

Artificial Saliva for Therapeutic Management of Xerostomia: A Structured Review

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ABSTRACT

Introduction: Artificial salivary substitutes are commonly used as mouth and throat lubricants. The purpose of this review is to describe the therapeutic role of artificial saliva for the symptomatic relief and preventive management of dry mouth.

Materials and methods: To review application of artificial saliva in dentistry, the electronic search was carried out in PubMed, Medline, Embase, Cochrane Library, Google Scholar, and the hand search was performed in journals published from 1987 to 2018. Further information was requested from corresponding authors. Inclusion criteria were a predefined hierarchy of evidence and objectives.

Results: Artificial saliva is considered to be simple to use and clinically effective, with the provision of immediate relief from the symptoms of dry mouth.

Conclusion: The therapeutic efficacy of artificial saliva substitute is often transient, because of rapid elimination from the oral cavity, and thus there is an unmet need to maintain a hydrated mucosa for a prolonged period.

Keywords: Dentist, Oral healthcare professionals.

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INTRODUCTION

Saliva is a watery substance which is located in the mouth animals and humans, secreted by the salivary glands.¹ It is an aqueous hypotonic solution which guards hard and soft tissues of the oral cavity.²

Saliva serves many purposes in the oral cavity. For instance, it initiates and takes part in digestion, enhances masticatory function, enables swallowing and speech, enhances taste, lubricates oral mucosa, and permits free motion of oral tissues and maintains mucosal integrity. Saliva assists irrigation and cleaning of the teeth and oral mucosa with buffering capacity. It also cushions teeth from demineralization and gives antimicrobial and immunological defense against oral infections in the oral cavity.³ Amal et al. studied a decrease in the flow of saliva or hyposalivation is often related with a numerous secondary effects, namely hampered actions of the lips and tongue, masticatory problems, and obstacles in swallowing, speech, and taste.⁴

Hyposalivation is generally accompanied by plaque-mediated diseases such as dental caries and gingivitis, which ultimately result in tooth loss.⁵

Saliva substitutes, also known as artificial saliva, structurally take measure by humidification and lubrication of the dehydrated oral mucosa. The biophysical properties of artificial saliva must be as near as feasible to natural saliva.⁶

Artificial saliva contains a mixture of buffering agents, cellulose derivatives (to increase stickiness and moistening ability), and flavoring agents (such as sorbitol).⁷

Saliva substitutes are available in various forms such as liquids, sprays, gels, oils, lozenges, mouthrinses, chewing gums, and toothpastes.⁸

Hence, the study was conducted with an aim to scrutinize the available literature knowledge currently available on saliva substitutes this topic and to suggest how this information could be used to provide sound recommendations for by clinicians to advise their patients on the ideal usage of the currently available products.

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MATERIALS AND METHODS

The present review was carried out to describe the therapeutic role of artificial saliva/saliva substitutes in dentistry. The electronic search was carried out in PubMed, Medline, Embase, Cochrane Library, and Google Scholar, and articles journals published from 1987 to 2018 were selected. A literature review was performed using MeSH terms saliva, artificial saliva, and xerostomia. A total of 334 relevant records were retrieved from seven databases. After exclusion of duplicated (75), 259 studies remained. By reviewing the title and abstract of these 259 studies, 226 studies were found to be irrelevant. Sixty five studies were chosen for a full-text analysis. Hence, in this review, a total of 33 records were finally included.

RESULTS

In the case of patients with chronic dry mouth, saliva substitutes or artificial saliva can be used for longer durations as palliative or coadjutant treatments that are the option of choice.

Contents of Artificial Salivary Substitutes

The artificial salivary substitute contains either carboxymethylcellulose (CMC) or hydroxyethyl cellulose as lubricants and a variety of artificial sweeteners, fluoride salts, preservatives, and chloride (Tables 1 and 2).^{9–14}

Table 1: Contents of artificial salivary substitutes

1	Lubrication and viscosity is provided by CMC
2	Viscosity/surface tension of artificial saliva is reduced using artificial mucins
3	Xylitol or sorbitol acts as a sweetener
4	To mimic the electrolyte content of natural saliva, mineral salts are added to artificial saliva
5	Remineralization effect is provided by fluorides (Gelhard et al.)

