aimed at eliminating the initial cause of cell injury, clearing out necrotic cells, and initiating tissue repair processes. (While acute inflammation is typically self-limiting and beneficial, chronic inflammation is often deleterious and has been implicated in the pathogenesis of various degenerative and metabolic disorders such as rheumatoid arthritis, atherosclerosis, type 2 diabetes, alzheimer's disease, and cancer (Xiao, 2017; Krüger *et al.*, 2019; Kumar, 2020). Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids remain the mainstay of anti-inflammatory therapy. However, their long-term use is frequently associated with adverse effects such as gastrointestinal ulceration, hepatotoxicity, nephrotoxicity, and increased cardiovascular risk (Eren *et al.*, 2016; Singgih *et al.*, 2020). This has driven the exploration of alternative therapies derived from medicinal plants that offer comparable efficacy with improved safety profiles. Herbal medicines have a longstanding history of use in traditional systems and are known for their multi-targeted actions with minimal side effects (Ghasemian *et al.*, 2016). *Tinospora sinensis* (Lour.) Merr., a climbing shrub from the family *Menispermaceae*, is extensively utilized in traditional Ayurvedic and Chinese medicine for treating fever, inflammation, metabolic disorders, and immunological conditions (Liang *et al.*, 2024). It is closely related to *Tinospora cordifolia*, which has been widely studied for its anti-inflammatory and immunomodulatory

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effects (Chaudhary *et al.*, 2024). Phytochemical studies of *T. sinensis* have revealed the presence of alkaloids, diterpenoid lactones, steroids, flavonoids, and polysaccharides, many of which have been associated with anti-inflammatory, antioxidant, and immunostimulant activities (Huyen *et al.*, 2025; Singh *et al.*, 2021). However, there is limited preclinical evidence supporting the anti-inflammatory potential of *T. sinensis* in validated experimental models, which justifies further pharmacological evaluation. The formalin-induced rat paw edema model is a reliable and widely accepted method for assessing anti-inflammatory activity. This model induces a biphasic inflammatory response: the early neurogenic phase (0-1 hr) is mediated by histamine and serotonin release, whereas the later tissue-mediated phase (1-6 hr) involves prostaglandins, bradykinin, and cytokines (Jalali *et al.*, 2024; Tahir *et al.*, 2025). Therefore, it serves as an effective platform for evaluating both central and peripheral anti-inflammatory actions of test substances. In this context, the current study aims to evaluate the anti-inflammatory efficacy of aqueous extract of *Tinospora sinensis* using the formalin-induced rat paw edema model. This investigation not only provides scientific validation to its traditional use but also paves the way for developing it as a potential plant-derived therapeutic agent for inflammatory conditions.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals utilized in the study were of analytical grade and procured from reputable sources. Diclofenac sodium tablets (50 mg) were obtained from a licensed local pharmacy. Formalin (37% solution) was purchased from Aatur Instrachem, Vadodara, India. Commercially available ELISA kits for the quantitative estimation of pro-inflammatory marker such as TNF-α and CRP were procured from Athenese-Dx Pvt. Ltd., Chennai, India.

Instruments

During the experimental procedures, several instruments were utilized to ensure accuracy and reliability of the results. A digital analytical weighing balance with a precision of ±0.001 g was employed for precise measurement of chemical reagents and test substances. The animal weighing balance was used to monitor the body weight of experimental animals throughout the study, which served as an important parameter for assessing general health and treatment effects. To evaluate inflammatory responses, a plethysmometer was employed for accurate measurement of paw volume in the paw edema model (John and Shobana, 2012). Additionally, a semi-automated cell analyzer was used for biochemical assessments, providing dependable and standardized analysis of hematological parameters.

Plant Material

Preparation of Plant Sample

Fresh stem parts of *Tinospora sinensis* were thoroughly washed with distilled water to eliminate adhering soil and other extraneous matter. The plant material was shade-dried for 28 days at ambient room temperature (25-28°C) to preserve thermo-labile phytoconstituents. The dried stems were subsequently pulverized into a coarse powder using an electric grinder. The powdered material was stored in an airtight container at room temperature until further use.

