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Feature Article

Influence of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus

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ABSTRACT

Dry mouth is common in elderly patients. However, the use of saliva substitute has been limited due to its inedibility. This study investigated the efficacy of oral moisturizing jelly (OMJ), a novel edible saliva substitute. A pre-post design was conducted in 118 elderly patients diagnosed with hypertension and/or diabetes mellitus. After using OMJ, signs and symptoms of dry mouth were compared with baseline data. The properties of saliva were compared between the OMJ use and non-use periods. The use of OMJ for 2 weeks significantly reduced symptoms of dry mouth, while the use for 1 month reduced the signs of xerostomia, prevented the decline of salivary pH(s) and improved buffering capacities. OMJ was equally effective in patients taking 1 to 2 and 3 to 7 medications. Furthermore, 65% of patients preferred OMJ over a commercial product. OMJ could be new edible saliva substitute for elderly patients suffering from dry mouth.

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Introduction

Xerostomia (dry mouth) is a common complaint of almost 50% of elderly population.¹ Although salivation decreases with age, the actual causes of xerostomia in elders are likely drug-induced

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hyposalivation, head and neck irradiation and systemic conditions, such as Sjögren's syndrome and type 2 diabetes mellitus.² Many types of medicine cause dry mouth as a side effect e.g. anti-hypertensive drugs, anti-diabetic drugs, psychotherapeutic drugs and anti-histamines.³ Owing to the multiple functions of saliva, hyposalivation leads to speech problems, taste disorders, chewing and swallowing difficulties, ill-fitting dentures and consequently poor qualities of life.^{4,5} Furthermore, hyposalivation results in decreased oral clearance, declined salivary pH and buffering capacity, and reduced immune defenses.⁶ These symptoms may increase risks of developing infectious oral diseases such as cervical caries, periodontitis and oral candidiasis.⁶ Current interventions for xerostomia include systemic therapies such as cholinergic agonists; topical interventions such as saliva

stimulants and saliva substitutes, and non-pharmacological interventions such as acupuncture and electrostimulation.^{7–9} Recent evidence-based reviews concluded that systemic salivary stimulants e.g. pilocarpine and cevimeline are recommended only for primary and secondary Sjögren's syndrome.⁷ No topical therapies have strong evidence to support their efficacies.⁸ Evidences for acupuncture or electrostimulation devices are insufficient.⁹ Thus, the development of novel effective approaches for alleviating xerostomia is essential.

In recent years, saliva substitutes have gained much attention. Saliva substitutes are available in various formulations e.g. lozenges, sprays, mouth rinses, gels, oils, chewing gums or toothpastes. However, no single product could adequately reproduce the properties of the natural saliva.¹⁰ This is likely due to the inedibility of those saliva substitutes. The saliva substitute products usually contain preservatives. Therefore, their uses are limited only to oral cavity and they are not recommended to be swallowed.¹⁰ This constraint has become critical and thus limited the uses of commercially available saliva substitutes. Saliva swallowing is a normal reflex to maintain a proper clearance by eliminating gram-negative bacilli from oropharynx.¹¹ In fact, oropharyngeal infection and sputum accumulation in patients with xerostomia could increase the risk of aspiration pneumonia.¹¹ Furthermore, saliva swallowing is critical for food ingestion since the flow of saliva through oropharyngeal isthmus stimulates swallowing process and taste perception in oropharyngeal area.¹² Therefore, the general properties of ideal saliva substitutes should be inexpensive, edible, hydrating, easy-to-swallow but retainable in the mouth.

Recently, oral moisturizing jelly (OMJ) was successfully developed by joint collaborators from various disciplines including dentistry, nursing, medicine and food sciences. OMJ is a ready-to-eat gel with semi-solid appearance but could be melted under oral environment temperature.¹³ Upon biting or spooning, the gel will release some water due to syneresis.¹⁴ Since patients with xerostomia often have chewing and swallowing problems,⁴ the texture and gel strength of OMJ were designed based on a previous research and development of Nutri-jelly,¹⁵ a nutritious edible gel proven to be effective in improving quality of life in head and neck cancer patients with chewing and swallowing difficulties.¹⁶ Unlike Nutri-jelly, OMJ has no nutrients but contains buffering agents and high water content. In addition, OMJ has neutral pH (6.8–7) and normal buffering capacity, imitating the natural saliva.¹³ The most severe xerostomia was found in head and neck cancer patients undergoing radiation therapy. A home-use-test of OMJ was conducted in 36 cancer patients with xerostomia.¹³ The patients used the OMJ products for two weeks and recorded their uses and satisfactions in their diaries. The study showed that 82.3% of the cancer patients were satisfied with the texture, flavor and moisture of OMJ.¹³ In addition, the satisfaction of OMJ was higher than that of a commercially available saliva gel.¹³ After taking one spoon of OMJ, most patients required an additional spoon after 2 h and 45 min, suggesting that OMJ can retain in the mouth for almost 3 h.¹³ Although dry mouth is common in elderly population, the intervention studies for treatment of dry mouth in these patients have been limited.¹⁷ Therefore, the aim of this study was to investigate the efficacy of OMJ in elderly patients.

Methods

Intervention

Oral moisturizing jelly (OMJ) products were provided by Dental Innovation Foundation under Royal Patronage, a non-profit organization. The OMJ products passed food safety test (free of pathogenic micro-organisms and hazardous metals), according to the

regulation of Thai Food and Drug Administration (FDA). The OMJ products were manufactured in a clean room by hot-filling. The OMJ products have 6-month shelf life at room temperature. Besides, the products are available in two flavors: strawberry and lime mint (Fig. 1a), and their biochemical properties are not different.¹³ The products are semi-solid with consistency comparable to National Dysphagic Diet (NDD) level 1,¹⁸ non-nutritive, water-releasing and ready-to-eat by spoon (Fig. 1b).

Participants

Patients were recruited from the out-patient departments of two hospitals located in Lamphang province of Thailand. Prior to the recruitment, all patients were screened based on the following inclusion criteria: being diagnosed with hypertension or diabetes mellitus and receiving medical therapies for at least 1 year; having complaint of xerostomia. Exclusion criteria were as follows: having subjective dry mouth score <3 or objective dry mouth score <2; having oral candidiasis; being unable to make reliable decisions or communications. All patients signed their written informed consents prior to data collection. Their identities had been protected, following Good Clinical Practice guidelines of International Conference on Harmonisation (ICH-GCP).

