ORIGINAL ARTICLE

The Effects of Ginger on Unstimulated Salivary Flow Rate: A Double-Blind, Randomized, Placebo-Control Trial

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Objective: To investigate the effects and safety of standardized ginger powder (SGP) on healthy volunteers' unstimulated salivary flow rate (USFR).

Materials and Methods: The present study was a single-visit, double-blind, randomized, placebo-control trial conducted in Thailand. Healthy volunteers aged 18 to 60 were eligible if they met all the criteria. They were allocated to four groups using block randomization to ensure an equal number in each group. The control group received a placebo, while the other three experimental groups received 1,000 mg, 1,500 mg, and 2,000 mg SGP, respectively. The primary outcome was the USFR, measured by a modified Schirmer test. The post USFR was measured 45 minutes after the intervention and was compared to the baseline USFR. The research assistants administered placebo and SGP capsules, identical in their appearance. The volunteers and the investigator were unaware of the assigned interventions.

Results: Total of 368 volunteers were randomly assigned to four groups, each consisting of 92 participants. All three experimental groups showed a change in USFR. However, only the 2,000 mg group showed a significant increase in the USFR (mean difference 9.47 mm/5 minutes, 95% CI 3.24 to 15.71, p=0.003). Approximately 32.6% of the volunteers reported side effects, mainly gastrointestinal events, such as belching (16.3%) and mild abdominal discomfort (7.9%).

Conclusion: Two thousand mg SGP significantly increased USFR, yet the effect size was modest. This may be due to the low concentration of bioactive compounds in the SGP used in the present study. All side effects were minor and temporary.

Keywords: Ginger; Unstimulated salivary flow rate; Modified Schirmer test

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Ginger (*Zingiber officinale* Roscoe) is one of the oldest medicinal herbs in human history[1]. It possesses many pharmacological effects[2-4]. Previous clinical trials showed positive results of using ginger as an antiemetic in early pregnancy[5], analgesic in primary dysmenorrhea[6], anti-inflammatory in elderly knee osteoarthritis[7], galactagogue in breastfeeding mothers[8], and antimicrobial in oral cavities[9]. Ginger is considered safe as a medicinal herb[10] and food ingredient[11]. Meta-analysis studies and systematic reviews also reported the safe use of ginger for osteoarthritis[12], primary dysmenorrhea[13], and as an antiemetic[14]. Most side effects of ginger are insignificant and consist of gastrointestinal-correlated symptoms[15]. Nevertheless, high dosage of ginger may modify the effects of some medications, such as antiplatelets[16].

According to Asian traditional medicine, ginger has long been known as a sialagogue[17]. However, there is little evidence to support this belief, especially in terms of scientifically based clinical research. Salivation in humans is regulated by the autonomous nervous system (ANS). Parasympathetic divisions of the seventh cranial nerve innervate lacrimal, nasal mucous, and salivary glands[18]. With the release of acetylcholine binding to muscarinic receptors by parasympathetic nerves, saliva secretion is stimulated[19]. Nonetheless, human salivation might be affected by other factors, such as systemic diseases, medications, mental health status, and some natural traits[19-21]. One study showed that ginger extract could stimulate salivary glands in mice[22]. So

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far, only three published clinical trials have described the effects of ginger on mouth dryness, and all of them show promising results[23-25].

It is essential to gather more empirical evidence, and conducting a clinical trial to establish the use of ginger as a sialagogue is a necessary step. To fill the knowledge gap, the authors aimed to investigate the effects of standardized ginger powder (SGP) on the unstimulated salivary flow rate (USFR) and its safety in healthy individuals. The authors hypothesized that ground ginger powder could increase saliva secretion.

Materials and Methods

The design was a single-center, equal randomized, double-blind, placebo-control, and multi-arm trial. The present study was conducted in a community hospital and four sub-district health promoting hospitals. The volunteers were randomly assigned to four parallel groups in a 1:1:1:1 ratio, receiving one of four interventions. The volunteer took the intervention only once and completed the trial in one visit. No significant protocol amendment occurred during the study. A minor protocol amendment was the setup of satellite sites to make the intervention more convenient for the volunteers.

