

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

Faisal Kuswandani 

Pharmacology and Pharmacy, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

Felisha Febriane Balafif 

Microbiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

Nuroh Najmi 

Anatomy Pathology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

Anggun Rafisa 

Physiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

Suggested Citation

Kuswandani, F., Balafif, F.F., Najmi, N., & Rafisa, A. (2024). Efficacy of Natural Artificial Saliva and Natural Saliva Stimulant in Xerostomia: A Review. *European Journal of Theoretical and Applied Sciences*, 2(4), 545-553. DOI: [10.59324/ejtas.2024.2\(4\).46](https://doi.org/10.59324/ejtas.2024.2(4).46)

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 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.

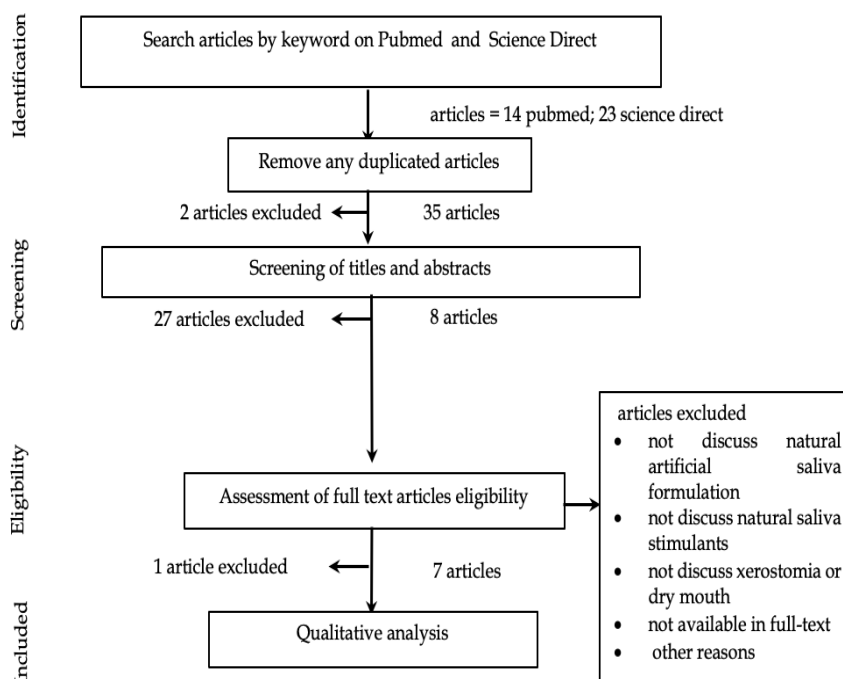


Figure 1. Flowchart of Article Search Based on the PRISMA Method

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

No	Author	Study design	Etiologies	Formulation and Treatment	Detail of patient, procedure, and evaluation	Important Result (conclusions)
1	Ameri et al., 2016	randomized clinical trial, double-blind,	radiation-induced xerostomia	Group 1 = <i>Maha sylvestris</i> and <i>Alcea digitata</i> powder	62 patients 20 to 70 years of age	Herbal compound effective for controlling

