

EXPLORATION OF THE EFFICACY AND SAFETY OF ORAL MOISTURIZING AGENTS FOR DRY MOUTH AND XEROSTOMIA: A SYSTEMATIC REVIEW

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ABSTRACT

This systematic review aimed to explore the efficacy and safety of oral moisturizing agents for dry mouth and xerostomia. Oral moisturizing agents improve the patient's quality of life by moisturizing the oral mucosa and maintaining the buffer capacity. The methods of this review was structured following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pubmed and Ebscohost-CINAHL Plus databases were used for article searching. The JADAD or Oxford quality scoring system was used to assess the risk of bias. Oral moisturizing agents tested were moisturizer mouthwash, Verramin gel, oral moisturizer jelly (OMJ), GC Dry Mouth Gel®, aloe vera mouthwash, and ginger mouthwash. All of them can reduce discomfort and dry mouth complaints in patients. Even OMJ could increase salivary pH and reduce the risk of candidiasis. There was no significant difference after using moisturizer mouthwash in patients with Sjogren's syndrome compared to giving natural water as a control. Mild to moderate adverse effects were found due to the use of moisturizer mouthwash. Oral moisturizing agents can overcome the problem effectively and safely for dry mouth or xerostomia, however, were less effective for patients with Sjogren's syndrome.

Keywords: Dry mouth, Oral moisturizing agents, Saliva substitutes, Xerostomia

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INTRODUCTION

The condition of a healthy human mouth is must always be always be moist with an adequate amount of saliva. The condition of lack of saliva will cause disturbances in oral functions, such as eating, swallowing, and speaking, so saliva is important in maintaining oral health. Saliva contains components of proline-rich glycoprotein, mucins, and water which have important roles to help moisturize the oral mucosa, maintain normal taste perception of food, and protecting the mucosa and teeth [1]. While the antimicrobial components of saliva consisting of histatin, lysozyme, and lactoferrin help prevent oral infectious diseases through the mechanism of regulation of host commensal microorganisms [2, 3]. Saliva can also help detect early oral diseases, such as dental caries and periodontal disease, because its protein content can be used as a biomarker [4].

Dry mouth or xerostomia is a common condition defined as an overall reduction in salivary output. Many causes of xerostomia were known as medications, autoimmune or systemic disease, and other conditions, including anxiety [5-8]. The role of aging and associated salivary dysfunction remains controversial [2, 9]. Dry mouth or xerostomia causes subjective complaints that are uncomfortable for the patient. Chronic decreased salivary flow often causes various oral diseases such as burning sensation, ulceration, and erosion due to lack of lubrication. Dental caries and infections also easy to occur due to dry mouth or xerostomia because of the decreased defense of the oral mucosa and teeth contained in saliva [2, 10]. Saliva also affects the composition and activity of the oral microbiota; if there is a disruption of salivary flow, it can result in dysbiosis. This dysbiosis affects oral health and increases the host's susceptibility to infection [11].

The background of xerostomia in the form of systemic diseases, such as diabetes, must also be treated, whereas if it is due to side effects of drugs, it can be suggested to replace with alternative drugs [2, 8]. If the condition of xerostomia is not treated, it can affect the patient's quality of life and even have the potential to cause depression [6]. Patients should be educated about efforts to avoid factors that may increase dryness and keep the mouth moist. Salivary substitutes may help symptomatically. A variety is available, including cevimeline or malic acid [6], water or ice chips, frequent sips of water that are generally effective, synthetic salivary substitutes [2], and peripheral and central sialogogues [1].

Salivary substitutes or artificial saliva, are topical agents that maintain lubrication of the mucosa and may or may not have a saliva-stimulating effect. There are several drug dosage forms available to treat dry mouth, namely: mouthwashes, gels, sprays, toothpaste, oral spray, and lozenges, but patients should be cautioned to avoid products containing alcohol, sugar, or strong flavors that may irritate sensitive, dry mucosa [2]. To prevent the occurrence of lesions due to friction, an agent that can moisturize or rehydrate the oral mucosa is needed, for example, preparations containing aloe vera or neutral edible oil. Although it is only temporary relief of discomfort, it can be recommended for use in patients before bedtime or around meals [5, 12].

For symptomatic treatment of dry mouth, saliva substitute agents should be lubricating, thickening, adhesive, and moisturizing, also been reported to help overcome this problem. The thickening agents, such as modified celluloses, polysaccharide gum, or polyethylene glycol, can relieve dry mouth, but because they cannot resemble the condition of human saliva, their effect is only temporary [13].

