

Evaluation of Efficacy of Citric Acid, Ginger Extract and Orange Peel Oil Mucoadhesive Tablets as Salivary Stimulants in Healthy Volunteers: A Randomized Three Way Crossover Study

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ABSTRACT

Background: Xerostomia is a common clinical problem, and different medications have been tried in its management. In the present study, herbal supplements like extract of ginger and orange peel are used to assess their effect on salivary quantity, salivary pH and buffering capacity. **Aim:** To evaluate and compare the efficacy of citric acid, extract of ginger and Orange peel oil mucoadhesive tablets as salivary stimulants in healthy volunteers. **Objective:** The main objective of study was to compare the quantity, pH and buffering capacity of saliva between inter and intra groups. **Methodology:** A total of 20 healthy volunteers (aged 20-30) were selected. Mucoadhesive tablets of citric acid, ginger and orange peel extract was prepared. A 3 way cross over was done to assess the impact of the stimulants on salivary quantity, pH and buffering capacity at baseline, 10 minutes, 30 minutes and 60 minutes. **Results:** Comparisons between inter and intra groups using the (ANOVA test) showed that there was a significant increase in quantity of saliva, pH and buffering capacity after treatment for both ginger and orange peel mucoadhesive tablets. **Conclusion:** Ginger being an herbal product can be tried as a novel, reasonable and available treatment as salivary stimulant for symptomatic oral dryness.

Keywords: Saliva, Dry mouth, Ginger, Orange peel, Citric acid, Mucoadhesive tablets

INTRODUCTION

Saliva plays a phenomenal role in the maintenance of oropharyngeal health. The salivary fluid is crucial for taste sensation. The buffering capacity of saliva is responsible for neutralising salivary pH, for remineralisation of dental enamel and dentine. The normal stimulated salivary flow rate averages 1.5–2.0 mL/min while the unstimulated salivary flow rate is approximately 0.3–0.4 mL/min. A diagnosis of hypo salivation is made when the stimulated salivary flow rate is <0.5–0.7 mL/min and the unstimulated salivary flow rate is <0.1 mL/min [1]. Xerostomia is a subjective sensation of mouth dryness that may occur in very old to very young during the course of several acute or chronic diseases, as a consequence of head and neck radiation therapy. Reduced secretory capacity, due to medications such as (e.g., psychotropic drugs, diuretics, β -blockers, calcium channel blockers, antidepressants), which are routinely prescribed. There exist many options for treatment and symptom management such as salivary stimulants topical agents, salivary substitutes and systemic sialogogues [2]. None proved to be effective in the long term management of xerostomia. Herbs which exhibit many medicinal and ethanomedicinal properties can be tried to as a salivary stimulant. Ginger is one such herb which exhibits parasympathetic activity along with many medicinal values [3].

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Receiving Date: July 01, 2020

Acceptance Date: July 31, 2020

Publication Date: August 08, 2020

The root of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is one of the widely used dietary substances in the world. Gingerols are the pungent compounds in fresh roots, contains [6]-gingerol predominantly. Shogaols, the dehydrated form of gingerols, are found in only small quantities in the fresh root with 6-shogaol being the most abundant. Because of their active mechanism in salivary gland acinar cells, ginger can be designed as a salivary stimulant to alleviate the dry mouth symptoms [3,4]. Citric acid (3%), sialic acid have been tried in the management of xerostomia. However, when an acid enters the mouth, whether from an intrinsic or extrinsic source, salivary flow rate normally increases, decreasing the pH and buffering capacity. Within minutes, the acid is neutralized and cleared from the oral cavity and the pH returns to normal [5].

Mucoadhesive polymers are hydrophilic macromolecules that are able to form hydrogen bonds. When used in an aqueous environment, they absorb water and become hydrated and turgid and thus stick to the adjacent mucosa. In recent years, they have been used as controlled-release drug delivery systems in different areas of the body. Some advantages of using mucoadhesives include the prolonged residence period of the drug, painless administration, and dosage reduction. This is because of site-specific targeting, diminishing salivary washout, easy drug withdrawal, fast onset of action, patient compliance, and the attractive alternative for the non-invasive delivery of some drugs [6].

