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ARTIFICIAL SALIVA IN XEROSTOMIA MANAGEMENT: RHEOLOGICAL LIMITATIONS AND EMERGING ELECTRO-RESPONSIVE THERAPEUTIC STRATEGIES

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Abstract

Xerostomia is a prevalent and clinically significant condition characterized by reduced salivary secretion and qualitative alterations of saliva, leading to impaired oral function, increased disease susceptibility, and diminished quality of life. Current management relies largely on conventional saliva substitutes and pharmacological sialogogues; however, these approaches remain limited by their palliative nature, lack of biological activity, poor adaptability to dynamic oral conditions, and frequent systemic adverse effects. This review analyzes the pathophysiological basis of xerostomia with a specific focus on the composition, rheological behavior, and clinical performance of artificial saliva formulations. Emphasis is placed on the intrinsic limitations of static saliva substitutes in replicating the viscoelastic and multifunctional properties of natural saliva. Furthermore, emerging electro-responsive and smart material–based systems are explored as innovative therapeutic strategies capable of dynamic interaction with the oral environment. These advanced systems offer potential advantages through adaptive modulation of lubrication, enhanced mucosal retention, and controlled local delivery of active agents. By integrating insights from oral medicine, biomaterials science, and translational research, this review highlights future directions aimed at transforming artificial saliva from a passive palliative agent into an adaptive, functionally integrated therapeutic platform for xerostomia management.
Keywords: xerostomia, artificial saliva, rheological properties, electro-responsive systems, smart biomaterials

Pathophysiology of xerostomia and clinical implications

Xerostomia represents a frequent and clinically significant condition defined as the subjective sensation of oral dryness, most often associated with objectively reduced salivary flow (hyposalivation). Saliva plays a fundamental role in maintaining oral homeostasis through lubrication, buffering capacity, antimicrobial activity, enamel remineralization, and facilitation of mastication, swallowing, and speech. Any quantitative or qualitative alteration of salivary secretion disrupts these functions, leading to a cascade of local and systemic consequences that substantially impair oral health and quality of life [1].

From a pathophysiological perspective, xerostomia arises from multiple mechanisms affecting salivary gland structure, neural regulation, or secretory capacity. Primary glandular dysfunction is characteristic of autoimmune diseases such as Sjögren's syndrome, where

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lymphocytic infiltration progressively destroys acinar tissue, resulting in irreversible hypofunction. In contrast, secondary xerostomia may occur due to systemic diseases, polypharmacy, dehydration, or iatrogenic damage following head and neck radiotherapy, where vascular injury and fibrosis severely compromise glandular regeneration [2]. Regardless of etiology, the final common pathway is a reduction in serous secretion, accompanied by qualitative changes in saliva composition.

Saliva is a complex biological fluid whose protective efficacy depends not only on volume but also on its rheological behavior. The viscoelastic properties of saliva, largely determined by mucins and electrolytes, enable effective mucosal coating and lubrication under dynamic oral conditions. Alterations in salivary flow are frequently associated with increased viscosity, reduced elasticity, and impaired spreading capacity, which exacerbate the sensation of dryness even when residual secretion is present [3]. This explains why some patients report severe xerostomia despite measurable salivary output, highlighting the importance of qualitative dysfunction.

Clinically, xerostomia manifests through a wide spectrum of symptoms, including burning sensation, dysphagia, dysgeusia, speech difficulties, and increased thirst. These symptoms are often accompanied by objective signs such as mucosal atrophy, fissuring of the lips and tongue, candidiasis, and rapid development of cervical and root caries. The absence of adequate salivary buffering promotes acidic oral environments, favoring enamel demineralization and dysbiosis of the oral microbiome [4]. Consequently, xerostomic patients exhibit a significantly higher prevalence of dental caries and periodontal disease.