So far, a review article has been found that discusses the efficacy of saliva substitutes and stimulants in the treatment of dry mouth for non-Sjogren syndrome patients [13]. Therefore, this systematic review was compiled to complement and update the previous articles, with a wider population that is not limited to non-Sjogren Syndrome sufferers and recent publications. This review will also be used as a guideline for selecting saliva substitutes and oral moisturizing agents in the management of dry mouth or xerostomia patients, so it is necessary to explore the efficacy and safety of the agents.

MATERIALS AND METHODS

This systematic review was following the Preferred Reporting Items for the guide Systematic Reviews and Meta-analyses (PRISMA). Determination of the research question using the Population, Intervention, Comparison, and Outcome (PICO) method [15]. In this systematic review, the population were patients who experienced xerostomia or dry mouth; the intervention was the provision of saliva substitutes or artificial saliva or oral moisturizer agents; placebo control gel or GC dry mouth was used as a comparison, and the outcome obtained was an assessment of therapeutic efficacy and safety.

Based on the research question, the keywords used were ((xerostomia) OR (dry mouth)) AND (((artificial saliva) OR (saliva substitute)) OR (oral moisturizer)). Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>) and Ebscohost-CINAHL Plus (<https://www.ebsco.com/products/research-databases/cinahl-database>) were used as the databases. Filters were used in the database, written in English, full-text articles available, clinical trial or randomized controlled trial (RCT) articles, and published in 10 recent years. Inclusion criteria were articles that describe the intervention of saliva substitute or artificial saliva or oral moisturizer agents; studies in humans; patients with xerostomia or dry mouth, and also according to the purpose of this systematic review writing. Pilot studies or not RCTs articles were excluded. The period of article collecting was carried out until May 20, 2022.

The Jadad scoring or Oxford quality scoring system was used for assessing the quality of articles or the risk of bias in the methodology used in the articles. The questions were as follows: (1) Does the article describe the randomization process of the research? (2) Is the process of randomization appropriate? (3) Does the article describe the double-blinding process? (4) Is the method of double blinding described and appropriated? (5) Is there a procedure for

the resignation of the respondent in the research article? A score of 0 was given to the answer "NO" and a score of 1 for the answer "YES" (questions 1, 3, and 5). If the randomization method or blinding process did not appropriate, then the points were deducted by 1 (questions 2 and 4). The total score between -2 and 2 showed the low quality of the article, while the total score between 3 and 5 showed the high quality of the articles [15]. Fig. 1 showed a flow chart of how articles were chosen. These articles will be analyzed qualitatively.

RESULTS

This systematic review resulted in an assessment of the risk of bias, distribution of research subjects by country, systemic disease, sample size, and research design, as well as measuring the efficacy and safety parameters of oral moisturizing agent intervention for xerostomia or dry mouth. Table 1 shows that of the five included articles, four are of good quality, while the other one is of low quality. The randomization domain (items 1 and 2) reached 100%, the domain regarding blinding (items 3 and 4) reached 80%, and the domain of the procedure for resigning or withdrawing from research (item 5) was 100%. Table 1 is shown regarding the risk of bias assessment.