Table 2: Artificial salivary products have been introduced in the market, which are presented

Product name	Active ingredients
Salivart	CMC
Oracare D	Glycerol
Salinum ⁴	Linseed
Oralbalance gel ⁹	LP3 protein enzyme
Luborant	CMC and fluoride (it comes in neutral, lemon, or peppermint flavors)
Glandosane	CMC
Saliva Orthana	Porcine gastric mucin (it comes in aerosol spray, and lozenge forms)
Salivix ¹⁰	Acacia and malic acid
Biotene	LP3 protein enzyme
Oral Seven	LP3 protein enzyme (it comes in toothpaste, mouthrinse, and gel forms)
BioXtra	LP3 protein enzyme (it is available in toothpaste, gel, mouthrinse, mouth spray, chewing gums, and lozenge forms)
GC dry mouth gel	CMC
Colgate dry mouth relief fluoride mouthwash ¹¹	Fluoride and cetylpyridinium chloride
Saliva natura ¹²	Natural mucins
XyliMelts ¹³	Xylitol, cellulose gum, and other natural ingredients (it comes in disk form)

Role of Artificial Salivary Substitutes in Oral Medicine

Xerostomia is defined as the stage of subjective sensation of oral dryness that may be associated with a decrease in the production of saliva and/or varied salivary composition. As a result of diminished lubrication, the oral mucosa appears dry in patients with chronically decreased salivary flow (hyposalivation). This causes patient discomfort and the first evidence of dysfunction that markedly affects quality of life, such as speech, chewing or swallowing difficulties, and even altered taste sensation. Similarly, these patients are more vulnerable to oral infections due to the adverse outcomes of reduced saliva output upon the five oral ecosystems. Diminished salivation and the appearance of dental caries are directly proportional.¹⁵

Artificial saliva substitutes such as Glandosane, Luborant, Biotene Oralbalance, AS Saliva Orthana, Salivace, and Saliveze. Alcohol-free mouthrinses (BioXtra and Biotène) and moisturizing gels (Oralbalance, BioXtra) are used in xerostomia, radiation therapy, and Sjögren's syndrome patient.^{9,15}

Oralbalance gel contains antimicrobial against *Streptococcus sanguis*, *S. salivarius*, *Neisseria mucosa*, *Stomatococcus mucilaginosus*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans* and imparts a moisturizing activity to alleviate symptoms of dry mouth.

Oralbalance gel contains antimicrobial enzymes such as lactoperoxidase, lysozyme, and lactoferrin which hinder the growth of bacteria that leads to bad breath. It further imparts defense against oral problems and helps cleanse the mouth gently. For holding denture in place, it can be used.⁹

Salivary substitutes are used in xerostomia, radiation therapy, hematopoietic cell transplantation, and end-stage renal disease patient.¹⁴ The salivary glands commonly get affected by various obstructive and inflammatory diseases and henceforth their glandular functions get altered.¹⁶ Recently, stem cell therapy and tissue engineering plays an important role for the treatment of atrophic salivary glands.¹⁷

Tissue Engineering of Salivary Gland

An alternative approach is required, if the gland damage is severe and the residual tissue can no longer be restored. The concept of artificial salivary gland is based on the principles of tissue engineering. Tissue engineering is one of the most interesting interdisciplinary approaches for this purpose, which uses cells, biodegradable scaffolds, and signals to reanimate tissues. The concept of tissue engineering has been considered as almost alike to, or a distinct area of, regenerative medicine in the history.¹⁷

The device similar to the natural duct system, constructed from porous, slowly biodegrade substratum, covered with matrix constituent on the inner surface of blind-end tube, in order to permit generation of polarized epithelial cell monolayer, presuming unidirectional fluid secretion and is surgically grafted in the buccal mucosa with an aperture in the oral cavity.¹⁶ Prior to administration of radiation therapy to treat head and neck carcinoma, if stem cells can be isolated from salivary glands of patients, it may be possible to transplant these cells back into patients to restore salivary gland function.¹⁷ Regeneration of salivary gland is a physiological function of living organisms, which allows the repair of lost or damaged tissue. Duct stem cells are used as a glandular regeneration for salivary gland tissue repair.¹⁸ Stem cells or progenitor cells are a characteristic group of cells which have self-renewal capability and pluripotency.¹⁹ Rius et al. have stated that in adult mice, the fully functional regeneration of a salivary gland through the orthotopic transplantation of a bioengineered salivary gland occurred. This recent study imparts a proof-of-concept for bioengineered salivary gland regeneration as a prospective therapy for xerostomia.¹⁸

