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Safety and effectiveness of topical dry mouth products containing olive oil, betaine, and xylitol in reducing xerostomia for polypharmacy-induced dry mouth

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SUMMARY Polypharmacy is a common cause of salivary hypofunction, producing symptoms of dry mouth or xerostomia, especially among older populations. As the number of older people continues to increase, polypharmacy-induced salivary hypofunction is becoming an increasing problem. Many over-the-counter products are available for relieving symptoms of dry mouth, but few have been tested in controlled clinical investigations. The purpose of this investigation was to evaluate the safety and efficacy of a group of topical dry mouth products (toothpaste, mouth rinse, mouth spray and gel) containing olive oil, betaine and xylitol. Forty adults were entered into this single-blinded, open-label, cross-over clinical study and 39 completed all the visits. Subjects were randomly assigned at baseline to using the novel topical dry mouth products daily for 1 week, or to maintain their normal dry mouth routine care. After 1 week, they were crossed over to the other dry mouth regimen. The results demonstrated that the use of the novel topical dry mouth products increased significantly unstimulated whole salivary flow rates, reduced complaints of xerostomia and improved xerostomia-associated quality of life. No clinically significant adverse events were observed. These data suggest that the daily use of topical dry mouth products containing olive oil, betaine and xylitol is safe and effective in relieving symptoms of dry mouth in a population with polypharmacy-induced xerostomia.

KEYWORDS: xerostomia, salivary hypofunction, dry mouth, polypharmacy, olive oil, betaine, xylitol

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Introduction

Saliva is an essential component for the maintenance of normal oral health (1, 2). Decreased saliva production results in difficulties in speech, mastication, swallowing, changes in taste, new and recurrent dental caries, impaired use of removable prostheses, microbial infections, unpleasant breath, deterioration of soft tissues and a compromised quality of life (3–6). While it was previously thought that decreased salivary function was a normal part of the ageing process, recent evidence demonstrates that most salivary loss is due to local and systemic diseases, immunologic disorders, external beam radiation, and multiple prescription and non-prescription medications (3, 7–10). The most common cause of salivary hypofunction and xerostomia (subjective complaint of a dry mouth), particularly in older aged populations, is polypharmacy-induced salivary hypofunction (11–14).

It is difficult to determine the global estimates of xerostomia and salivary gland dysfunction because of limited epidemiological studies, yet it is probable that ~30% of the population aged 65+ years experiences these disorders (15). Furthermore, because of the growing population of older adults, many of whom are susceptible to salivary gland disorders, xerostomia and its concomitant oral-pharyngeal sequelae will become increasingly more prevalent (15, 16).

Treatment of salivary hypofunction and xerostomia can be accomplished by multiple approaches,

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depending upon the aetiology of the disorder (17). Chewing gum (18–20), sugarfree lozenges (21), salivary substitutes and moisturizers (20, 22–24), toothpastes (25), intra-oral stimulatory devices (26), acupuncture (27) and cholinergic agonists (28) have all demonstrated some ability to improve xerostomia and promote salivary function, depending upon the underlying aetiology and the degree of salivary dysfunction. However, each technique has its drawbacks (29). Cholinergic agonists have side effects and are contraindicated for certain concomitant medical disorders; salivary glands may be severely atrophic and non-responsive to stimulants. It is not always feasible to continually sip water during the day, and not everyone enjoys chewing gum (15). Furthermore many medicaments have limited access for purchase (30).

Salivary-promoting oral moisturizers represent a strategy for reduction of xerostomic complaints in a wide variety of dry mouth patients. Three topical oral medicaments have been formulated together to develop a novel mouth rinse to reduce xerostomia. Olive oil has oral lubricating properties (31), betaine (a naturally-occurring amino acid and wetting agent) has been associated with improving symptoms of dry mouth (25, 32–34), and xylitol is a valuable asset in combating dental caries (35). The purpose of this investigation was to examine the safety and efficacy of topical dry mouth products containing olive oil, betaine and xylitol in a population of adults experiencing polypharmacy-induced salivary hypofunction and xerostomia. The null hypothesis was that there would be no difference in dry mouth symptoms in subjects using the novel topical dry mouth products (Xerostom®* products) compared with subjects' regular dry mouth routine.