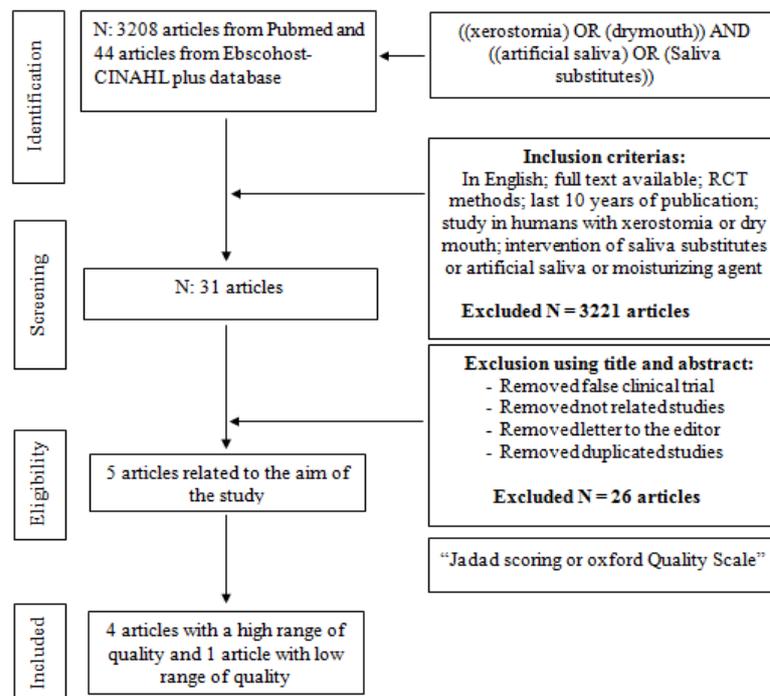


Fig. 1: Flow chart of the article selection

Table 1: Assessment of the risk of bias

No	Reference	Question no.					Total score	Result
		(1)	(2)	(3)	(4)	(5)		
1	Jose <i>et al.</i> , 2018 [16]	1	1	1	1	1	5	High range of quality
2	Athasi <i>et al.</i> , 2018 [17]	1	1	1	1	1	5	High range of quality
3	Nuchit <i>et al.</i> , 2019 [18]	1	1	1	1	1	5	High range of quality
4	Badooei <i>et al.</i> , 2021 [19]	1	1	1	1	1	5	High range of quality
5	Lam-ubol <i>et al.</i> , 2020 [20]	1	1	0	-1	1	2	Low range of quality
Domain assessment (%)		100	100	80	80	100	-	-

Note: Question Number (1) was the study described as random? (Yes=1, No = 0); (2) Was the randomization scheme described and appropriate? (Yes=1, No =-1); (3) was the study described as double-blind? (Yes=1, No = 0); (4) was the method of double-blinding appropriate? (Yes=1, No =-1); (5) was there a description of dropouts and withdrawals? (Yes=1, No = 0). Total Score -2 to 2 decided as the Low range of quality; 3-5 decided as the high range of quality.

Table 2 showed that research on the intervention of oral moisturizing agents for patients with a dry mouth or xerostomia has been carried out

in the United Kingdom (1 article), Iran (2 articles), and Thailand (2 articles). The age range of the patients was 18-85 y, with co-existing

systemic conditions/diseases: Sjogren's syndrome (28 people), non-Sjogren's syndrome (72 people), post-head and neck cancer patients who received radiotherapy (118 people), diabetes mellitus (105 people), and patients using endotracheal tubes (80 people). All included articles

used an RCT-study design, but only four articles carried out a proper blinding process. Table 2 regarding the distribution of research subjects by country, underlying systemic diseases/conditions, sample size, intervention, and study design, as shown below.

Table 2: Distribution of research subjects by country, systemic disease/condition, sample size, intervention, and study design

No	Reference	Country	Systemic disease/condition	Sample size and intervention	Study design
1	Jose <i>et al.</i> , 2018 [16]	United Kingdom	Patients aged 18-84 y with complaints of dry mouth accompanied by Sjogren's syndrome (SS) or non-SS.	100 patients were divided into 2 groups: - 28 patients SS - 72 patients with non-SS	● RCT ● Double-blinded
2	Athasi <i>et al.</i> , 2018 [17]	Iran	Patients aged 18-85 y, with dry mouth, were diagnosed by a dentist using an oral endotracheal tube.	80 patients were divided into 2 groups: - 40 patients were given Verramin gel - 40 patients were given placebo control of carboxy methyl cellulose (CMC).	● RCT ● Triple blinded
3	Nuchit <i>et al.</i> , 2019 [18]	Thailand	Patients aged 30-70 y, during minimum 1-month radiotherapy with head and neck cancer.	62 patients were divided into 2 groups: - 31 patients were given oral moisturizer jelly (OMJ) - 31 patients were given GC Mouth gel®	● RCT ● Double-blinded
4	Badooei <i>et al.</i> , 2021 [19]	Iran	Patients with xerostomia, Diabetes Mellitus, and no allergy to ginger and aloe vera.	105 patients were divided into 3 groups: - 35 patients were given aloe vera mouthwash - 35 patients were given ginger mouthwash - 35 patients as control.	● RCT ● Triple blinded
5	Lam-ubol <i>et al.</i> , 2020 [20]	Thailand	Post-radiotherapy patients with head and neck cancer.	56 patients were divided into 2 groups: - 30 patients were given OMJ - 26 patients were given GC dry mouth gel®	● RCT ● Single blinded

Note: RCT = randomized controlled trial.