The newer modalities for treating atrophic salivary gland are regenerative medicine and tissue engineering. An important role is being played by stem cell transplantation in salivary gland tissue regeneration.¹⁵ Nowadays, an artificial salivary gland was fabricated on the basis of tissue engineering principles. The new treatment modalities for atrophic salivary gland may thus be provided by stem cell therapy and tissue engineering.¹⁷

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In caries prevention, remineralization, and attrition of enamel, a significant role is played by artificial saliva.⁹

The daily usage of 1.1% sodium fluoride (NaF) dentifrice or gel may prevent or reduce the development of dental decay among the

patients with dry mouth. Fluoride application should be regulated according to the severity of the symptoms, degree of development of dental decay, and the underlying disease or the cause that steer to the dryness of the mouth.²⁰ Salivary substitute contains 0.4% stannous fluoride or 1.1% sodium fluoride.⁴

Remineralization effect of artificial saliva is mostly found in CMC than in mucin-based salivary substitute. It depends on the viscosity of artificial saliva. The viscosity of artificial saliva is inversely proportional to the remineralization effect. Remineralization effect of saliva substitutes prevents caries in dry mouth patient better than fluoride gel and mouthrinses.

Saliva natura is a salivary substitute, having demineralization effect on dentin, but it has neutral results on enamel when adding calcium, phosphate, and fluoride in Saliva natura leading to remineralization effect. It was also found that when increasing calcium in mucin-based salivary substitute, remineralization of artificial saliva will increase.

Demineralization effect depends on the pH value of artificial saliva. The pH value of artificial saliva substitute Glandosane is around 5.1. It damages the sound enamel structure of the tooth. Saliva Orthana lozenge, spray, and Salivix have low demineralization capacity. Demineralization effect of artificial saliva could be reduced when it is used with fluoride.⁹

A study revealed that a regimen of Caphosol (supersaturated remineralizing rinse based on calcium and phosphate ions) used daily with 1.1% sodium fluoride dentifrice and fluoride varnish treatment every 3 months was effective in preventing the progression of both root and coronal caries in xerostomic group patients.²⁰

Amal et al. in their article mentioned that the salivary substitute fluoride contains 0.4% stannous fluoride or 1.1% sodium fluoride⁴ and plays a significant role in remineralization, caries prevention, and attrition of enamel.¹⁴ Another study stated that a regimen of caphosol used daily with 1.1% sodium fluoride dentifrice and fluoride varnish treatment every 3 months was effective in preventing the progression of both root and coronal caries in xerostomic group.¹⁶ Patients with dry mouth have an enhanced chance of developing carious lesions. In patients with a high intake of acidic drinks or a high vomiting frequency and a decrease in the flow of saliva and insufficient buffering capacity will enhance clearance time of acids and durations with a low intraoral pH, and the chance of dental erosion might also be increased.²¹

Salivary flow plays a vital role in reducing enamel erosion by acid attack.²² Various artificial saliva substitutes in the forms of gels, mouthrinses, oils, sprays, viscous liquids, pastilles, and gums are obtainable to mitigate the pain and discomfort from chronic dry mouth and elevated salivary flow rate. Artificial saliva substitutes vary with respect to their chemical composition, base substance, and viscosity.⁸

All artificial saliva with a definite erosion-defensive potency showed a very towering viscosity due to numerous thickening agents such as glycerol, cellulose, and oil. Saliva substitute glandosane has erosive potential. In rehardening of softened dental enamel *in vitro*, saliva substitutes have been shown to act as an active agent.²¹

Some studies both *in vitro* and *in vivo* showed that reduction in enamel mineral loss, increase in enamel rehardening, and reduction in erosive lesion depth are carried out by natural saliva and its synthetic substitutes.²²

Mouth breathing has long been perceived as a crucial factor in persistent marginal gingivitis. More susceptible to infections, drying

itself may irritate soft tissues in the mouth. Patients complaining of a dry mouth and in those with insufficient salivary function, artificial saliva substitutes may be helpful and offer symptomatic relief. Oral dryness occurred due to inspired air may be avoided by the usage of a lubricant and moisturizer, which might help to protect the hydration status of the elementary investing tissues.²³

