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## Original Research Article

# Artificial saliva plus beta-glucan for treatment of xerostomia in older adults: The clinical study of effectiveness and salivary total antioxidant capacity levels

Pakawan Tanviruch<sup>1</sup>, Surawut Pongsiriwet<sup>2</sup>, Jitjiroj Ittichaicharoen<sup>2</sup>,  
Kanyarat Korwanich<sup>3</sup>, Kathawut Tachasuttirut<sup>1\*</sup>

<sup>1</sup>Dept. of Oral and Maxillofacial Surgery, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

<sup>2</sup>Dept. of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

<sup>3</sup>Dept. of Family and Community Dentistry, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand



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## ABSTRACT

**Background:** To evaluate the effectiveness of 2 artificial saliva formulations, sodium carboxymethylcellulose artificial saliva spray and sodium carboxymethylcellulose artificial saliva spray plus  $\beta$ -glucan.

**Materials and Methods:** This study was a double-blind randomized controlled trial and involved older adults with xerostomia. The xerostomia inventory score, clinical oral dryness score, oral moisture degree, unstimulated salivary flow rate, and salivary total antioxidant capacity were measured prior to and after treatment. The results were evaluated 4 weeks after taking both products.

**Results:** The study included 51 subjects in the control ( $n = 25$ ) and BG ( $n = 26$ ) groups. Xerostomia inventory score and clinical oral dryness score were significantly lower in both groups after 4 weeks of treatment ( $p < 0.00$ ). Additionally, both groups had significantly greater oral moisture degree and unstimulated salivary flow rate than before treatment ( $p < 0.05$ ). Only the increase in oral moisture degree in the BG group was significantly greater than that in the control group ( $p = 0.048$ ). Both groups tended to have decreased salivary total antioxidant capacity, but only the control group had a significant difference at 4 weeks ( $p = 0.004$ ). There was no significant difference in satisfaction score between the two groups. No serious side effects were found in the study.

**Conclusion:** The clinical signs and symptoms of xerostomia were improved by both control and artificial BG saliva. BG improved oral moisture more than the control. Furthermore, BG was more likely to prevent a decrease in salivary total antioxidant capacity than was the control.

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## 1. Introduction

Xerostomia, or dry mouth symptoms, may occur when there is a lack of saliva. Many factors can contribute to xerostomia. One of the most common causes is the adverse effects of drugs.<sup>1</sup> To a greater extent than any other age group, older adults experience xerostomia due to the greater frequency of concurrent diseases and increased use of

medications. Furthermore, certain studies have shown that as people age, the proportion of acinar cells in the major salivary glands decreases, and acinar cells are continuously replaced by fat and connective tissue.<sup>2</sup> Between the ages of 34 and 75, it is thought that the number of salivary gland acinar cells decreases by 30% to 40%.<sup>3</sup> For these reasons, older adults are typically affected by xerostomia.

Xerostomia affects important life activities, such as speaking, chewing, enjoying and ingesting food, and wearing dental prostheses. A lack of saliva may contribute

\* Corresponding author.

E-mail address: [kathawut.t@cmu.ac.th](mailto:kathawut.t@cmu.ac.th) (K. Tachasuttirut).

to the risk of several oral diseases, such as dental caries, candidiasis, bad breath, and burning sensation in the mouth. The adverse effects of oral dryness are caused by a deficiency of antioxidants.<sup>4,5</sup> Similarly, increasing evidence suggests that those who experience xerostomia or salivary hypofunction may benefit from antioxidants.<sup>6</sup>

Management of dry mouth can be achieved through 2 strategies: systemic and local treatments. Nevertheless, patients with damaged salivary glands may not benefit from systemic therapy. Additionally, older adults who take multiple medications may experience negative side effects from systemic drugs. As a result, the recommended treatment should focus on local therapy or alleviating symptoms. Artificial saliva has been developed to relieve dry mouth symptoms in xerostomia patients. The primary function of artificial saliva is to coat and lubricate oral soft tissues. Artificial saliva is available in various forms, including sprays, liquids and gels.

