Original Article

Innovative novel candy made from a low-solubility amorphous material promotes saliva secretion: a randomized, double-blind, placebo-controlled crossover comparative trial

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Saliva has antioxidant properties, washes away food residues, and helps maintain the oral environment; thus, decreased saliva secretion can have negative consequences. This study examined how slow-soluble innovative candy, named low-solubility amorphous material, affects oral indices such as saliva secretion and halitosis in a randomized, double-blind, placebo-controlled, crossover comparative study. Twenty-four healthy individuals with low saliva production were given one piece of low-solubility amorphous material or placebo candy and their saliva secretion was measured over 20 min. Before and after participants used the test food, we measured the concentrations of three volatile sulfur compounds involved in halitosis and the secretion rate of secretory immunoglobulin A, and participants completed the Profile of Mood States Second Edition (POMS2) and a visual analog scale (VAS). As a result, saliva secretion increased significantly in low-solubility amorphous material candy condition, compared to placebo candy. Furthermore, changes in the hydrogen sulfide concentration, POMS2 Total Mood Disturbance and Vigor-Activity scores, and oral "moisture" and "refreshed feeling" scores on the VAS were improved more by low-solubility amorphous material candy use than by placebo. Low-solubility amorphous material candy may help improve the oral environment by increasing saliva secretion and reducing halitosis-related substances and may improve mood.

***Key Words*: low-solubility amorphous material, slowly soluble candy, saliva secretion, oral environment**

Saliva plays a crucial role in maintaining oral health because it contains various antioxidant components such as superoxide dismutase, catalase, peroxidase, and uric acid,[1–3] and the antioxidant capacity of saliva is considered the first line of defense against oxidative stress within the oral cavity. Moreover, saliva helps protect the oral tissues from damage caused by reactive oxygen species (ROS) created during processes such as inflammation, infection, and exposure to environmental contaminants or radiation. Saliva also contains lactoferrin, lysozyme, and immunoglobulin, which protect the body from bacteria and viruses through their antibacterial effects,[4] In addition, saliva physically washes away food residues and cleanses the mouth. Thus, when saliva secretion decreases, the oral environment deteriorates. The percentage of people who experience xerostomia, i.e., dry mouth, due to decreased saliva secretion increases with age, and less saliva is secreted in older adults than in younger people.[5] The salivary flow rate and salivary overall antioxidant capacity were reportedly significantly decreased in elderly compared to younger individuals.[6] In addition to having negative effects on oral hygiene and digestion, decreased salivary secretion also leads to increased halitosis, worsening of infections, increased risk of dental caries, and decreased quality of life (QOL) due to difficulties eating, swallowing, and speaking.[7–9] Oral cavity bacteria produce volatile sulfur compounds (VSCs), such as H_2S, CH_3SH, and $(CH_3)_2S$,[10] the causative agents of halitosis,[11] and these compounds reportedly increase when saliva secretion decreases.[12,13] Furthermore, severe deterioration of the oral environment can lead to aspiration pneumonia.[14] Because decreased saliva secretion is involved in xerostomia, the maintenance of and improvement in saliva secretion are highly important.

Surveys in Europe and the United States revealed that approximately 25% of the population has symptoms related to xerostomia,[15] suggesting that a large number of people may have reduced saliva production. The estimated prevalence of xerostomia tends to be greater in women than in men,[16,17] and approximately 30% of the population older than 65 years has salivary disorders.[18] Medications for dry mouth, such as those used in Sjögren's syndrome, include muscarinic receptor agonists, which stimulate saliva secretion; however, these medications frequently have adverse effects such as increased sweating, polyuria, and diarrhea. Other methods of stimulating saliva secretion include massaging the salivary glands[19] and chewing gum.[20] Recently, functional ingredients such as Sichuan pepper oil,[21] coenzyme Q10,[22,23] and glucosylceramide[24] have been shown to stimulate saliva secretion, but additional new products that promote saliva secretion are needed.

