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1 **Could the use of saliva substitutes improve food oral processing in individuals with**
2 **xerostomia? A systematic review**

3
4 **Short title : Saliva substitutes and FOP**

5
6 Sophie Piaton^{1,2}, Anne Duconseille¹, Valérie Roger-Leroi^{1,2}, Martine Hennequin^{1,2}

7
8 ¹ Université Clermont Auvergne, CROC, F-63000 Clermont-Ferrand, France.

9 ² CHU de Clermont-Ferrand, Service d'Odontologie, F-63003 Clermont-Ferrand, France

10
11 **Corresponding author**

12 Prof Martine Hennequin

13 CROC EA4847 UFR d'Odontologie

14 2 rue de Braga

15 63000 Clermont-Ferrand

16 France

17 Email: martine.hennequin@uca.fr

18 Tel: 00 33 4 73 17 73 81

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ABSTRACT

Xerostomia ~~was is~~ associated with food avoidance and low nutritional assessment. This review seeks to document whether products called “saliva substitutes” or “artificial saliva” can really replace saliva in food oral processing. Pubmed and Science Direct were searched for articles using the keywords “saliva substitutes” and “artificial saliva”. An advanced search was applied using the terms “xerostomia” and/or “food oral processing” and/or “eating” and/or “mastication” and/or “chewing” and/or “swallowing”. The analysis methods and the inclusion criteria were documented in a protocol published in the International prospective register of systematic reviews (PROSPERO with the registration number CRD42019124585).

The search included 43 articles, published between 1979 and 2017. Among the included studies, 17 were observational studies, 5 were pilot studies, 21 were crossover studies and 14 of these studies were blinded. The Strobe score for the included articles varied from 7.5 to 20.

The possible effects of the use of saliva substitutes on the ingestion function were poorly investigated. No evidence was based on physiological studies. It is unknown whether using a saliva substitute has an effect on the composition and rheological properties of the food bolus, on the lubrication of the oral and laryngeal mucosa or on both phenomena. Moreover, saliva substitutes were not formulated to improve food oral processing and most of them are flavoured. New saliva substitutes and artificial saliva should be designed and formulated to improve food oral processing.

Keywords: Xerostomia, Sjögren’s syndrome, saliva substitutes, artificial saliva, Food oral Processing, review

48 1 INTRODUCTION

49 Xerostomia is a subjective feeling of dryness in the mouth related to possible quantitative and
50 qualitative changes in saliva composition (Fox, Busch, & Baum, 1987). It should be
51 differentiated from hyposalivation which results from an objective assessment of a reduced
52 salivary flow rate (Łysik, Niemirowicz-Laskowska, Bucki, Tokajuk, & Mystkowska, 2019).
53 The causes of xerostomia are heterogenous, and may or may not be related to saliva production
54 deficiencies. Among the origins of xerostomia, one can distinguish the consequences of salivary
55 diseases (salivary gland trauma, ~~and~~ tumor, surgery or radiotherapies), from the effects of
56 systemic chronic diseases (~~chronic, autoimmune~~, diabete mellitus, Sjogren's syndrome, lupus
57 erythematosus and others autoimmune disorders), dehydration, mouth breathing or the adverse
58 effects of drugs. More than 400 medicines are associated with xerostomia (Porter, Scully, &
59 Hegarty, 2004). Determining the epidemiology of xerostomia is complex due to the unclear
60 definitions of dry mouth being used and the different methods for measuring this condition
61 (Ying Joanna & Thomson, 2015). A systematic review reported that the prevalence of
62 xerostomia ranged from 8% to 42%, while the prevalence of hyposyalia varied from 12% to
63 47% (Hopcraft & Tan, 2010). Xerostomia prevalence is estimated to be approximately 20% in
64 the general population, with an increased prevalence in women (up to 30%) and in elderlies (up
65 to 50%) (Furness, Worthington, Bryan, Birchenough, & McMillan, 2011). Overall, 54% of
66 people complaining of xerostomia actually had objective evidence of hyposalivation after
67 salivary flow measurements were taken (Longman et al., 1997).

68 Various treatments were proposed to patients with xerostomia. Saliva stimulants and saliva
69 substitutes aim to alleviate the symptoms of xerostomia. Saliva stimulants activate the salivary
70 gland function. Their composition is based either on pilocarpine, a nonselective muscarinic
71 agonist, or on cemivaline, which has specific affinity for receptor subtypes. The indications of
72 saliva stimulants are restricted to individuals suffering from hyposalivation. Saliva substitutes

73 have no effect on saliva production. They are indicated for all patients suffering from
74 xerostomia, including those having hyposalivation. Artificial saliva products definitely are not
75 saliva. They were developed to imitate and act as saliva but they do not act as saliva for all of
76 its complex functions (antimicrobial, digestive/perceptive, teeth protection etc..). ~~are indicated~~
77 ~~for all patients suffering for xerostomia, including those having hyposalivation.~~

78 The effects of saliva substitutes have been reported in many studies measuring self-perception
79 of pain, comfort in mouth and quality of life related to oral health. However, it is not clear
80 whether saliva substitutes could improve eating capacities and the nutritional status. The
81 question is challenging, as saliva plays vital roles in maintaining oral health and in food oral
82 processing (FOP). Food oral processing covers all ingestive functions and includes sucking,
83 biting, chewing, manipulating the food with the tongue and swallowing. The dryness of the
84 mouth affects both the oral preparatory and oral phases of swallowing, and can lead to impaired
85 bolus formation and oropharyngeal bolus transport. This can cause chewing and swallowing
86 difficulty and may influence the quality and/or quantity of dietary intakes.