Table 3: Intervention, control, instruments, efficacy, and safety parameters

No	Reference	Intervention	Control	Instruments	Efficacy	Safety
1	Jose <i>et al.</i> , 2018 [16]	Moisturizer mouthwash contains glycerin, xylitol, sorbitol, propylene glycol, poloxamer 407, potassium sorbate, Natrosol 250-M, sodium phosphate monobasic anhydrous, Carboxy poly cellulose (CPC), and disodium phosphate anhydrous. Used 1-2 times, 15 ml/day.	Natural spring water (pH: 7.0), used 1-2 times, 15 ml/day.	Questionnaire on comfortability and symptom reduction.	The use of moisturizer Mouthwash was superior to natural spring water in non-Sjogren's syndrome patients but did not show any difference in patients with Sjogren's syndrome.	Mild to moderate Adverse effects occur due to the use of mouthwash, namely: oral paresthesia, oral discomfort, and throat irritation.
2	Athasi <i>et al.</i> , 2018 [17]	Verramin moisturizer gel contains 100% aloe vera jelly, 3% peppermint essential oil, Carboxymethylcellulose (CMC), 10% propylene glycol, and 0.1 % potassium sorbite.	Placebo contains CMC gel, 10% propylene glycol, 0.1% potassium sorbite, mint flavor, and water.	Challacombe score.	Verramin was better than placebo in reducing discomfort and improving oral health.	Not Available
3	Nuchit <i>et al.</i> , 2019 [18]	OMJ contains glycerin, water, sorbitol, xylitol, carbomer, hydroxyethyl cellulose (HEC), sodium hydroxide, and propylparaben, used for 2 mo (1-2 teaspoonfuls 6 x/day).	GC dry mouth gel® contains CMC, used for 2 mo (application every 3 h).	Challacombe score and questionnaire.	OMJ and GC dry mouth gel® showed improvement in symptoms, but OMJ showed a better effect than GC dry mouth gel®.	A mild adverse effect occurs with the use of GC dry mouth gel®. There was no adverse effect due to OMJ.
4	Badooei <i>et al.</i> , 2021 [19]	Aloe vera (50%) mouthwash (20 ml, 3x/day). Ginger (25%) mouthwash (20 ml, 3x. day).	Placebo (saline solution).	VAS scale for pain and questionnaire.	The use of ginger and aloe vera was better than saline solution, but ginger was better than aloe vera.	Not Available
5	Lam-ubol <i>et al.</i> , 2020 [20]	OMJ used for 2 mo (1-2 teaspoonfuls 6 x/day).	GC dry mouth gel® was used for 2 mo.	Questionnaire.	OMJ and GC could increase salivary pH and Reduce candidiasis. OMJ was better at increasing buffering capacity while GC was better at increasing saliva flow rate	Not Available

Table 3 shows the intervention materials, control materials, instruments, efficacy, and safety parameters. The tested moisturizer ingredients were carboxy polycellulose (CPC; 1 article), carboxy methyl cellulose (CMC; 1 article), and hydroxyethylcellulose (HEC; 2 articles), and in 1 article, it was not explained. Two articles tested aloe vera herbal ingredients (aloe vera mouthwash and Verramin) and one article reported testing ginger herbal ingredients. The

materials used as controls were natural spring water (1 article), saline solution (1 article), CMC placebo (1 article), and GC Dry Mouth gel® containing CMC (2 articles). The output parameter measuring instruments used were: a questionnaire about comfort and symptom reduction (4 articles), a visual analog scale (VAS for pain; 1 article), and objective measurements using the Challacombe scale (2 articles).

There was an increase in the degree of comfort and a decrease in symptoms in patients with dry mouth and non-Sjogren's syndrome after giving CPC mouthwash, which was better than the administration of natural spring water as a control. Verramin preparations containing CMC can reduce discomfort due to dry mouth and can improve oral health. Administration of oral moisturizing jelly (OMJ) can reduce symptoms in dry mouth patients, increase salivary pH, and reduce candidiasis better than administration of GC Dry Mouth Gel® containing CMC. OMJ is better at increasing buffer capacity, but GC dry mouth Gel® is better at increasing saliva flow rate. Measurement of safety parameters was only obtained from 2 articles that reported the occurrence of non-serious adverse effects. In table 3, the following information is given about the intervention materials, the control materials, the measuring tools, the efficacy, and the safety parameters.

DISCUSSION

Based on the 5 included articles [16-20], the most related conditions to dry mouth were not only in patients with systemic diseases such as Sjogren's syndrome [16], post-radiotherapy in head and neck cancer patients [18, 20], diabetes mellitus [19], and patients using endotracheal tubes [19] but can also be found in non-Sjogren's syndrome patients. This article review completes the previously published review articles, which already stated that dry mouth or xerostomia could be related to aging [1, 2, 7, 8, 21], burning mouth syndrome [1], and medication-induced. Saliva substitutes or oral moisturizing agents can be given to relieve oral discomfort due to dry mouth or xerostomia [5, 7, 8, 16-20].