Sample size calculation

Sample size was identified by priori power analysis using G Power 3.1.¹⁹ The effect size was calculated from the pilot data of 10 patients using their mean subjective dry mouth scores and standard deviations at baseline, 2 weeks and 1 month after OMJ use. Based on repeated measure analysis of variance (repeated measure ANOVA), it was necessary to enroll 70 patients to achieve 90% power at 2-sided 1% significance level. To account for an up to 30% drop-out rate, at least 100 patients were required. Initially, 126 patients agreed to be enrolled in the study. Finally, completed data were presented from 118 patients (93.6%).

Study procedures

This study was approved by the institutional ethic committee for research in human of Department of Health, Ministry of Health, Thailand, and performed according to Declaration of Helsinki. To investigate the possible benefits of OMJ, a pre-post design was used. At the beginning, all patients who passed the inclusion criteria signed their written informed consents. Then, all of them received their favorite flavored OMJ products in a volume of 50 ml (10 ml × 5 times) per day. After using the OMJ for 2 weeks and 1 month, their signs and symptoms of xerostomia were measured as objective and subjective dry mouth scores, respectively, and compared with their baseline data (prior to use). Their properties of saliva, including salivary pH(s), buffering capacities and flow rates, were subsequently compared with their baseline data. Since, the patients were also taking other medicines with potential side effects on saliva qualities during the study period, their changes of saliva properties during 'OMJ use period' were monitored and compared within the same patients during 'OMJ non-use' period. The data for 'OMJ non-use' period were collected within the same patients three months later. To ensure that the baseline data of "OMJ use and non-use" periods was comparable, the history of medication uses was rechecked. It was confirmed that all patients received similar medications and doses in both periods.

Measures

The primary outcome measures were satisfaction and subjective dry mouth scores. The secondary outcomes measures were

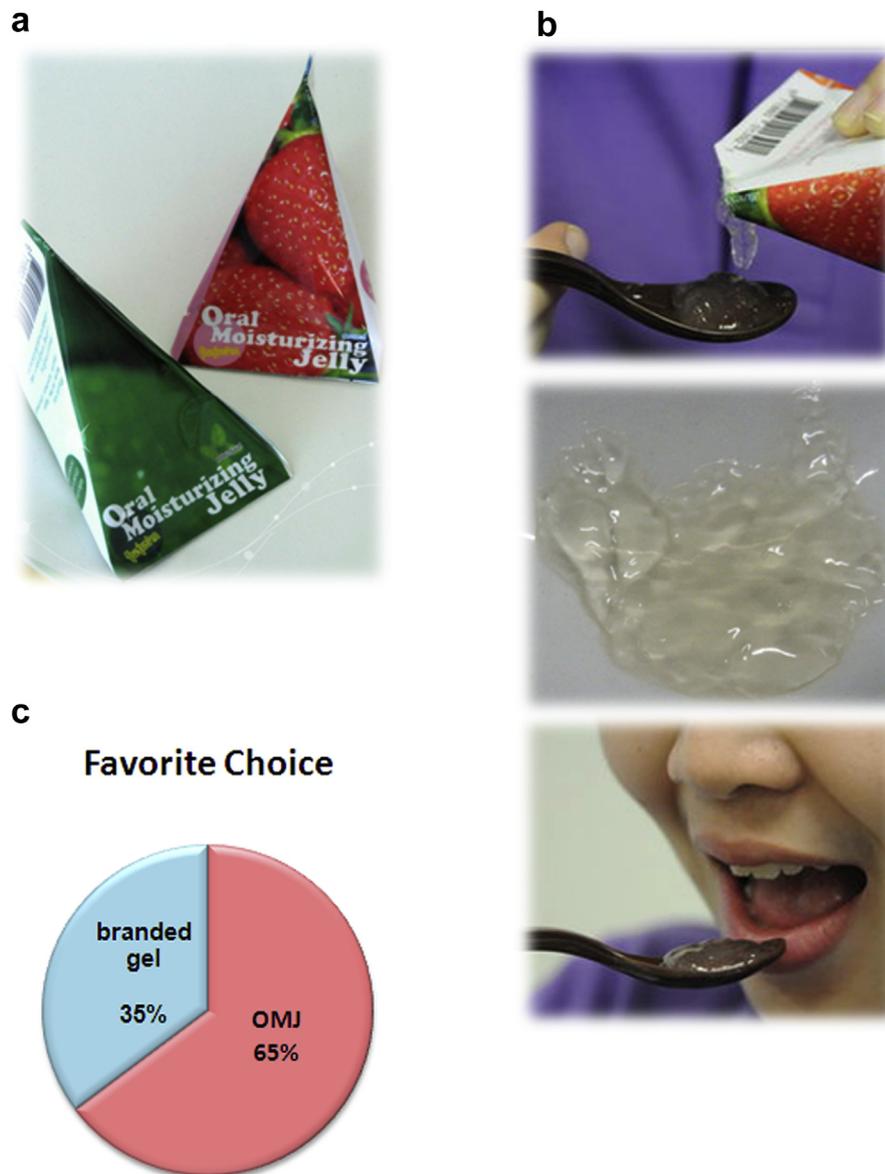


Fig. 1. Oral moisturizing jelly (OMJ). (a) The packages of OMJ in hot-filled pyramidal boxes: strawberry flavored (red labeled) and lime mint flavored (green labeled) products. (b) The consistency of OMJ is comparable to NDD level 1 with pudding-like texture, no-need-to-chew and easy-to-pour-out properties (Top image). Upon cut or bitten, the gel will release water (Middle image). OMJ can be taken by spoon, like regular food (bottom image). (c) The pie chart demonstrates the percentages of patients who selected either OMJ (red area) or a commercial saliva gel (blue area) as their favorite choices. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

objective dry mouth scores, salivary pH(s), buffering capacities and flow rates.

Satisfaction

At the beginning, all patients had few spoons of OMJ and a commercially available artificial saliva gel, in a random order. Then, they were asked to choose their favorite gel (either OMJ or the commercial one). At the end of the 'OMJ use' period, the patients were asked to rate their appreciation for OMJ in a scale of 0–10.

Subjective dry mouth score

The patients were interviewed for their symptoms of xerostomia including dry mouth, dry throat, chewing and swallowing difficulties, taste disturbances, speech problems, night-time water intakes and ill-fitting dentures.²⁰ The patients were advised to give the scores on the severity of symptoms in a scale ranging from 0 (not troublesome) to 10 (most troublesome).²⁰ The subjective dry

mouth scores of each patient were calculated as the mean of all item scores. Patients with a score less than 3 were excluded from data analysis.

Objective dry mouth score

The patients were examined for their signs of dry mouth including loss of pooled saliva, mouth mirror stickiness, stringy or foamy appearance, labial dehydration and irresponsiveness to parotid stimulation.²¹ Objective dry mouth scores were calculated as the number of observed dry mouth signs (0–5). Patients with a score less than 2 were excluded.

