

Evaluation of Effects of *Zingiber officinale* on Salivation in Rats

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Abstract- There are some herbal plants in Iranian traditional system of medicine which are believed to be excellent remedies to alleviate the symptoms of xerostomia. The aim of the present study was to evaluate the effect of systemic administration of seven different herbal extracts on the rate of salivation in rats. The extracts of 7 herbs; *Zingiber officinale* Roscoe (Zingiberaceae), *Citrus sinensis* (L.) Osbeck (Rutaceae), *Artemisia absinthium* L. (Asteraceae), *Cichorium intybus* L. (Asteraceae), *Pimpinella anisum* L. (Apiaceae), *Portulaca oleracea* L. (Portulacaceae), *Tribulus terrestris* L. (Zygophyllaceae) were prepared. Nine groups of animals (including negative and positive control groups) were used and seven rats were tested in each group. After the injection of extracts, saliva volume was measured gravimetrically in four continuous seven-minute intervals. The results showed that after injection of ginger extracts salivation was significantly higher as compared to the negative control group and other herbal extracts in all of the four intervals ($P < 0.01$). The peak action of the ginger was during the first 7-minute interval and following this, salivation decreased to some extent. The present study suggests that the extract of *Zingiber officinale* can increase the rate of salivation significantly in animal model. Further investigations on different constituents of ginger seem to be essential to identify the responsible constituent for stimulation of saliva secretion.

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Introduction

Xerostomia (dry mouth) is the most common long-standing problem for the majority of the patients who suffer from salivary gland diseases. Medications, exposure of the head and neck region to radiation, and connective tissue diseases are the most common causes of salivary gland dysfunction that may in turn lead to xerostomia (1).

Although xerostomia is usually managed symptomatically with saliva substitutes, a large number of potential systemic therapies for chronic xerostomia have emerged during the past decade. More than 24 agents have been proposed as the means of stimulating salivary output systemically (2). Most of the drugs used to increase salivary flow, stimulate saliva secretion through their cholinergic effects on functional acinar cells (3).

Several herbal drugs have been recently developed and used in clinical trials successfully to relieve xerostomia.

Herbal medications claiming to relieve xerostomia include *Cetraria islandica*, Bakumondo-to, LongoVital, hot aqueous extract of the rhizome of *Anemarrhena asphodeloides* and Byakko-ka-ninjin-to (4-8). There are some herbal plants in Iranian traditional system of medicine, which are believed to be excellent remedies to alleviate and help with the symptoms of chronic salivary gland diseases particularly xerostomia. However, lack of scientific papers published on these herbs, makes it difficult to determine either the validity of their effects or their mechanism of action. The present study was designed to evaluate the effect of seven herbal plants widely used to increase the rate of salivation in Iranian folk medicine.

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Materials and Methods

Animals

In this experimental study, 63 adult male rats (weight: 200-300 g) from NMRI strain were used. The animals were bred and housed at the animal facility of neuroscience research center of Kerman University of Medical Sciences. The animals were kept in a well cross ventilated room with controlled temperature and humidity and a standard 12h light: 12h dark cycle. Standard rodent food and tap water were available. Nine groups of animals (including negative and positive control groups) were used and seven rats were tested in each group. Approval for this study was obtained from the Animal Care Committee at Research Center of Kerman University.

Plants

Rhizome of *Zingiber officinale* Roscoe (Zingiberaceae), peels of the fruit of *Citrus sinensis* L. (Rutaceae), aerial parts of *Artemisia absinthium* L. (Asteraceae), roots of *Cichorium intybus* L. (Asteraceae), fruits of *Pimpinella anisum* L. (Apiaceae), seeds of *Portulaca oleracea* L. (Portulacaceae), and fruits of *Tribulus terrestris* L. (Zygophyllaceae) were used. The plant materials were identified and authenticated taxonomically by a botanist.

Parts of the plants selected for the present study (20 g) were washed with distilled water to remove dirt and soil, and shade dried. The dried materials submitted for a maceration process. The material was extracted twice with ethanol (80%). The extracts were filtered, pooled, and concentrated at high temperature (+50°C) on a rotary evaporator (Heidolph, Germany). The extracts were suspended in normal saline with ethanol 10% as co-solvent and stored in refrigerator within dark containers.

Saliva collection

Rats were anesthetized using a single intraperitoneal injection of 75 mgkg⁻¹ ketamine (Alfasan, Holland) and 5 mgkg⁻¹ xylazine (Alfasan, Holland). The unconscious rats were kept on a thermal pad to maintain their body temperature at the level of 37°C.