Materials and methods

Subjects

The study was reviewed and approved by the Institutional Review Board (IRB) in accordance with the Code of Ethics of the Declaration of Helsinki (36). A total of 40 participants (25 female and 15 male) were recruited and enrolled from the general population aged 50–67 years [60·6 ± 6·7 years; mean ± standard deviation (s.d.)]. All subjects reported a history of dry mouth symptoms because of polypharmacy. All subjects were screened according to the inclusion/exclusion criteria described below; subjects who matched were given an IRB-approved consent form to review and sign by a study-dedicated clinical research coordinator. Subjects were randomly divided into two groups; one group ($n = 20$) continued their current dry mouth routine for 7 days, while the other group ($n = 20$) received topical dry mouth products containing olive oil, betaine and xylitol (Xerostom®* products) to be used for 7 days.

Inclusion criteria

1 Subjects with a complaint of dry mouth as assessed by a response of 30 mm or greater on at least one of eight Dry Mouth Visual Analogue Scale (VAS) questions (37).
2 Subjects with an unstimulated whole salivary flow rate of ≤0·2 mL min^{-1} (38).
3 Subjects between 50 and 90 years of age.
4 Subjects taking a minimum of three drugs associated with causing salivary hypofunction or xerostomia (e.g. anxiolytics, anorexiants, anti-asthmatics, anti-cholinergics, anti-depressants, anti-emetics, anti-histamines, anti-hypertensives, anti-parkinsonians, anti-psychotics, decongestants, diuretics and sedatives) (39).
5 Subjects taking these medications (no. 4 above) for at least 1 week prior to study initiation and expected to be taking them for the duration of the study.
6 Subjects willing to use only the novel topical dry mouth products for dry mouth symptoms during that phase of the study.
7 Subjects willing to return for all study-associated visits.
8 Subjects able to read, understand and sign the IRB-approved informed consent form.

Exclusion criteria

1 Subjects who had received radiation therapy to the head and neck region.
2 Subjects with Sjögren's syndrome (40).
3 Subjects with insufficient manual dexterity to use the products appropriately.
4 Subjects unable to read and understand the consent form.
5 Subjects using any prescription medication for their dry mouth condition (pilocarpine, cevimeline) within 7 days prior to entrance into the study.

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6 Subjects requiring dental-alveolar surgery or extensive dental treatment during the course of the study.
7 Subjects requiring hospitalization for any medical problem during the course of the study.
8 Subjects with uncontrolled medical conditions that could interfere with study outcomes.
9 Subjects with an uncontrolled medical condition that required changes in medications during the course of the study.

Baseline measurements

Unstimulated whole saliva was collected by a previously described protocol (41) and a comprehensive standardized oral tissue exam was performed. All subjects were seen between 8 AM and noon after a 2 h fast during which eating, drinking, performing oral hygiene, smoking, chewing gum and using mints were prohibited. An eight item 100 mm dry mouth VAS questionnaire (37) and a xerostomia-related quality of life questionnaire were administered (42) by a single, study-dedicated research coordinator.

Study products

Topical dry mouth products (tooth paste, mouth rinse, spray and gel) containing three active ingredients (olive oil, betaine and xylitol) were used in this investigation (Xerostom®* products). Xerostom®* ingredients are formulated at a neutral pH, have a mild lemon aroma, and include olive oil, betaine, xylitol, fluoride, vitamin E and vitamin B5. Olive oil helps ameliorate oral conditions commonly found in dry mouth patients. It has anti-inflammatory (43), anti-microbial (44) and oral lubricating properties (31). Olive oil has inhibitory effects on cariogenic bacterial growth (45), assists in controlling oral malodour (46) and can reduce tooth demineralization (47). Its greatest value may be due to olive polyphenols that contribute to the modulation of the oxidative balance and are considered safe at high levels (48). Xylitol has proven anti-caries activity (35, 49), and vitamin E may help reduce mucosal irritation (50). Betaine (trimethylglycine) is a naturally-occurring amino acid in humans (51, 52). It has been demonstrated to reduce skin-irritating effects typically found in mouth products using sodium-lauryl-sulphate, and has been associated with improving symptoms of dry mouth (25, 32–34).

