Regular Article

Ginger Orally Disintegrating Tablets to Improve Swallowing in Older People

Ayumu Hirata,*[a,b] Hiroki Funato,[a] Megumi Nakai,[a,b] Michiro Iizuka,[a] Noriaki Abe,[a,b] Yusuke Yagi,[a,b] Hisashi Shiraishi,[a,b] Kohei Jobu,[a] Junko Yokota,[a] Kahori Hirose,[c] Masamitsu Hyodo,[c] and Mitsuhiko Miyamura[a,b]

[a] *Department of Pharmacy, Kochi Medical School Hospital; 185–1 Kohasu, Oko-cho, Nankoku, Kochi 783–8505, Japan:* [b] *Kochi Medical Graduate School; 185–1 Kohasu, Oko-cho, Nankoku Kochi 783–8505, Japan: and* [c] *Department of Otolaryngology, Head and Neck Surgery, Kochi Medical School; 185–1 Kohasu, Oko-cho, Nankoku, Kochi 783–8505, Japan.*

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We previously prepared and pharmaceutically evaluated ginger orally disintegrating (OD) tablets, optimized the base formulation, and carried out a clinical trial in healthy adults in their 20 s and 50s to measure their effect on salivary substance P (SP) level and improved swallowing function. In this study, we conducted clinical trials using the ginger OD tablets in older people to clinically evaluate the improvements in swallowing function resulting from the functional components of the tablet. The ginger OD tablets were prepared by mixing the excipients with the same amount of mannitol and sucrose to a concentration of 1% ginger. Eighteen healthy older adult volunteers aged 63 to 90 were included in the swallowing function test. Saliva was collected before and 15 min after administration of the placebo and ginger OD tablets. Swallowing endoscopy was performed by an otolaryngologist before administration and 15 min after administration of the ginger OD tablets. A scoring method was used to evaluate the endoscopic swallowing. Fifteen minutes after taking the ginger OD tablets, the salivary SP amount was significantly higher than prior to ingestion or after taking the placebo ($p<0.05$). Among 10 subjects, one scored 1–3 using the four evaluation criteria. Overall, no aspiration occurred and a significant improvement in the swallowing function score was observed ($p<0.05$) after taking the ginger OD tablets. Our findings showed that the ginger OD tablets increased the salivary SP amount and improved swallowing function in older people with appreciably reduced swallowing function.

Key words older people; dysphagia; ginger; orally disintegrating tablet; substance P; saliva

The Japanese population is aging rapidly with older people (≥65 years) making up greater than 22% with further increases anticipated. Older people often suffer reduced vital functions from a combination of underlying disease and reduced physical and cognitive abilities. In particular, dysphagia is a serious problem and combined with reduced cough reflex, leads to increased risk of aspiration pneumonia. Currently pneumonia is the third leading cause of death in Japan, and the cause of death in greater than 90% of older patients. Aspiration is the speculated cause in many of the pneumonia related deaths.[1–3] Dysphagia also leads to malnutrition, dehydration, and loss of pleasure in eating, decreasing the patients' quality of life. The swallowing reflex is controlled by substance P (SP). Secretion of SP from nerve endings in the bronchial mucosa and oral cavity[4,5] is essential to proper swallowing function and reduced SP secretion is the cause of dysphagia. Swallowing dysfunction can be caused by decreased production of dopamine and SP. Salivary SP levels in older people are reported to be significantly lower than in healthy younger individuals.[6] When basal ganglia are disturbed, such as with cerebral infarction, dopaminergic nerve function decreases and then SP secretion decreases. These effects combined with reduced cough and swallowing reflex increases the risk of aspiration pneumonia. Cerebral infarction lesions have been found in approximately half of older patients with pneumonia[7] and both reduced cough reflex and swallowing function are reported in these patients.[8] Increased SP levels lead to reduced aspiration and decreased pneumonia rates and SP levels increase in response to angiotensin converting enzyme inhibitors,[9,10] cilostazol,[11] amantadine,[12] and herbal remedies.[13] However, these compounds do not ensure dysphagia improvement and side effects are a concern. To address these problems, attention has turned to food components, including capsaicin (the pungent component of *Capsicum annuum*). Capsaicin is an agonist of transient receptor potential vanilloid type 1 (TRPV1)[14,15] and promotes SP release from nerve endings in the oral cavity, improving the swallowing reflex. Capsaicin activates the TRPV1 from unmyelinated airway C-fibers.[16] SP released from nerve endings in the mucosa and mouth is derived from the influx of Ca^{2+} into the cell because of activation of TRPV1 which then promotes secretion of SP.[17]