Numerous studies have shown the efficacy of several artificial saliva formulations for treating people affected by xerostomia; however, their effectiveness in treating xerostomia is still controversial.<sup>7–10</sup> Various components, either separately or in combination, can be found in the ingredients, including xylitol, sodium carboxymethylcellulose (SCMC), mucopolysaccharide, glycerate polymer gel base, and natural mucins. All commercially available saliva substitutes have moisturizing and lubricating properties intended to prolong the wetness of oral tissue. Beta-glucan ( $\beta$ -glucan) is recognized for its biological activities, such as lowering the glycemic index and serum cholesterol and its immunomodulatory, antitumor, antioxidant, and anti-inflammatory activities.<sup>11</sup> The antioxidant activity of  $\beta$ -glucan was noticeably greater than that of several polymers used as food additives. Moreover,  $\beta$ -glucan has a high capacity to hold water and plays a significant role in various food applications as a soluble fiber that helps prevent rotting, limits moisture migration, and reduces syneresis or weeping.<sup>12</sup>

Several researchers have reported that  $\beta$ -glucan has beneficial cosmeceutical properties, including moisture retention and skin revitalization.<sup>13</sup> However, no studies have been conducted on artificial saliva containing beta-glucan. Therefore, this study aimed to evaluate and compare the effectiveness of a new formula, artificial saliva containing  $\beta$ -glucan, with that of plain artificial saliva (without  $\beta$ -glucan) for treating xerostomia in older adults.

## 2. Aims

To evaluate and compare the effectiveness of 2 artificial saliva formulations, sodium carboxymethylcellulose (SCMC) artificial saliva spray and sodium carboxymethylcellulose (SCMC) artificial saliva spray plus  $\beta$ -glucan.

## 3. Objectives

1. To evaluate the effectiveness of SCMC artificial saliva spray plus  $\beta$ -glucan for treating of xerostomia.
2. To compare the effectiveness of SCMC artificial saliva spray and SCMC artificial saliva spray plus  $\beta$ -glucan for treating of xerostomia.
3. To compare the salivary TAC level in subjects with xerostomia before and after being treated with SCMC artificial saliva spray and SCMC artificial saliva spray plus  $\beta$ -glucan.
4. To compare the satisfaction of subjects with xerostomia after being treated with SCMC artificial saliva spray and SCMC artificial saliva spray plus  $\beta$ -glucan.

## 4. Material and Methods

### 4.1. Study design

This was a double-blind randomized controlled trial of older adults with xerostomia. The study was performed according to the Declaration of Helsinki and the ICH-GCP. The Ethics Committee of the Faculty of Dentistry, Chiang Mai University, Thailand (protocol No.054/2022), is registered in the Thai Clinical Trials Registry under the registration number TCTR20230206008. Prior to data collection, all subjects signed written informed consent.

### 4.2. Subjects

Fifty-one older adults with xerostomia were enrolled in the trial ( $n=26$  for the BG (study) group and  $n=25$  for the control group). The subjects in this study were adults aged 60 years or older who experienced subjective feelings of dry mouth for  $\geq 7$  days. The subjects were asked a single-item question: How often do you feel dry mouth? The available answers were 'never', 'sometimes', 'frequently', or 'always'. Those who answered 'frequently' or 'always' were considered to have subjective dry mouth. The exclusion criteria were previous radiation therapy (head and neck area), chemotherapy, cancer or tumor of the salivary gland, a history of systemic diseases explaining the diminished salivary flow (i.e., Sjögren syndrome, infection of the salivary glands), decompensated systemic disorders or cognitive problems, drug abuse, and allergies to fungi or yeast.

### 4.3. Sample size calculation

The sample size was calculated according to previously published data that compared the clinical efficacy of a topical sialagogue spray containing 1% malic acid for older adults with xerostomia by contrasting distinct XI scores at the beginning and final stages of the study.<sup>14</sup> A power of 90% and a type I error of 0.05 were used. The calculated total sample size was 20 (at least 10 in each group).

#### 4.4. Randomization, allocation and concealment

Subjects were randomly allocated into two groups using a web-based random sequence generator available at <http://www.sealedenvelope.com>. The allocation was conducted by an independent individual not affiliated with the study. The qualified subjects were assigned to receive either plain artificial saliva spray or artificial saliva spray plus  $\beta$ -glucan at a 1:1 ratio. All examiners involved in the data collection and statistical analysis were blinded.