		parallel-group, single-dose		Group 2 = Hypozalix artificial saliva 3 times per day for 4 weeks	Efficacy evaluated by VAS and dry mouth grade	symptoms of dry mouth in head and neck cancer patients.
2	Anabel NM., et al	randomized clinical trial, double-blind, parallel-group, single-dose	drug-induced xerostomia	Group 1 = lycopene-enriched virgin olive oil in spray Group 2 = placebo 3 times per day for 12 weeks	60 patient aged over 18 years Efficacy evaluated by VAS The Xerostomia Inventory (XI) and oral Health Impact Profile 14 (OHIP-14)	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.
3	Morales-Bozo I., et al	randomized clinical trial, double-blind, cross-sectional	xerostomia	Group 1 = chamomile- and linseed-based saliva substitute Group 2 = CMC based saliva substitute 4 times per day for 1 week followed by rotation in the sample use	74 elderly aged over 60 years Efficacy evaluated by Unstimulated whole saliva' test and VAS	chamomile- and linseed-based saliva substitute was effective in relieving xerostomia symptoms
4	Skrinjar I., et al.	randomized clinical trial, open-label, parallel-group, single-dose	xerostomia	Group 1 = Buccotherm® spray Group 2 = Xeros® saliva substitute Group 3 = marshmallow root-based mouth rinse 4 times per day for 2 weeks followed by rotation in the sample use	60 patient aged over 60 years VAS Croatian version of Oral Health Impact Profile	Buccotherm® has the biggest effect on quality of life in patients with hyposalivation. three saliva substitutes decreasing xerostomia symptoms
5	Yu I.C., et al.	randomized clinical trial, open-label, single-blind, parallel-group, single-dose	xerostomia in hemodialysis patients	Group 1 = pure water mouthwash Group 2 = licorice mouthwash Group 3 = no mouthwash 4 times per day for 2 weeks followed by rotation in the sample use	125 patient aged over 60 years unstimulated salivary flow rates	licorice mouthwash may effectively relieve feelings of xerostomia in hemodialysis patients
6	Heydarirad G., et al.	randomized clinical trial, double-arm, open-label,	radiation-induced xerostomia	Group 1 = <i>Mahva sylvestris</i> and <i>Alcea digitata</i> powder	62 patients 20 to 70 years of age	<i>Mahva sylvestris</i> and <i>Alcea digitata</i> powder potential for

		active-controlled, single-dose	in head and neck cancers	Group 2 = Hypozalix artificial saliva 3 times per day for 4 weeks	QOL evaluated by EORTC QLQ-H&N 35	xerostomia treatment and improving QOL in HNC patients with radiation-induced xerostomia
7	De Rossi S. et al	randomized clinical trial, double-blind, placebo-controlled, single-dose	xerostomia	Group 1 = catechin-lozenge Group 2 = xylitol-lozenge 1 lozenge every 4 h for 8 weeks	60 patients 21 to 72 years of age QOL evaluated by questionnaire and VAS	The catechin-based formula significant increase in unstimulated (3.8-fold) and stimulated (2.1-fold) saliva output and improvement in QOL

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 Heydarirad 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 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 (Kregielczak, 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 Kregielczak, 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 (Sulistiyan, 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

- Alhejoury, H. A., Mogharbel, L. F., Al-Qadhi, M. A., Shamlan, S. S., Alturki, A. F., Babatin, W. M., Mohammed Alaishan, R. A., & Pullishery, F. (2021). Artificial Saliva for Therapeutic Management of Xerostomia: A Narrative Review. *Journal of pharmacy & bioallied sciences*, 13(Suppl 2), S903–S907. https://doi.org/10.4103/jpbs.jpbs_236_21