The eligible volunteers were healthy, non-smoking, and non-drinking individuals aged 18 to 60 years with no known critical illness. The exclusion criteria were ginger allergy, pregnancy, breastfeeding, menstruation, history of head and neck radiotherapy, antithrombotic drugs, antihistamines, decongestants, nonsteroidal anti-inflammatory drugs (NSAIDs), history of or scheduled surgery within two weeks, history of gallstones or bile duct obstruction, herpes labialis, and a previous meal which may alter salivary secretion. Specific criteria were applied to ensure that the changes in the USFR resulted from the intervention. The history of the last meal was crucial. Some foods, such as sour or spicy foods, citrus fruits, high calcium carbonated vegetables, coffee, tea, or soft drinks, could alter salvation. Finally, all volunteers were required to take a COVID-19 risk assessment.

The present study was conducted in the government medical facilities in Khaosuankwang. Khon Kaen Zoo and a large urban water park have attracted tourists from nearby provinces, yet most people in the district work in agricultural-related jobs. As with other areas in Northeast Thailand, the district has a long hot season with unpredictable rainfall and a short winter.

The volunteers were informed of the research objectives, expected duration, the process, expected benefits, possible risks, and discomforts of the trial. The investigation began the process with body weight and height measurements. After the baseline USFR was measured, the volunteer was sent to meet the research assistants who delivered the intervention. The volunteers then returned to the waiting area. After approximately 45 minutes, the post USFR was measured. The investigator also interviewed the volunteers about ginger-related side effects. Each volunteer received about 4.5 U.S. dollars for travel expenses.

Four interventions occurred in the present study: one placebo and three doses of SGP. The ginger powder utilized in the trial was selected from commercial ginger supplements available in Thailand to meet three criteria: Thai Food and Drug Administration (FDA) approval, Good Manufacturing Practice (GMP) certification, and bioactive compound standardization. Capsule Ginger Tra KMP (produced by Kaewmungkornphaesaj Company Limited, based in Photharam, Ratchaburi, Thailand) was a 500 mg capsule of dried powder ginger standardized for at least 0.01 mL volatile oils and registered as traditional medicine (No. G131/54). Ten boxes of the same production code (Lot No. 546202) were purchased from a local pharmaceutical retailer. The authors claimed neither direct nor indirect benefits from selecting this product. The placebo was corn starch in an ivory-yellow capsule, representing the same color and size capsule of SGP. The control group received four capsules of the placebo. The first experimental group, 1,000 mg, received two capsules of SGP and two capsules of a placebo, while the second experimental group, 1,500 mg, received three capsules of SGP and one capsule of a placebo. Finally, the third experimental group, 2,000 mg, received four capsules of SGP. The intervention was delivered in an amber zip-lock bag together with a water bottle. The volunteers were advised to swallow four capsules with water. They were also encouraged to inform the investigator of any side effects.

The primary outcome was the USFR as measured by the modified Schirmer test, a method adapted from the Schirmer tear test[26], whereas the secondary outcome was a side effect of SGP as collected by observation and interview. The baseline USFR was measured before taking the intervention. Whatman filter paper no.41 (diameter 18 cm) was cut into a long strip of 1×17 cm and kept in an airtight container. A

digital stopwatch was used as a timing device, and the reading was conducted at five minutes. The wet length was measured using a standard Vernier scale, and the unit of measurement was mm/5 minutes. The process started at least two hours from the volunteer's last meal. The volunteers were kept informed and prepared for the measurement. After rinsing the mouth with bottled water and relaxing for five minutes, the volunteer sat upright at rest and minimized movement, especially in the mouth. The timing started with the swallowing of the saliva remaining in the mouth. The volunteer raised and slightly retracted the tongue, and the Whatman paper strip was placed on the floor of the mouth at the midline position and held gently without contacting other oral structures. The volunteer was informed to mildly rest the tongue on the strip (covering 1 cm) and could not swallow saliva during the process. A 30×30 cm paper napkin was placed around the neck in case of excessive saliva. After five minutes, the Whatman paper strip was removed and put on a dry, shallow stainless-steel tray. A standard Vernier scale (up to two decimal places) was used to measure the paper strip from the tip to the mid-end point of the wet length. Forty-five minutes after taking the intervention, the post USFR was measured. Food, caffeine or soft drinks, gum, and smoking were prohibited during the process. After the post USFR measurement, the volunteers were interviewed about ginger-related side effects.