In this study, we focused on ginger (*Zingiber officinale*) obtained from Kochi Prefecture, which is the leading area of ginger production in Japan. Ginger contains a vanillin derivative as a functional ingredient, similar to capsaicin, and also includes 6-, 8-, 10-shogaol and 6-, 8-, 10-gingerol as pungent components. Ginger has various medicinal effects, such as inhibition of hyperglycemia and antioxidant and antithrombotic activities.[18] The ginger components activate TRPV1.[19–21] The swallowing reflex improvement action of 6-gingerol has been reported.[22] However, this study was performed in rat.

We chose an orally disintegrating (OD) form for the tablets because they can be easily taken by both pediatric patients and older people with swallowing difficulties and can be maintained at a high concentration in the oral cavity, the site of action of the main component. We prepared and pharma-

* To whom correspondence should be addressed. e-mail: jm-hayumu@kochi-u.ac.jp

ceutically evaluated OD tablets containing ginger, optimized the base formulation, and conducted a clinical trial in healthy adults in their 20's and 50's to measure their effects on salivary SP level and improvement of swallowing function.[23] In this follow-up study, we conducted clinical trials in older people using ginger OD tablets to clinically evaluate improvement in swallowing function resulting from the functional components.

MATERIALS AND METHODS

The materials were those used in the general production of the ginger OD tablets[23] except that ginger powder from Kochi was added (Asano Co., Ltd., Kochi, Japan; lot: 2012.10.25). The 6-, 8-, and 10-gingerol and 6-shogaol components were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Acetonitrile and water were of high-performance liquid chromatography grade and other reagents were commercial guaranteed-grade products. Mannitol and sucrose were purchased from Roquette (Keokuk, IA, U.S.A.) and Yoshida Pharmaceutical Co., Ltd. (Tokyo, Japan), respectively. Cornstarch binder was obtained from Nihon Shokuhin Kako (Tokyo, Japan), and calcium stearate lubricant was obtained from Taihei Chemical Industry Co., Ltd. (Osaka, Japan). Other reagents were of the highest grade commercially available.

Quantitative Determination of TRPV1 Agonist in the Ginger Examination of the 6-, 8-, and 10-gingerol and 6-shogaol composition of ginger powder was performed using a HPLC method.[24] Five grams of ginger powder were placed in a centrifuge tube and twice the sample mass of 99% ethanol was added. The preparation was sonicated for 20 min (Ultrasonic Cleaner; Yamato Scientific Co., Ltd., Tokyo, Japan) and subsequently centrifuged for 5 min at 4000 rpm (Centrifugal Separator; Kubota Corporation, Tokyo, Japan). The supernatant was transferred, stored at 4°C, and filtered through a Merck Millipore Filter (Millex-FG Filter Unit, 0.2 μm, hydrophobic PTFE membrane; Kyoto, Japan) before being injected onto the HPLC column. HPLC was performed using a HITACHI HPLC (L-2130 PUMP; Kyoto, Japan) with a diode array detector (L-7450H Plus). Chromatographic separation was performed as follows: column (Cosmosil 5C18-MS-II, 4.6 mm i.d.×150 mm; Nacalai Tesque Inc.), mobile phase A [water–acetonitrile–trifluoroacetic acid (69.95 : 30 : 0.05)]; mobile phase B [water–acetonitrile–trifluoroacetic acid (9.95 : 90 : 0.05)], gradient: 0–20 min, 100 to 10% A, 20–30 min 10% A, flow rate: 1.0 mL/min, column temperature: 40°C, detection: UV 228 and 280 nm, and injection volume: 10 μL. Experiments were performed five times and the standard error (S.E.) was calculated.