The properties of saliva

The various parameters of saliva including salivary pH(s), buffering capacities and flow rates were measured in all patients during OMJ use and non-use periods. As depicted in Fig. 2, the salivary pH(s), buffering capacities and flow rates were measured

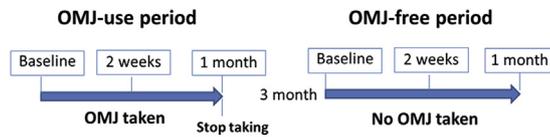


Fig. 2. The measurement of saliva qualities in OMJ use and OMJ non-use periods. This diagram shows time points where salivary pH(s), buffering capacities and flow rates were measured. The OMJ use period started three months after the OMJ non-use period ended.

at baseline (prior to OMJ use), and after 2 weeks and 1 month of OMJ use period. Then, all subjects were advised to stop their uses of OMJ for 3 months; thereafter, the measurements were collected as baseline, and after 2 weeks and 1 month of OMJ non-use period. For the measurement of saliva's properties, whole saliva samples were collected within 10 min after stimulation by paraffin chewing. Stimulated salivary flow rates, pH(s) and buffering capacities were measured by using commercially available GC Saliva Check-Buffer kits (GC Asia, Singapore).²² This method was feasible in dental offices and was proven to be well-correlated with laboratory titrations.²³ As instructed on the product sheet, salivary flow rates less than 1 ml/min and salivary pH(s) < 6.8 were considered abnormal. Salivary buffering capacities were categorized into very low (score 0–5), low (6–9) and normal (≥ 10) capacities. The buffering capacities of each patient after using the OMJ for 2 weeks and 1 month were compared with that of his baseline data. Then, they were represented by improved, unchanged or worse buffering capacities. For example, a patient had low buffering capacity at baseline, very low buffering capacity at 2 weeks and low buffering capacity at 1 month. The changes of buffering capacity in this patient would be categorized as worse capacity at 2 weeks and unchanged capacity at 1 month. The percentages of patients in each category (improved, unchanged or worse buffering capacities) were calculated as the number of patients in each category divided by the number of total patients.

Patients with baseline saliva qualities in a normal range i.e. flow rate of ≥ 1 ml/min, pH ≥ 6.8 and buffering capacity score ≥ 10 were excluded from data analysis.

Statistical analysis

The sample size and power were calculated by G Power 3.1. Data from 118 patients yield a post-hoc power of 0.95 for repeated measure ANOVA. Graphing and statistical analyses were performed by using Graph Pad Prism 5.0. Descriptive statistics were used to summarize data as followings: mean of subjective and objective dry mouth scores, salivary pH(s) from all patients. The normality of data distributions was verified by the D'Agostino & Pearson omnibus test. Parametric statistical tests were used only when the data passed normality test ($p > 0.05$). Comparisons of subjective and objective dry mouth scores between 2 weeks, 1 month and baseline measurements were analyzed by using repeated measure ANOVA. The Bonferrini tests identified time points with significance differences from the baseline data. Comparisons of changes in salivary pH(s) between OMJ use and non-use periods were analyzed by using Two-way ANOVA, followed by Tukey's multiple comparisons. Comparisons of changes in salivary buffering capacities between "OMJ use" and "OMJ non-use" periods or between patients taking 1 to 2 and 3 to 7 medications were analyzed by chi-square tests. Comparisons of subjective and objective dry mouth scores, and salivary pH(s) at different time points between patients taking 1–2 and 3–7 medications were analyzed by Two-way ANOVA. All tests were performed with two-tailed methods (where possible), $\alpha = 0.05$. p -values < 0.05 were considered statistically significant.

Results

Baseline data

Initially, 126 patients agreed to participate in the study. Finally, completed data were obtained from 118 patients (93.6%). The demographic data and illness characteristics of the patients were shown in Table 1. Seventy one percent of the patients were female with average age of 71.2 years. Ninety-eight percent of the patients were non-smokers. Eighty five percent of the patients had been diagnosed as hypertensive (HT) along with or without diabetes mellitus (DM). Some patients had only DM. Almost fifty percent of the patients were suffering from dyslipidemia and required hypolipidemic drugs; e.g. Simvastatin. Eighty two percent of the patients had taken more than one type of drugs consistently. A calcium channel blocker; i.e. Amlodipine 10 mg and an anti-type 2 diabetic drug; i.e. Metformin 500 mg were most common drugs used for treatment of HT and DM, respectively. At baseline, the patients had signs and symptoms of xerostomia with high average objective and subjective dry mouth scores, respectively. Furthermore, their saliva

Table 1
Descriptive characteristic of the study samples.

Characteristic	N	%	Mean \pm sd.	Range
Age			71.22 \pm 6.8	58–88
Gender				
Female	84	71.19		
Male	34	28.81		
Systemic condition				
Only Hypertension (HT)	73	61.86		
Both HT and DM	28	23.73		
Only Diabetes Mellitus (DM)	13	11.02		
Other e.g. gout, seizure	4	3.39		
With dyslipidemia				
Yes	51	43.22		
No	67	56.78		
Medication(s)				
Single drug ^a	21	17.80		
Combination of two drugs ^b	28	23.73		
Combination of three drugs ^b	32	27.12		
Combination of four drugs ^b	18	15.25		
Combination of five to seven drugs ^b	19	16.10		
Smoking				
Yes	2	1.69		
No	116	98.31		
Baseline subjective dry mouth score (0–10)			5.15 \pm 1.57	3.0–9.2
Baseline objective dry mouth score (0–5)			3.42 \pm 1.01	2.0–5.0
Baseline stimulated salivary flow rate (ml/min)			0.216 \pm 0.118	0.1–0.6
Baseline salivary pH			6.15 \pm 0.34	5.6–6.6
Baseline salivary buffering capacity			5.75 \pm 1.95	2.0–9.0
Oral lesions associated with xerostomia				
Cervical caries	65	55.08		
Coated tongue	56	47.46		
Petechiae	18	15.25		
Fissured tongue	13	11.02		
Depapillated tongue	6	5.08		
Daily water drink (servings/day)			7.36 \pm 2.73	4.0–15.0

^a Included calcium channel blocker (Amlodipine), Beta-adrenergic blocker (Atenolol), Angiotensin converting enzyme inhibitor (Enalapril), Anti-type 2 diabetic (Metformin), Thiazide diuretic (HCTZ), Angiotensin II receptor antagonist (Losartan).