The relationship between salivary hypofunction and oral microbiota alterations has been increasingly emphasized. Reduced salivary flow diminishes mechanical clearance and antimicrobial activity, allowing pathogenic species to proliferate. Changes in carbohydrate metabolism and microbial composition further accelerate caries progression and mucosal infections, particularly in patients with chronic xerostomia [5]. These microbial shifts contribute not only to dental pathology but also to halitosis and persistent oral discomfort.

Neural regulation of salivary secretion represents another critical pathophysiological dimension. Salivary glands are under autonomic control, predominantly parasympathetic, with acetylcholine-mediated stimulation inducing fluid secretion. Sensory stimuli such as taste, mastication, and chemical irritation can modulate salivary flow and composition. Experimental data indicate that specific gustatory or chemical stimuli may transiently enhance salivary rheology by increasing endogenous citrate and other components, although these effects are short-lived and dependent on residual glandular function [6].

Beyond physiological stimuli, alternative therapeutic approaches targeting neural pathways have been explored. Acupuncture has been proposed as an adjunctive therapy capable of modulating autonomic activity and improving salivary flow in selected patients. While the underlying mechanisms remain incompletely elucidated, proposed effects include increased parasympathetic tone and local neurovascular modulation [7]. Clinical studies suggest potential benefits, particularly in radiation-induced xerostomia, although heterogeneity in treatment protocols limits reproducibility [8].

Efforts toward standardizing acupuncture protocols have highlighted the need for consistent point selection and treatment duration to achieve reliable outcomes. Nevertheless, even under optimized conditions, the efficacy of such interventions appears contingent on the presence of functional glandular tissue, limiting their applicability in advanced glandular destruction [9]. Systematic reviews focusing on oncological patients further underscore modest but clinically relevant improvements in subjective symptoms rather than complete restoration of salivary function [10].

Pharmacological sialogogues remain a cornerstone in the management of xerostomia when viable glandular tissue persists. Pilocarpine, a non-selective muscarinic agonist, has demonstrated efficacy in increasing salivary flow in patients with Sjögren's syndrome and post-

radiation xerostomia. However, its systemic administration is frequently associated with adverse effects such as sweating, gastrointestinal discomfort, and cardiovascular symptoms, which limit long-term adherence [11]. These limitations have driven research toward localized delivery systems aimed at enhancing efficacy while minimizing systemic exposure [12].

Composition and rheological properties of artificial saliva

Artificial saliva has been developed as a symptomatic therapeutic option for patients with xerostomia, aiming to reproduce, at least partially, the lubricating and protective functions of natural saliva. However, unlike physiological saliva, which is a highly dynamic and biologically active fluid, saliva substitutes are static formulations whose efficacy largely depends on their composition and rheological properties. Understanding these properties is essential for critically evaluating their clinical performance and inherent limitations [13].

The primary objective of artificial saliva formulations is to restore oral lubrication and reduce mucosal friction. To achieve this, most commercially available products rely on hydrophilic polymers designed to mimic the viscoelastic properties of natural saliva. Early formulations incorporated mucins, carboxymethylcellulose (CMC), or polyethylenoxide as key constituents, each influencing viscosity, elasticity, and spreading capacity in distinct ways. Mucin-based substitutes most closely resemble the lubricative behavior of natural saliva due to their glycoprotein structure, which enables effective boundary lubrication. In contrast, cellulose-derived agents primarily increase bulk viscosity without fully replicating salivary elasticity [14].

