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Evaluation of the Anti-inflammatory Potential of a Combined *Ocimum sanctum* and *Cinnamomum zeylanicum* Polyherbal Formulation: An In Vitro Study

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ABSTRACT

Background: Inflammation plays a pivotal role in endodontic diseases, leading to pain, tissue damage, and impaired healing. While synthetic medicaments and irrigants are widely used to manage endodontic infections and inflammation, they have limitations, including cytotoxicity and adverse effects. This study explores a combined polyherbal extract of *Ocimum sanctum* and *Cinnamomum zeylanicum*, each known for its anti-inflammatory properties, as a biocompatible natural alternative for managing endodontic inflammation through various in vitro assays.

Methods: The polyherbal extract was prepared from authenticated plant materials. Anti-inflammatory activity was assessed via three in vitro assays: Bovine Serum Albumin (BSA) denaturation, egg albumin denaturation, and membrane stabilization assays at concentrations of 10-50 µg/mL. Diclofenac sodium served as the reference standard. Percentage inhibition of protein denaturation and membrane stabilization was calculated, with statistical significance determined using one-way ANOVA ($p < 0.05$).

Results: The combined extract exhibited significant, dose-dependent synergistic anti-inflammatory effects across all three assays. Higher concentrations (10-50 µg/mL) led to progressively increased inhibition of inflammation indicators, demonstrating the formulation's

potency. Statistical analysis confirmed significant anti-inflammatory activity across all assays ($p < 0.05$), indicating the extract's potential as a potent natural anti-inflammatory agent.

Conclusion: The combined *Ocimum sanctum* and *Cinnamomum zeylanicum* polyherbal formulation demonstrated strong anti-inflammatory activity, suggesting its potential as a natural adjunct or alternative to conventional agents used in endodontic therapy. Further in vivo research is needed to confirm its efficacy and optimize clinical application.

Keywords: *Ocimum sanctum*, *Cinnamomum zeylanicum*, anti-inflammatory, endodontics, polyherbal, intracanal medicament, irrigants

INTRODUCTION

Inflammation is a key defense mechanism in the body, but chronic inflammation is linked to various diseases, including those affecting the dental pulp and periapical tissues.[1] Inflammation in endodontics typically arises as a response to microbial invasion, most commonly due to deep carious lesions or trauma. When bacteria infiltrate the dental pulp, the immune system responds by releasing pro-inflammatory mediators such as cytokines (TNF-α, IL-6), chemokines, and prostaglandins.[2] This inflammatory response, known as pulpitis, is initially aimed at neutralizing the infection but can progress to irreversible tissue damage if inflammation becomes chronic.[3] In cases of irreversible pulpitis, the pulp tissue undergoes necrosis, leading to the spread of bacteria and toxins to the periapical region. Once inflammation reaches the periapical tissues, a more extensive immune response is triggered, resulting in the formation of abscesses, granulomas, or cysts. Chronic periapical inflammation can cause significant bone resorption, tissue destruction, and ultimately the development of apical periodontitis.[4] Therefore, controlling inflammation is essential not only to manage pain and tissue damage but also to promote healing and prevent further complications.

The role of inflammation in endodontic treatment is two-fold: it represents both a biological defense mechanism and a target for therapeutic intervention.[2] Traditional endodontic treatments involve root canal therapy, where mechanical debridement is used in combination with chemical irrigants to eliminate pathogens and inflamed tissue. Despite successful bacterial elimination, it is equally essential to address the underlying inflammatory process to ensure complete resolution of the infection and healing of periapical tissues.

In endodontic treatment, anti-inflammatory agents are employed to reduce periapical inflammation, promote healing, and manage pain. These agents are delivered through intracanal medicaments and irrigants, which are placed directly into the root canal system during treatment.[5] Traditionally, sodium hypochlorite (NaOCl) and chlorhexidine (CHX) have been the most commonly used irrigants for their antimicrobial properties.[6] However, these agents have limited anti-inflammatory effects and, in some cases, may exacerbate tissue damage due to their cytotoxicity.[7] Intracanal medicaments, such as calcium hydroxide, have been widely used for their anti-inflammatory properties. [8] Calcium hydroxide induces a high pH environment, which has been shown to reduce microbial load and inhibit the activity of pro-inflammatory cytokines, thereby minimizing inflammation in the periapical tissues. However, its direct impact on modulating the inflammatory response is limited.[9] Other commonly used medicaments such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs),[9], [10] directly target inflammation by inhibiting prostaglandin synthesis and reducing the recruitment of immune cells to the site of infection. However, their long-term effects carry potential side effects, including delayed healing and immune suppression. Thus,