- Ameri, A., Heydarirad, G., Rezaeizadeh, H., Choopani, R., Ghobadi, A., & Gachkar, L. (2016). Evaluation of Efficacy of an Herbal Compound on Dry Mouth in Patients With Head and Neck Cancers: A Randomized Clinical Trial. *Journal of evidence-based complementary & alternative medicine*, 21(1), 30–33. <https://doi.org/10.1177/2156587215590232>
- Austin, W., Hdeib, M., Fraser, P., Goldchtaub, M., Shams, E., Han, Ti., Michaud, P.-L., & Adibnia, V. (2024). Oral Lubrication, Xerostomia, and Advanced Macromolecular Lubricants for Treatment of Dry Mouth. *Lubricants*, 12, 126. <https://doi.org/10.3390/lubricants12040126>
- Aykut-Yetkiner, A., Wiegand, A., & Attin, T. (2014). The effect of saliva substitutes on enamel erosion in vitro. *Journal of dentistry*, 42(6), 720–725. <https://doi.org/10.1016/j.jdent.2014.03.012>
- Biswal, B. N., Das, S. N., Das, B. K., & Rath, R. (2017). Alteration of cellular metabolism in cancer cells and its therapeutic prospects. *Journal of oral and maxillofacial pathology : JOMFP*, 21(2), 244–251. https://doi.org/10.4103/jomfp.JOMFP_60_17
- Bugarin-Castillo, Y., Bou-Fadel, P., Mohamed-Ismail, S., Huang, N., Saint-Eve, A., Mathieu, V., & Ramaioli, M. (2024). On the rheological and sensory properties of a novel natural salivary substitute. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 199, 106802. <https://doi.org/10.1016/j.ejps.2024.106802>
- Cavallo, A., Iacovelli, N. A., Facchinetti, N., Rancati, T., Alfieri, S., Giandini, T., Cicchetti, A., Fallai, C., Ingargiola, R., Licitra, L., Locati, L., Cavalieri, S., Pignoli, E., Romanello, D. A., Valdagni, R., & Orlandi, E. (2021). Modelling Radiation-Induced Salivary Dysfunction during IMRT and Chemotherapy for Nasopharyngeal Cancer Patients. *Cancers*, 13(16), 3983. <https://doi.org/10.3390/cancers13163983>
- Chen, Y.C., Viet-Nhi, N.K., Dang, L.H., Su, C.H., Hung, S.H. (2024). Efficacy of Office-Based Salivary Ductal Steroid Irrigation for Managing Post-Irradiation Xerostomia in Head and Neck Cancer Patients: A Retrospective Study. *Biomedicines*, 12, 1033. <https://doi.org/10.3390/biomedicines12051033>
- De Rossi, S. S., Thoppay, J., Dickinson, D. P., Looney, S., Stuart, M., Ogbureke, K. U., & Hsu, S. (2014). A phase II clinical trial of a natural formulation containing tea catechins for xerostomia. *Oral surgery, oral medicine, oral pathology and oral radiology*, 118(4), 447–454.e3. <https://doi.org/10.1016/j.oooo.2014.06.015>
- El Mihyaoui, A., Esteves da Silva, J. C. G., Charfi, S., Candela Castillo, M. E., Lamarti, A., & Arnao, M. B. (2022). Chamomile (*Matricaria chamomilla* L.): A Review of Ethnomedicinal Use, Phytochemistry and Pharmacological Uses. *Life (Basel, Switzerland)*, 12(4), 479. <https://doi.org/10.3390/life12040479>
- Farooq, I., & Bugshan, A. (2020). The role of salivary contents and modern technologies in the remineralization of dental enamel: a narrative review. *F1000Research*, 9, 171. <https://doi.org/10.12688/f1000research.22499.3>
- Fracasso, J. A. R., Ibe, M. B., da Costa, L. T. S., Guarnier, L. P., Viel, A. M., Brito, G. R., Parron, M. C., Pereira, A. E. D. S., Pegorin Brasil, G. S., Farias Ximenes, V., Fraceto, L. F., Malacrida Mayer, C. R., Ribeiro-Paes, J. T., Ferreira, F. Y., Zoppe, N. A., & Santos, L. D. (2023). Anti-Inflammatory Effect and Toxicological Profile of Pulp Residue from the *Caryocar Brasiliense*, a Sustainable Raw Material. *Gels (Basel, Switzerland)*, 9(3), 234. <https://doi.org/10.3390/gels9030234>
- Garrido, M., González-Flores, D., Marchena, A. M., Prior, E., García-Parra, J., Barriga, C., & Rodríguez Moratinos, A. B. (2013). A lycopene-enriched virgin olive oil enhances antioxidant status in humans. *Journal of the science of food and agriculture*, 93(8), 1820–1826. <https://doi.org/10.1002/jsfa.5972>
- Heydarirad, G., Rezaeizadeh, H., Choopani, R., Mosavat, S. H., & Ameri, A. (2017). Efficacy of a traditional Persian medicine preparation for radiation-induced xerostomia: a randomized, open-label, active-controlled trial. *Journal of*

integrative medicine, 15(3), 201–208.
[https://doi.org/10.1016/S2095-4964\(17\)60333-9](https://doi.org/10.1016/S2095-4964(17)60333-9)