87 Previous research showed that a reduced salivary flow rate and/or subjective oral dryness were
88 associated with food avoidance and low nutritional assessment. It was shown that the use of a
89 mucin-containing saliva substitute three times a day before meals treats xerostomia and oral
90 mucosa disorder in elderlies (Blixt-Johansen, Sjöholm, Wiesel, & Ek, 1992). Moreover, meals
91 duration was longer after the treatment period than before. The consequences of xerostomia on
92 swallowing depend on the food type. For friable and non hydrophilic foods, the collection of
93 particles into a single bolus could be affected, as could its transportation towards the pharynx
94 (Liedberg, Ekberg, & Owall, 1991). Indeed, there is little information about the association
95 between hyposalivation and actual nutrient intake (Iwasaki et al., 2016). A systematic review
96 and meta-analysis identified a clear gap in knowledge on the influence of saliva incorporation
97 and oral lubrication on appetite ratings and food intake (Krop et al., 2018). The influence of the

lubrication parameters of food on appetite and food intake remains largely unquantified. This review seeks to document whether the products called “saliva substitutes” or “artificial saliva” can really replace saliva during food oral processing.

2 MATERIALS AND METHODS

A systematic review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-analyses Protocol (PRISMA-P) statement (Moher et al., 2015). The analysis methods and inclusion criteria were documented in a protocol published in the International prospective register of systematic reviews (PROSPERO with the registration number CRD42019124585).

2.1 Search

The search was designed to find articles reporting the use of saliva substitutes in individuals with xerostomia, in order to answer the question: Could the use of saliva substitutes improve food oral processing?

2.2 Information sources

Pubmed and Science Direct were searched for articles using the keywords “saliva substitutes” and “artificial saliva”. An advanced search was applied using the terms “xerostomia” and/or “food oral processing” and/or “eating” and/or “mastication” and/or “chewing” and/or “swallowing”. The PRISMA protocol was applied for article selection reviews (Moher et al., 2015). Criteria for exclusion were: articles not written in English, animal studies, in vitro studies, articles with off-topics and reviewed articles. The remaining records were assessed for screening and abstracts were read. Any article reporting an evaluation of saliva substitute was included in the eligibility phase. The remaining records were assessed for eligibility and full texts were read. The Strobe Grade approach (Cuschieri, 2019) was used to grade the quality of the evidence in the different studies. Three systematic reviews aimed at evaluating the efficacy

122 of interventions for management of dry mouth were excluded (Furness, Bryan, McMillan,
123 Birchenough, & Worthington, 2013; Furness et al., 2011; Hahnel, Behr, Handel, & Bürgers,
124 2009).

125 **2.3 Data extraction**

126 A Microsoft Excel® chart file was created and a pre-piloted form was tested for 10 articles by
127 two investigators. Any quantitative or qualitative variable was considered as one item and noted
128 as a column label while the articles included were listed in the rows. Depending on the
129 articles, some items were either not described or not available. Finally, twenty eight items were
130 listed for data extraction: design trial; population description (number of subjects, number of
131 females, number of males, age, number of groups of individuals, number of treatment per
132 groups, aetiology of xerostomia, exclusion criteria, salivary flow); treatment (saliva substitute
133 name, form, composition, posology); study parameters (duration, measurement frequency,
134 control group, placebo, primary outcomes, secondary outcomes); objective and/or subjective
135 measurements; significant results for primary and secondary outcomes; subjects' preferences
136 for using a substitute; study grade. A last column was added to check whether saliva substitutes
137 had an effect on one or more FOP functions such as biting, chewing, manipulating food between
138 tongue, palate, teeth and cheek and /or swallowing.

139 **2.4 Strategy for data synthesis**

140 Qualitative results were written as a narrative review. The term “saliva substitute” was used to
141 refer to both “saliva substitute” and “artificial saliva”.