^b Combination between: 1) Calcium channel blockers (i.e. Amlodipine) and other drugs e.g. hypolipidemic (Simvastatin), Anti-type 2 diabetic (Metformin), Anti-platelet (Aspirin (ASA)), Beta-blocker (Atenolol), Diuretic (HCTZ, Furosemide, Moduretic), Vitamin (Folic acid), Anti-gout (Allopurinol), Angiotensin Converting Enzyme Inhibitor (Enalapril), 2) Beta-adrenergic blockers (Atenolol) and other drugs e.g. anti-type 2 diabetic (Glipizide), thiazide diuretic (HCTZ), 3) Hypolipidemic (Simvastatin) and others such as anti-type 2 diabetic (Glibenclamide), Angiotensin II receptor antagonist (Losartan), 4) Diuretic (Furosemide) and Angiotensin converting enzyme inhibitor (Enalapril), 5) Beta-adrenergic blocker (Metoprolol) and thiazide diuretic (Tritazide), 6) Insulin injection (Mixtard 30 HM Penfill) and Minerals (Calcium carbonate).

qualities were poor with abnormally low flow rates, acidic pH(s) and low buffering capacities. Consequently, fifty-five percent of them had cavities at the neck of tooth (cervical caries) and forty-seven percent of them had microbial plaque accumulations on their tongues (tongue coating). Due to their dry mouth problems, the patients drank water frequently and their water intakes ranged from 4 to 15 servings/day.

Satisfaction

As shown in Fig. 1c, sixty-five percent of the patients selected OMJ as their favorite gels, while 35% preferred the commercial artificial saliva gel. The highest preference of OMJ was correlated with easily swallowing, extra deliciousness and more hydrating. An example of quotes from the patients was, “OMJ is my favorite gel because it can be swallowed similar to natural saliva. Compared to the other brand, OMJ keeps mouth and throat more moisten.” At the end of OMJ use period, the patients provided average appreciation score of 7.98 ± 2.6 (out of 10). Examples of quotes from the patients were; “After using OMJ, I don’t choke while eating”; “OMJ is very

helpful. My mouth and throat are no longer dry”; “Previously, frequent water sipping was required when swallowing food. With OMJ, I can freely swallow the food.” Three months later, most patients complained that their dry mouth symptoms returned after stopping OMJ and they had simultaneously requested for OMJ. A great example of quotes from patients was, “Without OMJ, I had dry and sore throat, and excessive coughing with sputum. It was difficult to endure without OMJ and frequent water sipping was required for swallowing of food. I really would like to have OMJ once more.”

Effect of oral moisturizing jelly on subjective and objective dry mouth scores

To evaluate the effects of OMJ on symptoms and signs of xerostomia, subjective and objective dry mouth scores after using OMJ were compared with their baseline scores. As shown in Fig. 3a, the average subjective dry mouth scores had 73% and 88% reduction from their baseline data, after using OMJ for 2 weeks and 1 month, respectively ($p < 0.0001$). The results suggested that the repeated uses of OMJ could significantly decrease the symptoms of dry mouth.