Artificial salivary substitutes are function oriented. The required properties of artificial saliva substitutes include excellent lubrication, surface wetting, inhibition of overgrowth of pathogenic microorganisms, maintenance of the hardness of dental structure, pleasant taste, long duration of effect, extended shelf life, and low cost.⁴

Artificial saliva substitutes generally contain cellulose, derivatives that elevate their stickiness and moistening ability.²³ Some studies have showed that salivary glycoproteins, including mucins, were mainly responsible for the lubricating characteristics of saliva.¹⁴ Humidification and lubrication properties are exhibited by the glycerin component of the saliva substitute. Although such preparations can be used as often as needed, artificial saliva substitutes are rapidly swallowed, and hence, frequent application may be mandatory as their moistening and lubricating measures have restricted time span.²³

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In prosthodontics, saliva plays a main role in the retention of complete denture.²⁴ It forms a thin film between denture and the oral cavity, and its absence leads to decreased retention and increased chances of ulceration in oral mucosa. Denture retention depends on various factors such as adhesion, cohesion, interfacial surface tension, and saliva. Saliva plays a significant role for these factors to be effective. The biological and rheological properties of artificial salivary substitutes help in retention of denture in patients with xerostomia. Rheological properties of artificial salivary substitutes are important in fixation of dentures. Artificial saliva substitutes are delivered through salivary reservoirs. Salivary reservoir is a chamber integrated into a removable prosthesis that imparts a flow of artificial saliva for a definite time period.

Artificial saliva substitutes preserve the underlying mucosa beneath the intaglio surfaces of the prosthesis by flushing the food debris collected due to xerostomia and also reintegrate the health of denture bearing mucosa by its healing and nutritive properties.

Composition of Artificial Salivary Substitutes Used in Prosthodontics

Sodium chloride, sodium CMC, potassium chloride, magnesium chloride, calcium chloride, sorbitol, di-potassium hydrogen orthophosphate, potassium di-hydrogen orthophosphate, sodium fluoride, methyl *p*-hydroxybenzoate, and spirit of lemon are the composition of artificial saliva substitutes used in prosthodontics.⁹ Commonly used artificial salivary substitutes in prosthodontics:

- Saliva Orthana spray,
- Saliva Orthana gel,
- Salivix pastes,
- Salivace,
- Glandosane,
- Moisties.⁹

Saliva plays as the most important environmental factor affecting the performance of the orthodontic appliances, affecting their success or failure.²⁵ Artificial saliva serves as mouth and throat lubricants. The artificial saliva substitutes have rheological characteristics that restrict their capacity of adsorption and film formation. Mucin-containing artificial saliva has rheological properties contiguous to human saliva, involving the capacity to structure a superficial film, which is an important attribute in its proficiency as a lubricant. The mucin-based artificial saliva substitutes have viscoelasticity similar to human saliva and have an elevated adsorption capacity, thus producing superior lubrication. While CMC-containing artificial saliva could have an inferior ability to form a superficial film, thus compromising their potency to stimulate the lubrication obtained from natural human saliva.

A study showed that lubrication has a part in friction forces between self-ligating brackets and CuNiTi wires, with mucin- and CMC-based artificial saliva imparting a dependable adjunct to natural human saliva.²⁶ The after-effect of artificial saliva on the static and kinetic frictional forces of stainless steel (Dentaurum) and polycrystalline ceramic (Transcend) brackets was examined by Downing et al. in combination with 0.018 inch round and 0.019 × 0.025 inch Edgewise archwire sizes and stainless steel, nickel–titanium, and β-titanium archwire materials, under a continuous ligature force were investigated. Artificial saliva had the outcome of increasing the frictional force when compared with the dry state in all the cases.¹⁹

DISCUSSION

The therapeutic role of artificial saliva in dentistry was reported by this review. Artificial saliva substitutes are used as a replacement therapy instead as treatment for dry mouth.⁴ Artificial saliva can be used whenever needed. Artificial saliva substitutes are swallowed swiftly, and hence, the moistening and lubricating measures have definite timespan.²⁷ In alleviating discomfort and to help in maintaining the integrity of the teeth, artificial saliva is used. The saliva substitutes must be as near as attainable to the natural saliva in terms of biophysical properties such as viscosity, mineral content, preservatives, and palatability.⁴