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145 **3 RESULTS**

146 **3.1 Search results**

147 The flow chart for inclusions is presented in Figure 1. The search included 43 articles, published
148 between 1979 and 2017 (Aliko, Alushi, Tafaj, & Isufi, 2012; Alpöz et al., 2015, 2008; Alves,
149 Motta, Messina, & Migliari, 2004; Andersson et al., 1995; Apperley, Medlicott, Rich, Hanning,
150 & Huckabee, 2017; Blixt-Johansen et al., 1992; Bots et al., 2005; Dalodom et al., 2016; Davies
151 & Singer, 1994; Dirix, Nuyts, Vander Poorten, Delaere, & Van den Bogaert, 2007; Donath,
152 Tonner, Chavda, Gatignol, & Bouyrie, 2016; Duxbury, Thakker, & Wastell, 1989; Epstein,
153 Emerton, Le, & Stevenson-Moore, 1999; Epstein & Stevenson-Moore, 1992; Frost, Shirlaw,
154 Walter, & Challacombe, 2002; Furumoto, Barker, Carter-Hanson, & Barker, 1998; Gil-
155 Montoya, Subirá, Ramón, & González-Moles, 2008; Heydarirad, Rezaeizadeh, Choopani,
156 Mosavat, & Ameri, 2017; Jellema et al., 2001; Johansson, Andersson, Attström, Glantz, &
157 Larsson, 1994; Klestov et al., 1981; Matear & Barbaro, 2005; McMillan, Tsang, Wong, & Kam,
158 2006; Momm, Volegova-Neher, Schulte-Mönting, & Guttenberger, 2005; Morales-Bozo et al.,
159 2017; Mouly, Orlor, et al., 2007; Mouly, Salom, et al., 2007; Nakamoto, 1979; Oh, Lee, Kim,
160 & Kho, 2008; Regelink, Vissink, Reintsema, & Nauta, 1998; Rogus-Pulia, Gangnon, Kind,
161 Connor, & Asthana, 2018; Salom et al., 2015; Shahdad, Taylor, Barclay, Steen, & Preshaw,
162 2005; Silvestre, Minguez, & Suñe-Negre, 2009; Skrinjar et al., 2015; Stewart et al., 1998;
163 Sweeney, Bagg, Baxter, & Aitchison, 1997; Temmel, Quint, Schickinger-Fischer, & Hummel,
164 2005; van der Reijden, van der Kwaak, Vissink, Veerman, & Amerongen, 1996; Visch,
165 Gravenmade, Schaub, Van Putten, & Vissink, 1986; Vissink et al., 1983)

166 Among the included studies, 17 were observational studies, 5 were pilot studies, 21 were cross-
167 over studies and 14 of these studies were blinded. The Strobe score for the included articles
168 varied from 7.5 to 20. Xerostomia aetiologies and methods used to assess Food Oral Processing
169 in included studies are reported in Table 1.

3.2 Review

There are few objective and direct evaluations of the impact of the use of saliva substitutes on Food Oral Processing. Overall, 30 studies used visual analogue scales and /or Likert scales to evaluate the self-perception of subjects for the level of dryness of their mouth or throat, swallowing, chewing and speaking difficulties, level of thirst, taste disturbance, or denture retention (Aliko et al., 2012; Alpöz et al., 2015, 2008; Dalodom et al., 2016; Davies, Daniels, Pugh, & Sharma, 1998; Davies & Singer, 1994; Dirix et al., 2007; Donath et al., 2016; Epstein et al., 1999; Frost et al., 2002; Johansson et al., 1994; Matear & Barbaro, 2005; Nakamoto, 1979; Regelin et al., 1998; Temmel et al., 2005; Visch et al., 1986; Vissink, Burlage, Spijkervet, Veerman, & Nieuw Amerongen, 2004). Four studies asked subjects to report on the improvement in dryness related to the use of saliva substitutes (Salom et al., 2015; Silvestre et al., 2009; Stewart et al., 1998; van der Reijden et al., 1996). Six studies reported the impact of xerostomia on Quality of life (GOHAI (McMillan et al., 2006), OHIP 14 (Gil-Montoya et al., 2008; Skrinjar et al., 2015), EORTC - QLQ + H&35 (Heydarirad et al., 2017; Jellema et al., 2001), QoL (Dirix et al., 2007)). In one observation report, the staff of an establishment for elderlies measured meal duration, reported the residents' pain complaints and subjectively assessed their ability to speak, eat and swallow (Blixt-Johansen et al., 1992). Sixteen studies globally measured the impact of xerostomia using validated (Apperley et al., 2017; Bots et al., 2005; McMillan et al., 2006; Morales-Bozo et al., 2017), or non validated (Alves et al., 2004; Andersson et al., 1995; Frost et al., 2002; Furumoto et al., 1998; Gil-Montoya et al., 2008; Klestov et al., 1981; Momm et al., 2005; Mouly, Orlor, et al., 2007; Mouly, Salom, et al., 2007; Oh et al., 2008; Shahdad et al., 2005; Sweeney et al., 1997) comprehensive questionnaires.

Xerostomia was described in different conditions of gender, age and medical condition. The age range was from 18 to 94 and gender was not a criterion for inclusion. The medical conditions observed were: radiotherapy and/or chemotherapy after head and neck cancers

195 (Andersson et al., 1995; Apperley et al., 2017; Dirix et al., 2007; Epstein & Stevenson-Moore,
196 1992; Epstein et al., 1999; Jellema et al., 2001; Momm & Guttenberger, 2002; Nakamoto, 1979;
197 Regelin et al., 1998; Shahdad et al., 2005), systemic auto immune disease (Aliko et al., 2012;
198 Alpöz et al., 2008; Alves et al., 2004; Klestov et al., 1981; van der Reijden et al., 1996); drug
199 consumption (Donath et al., 2016; Mouly, Orler, et al., 2007; Skrinjar et al., 2015); elderlies
200 (Mouly, Salom, et al., 2007; Rogus-Pulia et al., 2018); final stage renal disease on
201 haemodialysis (Bots et al., 2005). Regardless of the aetiology of xerostomia, controlling the
202 effect of saliva substitutes on the production of a swallowable food bolus is of importance.