The number of volunteers participating in the present study was calculated based on the statistical method used to obtain the mean difference of USFRs under a linear regression framework. This statistical methodology required 92 volunteers in each group, resulting in 368 volunteers required for the study. A computer-generated randomization code was prepared using the Stata, version 14 (StataCorp LP, College Station, TX, USA). Block randomization with a block size of four and eight was used to ensure an equal number of 92 volunteers per group. A copy version was made and masked by four-color codes. Color stickers were placed on the zip lock bag based on the code. The original randomization and color codes were kept confidential to preserve masking implementation until the end of the enrollment by one assistant who did not participate in the clinical process. The investigator was responsible for enrollment, eligibility screening, oral examination, and USFR measurement. Other research assistants were responsible for delivering the intervention. Therefore, the investigator was unaware of the assignment. The placebo and SGP capsules were identical in appearance. The placebo capsules were stored in a bottle that had previously been used to contain ginger supplements to imbue the placebo with the herb's unique scent. However, the volunteers were unaware of the interventions. An online case report form was developed using a research management engine provided by the National Clinical Research Center (www.ncrc.in.th). There was no interim analysis in the present trial.

The mean differences and 95% confidence intervals (CIs) for the post USFRs between the three intervention groups and the control group were estimated using the analysis of covariance (ANCOVA). The linear regression framework incorporated the baseline USFR and other covariates into the model. The side effects of SGP were analyzed using frequency and percentage. The characteristics of the volunteers, namely age, body mass index (BMI), and USFRs, were described using mean, standard deviation (SD), and minimum and maximum values. Gender was represented using frequency and percentage. The Stata, version 14 (StataCorp LP, College Station, TX, USA) was employed to analyse the data. A p-value of less than 0.05 was considered to be of statistical significance.

The present trial followed principles of ethical research: individual rights, respect, beneficence, and justice. Firstly, the volunteers had the right to stop participating at any time. Secondly, their decisions would have no consequence on the medical and health services at the hospital. Thirdly, the volunteers acknowledged that the trial did not directly benefit them. Fourthly, the data were treated as confidential. Fifthly, the findings were reported and presented summarily, not individually. In addition, the present study applied preventive measures towards the COVID-19 pandemic based on the World Health Organization (WHO) and Ministry of Public Health (MOPH) guidelines.

The present study was a self-funded trial commenced after being approved by the Khon Kaen University Ethics Committee for Human Research (reference No. HE631359) and registered at the Thai Clinical Trials Registry (reference No. TCTR20200915004). Recruitment posters were distributed to the community about one week before enrollment. The poster provided information about the study, including volunteer characteristics, volunteer preparation, and the researcher's contact number.

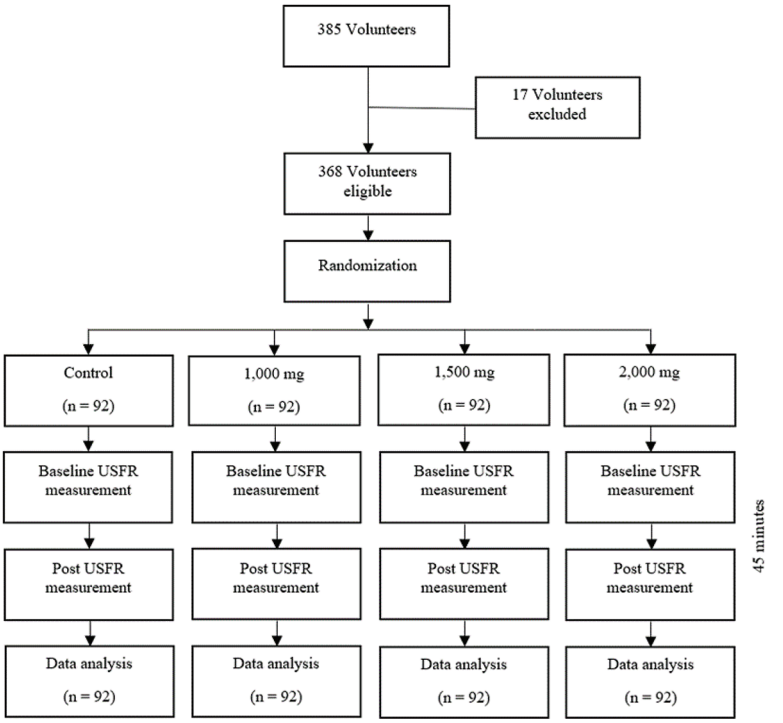

Figure 1. Flow diagram of the study.