Study design

Subjects were randomized to receiving Xerostom®* products first, or to continue in their normal daily regimen for dry mouth. The Xerostom®* regimen consisted of: (i) use of the tooth paste/mouth rinse three times daily after main meals, (ii) use of the spray and gel between meals and as often as desired, but a minimum of eight times daily. Subjects on the Xerostom®* regimen kept a product use diary and compliance was determined to be >80% of the recommended daily use. Subjects in the normal daily regimen group were instructed to continue their everyday typical practices for the treatment of dry mouth, excluding any use of pharmacological stimulants. A product use diary was also kept by these subjects. On day 8, all subjects returned to the research centre, baseline measurements were repeated and records of any adverse events were taken.

Cross-over subjects in the normal dry mouth regimen group were then placed on the Xerostom®* regimen, while subjects in the Xerostom®* regimen were given instructions to discontinue the use of the Xerostom®* products and instructed not to use any dry mouth products (washout period). On day 15, all subjects returned to the research centre, baseline measurements were repeated and records of any adverse events were taken. Subjects who were initially in the no treatment group were dismissed from the study. Subjects who completed that washout week were instructed to resume their normal daily regimen and initiate their everyday typical practices for the treatment of dry mouth, excluding any use of pharmacological stimulants. A product use diary was also kept by these subjects. On day 22, this group returned to the research centre, baseline measurements were repeated and records of any adverse events were taken. Afterwards these subjects were also dismissed from the study.

VAS questionnaire

A validated VAS questionnaire was used which contains eight items regarding oral dryness (37). Subjects were asked to mark a vertical line through a 100 mm horizontal line to indicate their level of dryness. Two of the items (nos 2, 3) have been correlated with objective findings of salivary gland hypofunction (53). Three of the items (nos 6,7 and 8) have been previously used in the investigations of dry mouth (53, 54), and dryness of

lips (no. 6) successfully predicted salivary gland hypofunction (55). The eight items were:

1 Rate the difficulty you experience in speaking because of dryness.
2 Rate the difficulty you experience in swallowing because of dryness.
3 Rate how much saliva is in your mouth.
4 Rate the dryness of your mouth.
5 Rate the dryness of your throat.
6 Rate the dryness of your lips.
7 Rate the dryness of your tongue.
8 Rate the level of your thirst.

Xerostomia-related quality of life questionnaire

The validated xerostomia-related quality of life questionnaire (42) includes 15 questions regarding how dry mouth affects a person's quality of life, with subdivisions for the four major domains of quality of life: physical function, personal function, social function and pain. The questions were:

1 My mouth/throat dryness limits the kinds or amounts of food I eat.
2 My mouth/throat dryness causes discomfort.
3 My mouth/throat dryness causes a lot of worry or concern
4 My mouth/throat dryness keeps me from socializing (going out).
5 My mouth/throat dryness makes me uncomfortable when eating in front of other people.
6 My mouth/throat dryness makes me uncomfortable speaking in front of other people.
7 My mouth/throat dryness makes me nervous.
8 My mouth/throat dryness makes me concerned about the looks of my teeth and mouth.
9 My mouth/throat dryness keeps me from enjoying life.
10 My mouth/throat dryness interferes with my daily activities.
11 My mouth/throat dryness interferes with my intimate relationships.
12 My mouth/throat dryness has a bad effect on tasting food.
13 My mouth/throat dryness reduces my general happiness with life.
14 My mouth/throat dryness affects all aspects of my life.
15 If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?

Five response categories are used for items 1–14: (i) not at all, (ii) a little, (iii) somewhat, (iv) quite a bit and (v) very much. For item 15, five different responses were used: (i) delighted, (ii) mostly satisfied, (iii) mixed satisfied/dissatisfied, (iv) mostly dissatisfied and (v) terrible.

Statistical analyses

Data were entered and checked into a password protected data base. Baseline demographic characteristics were computed, and comparisons conducted between the two groups randomized at baseline with Student's *t*-tests. Paired *t*-test analyses were performed for salivary flow rates and responses to the two questionnaire measurements for the group using Xerostom®* products compared with the group using their normal dry mouth routine. As the study was a cross-over design during which one group received the Xerostom®* products during week 1, while the other group received the Xerostom®* products during week 2, some programming was necessary to select responses during Xerostom®* products use at weeks 1 and 2 and combine them as one field to test the hypothesis. Analyses were carried out using SAS version 9[†]. A *P*-value was accepted for statistical significance at $P \leq 0{\cdot}05$.