Preparation of Aqueous Extract of *T. sinensis* (TSAE)

The aqueous extract was prepared by macerating 20 g of powdered stem material in 100 mL of distilled water in a 500 mL conical flask. The mixture was heated on a heating mantle at 60°C for 20 min with intermittent stirring to facilitate extraction of water-soluble phytochemicals. After cooling to room temperature, the mixture was filtered through Whatman No. 1 filter paper to remove insoluble residues. The filtrate was transferred to a porcelain china dish and evaporated to dryness on a heating mantle to obtain the crude aqueous extract. The dried extract was weighed to determine yield and stored in a desiccator until further experimental use (Das *et al.*, 2020).

Phytochemical Screening

Preliminary phytochemical screening of the aqueous extract was carried out to identify the presence of various classes of secondary metabolites such as carbohydrates, alkaloids, flavonoids, tannins, saponins, glycosides, terpenoids, and triterpenoids using standard qualitative methods as described in authoritative pharmacognostic literature (Gokhale and Kokate, 2008; Evans and Trease, 1996).

Experimental Animals

Adult female Wistar rats weighing 200-250 g were employed in this study. The animals were housed in polypropylene cages under standard environmental conditions, including a 12 hr light/dark cycle, controlled temperature of 25±1°C, and relative humidity of 50-60%. Rats were maintained on a standard pellet diet (rat chow) and had free access to water throughout the experimental period. All procedures involving animals were conducted following the ethical guidelines laid down by the Committee for Control and Supervision of Experiments on Animals (CCSEA). Prior approval for the study protocol was obtained from the Institutional Animal Ethics Committee (IAEC) (Approval No.: SVU/DP/IAEC/2024/11/77).

Induction of Acute Inflammation

Acute inflammation was induced in the right hind paw of each rat using the formalin-induced paw edema model. A volume of 0.1 mL of 1% formalin solution was injected subcutaneously into the

plantar surface of the right hind paw to provoke localized edema. The paw volume was measured using a digital plethysmometer at 0, 30, 60, 90, and 120-min post-formalin injection. The anti-inflammatory effect was assessed by comparing the paw volume of treated groups with the control group at each time point (John and Shobana, 2012).

Experimental Design

To evaluate the anti-inflammatory potential of the Aqueous Extract of *Tinospora sinensis* (TSAE), a total of 30 female Wistar rats were randomly allocated into five groups, with six animals per group (n=6). The grouping, dosage, and treatments are summarized in Table 1.

To comprehensively evaluate the anti-inflammatory efficacy of *Tinospora sinensis* extract in the formalin-induced inflammation model, a range of hematological, inflammatory, and physiological parameters were assessed. Paw volume measurement using a digital plethysmometer served as the primary physiological indicator of acute localized inflammation, allowing quantification of edema formation over time and the degree of inflammation suppression following treatment. Total White Blood Cell (WBC) count was evaluated to assess the systemic immune response, as elevated WBC levels are a hallmark of acute inflammation and leukocyte mobilization (Chmielewski and Strzelec, 2018). Red Blood Cell (RBC) count was measured to detect anemia or hem dilution, conditions frequently associated with chronic inflammatory states and tissue hypoxia. Restoration of these parameters indicated hematological recovery and systemic protective effects of the extract (Chmielewski and Strzelec, 2018; Kounis *et al*., 2015). To investigate the molecular and immunological mechanisms underlying the anti-inflammatory response, serum levels of Tumor Necrosis Factor-alpha (TNF-α) key pro-inflammatory cytokine involved in the initiation and amplification of the inflammatory cascade were quantified using Enzyme-Linked Immunosorbent Assay (ELISA) kits (Feuerstein *et al*., 1994). Additionally, C-reactive Protein (CRP), an acute-phase reactant synthesized by the liver in response to IL-6, was measured as a general marker of systemic inflammation and tissue damage (Kramer *et al*., 2008; Sproston and Ashworth, 2018).

Statistical analysis

All experimental results will be expressed as mean ± Standard Error of the Mean (SEM). Statistical analysis will be carried out using One-Way Analysis of Variance (ANOVA) to determine the significance of differences among the groups. Following ANOVA, the Bonferroni *post hoc* test will be applied for multiple comparisons between groups. A p-value of less than 0.05 will be considered statistically significant for all analyses, indicating a meaningful difference between treatment and control groups.