Table 1. Composition and Rheological Characteristics of Conventional Artificial Saliva Formulations

Component / Agent	Primary function	Rheological behavior	Clinical advantages	Main limitations	Notes
Mucin-based polymers	Boundary lubrication, mucosal coating	Viscoelastic, shear-thinning	Closest mimic of natural saliva lubrication	Limited stability, short duration	High biomimetic potential
Carboxymethylcellulose (CMC)	Increase bulk viscosity	Predominantly Newtonian	Low cost, widely available	Sticky sensation, poor elasticity	Commonly used
Polyethylenoxide	Lubrication enhancement	Moderate viscoelasticity	Improved spreading	Incomplete biomimicry	Intermediate performance
Electrolytes (Ca^{2+}, PO_4^{3-})	Buffering, remineralization	Minimal impact	Support enamel protection	Low long-term efficacy	Adjunctive role
Flavoring agents	Sensory acceptance	No rheological role	Improved compliance	No therapeutic effect	Optional additives

Table 1 summarizes the main components used in conventional artificial saliva formulations, highlighting their primary functions, rheological behavior, clinical advantages,

and inherent limitations. The data emphasize the gap between static saliva substitutes and the dynamic properties of natural saliva.

Rheological properties, such as viscosity, shear-thinning behavior, and elastic modulus, play a crucial role in determining patient comfort. Physiological saliva exhibits non-Newtonian, shear-thinning characteristics, allowing it to remain sufficiently viscous at rest while becoming less resistant during mastication and speech. Many artificial saliva formulations fail to adequately reproduce this behavior, resulting either in excessive thickness, perceived as unpleasant or sticky, or in rapid clearance from the oral cavity, limiting their duration of action [15]. This mismatch between formulation rheology and functional demands represents a central challenge in saliva substitute design.

In addition to lubrication, saliva contributes to enamel protection, buffering capacity, and microbial homeostasis. Most artificial saliva products lack enzymes, immunoglobulins, and antimicrobial peptides, rendering them biologically inert. While some formulations include electrolytes such as calcium and phosphate to support remineralization, their concentrations are often insufficient to exert a sustained protective effect. Consequently, saliva substitutes should be regarded primarily as palliative agents rather than true functional replacements [16].

Pharmacologically enhanced saliva production remains preferable when residual glandular function exists. Agents such as pilocarpine and cevimeline stimulate endogenous secretion, thereby preserving the complex rheological and biological properties of natural saliva. Nevertheless, their systemic administration is associated with dose-dependent adverse effects, including sweating, gastrointestinal disturbances, and cardiovascular reactions, which limit their long-term use [17]. These constraints underscore the ongoing reliance on artificial saliva in patients for whom pharmacological stimulation is contraindicated or ineffective.

The rheological inadequacy of conventional saliva substitutes becomes particularly evident in patients with severe hyposalivation, where continuous mucosal hydration is required. Frequent reapplication is often necessary, reflecting poor retention and limited mucoadhesive capacity. Moreover, static viscosity enhancement alone does not compensate for the absence of adaptive responses to mechanical stress or changes in oral pH and temperature. This explains the frequent discrepancy between short-term symptom relief and persistent functional impairment reported by xerostomic patients [18].

Recent perspectives on salivary enhancement emphasize the need for formulations capable of dynamic interaction with the oral environment. Fox highlighted that future therapeutic strategies should move beyond simple lubrication toward approaches that either stimulate residual glandular tissue or provide more functionally integrated substitutes [19]. Within this framework, optimizing rheological properties remains a foundational requirement, but it must be complemented by adaptive and responsive mechanisms to better approximate physiological conditions.

In summary, artificial saliva formulations represent an essential but inherently limited component of xerostomia management. Their composition and rheological properties largely determine clinical acceptability, yet current products fail to fully replicate the complex viscoelastic and biological behavior of natural saliva. These limitations provide a strong rationale for exploring advanced materials and smart systems capable of delivering adaptive lubrication and enhanced functional performance in xerostomic patients.

Clinical performance and limitations of conventional saliva substitutes

Conventional saliva substitutes are commonly prescribed as first-line symptomatic interventions for patients suffering from xerostomia, particularly in cases of irreversible salivary gland damage or when pharmacological stimulation is contraindicated. Their primary clinical objective is to alleviate the subjective sensation of oral dryness by providing temporary lubrication of the oral mucosa. While short-term symptomatic benefits are frequently reported,

the overall clinical performance of these agents remains limited and largely palliative in nature [1,2].

