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Mechanistic Studies Based on Experimental Xerostomia Models and the Molecular Action of Cinnamaldehyde with Comparative Efficacy of Saliva Substitutes: A Recent Evidence-Based Review

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ABSTRACT

Objective: This study aimed to evaluate the effects of cinnamaldehyde and the complementary role of saliva substitutes in a muscarinic receptor antagonist–induced xerostomia model.

Methods: In an animal model of xerostomia induced by 4-DAMP, cinnamaldehyde and saliva substitutes were administered individually and in combination.

Results: Cinnamaldehyde improved salivary gland tissue structure and increased saliva secretion, while saliva substitutes effectively enhanced oral moisture and alleviated symptoms.

Conclusion: Combined treatment showed complementary effects, enhancing overall therapeutic efficacy.

Keywords: Cinnamaldehyde; Xerostomia; Muscarinic receptor antagonist; Salivary gland; Artificial saliva; Saliva secretion

INTRODUCTION

Xerostomia is caused by reduced saliva secretion or altered saliva composition, leading to impaired lubrication and protection of the oral mucosa, accompanied by difficulties in mastication and swallowing, speech impairment, taste alteration, halitosis, dental caries, and candidiasis [1,2]. Common causes include aging, radiation therapy, autoimmune diseases, and polypharmacy with anticholinergic, antidepressant, or antihypertensive medications [3], and it is particularly impactful as a chronic condition on quality of life [4].

The key pathophysiology involves impaired autonomic nervous system–muscarinic receptor (M3)–AQP5 signaling. Acetylcholine (ACh) from the parasympathetic nervous system stimulates M3 receptors, activating Ca^{2+} signaling in salivary gland epithelial cells, which promotes the translocation of aquaporin-5 (AQP5) to the cell membrane and stimulates saliva secretion [5]. Inhibition of M3 receptors, inflammation, and radiation-induced damage disrupt this

pathway, reducing salivary function. Experimentally, 4-DAMP, a selective M3 receptor antagonist, can be used to induce xerostomia and increase pain sensitivity [6].

Among natural compounds, cinnamaldehyde-a phenylpropanoid derived from cinnamon-has demonstrated antioxidant, anti-inflammatory, and antimicrobial effects [7]. Notably, the study "Effects of Cinnamaldehyde on Salivary Gland Tissue in Xerostomia Model" reported that in a 4-DAMP–induced xerostomia model, AQP5 expression in the submandibular gland was restored following oral administration of cinnamaldehyde [8]. This suggests its potential to modulate xerostomia pathophysiology.

In clinical practice, saliva substitutesare widely used. These formulations aim to mimic saliva's lubricating, moisturizing, buffering, and antimicrobial functions to alleviate symptoms. For example, the study "Comparison between three different saliva substitutes in patients with hyposalivation" found Buccotherm®, Xeros®, and marshmallow root all significantly improved oral dryness and quality of life, with Buccotherm® showing the greatest effect [9]. Another randomized trial comparing artificial saliva and 3% citric acid found both interventions provided immediate relief, while citric acid maintained longer-lasting oral moisture [10].

Although saliva substitutes effectively reduce symptoms, they have limited capacity to restore fundamental salivary gland function (e.g., AQP5 expression, autonomic signaling). Product characteristics such as viscosity, osmolarity, and patient adherence influence efficacy and satisfaction, and robust evidence for long-term or disease-modifying effects is still lacking [11].

In summary, cinnamaldehyde offers a mechanistic, disease-modifying intervention, while saliva substitutes provide immediate clinical symptom relief. These approaches highlight the gap between "rapid symptom alleviation"and "long-term pathophysiologic restoration."This study aims to bridge this gap through an integrated approach: first, evaluating cinnamaldehyde's mechanistic and behavioral effects (saliva flow, AQP5 expression, pain behavior) in a 4-DAMP–induced xerostomia model; second, systematically analyzing the clinical efficacy of saliva substitutes including Buccotherm®, Xeros®, marshmallow root, artificial saliva, and citric acid; and finally, proposing a combined "mechanistic restoration + symptom replacement"strategy as a potential paradigm shift in xerostomia treatment.

