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Effects of dihydrocapsiate on salivary secretion in healthy subjects: A randomized, double-blind, placebo-controlled, crossover study

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ABSTRACT

Purpose: We aimed to assess the effects of dihydrocapsiate (DHC), a non-pungent capsaicin analog, on salivary secretion in individuals experiencing mild dry mouth symptoms. Given the function of transient receptor potential vanilloid 1 (TRPV1) in salivation, we hypothesized that DHC, which activates TRPV1 with minimal irritation, could serve as a novel therapeutic agent for dry mouth (xerostomia).

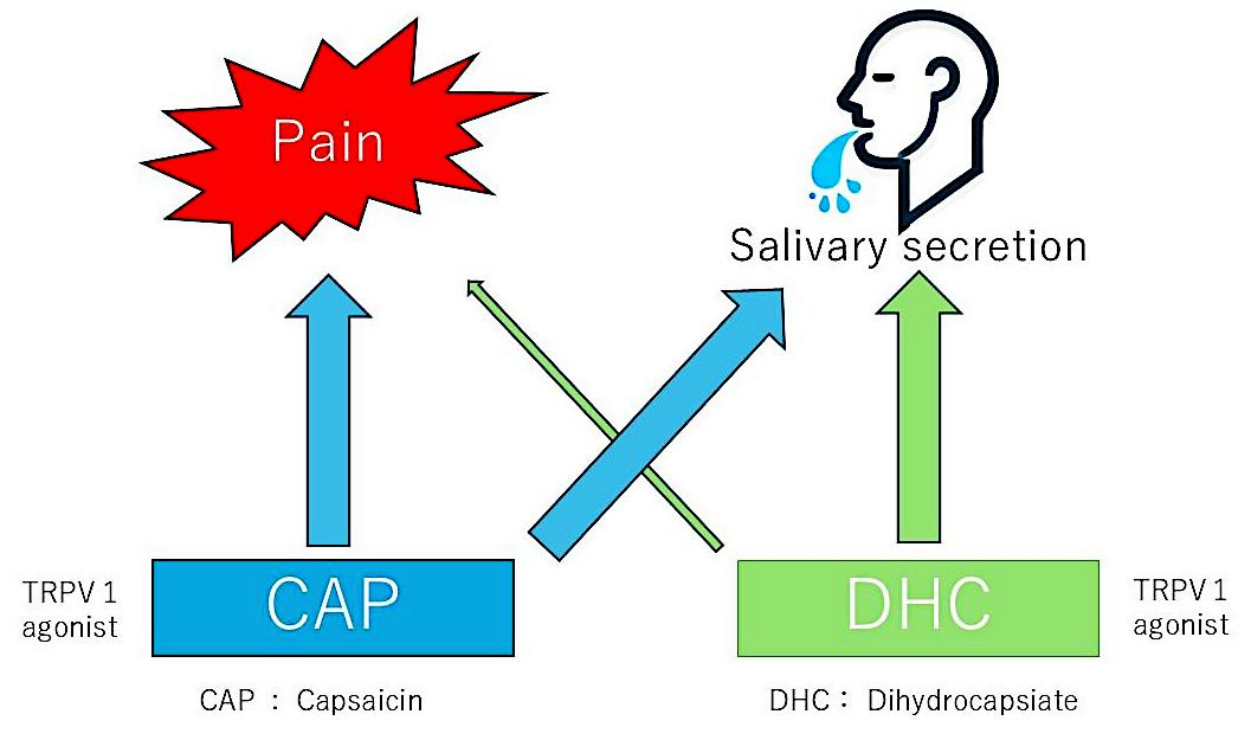
Methods: A randomized, double-blind, crossover trial was conducted involving healthy adults aged 40 to 70 years who reported a tendency toward dry mouth. Participants were randomly assigned to receive either a test tablet containing 0.8 mg DHC or a placebo tablet. Saliva secretion was measured using a spitting method before and after tablet administration, with assessments conducted in the morning to minimize diurnal variations. For statistical comparisons, paired Student's t-tests were applied.

Results: DHC intake significantly increased salivary secretion relative to the placebo group ($p < 0.05$). No adverse events or significant changes in safety parameters, including body weight, BMI, or blood pressure, were recorded during the study.

Conclusion: DHC effectively enhanced salivary secretion while minimizing the pungency associated with capsaicin. Its ability to stimulate TRPV1 with low irritation suggests potential as a safe and convenient therapeutic option for individuals experiencing dry mouth.