From a functional perspective, saliva substitutes may improve speech articulation, facilitate swallowing, and reduce mucosal irritation immediately after application. These effects are typically short-lived, as most formulations are rapidly cleared from the oral cavity through swallowing, evaporation, or mechanical displacement during mastication and phonation. Consequently, patients often require repeated applications throughout the day, which negatively impacts adherence and long-term satisfaction [1,3]. This limitation is particularly evident in patients with severe hyposalivation, where continuous lubrication would be necessary to maintain oral comfort.

A fundamental shortcoming of conventional saliva substitutes is their inability to reproduce the dynamic adaptive behavior of natural saliva. Physiological salivary secretion varies in response to mechanical stimulation, gustatory input, and circadian rhythms, adjusting both flow rate and composition. In contrast, artificial saliva products are static systems characterized by fixed viscosity and limited responsiveness to shear stress or environmental changes. This lack of adaptability results in suboptimal lubrication under functional conditions and contributes to persistent discomfort during eating or speaking [1,4].

In addition to rheological constraints, saliva substitutes are biologically inert when compared to natural saliva. They do not contain immunoglobulins, antimicrobial enzymes, or peptides involved in innate oral defense, nor do they support enzymatic digestion or effective buffering. As a result, their use does not mitigate the increased risk of dental caries, periodontal disease, or fungal infections associated with xerostomia. Clinical studies consistently show that saliva substitutes alone are insufficient to prevent disease progression and must be supplemented with intensive preventive strategies [2,5].

Patient-reported outcomes further highlight the limitations of these products. Complaints related to unpleasant taste, excessive stickiness, or inadequate duration of action are common and vary depending on formulation. Highly viscous substitutes may impair speech or be perceived as uncomfortable, whereas low-viscosity products fail to provide sustained relief. This delicate balance between viscosity and acceptability underscores the difficulty of achieving an optimal formulation using conventional materials [1,4].

Table 2. Clinical Performance and Limitations of Conventional Saliva Substitutes

Clinical aspect	Observed performance	Underlying mechanism	Clinical consequence
Symptomatic relief	Short-term improvement	Temporary lubrication	Frequent reapplication
Retention time	Low	Rapid clearance	Poor adherence
Functional adaptation	Absent	Static rheology	Ineffective during mastication
Biological protection	Minimal	Lack of enzymes and antimicrobials	Caries and infection risk
Prosthodontic compatibility	Limited	Increased friction	Reduced denture comfort
Patient satisfaction	Variable	Taste/viscosity issues	Discontinuation risk

Table 2 outlines the clinical performance of conventional saliva substitutes in xerostomia management, focusing on their symptomatic benefits, functional limitations, and consequences for long-term oral health and prosthodontic rehabilitation.

Overall, while conventional saliva substitutes remain an essential component of xerostomia management, their clinical performance is constrained by limited retention, lack of biological functionality, and poor adaptability to oral dynamics. These shortcomings justify the growing interest in advanced delivery systems and smart materials designed to overcome the inherent limitations of traditional saliva replacement therapies [2,6].

Electro-responsive and smart systems in xerostomia therapy

The limitations of conventional saliva substitutes have prompted growing interest in advanced therapeutic approaches capable of dynamically interacting with the oral environment. Electro-responsive and smart material–based systems represent an emerging field with significant potential to address the functional inadequacies of static saliva replacement therapies. These systems are designed to modify their physical or chemical properties in response to external stimuli, such as electrical signals, pH changes, or mechanical stress, thereby more closely approximating the adaptive behavior of physiological saliva [19].