Table 1. Volunteer characteristics

Characteristics	n=368	Control	1,000 mg	1,500 mg	2,000 mg
Sex; n (%)					
Male	69 (18.8)	20 (21.7)	15 (16.3)	18 (19.6)	16 (17.4)
Female	299 (81.2)	72 (78.3)	77 (83.7)	74 (80.4)	76 (82.6)
Age (years); mean±SD	39.64±12.51	40.05±13.14	37.85±12.88	40.09±11.86	40.58±12.15
Median=41, min=18, max=60					
BMI (kg/m^2); mean±SD	24.70±4.60	24.64±4.88	23.66±3.93	25.79±4.86	24.72±4.48
Median=24.26, min=16.16, max=42.57					

BMI=body mass index; SD=standard deviation

Results

The enrollment began on September 25 and ended on December 23, 2020. Data analyses started after obtaining the 368th primary outcome. Three hundred and eighty-five volunteers were screened for eligibility. Seventeen volunteers were excluded as they failed to meet the criteria. Three hundred and sixty-eight volunteers were randomly allocated to four groups, and their baseline USFRs were measured. Personal attributes were recorded: age, gender, body weight, and height. Approximately 45 minutes after taking the intervention, the post USFR was measured. The study's procedure was shown in Figure 1.

Volunteer characteristics

Table 1 showed the demographic characteristics of the volunteers. The majority were female (81.2%), the average age was 39.64±12.51 years, and the average BMI was 24.70±4.60 kg/m^2. There was no statistically significant difference in the characteristics among groups.

Effects of standardized ginger powder on USFR

ANCOVA was carried out to analyze the effect of SGP on USFR with adjustment for four covariates, namely: baseline USFR, age, gender, and BMI. The mean differences and their 95% CIs were estimated to indicate the effect's magnitude. As

Table 2. Mean differences in USFR for each experimental group using the placebo as the reference

Groups	Baseline USFR; mean±SD	Post USFR; mean±SD	Mean difference*	95% CI	p-value
Control	63.93±34.43	59.79±28.98	0.00		
1,000 mg	62.09±30.86	60.46±26.90	–1.28	–4.98 to 7.54	0.689
1,500 mg	58.77±20.59	62.35±27.65	5.99	–0.25 to 12.24	0.060
2,000 mg	57.42±18.88	64.81±30.88	9.47	3.24 to 15.71	0.003

USFR=unstimulated salivary flow rate; SD=standard deviation; CI=confidence interval

* Adjusted for baseline USFR, age, gender, and BMI

Table 3. Side effects of SGP

Side effects	n=368; n (%)	Control; n (%)	1,000 mg; n (%)	1,500 mg; n (%)	2,000 mg; n (%)
Yes	120 (32.6)	24 (26.1)	34 (37.0)	26 (28.3)	36 (39.1)
Heartburn	5 (1.4)	0 (0.0)	3 (3.3)	0 (0.0)	2 (2.2)
Oral irritation	9 (2.5)	3 (3.3)	1 (1.1)	2 (2.2)	3 (3.3)
Belching	60 (16.3)	11 (12.0)	16 (17.4)	13 (14.1)	20 (21.7)
Abdominal discomfort	29 (7.9)	9 (9.8)	9 (9.8)	5 (5.4)	6 (6.5)
Hot flash	2 (0.5)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)
Tingling tongue	3 (0.8)	0 (0.0)	1 (1.1)	2 (2.2)	0 (0.0)
Sweating	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Heartburn & belching	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Heartburn & oral irritation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Oral irritation & abdominal discomfort	1 (0.3)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Belching & abdominal discomfort	7 (1.9)	1 (1.1)	1 (1.1)	2 (2.2)	3 (3.3)
Heartburn & belching & abdominal discomfort	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

shown in Table 2, the 1,000 mg group and the 1,500 mg group demonstrated decreasing and increasing USFRs without attaining statistical significance, respectively (mean difference –1.28, 95% CI –4.98 to 7.54, p=0.689 and mean difference 5.99, 95% CI –0.25 to 12.24, p=0.060). Only the 2,000 mg group showed a statistically significant increase in the USFR (mean difference 9.47, 95% CI 3.24 to 15.71, p=0.003).