203 The possible effects of saliva substitutes on FOP were reported in 44 articles for swallowing
204 only (Blixt-Johansen et al., 1992; Davies et al., 1998; Davies & Singer, 1994; Dirix et al., 2007;
205 Donath et al., 2016; Epstein et al., 1999; Jellema et al., 2001; Klestov et al., 1981; Matear &
206 Barbaro, 2005; Morales-Bozo et al., 2017; Nakamoto, 1979; Rogus-Pulia et al., 2018; van der
207 Reijden et al., 1996) and in one article for mastication with objective measurements (Apperley
208 et al., 2017). Evaluation of difficulties/easiness to swallow, to chew, to eat and/or to sip liquids
209 were reported in 22 studies. Positive effects on FOP based on statistical analysis were assessed
210 in 14 studies (Aliko et al., 2012; Alpöz et al., 2008; Alves et al., 2004; Andersson et al., 1995;
211 Frost et al., 2002; Heydarirad et al., 2017; McMillan et al., 2006; Momm et al., 2005; Morales-
212 Bozo et al., 2017; Mouly, Orler, et al., 2007; Mouly, Salom, et al., 2007; Rogus-Pulia et al.,
213 2018; Salom et al., 2015; Shahdad et al., 2005). Only one clinical trial measured xerostomia
214 with a validated questionnaire and compared the effects of three different saliva substitutes on
215 the chewing kinematics during ingestion of crackers (Apperley et al., 2017). The Test of
216 Mastication and Swallowing Solids (TOMASS) required ingestion of a cracker as quickly
217 and as comfortably as possible (Hägglund, Blom, Thoden, & Karlsson, 2020; Huckabee et al.,
218 2018). During mastication, the number of cycles, chewing time, and swallows per bite were
219 measured. It was found that the use of saliva substitutes slightly improved xerostomia but had

Mis en forme : Anglais (États-Unis)

no effect on chewing kinematic parameters during the cracker eating. The authors suggested that TOMASS test was not appropriate to evaluate mastication in subjects with xerostomia.

4 DISCUSSION

This review ~~demonstrated~~ showed that the possible effects of the use of saliva substitutes on the ingestion function were poorly investigated. No evidence ~~is~~ was based on physiological studies. Saliva participates in food bolus constitution, affects its rheological properties and initiates digestion. Food bolus rheology has a dominant influence on mastication and swallowing (Chen, 2007). During FOP, saliva gradually fills the gap between food particles and increases their viscous cohesion. The swallowing threshold is defined as the moment when the food bolus reaches the maximum cohesive force (Prinz & Lucas, 1997). It is unknown whether the use of a saliva substitute has an effect on the composition and the rheological properties of the food bolus, on the lubrication of the oral and laryngeal mucosa or on both these phenomena. Moreover, it is clear that saliva substitutes are not developed to improve FOP. For example, most of the saliva substitute listed in Table 1 have mint, grapefruit, lemon or sweet flavouring. A flavoured saliva substitute could affect the perception of food and could limit the use of the saliva substitute during meals. Spontaneous food consumption could be altered for individuals using a saliva substitute, independently of the consequences of xerostomia.

Natural saliva is a non-Newtonian fluid. This characteristic ensures bolus aggregation and the lubrication of the oral and laryngeal mucosa during FOP. It could be suggested that a saliva substitute should be a non-Newtonian fluid. However, among the saliva substitutes used within the 14 studies reporting a possible positive effect of saliva substitutes on FOP, seven were based on mucine and/or xanthan gum and could be considered as natural saliva simulators (NSS), six were Newtonian fluids based on carboxymethyl cellulose or glycerol and two were

uncategorized (Table 42). In most cases, non-Newtonian saliva substitutes contain substances of natural origin (salivary macromolecules such as mucins, lysozyme, lactoferrin) that provide high biocompatibility. However, mucines have pig or cow origins, which can affect the uses of the corresponding saliva substitute in some individuals for cultural reasons. The challenges of treating xerostomia are to mimic all properties of natural saliva definitely in order to improve oral comfort between and during meals.