Novelty: This study is the first randomized, placebo-controlled trial to demonstrate that dihydrocapsiate (DHC), a non-pungent capsaicin analog, significantly enhances salivary secretion in healthy individuals. These findings suggest that DHC may serve as a novel and tolerable functional ingredient for the management of oral dryness.

Keywords: dihydrocapsiate (DHC), capsaicin, TRPV1, salivary secretion, xerostomia, dry mouth.



Graphical abstract: Effects of dihydrocapsiate on salivary secretion in healthy subjects: A randomized, double-blind, placebo-controlled, crossover study

INTRODUCTION

Dry mouth (xerostomia) refers to a condition in which reduced saliva secretion results in dryness within the oral cavity. The causes of dry mouth are varied with systemic factors including aging, medication side effects, radiation therapy for cancer, etc.[1, 2], Prolonged dry mouth can lead to an increased risk of dental caries and periodontal disease, as well as difficulties in eating and swallowing, ultimately resulting in a decline in quality of life.[3, 4] Currently, treatments for dry mouth include artificial saliva and salivary secretion stimulants, such as pilocarpine, a known muscarinic receptor agonist.[5-8]

However, artificial saliva provides only temporary and limited relief, and salivary stimulants often have significant side effects. [7] For this reason, salivary stimulants are typically used only for patients with Sjögren's syndrome or severe xerostomia following head and neck radiation therapy. Therefore, there is a strong need for the development of new treatment options that are both safe and convenient for broader patient use.

The transient receptor potential vanilloid 1 (TRPV1) is a non-selective cation channel, and recent studies have suggested that TRPV1 plays a role not only in sensory perception but also in the regulation of various physiological processes [11-12], including salivary secretion.[13] This is because TRPV1 is expressed in the salivary glands [15], and its direct stimulation in these glands is thought to contribute to saliva secretion.[15, 19] Given these findings, the regulation of TRPV1 may provide valuable insights into potential therapeutic targets for conditions associated with impaired salivary secretion, such as dry mouth. TRPV1 is known to be activated by stimuli such as heat and low pH.[9, 10] Application of capsaicin, the active component in chili peppers and a TRPV1 agonist, is also reported to induce saliva secretion in rabbits, rats, and humans.[13-15] The salivary secretion effect of capsaicin is primarily mediated via the trigeminal-parasympathetic pathway.[16-18]

Capsinoids, capsaicin analogs, are found in a non-pungent cultivar of red pepper known as "CH-19 Sweet." Dihydrocapsiate (DHC) is one of the compounds in the capsinoid family, so it activates TRPV1 like capsaicin. [10, 20] However, DHC has a hot taste threshold estimated at approximately 1,000 times that of capsaicin.[21] Therefore, DHC may promote saliva secretion with less stimulation than capsaicin. In this study, we investigated the effect of DHC on saliva secretion.

MATERIALS AND METHODS

Study design: To investigate the effects of DHC on salivary secretion, a randomized, double-blind, crossover trial was conducted. The subjects were randomly allocated to group I or II by an independent third party, with consideration given to age, sex, and saliva secretion levels to ensure comparable group composition. Randomization was performed by a doctor not involved in the trial, and blinding was maintained throughout the study until data analysis..

This study adhered to the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments. Approval was obtained from the Ethics Committee of Chiyoda Paramedical Care Clinic (IRB Approval Number: 24101803), and the trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMINCTR: UMIN000056070).

Participants: The selection criteria of this study were as follows: (1) Male and female aged 40 to 70 years at the time of consent acquisition; (2) Individuals who are aware that their mouth tends to dry out easily; (3) Individuals with a baseline resting saliva secretion of 1.5 g/15 min or more in the spitting method,[22] during preliminary testing; and (4) Individuals capable of giving informed consent to participate in the study after receiving a detailed explanation of the protocol and understanding its contents. The exclusion criteria were as follows: (1) Individuals who consume, more than once a week and could not discontinue their consumption from the time of consent, foods or supplements containing DHC, coenzyme Q10, eriodictyol-6-C-glucoside, or similar

compounds that could affect the trial, including Foods with Function Claims, functional food labels, and health supplements; (2) Individuals who are taking medications that could affect the trial, such as antihypertensives, antihistamines, antiepileptics, anti-Parkinson drugs, and sedatives; (3) Individuals who are participating in, planning to participate in, or had participated in clinical trials for pharmaceuticals and health foods within four weeks prior to this trial; (4) Smokers, except for those who have abstained from smoking for more than one year; (5) Individuals with excessive alcohol intake; (6) Participants with existing or prior severe conditions related to cardiovascular, hepatic, renal, or gastrointestinal systems; (7) Females who are pregnant or lactating, and those who intend to become pregnant while the study is ongoing; (8) Individuals with allergies to medications and/or food; (9) Individuals deemed unsuitable for participation in the trial by the principal investigator or sub-investigator.