despite the effectiveness of these conventional treatments, there is growing interest in natural, biocompatible alternatives that not only offer antimicrobial activity but also possess anti-inflammatory properties with minimal side effects. Several herbal extracts have been studied for their potential use as anti-inflammatory agents in endodontics.[11] Ocimum sanctum (holy basil) and Cinnamomum zeylanicum (cinnamon) are well-known medicinal plants traditionally used for their anti-inflammatory, antioxidant, and antimicrobial properties.[12], [13] In the context of endodontics, their potential as natural alternatives to conventional anti-inflammatory agents is of particular interest.[14] Individually, these plants have demonstrated efficacy in reducing inflammation, but their combined effect has not been extensively studied. Polyherbal formulations, in particular, are gaining attention due to their potential to exert synergistic effects, where the combined action of two or more plants results in enhanced therapeutic efficacy compared to individual extracts.[15] This study aims to evaluate the synergistic anti-inflammatory potential of a combined *Ocimum sanctum* and *Cinnamomum zeylanicum* formulation through a series of in vitro assays. By assessing the formulation's effects on protein denaturation and membrane stabilization, this study seeks to provide a scientific basis for its potential application in endodontic therapy.

MATERIALS AND METHODS

Polyherbal extract preparation: Fresh *Ocimum sanctum* leaves and *Cinnamomum zeylanicum* bark were sourced from a local market in Chennai, and their identity was confirmed by a botanist. The plant materials were washed with distilled water, air-dried for 48 hours, and ground into a fine powder. Five grams of each powder were combined with 50 mL of distilled water and heated at 70°C for 10 minutes with continuous stirring. The mixture was cooled and filtered to remove residues. The filtrate was concentrated by heating until the volume reduced to 5 mL. The concentrated extract was dried, reconstituted with distilled water, and shaken at 100 rpm for 24 hours. The final extract was stored in an airtight container at 4°C for use in the assays.

Evaluation of antiinflammatory activity: The evaluation of antiinflammatory activity of the polyherbal extract encompassed 3 tests: Bovine Serum Albumin (BSA) denaturation, egg albumin (EA) denaturation, and membrane stabilization assays.

Bovine Serum Albumin (BSA) Denaturation Assay: The anti-inflammatory effect of the polyherbal extract sample was assessed by its ability to inhibit protein denaturation. A mixture of 0.45 mL BSA solution (1% w/v) and 0.05 mL extract (10-50 µg/mL) was adjusted to pH 6.3 using phosphate buffer. The samples were incubated for 10 minutes at room temperature, followed by heating at 55°C for 30 minutes. Diclofenac sodium (10 µg/mL) served as the positive standard, and dimethyl sulphoxide (DMSO) as the negative control. Absorbance was measured at 660 nm, and amount of protein denaturation was calculated as percentage using the formula:

$$\% \text{ inhibition} = [B_{control} - B_{sample}) / B_{control}] \times 100$$

where $B_{control}$ represents the absorbance of the control solution and B_{sample} is the absorbance of the polyherbal extract

Egg Albumin Denaturation Assay : The anti-inflammatory potential was also assessed using the egg albumin denaturation method. In this procedure, 0.2 mL of fresh egg albumin was combined with 2.8 mL of phosphate buffer (pH 6.3) and varying concentrations of the extract (10-50 µg/mL). The mixture was left to incubate at room temperature for 10 minutes, followed by heating at 55°C for 30 minutes in a waterbath. Absorbance was recorded at 660 nm, and the percentage of protein denaturation inhibition was calculated similarly to the BSA assay.

Diclofenac sodium (10 µg/mL) served as the positive standard, and dimethyl sulphoxide (DMSO) as the negative control.

Membrane Stabilization Assay : The membrane stabilization effect was assessed using human RBCs. Fresh blood was centrifuged at 1000 g for 10 minutes to isolate RBCs, which were washed with PBS and resuspended in Tris-HCl buffer to a 10% RBC suspension. A mixture of 1 mL RBC suspension and extract (10-50 µg/mL) was incubated at 37°C for 30 minutes. After centrifugation, the supernatant absorbance was measured at 540 nm. The percentage inhibition of hemolysis was calculated using:

$$\% \text{ inhibition} = [(A_{control} - A_{sample}) / A_{control}] \times 100$$

where $A_{control}$ represents the absorbance of RBC suspension without the extract and A_{sample} is the absorbance of the RBC suspension with polyherbal extract.