The selection criteria of this review excluded the “saliva stimulant” keyword. Saliva stimulants are parasympathomimetics such as Pilocarpine or Cevimeline. These substances are indicated to improve the production of saliva compared with a placebo (LeVeque et al., 1993). The use of chewing gum was also described to increase saliva production. However, chewing a gum can be indicated only for persons whose salivary glands respond to stimulation. Saliva stimulant cannot meet the needs of all patients with xerostomia, contrary to saliva substitutes. It can be difficult to determine the amount of saliva that is indicative of the dysfunction of the salivary glands. The measurement of the salivary flow is the basis for the diagnosis of xerostomia/hyposalivation. Among the included studies, 28 reported a measure of saliva flow (Aliko et al., 2012; Alpöz et al., 2015, 2008; Andersson et al., 1995; Bots et al., 2005; Daloddom et al., 2016; Donath et al., 2016; Duxbury et al., 1989; Epstein et al., 1999; Epstein & Stevenson-Moore, 1992; Frost et al., 2002; Furumoto et al., 1998; McMillan et al., 2006; Morales-Bozo et al., 2017; Mouly, Orler, et al., 2007; Mouly, Salom, et al., 2007; Oh et al., 2008; Regelink et al., 1998; Silvestre et al., 2009; Skrinjar et al., 2015; Stewart et al., 1998; Sweeney et al., 1997; van der Reijden et al., 1996). Overall, hyposalivation was observed when salivary flow rate at rest falls below 0.1 mL per minute and stimulated saliva (Sreebny, 2000) below 0.5–0.7 mL per minute; (Navazesh, Christensen, & Brightman, 1992; Ship, DeCarli, Friedland, & Baum, 1990). However, the sialometric techniques used to measure the salivary flow varied a lot, the spitting method being the most often reported. Moreover, the salivary flow rate threshold as an

inclusion/exclusion criterion was set at different levels in different studies. Overall, the saliva flow was measured in 22 studies, while only seven studies considered the value of the saliva flow as an inclusion criterion (Table 23).

To conclude, this review underscores the need to develop new saliva substitutes to improve the rheological properties of the bolus and the lubrication of the laryngeal mucosa. Flavours should be excluded from their composition.

ETHICAL STATEMENT

Declarations of interest: The authors declare that they do not have any conflict of interest

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Table 1: Aetiologies for xerostomia and criteria for evaluation of FOP functions in included studies

Studies	Xerostomia aetiology	FOP function targeted	Objectives measures	Subjectives measures
(Aliko et al., 2012)	Sjögren's Syndrome	Mastication Swallowing Taste	Salivary flow Quantity of SS' use	VAS
(Alpöz et al., 2008)	Sjögren's Syndrome	Taste Mastication Sipping Speech Swallowing	Salivary flow	VAS
(Alpöz et al., 2015)	Mixed, unspecified	Chewing Sipping Swallowing Taste	Salivary flow Oral examination	Questionnaire
(Alves et al., 2004)	Sjögren's syndrome	Mastication Swallowing	Salivary flow	Questionnaire
(Andersson et al., 1995)	Radiotherapy	Chewing Swallowing Taste	Oral examination Salivary flow	Questionnaire
(Apperley et al., 2017)	Radiotherapy	Mastication Swallowing	Chewing cycles Chewing time Swallows/bite (TOMASS)	Questionnaire
(Blixt-Johansen et al., 1992)	Drugs Other unspecified	Eating Swallowing	Oral examination	Reports of frequency by Staff
(Bots et al., 2005)	Kidney failure	ND	Salivary flow	Questionnaire
(Dalodom et al., 2016)	Mellitous diabetes Hypertension	Chewing Swallowing Taste disturbance	Oral examination Salivary flow	VAS
(Davies & Singer, 1994)	Radiotherapy	Dysphagia Dysgeusia	ND	Questionnaire VAS
(Davies et al., 1998)	Cancer	Dysphagia Dysgeusia	ND	Questionnaire VAS
(Dirix et al., 2007)	Radiotherapy	Swallowing Taste	ND	Questionnaire VAS
(Donath et al., 2016)	Drugs	Swallowing	Oral examination Salivary flow	VAS
(Duxbury et al., 1989)	Drugs Diabetes Radiotherapy Sjögren's syndrome Smoking	Eating Taste	Frequency of SS' use Salivary flow	VAS
(Epstein & Stevenson-Moore, 1992)	Radiotherapy	ND	Frequency of SS' use Salivary flow	Questionnaire
(Epstein et al., 1999)	Radiotherapy	Swallowing Taste	Salivary flow	VAS
(Frost et al., 2002)	Buccal respiration Drugs Sjögren's syndrome Other	Chewing Swallowing	Oral examination Salivary flow	Questionnaire
(Furumoto et al., 1998)	Mixed, unspecified	Eating	Salivary flow	Questionnaire