#### 4.5. Intervention and materials

Subjects in both groups were instructed to spray one dose (3-4 sprays) of artificial saliva into the mouth 3 times a day (morning-noon-evening) for 4 weeks. Edible artificial saliva was obtained from Chiang Mai University. Both formulations of artificial saliva were prepared as an oral spray. Methylparaben was used as a preservative. (Table 1)

**Table 1:** Artificial saliva solution developed by Chiang Mai University (Control)

Ingredient	Amount
1.Sodium carboxymethylcellulose	1%
2. Glycerin	5%
3. Sweetening	2%
4. Preservative	0.1%
5. Lemon Flavor	1%
6. Distillated water q.s.	100 ml
Artificial saliva solution developed by Chiang Mai University plus 1.5% $\beta$ -glucan (w/v) (BG)	
Ingredient	Amount
1.Sodium carboxymethylcellulose	0.5%
2. 1.5% beta glucan	50%
3. Glycerin	5%
4. Sweetening	2%
5. Preservative	0.1%
6. Lemon Flavor	1%
7. Distillated water q.s.	100 ml

The control group (Control) received plain artificial saliva (sodium carboxymethylcellulose-base).

The study group (BG) received plain artificial saliva (sodium carboxymethylcellulose-base) plus 1.5%  $\beta$ -glucan (w/v).

#### 4.6. Data collection

After using both artificial saliva sprays for 4 weeks. The subjective and objective dry mouth scores and the degree of oral moisture were evaluated and compared with the baseline data. Subsequently, an analysis was performed to compare the unstimulated salivary flow rate and salivary level of total antioxidant capacity with the baseline data.

#### 4.7. Subjective dry mouth

Subjects were asked to assess the severity of dry mouth using the XI, an 11-item questionnaire. XI scores can represent the severity of chronic xerostomia, and higher scores represent more severe symptoms. This questionnaire has been indicated as a reliable method for assessing how an intervention affects the severity of xerostomia.<sup>15</sup>

#### 4.8. Objective dry mouth

Clinical oral dryness (COD) scores<sup>16</sup> were obtained by a single oral medicine specialist to assess the objective of dry mouth. The oral moisture degree (OMD) was measured by an oral moisture-checking device (Mucus® Life).<sup>17</sup> Unstimulated salivary flow rate (USFR) data were collected via the draining and spitting method. The subjects were asked to avoid eating or drinking anything (except water) for one hour prior to the test. Then, individuals were instructed to stay motionless and allow the saliva to drain passively for 5 minutes through the lower lip into a 10 ml tube fitted with a funnel. The saliva samples were stored at -4 °C until analysis.

#### 4.9. Biological analysis

The total antioxidant capacity of saliva was determined by using a total antioxidant assay kit (Ref. CS0790, Sigma–Aldrich Co.) based on the conversion of  $\text{Cu}^{2+}$  to  $\text{Cu}^{+}$  by both small molecules and protein antioxidants for colorimetric detection at 570 nm. The antioxidant concentration is shown in mM Trolox.

#### 4.10. Satisfaction

After both artificial saliva sprays were used, we assessed satisfaction on a Likert scale ranging from 1 to 5.

#### 4.11. Statistical analysis

IBM SPSS, version 26, was used for the statistical analysis. The pretreatment variables were analyzed using descriptive statistics. Fisher's exact test was used for categorical variables such as sex. Independent t tests were used to compare pretreatment characteristic variables such as age, XI, COD, OMD, and satisfaction score. The Mann–Whitney U test was used to compare pretreatment characteristic variables such as the USFR and salivary TAC. A paired t test was used to compare the outcome measures of the same group at baseline and after four weeks for the XI, COD, and OMD. The Wilcoxon signed rank test was used to compare outcome measures between the same group at baseline and after four weeks in terms of the USFR and salivary TAC. Independent t tests were used to compare differences in the XI, COD, OMD and satisfaction scores. The Mann–Whitney U test was used to compare differences in the USFR, salivary TAC and satisfaction score between

the two groups. Spearman correlation coefficients were used for statistical analysis. All the statistical tests were performed using a significance level of  $p < 0.05$ . The normality of the distributions was confirmed using the Kolmogorov–Smirnov test.