Table 3 showed that saliva substitutes or oral moisturizing agents were contained with cetyl pyridinium chloride (CPC), carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), oral moisturizing jelly (OMJ), aloe vera, and ginger. These ingredients have already been proven to reduce dry mouth symptoms and oral discomfort, which also increases the patient's quality of life [16-20].

CPC was a well-known antiseptic that contained anti-inflammatory properties [16]. It also has a high potential, both for antibacterial effect as well as the absence of a serious adverse effect. This material can be used for shorter periods than chlorhexidine for antibacterial effects [26]. CMC was a polymer-based that was commonly used in saliva substitute's agent. CMC was not a natural moisturizer but has already been proven as the best choice for saliva substitute material because it can improve the viscoelastic formulation of the agent [23]. HEC has a higher mechanical characteristic and could reduce evaporation [24]. Even though one article did not mention the ingredients of the agent, the other two articles tested aloe vera herbal as a saliva substitute or moisturizer agent. Aloe vera leaf jelly contains about 99 % of water and therefore, it has a strong moisture effect. The mucopolysaccharide in aloe vera also helps bind moisture into the skin and mucosa, so it can improve skin and mucosa hydration through the humectant mechanism. Aloe vera mouthwash has anti-inflammatory and wound-healing properties [17, 19]. Only one article reported ginger herbal as the ingredient of the tested agent. Ginger was believed to reduce pain and have anti-inflammatory and antioxidant properties. The presence of ginger increased salivation and stimulates the salivary glands to produce more saliva [19]. On the other hand, the materials controls used were natural spring water (1 article), saline solution (1 article), CMC placebo (1 article), and GC Dry Mouth Gel® which contained CMC (2 articles).

Saliva substitutes or oral moisturizing agents were available in several formulations, such as sprays, mouthwash, gels, lozenges, chewing gum, or toothpaste. Saliva substitute spray is used in a minimum amount so that it will less effective, but this formulation is the best for larynx or pharynx area lubrication. Mouthwash formulation can quickly reduce the symptoms but is only effective in the short term. Meanwhile, the use of a gel-based formulation is more comfortable and significantly reduces the symptoms while also assisting with swallowing due to low retention. Another is the use of a lozenges formulation that can increase the saliva pH [11, 22, 23].

In this review, we also found that the parameters used for efficacy and safety determination were instruments such as a questionnaire

about discomfort and symptom reduction (4 articles) [16, 18-20], a visual analog scale (VAS for pain; 1 article) [19], and the Challacombe scale (2 articles) [19, 20] as the objective instrument. Other researchers also used these parameters [13, 21]. The safety determination was only observed by two articles [16, 18] and there were no serious adverse effects reported. Mild to moderate adverse effects occur due to the use of mouthwash, namely: oral paresthesia, oral discomfort, and throat irritation [16]. A mild adverse effect occurs with the use of GC Dry Mouth Gel®, but there was no adverse effect due to OMJ use [18].

Based on the qualitative analysis in this review article, we can recommend the use of saliva substitutes or oral moisturizing agents containing CMC polymer-based ingredients. This is because CMC has proven to be effective and can be easily supplied or manufactured. Although OMJ is more effective and better when compared to CMC ingredients, OMJ has not been sold widely and is still in the research stage. Administration of OMJ can reduce symptoms in dry mouth patients, increase salivary pH, and reduce candidiasis better than administration of GC Dry Mouth Gel® containing CMC. OMJ is better at increasing buffer capacity, but GC dry mouth Gel® is better at increasing salivary flow rate [18, 20]. Currently, OMJ is the best agent that can be used because it contains ingredients that are safe if swallowed, have no preservatives detected, and can be swallowed and provide lubricant from the oral cavity through the throat, similar to natural saliva [20]. The wetting and anti-evaporation effects of CMC on human enamel were better and comparable to those of human saliva [24].

The limitation of this review is that the research analyzed in this review was mostly done in Asia, so it is necessary to explore similar research conducted in other continents. Although the risk of the bias assessment process, one of the articles has low quality, so far our review is an update for dental practitioner's guidelines in prescribing oral moisturizing agents as dry mouth therapy.

CONCLUSION

Saliva substitutes or oral moisturizing agents can overcome the problem effectively and safely for dry mouth or xerostomia. However, they were less effective for patients with Sjogren's syndrome.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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