Statistical Analysis: *Results were expressed as the mean ± standard deviation (SD). Statistical significance between groups was determined using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS version 2.0 software.*

RESULTS

The combined *Ocimum sanctum* and *Cinnamomum zeylanicum* polyherbal extract displayed consistent and notable anti-inflammatory effects across all three assays (Figure 2). The results indicated a clear dose-dependent trend, with increased concentrations of the extract correlating with enhanced anti-inflammatory activity. The statistically significant findings across all assays ($p < 0.05$) underscore the extract's strong potential as an effective anti-inflammatory agent.

Bovine Serum Albumin (BSA) Denaturation Assay: *The combined formulation of Ocimum sanctum and Cinnamomum zeylanicum demonstrated a dose-dependent inhibition of protein denaturation in the BSA assay. The polyherbal formulation of Ocimum sanctum and Cinnamomum zeylanicum exhibited a dose-dependent inhibition of protein denaturation in the BSA assay, demonstrating significant anti-inflammatory activity. The percentage inhibition at concentrations of 10, 20, 30, 40, and 50 µg/mL was recorded as 47.6%, 56.3%, 68.8%, 76.5%, and 86.4%, respectively. Diclofenac sodium, used as the positive control, achieved 82.5% inhibition at the highest concentration of 50 µg/mL. Statistical analysis revealed that the combined extract's inhibition was significantly higher ($p < 0.05$), indicating a strong synergistic anti-inflammatory effect.*

Egg Albumin Denaturation Assay: *The combined extract exhibited a concentration-dependent inhibition of egg albumin protein denaturation. The inhibition percentages for concentrations ranging from 10 to 50 µg/mL were observed to be 52.1%, 58.9%, 66.5%, 70.2%, and 81.3%, respectively. Diclofenac sodium, used as the positive control, demonstrated 78.7% inhibition. These results reinforce the synergistic anti-inflammatory potential of the polyherbal formulation in preventing protein denaturation.*

Membrane Stabilization Assay: *The membrane stabilization assay evaluated the ability of the combined formulation to protect red blood cell (RBC) membranes from hemolysis, which is indicative of anti-inflammatory potential. The results indicated effective inhibition of hemolysis in a dose-dependent manner. The percentage inhibition of hemolysis at 10, 20, 30, 40, and 50 µg/mL concentrations was found to be 54.7%, 66.2%, 73.6%, 80.1%, and 85.4%, respectively. The standard reference, diclofenac sodium, exhibited 82.8% inhibition. The combined extract*

showed significantly higher membrane stabilization activity, indicating its superior ability to protect cell membranes from lysis under stress.

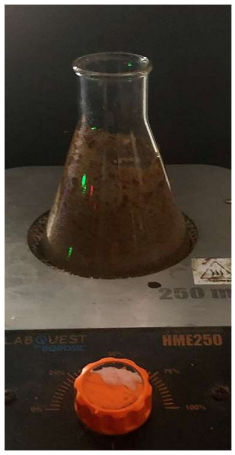

Figure 1: *Concentration of filtered polyherbal extract in a laboratory heating mantle to a volume of 5 ml.*