Side effects of standardized ginger powder

As shown in Table 3, about 32.6% of the volunteers reported at least one side effect. The top three side effects were belching (16.3%), followed by abdominal discomfort (7.9%), and oral irritation (2.5%). Eleven volunteers reported more than one side effect (3.0%). The highest number of volunteers with side effects was in the 2,000 mg group (39.1%), followed by the 1,000 mg group (37.0%), the 1,500 mg group (28.3%), and then the control group (26.1%). The side effects in the latter group (26.1%) were lower than in the experimental groups (34.8%). Moreover, no volunteers with side effects required treatment, and those conditions did not last long. Rare side effects, such as hot flushes, a tingling tongue, and sweating, were only found in the experimental groups.

Discussion

There is a long-held belief that ginger root can stimulate salivation[27]. Nevertheless, evidence for its systemic effect on salivation has to date, primarily relied on folk beliefs. The pungent taste of this herb might trigger salivary flow. Specifically, some compounds in ginger root extract may involve the ANS, which regulates salivation[28]. Still, there has to date been minimal evidence-based research, especially findings from clinical trials, to support any claims regarding causation.

The findings showed that the USFR decreased as time went by 45 minutes in the control group. However, the USFRs in the two experimental groups increased. These findings indicated that SGP seemed to have a systemic effect in stimulating salivation. The results were in line with the following previous studies. One clinical trial in 40 radiotherapy-induced xerostomia patients, who took 2,000 ginger root powder or placebo, concluded that both the USFRs in experimental and control groups significantly increased[24]. Nevertheless, the USFR

of the experimental group (2.051 gr/5 minutes) was significantly higher than the USFR of the control group (0.997 gr/5 minutes) ($p<0.001$). A second clinical trial, investigating the effects of ginger infusion on salivation in 16 smokers, reported that the USFR after drinking a ginger infusion (0.24±0.05 mL/minute) and the USFR before drinking the ginger infusion (0.12±0.05 mL/minute) were statistically different ($p<0.001$)[29]. Ginger appeared to deliver significant changes in these two studies as the USFRs increased by a factor of approximately two. However, SGP in the present trial reported herein seemed to deliver a small change. Likely of relevance is the fact that the bioactive compounds of SGP used in the present study were relatively low (500 mg SGP is equivalent to 0.01 mL volatile oils). A third clinical trial was conducted with 20 Type 2 diabetes patients with xerostomia[23]. The findings concluded that oral ginger spray could significantly increase the salivary flow rate ($p<0.001$). The mean difference in the USFR in male patients was 7.6±3.4 mm/3 minutes, while that of female patients was 9.1±3.9 mm/3 minutes.

About 32.6% of the volunteers reported side effects that were not harmful and temporary, such as belching, abdominal discomfort, oro-esophageal tube irritation, and heartburn. No side effects required further investigation or treatment. These gastrointestinal conditions were similar to the findings of the previous studies[30,31]. Approximately one-fifth of the volunteers in the control group reported side effects compared to one-third in the experimental groups. Additionally, more than one side effect was more likely found in the experimental groups than in the control group.

There were several limitations of the present trial. Certain mental health conditions, such as stress, anxiety, or depression, may affect the USFR. Even though no volunteers had severe illness, approximately half were overweight or obese. Thus, the sample may not be an ideal representation of a healthy population. In addition, salivary measurement was conducted in both morning and afternoon sessions; thus, the circadian rhythm may affect the USFR[32]. The results may not apply to a specific population since it applied eligibility criteria.

Conclusion

In summation, the 2,000 mg SGP dose could stimulate the USFR in healthy individuals. However, the rate was not substantial. Since there still exists no clear evidence for a clinically meaningful cut point for increasing the USFR, the applications of the findings remain debatable. All the side effects of ginger were minor and temporary. Thus, future research may employ a higher concentration of volatile oils and oleoresins. Future research may also focus on specific populations, such as chemotherapy patients who take ginger supplements to relieve nausea and vomiting and who may benefit from managing hyposalivation or xerostomia.

What is already known on this topic?

The fresh ginger root acts as a natural sialagogue when chewing.

What this study adds?

Ground ginger powder also possesses sialagogic action. Consuming four capsules of ground ginger (one capsule contains at least 0.01 mL of volatile oils) mildly increases the USFR.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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