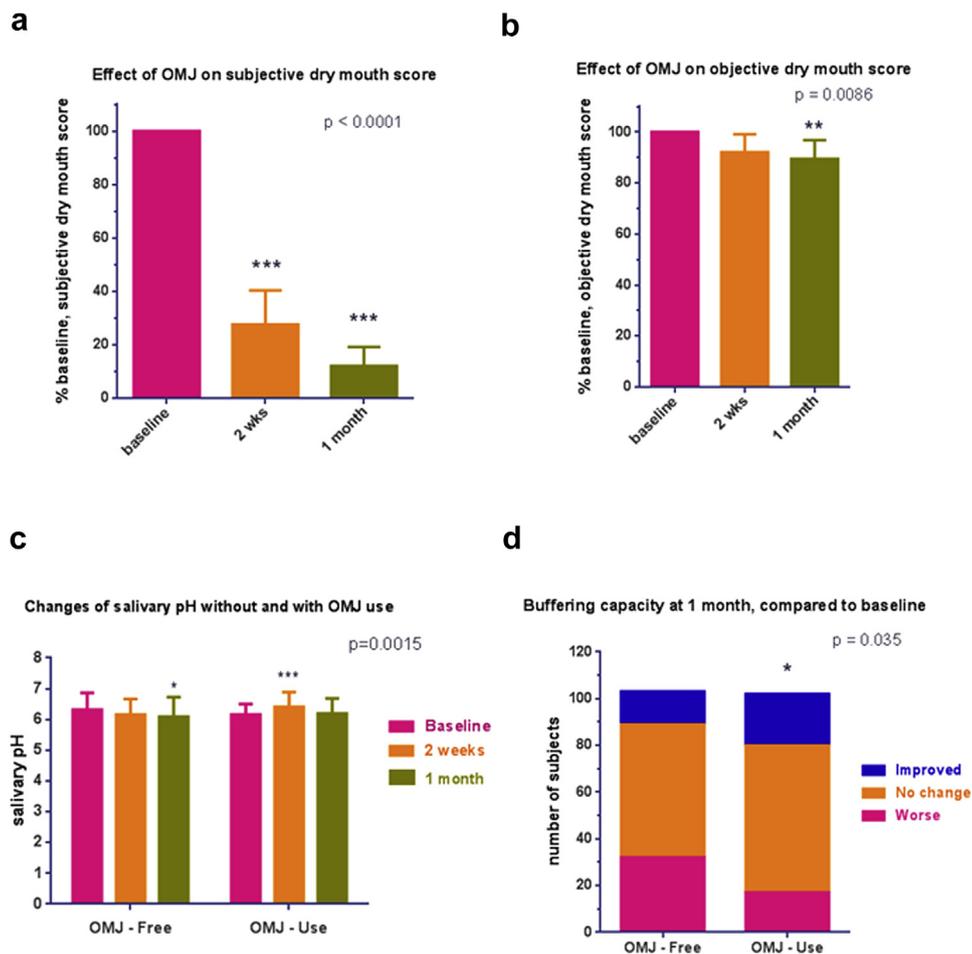


Fig. 3. The effect of OMJ on signs and symptoms of dry mouth and saliva's properties. (a and b) The changes of subjective (a) and objective (b) dry mouth scores during OMJ use period reflected the effect of OMJ on symptoms and signs of dry mouth, respectively. Each bar represented the percentage of the respective scores compared with their baseline scores. Error bars indicated 95% confidence interval. Repeated measured ANOVA tests showed significant changes in subjective ($p < 0.0001$) and objective ($p = 0.0086$) dry mouth scores, compared with baseline data. Bonferrini tests identified time points with significant differences from baseline. (***) = $p < 0.001$; (**) = $p < 0.01$; (*) = $p < 0.05$; (****) = $p < 0.0001$. (c) Comparisons of salivary pH(s) between OMJ use and OMJ non-use periods. Each bar represented the mean of salivary pH(s) at various time points; pink = baseline, orange = 2 weeks, green = 1 month. Error bars indicated 95% confidence interval. Two-way ANOVA showed a significant difference between the periods ($p = 0.0015$). Tukey's tests identified time points with significant differences from baseline. (*) = $p < 0.05$; (****) = $p < 0.0001$. (d) Comparisons of buffering capacities in all patients between OMJ use and OMJ non-use periods. Each stacked bar represented the percentage of patients who had improved (blue), unchanged (orange) and worse (pink) buffering capacities during 1 month of OMJ use or OMJ non-use periods. The chi-square test showed a significant difference between the two periods ($p = 0.035$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Interestingly, as shown in Fig. 3b, there was about 16% reduction of objective dry mouth scores ($p < 0.0086$), after using OMJ for 1 month, while its 2-week use showed a slight (but not significant) decrease of dry mouth signs. These results suggested that the alleviation of dry mouth signs required repeated uses of OMJ for at least 1 month.

Effect of oral moisturizing jelly on saliva's properties

Since all patients were allowed to take their medications for hypertension/diabetes mellitus during 'OMJ use' period, their saliva properties could be fluctuated. To evaluate the actual effect of OMJ on saliva's properties, their changes in salivary pH(s) and buffering capacities were compared between OMJ use and OMJ non-use periods within the same patients. As shown in Fig. 3c, the mean salivary pH(s) were decreased in a time-dependent manner and become significantly decreased at 1 month during OMJ non-use period. In contrast, the average salivary pH(s) were not decreased during "OMJ use" period. Interestingly, the significant increase in salivary pH(s) toward the normal level was noted after using the OMJ for 2 weeks. Two-way ANOVA analyses showed that salivary pH(s) of OMJ use period were significantly better than that of OMJ non-use period ($p = 0.0015$). Similarly, as shown in Fig. 3d, the number of patients with worse buffering capacities was decreased from thirty two percent in OMJ non-use period, to fifteen percent in OMJ use period. Furthermore, the number of patients with improved

buffering capacities was increased from ten percent in OMJ non-use period, to twenty percent in OMJ use period. Statistical analyses showed that salivary buffering capacities of OMJ use period were significantly better than that of OMJ non-use period ($p = 0.035$). Since the patients were a mixed group of very low- (score 0–5) and low- (score 6–9) baseline buffering capacities, separate analyses for each group were performed. As shown in Fig. 4, in the very-low-baseline group salivary buffering capacities after using OMJ for both 2 weeks and 1 month were significantly better than that of OMJ non-use period. In contrast, in the low-baseline group the significance was found only after using OMJ for 1 month. These results suggested that the patients with very-low-baseline buffering capacities were more responsive to OMJ. A slight increase in the salivary flow rates was observed after OMJ use. The average salivary flow rates after 2 week and 1 month OMJ uses were 0.69 ± 0.53 ml/min and 0.75 ± 0.57 ml/min, respectively, while that of baseline was 0.63 ± 0.51 ml/min. However, statistical analyses showed that these differences were not significant ($p = 0.2782$, Kruskal–Wallis test).

Effect of OMJ in the patients based on the number of their medications

The patients were stratified into two groups based on the number of medications consumed by the patients: (1) taking 3–7 medications ($n = 69$), (2) taking 1–2 medications ($n = 49$). To

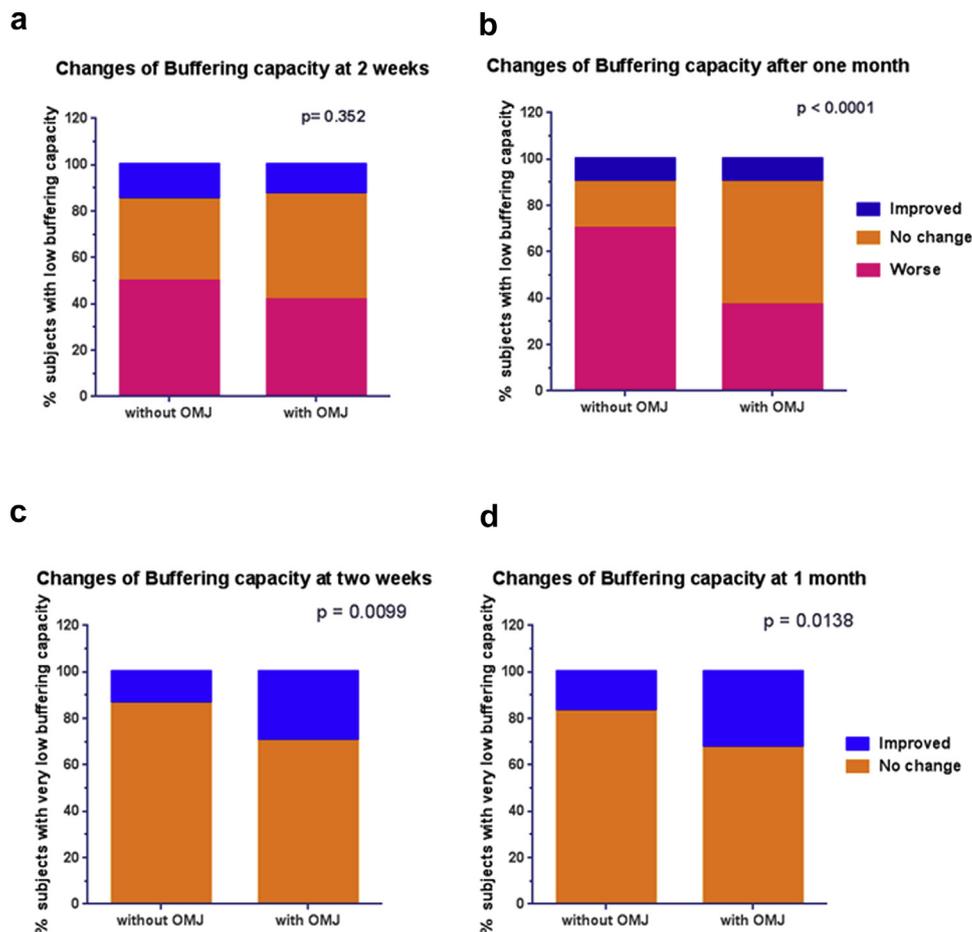


Fig. 4. The effect of OMJ on saliva buffering capacity. Comparisons of buffering capacities between OMJ use and OMJ non-use periods in elderly patients, with low (a and b) and very low (c and d) baseline buffering capacities. (a and b) Each stacked bar represented the percentage of patients who had improved (blue), unchanged (orange) and worse (pink) buffering capacities, during 2 weeks (a) and 1 month (b) of OMJ use or OMJ non-use periods. (c and d) Each stacked bar represented the percentage of patients who had improved (blue) and unchanged (orange) buffering capacities, during 2 weeks (c) and 1 month (d) of OMJ use or OMJ non-use periods. p -value(s) calculated from chi-square tests were shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