Determination of the sample size: The sample size was determined based on a preliminary study, using the mean difference and standard deviation in saliva secretion between the test tablet, containing DHC, intake group and the placebo tablet intake group as the primary endpoints, and the sample size was estimated to achieve 80% power at a 5% significance level. As a result, the calculated sample size for each group was 30 individuals. Although the calculated sample size per group was 30 individuals, a total of 40 participants were enrolled due to limitations in recruitment capacity and study timeline. Consequently, the final number of participants analyzed was slightly below the initially estimated number. Nonetheless, the achieved sample size was sufficient to detect a statistically significant difference in salivary secretion between the DHC and placebo groups, supporting the validity of the findings.

Preparation of the tablets: The test tablet included 0.8 mg DHC (Ajinomoto Healthy Supply Co., Inc., Tokyo, Japan). The test tablet also contained maltose, maltitol, cellulose powder, calcium stearate, and silica dioxide. The placebo tablets were identical in composition to the test tablets, except that they did not contain DHC. The weight of the tablets was adjusted to 0.85 g.

Randomization: Participants were randomly assigned (1:1) to one of two study sequences using a computer-generated randomization list created by staff at a contract research organization who were not otherwise involved in the study. The randomization process was stratified by age, sex, and baseline saliva secretion in preliminary testing at the screening stage. The randomization list and associated documentation were securely stored at the contract research organization. The sequence allocation codes remained blinded to the investigator, clinical personnel, participants, and all individuals involved in the study procedures, including outcome assessors, until the database was locked.

Schedule: The study schedule is presented in Fig. 1. Healthy individuals aged 40 to 70, presenting symptoms such as a slight decrease in saliva production, were enrolled in the study. Before screening, participants received a full explanation of the study procedures and objectives and provided their written informed consent. The participants visited the clinic on three occasions: at the baseline assessment period (screening test), and at the test assessment periods immediately after the 1st and 2nd intakes of the test food.

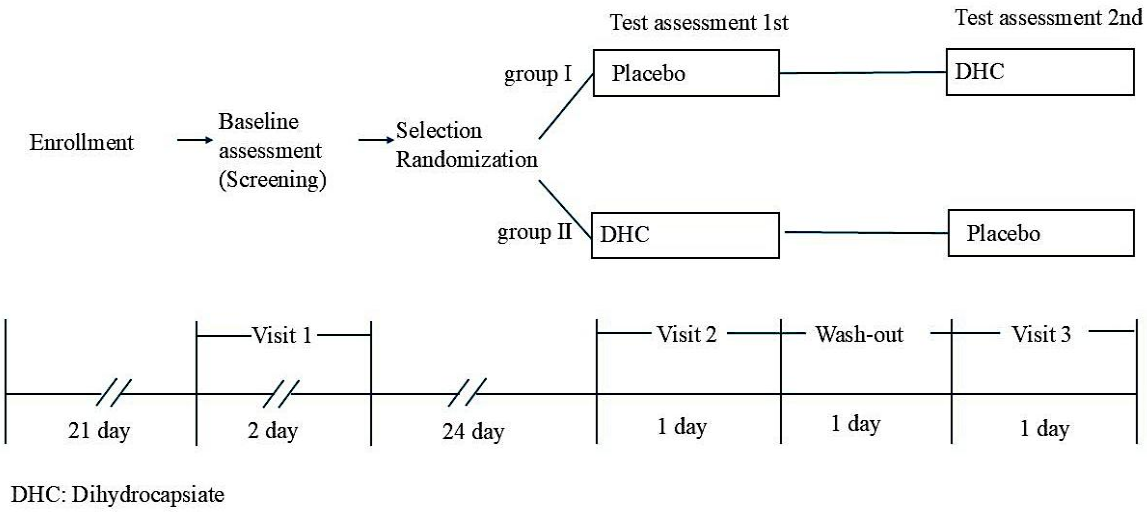


Figure 1. Schematic overview of the study design**.**

Assessment: All assessments were carried out between 9:30 and 11:30 AM. The primary assessment endpoint of this study was saliva secretion. Resting saliva volume was evaluated (Visit 1, in Fig. 1) for 15 min using a spitting method19 at the baseline assessment period. During the test assessment (Visits 2 and 3), saliva volume was evaluated for 15 min using the same method as for resting saliva after placing a tablet (placebo or DHC test tablet) on the tip of the tongue. The secondary assessment endpoint of this study was subjective mouth dryness, evaluated using the VAS method. The VAS assessment utilized the pre-intake perception of oral dryness as the baseline and evaluated subjective improvements following the salivary secretion test.