Results

Forty subjects were randomized upon entry into the study and 39 subjects completed all visits. The one subject did not return for his last visit resulting in 14 males and 25 females who completed the study. At baseline the two groups (Xerostom®* products, normal dry mouth routine) had similar mean ages (58·9 and 62·3 years, respectively; $P > 0{\cdot}05$). There were 19 Caucasians, 18 African-Americans and three Hispanics. Subjects were taking between 3 and 21 prescription medications and between 3 and 13 medications associated with salivary hypofunction or xerostomia. The numbers of xerostomic medications used at baseline by those who began the Xerostom®* regime ($5{\cdot}1 \pm 2{\cdot}5$, mean $\pm$ s.d.) were similar to those who continued their normal dry mouth routine ($4{\cdot}4 \pm 1{\cdot}4$, mean $\pm$ s.d.; $P > 0{\cdot}05$).

Initially the baseline unstimulated whole salivary flow rates were compared between the two groups to assure that the randomization did not result in initial

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differences before the start of therapy. The analysis of variance indicated that at baseline (day 0), there were no statistically significant differences in mean unstimulated whole salivary flow rates for the subjects who began using the Xerostom®* regime (0·046 mL min^{-1}) versus those who continued their normal dry mouth routine (0·047 mL min^{-1}).

Paired *t*-test analyses were then used to test the hypothesis. Results showed that the use of Xerostom®* products for 1 week resulted in a significantly greater increase in unstimulated whole salivary flow rates than subjects' normal dry mouth routine for 1 week ($P = 0·033$). In the Xerostom®* products group, flow rates increased from a baseline of 0·05 ± 0·05 mL min^{-1} (mean ± s.d.) to 0·140 ± 0·26 mL min^{-1} (mean ± s.d.) during the week when they used Xerostom®* products (Fig. 1), while flow rates in those subjects using normal dry mouth routine products remained the same over the 7-day period (0·047 ± 0·05 mL min^{-1} vs. 0·05 ± 0·05 mL min^{-1}; mean ± s.d.).

Dry mouth symptoms were assessed by an eight-item VAS questionnaire, and the results demonstrated that use of the Xerostom®* products produced greater ($P = 0·011$) overall improvement compared with subjects' normal dry mouth routine for the same period of time (Fig. 2). All eight individual VAS items demonstrated improvement in both groups, but there was greater improvement in the Xerostom®* product group. Three of the eight items (overall dryness of the mouth, tongue dryness and level of thirst) demonstrated significantly greater improvements in the Xerostom®* products group: overall dryness of the mouth ($P = 0·038$), overall dryness of the tongue ($P = 0·002$) and level of thirst ($P = 0·0001$).

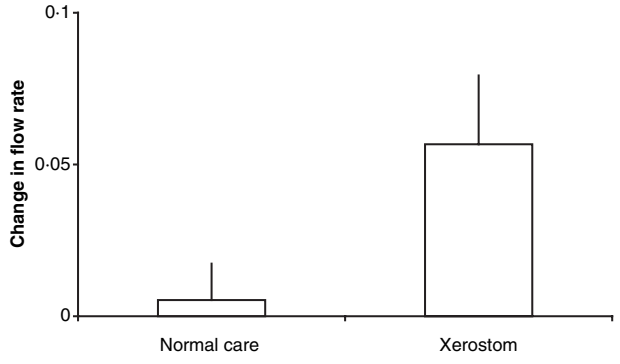

Fig. 1. Change in unstimulated whole salivary flow rates over 1 week in subjects who used novel topical dry mouth products (Xerostom®*) compared with the same subjects who used their normal daily dry mouth products. Results expressed as mean ± standard deviation. Differences between groups are statistically significant at $P = 0·033$.