## 5. Results

The demographic characteristics and baseline data of the subjects are presented in (Table 2). The XI, COD, OMD, USFR and salivary TAC of the subjects in the BG and control groups were not significantly different. ( $P < 0.05$ )

**Table 2:** Demographic characteristics and baseline data of the subjects

	BG (N = 26)	Control (N =25)	p value
<b>Sex, N (%)</b>			1.000 <sup>F</sup>
Male	3(11.54)	3(12)	
Female	23(88.46)	22(88)	
<b>Age</b>	70.35±5.12	71.48±7.29	0.522 <sup>I</sup>
<b>XI</b>	30.38 ± 8.38	27.44 ± 8.48	0.227 <sup>I</sup>
<b>COD</b>	3.31 ± 1.23	3.16 ± 1.21	0.667 <sup>I</sup>
<b>OMD</b>	26.07 ± 3.49	26.97 ± 3.19	0.339 <sup>I</sup>
<b>USFR</b>	0.237 ± 0.18	0.258 ± 0.209	0.785 <sup>M</sup>
<b>Salivary TAC (mM)</b>	0.58 ± 0.95	0.36 ± 0.69	0.509 <sup>M</sup>

<sup>F</sup> By Fisher's exact test

<sup>I</sup> By Independent t test

<sup>M</sup> By Mann–Whitney Utest

(\*) Statistically significant difference ( $p < 0.05$ )

### 5.1. Xerostomia inventory (XI) and clinical oral dryness (COD) score

There was a statistically significant reduction in the XI score and COD score from baseline to week 4 in both the BG and control groups. ( $P < 0.05$ ) However, there was no statistically significant difference between the BG and control groups in terms of the reduction in the XI score or COD score. (Table 3)

### 5.2. Oral moisture degree (OMD)

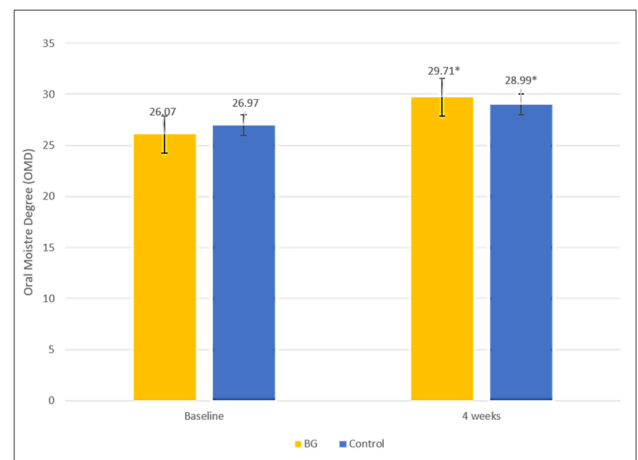
There was a statistically significant increase in the degree of oral moisture from baseline to week 4 in both the BG and control groups. ( $P < 0.05$ ) (Figure 1) & (Table 3). The degree of oral moisture was significantly greater in the BG group than in the control group. ( $P < 0.05$ ) (Figure 2)

### 5.3. Unstimulated salivary flow rate (USFR)

There was a statistically significant increase in the USFR from baseline to week 4 in the BG and control groups. ( $P < 0.05$ ) However, there was no statistically significant difference in the reduction in the USFR between the BG group and the control group. (Table 3)



**Figure 1:** Artificial saliva spray Left: Control. Right BG



**Figure 2:** Mean OMD of subjects in the BG and control groups at baseline and after 4 weeks of intervention

### 5.4. Salivary total antioxidant capacity (salivary TAC)

The salivary TAC in the control group decreased significantly from baseline to week 4. ( $P < 0.05$ ) (Table 3) However, salivary TAC decreased in the BG group, but the difference was not statistically significant. (Figure 3) Nevertheless, there was no statistically significant difference in the total change in salivary TAC between the BG group and the control group. (Figures 4 and 5)

### 5.5. Satisfaction score

There was no statistically significant difference in the satisfaction score between the BG group and the control group. (Table 3)

**Table 3:** XI, COD, OMD, USFR, salivary TAC and satisfaction score before and after 4 weeks using artificial saliva plus  $\beta$ -glucan and normal artificial saliva