Safety Assessment: The following parameters were defined as safety endpoints. Body weight, body mass index (BMI), and blood pressure were measured during physical examinations. Fluctuations in body weight, blood pressure, and BMI were monitored during the intake period to detect any abnormal changes.

Statistical analysis: Results are presented as the mean ± standard deviation. Comparison of saliva secretion volume (primary assessment endpoint) and mouth dryness (secondary assessment endpoint) using VAS methods was analyzed using paired Student's t-tests.

RESULTS

Subject Background: The participant flow diagram is presented in Figure 2. A total of 100 individuals were screened, and 40 were selected for inclusion in the study. These 40 participants were then randomly allocated to either Group I or Group II by the allocation manager. During the trial, one participant from Group I and one from Group II withdrew from the study due to personal reasons. Additionally, one participant in group II was excluded due to a failed saliva measurement. As a result, the final number of participants was 37. Twenty-eight participants in the active group and 29 in the placebo group were eligible for analysis.

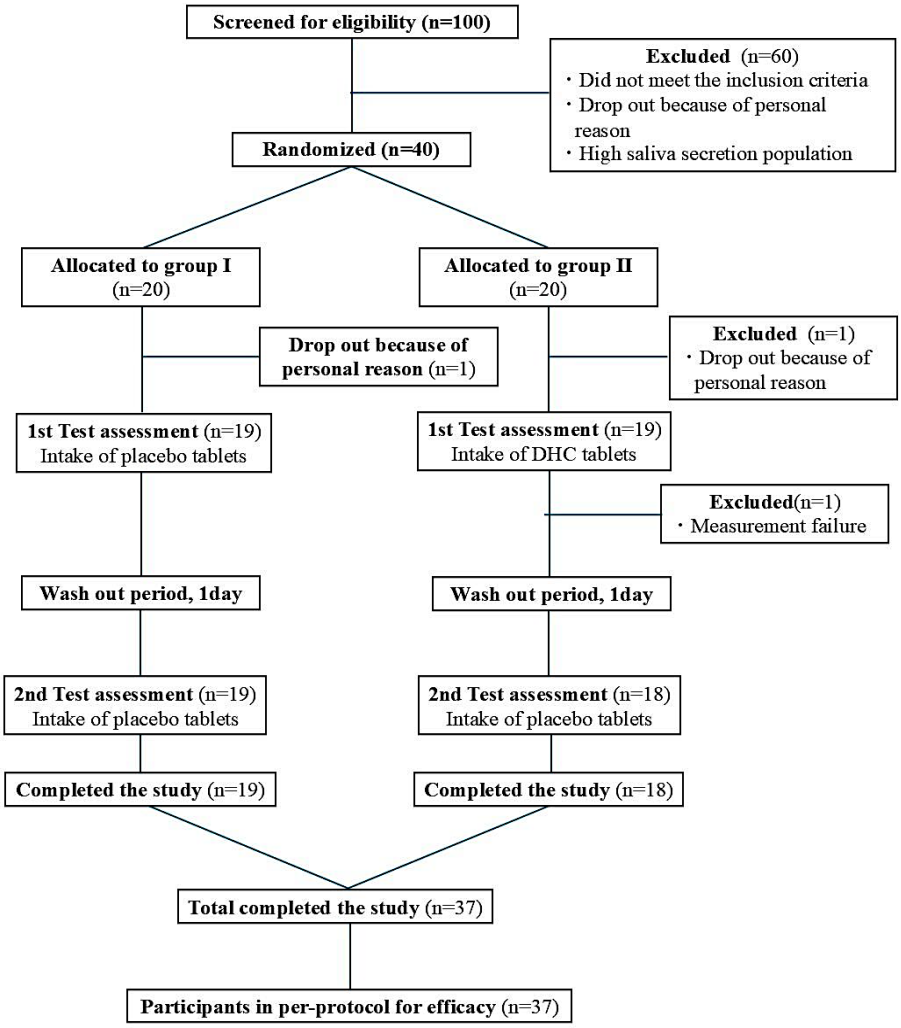


Figure 2. Flow of participants through the study.