RESULTS

Effect of *Tinospora sinensis* extract on paw volume in formalin-induced inflammation

At baseline, all experimental groups exhibited comparable paw volumes, indicating uniformity prior to inflammation induction which shown in Figure 1(A). In the disease control group, paw volume progressively increased and remained significantly elevated throughout the observation period, confirming a sustained inflammatory response in the absence of treatment. Rats treated with *T. sinensis* extract at 150 mg/kg (Treatment Group 1) demonstrated a moderate reduction in paw volume compared to the disease control which shown in Figure 1(B), indicating partial suppression of edema. The 300 mg/kg dose (Treatment Group 2) exhibited a more substantial reduction, suggestive of a dose-dependent anti-inflammatory effect. The standard group, which received Diclofenac sodium (10 mg/kg), showed the marked attenuation in paw swelling, validating the model and serving as a positive therapeutic benchmark.

Effect of *Tinospora sinensis* extract on RBC in formalin-induced inflammation.

RBC count, expressed as $\times 10^6$ cells/mm^3, was significantly affected by formalin-induced inflammation. The normal control group-maintained baseline RBC levels, whereas the disease control group exhibited a marked decrease, as shown in Figure 2 (A), indicating anemia or hemodilution secondary to inflammation (Straat *et al*., 2012). Both treatment groups receiving *T. sinensis* (150 and 300 mg/kg) exhibited statistically significant restoration of RBC count. Notably, the 300 mg/kg dose achieved near-complete recovery, with RBC levels closely approaching normal values (p<0.01). The standard group also showed significant improvement, consistent with

Table 1: Experimental Design.

Sl. No.	Animal Group	No. of Animals	Treatment Administered
1.	Normal Control	6	No treatment; standard diet and water only
2.	Disease Control	6	1% Formalin injection (0.1 mL, s.c., right hind paw)
3.	Treatment Group 1	6	1% Formalin + TSAE 150 mg/kg (p.o.) (Naik *et al*., 2013)
4.	Treatment Group 2	6	1% Formalin + TSAE 300 mg/kg (p.o.)
5.	Standard Group	6	1% Formalin + Diclofenac sodium 10 mg/kg (p.o.)

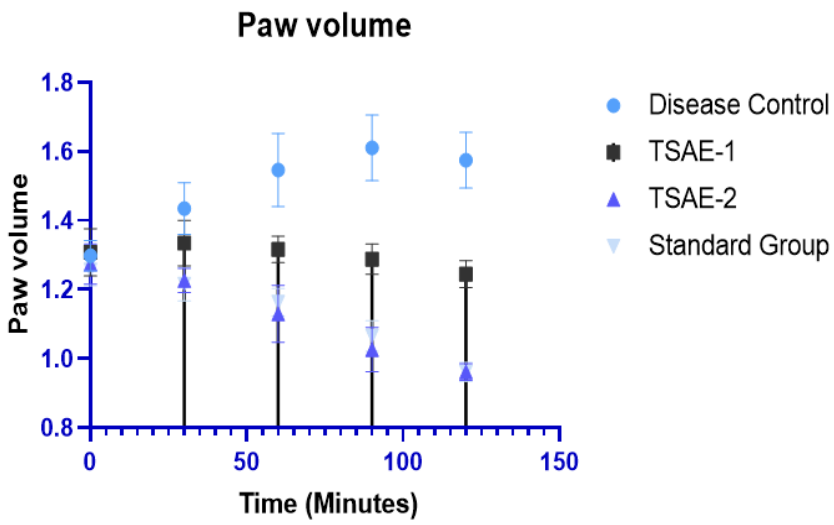


Figure 1(A): Effect of TSAE on paw volume against formalin-induced inflammation in rat paw edema.



Figure 1(B): Measurement of Paw edema using plethysmometer.

effective anti-inflammatory therapy. These findings support the hematoprotective potential of *T. sinensis*, particularly in mitigating inflammation-induced RBC depletion.

