Efficacy of Natural Artificial Saliva and Natural Saliva Stimulant in Xerostomia: A Review

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Abstract:
Xerostomia, characterized by reduced salivary flow, leads to significant health issues that compromise oral health-related quality of life (OHRQOL). Current therapeutic approaches for xerostomia include artificial saliva and saliva stimulants, which aim to restore moisture and lubrication to oral surfaces. Natural products have been utilized in medical applications for centuries due to their bioactive compounds that exhibit a wide range of pharmacological activities. However, their efficacy in treating xerostomia remains unclear. This review aims to assess the efficacy of natural artificial saliva and natural saliva stimulants in treating xerostomia. Methods, the data synthesis followed a rapid review protocol by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). Electronic databases were searched for articles published from 2004 to 2024 that evaluated the efficacy of natural artificial saliva and natural saliva stimulants for xerostomia. Results obtained from PubMed and ScienceDirect databases identified 37 scientific articles, of which 7 met the inclusion criteria. This review study found that a combination of Malva sylvestris and Alcea digitata, lycopene-enriched virgin olive oil, a combination of Matricaria chamomilla and Linum usitatissimum, Althaea officinalis, and licorice improved xerostomia-related symptoms and enhanced patient quality of life. Conclusion, natural compounds exhibit pharmacological activity in reducing xerostomia symptoms and improving quality of life (QoL). They show potential as constituents of artificial saliva and saliva stimulants.

Keywords: artificial saliva, saliva stimulant, herbal, natural, xerostomia.

Introduction
Xerostomia affects around 20% of the global population, predominantly occurring in menopausal women and geriatric individuals with comorbidities and polypharmacy (Austin, et al., 2024; Kontogiannopoulos, et al., 2023). It is characterized by a subjective sensation of dry mouth, often accompanied by quantitative and qualitative changes in saliva (Piaton, et al., 2021;
Wan, Vissink, & Sharma, 2020). Xerostomia, also referred to as hyposalivation, is typically defined by a resting salivary flow rate of less than 0.1 mL per minute and a stimulated saliva flow rate ranging from 0.5 to 0.7 mL per minute (Kapourani, et al., 2022). This condition leads to serious health problems such as difficulty in speaking, altered taste and smell perception, swallowing problems, dental caries, candidiasis, dysphagia and a burning sensation on the tongue (Łysik, et al., 2019). Xerostomia mostly induced by medication, radiotherapy, chemotherapy, and systemic disease (diabetes mellitus, sarcoidosis, systemic lupus erythematosus, and Sjögren's syndrome) all of which negatively impact oral health-related quality of life (OHRQOL) (Kapourani, et al., 2022; Łysik, et al., 2019).

The most effective therapy for xerostomia is managed by artificial saliva, which significantly reduces dry mouth symptoms and alleviates oral discomfort (Purdie, et al., 2023; Vinke, et al., 2020; Alhejoury, et al., 2021; Marimuthu, et al., 2021). Artificial saliva can provide sufficient hydration, lubrication and viscosity similar to natural saliva (See, et al., 2019). The formulations may be derived from synthetic materials or natural sources. An ideal artificial saliva should mimic the properties of human natural saliva, particularly its viscosity for effective mouth lubrication. Therefore, formulations must satisfy both biological and rheological requirements, such as viscosity and film-forming ability, crucial for tissue protection, speech, and swallowing (Austin, et al., 2024; Kontogiannopoulos, et al., 2023). They are important in the tissue protection, speech and swallowing (Łysik, et al., 2019). The protective capabilities of artificial saliva, including antimicrobial and remineralizing properties, are critical considerations. The oral cavity contain over 700 bacterial species, highlighting the need for formulations that inhibit bacterial adhesion (Biswal, et al., 2017). However commercially available artificial saliva doesn't inhibit the adhesion of bacteria (Łysik, et al., 2019). Additionally, remineralizing properties are essential as saliva plays a pivotal role in enamel structure maintenance and remineralization cycles. Reduced saliva flow can impair these functions (Farooq, & Bugshan, 2020). Moreover, some artificial saliva products contain citric acid, which lowers pH and increases the risk of enamel erosion (Aykut-Yetkiner, Wiegand, & Attin, 2014). Saliva stimulant is one of the alternative for xerostomia treatment when salivary gland partially impaired. This stimulant including acid stimulation (e.g., citric acid), mechanical stimulation (e.g., chewing gum, acupuncture, electrostimulation, and lozenges), and pharmaceutical agents (e.g., pilocarpine and cevimeline) (Kapourani, et al., 2022).