Artificial saliva substitutes help in retention of denture in patients with dry mouth.⁹ Artificial saliva substitute is categorized as two groups: mucin and CMC based. Carboxymethylcellulose is used to provide lubrication and viscosity. Best wetting properties on the denture base and the oral mucosa are exhibited by mucin-based salivary substitutes.²⁸

Artificial saliva substitutes generally consist of enzymes with antimicrobial action or mucins as lubricants. Similarly, these formulations sometimes compose elements that provide extra protection, circumvent buccodental over-colonization, and thus the progression of dental decay.²⁹ Artificial saliva substitute should specifically interact with microorganism. An artificial saliva substitute plays a main role in patients with xerostomia, radiation therapy, hematopoietic cell transplantation, and end-stage renal disease patient.⁹

Most researchers have showed that mucin-containing artificial saliva substitutes are considerably superior to CMC formulations. Patients preferred a mucin-containing artificial saliva over a CMC formulation because of the large upgradation of oral functioning, large retention time, and less amount required daily as found by Amal et al.⁴

Carboxymethylcellulose-based salivary substitute as a supplement to standard periodontal treatment may decrease

gingival inflammation and bleeding on probing in the anterior oral regions in mouth breathing patients with periodontitis as examined by Bhatia et al.²³ Linseed mucilage salinum emerged to be an appropriate artificial saliva replacement in dry mouth patients as found by Andersson Johansson et al.³⁰

Restorative materials are also generally used in dental practice.³¹ The outcomes of artificial saliva contamination on three restorative materials, that is, a glass ionomer cement (GIC), a resin-modified GIC (RMGIC), and a composite resin, were evaluated by a recent study. It was suggested that contamination of artificial saliva did not affect the shear bond strengths of GIC and RMGIC or their degrees of micro leakage.³²

Various studies showed that artificial saliva substitutes play a major role in orthodontics. A decrease in friction in the presence of artificial saliva was observed by Baker et al., whereas Stannard et al. have shown an increased friction in the existence of artificial saliva.²⁵

The use of saliva as a significant factor in removable prosthodontics treatment is described by Singh et al.²⁸

Biotene and BioXtra products had shown some potency in lowering the symptoms corresponding with xerostomia. Superior antimicrobial properties compared with Biotene products were claimed by BioXtra.¹¹

A study on facilitated saliva secretion and decreased oral inflammation by a novel artificial saliva system in the management of salivary hypofunction was conducted by Kang et al.³³ Authors concluded that the novel artificial saliva was contemplated to assist salivary secretion and reestablish physiological conditions in the mouth of patients with salivary hypofunction.³³

The artificial saliva substitute also act as an efficacious agent for rehardening of softened dental enamel. An artificial saliva substitute can be recommended that patients suffering from xerostomia and at high risk for dental erosion should use high-viscous saliva substitutes, but should avoid saliva substitutes with low pH or containing citric acid.²¹ The advantages of artificial saliva substitutes are in the covering and moisturizing oral mucosa and teeth, and disadvantages are their short-term activity in the absence of precautionary effect on the tissue.

Hence, all oral health professionals must requisitely have a good understanding of variable products available and be capable to discuss the benefits and limitation of these with their patients. Artificial saliva has been proven to be satisfactory efficacious clinically with the supply of instant relief from the symptoms of dry mouth symptoms.

CONCLUSION

Depending on the severity of symptoms, it was concluded that saliva substitutes or artificial saliva can be used as palliative or coadjuvant therapy of dry mouth symptoms. Among the patients who suffer from hyposalivation, this method proved to be productive in improving the oral health, self-confidence, and consequently upgraded the quality of life. Artificial saliva is considered to be easy to use and clinically systematic, with the provision of instant relief from the dry mouth symptoms. Depending on the severity of symptoms from the present review, evidence was found that saliva substitutes or artificial saliva can be used as palliative or coadjuvant therapy of dry mouth symptoms. This approach proved to be effective in recovering the oral health and self-confidence. Hence, the quality of life of the patient is upgraded.

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