Kapourani, A., Kontogiannopoulos, K. N., Manioudaki, A. E., Pouloupoulos, A. K., Tsalikis, L., Assimopoulou, A. N., & Barmapalexis, P. (2022). A Review on Xerostomia and Its Various Management Strategies: The Role of Advanced Polymeric Materials in the Treatment Approaches. *Polymers*, 14(5), 850.
<https://doi.org/10.3390/polym14050850>

Kontogiannopoulos, K. N., Kapourani, A., Gkougkourelas, I., Anagnostaki, M. E., Tsalikis, L., Assimopoulou, A. N., & Barmapalexis, P. (2023). A Review of the Role of Natural Products as Treatment Approaches for Xerostomia. *Pharmaceuticals* (Basel, Switzerland), 16(8), 1136.
<https://doi.org/10.3390/ph16081136>

Kręgielczak, A., Łukaszewska-Kuska, M., Mania-Końsko, A., & Dorocka-Bobkowska, B. (2023). Flaxseed (*Linum usitatissimum*), Chamomile (*Matricariae flos*) and Marshmallow (*Althaea officinalis*) Mouth Rinses in the Therapy of Oral Mucosa Diseases – A Review. *Journal of Natural Fibers*, 20(2).
<https://doi.org/10.1080/15440478.2023.2228487>

Kwon, Y. J., Son, D. H., Chung, T. H., & Lee, Y. J. (2020). A Review of the Pharmacological Efficacy and Safety of Licorice Root from Corroborative Clinical Trial Findings. *Journal of medicinal food*, 23(1), 12–20.
<https://doi.org/10.1089/jmf.2019.4459>

Łysik, D., Niemirowicz-Laskowska, K., Bucki, R., Tokajuk, G., & Mystkowska, J. (2019). Artificial Saliva: Challenges and Future Perspectives for the Treatment of Xerostomia. *International journal of molecular sciences*, 20(13), 3199.
<https://doi.org/10.3390/ijms20133199>

Marimuthu, D., Han, K. M., Mohamad, M. S. F., & Azman, M. (2021). Saliva substitute mouthwash in nasopharyngeal cancer survivors with xerostomia: a randomized controlled trial. *Clinical oral investigations*, 25(5), 3105–3115.
<https://doi.org/10.1007/s00784-020-03634-5>

Mocini, R., Farhan, F., Mofid, B., Rezaeizadeh, H., Gorji, N., Ghobadi, A., Jaladat, A., & Khanavi, M. (2018). The effect of the combination of *Malva sylvestris* L. and *Althaea digitata* Boiss. on prevention of acute radiation proctitis in patients with prostate cancer. *Journal of Herbal Medicine*, 1(12), 20–26.
<https://doi.org/10.1016/j.hermed.2018.01.005>

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A., & PRISMA-P Group (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*, 4(1), 1.
<https://doi.org/10.1186/2046-4053-4-1>

Morales-Bozo, I., Ortega-Pinto, A., Rojas Alcayaga, G., Aitken Saavedra, J. P., Salinas Flores, O., Lefimil Puente, C., Lozano Moraga, C., Manríquez Urbina, J. M., & Urzúa Orellana, B. (2017). Evaluation of the effectiveness of a chamomile (*Matricaria chamomilla*) and linseed (*Linum usitatissimum*) saliva substitute in the relief of xerostomia in elders. *Gerodontology*, 34(1), 42–48.
<https://doi.org/10.1111/ger.12220>

Navarro Morante, A., Wolff, A., Bautista Mendoza, G. R., & López-Jornet, P. (2017). Natural products for the management of xerostomia: a randomized, double-blinded, placebo-controlled clinical trial. *Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 46(2), 154–160.
<https://doi.org/10.1111/jop.12487>

Piaton, S., Duconseille, A., Roger-Leroi, V., & Hennequin, M. (2021). Could the use of saliva substitutes improve food oral processing in individuals with xerostomia? A systematic review. *Journal of texture studies*, 52(3), 278–293.
<https://doi.org/10.1111/jtxs.12591>

Purdie, M. J., Carpenter, M. D., Noll, J. L., Stephens, C. L., Taylor, Y. J., Hammitt, K. M., Napenas, J. J., & Brennan, M. T. (2023). Patient satisfaction and impact of salivary flow rate on effectiveness of xerostomia products. *Oral surgery, oral medicine, oral pathology and oral*

radiology, 135(2), 236–241.