Natural products have been employed in medicine for centuries due to their bioactive compounds that exhibit a broad spectrum of pharmacological activities, often with fewer side effects compared to synthetic drugs. Therefore, they now play a pivotal role in pharmaceutical research and development (Kapourani, et al., 2022). Recent study shows artificial saliva containing natural substances has promising efficacy, but the data on their effectiveness in patients with xerostomia remain limited (Bugarin-Castillo, et al., 2024). Therefore, the primary objective of this study was to examine the efficacy of natural artificial saliva formulations in xerostomia.

Materials and Methods
The search was designed to find articles reporting the use of natural saliva artificial in individuals with xerostomia, and their impact on oral functions. The data synthesis protocol for a rapid review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) guidance (Moher, et al., 2015).

Study selection Criteria.
The focused question was formulated following the PICO (Roever, 2018):

- Population: Xerostomia patient.
- Interventions: Treatment with natural artificial saliva formulations or natural saliva stimulants.
- Control: Placebo or other artificial saliva
Outcomes: Improvement in oral health from xerostomia.

Literature Search Strategy

To identify studies a systematic search of the literature was conducted using PubMed and Science Direct database using Boolean operators and keywords ((saliva substitutes or artificial saliva or saliva artificial or saliva stimulant) AND (xerostomia or dry mouth)) AND (natural or herbal or extract). Inclusion criteria were articles published in 2014 - 2024, available in full text, RCTs, clinical study and published in English. The Criteria for exclusion were: articles not written in English, preclinical studies, articles with off-topics and reviewed articles. The remaining records were assessed for screening and abstracts were read.

Results

A total of 37 scientific articles were identified from the two databases used were screened using the PRISMA method according to the established criteria. The final number of articles that entered the qualitative data synthesis stage was 7 articles. The selected articles were then extracted, and qualitative analysis was carried out using a narrative approach. The research procedure is briefly shown in Figure 1 and 7 Articles were selected as they were related to the topic (Table 1).