Table 1. Baseline characteristics of the participants.

	All participants	Group 1	Group 2
Participants, n	37	19	18
Sex (F/M), n	20/17	11/8	10/9
Age	54.9 ± 7.6	54.9 ± 7.3	54.9 ± 7.8
BMI kg/m²	22.4 ± 2.9	22.4 ± 3.1	22.3 ± 2.7
Saliva flow rate (g/15 min)	3.01 ± 0.91	3.02 ± 0.95	3.00 ± 0.90

Data are presented as the mean ± SD.

The backgrounds of the study participants are listed in the Table. 1. There were no significant differences in the background factors between the two groups.

Salivary Secretion: The saliva secretion results are presented in Table 2. After the treatment, a significantly higher salivary flow rate was observed in the DHC group than in the placebo group (DHC group: 9.64 ± 4.00 g/15 min, placebo group: 8.16 ± 3.18 g/15 min). In addition, compared to the placebo group (295 ± 154%), the DHC group showed a significantly higher percentage increase from baseline (352 ± 189%).

Table 2. Effects of *Dihydrocapciate* on saliva flow rate.

	Resting saliva (Baseline)	Placebo group	DCH group	p-Value
Saliva Flow Rate (g/15 min)	3.01 ± 0.90	8.16 ± 3.18	9.64 ± 4.00	0.0006
Percentage Increase from Baseline (%)	-	295 ± 154	352 ± 189	0.0003

Data are presented as the mean SD. *Student's t-test, the placebo group vs DCH group.

Assessment of Subjective Dryness (VAS Score): The VAS scores for subjective dryness showed no significant differences between the groups. One possible reason for the lack of significant differences in the VAS assessment of salivary function is that symptom perception is inherently subjective and may vary considerably among individuals. Furthermore, subtle physiological changes in salivary secretion may not be readily perceived or accurately self-reported by participants, which could have reduced the sensitivity of the VAS as a tool for evaluating short-term changes in salivation.

Safety Assessment: Body weight, BMI, and blood pressure remained stable throughout the study, with no medically relevant changes noted.

DISCUSSION

The present study demonstrated that DHC significantly enhanced salivary secretion compared to the placebo group, indicating its potential utility in the management of dry mouth (xerostomia). Given the increasing prevalence of xerostomia due to aging, medication use, and underlying conditions such as Sjögren's syndrome, the identification of safe and effective stimulants for salivary secretion is of great clinical importance.

Mechanism of Action and Advantages of DHC: Previous research has established that capsaicin, a well-known activator of TRPV1, promotes salivation by stimulating TRPV1-expressing sensory nerves in the oral mucosa [16-18]. Our findings suggest that DHC, which structurally resembles capsaicin and activates TRPV1, can also induce salivation in a similar manner. However, unlike capsaicin, DHC is known for its low pungency and reduced nociceptive stimulation [20], making it a more tolerable alternative for therapeutic applications. This reduced irritation is particularly beneficial for individuals who may be sensitive to spicy compounds or those requiring long-term salivation enhancement without discomfort.

A modest increase in salivary secretion was also observed in the placebo group. This may be explained by several factors. First, the act of placing a tablet on the tongue—regardless of its active ingredients—may provide mechanical stimulation that triggers salivary reflexes. Additionally, psychological factors such as expectation or placebo effects may also enhance salivation. These factors may have contributed to the increase in salivary secretion observed in the placebo group; however, the significantly greater impact in the DHC group supports the specific action of DHC on salivary secretion.

While both DHC and capsaicin activate TRPV1, they differ markedly in their sensory effects and pharmacological profiles. Capsaicin, the pungent compound in chili peppers, is known to stimulate salivary secretion via the trigeminal-parasympathetic reflex [16-18]. Still, its intense irritant properties limit its long-term usability in clinical or dietary contexts. In contrast, DHC, derived from the non-pungent "CH-19 Sweet" pepper, activates TRPV1 without causing significant irritation [20,

23].

The threshold dose for pungency of DHC is approximately 1,000 times higher than that of capsaicin [21], making it suitable for sensitive populations. Furthermore, TRPV1 has been reported to be expressed in the salivary glands themselves. [15, 19] Therefore, it is also possible that DHC promotes salivary secretion by directly acting on TRPV1 receptors in the salivary glands. This study suggests that, in addition to neural pathways, DHC may stimulate secretory cells through direct activation of TRPV1 in the salivary glands, representing an essential perspective for future investigations into its underlying mechanisms.