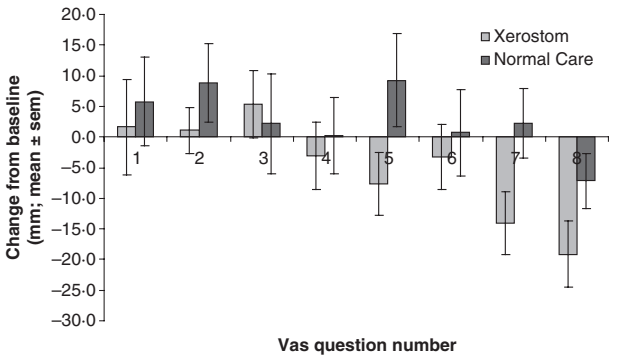

Fig. 2. Change in xerostomic complaints [eight Visual Analogue Scale (VAS) items] over 1 week in subjects who used novel topical dry mouth products (Xerostom®*) compared with the same subjects who used their normal daily dry mouth products. Positive changes in VAS results denoted greater xerostomic complaints, negative changes denoted decreased xerostomic complaints, and zero changes denoted no changes in xerostomic complaints. Results expressed as mean ± standard error of the mean. Statistically-significant differences between groups were detected for overall dryness of the mouth (no. 4), tongue dryness (no. 7) and level of thirst (no. 8).

To determine if baseline total medications or total xerostomic medications influenced changes in VAS scores, the analysis of covariance was conducted on each of the above analyses while controlling for total number of baseline xerostomic medications. The results demonstrated that statistics for all eight VAS items reported above did not change as the covariate was not significant ($P > 0·05$). The same analysis of covariance was conducted on each of the above analyses while controlling for total number of baseline medications. The results indicated that the total number of medications was not related to any of the VAS change scores ($P > 0·05$).

The effect of xerostomia on a subject's quality of life was assessed with a 15-item survey, and overall, results demonstrated a greater improvement in the group that used the Xerostom®* products regimen compared with their normal dry mouth routine (Fig. 3). The overall changes for 15 items combined did not demonstrate significant differences between the two groups ($P = 0·17$), yet 14 of 15 items favoured the Xerostom®* product groups, with four items showing statistical significance ($P < 0·05$) and two items showing borderline significance ($P < 0·10$). A subsequent analysis

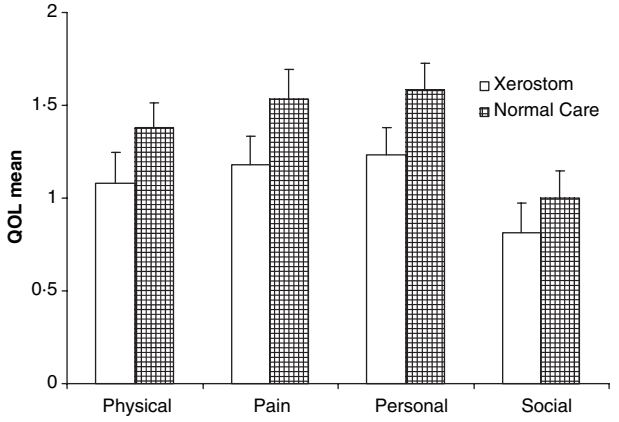

Fig. 3. Change in xerostomia-related quality of life over 1 week in subjects who used novel topical dry mouth products (Xerostom®*) compared with the same subjects who used their normal daily dry mouth products. Results expressed as mean ± standard deviation. Statistically-significant differences between groups were detected for physical function ($P = 0{\cdot}03$), pain ($P = 0{\cdot}03$) and personal function ($P = 0{\cdot}01$), but not for social function ($P = 0{\cdot}2$).

categorized the 15 items into the four primary quality of life areas (42). Three of the areas demonstrated significantly greater improvement after the use of Xerostom®* products compared with normal dry mouth routine: physical function (items: 1, 6, 10 and 12; $P = 0{\cdot}03$), pain (items: 2, 3, 7 and 9; $P = 0{\cdot}03$), personal function (items: 8, 13, 14 and 15; $P = 0{\cdot}01$) (Fig. 3). Social function changes were indistinguishable between the two groups (items: 4, 5 and 11; $P = 0{\cdot}2$), which accounted for the lack of overall statistical differences for all four areas between the two groups.