		Baseline	4 weeks	p value <sup>P</sup>	Mean difference	p value <sup>I</sup>
<b>XI</b>	BG	30.38 ± 8.38	20.46 ± 6.52	0.000*	9.92 ± 7.66	0.727
	Control	27.44 ± 8.48	18.4 ± 5.73	0.000*	9.12 ± 8.68	
<b>COD</b>	BG	3.31 ± 1.23	2.12 ± 0.90	0.000*	0.88 ± 0.77	0.731
	Control	3.16 ± 1.21	2.20 ± 0.91	0.000*	0.96 ± 0.79	
<b>OMD</b>	BG	26.07 ± 3.49	29.71 ± 2.17	0.000*	3.64 ± 2.97	0.048*
	Control	26.97 ± 3.19	28.99 ± 2.24	0.001*	2.02 ± 2.73	
		Baseline	4 weeks	p value <sup>W</sup>	Mean difference	p value <sup>M</sup>
<b>USFR</b>	BG	0.237 ± 0.18	0.31 ± 0.22	0.005*	0.69 ± 0.15	0.445
	Control	0.258 ± 0.209	0.34 ± 0.24	0.027*	0.83 ± 0.17	
<b>Salivary TAC (mM)</b>	BG	0.58 ± 0.95	0.55 ± 0.81	0.241	0.03 ± 1.14	0.575
	Control	0.36 ± 0.69	0.31 ± 0.075	0.004*	0.05 ± 0.71	
<b>Satisfaction score</b>	BG		4.65 ± 0.56			0.316
	Control		4.40 ± 0.82			

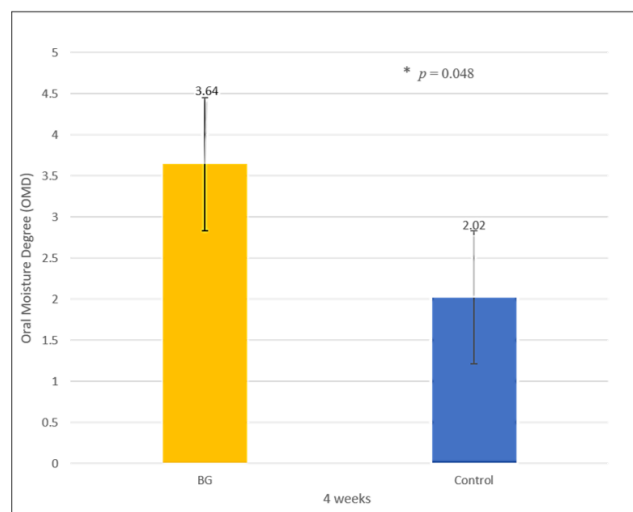
<sup>P</sup> By Paired-sample test.

<sup>I</sup> By Independent t test.

<sup>W</sup> By Wilcoxon signed-rank test was used.

<sup>M</sup> By Mann–Whitney U test

(\*) Statistically significant difference (p < 0.05)



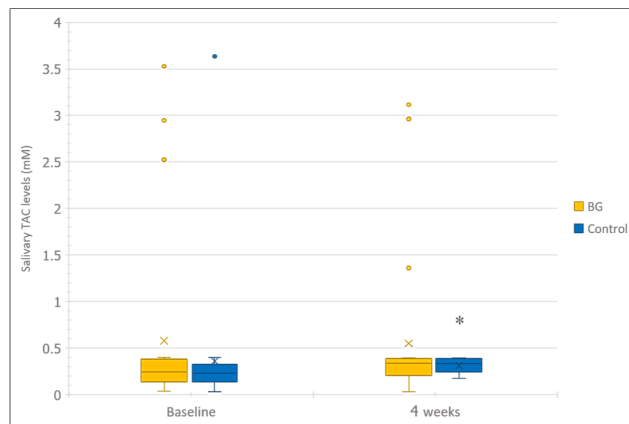
**Figure 3:** Differences in the mean OMD between the two groups after 4 weeks

### 5.6. Relationships among XI, COD, OMD and USFR

The correlation coefficients of COD with OMD and USFR were -0.360 and -2.92, respectively, indicating negative correlations. (P < 0.05) (Table 4)

## 6. Discussion

The most important and challenging goal for older adults with xerostomia is symptom and discomfort relief. Therefore, the primary result of this study was the XI, which was found to be a reliable multi-item questionnaire for assessing the severity of dry mouth symptoms in clinical and epidemiologic studies. According to the XI,