Effect of *Tinospora sinensis* extract on WBC in formalin-induced inflammation

Total WBC count, a key marker of systemic immune activation, was markedly elevated in the disease control group shown in Figure 2(B), likely due to the release of pro-inflammatory cytokines such as interleukins and granulocyte/macrophage colony-stimulating factors (Oda and Kawai, 2010). Treatment with *T. sinensis* extract led to a dose-dependent reduction in WBC count. The 150 mg/kg dose showed a modest decrease, whereas the 300 mg/kg dose resulted in a statistically significant reduction in WBC levels ($p<0.05$). The Diclofenac-treated group also demonstrated significant suppression of leukocytosis, further corroborating the anti-inflammatory effect. These results highlight the immunomodulatory properties of *T. sinensis*, suggesting its role in controlling inflammatory leukocyte proliferation.

Effect of *Tinospora sinensis* extract on TNF-α in formalin-induced inflammation

Serum levels of TNF-α, a central pro-inflammatory cytokine, were significantly elevated in the disease control group, validating the induction of systemic inflammation (Olsen *et al.*, 2007). Administration of *T. sinensis* resulted in a dose-dependent attenuation of TNF-α levels. The 150 mg/kg group showed the most pronounced decrease, restoring TNF-α levels nearly to baseline which shown in Figure 3(A). The 300 mg/kg group also demonstrated a significant reduction, though slightly less pronounced. TNF-α levels in the standard group were comparable to the treatment groups, reaffirming the efficacy of *T. sinensis* in modulating cytokine-mediated inflammation.

Effect of *Tinospora sinensis* extract on CRP in formalin-induced inflammation

CRP, a sensitive acute-phase protein and systemic marker of inflammation, was significantly increased in the disease control group compared to the normal control group, indicating active inflammatory response (Straat *et al.*, 2012). Treatment with *T. sinensis* extract led to a dose-dependent reduction in CRP levels. While the 150 mg/kg dose produced a modest, non-significant decrease, the 300 mg/kg group demonstrated a statistically significant reduction in CRP concentration, nearing values observed in the normal control which shown in Figure 3(B). The Diclofenac-treated group showed a comparable decline, validating both the experimental model and the therapeutic potential of *T. sinensis*. These findings underscore the systemic

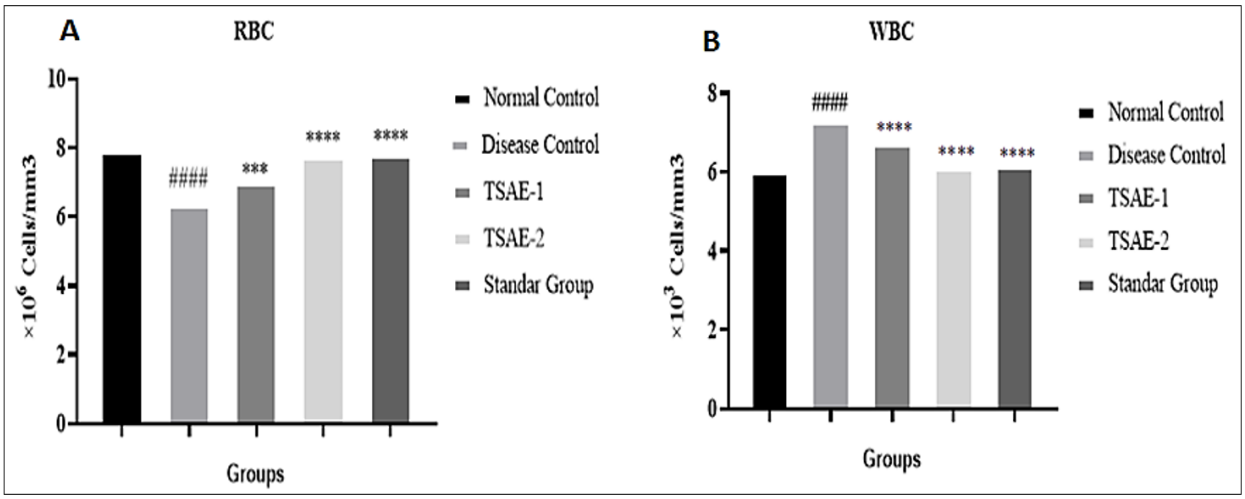


Figure 2: Effect of TSAE on (A) RBC (B) WBC levels against formalin induced inflammation in rat paw edema The Mean ± SEM is used to express all values (*n*=6). ####*p*<0.0001 compared to normal control; ***p<0.001, ****p<0.0001 compared to Disease control.