By using processed starch, we developed a new, less-soluble type of candy, which we named low-solubility amorphous material (LSA) candy because of its amorphous material structure. LSA candy is made by drying starch in its starchy state, which makes it hard and slowly soluble. When the surface of the candy comes into contact with moisture, the starch absorbs water and swells, forming a barrier that allows water to infiltrate the candy only slowly, meaning that the candy dissolves slowly. This amorphous starch structure is also resistant to degradation by digestive enzymes and has been applied in drug release kinetics research.[25]

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Physical stimulation of the oral cavity is known to induce salivation.[26] Stimulation of mechanoreceptors in the oral cavity is transmitted to the salivary glands by the parasympathetic reflex arc via the trigeminal nerve, and saliva is secreted.[27] Because LSA candy stays in the mouth for a long time, it is expected to stimulate the oral cavity and promote saliva secretion. Furthermore, research has shown that chewing starch-rich bread promotes saliva secretion more than chewing Parafilm does,[28] suggesting that starch-rich foods may promote saliva secretion. However, how LSA candy affects salivary secretion is unclear. Therefore, this study examined the effects of LSA candy use on saliva secretion and saliva-related parameters in a randomized, double-blind, placebo-controlled, crossover comparative trial.

Materials and Methods

Dissolution test of candies. The solubilities of LSA and other candies were compared with that of a disintegration tester (Toyama Sangyo Co., Ltd., Japan). The tank was filled with distilled water at 37°C, one piece of each type of candy was added, and the time until complete dissolution was measured.

Study design. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki (revised in 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare, Japan). This study was approved by the Institutional Review Board of Chiyoda Paramedical Care Clinic (IRB No. 15000088; date of approval, April 16, 2021). Participants were fully informed about the purpose, details, and methods of the study, and they provided written informed consent prior to participating in the study.

Participants were recruited and managed by CPCC Company Ltd., and measurements were conducted at the Chiyoda Oral Health Care Clinic. The study was registered in the UMIN Clinical Trials Registry (UMIN ID: UMIN000044473) and was conducted in May and June of 2021. No changes were made to the protocol during the study.

Participants. Individuals were invited to participate in the study if they met the inclusion criteria and did not meet the exclusion criteria. The following individuals were eligible for the study: 1) healthy men and women aged >20 to 64 years at the time of informed consent; 2) individuals with saliva secretion (assessed by the Saxon method) of more than 2 g but less than 6 g at the preliminary examination; and 3) individuals who received sufficient explanation and understood the study and were able to provide written informed consent. Individuals were excluded if they fulfilled any of the following criteria: 1) had full or partial dentures, were in the process of straightening their teeth, or experienced a stinging sensation in their teeth upon eating sweet foods; 2) had a history of hospital treatment or oral cleaning within one month prior to the beginning of the study or planned to visit the hospital before the end of the study; 3) had any difficulty in refraining from continuous intake (i.e., intake ≥3 times a week) of medicines or health-related, functional, or health foods that might affect the test results, i.e., those related to salivary secretion, halitosis control, and immunity; 4) had a smoking habit (i.e., smoked approximately 20 cigarettes or more per day); 5) had a probable seasonal allergy such as pollinosis during the study period; 6) expected a lifestyle change during the study period; 7) were receiving medical treatment (in particular for Sjögren's syndrome and similar diseases); 8) had previous or current digestive diseases (individuals with a previous digestive disease were permitted to participate in the study if the principal investigator did not expect the disease history to influence the study results); 9) had been hospitalized and received treatment in the past 6 months or expected to be hospitalized during the study period; 10) were definitely or possibly pregnant or breastfeeding; 11) had a previous or current serious disease, e.g., of the heart, liver, and kidney; 12) had excessive alcohol intake (i.e., on average, >60 g/day in a week); 13) had a drug or food allergy; 14) were currently participating in another clinical trial with some kind of medicine or food, had participated in such a trial within 4 weeks prior to this study, or were planning to join such a trial after giving informed consent to participate in this study; and 15) were determined as ineligible for participation according to the opinion of the principal investigator or subinvestigator.

Experimental protocol. This was a randomized, double-blind, placebo-controlled, crossover comparative study. The rationale for the number of participants was based on studies examining the effects of test food consumption on salivary secretion.[23,29,30] In these studies, salivary secretion was adequately assessed in approximately twenty-five participants, and the number of participants in this study was set at twenty-four.

The test food was LSA candy made from processed starch as the main ingredient; each piece of LSA candy contained 0.09 g of slowly soluble processed starch. The placebo was a piece of candy in which the carbohydrates in the LSA candy were replaced mainly by sugar and syrup; the placebo candy did not contain any slowly soluble processed starch. The LSA and placebo candies were the same size (0.5 g per piece) and had the same appearance.