Preparation of the Ginger OD Tablets To prepare the ginger OD tablets, the excipients were mixed with the same amount of mannitol and sucrose to a concentration of 1% ginger. The ginger concentration was selected based on the studies by Ebihara *et al.*[14] and Sugiyama *et al.*[22] Furthermore, we previously reported the results from a clinical trial in healthy adults in their 20 s and 50s to measure the effect of ginger OD tablets on salivary SP level and improved swallowing function.[23]

The ginger OD tablet consisted of 2 mg ginger powder, 177.1 mg excipient mixed with the same amount of mannitol and sucrose, 19.9 mg cornstarch (binder), and 1.0 mg calcium stearate (lubricant). A hand press (NPa Systems, Saitama, Japan) was used to produce ginger OD tablets at a compression pressures of 8 kN. The final product consisted of flat ginger OD tablets (200 mg) with an 8-mm diameter and 3-mm thickness.[23] Placebo tablets consisted of 179.1 mg excipient mixed with the same amount of mannitol and sucrose, 19.9 mg cornstarch (binder), and 1.0 mg calcium stearate (lubricant). The placebo tablets did not include the ginger and were produced in the same manner as the ginger OD tablets.

Clinical Trial This study was conducted according to the regulations and approval of the Ethical Review Board of Kochi Medical School (approval No. 23–89) and was in accordance with the principles of the Helsinki Declaration. All subjects gave their written and oral informed consent to participate in the study.

Background of the Subjects Subjects included 13 men and 5 women. We excluded subjects with liver disease, serious kidney, heart, or hematologic disease, drug hypersensitivity, and those who were pregnant or possibly pregnant. We also excluded subjects taking drugs with a significant impact on swallowing function.

Assessing Effects on Salivary SP Amount The 18 subjects included 13 men and 5 women with an average age of 71.2±7.7 years. Saliva was collected before and 15 min after separate administration of the placebo OD tablets and the ginger OD tablets. The salivary SP amount was measured with an SP ELISA kit (R&D Systems, Minneapolis, MN, U.S.A.) using a microplate reader (VersaMax; Molecular Devices, Sunnyvale, CA, U.S.A.). The saliva was collected in a saliva collection tube (Sarstedt, Humbrecht, Germany) and the volunteers were prohibited from eating and drinking prior to the test and after taking the placebo OD tablets and the ginger OD tablets.

Assessing Impact on Swallowing Function

Swallowing Screening Assessment

Eighteen subjects described above, a further 10 subjects including 5 men and 5 women with an average age of 74.8±8.4 years were evaluated using the repetitive saliva swallowing test,[25] and a drinking test (Kubota testing[26]) before separately taking the placebo and the ginger OD tablets and 15 min after examination by a speech therapist. The repetitive swallowing saliva test involved recording how many times a patient could perform empty swallowing over 30 s. Dysphagia may be experienced by a patient if his/her rate of swallowing is less than three times over 30 s. The Kubota water swallowing test was used to observe the middle stage of swallowing and to record the time to drink 30 mL of water. The test was evaluated based on five stages: (1) it is possible to swallow the water without choking once; (2) it is possible to swallow the water in two or more portions and without choking; (3) although it is possible to swallow the water in one portion, choking may occur; (4) despite swallowing the water in two or more portions, choking sometimes occurs; (5) choking occurs often and it is difficult to swallow the total amount of water.

Evaluation of Swallowing Function by Swallowing Endoscopy Swallowing endoscopy was performed on 10 subjects by an otolaryngologist before administration and 15 min after separate administration of placebo and the ginger OD tablets to evaluate swallowing function. Methylrosanilinium chloride was used to prepare 3 mL of blue-dyed water and the nasopharynx, hypopharynx, and larynx were then examined

Table 1. Scoring in Swallowing Endoscopy

Parameters		Normal←Score→Severe
Four parameters	The degree of salivary pooling at the vallecula and piriform sinuses	0・1・2・3
	The glottal closure reflex induced by touching the epiglottis or arytenoid with the endoscope	0・1・2・3
	Swallowing reflex initiation assessed by "white-out" timing	0・1・2・3
	Pharyngeal clearance after blue-dyed water is swallowed	0・1・2・3
	Aspiration	None・Mild・Severe
	Associated feature	Nasopharyngeal regurgitation
		Early pharynx influx
		Vocal cord paralysis・( )

endoscopically before and after swallowing the blue-dyed water. Evaluation was performed according to the scoring method proposed for endoscopic swallowing evaluation.[27] This clinical scoring system was developed for flexible endoscopic evaluation of swallowing and assesses four factors: (1) the degree of salivary pooling at the vallecula and piriform sinuses; (2) the glottal closure reflex induced by touching the epiglottis or arytenoid with the endoscope; (3) swallowing reflex initiation assessed by "white-out" timing; and (4) pharyngeal clearance after blue-dyed water is swallowed, categorized as 0 for normal, 1 for mildly impaired, 2 for moderate, or 3 for severe. According to the authors of the study, scores given by experienced otolaryngologists with expert-level experience in treating dysphagic subjects correlated significantly with those given by nonexpert otolaryngologists and speech-language-hearing therapists. Pharyngeal clearance evaluated by swallowing endoscopy correlated with the test scores to a statistically significant degree, as did aspiration severity with total scores. We considered a score of 4 to 5 points as normal, independent oral intake and that oral intake should be discontinued with a score of ≥9 to 10. Table 1 shows the scoring system for the swallowing endoscopy test.