Ginger, known for its richness in medicinal values has a parasympathetic and cholinergic activity [4]. This unexplored property of ginger was tried in our study in the of mucoadhesive tablet for stimulating saliva. The present novel study was performed in an attempt to assess the quantity, pH and buffering capacity between intra & inter groups at different intervals.

MATERIALS AND METHODS

The present study was undertaken in the Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, Karnataka, India. The study group comprised of 20 healthy volunteers of 20-30 years of either sex. Study Design: comparative, randomized, crossover study. The three way crossover-per-patient study design was chosen.

Inclusion Criteria

1. Subjects in the age group of 20-30 years having good health
2. Subjects who were not complaining of oral dryness
3. Subjects who are free from acute or chronic diseases of the oral mucosa or salivary glands

Exclusion Criteria

1. Individuals with adverse habits like smoking, alcohol, tobacco and areca nut
2. Subjects who were on xenogeneic medications

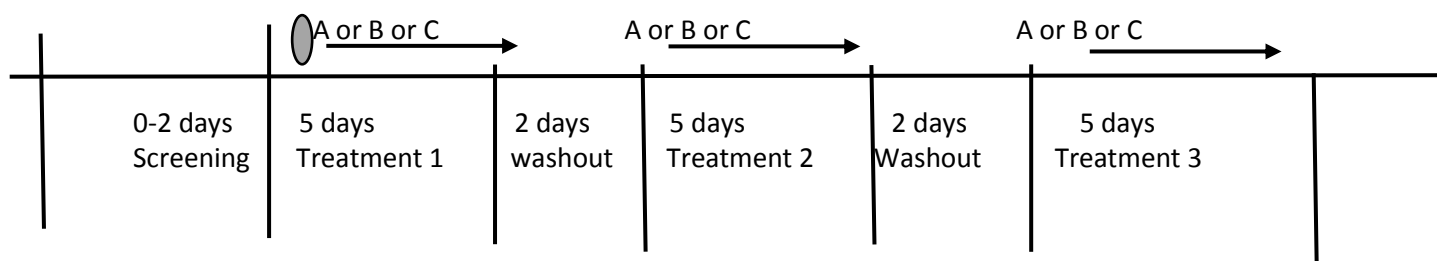
Mucoadhesive tablets of Citric acid, extract of Ginger and Orange peel oil were prepared at Bapuji Pharmacy College, Davangere.

Composition of each tablet

The main composition of citric acid tablets was citric acid (100mg) and other ingredients were HPMC (Hydroxypropylmethylcellulose) (400gm), Saccharin Na (2mg), talc (2%) (10mg), menthol (1mg). The ginger and orange peel mucoadhesive tablets had ginger extract (ginger powder (100mg) and orange peel oil (orange peel oil-3ml, lactose-2.7g) as prime constituents respectively. The other ingredients were same as that of citric acid tablets [2].

Collection of saliva

All subjects were refrained from eating for a minimum period of 2 hours before saliva collection. They were comfortably seated and, after a few minutes of relaxation, trained to avoid swallowing saliva and asked to lean forward and spit all the saliva they collected at 1 minute interval for a period of 5 minutes [5].



A-Citric acid B-Ginger C-Orange peel oil

Method of Mucoadhesive tablet application

The application site was first cleaned with a cotton roll, and then the mucoadhesive tablet was placed either on the right or left side of buccal mucosa applying pressure for 30 sec, weighing 500mg. Subjects were instructed to maintain the tongue in rest position [7].