		Swallowing			
(Gil-Montoya et al., 2008)	Aging	Biting Chewing Eating Swallowing	ND	Questionnaire	
(Heydarirad et al., 2017)	Radiotherapy	Eating Swallowing Taste	ND	Questionnaire	
(Jellema et al., 2001)	Radiotherapy	Swallowing	Frequency of SS' use	Questionnaires	
(Johansson et al., 1994)	Drugs Radiotherapy Sjögren's Syndrome	Mastication Swallowing Taste	Oral examination	Questionnaire	
(Klestov et al., 1981)	Sjogren's syndrome	Chewing Drinking Swallowing	ND	Questionnaire	
(Matear & Barbaro, 2005)	Aging Drugs Systemic diseases	Swallowing	ND	Questionnaire	
(McMillan et al., 2006)	Radiotherapy	Biting Chewing Eating Swallowing	Salivary flow	Questionnaire	
(Momm et al., 2005)	Radiotherapy	Chewing Eating Swallowing	ND	Questionnaire	
(Morales-Bozo et al., 2017)	Various	Swallowing	Salivary flow	VAS	
(Mouly, Orlor, et al., 2007)	Aging	Chewing Swallowing Taste	Oral examination Salivary flow	VAS	
(Mouly, Salom, et al., 2007)	Drugs	Chewing Swallowing Taste	Frequency of SS' use Oral examination Salivary flow	Questionnaire VAS	
(Nakamoto, 1979)	Radiotherapy	Eating Swallowing Taste	ND	Questionnaire	
(Oh et al., 2008)	Sjögren's syndrome Autoimmune disorders Radiotherapy	Chewing Eating Sipping Swallowing	Salivary flow	Questionnaire	
(Regelink et al., 1998)	Radiotherapy		Salivary flow	Questionnaire	
(Rogus-Pulia et al., 2018)	Aging	Swallowing	ND	One single question	
(Salom et al., 2015)	Autoimmune disorders Drugs Radiotherapy Sjögren's syndrome Other various medical conditions	Chewing Swallowing Taste	ND	Questionnaire VAS	
(Shahdad et al., 2005)	Radiotherapy	Chewing Swallowing Taste	ND	Questionnaire VAS	
(Silvestre et al., 2009)	Drugs Radiotherapy	Eating Swallowing	Frequency of SS' use Salivary flow	VAS	
(Skrinjar et al., 2015)	Drugs	Taste Mastication	Salivary flow	Questionnaire VAS	

(Stewart et al., 1998)	Auto-immune disease Drugs Radiotherapy	Eating Sipping Swallowing Taste	Salivary flow	Questionnaire VAS	
(Sweeney et al., 1997)	Motor neurone disease cancer	Eating Taste	Salivary flow	VAS	
(Temmel et al., 2005)	Sjögren's syndrome Menopause	Taste	Frequency of SS' use Oral examination	Questionnaire	
(van der Reijden et al., 1996)	Sjögren's syndrome Autoimmune disorders	Eating Swallowing Taste	Salivary flow	Questionnaire	
(Visch et al., 1986)	Radiotherapy Sjögren's syndrome	Chewing Swallowing	ND	Questionnaire	
(Vissink et al., 1983)	Drugs Radiotherapy Sjögren's syndrome Other unspecified	Mastication Swallowing Taste	Oral examination Salivary presence	Questionnaire	

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Table 2 Composition of saliva substitute used in the included studies (NSS: Natural saliva simulators: saliva substitutes containing mucin or mucin with xanthan or guar gum

Name	Composition	NSS	Form	Aromas	Instructions for use	Placebo or Control	References
Aequasyl®	94.4% triesters of glycerol; Oxidized fatty acids of vegetal origin (corn oil) Silicium dioxide Aspartame	No	Spray	Orange, Grapefruit, And mint Aspartam	2 spray (one by cheek then swill the product with the tongue until it had coated oral mucosa, after breakfast, and 15 min before a standard meal		(Donath et al., 2016)
					At least 5 times/day		(Mouly, Orlor, et al., 2007)
					1 or 2 spray up to 4 times a day		(Mouly, Salom, et al., 2007)
Novasial®			Sticks		One stick 4 times a day	Aequasyl® Biotène®	(Salom et al., 2015)
			Spray		One spray four times a week		
DC161- DP0293	Paraffin liquid, Cotton refine oil, Alphonatocopheryle acetate (oily solution)	No	Spray	Orange flavor	3 sprays (one by cheek, one on the tongue,) twice a day. One after breakfast, and one 15 min before a standard meal		(Donath et al., 2016)
DC161- DP0291	Glycerol, Polysorbate 80, Soja lecithin, Sodium hyaluronate, Xanthan gum, Potassium chloride, Xylitol, Anhydrous disodiumhydrogen phosphate, potassium dihydrogen, phosphate, sucralose, macrogolglycerol 40 hydroxystearate, benzylic, alcohol, Sodium benzoate, Cetylpyridinium chloride, alpha, tocopheryle	Yes	Spray	soft mint flavor	3 sprays (one by cheek, one on the tongue,) twice a day. One after breakfast, and one 15 min before a standard meal		(Donath et al., 2016)

	acetate, Water. (Aqueous solution)						
DC161-DP0292	Glycerol, Povidone K30, Copovidone, xanthan Gum, Potassium chloride, Xylitol, Marshmallow concentrated hydroglycerined extract, Anhydrous disodium hydrogen phosphate, potassium dihydrogen phosphate, Macrogolglycerol 40 hydroxystearate, Potassium sorbate, benzylic alcohol, Water	Yes	Spray		3 sprays (one by cheek, one on the tongue,) twice a day. One after breakfast, and one 15 min before a standard meal		(Donath et al., 2016)
Biotene Oral Balance®	Lactoperoxidase, Lysozyme Glucose oxidase, Lactoferrin, Hydrogenated starch, Polymethacrylate, Xylitol sweetening; Hydroxyethyl sweetening Cellulose, Potassium thiocyanate, Aloe vera.	No	Gel	Sweetening	1 cm of gel on tongue and oral mucosa		(Aliko et al., 2012; Frost et al., 2002; Regelink et al., 1998; Rogus-Pulia et al., 2018; Shahdad et al., 2005)
						Carboxymethylen : 0.8% Triethanolamine Xylitol Nipagim : 0.3%	(Alves et al., 2004)
Biotene mouthwash® and Oral Balance gel®	Lactoperoxidase, Lysozyme, Glucose oxidase, Lactoferrin		Mouthwash	Slightly mentholed flavour and xylitol sweetening	Three times a day after brushing the teeth and/or dentures (12 ml) during 30 seconds	Aqueous solution with mint essence	(Gil-Montoya et al., 2008)
			Gel		Following the mouthrinse, 1 cm of gel on tongue and oral mucosa	Cream of similar appearance and flavor was prepared using carboxymethyl cellulose	