investigate whether the number of medications had any effects on the efficacy of OMJ, the changes in subjective and objective dry mouth scores, salivary pH(s) and buffering capacities during 'OMJ use' period were compared between the two groups. As shown in Fig. 5, OMJ was very effective in both groups. No significant differences were noted between the two groups after using the OMJ. The buffering capacities were significantly improved in both groups after using OMJ for 2 weeks, as compared to OMJ non-use period (Fig. 6a). In addition, the improved buffering capacities were noted in the 1-2-medication group after using OMJ for 1 month (Fig. 6b right). While in case of the 3–7-medication group, the buffering capacities at 1 month were improved but not significantly, when compared to OMJ non-use period (Fig. 6b left). These results suggested that OMJ might be effective regardless of the number of medications.

Intervention fidelity

To ensure treatment fidelity according to NIH Behavioral Change Consortium (BCC),²⁴ treatment designs for dose, duration and outcome measures were reviewed and agreed by a team of six professional dentists. All patients visited the same hospital for data collections on the same day. On each visit, the data were collected by the same team of researchers to ensure the consistency of the protocol. The assessments of all parameters on each visit were performed by the same researchers in all patients (one researcher for each parameter). The same team of researchers collected data of subjects from the two different hospitals. To enhance the adherence of intervention deliveries, a food sensory testing was performed at the first visit. All patients had few spoons of OMJ (both flavors) and selected their favorite one for further home use.

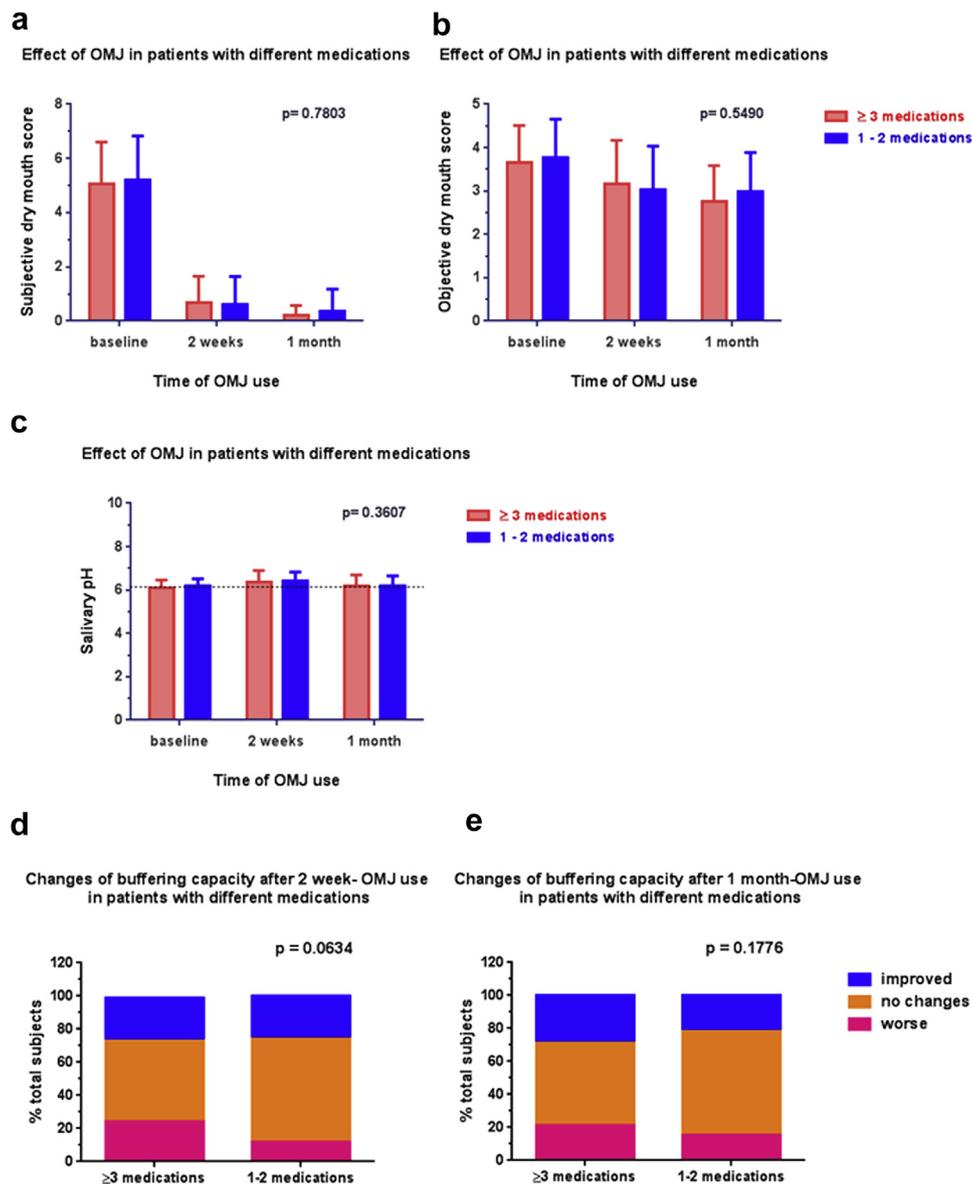


Fig. 5. Comparisons of OMJ effects between patients taking 3–7 medications ($n = 69$) and those taking 1–2 medications ($n = 49$). (a and c) Comparisons of changes in subjective (a) and objective (b) dry mouth scores and salivary pH(s) (c) during OMJ use period, between patients taking 3–7 medications (red bar) and those taking 1–2 medications (blue bar). Each bar represented the mean of respective scores at various time points. Error bars indicated standard deviations. Two-way ANOVA showed no significant differences between the two groups in either subjective or objective scores ($p = 0.7803, 0.549, 0.3607$, respectively). (d and e) Comparisons of changes in buffering capacities of patients after using OMJ for 2 weeks (d) and 1 month (e), between patients taking 3–7 medications and those taking 1–2 medications, as labeled. Each stacked bar represented the percentage of patients who had improved (blue), unchanged (orange) and worse (pink) buffering capacities. p -value(s) calculated from chi-square tests were shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