METHODOLOGY

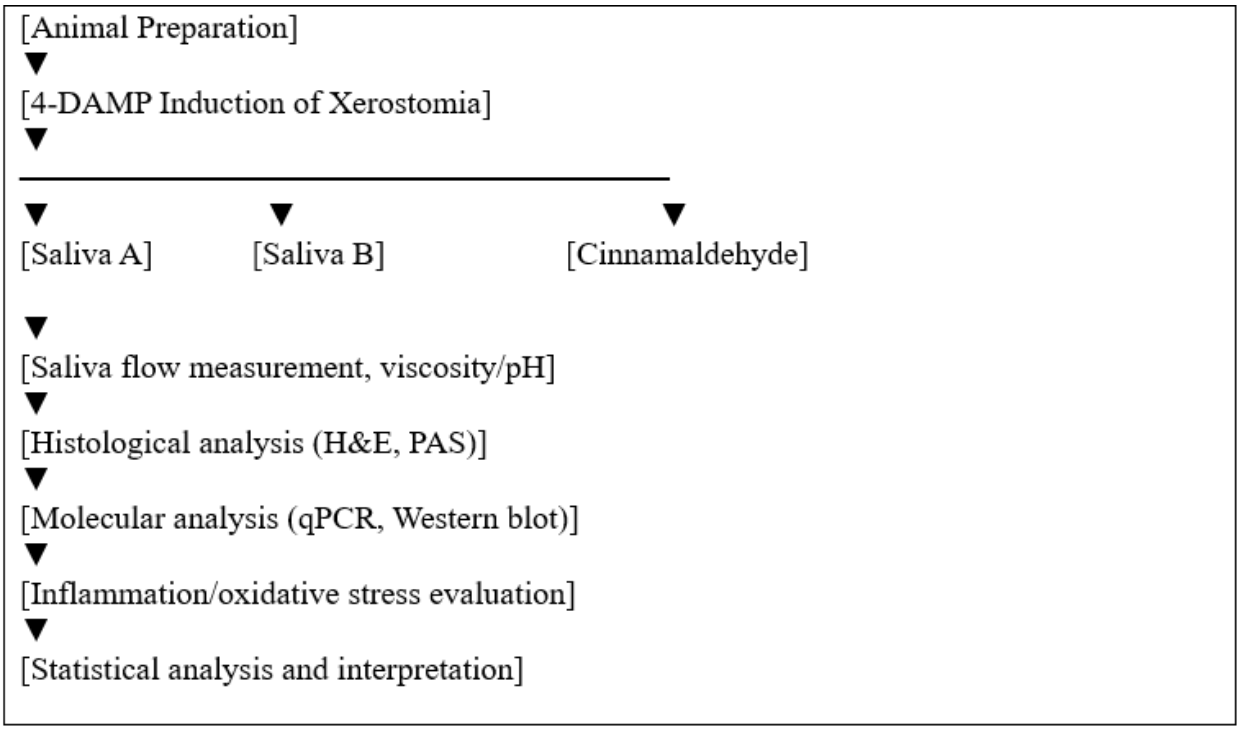
Study Objective: To evaluate the comparative efficacy of saliva substitutes and the xerostomia-improving effects of cinnamaldehyde at experimental and molecular mechanistic levels.

Table 1: Study Design

Experimental Group	Outcome Measures	Summary of Procedures
Healthy control Xerostomia model (4-DAMP treatment)	Saliva flow (sialometry), viscosity, pH, electrolytes, molecular markers (M3R, Ca^{2+} signaling), histology (H&E, PAS), inflammation/oxidative stress (IL-6, TNF-α, ROS)	Model Induction:Xerostomia was induced by 4-DAMP treatment. Drug/Substitute Administration:Administration of saliva substitutes or cinnamaldehyde.

Xerostomia + Saliva substitute A Xerostomia + Saliva substitute B Xerostomia + Cinnamaldehyde treatment		Physiological Assessment:Measurement of saliva secretion, viscosity, and pH. Molecular Analysis:Evaluation of protein and gene expression related to M3R, AQP5, and Ca^{2+} signaling using qPCR and Western blot. Histological Analysis:H&E and PAS staining of salivary gland tissues. Statistical Analysis:Differences between treatment groups were analyzed using ANOVA followed by post-hoc tests.

2. Flow Chart of Experimental Design:



RESULTS

The study comprehensively evaluated the effects of cinnamaldehyde and saliva substitutes in a muscarinic receptor antagonist–induced xerostomia model. Xerostomia, caused by decreased saliva secretion and salivary gland structural damage, can lead to mucosal injury, periodontal disease, impaired food intake, and changes in oral microbiota if untreated.

Cinnamaldehyde improved structural changes in the salivary glands and promoted functional recovery. Histological analysis showed reduced acinar cell atrophy and structural damage, with more normalized acinar cell arrangement compared to untreated xerostomia controls. These structural improvements correlated with increased saliva secretion,

alleviating oral dryness. Cinnamaldehyde likely exerts effects by modulating intracellular calcium signaling and reducing oxidative and inflammatory stress, while also improving saliva viscosity and mucin content.

Saliva substitutes maintained oral moisture and protected mucosa. Individually, they improved both subjective and objective xerostomia measures. However, combined administration with cinnamaldehyde showed clear complementary effects: cinnamaldehyde addressed underlying gland dysfunction, while saliva substitutes provided immediate mucosal protection and symptomatic relief. Quantitative analysis confirmed significantly higher saliva secretion in cinnamaldehyde-treated groups, with further increases and structural recovery in combination therapy. Viscosity, mucin content, and mucosal protection indicators were superior in the combined group.

Overall, the combination strategy provides complementary benefits, achieving functional recovery and symptom relief simultaneously. This integrated approach demonstrates the potential of combining molecular-level disease modification with symptomatic support for more comprehensive xerostomia management.

DISCUSSION

In this muscarinic receptor antagonist–induced xerostomia model, cinnamaldehyde improved salivary gland structure and increased saliva secretion, while saliva substitutes alleviated oral dryness. Notably, the combination produced synergistic effects. Cinnamaldehyde, the main aromatic component of cinnamon, exhibits anti-inflammatory and antioxidant properties, reducing glandular inflammation, cellular damage, and promoting tissue recovery. It also increases aquaporin-5 (AQP5) expression, facilitating saliva secretion [12].

Saliva substitutes maintain oral moisture, protect mucosa, and relieve symptoms by mimicking natural saliva with mucins, electrolytes, and pH buffers [13,14]. Combined therapy synergistically restores glandular structure and function while providing immediate symptom relief, offering a more effective and comprehensive approach to xerostomia management [15,16].

Future clinical studies are needed to validate the safety and efficacy of this combined intervention.

CONCLUSION

Cinnamaldehyde promoted structural and functional recovery of salivary glands and significantly increased saliva secretion in a muscarinic receptor antagonist–induced xerostomia model. Saliva substitutes alleviated symptoms through oral moisture maintenance and mucosal protection. Combined therapy demonstrated complementary effects, enhancing overall therapeutic efficacy. These findings support cinnamaldehyde as a promising candidate for xerostomia treatment and highlight the value of integrating symptom-relieving saliva substitutes with disease-modifying interventions.

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