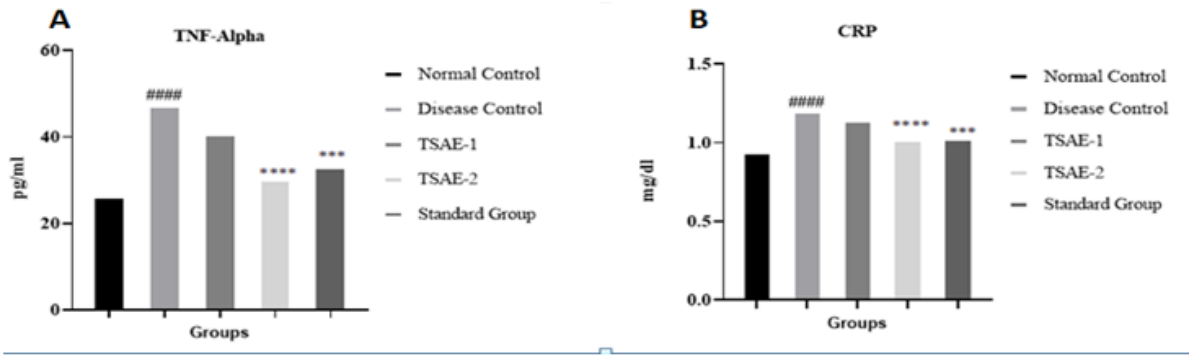


Figure 3: Effect of TSAE on (A) TNF-α (B) CRP levels against formalin induced inflammation in rat paw edema. The Mean ± SEM is used to express all values (*n*=6). ####*p*<0.0001 compared to normal control; ***p<0.001, ****p<0.0001 compared to Disease control.

anti-inflammatory efficacy of the extract, particularly at higher doses.

DISCUSSION

The findings of this investigation confirm that *Tinospora sinensis* possesses significant anti-inflammatory properties, which substantiate its ethnopharmacological use in traditional medicine. The formalin-induced paw edema model employed in this study provides a reliable biphasic response, allowing evaluation of both neurogenic and tissue-mediated components of inflammation. The aqueous extract of *T. sinensis* produced a marked reduction in paw swelling, particularly at the 300 mg/kg dose, suggesting that it acts through modulation of multiple inflammatory mediators. The reduction of paw edema parallels that observed with the standard drug diclofenac sodium, a known cyclooxygenase inhibitor, implying that *T. sinensis* may exert its effect through similar prostaglandin-inhibitory mechanisms. The extract's ability to restore RBC levels and normalize WBC counts further supports its hematoprotective and systemic stabilizing effects during inflammation. Mediators such as TNF-α and IL-6, which drive inflammatory processes, hold central importance in initiating and propagating inflammatory cascades, leading to activation of acute-phase proteins like CRP. The significant attenuation of TNF-α and CRP levels by *T. sinensis* suggests that the extract effectively modulates cytokine signaling pathways. These findings align with previous reports on *Tinospora cordifolia*, a related species known for similar pharmacological activities, indicating that both species share comparable phytochemical constituents responsible for their therapeutic effects. Phytochemical analysis revealed the presence of alkaloids, flavonoids, diterpenoid lactones, tannins, and phenolics, compounds known for their antioxidant and anti-inflammatory properties (Ilaiyaraja and Khanum, 2011; Khan, 2019). Flavonoids and polyphenols can scavenge reactive oxygen species, suppress cyclooxygenase and lipoxygenase activities, and inhibit nitric oxide production collectively reducing oxidative stress and inflammatory mediator synthesis. The combined action of these bioactive compounds likely contributes to the observed effects of the extract (Hussain *et al.*, 2016; Shukla *et al.*, 2019). Overall, the study provides compelling evidence that *T. sinensis* exerts its anti-inflammatory activity through multiple pathways: inhibition of pro-inflammatory cytokines, reduction of acute-phase

reactants, and preservation of hematological integrity. These multi-targeted actions emphasize the therapeutic potential of *T. sinensis* as a phytotherapeutic candidate for treating inflammatory and immune-mediated conditions.