**Figure 4:** Median and interquartile range (IQ) of salivary TAC in each group at baseline and after 4 weeks

the feeling of oral dryness decreased significantly in both the intervention and control groups at the end of the trial (the average decreases in the XI score were 9.92 and 9.12 points, respectively). Nonetheless, when the mean reduction in the XI in both groups was analyzed, there was no statistically significant difference. In earlier research, artificial saliva based on sodium carboxymethylcellulose (SCMC) was frequently used to treat the symptoms of xerostomia, owing to its moderate efficacy in relieving dry mouth symptoms.<sup>18,19</sup> Oh et al. discovered that a saliva substitute made of carboxymethylcellulose may reduce the suffering of patients from dry mouth both during the day and at night, with significantly greater efficacy shown for patients with functional residual secretory capacity.<sup>7</sup> In this study, we mainly recruited people whose secretory glands

**Table 4:** Correlation analysis of the XI, COD, OMD, and USFR

Variable	With variable	Spearman p	P value
XI	COD	0.125	0.380
OMD	COD	-0.360*	0.009
XI	OMD	-0.110	0.441
USFR	COD	-2.920*	0.037
USFR	OMD	1.420	0.320
USFR	XI	-0.150	0.293

**Figure 5:** Differences in the median and interquartile range (IQ) of salivary TAC between the two group after 4 weeks

were still functional. As a result, we clearly observe the effects of both artificial saliva methods.

Our results revealed that both the BG and control groups exhibited significant improvements in clinical outcomes, such as COD and the degree of oral moisture. Interestingly, the mean increase in the BG group was significantly greater than that in the control group. This might be related to the moisturizing properties of  $\beta$ -glucan. According to several studies,  $\beta$ -glucan has a high water holding capacity and good gelling properties. Cao et al. discovered that  $\beta$ -glucan-containing skin care regimens may help heal skin inflammation and barrier function following fractional laser therapy.<sup>20</sup> According to the study of Natakankitkul et al.,  $\beta$ -glucan extract from yeast waste has positive cosmeceutical qualities, such as moisture retention and skin regeneration.<sup>21</sup> The amount of saliva that is retained on and moistens the oral surface appears to be a critical factor in oral pain, and its decrease is related to a worsening sensation of dryness.<sup>22</sup> Our findings indicate that artificial saliva containing  $\beta$ -glucan is more effective than typical artificial saliva in promoting moisture maintenance in the oral mucosa.

According to most studies, oral dryness is more often determined by the unstimulated salivary flow rate than by the stimulated flow rate.<sup>23</sup> In this study, the USFR significantly increased in the BG and control groups at

the end of the study. Similarly, Sarideechaigul et al. reported that the USFR and SSFR significantly increased following treatment with the SCMC formula.<sup>19</sup> Our results are supported by earlier research showing that 1% malic acid, SCMC artificial saliva, and OMJ could increase the salivary flow rate within one or two months.<sup>14,19,24</sup> In this study, a COD was correlated with both salivary flow rates and mucosal moisture. The correlation coefficients between COD and OMD showed moderate to substantial negative relationships. Additionally, there were moderate negative correlations between COD and USFR. Therefore, the results obtained in this study indicate that decreased USFR and OMD are related to increased COD. The outcome agrees with that of previous studies revealing a significant inverse relationship between lingual moisture and mouth dryness.<sup>17,25</sup>

Since oxidative stress contributes to worsening of the associated oral disease, the use of antioxidant products is related to xerostomia. Our study revealed that artificial saliva plus  $\beta$ -glucan has the potential to prevent a reduction in salivary TAC. The differences between the two groups led to interesting questions regarding the possible function of  $\beta$ -glucan in preventing the decrease in salivary TAC associated with xerostomia. Salivary TAC levels have been studied in a variety of oral diseases, including caries, periodontitis, and oral cancer.<sup>26,27</sup> Since all antioxidants work as a single unit, our research chose to assess salivary TAC. Previous research also showed that TAC was significantly different from that of different antioxidants.<sup>28</sup> To date, numerous studies have investigated the antioxidant properties of  $\beta$ -glucan; however, the majority of these studies were conducted in vitro and in vivo.<sup>29–31</sup> Slamová et al. supported our findings by investigating the protective effect of yeast-derived  $\beta$ -glucan and fungus-derived  $\beta$ -glucan-chitin complexes against oxidative DNA damage induced by H<sub>2</sub>O<sub>2</sub> and visible light-excited methylene blue in V79 hamster lung cells; they concluded that  $\beta$ -glucan protects DNA from oxidative damage by scavenging both OH radicals and singlet oxygen.<sup>29</sup> Krizkova et al. discovered the antigenotoxic and antioxidant activity of yeast-derived mannan and mannan conjugates with human serum albumin in *Euglena gracilis*. The tested  $\beta$ -glucan showed strong antigenotoxic and antioxidant activity against acridine orange and ofloxacin.<sup>30</sup> Few animal research investigations have been undertaken. Yuan et al.<sup>31</sup> used a lymphocyte