Participants visited the clinic three times in total. At the first visit, the patients were informed about the study, and written informed consent was obtained. After a medical interview, saliva secretion was measured by the Saxon method. In this method, patients chew sterile gauze for 2 min, and the amount of saliva produced was calculated from the change in the weight of the gauze before and after chewing. Twenty-four individuals who met the selection criteria for saliva production according to the Saxon method and who were judged by the principal investigator to be eligible to participate in the study were selected. The allocation manager, who was independent of the study and analysis, used stratified randomization to allocate eligible participants to two groups based on sex and the amount of saliva measured during the screening test, and each group was assigned to receive either the LSA candy on the first measurement day and the placebo candy on the second measurement day or *vice versa*. Information on the assigned test foods was kept confidential until the analysis was completed.

On each measurement day, halitosis-causing VSCs were measured, saliva was collected for sIgA analysis, and participants completed the POMS2 and VAS questionnaires. Then, one piece of test candy was placed in the participant's mouth, and saliva was collected for 20 min and subsequently weighed. Thereafter, post-consumption assessments were performed, which included assessment of halitosis-causing VSCs, saliva collection for sIgA analysis, and completion of the POMS2 and VAS. After a washout period of one week, the same assessments were conducted with the other test candy.

Evaluations. To evaluate the effects of LSA candy, salivary secretion, halitosis-causing VSCs, and salivary sIgA were measured, and questionnaire evaluations were performed. The details are provided below:

Salivary secretion. All saliva secreted during 20 min after consumption of the test food was collected by spitting into a collection tube. 20 min later, the weight of the total collected saliva sample was measured and the salivary flow rate calculated. Even if the test food was finished within 20 min, saliva was collected for 20 min.

VSC measurement. The concentrations of the VSCs hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide [$(CH_3)_2S$], the major causative agents of halitosis, were measured by Oral Chroma™ (Nissha FIS, Inc., Japan). VSC measurements were conducted before and after the intake of the test food, and the changes in the concentrations of the three VSCs from before

to after the test food was consumed were calculated.

Salivary sIgA measurement. Approximately 1 ml of resting saliva was collected before and after the use of the test food. The time taken for saliva collection was recorded. The concentration of sIgA was measured with a salivary secretory IgA indirect enzyme immunoassay kit (Salimetrics, CA), and the sIgA secretion rate was calculated by using the saliva collection time.

Questionnaire evaluations. Participants subjectively rated their mood profile with the POMS2, which consists of the following subscales: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, Vigor-Activity, Friendliness, and Total Mood Disturbance. In addition, they used a VAS to rate "moisture", "refreshed feeling", and "unpleasant taste" in the mouth. The POMS2 and VAS were administered before and after test food consumption.

Statistical analysis. The participants' background data are presented as the means ± SDs, and other data are presented as the means ± SEMs. Differences between LSA candy and placebo use were analyzed with paired *t* test or Wilcoxon signed-rank test. A *p* value of less than 0.05 indicated statistical significance. The effect size was calculated as Cohen's d. Statistical analyses were performed with Microsoft Excel (Microsoft Corporation) and SPSS software ver. 26 (IBM Japan).

Results

Dissolution time of LSA candies. We performed dissolution tests to confirm that LSA candy dissolves slowly. As shown in Table 1, the dissolution time of LSA, which has an amorphous structure and is composed mainly of processed starch, was noticeably longer than that of commercially available hard candy (amorphous structure), soft candy (mixed structure of crystalline and amorphous), and sugar-coated soft candy (mixed structure of crystalline and amorphous).

Table 1. Dissolution times of different types of candy

	Weight (g)	Dissolution time (min)
LSA	0.5	>600
Hard candy	2.7	12
Soft candy	4.6	24
Sugar-coated soft candy	2.7	83

LSA, low-solubility amorphous material; hard candy, Ryukakusan (RYUKAKUSAN Co., Ltd.; soft candy, Hi-Chew (Morinaga & Co., Ltd.); and sugar-coated soft candy, Mentos (Perfetti Van Melle Japan).

Table 2. Participants' background

	Subjects (*n* = 24)
Age (years)	52.3 ± 4.4
Male/Female (number)	7/17
Height (cm)	161.2 ± 6.5
Body weight (kg)	57.9 ± 12.1
Amount of saliva (g)	4.7 ± 0.7

The data are shown as the means ± SDs.