Electro-responsive systems operate on the principle that external electrical stimulation can induce controlled changes in wettability, viscosity, or drug release. In the context of xerostomia, such mechanisms are particularly relevant, as oral conditions are highly dynamic and require rapid adaptation to shear forces generated during speech and mastication. Modulation of fluid spreading and surface interaction under low-energy stimulation may enhance mucosal coating and prolong the residence time of saliva-like formulations, addressing one of the core functional limitations of conventional substitutes [1,6].

Beyond surface wettability, electrically responsive polymers and hydrogels have been investigated for their ability to reversibly alter swelling behavior and lubrication properties. These materials are capable of transitioning between different rheological states, providing low resistance during functional movements while maintaining sufficient viscosity at rest. Such adaptive behavior directly targets the mismatch between static saliva substitutes and the dynamic biomechanical demands of the oral cavity, which has been consistently highlighted as a major cause of limited clinical efficacy [1,19].

A particularly promising application of electro-responsive systems lies in controlled local drug delivery. Electrospun nanofiber matrices and electrically sensitive carriers have demonstrated the capacity to release sialogogues, such as pilocarpine, in a spatially and temporally controlled manner. Localized delivery strategies are of particular relevance in xerostomia management, as they may enhance therapeutic efficacy while minimizing systemic adverse effects associated with oral administration. Experimental ex vivo and in vivo data indicate that such systems can achieve sustained stimulation of hypofunctional salivary glands under controlled conditions [12].

The integration of electro-responsive materials with mucoadhesive platforms further expands their clinical potential. Enhanced adhesion to oral mucosa or prosthetic surfaces may enable prolonged hydration and lubrication, improving patient comfort and functional outcomes. This approach is especially relevant in prosthodontic rehabilitation, where xerostomia negatively affects denture retention, mucosal tolerance, and overall treatment success [19].

Despite their theoretical and experimental advantages, electro-responsive systems for xerostomia therapy remain largely at the preclinical or early translational stage. Critical

challenges include ensuring long-term biocompatibility, safety under repeated stimulation, and the feasibility of integration into practical, patient-friendly oral devices. Furthermore, the lack of standardized stimulation protocols and performance benchmarks currently limits clinical extrapolation [12,19].

In summary, electro-responsive and smart systems represent a conceptual shift from passive lubrication toward adaptive, functionally integrated xerostomia therapies. By enabling dynamic modulation of rheological properties and targeted local delivery of active agents, these technologies offer a promising strategy for overcoming the intrinsic limitations of conventional saliva substitutes. Their successful translation into routine clinical practice will depend on rigorous validation and close interdisciplinary collaboration between material science, bioengineering, and oral medicine [19].

Future perspectives and translational potential in clinical practice

The evolving understanding of xerostomia as a complex, multifactorial condition highlights the need for therapeutic strategies that extend beyond symptomatic lubrication. Future approaches are expected to focus on translational solutions capable of integrating advanced biomaterials, smart delivery systems, and individualized clinical management. In this context, artificial saliva is likely to evolve from a passive palliative agent into an adaptive therapeutic platform designed to interact dynamically with the oral environment [19].

One of the most promising directions involves the clinical translation of electro-responsive and stimuli-sensitive materials. These systems may allow real-time modulation of rheological properties in response to functional demands such as mastication and speech, thereby more closely approximating the behavior of physiological saliva. Adaptive control of viscosity and surface interaction could significantly improve mucosal coverage and patient comfort, particularly in individuals with severe or permanent salivary gland dysfunction [1,6].

Localized and controlled drug delivery represents another critical area of development. Technologies enabling site-specific release of sialogogues or anti-inflammatory agents may reduce systemic exposure while preserving therapeutic efficacy. Experimental models employing electrospun matrices have demonstrated the feasibility of delivering pilocarpine directly to hypofunctional salivary glands, offering a promising alternative to systemic administration in selected patient populations [12]. Such approaches are particularly relevant for patients with contraindications to long-term pharmacological stimulation or those experiencing significant adverse effects [13,17].