proliferation test to assess the anti-inflammatory and immunological effects of  $\beta$ -glucan from *Phellinus ribis* in mice. They concluded that  $\beta$ -glucan administration increased the activity of antioxidant enzymes (SOD and GSH-Px) and decreased the amount of TBARS in blood. Unfortunately, only one study evaluated the antioxidant properties of  $\beta$ -glucan in human clinical research.<sup>32</sup> Preus et al. revealed the effect of soluble  $\beta$ -glucan as a mouth rinse and swallowed on gingivitis in humans. According to the study, GCF levels in swallowed soluble-glucan groups increased significantly within the first week. The increased GCF secretion in the swallow group may thus be evidence of an improved mucosal immune response. However, the antioxidative mechanism of  $\beta$ -glucan has not been widely studied. The Dectin-1/Nrf2/HO-1 signaling pathway was shown to be the mechanism underlying the stimulation of antioxidants in xerostomia patients.<sup>33</sup>

Our study revealed that both artificial saliva formulations had very high levels of satisfaction, with mean satisfaction scores of 4.65 and 4.4 in the intervention and control groups, respectively. According to Perimentel et al., a score ranging from 4.21 to 5.00 indicates strongly agree or very satisfied, respectively.<sup>34</sup> Silvestre et al. reported that a saliva substitute in spray form was simple to use and clinically effective, providing immediate relief from dry mouth symptoms.<sup>35</sup> The spray design, texture, taste, and smell of artificial saliva, together with its immediate effectiveness for relieving dry mouth, may be the reasons why both types of artificial saliva tend to be satisfactory.

Due to the limited data available for evaluating antioxidant properties in human clinical research, our study is the first to evaluate the effect of  $\beta$ -glucan in artificial saliva. No serious adverse effects were found throughout the period during which the subjects used artificial saliva. This study showed that both artificial saliva formulations achieved favorable outcomes in the treatment of xerostomia. Additionally, our study demonstrated that the addition of  $\beta$ -glucan to artificial saliva may have antioxidative effects on older adults. In future studies, more extended periods of follow-up and monitoring might provide additional information and evidence regarding the effects of  $\beta$ -glucan-containing artificial saliva. Additionally, other concentrations of  $\beta$ -glucan may provide more visible antioxidant effects to the oral mucosa. Therefore, further studies are needed to investigate the potential of  $\beta$ -glucan as an active component of artificial saliva for treating xerostomia.

## 7. Conclusion

We concluded that “artificial saliva” and “artificial saliva plus  $\beta$ -glucan” can help to reduce the XI score and COD and improve the OMD and the USFR in older adults with xerostomia after 4 weeks of use. Artificial saliva plus  $\beta$ -glucan could provide more moisture than normal artificial saliva. Furthermore, in older adults with

xerostomia, artificial saliva spray plus  $\beta$ -glucan was more likely to prevent a decrease in salivary TAC than was normal artificial saliva.

## 8. Source of Funding

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## 9. Conflicts of Interest

All authors declare no conflicts of interest.

## 10. Acknowledgement

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#### Author biography

**Pakawan Tanviruch**, PG Dental Student  <https://orcid.org/0009-0001-0687-6906>

**Surawut Pongsiriwet**, -  <https://orcid.org/0009-0005-7914-043X>

**Jitjiroj Ittichaicharoen**, -  <https://orcid.org/0000-0002-0805-9432>

**Kanyarat Korwanich**, -  <https://orcid.org/0000-0002-9112-6797>

**Kathawut Tachasuttirut**, -  <https://orcid.org/0009-0003-9352-3192>

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