Participants. We performed a clinical study to examine the effects of LSA intake on salivary secretion. The study flowchart, from participant selection to statistical analysis, is shown in Fig. 1. Screening test was performed on sixty-eight individuals who agreed to participate in the study, and twenty-four individuals who met the selection criteria were chosen to participate in the study. All twenty-four participants underwent all the study measurements; i.e., there were no dropouts, and all were suitable for inclusion in the data analysis. The participant background characteristics are shown in Table 2. All participants were nonsmokers. No adverse events were reported during the study.

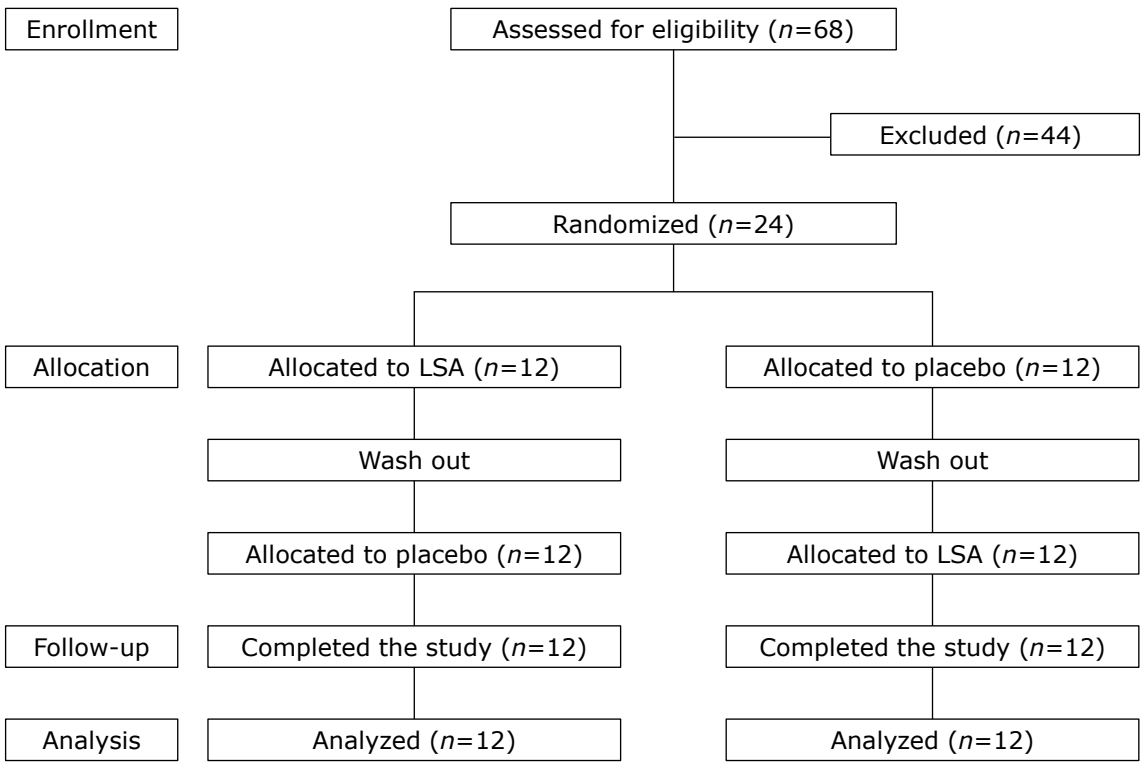

Fig. 1. Flow diagram of the study. LSA, low-solubility amorphous material.

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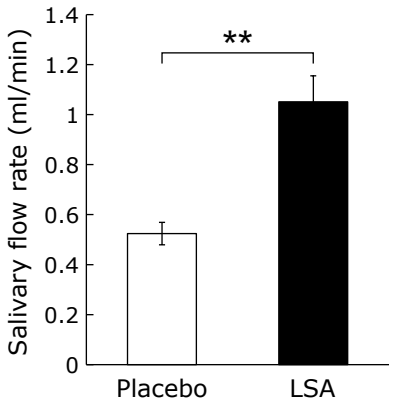

Fig. 2. Salivary flow rate at 20 min after ingestion of test food. All saliva secreted during 20 min period after consumption of the test food was collected by spitting into a collection tube. The weight of the entire saliva sample collected over the 20 min period was measured, and the salivary flow rate was calculated. Data are shown as means ± SEMs. **p<0.01, paired t test. LSA, low-solubility amorphous material.