Finally, a safety analysis was conducted for all subjects enrolled in the study. There were a very small number of adverse events reported by subjects that were not considered to be related to any of the products used, and no differences were detected in adverse events between the subjects when using Xerostom®* products or when using their normal dry mouth routine.

Discussion

Salivary output and constituents are critically important components of oral health. Clinically significant detriments in salivary function reduce the health of the oral cavity and pharynx, and can impair a person's quality of life (6, 8). The most common cause of salivary hypofunction, particularly amongst older populations, is medications (3, 7, 39, 56). As the elderly are the most rapidly growing segment of the population, and most older individuals are taking at least one drug, polypharmacy-induced salivary hypofunction and xerostomia are predicted to become more prevalent in the future (13, 15, 57). Therefore, it is important to have a wide variety of products that can help modify the xerostomic effects of multiple medications (28). Importantly, these products should be convenient to use, safe, with minimal side effects, and tested for safety and efficacy in controlled clinical trials.

The results of this investigation demonstrate that topical dry mouth products containing olive oil, betaine and xylitol, designed to reduce symptoms of xerostomia, are safe to use in a group of adults experiencing polypharmacy-induced dry mouth. There were no adverse events observed during the clinical investigation demonstrating a good safety profile in the subjects who used these dry mouth products for a week. Olive oil has many properties helpful in ameliorating oral conditions commonly found in dry mouth patients, including anti-microbial, lubrication, anti-inflammatory and anti-caries activities (31, 43–46, 48). Betaine is a naturally occurring amino acid derivative, obtained from sugar beet molasses during sugar production (58, 59). Betaine is also called trimethylglycine, but betaines can be any of the trimethyl amino acids. Betaine is found at different concentrations in all living organisms. In humans, as it has surface active properties, betaine participates in many functions, including lubrication. Betaine has osmoprotectant capabilities (59, 60), is also able to bind humidity from the air, so that it has an osmoprotecting effect on the skin and oral mucosa against chemical and mechanical irritation (61). Betaine-containing detergent-free toothpaste was found to cause no epithelial desquamation compared with a sodium-lauryl-sulphate containing toothpaste (62). Currently, it is used in skin, cosmetic and hair care products as well as in toothpastes as a preventative, soothing and osmoprotective component (61). Betaine has also been demonstrated to provide relief against oral irritants (25, 32). Accordingly, it has been suggested that it could assist in the reduction of dry mouth complaints because of its osmoprotective qualities (25, 32, 34). Xylitol, a widely used natural carbohydrate sweetener of the pentitol type, has proven anti-caries activities (35, 49) and has been used effectively in older patients to help stimulate saliva (63).

The purpose of this cross-over clinical investigation was also to determine the efficacy of a week-long regimen of topical dry mouth products containing olive oil, betaine and xylitol compared with a person's normal dry mouth regimen for polypharmacy-induced xerostomia. The results suggest that daily use of these novel topical dry mouth products increased significantly unstimulated whole saliva during the week of product use compared with the saliva produced when subjects continued their normal dry mouth routine. Subjects also showed improvements in xerostomia and quality of life issues as assessed by VAS and xerostomia-associated quality of life questionnaires. The VAS showed statistically significant improvements in the dryness of the mouth and tongue and a decrease in thirst when using Xerostom®* products as compared with their normal dry mouth routine. Subjects showed improvement in the other five VAS items, although with less significance. There was a statistically significant improvement in the quality of life issues relating to physical, personal function and pain when using Xerostom®* products compared with their normal dry mouth routine. Interestingly, Xerostom®* products did not significantly improve social functions versus subjects' normal dry mouth routine ($P = 0{\cdot}2$) which could have been partially because of normal dry mouth routines that include chewing gum or sipping liquids.

These findings are consistent with many other studies that have demonstrated that topical dry mouth products can improve symptoms of dry mouth in a variety of patient populations (20–24, 64–73). However, the vast majority of these clinical investigations were conducted in patients with radiotherapy-induced salivary hypofunction or Sjögren's syndrome. There are limited clinical trial data for adults with polypharmacy-induced dry mouth, despite the prevalence of drug-induced dry mouth symptoms amongst older adults (13, 74). Therefore, the results from this study could help subjects experiencing dry mouth symptoms as a result of concomitant medication use.

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