From a clinical standpoint, integration of smart saliva substitutes into prosthodontic and oral rehabilitation protocols may substantially improve treatment outcomes. Xerostomia compromises denture retention, mucosal tolerance, and implant-supported prostheses by altering lubrication and increasing frictional forces. Adaptive saliva-mimicking systems incorporated into removable appliances or prosthetic interfaces could provide continuous hydration and functional lubrication, thereby enhancing comfort and prosthetic stability [19].

Despite their potential, several barriers to clinical implementation must be addressed. Ensuring long-term biocompatibility, material stability, and safety under repeated stimulation remains a priority. Additionally, the absence of standardized clinical endpoints and regulatory pathways for electro-responsive oral devices complicates translational progress. Well-designed clinical trials are essential to establish efficacy, safety, and cost-effectiveness before routine clinical adoption can be considered [12,19].

Interdisciplinary collaboration will play a decisive role in advancing these technologies from experimental concepts to clinically viable therapies. Effective translation will require coordinated efforts between material scientists, bioengineers, and clinicians specializing in oral medicine, prosthodontics, and oncology. Standardized outcome measures, including patient-reported outcomes and objective functional assessments, will be necessary to validate the real-world impact of smart xerostomia therapies [19].

Future management of xerostomia is likely to be shaped by the development of adaptive, biologically informed, and clinically integrated therapeutic systems. By leveraging electro-responsive technologies and advanced biomaterials, artificial saliva may evolve into a multifunctional platform capable of addressing both the functional and biological consequences of salivary gland hypofunction. Successful clinical translation of these innovations holds the potential to significantly improve long-term outcomes and quality of life for patients affected by xerostomia [19].

Conclusions

Xerostomia represents a complex clinical entity in which quantitative salivary deficiency, qualitative rheological alterations, and loss of biological function converge to significantly impair oral health and quality of life. Conventional saliva substitutes provide only transient symptomatic relief, as their static composition and limited adaptability fail to replicate the dynamic, multifunctional behavior of natural saliva. Pharmacological stimulation remains effective in selected cases but is frequently constrained by systemic adverse effects and contraindications, underscoring the unmet need for innovative, locally acting, and functionally adaptive therapeutic strategies.

The integration of electro-responsive and smart material–based systems offers a promising paradigm shift in xerostomia management by enabling dynamic modulation of lubrication, improved mucosal retention, and controlled local delivery of active agents. Such technologies have the potential to bridge the gap between passive saliva replacement and true functional restoration, particularly in patients with irreversible salivary gland damage. Continued interdisciplinary research, coupled with rigorous translational and clinical validation, will be essential to transform these emerging concepts into safe, effective, and clinically applicable solutions for long-term xerostomia care.

Bibliography

1. Vissink A, Waterman HA, S-Gravenmade EJ, Panders AK, Vermey A. *Rheological properties of saliva substitutes containing mucin, carboxymethylcellulose or polyethylenoxide*. **J Oral Pathol.** 1984;13:22–8. doi: 10.1111/j.1600-0714.1984.tb01397.x
2. Horst JA, Tanzer JM, Milgrom PM. *Fluorides and other preventive strategies for tooth decay*. **Dent Clin North Am**. 2018;62:207–34. doi: 10.1016/j.cden.2017.11.003
3. Karami-Nogourani M, Kowsari-Isfahan R, Hosseini-Beheshti M. *The effect of chewing gum's flavor on salivary flow rate and pH*. **Dent Res J (Isfahan)** 2011;8:S71–5
4. Novianti Y, Hidayat W, Rosa DE. *Severe Xerostomia Induced by Multiple Systemic Diseases in a Patient with Psoriasis Vulgaris: A Case Report and Literature Review*. ***Int Med Case Rep J.*** 2024;17:77-88 https://doi.org/10.2147/IMCRJ.S453097