CONCLUSION

The current study demonstrated that the aqueous extract of *Tinospora sinensis* significantly reduces inflammation in formalin-induced rat paw edema, restores hematological balance, and suppresses key inflammatory mediators such as TNF-α and CRP. The dose-dependent response and comparable efficacy with diclofenac sodium highlight its strong pharmacological potential. The anti-inflammatory activity is likely attributed to its rich phytoconstituent profile, including flavonoids, alkaloids, and diterpenoid lactones, which act synergistically to modulate inflammatory signaling pathways. These results validate the traditional claims regarding *T. sinensis* and encourage further research focused on isolating active compounds, elucidating molecular mechanisms, and evaluating its efficacy in chronic inflammation models. With additional studies, *T. sinensis* could emerge as a promising natural alternative to synthetic anti-inflammatory agents with fewer adverse effects.

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ABBREVIATIONS

TSAE: Aqueous Extract of *Tinospora sinensis*; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **WBC:** White Blood Cell; **RBC:** Red Blood Cell; **CCSEA:** Committee for Control and Supervision of Experiments on Animals; **IL-6:** Interleukin-6; **SEM:** Standard Error of the Mean; **s.c.:** Subcutaneous; **p.o.:** Per os (Oral administration); **TNF-α:** Tumor Necrosis Factor-Alpha; **ELISA:** Enzyme-Linked Immunosorbent Assay; **CRP:** C-Reactive Protein; **IAEC:** Institutional Animal Ethics Committee; **ANOVA:** Analysis of Variance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

The study protocol (SVU/DP/IAEC/2024/11/77) received approval from the Institutional Animal Ethics Committee of SBKS MI and RC and followed prescribed ethical guidelines.

AUTHORS CONTRIBUTION

Dr. Kinjal P. Patel conceptualized and designed the study, supervised the experimental work, interpreted the data, and drafted and critically revised the manuscript for important intellectual content. Navneet Rajput and Simran Dimri carried out the experimental procedures, collected and analyzed the data, and contributed to the preparation of the manuscript. Rahul Trivedi participated in reviewing the manuscript. Rajesh A. Maheshwari provided overall guidance, critically reviewed the manuscript for publication. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

SUMMARY

Inflammation is a fundamental protective response of the innate immune system; however, its persistence contributes to the development of several chronic and degenerative diseases. Although non-steroidal anti-inflammatory drugs remain the cornerstone of therapy, their prolonged use is associated with serious adverse effects, necessitating the search for safer alternatives. The present study investigated the anti-inflammatory potential of the Aqueous Extract of *Tinospora sinensis* (TSAE), a medicinal plant traditionally used for inflammatory and immune-related disorders, using the formalin-induced rat paw edema model. The aqueous extract was prepared from the stem of *T. sinensis* and subjected to preliminary phytochemical screening, which revealed the presence of alkaloids, flavonoids, tannins, diterpenoid lactones, and phenolic compounds. Acute oral toxicity studies confirmed the safety of TSAE at the tested doses. Female Wistar rats were divided into five groups and treated with TSAE at doses of 150 and 300 mg/kg, with diclofenac sodium used as the standard drug. Acute inflammation was induced by subcutaneous injection of formalin into the hind paw, and inflammatory responses were evaluated through paw volume measurement, hematological parameters, and serum inflammatory markers. TSAE produced a dose-dependent reduction in paw edema, with the 300 mg/kg dose showing significant inhibition comparable to diclofenac. Treatment with TSAE also restored red blood cell counts and significantly reduced elevated white blood cell levels, indicating hematoprotective and immunomodulatory effects. Additionally, TSAE markedly suppressed serum levels of Tumor Necrosis Factor-α and C-reactive protein, demonstrating effective modulation of systemic inflammatory mediators. Overall, the findings validate the traditional use of *Tinospora sinensis* as an anti-inflammatory agent and highlight its multi-targeted mechanism of action. TSAE shows promise as a safe, plant-derived therapeutic candidate for the management of inflammatory conditions, warranting further mechanistic and chronic inflammation studies.

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