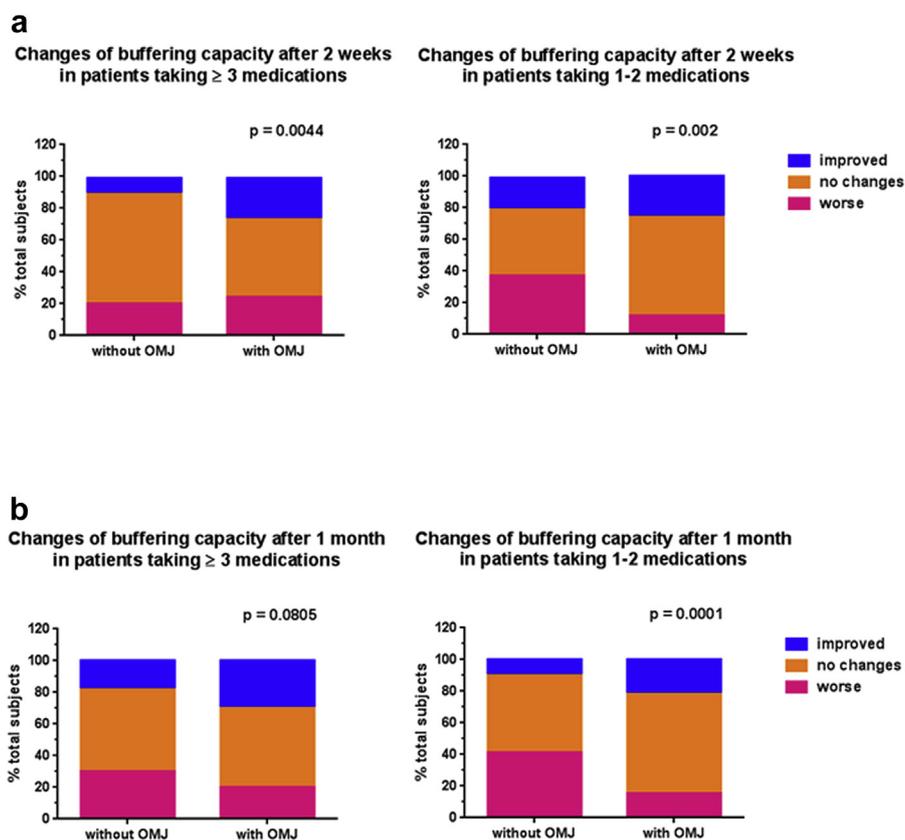


Fig. 6. The effect of OMJ on saliva buffering capacities in patients taking 3–7 medications and those taking 1–2 medications. Comparisons of changes in the buffering capacities between OMJ use and OMJ non-use periods after 2 week (a) and 1 month (b). Each stacked bar represented the percentage of patients who had improved (blue), unchanged (orange) and worse (pink) buffering capacities, in patients taking 3–7 medications (left) and those taking 1–2 medications (right). *p*-value(s) calculated from chi-square tests were shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Instructions for using OMJ were carried by a researcher for all patients to ensure consistent deliveries. The treatment receipts (their uses of OMJ) were evaluated by patient diaries (daily records) and patients' interviews at follow-up visits. The treatment enactment focused on the degree to which the patients continuously received OMJ and returned for dental follow-up visits. Among 126 patients agreed to be enrolled in this study, 118 patients (93.6%) returned for complete follow-up visits and reported continuous daily intake of 50 ml (10 ml \times 5 times) of OMJ. However, a very small percentage of patients did not adhere to protocols and did not return for follow-up visits.

Discussion

Dry mouth is a critical problem in elderly people with poly pharmacy. It could increase the risk of oral diseases, taste dysfunctions, chewing and swallowing difficulties, speech problems and poor qualities of life.^{25,26} Intra-oral topical agents are among the most commonly recommended treatments for the management of xerostomia.²⁷ Currently, no interventions were proven effective in elderly people diagnosed with systemic diseases.^{7,8} In general, xerostomia causes dryness in both oral and oropharyngeal mucosa(s), and currently available saliva substitutes are preservative-containing and unsuitable to eat.²⁸ Therefore, they lack bathing effect to oropharynx and their efficacies are limited. Recently, "oral moisturizing jelly (OMJ)," a novel edible gel, was developed to overcome these limitations.¹³ In this study, a pre-post design was conducted in 118 older people taking medications for hypertension and/or diabetes mellitus. Continuous daily uses of

OMJ for 1 month were found to reduce signs and symptoms of dry mouth and improved the saliva's qualities of elderly patients. Furthermore, OMJ was equally effective in patients taking various medications. This intriguing findings of this investigation demand further randomized control studies.

The efficacy of OMJ more likely resulted from its unique physical and biochemical properties. Unlike other available saliva substitutes, OMJ is edible, easy-to-swallow and hydrating to mouth and throat.¹³ The design of OMJ's consistency was based on an insight from research and development of Nutri-jelly, a food gel suitable for cancer patients with chewing and swallowing difficulties.^{15,16} According to National Dysphagia Diet (NDD) standards for texture modified diets,¹⁸ the consistencies of Nutri-jelly and OMJ were likely NDD level 1. Since Nutri-jelly was proved edible by head and neck cancer patients with swallowing difficulties,¹⁶ OMJ might also be suitable for individuals with chewing or swallowing difficulties. Since older people often had chewing and swallowing difficulties due to tooth loss and dry mouth,²⁹ future studies should address the effects of OMJ on the improvement of dietary intake in dysphagic older patients.

The moisturizing effect of OMJ more likely resulted from syn-eresis property; i.e. the release of water from gel upon biting or spooning,¹⁴ which rehydrated the dry mouth.¹³ This was consistent with a previous report showing that the gel formulation appeared to be the most efficient and appreciated by patients among other oral lubricants.³⁰ In addition, the 3-h mouth retention property of OMJ likely allowed continuously hydrating and buffering effects, as shown in other oral care products.³¹ The use of OMJ for 1 month significantly improved the buffering capacities, when compared to

OMJ non-use period. This finding suggested an efficacy of OMJ. However, it is worth noting that the major proportion of the patients remained unchanged in their buffering capacities after using OMJ (Figs. 3d and 4). This is more likely due to the lack of bicarbonate buffering agents in the OMJ product. Dry mouth problems in the patients of the current study were mainly caused by the side effects of anti-hypertensive/anti-diabetic drugs on autonomic nervous systems.³² The autonomic nerves stimulate the release of parotid saliva containing bicarbonate buffer. These medications affect the autonomic nervous system and thereby decrease the release of bicarbonate in the saliva.³³ Currently, OMJ contains only phosphate but not bicarbonate buffer systems. Thus, future research to improve the efficacy of OMJ should consider including bicarbonate buffer into this product.