Table 1. Summary of the Results from Selected Article

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Study design</th>
<th>Etiologies</th>
<th>Formulation and Treatment</th>
<th>Detail of patient, procedure, and evaluation</th>
<th>Important Result (conclusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ameri et al, 2016</td>
<td>randomized clinical trial, double-blind, radiation-induced xerostomia</td>
<td>Group 1 = Malva sylvestris and Alcea digitata powder</td>
<td>62 patients 20 to 70 years of age</td>
<td>Herbal compound effective for controlling</td>
<td></td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Design</td>
<td>Drug or Treatment</td>
<td>Efficacy Evaluation</td>
<td>Patient Characteristics</td>
<td>Study Outcome</td>
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<tr>
<td>Anabel NM., et al</td>
<td>Randomized clinical trial, double-blind, parallel-group, single-dose</td>
<td>Drug-induced xerostomia</td>
<td>Efficacy evaluated by VAS and dry mouth grade</td>
<td>Group 1 = lycopene-enriched virgin olive oil in spray, Group 2 = placebo</td>
<td>The topical application of lycopene-enriched virgin olive oil and its placebo counterpart improved xerostomia-related symptoms significantly (but not salivary flow rate) in patients with drug-induced xerostomia.</td>
<td></td>
</tr>
<tr>
<td>Morales-Bozo I., et al</td>
<td>Randomized clinical trial, double-blind, cross-sectional</td>
<td>Xerostomia</td>
<td>Efficacy evaluated by VAS The Xerostomia Inventory (XI) and Oral Health Impact Profile 14 (OHIP-14)</td>
<td>Group 1 = chamomile- and linseed-based saliva substitute, Group 2 = CMC based saliva substitute</td>
<td>Chamomile- and linseed-based saliva substitute was effective in relieving xerostomia symptoms.</td>
<td></td>
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<tr>
<td>Skrinjar I., et al.</td>
<td>Randomized clinical trial, open-label, parallel-group, single-dose</td>
<td>Xerostomia</td>
<td>Efficacy evaluated by Unstimulated whole saliva test and VAS</td>
<td>Group 1 = Buccotherm® spray, Group 2 = Xeros® saliva substitute, Group 3 = marshmallow root-based mouth rinse</td>
<td>Buccotherm® has the biggest effect on quality of life in patients with hyposalivation. three saliva substitutes decreasing xerostomia symptoms.</td>
<td></td>
</tr>
<tr>
<td>Yu I.C., et al.</td>
<td>Randomized clinical trial, open-label, single-blind, parallel-group, single-dose</td>
<td>Xerostomia in hemodialysis patients</td>
<td>Efficacy evaluated by VAS Croatian version of Oral Health Impact Profile</td>
<td>Group 1 = pure water mouthwash, Group 2 = licorice mouthwash, Group 3 = no mouthwash</td>
<td>Licorice mouthwash may effectively relieve feelings of xerostomia in hemodialysis patients.</td>
<td></td>
</tr>
<tr>
<td>Heydarirad G., et al.</td>
<td>Randomized clinical trial, double-arm, open-label</td>
<td>Radiation-induced xerostomia</td>
<td>Efficacy evaluated by VAS</td>
<td>Group 1 = Malva sylvestris and Alcea digitata powder</td>
<td>Malva sylvestris and Alcea digitata powder potential for</td>
<td></td>
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</tbody>
</table>
**Discussion**

The objectives of xerostomia treatment include alleviating symptoms, stimulating salivary secretion, and enhancing oral quality of life with minimal side effects. In this study several herbal plants including *Malva sylvestris*, *Alcea digitata*, lycopene-enriched virgin olive oil, *Matricaria chamomilla*, *Linum usitatissimum*, *Althaea officinalis*, and *Glycyrrhiza glabra* were found to be effective for improving xerostomia symptoms, salivary flow rate, and oral quality of life.

Xerostomia is a common side effect of radiation therapy for head and neck cancer, affecting approximately 93% of patients. It primarily results from major salivary gland damage due to radiation (Cavallo, et al., 2021; Chen, et al., 2024). *Malva sylvestris* and *Alcea digitata* are mucilaginous plants known for their emollient and laxative properties. Moreover, *Alcea digitata* exhibits antioxidant, anti-inflammatory, and antimicrobial activities. Recent studies shows its potential in treating irritated mucous membranes and promoting tissue regeneration (Moeini, et al., 2018). Research by Ameri A., et al. (2016) *Malva sylvestris* and *Alcea digitata* combination had a synergistic effect to improve xerostomia symptoms in head and neck cancer patients undergoing radiotherapy as assessed by VAS score after 4 weeks of therapy. Furthermore, a study by Heydariad G., et al. (2017) showed that this herbal improves QOL in HNC patients with radiation-induced xerostomia.

Lycopene is a carotenoid known for its beneficial effects in treating oral mucosal lesions (such as leukoplakia, oral lichen planus, oral submucous fibrosis, leukoplakia), periodontitis, burning mouth syndrome, and anti-carcinogenic (Salehi, et al., 2019). Combination of lycopene and virgin olive oil has been reported to increase its bioavailability and antioxidant activity (Garrido, et al., 2013). Recent studies revealed that lycopene-enriched virgin olive oil enhances antioxidant levels. Antioxidants can increase salivary secretion by enhancing adenosine triphosphate (ATP) production, resulting in activating the secretory ability and water secretion mechanisms in the salivary gland. Study by Navarro Morante, et al. (2017) found that lycopene-enriched virgin olive oil in spray improves oral quality of life and reduces xerostomia symptoms in patients with drug-induced xerostomia. However, the statistical intergroup comparative analysis revealed no difference between the treatment and the placebo, necessitating further research for confirmation.