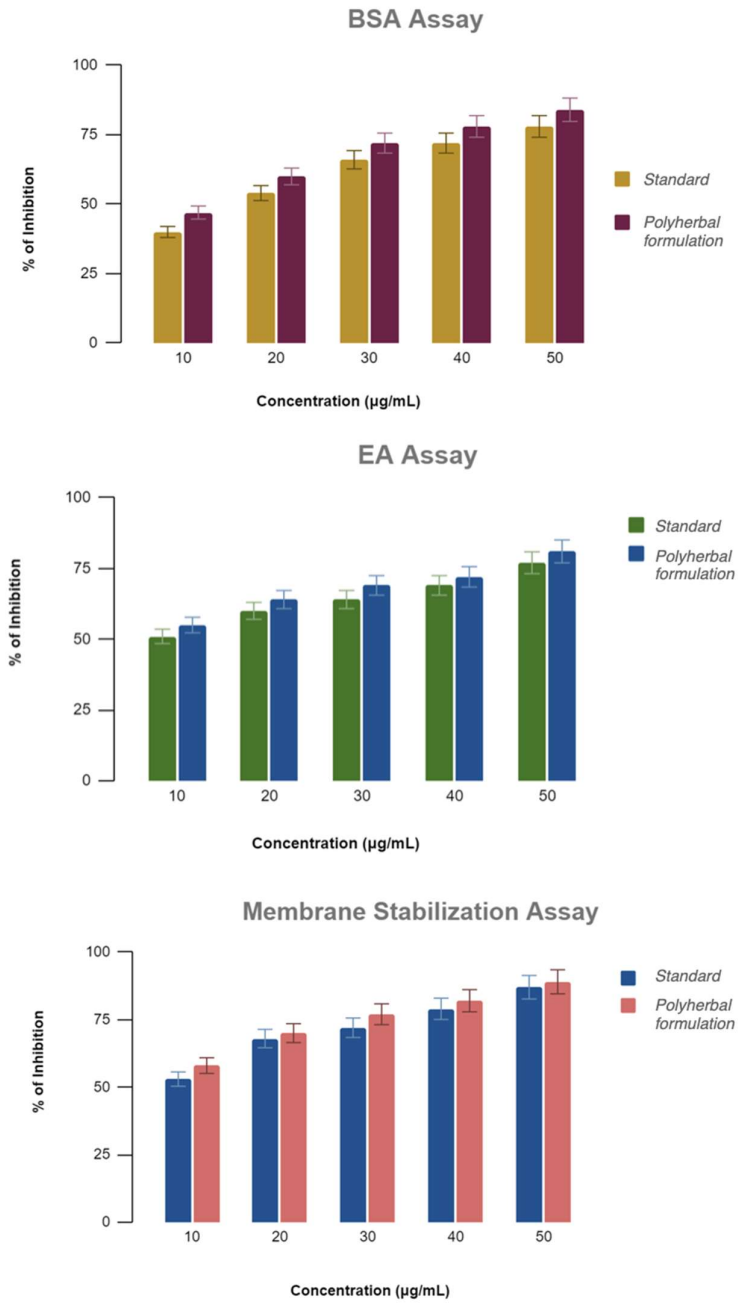

Figure 2: *Results of anti inflammatory properties of the polyherbal extract in the conducted assays compared to standards:* ***(A)*** *BSA (Bovine Serum Albumin Denaturation) assay;* ***(B)*** *EA (Egg Albumin Denaturation) assay;* ***(C)*** *Membrane Stabilization assay.*

DISCUSSION

Endodontic procedures require precision in the removal of infected tissue and the disinfection of the root canal system to ensure long-term success. One of the critical challenges in endodontic therapy is managing inflammation, which is a key driver of tissue damage and disease progression. Inflammation is a fundamental pathological process in endodontic disease, arising as a response to bacterial invasion, trauma, or chemical irritation.[1] When bacteria enter the pulp through caries or fractures, the host immune system activates an inflammatory

response characterized by the release of pro-inflammatory mediators, such as cytokines (e.g., IL-6, TNF-α) and prostaglandins. These mediators contribute to vasodilation, increased vascular permeability, and recruitment of immune cells, which aim to eliminate the infection.[2] However, if the inflammation becomes uncontrolled and chronic, it can lead to pulp necrosis and extend to the periapical tissues, causing the development of apical periodontitis.[3] Successful endodontic therapy not only requires the eradication of microorganisms from the root canal system but also involves managing inflammation to prevent further tissue damage and promote healing. Persistent inflammation in the periapical region can contribute to bone resorption and delayed healing, emphasizing the need for therapeutic strategies that address both microbial control and inflammation modulation.[16]