After adhesion, stimulated Saliva at 5 minutes, 30 minutes and 60 minutes interval was collected by spitting method in a preweighed container. Salivary quantity, pH and buffering capacity for each sample were assessed for all the groups and also at each interval. Quantity was assessed by preweighing the empty salivary containers prior to the test. After collection of saliva, resultant difference in weight is taken as quantity in grams (1gm=1mL) [8]. pH was assessed by digitometer. Saliva samples were titrated with 0.1N HCl to evaluate the buffering capacity and assessed by Digitometer

Statistical analysis

SPSS version 21 used for statistical analysis. All the data in the tables are shown as mean ± SD. Repeated measures of Anova was used for intergroup comparison. Unpaired T tests for intragroup. P value was considered significant if it is ≤ 0.05.

Table 1: Showing salivary quantity mean values of all the groups at different time intervals

Time Interval	Quantity (Mean+ SD) Ginger	Quantity (Mean+ SD) Orange	Quantity (Mean+ SD) Citric acid
Base Line	1.09(0.75)	1.07(0.61)	1.01(0.64)
5 Minutes	3.07(1.62)	3.04(1.79)	2.25(1.61)
30 Minutes	4.81(3.36)	3.80(2.37)	3.43(2.38)
60 Minutes	5.49(3.95)	4.09(2.51)	3.27(2.82)

RESULTS

In this study, 20 healthy volunteers (aged between 20 and 29 years) were enrolled. Comparisons between baseline saliva quantity and the saliva secretions induced by all the three mucoadhesive

tablets at 5,30 & 60 minutes (using the ANOVA test) showed that there was a significant increase after treatment at the end of the experiment for all the three groups.

The mean values of baseline salivary values of quantity, pH and buffering capacity with all the three groups were found to be non-significant. Mean values with Ginger>Orange peel>Citric acid in terms of quantity as shown in Table 1. Mean values of pH significantly decreased with Citric acid compared to Ginger & orange peel as shown in below Figures (1.1 and 1.2). There was no significant difference in mean buffering capacity between the groups.

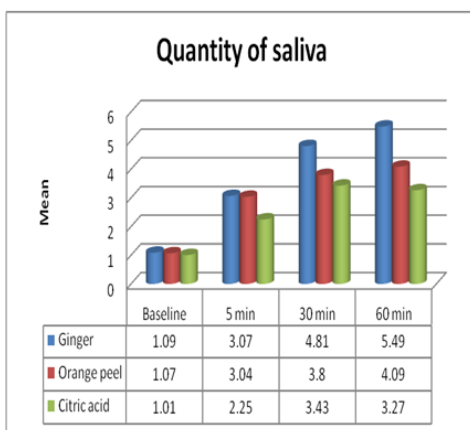


Figure 1.1: Inter groups quantity of saliva

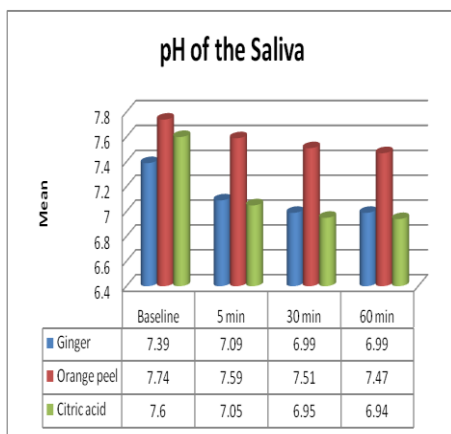


Figure 1.2: Inter groups pH of saliva

DISCUSSION

There were few studies where herbal drugs have been tried in xerostomia management [1]. The present holistic approach was to assess the localised effect of ginger mucoadhesive tablets on salivation in healthy volunteers. Ginger containing gingerol & shogaols as major constituents proved to have a role on salivary acinar cells [4]. In the present crossover study, the mean improvement in salivary quantity was 4.4 mL for ginger, 3.02 mL for orange peel, and 2.26 mL for citric acid from baseline to 60 minutes. This shows an effective salivary secretion in ginger followed by orange peel and citric acid. Ginger proved to be superior in increasing salivation without a drastic decline pH followed by orange peel and citric acid.