Salivary secretion. Salivary secretion during testing is shown in Fig. 2. Salivary flow rate over 20 min was significantly greater in the LSA candy treatment group (1.05 ± 0.10 ml/min) than in the placebo group (0.52 ± 0.04 ml/min; $p = 0.000$, d = 1.35).

Volatile sulfur compounds involved in halitosis and salivary secretory immunoglobulin A. The concentrations of three volatile sulfur compounds (VSCs) involved in halitosis were measured before and after the test foods were consumed. The amount of change after consumption of the test food is shown in Table 3. We found a significant difference in the change in hydrogen sulfide (H_2S) concentration between LSA candy use and placebo use but no significant difference in the change in methyl mercaptan (CH_3SH) or dimethyl sulfide [$(CH_3)_2S$] concentration between the test foods. The change in secretion rate of secretory immunoglobulin A (sIgA) in saliva did not differ between the test food groups (Table 3).

Questionnaire evaluations. The results of the Profile of Mood States Second Edition short version (POMS2) are shown in Table 4. None of the baseline indices were significantly different between testing conditions before the test foods were consumed. However, after the test foods were used, there was a significant decrease in the POMS2 Total Mood Disturbance score and a significant increase in the Vigor-Activity score during LSA candy use compared with those during placebo use. These results indicate that LSA candy use suppressed negative mood and increased vitality and vigor.

The results of the VAS questionnaire are presented in Table 5. There was a significant difference in the between-condition changes in the items "moisture" and "refreshed feeling" in the mouth before and after the test foods were consumed, but there was no significant between-condition difference in change scores for the item "unpleasant smell".

Discussion

We examined the effects of the use of a single piece of LSA candy on oral indices in a randomized, double-blind, placebo-controlled, crossover comparative trial in healthy individuals with low saliva secretion, and the results showed that, compared with placebo candy, LSA candy increased saliva secretion. Stimulation of saliva secretion by continuous consumption of carbohydrate-rich candies leads to excessive carbohydrate intake and increases the risk of dental caries.[31] In contrast, LSA candy, which can be administered in small doses and lasts for a longer time, is an innovative means of stimulating saliva secretion and has a low risk of excessive carbohydrate intake and diabetes.[32] LSA dissolves slowly, so individuals are expected to have a low

Table 3. The amounts of changes in the VSC concentration and sIgA secretion rate after ingestion of test food

	Placebo	LSA	p value	Effect size
ΔVSC concentration (ppm)				
H_2S	−105.7 ± 3.9	−291.1 ± 68.3	0.049*	0.52
CH_3SH	−135.9 ± 56.0	−105.8 ± 26.0	0.567	0.15
$(CH_3)_2S$	−46.2 ± 13.5	−15.9 ± 18.1	0.153	0.37
ΔsIgA secretion rate (μg/min)	−1.2 ± 5.4	16.5 ± 23.2	0.520	0.21

The data are shown as the means ± SEMs. VSC, volatile sulfur compound; H_2S, hydrogen sulfide; CH_3SH, methyl mercaptan; $(CH_3)_2S$, dimethyl sulfide; LSA, low-solubility amorphous material; *p<0.05 vs placebo (paired t test).

Table 4. Results of the profile of mood states

	Before test food intake			After test food intake			
	Placebo	LSA	p value	Placebo	LSA	p value	Effect size
TMD	44.7 ± 1.8	43.5 ± 1.8	0.094	43.3 ± 1.7	42.0 ± 1.7	0.004**	0.16
AH	45.1 ± 1.6	43.5 ± 1.5	0.200	42.9 ± 1.3	42.3 ± 1.6	0.228	0.09
CB	46.2 ± 1.9	45.3 ± 2.0	0.366	44.5 ± 1.9	43.8 ± 1.7	0.552	0.08
DD	45.5 ± 1.7	45.3 ± 1.3	0.788	44.3 ± 1.4	44.5 ± 1.4	1.000	0.03
FI	43.6 ± 2.0	42.3 ± 1.8	0.220	42.1 ± 2.0	40.6 ± 1.9	0.079	0.18
TA	43.9 ± 2.0	43.6 ± 2.0	0.700	41.8 ± 1.9	41.0 ± 1.8	0.391	0.09
VA	49.5 ± 1.9	50.8 ± 1.8	0.286	47.3 ± 2.0	49.6 ± 1.8	0.043*	0.25
F	48.9 ± 2.0	49.2 ± 1.7	0.476	48.2 ± 1.8	50.0 ± 1.9	0.180	0.20

The data are shown as the means ± SEMs. LSA, low-solubility amorphous material; *p<0.05, **p<0.01 vs placebo (Wilcoxon signed-rank test).