Statistical Analysis Paired *t*-tests were used to analyze the data and the significance was set at $p<0.05$. The Mann–Whitney *U*-test with Bonferroni correction was set at $p<0.05$.

RESULTS

Quantitative Determination of the TRPV1 Agonist in the Ginger Table 2 shows the content of each component of the TRPV1 agonist of the ginger. The 6-, 8-, and 10-gingerol and 6-shogaol were quantitated at 10.56±1.26, 1.12±0.06, 6.05±0.58, and 0.99±0.05 mg contained in 1 g ginger powder, respectively.

Impact on Swallowing Function

Effects on Salivary SP

The effects of taking the ginger OD tablets on salivary SP are shown in Table 3. The average salivary SP amount was 497.0±201.3 pg/mg protein before and 504.8±189.8 pg/mg protein 15 min after ingesting the placebo OD tablets. The average salivary SP amount was 833.0±203.8 pg/mg protein 15 min after the ginger OD tablets. Fifteen minutes after taking the ginger OD tablets, the salivary SP amount was significantly higher compared with prior to the ingestion and the ingestion of the placebo OD tablets ($p<0.05$).

Swallowing Screening Assessment

The results from the swallowing screening assessment are shown in Table 4. The results of the repetitive saliva swallowing test showed that three times more swallowing occurred before and 15 min after taking the placebo compared with the ginger OD tablets. However, one subject required less time to perform the empty swallowing test. For the drinking test, subjects were divided into two groups: those swallowing two or more times, and those who could drink water without choking. No differences in the swallowing screening test results were observed before or 15 min after taking the placebo or the ginger OD tablets.

Table 2. Content of the TRPV1 Agonist of Ginger

Component	Content (mg/g pow)	C.V.
6-Gingerol	10.56±1.26	0.27
8-Gingerol	1.12±0.06	0.12
10-Gingerol	6.05±0.58	0.22
6-Shogaol	0.99±0.05	0.11

Results are expressed as the mean±S.E. of 5 expeiments.

Evaluation of Swallowing Function by Swallowing Endoscopy The results of the evaluation of swallowing function by swallowing endoscopy are shown in Table 5. Of the 10 subjects, one scored 1–3 in the four evaluation criteria. The median of the swallowing endoscopy score was 2 before taking the ginger OD tablets, and 2 at 15 min after taking the placebo and 1 at 15 min after taking the ginger tablets. No aspiration occurred and improvement in the swallowing function score was observed after taking the ginger OD tablets ($p<0.05$).

DISCUSSION

In an effort to quantitatively determine the identity of the TRPV1 agonist in the ginger, the functional ingredients were analyzed. Six-gingerol was believed to be responsible for the improvement in swallowing function, possibly by acting as a TRPV agonist in a similar manner as capsaicin, the pungent component of *Capsicum annuum*. Both Ebihara *et al.*[14] and Sugiyama *et al.*[22] and Abe *et al.*[23] have previously explored the benefits of food components, including ginger, in the improvement of swallowing function.

Compared with healthy people over the age of 70, our clinical trial subjects suffered decreased swallowing function related to aging. Using our simplified examination of swallowing function, the drinking test, and the repetitive saliva swallowing test, the risk of aspiration was small, but the uncertainty about the presence of dysphagia was a concern. We also observed mild swallowing dysfunction during endoscopy.