Oral Balance gel and Biotene toothpaste®		No	Gel Toothpaste			CMC gel and commercial toothpaste	(Epstein et al., 1999)
Oral Balance gel and Biotene toothpaste and Mouthwash®		No	Gel Toothpaste Mouthwash				(Matear & Barbaro, 2005; Shahdad et al., 2005)
Device and Oral Balance gel		No	Gel		At night		(Frost et al., 2002)
					Gel alone in the form of an oral bolus Gel on demand via an intra-oral device(at least 4hours per day and remove it at night)		(McMillan et al., 2006)
Xialine®	Polysaccharide xanthan gum, sodium fluoride	Yes	Spray	Mint-taste	At least 6 times a day	Water Dilued tea	(Alpöz et al., 2008)
				Mint-taste	At least 6 times/ day		(Bots et al., 2005)
				Neutral taste	At least 4 times a day	Xialine without Xanthan gum	(Jellema et al., 2001)
Xanthan gum high viscosity	KCl,NaCl,MgCl ₂ ,CaCl ₂ , Methylhydroxybenzoate, Benzalkonium chloride, Keltrol KTL, Distilled water	Yes		Peppermint flavour			(van der Reijden et al., 1996)
Xanthan gum low viscosity	KCl,NaCl,MgCl ₂ ,CaCl ₂ , Methylhydroxybenzoate, Benzalkonium chlorid, Keltrol KTL, Distilled water	Yes		Peppermint flavour			(van der Reijden et al., 1996)
Polyacrylic acide	KCl,NaCl,MgCl ₂ ,CaCl ₂ , Methylhydroxybenzoate, Benzalkonium chloride, Carbopol, Distilled water	No		Peppermint flavour			(van der Reijden et al., 1996)
Saliva Orthana®	Mucin, xylitol, Potassium chloride, sodium chloride,	Yes	Mouthwash	Neutral-tasting	Rince + swallow with 5ml 3 times/day before meal		(Blixt-Johansen et al., 1992)

	magnésium, calcium, dipotassium hydorgenophosphate, Methagine, Benzalconchloride, Sodium-EDTA			Peppermint flavor	Ad libitum	KCl,NaCl,MgCl ₂ ,CaCl ₂ , methylhydroxybenzoate, benzalkonium chloride, distilled water	(van der Reijden et al., 1996)
				Peppermint flavor	Ad libitum		(Visch et al., 1986)
					Ad libitum		(Vissink et al., 1983)
			Spray	Peppermint flavor	2-3 sprays when required	Saliva Orthana® its no-mucin base Flavored distilled water	(Duxbury et al., 1989)
							(Davies et al., 1998; Davies & Singer, 1994; Sweeney et al., 1997)
					At least twice per day	Saliva Orthana® its no-mucin base	
BioXtra®	Hydroxyethylcellulose, Polyglyceryl methacrylate, Lactoperoxidase, Glucose oxidase, Lactoferrin, lysozyme and Monofluorophosphate and Xylitol (=oralbalance gel)+ peptides and Immunoglobulins	No	System: toothpaste mouthwash gel	Sweetening (less than OB)	Apply to your tongue and gums with your fingertip or a cotton swab Ad libitum		(Dirix et al., 2007; Shahdad et al., 2005)
HCC Spray		No	spray		Ad libitum		(Furumoto et al., 1998)
Hydroxyethylcellulose citric acid spray		No	gel		Ad libitum		
Salinum®	Linseed mucilage: 54% Protein: 9%		Mouthwash		Dosage of 2 ml of fluid Ad libitum		(Andersson et al., 1995; Johansson et al., 1994)

Plant mucilage	Matricaria chamomilla Linseed (linum usitatissimum)		Mouthwash		2ml 4 times a day		(Morales-Bozo et al., 2017)
Carboxyméthyl Cellulose (Original preparations: CMC, MAS-84, CMC-NZ, CMC Spray)	Sodium carboxymethylcellulose	No		Peppermint flavor	Plastic bottle 2 ml portion		(Andersson et al., 1995; Apperley et al., 2017)
					2ml 4 times a day		(Morales-Bozo et al., 2017; Temmel et al., 2005)
					Ad libitum		(Visch et al., 1986)
					Ad libitum		(Furumoto et al., 1998)
					Ad libitum		(Vissink et al., 1983)
					2ml Ad libitum		(Oh et al., 2008)
VA-Oralube®	Carboxymethylcellulose Water Sorbitol Preservative Fluorure, Ions	No	Squeeze bottle		Ad libitum		(Epstein & Stevenson-Moore, 1992)
				Peppermint flavor	Ad libitum		(Vissink et al., 1983)
	Dry concentrate			Peppermint flavor	Ad libitum		(Nakamoto, 1979)
Salivart	Carboxymethylcellulose	No	Spray		Ad libitum		(Epstein & Stevenson-Moore, 1992)
Moistir	Carboxymethylcellulose	No	Spray		Ad libitum		(Epstein & Stevenson-Moore, 1992)
Polyox	Polyethylene oxide 1% Water		Glassbottle	Tasteless	Ad libitum		(Epstein & Stevenson-Moore, 1992)
New oily formulation	Rice bran oil (RBO Alfa One®) : 30% w/w	No	Spray	Flavoring	At least 4 times a day	Distilled water	(Apperley et al., 2017)