In a study, clinical efficacy, safety, and acceptability of a Novasial, new oral salivary equivalent administered four times daily in the treatment of xerostomia in various medical conditions was compared with that of oxygenated glycerol triester oral spray (Aequasyl) and a moisturizing spray (Biotene) in a 2-week, multicenter, randomized, crossover study. The overall efficacy of Novasial and

Aequasyl were similar with respect to xerostomia. Novasial was preferred to Aequasyl and Biotene in alleviating taste alteration and chewing difficulty [8].

A study in Iran, where 20 diabetic patients were taken and given placebo and ginger herbal spray at different times to the same patients. Schirmer test was done for salivary flow before the treatment and after treatment. Mean dry mouth score was 8.3 ± 2.2 before the treatment, 7.9 ± 2 after taking the placebo, 2.4 ± 1.2 after taking the drug. P-value was considered significant for reducing dryness of mouth in post treatment with ginger group and non-significant with placebo group [9].

A study was done to assess the efficacy of yogurt and lemon juice on increase in salivation and its comparison with that of unstimulated saliva in healthy volunteers. The average salivary flow after lemon juice intake was 0.8529 mL/min where as 1.0147 mL/min for yogurt over a period of 5 min [5]. In our study we have assessed the parameters over a period of 60 minutes for all the 3 groups.

The present study showed that extract of Ginger as mucoadhesive tablet has shown to have increased salivary quantity at different time intervals from baseline compared with extract of Orange peel and citric acid. Salivary pH was drastically declined with Citric acid compared to Ginger & Orange peel oil. Dissolution time of the tablet in the oral cavity varied from 50 to 70 minutes with ulcerations seen observed at site of tablet with citric acid tablets.

In a study, the effects of [6]-gingerol, which is an ingredient of ginger, on the dedifferentiation of parotid acinar cells was examined. It was found that the increase of expression level of claudin-4 mRNA during the culture was suppressed by addition of [6]-gingerol. Claudin-4 is responsible for decreased permeability of TJ in salivary cells, the absence of claudin-4 expression in acinar cells may be important for production of saliva. The effect was confirmed by immunoblot analysis [10]. In addition, the decrease of amylase and aquaporin-5 during the culture was also suppressed by [6]-gingerol. Amylase and Aquaporin 5 were considered as salivary acinar markers. Aquaporin-5 is a major water channel in salivary glands and it was reported that knockout of aquaporin-5 results in remarkable decrease of saliva secretion. These results suggest that [6]-gingerol has a protective effect against the cellular stresses that induce dysfunction of salivary glands [11].

In an animal study, effect of ginger on salivary secretion was proved to be highest at 7 minutes [4]. In a study, they compared the effect of orange and lavender odor with a music condition and a control condition and demonstrated that odors are capable of reducing anxiety and altering emotional states in dental patients. Recently, contemporary and alternative medicine approaches such as aromatherapy (use of essential oils, scented, volatile liquid substances for therapeutic purposes) have been considered in dental and medical settings [13-15].

In our study, we used ginger as mucoadhesive tablet because of its rapid localised action and minimal side effects. Out of 20 subjects, 7 complained of localised ulceration at the site of tablet with citric acid. Many reported with poor compliance with taste for all the 3 tablets. The results of this study emphasize the positive role of extract of ginger and orange peel on saliva secretion, independent of their acidic taste or pH. The pH is not the only factor that is responsible for the increase in saliva secretion for Ginger and Orange. They have considered as major herbal supplement which has got several medicinal values in literature [9].

CONCLUSION

Through this study, it is concluded that ginger & orange peel can be tried as effective localised salivary stimulant with minimal side effects and acceptable taste. In future, it can be tried in patients complaining of xerostomia, patients on xenogeneic drugs on a larger sample.

FUTURE RECOMMENDATIONS

Fluoride can be incorporated in the composition to avoid demineralisation of teeth in the oral cavity. Ginger can be used as herbal spray in patients complaining of dryness of mouth.

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