Table 5. Amount of change in the VAS score after ingestion of test food

	Placebo	LSA	*p* value	Effect size
Moisture	15.6 ± 3.9	26.5 ± 4.7	0.015*	0.52
Refreshed feeling	16.6 ± 3.3	44.2 ± 4.6	0.000**	1.43
Unpleasant smell	–9.1 ± 3.6	–15.5 ± 6.6	0.246	0.24

The data are shown as the means ± SEMs. *p<0.05, **p<0.01 vs placebo (paired t test).

risk of a rapid increase in blood glucose levels and an increase in salivation without increasing carbohydrate intake.

It has been reported that VSCs such as H_2S, CH_3SH, and $(CH_3)_2S$ are the causative agents of halitosis.[11] These VSCs are produced by bacteria in the oral cavity using amino acids, such as cysteine and methionine.[10] Saliva acts as an oral cleanser and inhibits the growth of oral bacteria that produce substances that cause halitosis, and it has been reported that when saliva secretion decreases, the concentrations of H_2S and CH_3SH increase.[12,13] In the present study, a significant decrease in H_2S concentration was observed after the use of LSA candy. The use of gum has also been shown to transiently reduce the concentrations of VSCs[33] and to have a cleaning effect on the mouth by increasing saliva secretion, which is thought to be a factor in the reduction of halitosis through chewing gum.[34] Saliva acts as an oral cleanser and inhibits the growth of oral bacteria that produce halitosis-causing substances, and the concentrations of H_2S and CH_3SH reportedly increase when saliva secretion decreases.[12,13] These results suggest that LSA candy stimulates saliva secretion, which washes away the substrates of halitosis components in the oral cavity and reduces the H_2S concentration, thus improving halitosis and the oral environment.

In the present study, LSA candy was found to improve mood scale (POMS2) and subjective index (VAS) scores. Decreased saliva secretion leads to deterioration of the oral environment, which in turn leads to increased halitosis and, in severe cases, worsens QOL by impairing eating and speaking.[7–9] One possible explanation for the improvement in the mood state with LSA candy is that it stimulates saliva secretion, which moistens the mouth and reduces oral discomfort, e.g., due to dryness, leading to beneficial effects on the mood state, such as an improvement in negative mood.

In the future, other ingredients that promote saliva secretion could be added to LSA candy to enhance its saliva-promoting effect. Furthermore, research has shown that a sour taste promotes transient salivary secretion and that an umami taste promotes sustained salivary secretion;[35] therefore, improving the ingredients and taste of candies can be expected to further promote salivary secretion. The ability to enjoy one's favorite flavors for a long time is one of the best parts of eating candy, and candy use is expected to contribute to the improvement of QOL. People who engage in speaking for work or who are concerned about halitosis can keep a thin, small LSA candy in their mouth, allowing them to talk without worrying about thirst, the loss of their active voice because of dry mouth, or bad breath.

One limitation of our study was that a single use of LSA candy was evaluated; the effect of continuous use of LSA candy has not yet been evaluated. Since a single use of LSA candy increases salivary secretion and suppresses H_2S concentrations, continuous intake of LSA candy may improve the oral environment by, for example, increasing resting salivation and improving halitosis.

In summary, LSA candy, which stays in the oral cavity for a long time because it is made from processed starch, is expected to keep the mouth moist, to contribute to oral health by promoting saliva secretion and reducing H_2S concentration. Further investigations of the effects of this innovative candy are warranted.

Author Contributions

IS and SM designed the study; SKawakami, SM, and SKawasaki contributed to the collection and analysis of study data; IS, SKawakami, SM, SKawasaki, EN, MY, AY, YM, and TK interpreted the data; and IS, SKawakami, MY, and YM wrote the article. All authors approved the final manuscript after critical revision of the manuscript and agree to accept responsibility for its scientific accuracy and consistency.

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Conflict of Interest

SKawakami, SM, SKawasaki, EN, MY, AY, YM, and TK are employees of Morinaga & Co., Ltd. IS is a representative director of Cranescience Co., Ltd., Tokyo, Japan, and receives compensation and stock ownership. This research was partially funded by Morinaga & Co., Ltd. The sponsor had no control over the interpretation, writing, or publication of this work.

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