Table 3. The Effects of Taking the Ginger OD Tablets on Salivary SP

Subject No. (pg/mg protein)	1	2	3	4	5	6	7	8	9	10
Control	763.0	856.6	696.6	507.4	360.6	374.2	788.2	621.0	511.7	256.7
Placebo	547.8	868.0	850.1	541.4	435.8	364.7	505.9	732.9	344.4	251.8
Ginger	968.5	860.8	1030.5	928.4	369.5	576.1	619.6	979.9	688.9	867.3

Subject No. (pg/mg protein)	11	12	13	14	15	16	17	18	Average
Control	455.4	268.5	536.3	454.5	116.2	365.4	704.6	308.7	497.0±201.3*
Placebo	797.6	265.6	532.5	466.5	236.1	426.1	469.1	450.7	504.8±189.8*
Ginger	916.6	645.6	817.9	1122.3	705.9	709.5	1185.7	1001.1	833.0±203.8

Paired *t*-tests were used to analyze the data and significance was set at $*p<0.05$.

Table 4. Swallowing Screening Assessment

1) Repetitive saliva swallowing test

Subject No. (times)	1	2	3	4	5	6	7	8	9	10
Before	6	8	3	12	5	3	3	8	6	4
Placebo	5	7	4	11	4	3	3	7	6	5
Ginger	6	7	4	10	4	4	4	8	6	5

2) A drinking test (Kubota testing)

Subject No. (stage)	1	2	3	4	5	6	7	8	9	10
Before	2	2	2	2	1	2	2	2	1	2
Placebo	2	2	2	2	1	1	2	2	1	2
Ginger	2	2	2	2	1	1	2	2	1	2

Table 5. Evaluation of Swallowing Function by Swallowing Endoscopy

Subject No. (score)	1	2	3	4	5	6	7	8	9	10	Median
Before	3	1	2	2	1	2	1	1	2	2	2
Placebo	3	0	2	2	1	2	1	1	2	2	2
Ginger	2	0	1	1	0	1	1	1	1	2	1*

Mann–Whitney *U*-test with Bonferroni correction was set at $*p<0.05$.

Both of these findings are consistent with reduced swallowing function with age, which could lead to further reduction in swallowing function in the future, aspiration pneumonia, malnutrition, and dehydration.

Several methods have been studied to prevent aspiration pneumonia related to dysphagia. Capsaicin is the pungent component of chili peppers and it induces the swallowing reflex by acting as an agonist of TRPV1. In fact, lozenges and films containing capsaicin are now on the market.[14] We have studied the amount of salivary SP induced when taking capsaicin film and reported that in adults over the age of 65, the salivary SP content was increased following its ingestion.[28] However, irritation and a residual burning sensation have been problematic. The ginger OD tablets did not cause irritation and no subjects complained of any side effects.

Our results showed that the salivary SP amount was significantly increased in healthy older adults taking the ginger OD tablets as a result of the gingerol and shogaol components stimulating TRPV1 and affecting swallowing function. Compared with the results of Abe *et al.*,[23] the salivary SP amount was increased in healthy older adults to near the levels observed in healthy young adults. From the swallowing screening assessment, a significant difference between the placebo and the ginger OD tablets was not observed. Since the swallowing screening assessment is used to test for the presence or absence of dysphagia, it is possible that administration of a single dose of ginger OD tablets is not sufficient to significantly affect swallowing as measured by the scoring system. From the evaluation of the swallowing function by swallowing endoscopy, it was evident that ingestion of the ginger OD tablets helped to reduce the swallowing endoscopy score, suggesting an improvement in function. From these results, there was a correlation in the swallowing function and the saliva SP amount and the possibility that the salivary SP amount was a biomarker of the swallowing function. Similar results have been reported by Abe *et al.*[23] A correlation of the level of SP in blood and saliva and aspiration pneumonia has been reported by Nakamori *et al.*[29] Patients with low levels of SP in blood and saliva have a greater tendency to experience aspiration pneumonia. The results from both of our studies show a similar trend,[29] and SP levels in saliva may be a useful marker of swallowing function. We consider that the swallowing function in older adults could be improved as much as young adults by taking the ginger OD tablets.

Salivary SP can be measured in a minimally invasive way and is a useful biomarker for swallowing function. Future work includes plans to expand the clinical trials to establish the efficacy of measuring salivary SP for assessing improved swallowing function and the safety of the ginger OD tablets in repeated dose studies. We are also planning studies on a percutaneous ginger preparation suitable for dysphagia patients to assess its effectiveness in improving swallowing function and its pharmacodynamics and safety.

In conclusion, the mechanism responsible for improving swallowing function is believed to be a result of the gingerol compound acting as a TRPV1 agonist. The ginger OD tablets increased the salivary SP amount in older people with appreciable deterioration of swallowing function related to aging.

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Conflict of Interest The authors declare no conflict of interest.

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