<https://doi.org/10.1016/j.o000.2022.08.017>

Roever, L. (2018). PICO: Model for clinical questions. *Evidence-Based Medicine*, 3(2), 1-2.

<https://doi.org/10.4172/2471-9919.1000115>

Salehi, B., López-Jornet, P., Pons-Fuster López, E., Calina, D., Sharifi-Rad, M., Ramírez-Alarcón, K., Forman, K., Fernández, M., Martorell, M., Setzer, W.N., Martins, N., Rodrigues, C.F., & Sharifi-Rad, J. (2019). Plant-Derived Bioactives in Oral Mucosal Lesions: A Key Emphasis to Curcumin, Lycopene, Chamomile, Aloe vera, Green Tea and Coffee Properties. *Biomolecules*, 9. <https://doi.org/10.3390/biom9030106>

See, L., Mohammadi, M., Han, P. P., Mulligan, R., & Enciso, R. (2019). Efficacy of saliva substitutes and stimulants in the treatment of dry mouth. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*, 39(3), 287–297. <https://doi.org/10.1111/scd.12370>

Skrinjar, I., Vucicevic Boras, V., Bakale, I., Andabak Rogulj, A., Brailo, V., Vidovic Juras, D., Alajbeg, I., & Vrdoljak, D. V. (2015). Comparison between three different saliva substitutes in patients with hyposalivation. *Clinical oral investigations*, 19(3), 753–757. <https://doi.org/10.1007/s00784-015-1405-8>

Sulistiyan, E., Brimson, J. M., Chansaenroj, A., Sariya, L., Urkasemsin, G., Oonsiri, S., Tencomnao, T., Vacharaksa, A., Chaisuparat, R., & Ferreira, J. N. (2021). Epigallocatechin-3-Gallate Protects Pro-Acinar Epithelia Against Salivary Gland Radiation Injury. *International journal of molecular sciences*, 22(6), 3162. <https://doi.org/10.3390/ijms22063162>

Tulain, U. R., Mahmood, A., Aslam, S., Erum, A., Shamshad Malik, N., Rashid, A., Kausar, R., & Alqahtani, M. S. (2021). Formulation and Evaluation of *Linum usitatissimum* Mucilage-Based Nanoparticles for Effective Delivery of Ezetimibe. *International journal of nanomedicine*, 16, 4579–4596.

<https://doi.org/10.2147/IJN.S308790>

Vinke, J., Kaper, H. J., Vissink, A., & Sharma, P. K. (2020). Dry mouth: saliva substitutes which adsorb and modify existing salivary condition films improve oral lubrication. *Clinical oral investigations*, 24(11), 4019–4030. <https://doi.org/10.1007/s00784-020-03272-x>

Wahab, S., Annadurai, S., Abullais, S. S., Das, G., Ahmad, W., Ahmad, M. F., Kandasamy, G., Vasudevan, R., Ali, M. S., & Amir, M. (2021). *Glycyrrhiza glabra* (Licorice): A Comprehensive Review on Its Phytochemistry, Biological Activities, Clinical Evidence and Toxicology. *Plants (Basel, Switzerland)*, 10(12), 2751. <https://doi.org/10.3390/plants10122751>

Wan, H., Vissink, A., & Sharma, P. K. (2020). Enhancement in Xerostomia Patient Salivary Lubrication Using a Mucoadhesive. *Journal of dental research*, 99(8), 914–921. <https://doi.org/10.1177/0022034520917675>

Yu, I. C., Tsai, Y. F., Fang, J. T., Yeh, M. M., Fang, J. Y., & Liu, C. Y. (2016). Effects of mouthwash interventions on xerostomia and unstimulated whole saliva flow rate among hemodialysis patients: A randomized controlled study. *International journal of nursing studies*, 63, 9–17.

<https://doi.org/10.1016/j.ijnurstu.2016.08.009>