Endodontic irrigants are essential in root canal therapy for their roles in cleaning, disinfecting, and shaping the root canal system.[6] They help reduce the microbial load and remove debris that could harbor bacteria, which is crucial for preventing the recurrence of infection. However, when it comes to managing inflammation, the effects of conventional irrigants can be limited or even detrimental, depending on the chemical agents used.[7] Sodium Hypochlorite (NaOCl) is one of the most commonly used endodontic irrigants due to its strong antimicrobial properties and ability to dissolve organic tissue.[17] While it is effective in reducing the microbial burden within the canal, NaOCl's role in modulating inflammation is limited, making it insufficient to resolve periapical inflammation. It does not directly address inflammation and may, in some cases, exacerbate it.[18] If NaOCl is extruded beyond the apex, it can cause severe periapical inflammation and damage due to its cytotoxic nature, high pH and oxidative potential if extruded.[19] Inflammation caused by NaOCl extrusion can manifest as intense pain, swelling, and tissue necrosis, which complicates and delays healing.[20] Chlorhexidine (CHX) is often used as an alternative or supplement to NaOCl due to its broad-spectrum antimicrobial activity and substantivity.[21] However, CHX lacks tissue-dissolving capabilities and has minimal direct anti-inflammatory effects. Furthermore, its cytotoxicity to human cells can contribute to inflammation, especially if it contacts periapical tissues directly.[22] This makes it less than ideal as a sole agent for treating cases with significant periapical inflammation. It also forms an insoluble precipitate with sodium hypochlorite. [23] EDTA (Ethylene Diamine Tetraacetic Acid) is often used to remove the smear layer from root canal walls, which can enhance the penetration of other irrigants and intracanal medicaments.[7] While effective in aiding disinfection, EDTA does not have any direct anti-inflammatory properties, thus, does not contribute to the management of the inflammatory process itself.[24] These limitations suggest that while traditional irrigants play a vital role in cleaning and disinfecting the canal, they may not fully address the needs of cases where inflammation management is critical, which may require adjunctive strategies.

Intracanal medicaments are commonly employed during endodontic treatment to eliminate residual bacteria, reduce inflammation, and promote healing of periapical tissues.[8] However, each conventional medicament comes with its own set of limitations when it comes to managing inflammation effectively. Calcium hydroxide is one of the most widely used intracanal medicaments due to its high pH, which creates an unfavorable environment for most endodontic pathogens and neutralizes acidic conditions that promote inflammation.[25] It also exerts a mild anti-inflammatory effect by inhibiting the activity of pro-inflammatory cytokines.[9] However, its anti-inflammatory action is limited, as it does not directly target key mediators of the inflammatory process, such as COX-2 enzymes or specific inflammatory cytokines. [26], [27] Furthermore, calcium hydroxide’s effectiveness can be reduced in cases of persistent periapical infections with extensive bone resorption, as some bacteria may resist its high pH, resulting in incomplete resolution of inflammation.[25] Corticosteroids, such as

dexamethasone, are sometimes used as intracanal medicaments. They work by inhibiting the synthesis of pro-inflammatory mediators like prostaglandins and leukotrienes and reducing immune cell recruitment. While effective in decreasing pain and swelling in the short term, [28]long-term use of corticosteroids can suppress the immune system, potentially leading to secondary infections and delayed wound healing. Moreover, the systemic side effects associated with corticosteroids limit their use as routine intracanal medicaments.[29] Antibiotic pastes, often used in conjunction with other medicaments, provide antimicrobial coverage but are not primarily designed to modulate inflammation. Additionally, the overuse of antibiotics poses risks such as the development of antibiotic-resistant bacteria, allergic reactions, and alterations in the normal oral and gut flora.[30] These limitations highlight the need for safer alternative or adjunctive therapies that can control inflammation without relying on systemic effects.

Herbal alternatives are particularly appealing in endodontic therapy for their ability to support the body's natural healing process.[11] Plant-based therapies, particularly those with antioxidant and anti-inflammatory properties, [14] have garnered significant interest in recent years. Among them, *Ocimum sanctum* (holy basil) and *Cinnamomum zeylanicum* (Ceylon cinnamon) are two well-documented medicinal plants recognized for their extensive therapeutic applications.[31], [32] Both plants are known for their ability to reduce oxidative stress and inhibit the production of pro-inflammatory mediators, making them ideal candidates for addressing the dual challenges of microbial control and inflammation management in endodontic therapy.[12], [33], [34] Despite extensive research on the individual properties of these plants, limited studies have explored their combined effects. The concept of synergism—where the interaction of multiple agents produces a greater effect than the sum of their individual effects—underpins the rationale for using polyherbal formulations in therapeutic interventions[13], [15]. The synergistic interaction between *Ocimum sanctum* and *Cinnamomum zeylanicum* may enhance their ability to modulate inflammatory responses and promote tissue healing in endodontic applications.