A similar attempt to use a saliva gel in elderly people with abnormal salivary flow rates and buffering capacities had been made. Unfortunately, no significant results were obtained. For example, a prophylactic gel effective in adults with normal salivary secretion failed to alleviate dry mouth in patients with polypharmacy.³⁴ The authors discussed that the problems were caused by the lack of compliances due to the changeover of personnel/or the inconvenience of uses during weekend travels.³⁴ In this pre-post study, the success of intervention likely resulted from the appreciations and adherences of the patients to the continuous daily uses of OMJ, evidenced by the high appreciation scores and the high follow-up returns.

Conclusion

Continuous daily uses of OMJ for 1 month reduced the signs and symptoms of xerostomia and improved saliva's properties of the elderly patients who were taking multiple medications. OMJ is a new edible salivary substitute with potential clinical applications, and thus deserving further exploration in a larger population with a randomized-controlled design.

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References

- Mortazavi H, Baharvand M, Movahhedian A, et al. Xerostomia due to systemic disease: a review of 20 conditions and mechanisms. *Ann Med Health Sci Res.* 2014;4(4):503–510.
- Gupta A, Epstein JB, Sroussi H. Hyposalivation in elderly patients. *J Can Dent Assoc.* 2006;72(9):841–846.
- Liu B, Dion MR, Jurasic MM, et al. Xerostomia and salivary hypofunction in vulnerable elders: prevalence and etiology. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;114(1):52–60.
- Gerdin EW, Einarson S, Jonsson M, et al. Impact of dry mouth conditions on oral health-related quality of life in older people. *Gerodontology.* 2005;22(4):219–226.
- Cho EP, Hwang SJ, Clovis JB, et al. Enhancing the quality of life in elderly women through a programme to improve the condition of salivary hypofunction. *Gerodontology.* 2012;29(2):e972–e980.
- Turner MD, Ship JA. Dry mouth and its effects on the oral health of elderly people. *J Am Dent Assoc.* 2007;138(suppl):155–20S.
- von Bültzingslöwen I, Sollecito TP, Fox PC, et al. Salivary dysfunction associated with systemic diseases: systematic review and clinical management recommendations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(suppl):S57.e1–S57.e15.
- Furness S, Worthington HV, Bryan G, et al. Interventions for the management of dry mouth: topical therapies. *Cochrane Database Syst Rev.* 2011;12:CD008934.
- Bakarman EO, Keenan AV. Limited evidence for non-pharmacological interventions for the relief of dry mouth. *Evid Based Dent.* 2014;15(1):25–26.
- Dost F, Farah CS. Stimulating the discussion on saliva substitutes: a clinical perspective. *Aust Dent J.* 2013;58(1):11–17.
- Kikawada M, Iwamoto T, Takasaki M. Aspiration and infection in the elderly: epidemiology, diagnosis and management. *Drugs Aging.* 2005;22(2):115–130.
- Halpern BP. Tasting and smelling as active, exploratory sensory processes. *Am J Otolaryngol.* 1983;4(4):246–249.
- Kongkaew W. *Development of Artificial Saliva Gel for Hyposalivation and Xerostomia Patients* [Thesis]. Mahidol University; 2014.
- Kunitz M. Syneresis and swelling of gelatin. *J Gen Physiol.* 1928;12(2):289–312.
- Kanjanatiwat P. *Development of Nutritious Gel for Patients With Chewing and Swallowing Difficulties* [Thesis]. Mahidol University; 2013.
- Trachootham D, Songkaew W, Hongsachum B, et al. Nutri-jelly may improve quality of life and decrease tube feeding demand in head and neck cancer patients. *Support Care Cancer.* 2015;23(5):1421–1430.
- Han P, Suarez-Durall P, Mulligan R. Dry mouth: a critical topic for older adult patients. *J Prosthodont Res.* 2015;59(1):6–19.
- National Dysphagia Diet: Standardization for Optimal Care.* Chicago: American Dietetic Association; 2002.
- Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39:175–191.
- Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91(3):311–316.
- Osailan S, Pramanik R, Shirodaria S, et al. Investigating the relationship between hyposalivation and mucosal wetness. *Oral Dis.* 2011;17(1):109–114.
- Mahesh DR, Komali G, Jayanthi K, Dinesh D, Saikavitha TV, Dinesh P. Evaluation of salivary flow rate, pH and buffer in pre, post & post menopausal women on HRT. *J Clin Diagn Res.* 2014;8(2):233–236.
- Maldupa I, Brinkmane A, Mihailova A. Comparative analysis of CRT Buffer, GC saliva check buffer tests and laboratory titration to evaluate saliva buffering capacity. *Stomatologia.* 2011;13(2):55–61.
- Bellg AJ, Borrelli B, Resnick B, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. *Health Psychol.* 2004;23(5):443–451.
- Singh ML, Papas A. Oral implications of polypharmacy in the elderly. *Dent Clin North Am.* 2014;58(4):783–796.
- Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AM. Associations between labial and whole salivary flow rates, systemic diseases and medications in a sample of older people. *Community Dent Oral Epidemiol.* 2010;38(5):422–435.
- Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. *Ther Clin Risk Manag.* 2014;11:45–51.
- Visvanathan V, Nix P. Managing the patient presenting with xerostomia: a review. *Int J Clin Pract.* 2010;64(3):404–407.
- Yiengprugsawan V, Somkotra T, Seubsman SA, et al. Longitudinal associations between oral health impacts and quality of life among a national cohort of Thai adults. *Health Qual Life Outcome.* 2013;11:172.
- Furumoto EK, Barker GJ, Carter-Hanson C, et al. Subjective and clinical evaluation of oral lubricants in xerostomic patients. *Spec Care Dentist.* 1998;18(3):113–118.
- Gaffar A, Hunter CM, Mirajkar YR. Applications of polymers in dentifrices and mouthrinses. *J Clin Dent.* 2002;13(4):138–148.
- Moore PA, Guggenheimer J. Medication-induced hyposalivation: etiology, diagnosis, and treatment. *Compend Contin Educ Dent.* 2008;29(1):50–55.
- Almståhl A, Wikström M. Electrolytes in stimulated whole saliva in individuals with hyposalivation of different origins. *Arch Oral Biol.* 2003;48(5):337–344.
- Persson A, Lingström P, Bergdahl M, et al. Buffering effect of a prophylactic gel on dental plaque in institutionalised elderly. *Gerodontology.* 2007;24(2):98–104.