Chamomile (*Matricaria chamomilla*), a medical plant from the Asteraceae family, contains over 120 constituents including phenolic acid, flavonoid, coumarin, and terpenoid. It is known for its antioxidant, sedative, antispasmodic, anti-inflammatory, and antimicrobial effects. It also contains mucilage. Chamomile shows potential activity in protecting or repairing human oral mucosal lesions, alleviating oral discomfort, and managing mucositis (El Mihyaoui, et al., 2022). It induces wound healing through the formation
of the inhibitory zone by repositioning collagen fibers. Its luteolin and apigenin have the highest capacity in the development of new blood vessels (Kręgielczak, et al., 2023). Meanwhile, Linseeds (*Linum usitatissimum*) are rich in proteins, unsaturated oils, insoluble fibers, and soluble fibers or mucilages with viscoelastic properties. Polysaccharides in linseed mucilages have unique and dynamic properties like swelling (pH-dependent), swelling–dwelling ability due to stimuli, reduction of silver, and capping capability (Tulain, et al., 2021). Clinical studies in the elderly population have shown that the combination of chamomile and linseed saliva substitute relieves the xerostomia symptoms such as dry mouth sensation, thick saliva, burning tongue, and difficulty swallowing (Morales-Bozo, et al., 2017).

Marshmallow (*Althaea officinalis*) contains flavonoids, acidic polysaccharides, polyphenols, coumarin, pectin, starch, and tannins as bioactive compounds. It has antiseptic, anti-inflammatory, and immunomodulatory activity. *Althaea officinalis*’s root extract creates a protective film that induces a faster regeneration of lesioned mucosa Kręgielczak, et al., 2023, compare the efficacy of Buccotherm, Xeros, and marshmallow root in alleviating hyposalivation symptoms measured by VAS and improvement in QOL. Buccotherm contains sulfate, bicarbonates, calcium, sodium, chlorides, magnesium, fluorides, strontium, lithium, and metallo-enzymes. It has anti-inflammatory, healing, and hemostatic activity and stimulates salivary secretion. Xeros containing betaine, sodium fluoride, and hydroxyethyl cellulose. The research found that all three saliva substitutes decreased the xerostomia symptoms, with Buccotherm demonstrating superiority over the other two (Skrinjar, et al., 2015).

Licorice root (*Glycyrrhiza glabra*) is commonly used to alleviate heat, improve dry throat, and relieve throat pain. It exhibits a wide spectrum of pharmacological activity including anti-inflammatory, antioxidative, anti-ulcer, antimicrobial, immunodeficiency, anti-cancer, and anti-allergic with flavonoid as a major bioactive compound (Wahab, et al., 2021; Kwon, et al., 2020). A Study by Yu et al. (2016) evaluates the efficacy of licorice mouth rinse in improving xerostomia and salivary flow rates in hemodialysis patients. The study showed that pure water and a licorice mouthwash improved the salivary flow rates, whereas only the licorice mouthwash may effectively alleviate xerostomia symptoms in these patients.

Epigallocatechin-3-gallate (EGCG) is the main active constituent in green tea (*Camellia sinensis*). Previous studies have shown its potential activity in mice salivary gland epithelial cells. A study by De Rossi S. et al. (2014) evaluated the efficacy of catechin for the treatment of xerostomia. After 8 weeks of therapy, the catechin formulation resulted in a statistically significant increase in both unstimulated and stimulated saliva output compared to baseline, leading to improvements in patient quality of life. EGCG exhibits antioxidant and cytoprotective activities, promoting epithelial proliferation and the development of pro-acinar buds and ducts (Sulistiyani, et al., 2021).

**Conclusion**

Natural compounds demonstrate pharmacological activity in alleviating symptoms of xerostomia and improving quality of life (QoL). They hold promise as components of both artificial saliva formulations and saliva stimulants.

**Conflict of interests**

No conflict of interest.

**References**


radiology, 135(2), 236–241. https://doi.org/10.1016/j.oooo.2022.08.017