5. Rafeek R, Carrington CV, Gomez A, Harkins D, Torralba M, Kuelbs C, et al. *Xylitol and sorbitol effects on the microbiome of saliva and plaque*. **J Oral Microbiol.** 2019;11:1536181. doi: 10.1080/20002297.2018.1536181
6. Gardner A, So PW, Carpenter G. *Endogenous salivary citrate is associated with enhanced rheological properties following oral capsaicin stimulation*. **Exp Physiol.** 2020;105:96–107. doi: 10.1113/EP088166
7. Gupta D, Dalai DR, Swapnadeep, Mehta P, Indra BN, Rastogi S, et al. *Acupuncture (zhēn jiŭ) – An emerging adjunct in routine oral care***. J Tradit Complement Med**. 2014;4:218–23. doi: 10.4103/2225-4110.139113
8. Assy Z, Brand HS. *A systematic review of the effects of acupuncture on xerostomia and hyposalivation*. **BMC Complement Altern Med**. 2018;18:57. doi: 10.1186/s12906-018-2124-x
9. Li LX, Tian G, He J. *The standardization of acupuncture treatment for radiation-induced xerostomia: A literature review*. **Chin J Integr Med**. 2016;22:549–54. doi: 10.1007/s11655-015-2145-y
10. Zhuang L, Yang Z, Zeng X, Zhua X, Chen Z, Liu L, et al. *The preventive and therapeutic effect of acupuncture for radiation-induced xerostomia in patients with head and neck cancer: A systematic review*. **Integr Cancer Ther**. 2013;12:197–205. doi: 10.1177/1534735412451321
11. Wu CH, Hsieh SC, Lee KL, Li KJ, Lu MC, Yu CL. *Pilocarpine hydrochloride for the treatment of xerostomia in patients with Sjögren's syndrome in Taiwan – A double-blind, placebo-controlled trial.* **J Formos Med Assoc**. 2006;105:796–803. doi: 10.1016/S0929-6646(09)60266-7
12. Muthumariappan S, Ng WC, Adine C, Ng KK, Davoodi P, Wang CH, et al. *Localized delivery of pilocarpine to hypofunctional salivary glands through electrospun nanofiber mats: An ex vivo and in vivo study*. **Int J Mol Sci**. 2019;20:541. doi: 10.3390/ijms20030541
13. Nusair S, Rubinow A. *The use of oral pilocarpine in xerostomia and Sjögren's syndrome.* **Semin Arthritis Rheum**. 1999;28:360–7. doi: 10.1016/s0049-0172(99)80002-x
14. Leung KC, McMillan AS, Wong MC, Leung WK, Mok MY, Lau CS. *The efficacy of cevimeline hydrochloride in the treatment of xerostomia in Sjögren's syndrome in southern Chinese patients: A randomised double-blind, placebo-controlled crossover study.* **Clin Rheumatol.** 2008;27:429–36. doi: 10.1007/s10067-007-0723-x
15. Voskoboynik B, Babu K, Hack JB. *Cevimeline (Evoxac ®) overdose.* **J Med Toxicol**. 2011;7:57–9. doi: 10.1007/s13181-010-0112-8
16. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. *A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca.* **Arthritis Rheum**. 2002;46:748–54. doi: 10.1002/art.510
17. Chambers MS, Posner M, Jones CU, Biel MA, Hodge KM, Vitti R, et al. *Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer*. **Int J Radiat Oncol Biol Phys**. 2007;68:1102–9. doi: 10.1016/j.ijrobp.2007.01.019
18. Hamada T, Nakane T, Kimura T, Arisawa K, Yoneda K, Yamamoto T, et al. *Treatment of xerostomia with the bile secretion-stimulating drug anethole trithione: A clinical trial*. **Am J Med Sci.** 1999;318:146–51. doi: 10.1097/00000441-199909000-00009

19. Fox PC. *Salivary enhancement therapies*. **Caries Res**. 2004;38:241–6. doi: 10.1159/000077761