The combined *Ocimum sanctum* and *Cinnamomum zeylanicum* formulation in the present study demonstrated consistent and significant anti-inflammatory activity across all three assays. The results indicated a clear dose-dependent trend, where increasing concentrations of the extract led to progressively stronger anti-inflammatory effects. The statistically significant outcomes across all assays ($p < 0.05$) emphasize the extract's strong potential as an effective anti-inflammatory agent. The findings indicate that the polyherbal formulation effectively inhibits protein denaturation and stabilizes cell membranes, suggesting a strong potential for managing inflammation and facilitating tissue healing in endodontic therapy. This enhanced efficacy may be due to the complementary mechanisms of action of their bioactive compounds, which target multiple pathways involved in the inflammatory process. Both herbs are rich in phenolic compounds, flavonoids, and other secondary metabolites [35] known for their anti-inflammatory properties. In *Ocimum sanctum*, compounds like eugenol, ursolic acid, and rosmarinic acid have been shown to inhibit pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[31] These cytokines play a pivotal role in the inflammatory cascade that leads to periapical tissue damage in endodontic infections. Similarly, *Cinnamomum zeylanicum* contains cinnamaldehyde and eugenol, which have demonstrated the ability to inhibit the cyclooxygenase-2 (COX-2) enzyme, thus reducing prostaglandin synthesis and alleviating inflammation. The inhibition of these enzymes reduces the overall inflammatory burden, leading to decreased pain and swelling in the affected tissues.[36] The complementary mechanisms of action between these two herbs suggest that their combination could provide a more holistic approach to managing endodontic

inflammation than using single agents.[37] Previous in vitro studies have also demonstrated that *Ocimum sanctum* can effectively reduce oxidative stress by scavenging free radicals, thereby limiting the inflammatory response.[38] This antioxidant activity is particularly relevant in the context of endodontics, where oxidative stress and the subsequent release of reactive oxygen species (ROS) contribute to periapical inflammation and tissue destruction. By neutralizing ROS, *Ocimum sanctum* may help create a more favorable environment for tissue healing following root canal therapy.[39], [40] Additionally, *Ocimum sanctum* has been shown to possess antimicrobial properties, making it a potential candidate for use as an intracanal medicament or irrigant. Its ability to target both microbial pathogens and the inflammatory response positions it as a versatile tool in endodontic therapy.[41] Similarly, cinnamon's antimicrobial activity makes it an ideal candidate for combating common endodontic pathogens such as *Enterococcus faecalis*,[12] which is known to persist in root canal systems despite conventional disinfection methods. The findings of this study suggest that the *Ocimum sanctum* and *Cinnamomum zeylanicum* polyherbal formulation could serve as an effective adjunct to conventional endodontic irrigants and intracanal medicaments. Moreover, incorporating herbal formulations into endodontic practice could potentially reduce the need for high concentrations of cytotoxic irrigants like sodium hypochlorite (NaOCl), thus minimizing tissue damage.[41] Thus, the use of biocompatible herbal alternatives may help to promote a more favorable healing environment and reduce post-operative complications such as flare-ups and periapical inflammation.

While the in vitro results are promising, it is important to note that the efficacy of the combined *Ocimum sanctum* and *Cinnamomum zeylanicum* formulation needs to be validated in clinical settings. Future studies can focus on in vivo models and clinical trials to confirm the anti-inflammatory efficacy and safety of this polyherbal formulation for endodontic applications. Additionally, the optimal concentration, dosage, application methods for the polyherbal extract and its potential combinations with other herbal agents can be explored to maximize its therapeutic effects in endodontic therapy. The results of this study could pave the way for the development of new, plant-based endodontic protocols that prioritize biocompatibility, safety and long-term treatment success.

CONCLUSION

The combined polyherbal extract of *Ocimum sanctum* and *Cinnamomum zeylanicum* demonstrated significant anti-inflammatory activity across multiple in vitro assays, indicating its potential as a natural therapeutic agent for managing inflammation in endodontic treatment. The dose-dependent inhibition of protein denaturation and effective membrane stabilization highlight the extract's ability to target key mechanisms involved in the inflammatory process. These results suggest that the polyherbal formulation could serve as a promising adjunct or alternative to conventional synthetic agents, offering a more biocompatible, holistic and multi-targeted approach for treating endodontic inflammation in clinical practice. However, further in vivo studies and clinical trials are essential to validate these results for its effective application in current endodontic protocols.

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