	Soy lecithin 30% w/w Propylene glycol Water: 40% w/w						
OMJ® (Oral Moisturizing Jelly)	Water-releasing (jelly)		Gel	Strawberry flavour or lime mint flavour	10 ml (spoon) 5 times/ day		(Dalodom et al., 2016)
New preparation saliva substitute	Distilled water Methylcellulose Spirit of chloroform KCl, NaF, CaCl.		Mouthwash 5ml	Essence of lemon	Ad libitum	Glycerine mouthwash Distilled water Spirit of chloroform	(Klestov et al., 1981)
Aldiamed® gel	Aloe vera gel				Ad libitum		(Momm et al., 2005)
Glandosane® spray	Carboxymethylcellulose	No			Ad libitum		(Momm et al., 2005)
Rape spray	Rape oil pressed		Spray		Ad libitum		(Momm et al., 2005)
Margarine	Liquid margarine				Ad libitum		(Furumoto et al., 1998)
Saliva Medac® spray	containing mucin extracted from pig stomach	Yes	Spray		Ad libitum		(Momm et al., 2005)
Salivèze®	aqueous electrolyte-containing solution calcium chloride 0.15 mg/mL, magnesium chloride 0.05 mg/mL, sodium chloride 0.05 mg/mL, potassium chloride 1.2 mg/mL, sodium phosphate 0.28 mg/mL and sorbitol 30 mg/mL in purified water		Spray		At least 5 times/day 1 or 2 spray up to 4 times a day		(Mouly, Orler, et al., 2007; Mouly, Salom, et al., 2007)
New artificial saliva formulation	aqueous solution of potassium thiocyanate, potassium chloride, sodium chloride, calcium chloride, magnesium chloride, potassium dihydrogen phosphate, xylitol and citric acide		Spray	Flavor	At least 2 times / day		(Silvestre et al., 2009)

Buccotherm®	Thermal spring water		Spray		4 times daily		(Skrinjar et al., 2015)
					6 times daily	1/10 diluated black tea(plain water and Lipton tea)	(Alpöz et al., 2015)
Xeros®	Betaine, Sodium fluoride, Hydroxyethylcellulose	No	Mouthwash		4 times daily		(Skrinjar et al., 2015)
Marshmallow root	Infusion of marshmallow root into 2 dcl of cold water		Mouthwash		Rinsing with one large spoon 4 h after preparation		(Skrinjar et al., 2015)
Mouth-Kote®	Yerba santa (Eriodictyon californicum), Xylitol		Spray	Lemon flavor(sorbitol/xylitol-sweetened)	Ad libitum		(Stewart et al., 1998)
TPM (Traditional Persian Medecine)	Sachet 4 g of mixed powder of A. digitata and M. Sylvestris (in a proportion of 1:1), in a glass of boiled water (250 mL) as one dose. After 10 min, when the herbal infusion somewhat cooled, the patients were to sip the entire		Sip/Drink				(Heydarirad et al., 2017)
			Spray			Hypozaix spray (sodium carboxymethyl cellulose)	

Code de champ modifié

Table 3: Values of saliva flow rate in the set of seven studies considering saliva flow rate as inclusion criteria

REFERENCES	Unstimulated saliva method	flow rate
(Alpöz et al., 2008)	Spitting method 5 min	<0.3mL/min
(Andersson et al., 1995)	Spitting method 15 min	<1.5mL
(Donath et al., 2016)	Swab/test of saliva weight absorbed 5 min	≤0.5g
(Furumoto et al., 1998)	Spitting method 5 min	<0.2 mL/min
(Mouly, Orler, et al., 2007; Mouly, Salom, et al., 2007)	Swab/test of saliva weight absorbed 5 min	≤0.5g
	Spitting method	≤0.16 mL/min
	Stimulated saliva method	flow rate
(Alpöz et al., 2008)	Drops of acid citric spitting method	<1mL/min
(Alves et al., 2004)	Acid citric on cotton swab 5 min test spitting	<0.5mL/min
(Andersson et al., 1995)	Paraffin chewing 5 min	<3.5mL
(Gil-Montoya et al., 2008)	Chewing paraffin 5 min	≤0.7mL/min
(Mouly, Orler, et al., 2007; Mouly, Salom, et al., 2007)	Chewing paraffin	≤0.5mL/min
	Spitting method	≤0.5mL/min