Differential Tissue Permeability and Sustained TRPV1 Activation: Another important aspect of DHC is its differential tissue permeability compared to capsaicin.[23] Capsaicin readily penetrates biological membranes and accumulates in tissues, leading to prolonged desensitization of TRPV1-expressing neurons. In contrast, DHC exhibits a distinct tissue migration profile, which may allow for a more sustained and controlled activation of TRPV1 without excessive receptor desensitization. This characteristic could be advantageous for maintaining consistent salivary stimulation over time, reducing the risk of receptor downregulation that is sometimes observed with repeated capsaicin exposure.

Clinical Implications and Safety Considerations: From a clinical perspective, the potential of DHC as a treatment for xerostomia is highly promising. Many current treatments, such as artificial saliva and systemic sialagogues, have limitations, including transient relief, undesirable side effects [5-6], or lack of physiological stimulation of the salivary glands. DHC, by directly stimulating endogenous salivation, may offer a more natural and effective approach to managing dry mouth symptoms. Moreover, its favorable safety profile supports its potential application in functional foods or pharmaceutical products designed to improve salivary gland function.

DHC has already been studied and marketed as a thermogenic agent that enhances resting energy expenditure, a component of energy metabolism.[24-26] These products are commercially available not only in Japan but also in the USA, Europe, Brazil, and Australia, and gradual safety evaluations have been conducted to confirm their suitability for human consumption.[24] Notably, the dosage used for oral application (salivary stimulation) in this study is approximately one-tenth of the dosage used for enhancing energy metabolism.[24] Given this significantly lower dose, DHC is expected to maintain a high safety profile for oral use.

Limitations of the Study: Despite the promising findings, this study has several limitations. One notable limitation is that the study was conducted over a short period, and the long-term effects of DHC on salivary secretion remain unknown. While this study demonstrated an acute increase in saliva secretion, it is unclear whether prolonged intake would maintain or enhance this effect. Future studies should investigate the sustained impact of repeated DHC administration over weeks or months.

Additionally, the study population consisted of healthy adults aged 40 to 70 years who experienced mild symptoms of dry mouth. As a result, the findings may not be directly generalizable to patients with severe xerostomia, such as those with Sjögren's syndrome or individuals undergoing radiation therapy for head and neck cancer. To confirm DHC's effectiveness in these populations, clinical trials involving patients with different underlying causes of xerostomia are necessary.

Furthermore, although TRPV1 activation is presumed to be the mechanism behind DHC-induced salivation, this study did not directly investigate the

intracellular signaling pathways or neural mechanisms involved in the process. Further research should focus on elucidating the molecular pathways through which DHC influences salivary secretion, including possible secondary messengers and interactions with the autonomic nervous system.

Scientific Significance and Practical Implications: This study expands the current understanding of TRPV1 activation and salivary regulation by demonstrating that dihydrocapsiate (DHC), a non-pungent TRPV1 agonist, effectively stimulates saliva secretion. Unlike capsaicin, DHC offers a more tolerable sensory profile, which broadens the potential application of TRPV1-mediated interventions to individuals who are sensitive to pungent stimuli.

These findings suggest that DHC may be developed as a functional food ingredient or supplement to support oral hydration, particularly for individuals experiencing mild dry mouth due to aging, medication use, or environmental factors. Its low pungency not only enhances user compliance but also makes it a promising candidate for long-term use in both clinical and general health settings.

CONCLUSION

This study provides strong evidence that DHC can effectively stimulate salivary secretion through TRPV1 activation while avoiding the discomfort associated with capsaicin. Given its low irritant properties, differential tissue permeability, and potential for long-term use, DHC represents a promising candidate for managing xerostomia. Additionally, existing safety data from energy metabolism applications, combined with the significantly lower dosage required for oral use, further support its safety profile.

Abbreviations: DHC, dihydrocapsiate; TRPV1, transient receptor potential vanilloid 1; BMI, body mass index; SD, standard deviation.

Competing Interests: Keisuke Yoshida and Osamu Sakai are employees of Senju Pharmaceutical Co., Ltd. They were responsible for the test supplements but were not involved in the investigation, formal analysis, or data curation. The results of this study are as follows: clearly and without fabrication, falsification, or inappropriate data manipulation.

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