Before saliva collection, the oral cavity was wiped and dried with a cotton pellet and then 4 pre-weighed cotton pellets were inserted into the mouth of each animal: two cotton pellets underneath the tongue and one between the cheek and the teeth on either side. After seven minutes, the cotton pellets were removed and weighed again on a precision weighing balance (Sartorius, Germany). The difference of the weight of

the cotton pellets between two determinations was considered as the baseline weight of the saliva secreted. The flow rate of saliva was determined gravimetrically, assuming that the specific gravity of saliva is 1 (i.e. 1 g equals 1ml of saliva).

Following measurement of the baseline secreted saliva, the extracts were injected (10 mgkg⁻¹ body weight) intraperitoneally. The rate of saliva secretion was determined at four continuous seven-minute intervals. The investigator was blinded to all of the injected solutions in this study. The experiment was run in parallel with a negative control (10 mlkg⁻¹ normal saline mixed with co-solvent) and a positive control (4 μmolkg⁻¹ pilocarpine dissolved in distilled water and co-solvent). At the end of the experiments the rats were sacrificed by pentobarbital overdose.

Statistics

All the data were analyzed by the analysis of variance for comparing groups and Bonferroni for multiple comparisons. A value of $P < 0.05$ was considered statistically significant.

Results

The present study showed that the secretion of saliva increased dramatically after injection of extract of *Zingiber officinale*. The peak action of *Zingiber officinale* appeared during the first 7-minute interval and after that salivation decreased to some extent. Statistical analysis showed that the mean rate of saliva secretion induced by *Zingiber officinale* in all of the 7-minute intervals was significantly higher than that of other herbal extracts and negative control ($P < 0.05$) (Table 1 and Figure 1).

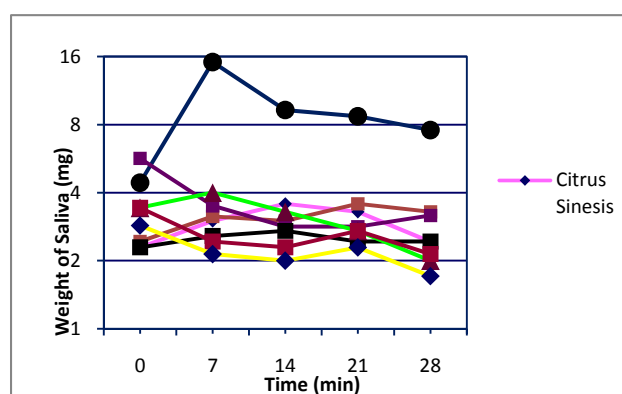


Figure 1. Saliva secretion before and after injection of seven herbal extracts in four continuous seven-minute intervals

Table 1. Saliva secretion (Mean \pm SD) before and after injection of seven herbal extracts in four continuous seven-minute intervals

Drug	Time (Minutes)									
	0		7		14		21		28	
	Weight of the Saliva (mg)									
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Citrus sinensis</i> ¹	2.3	0.8	3.0	1.4	3.6	1.7	3.3	1.0	2.4	0.5
<i>Artemisia absinthium</i> ²	2.4	0.8	3.1	1.2	3.0	1.7	3.6	1.3	3.3	1.4
<i>Zingiber officinalis</i>	4.4	1.9	15.1	8.1	9.3	6.6	8.7	6.6	7.6	7.0
<i>Cichorium intybus</i> ³	7.7	5.9	8.4	13.2	6.1	8.8	6.0	8.5	4.1	3.0
<i>Pimpinella anisum</i> ⁴	2.3	0.5	2.6	1.1	2.7	0.8	2.4	0.8	2.4	0.5
<i>Tribulus terrestris</i> ⁶	3.4	0.5	4.0	0.6	3.3	0.8	2.7	0.5	2.0	0.6
<i>Portulaca oleracea</i>	3.4	1.4	2.4	0.5	2.3	1.0	2.7	0.8	2.1	0.4
Negative control	2.9	1.9	2.1	0.7	2.0	0.8	2.3	1.4	1.7	1.0
Pilocarpine	3.1	0.7	129.3	51.5	201.7	23.1	169.0	28.9	129.9	42.9

1. Peels of the fruit of *Citrus sinensis* L. (Rutaceae)
2. Aerial parts of *Artemisia absinthium* L. (Asteraceae)
3. Roots of *Cichorium intybus* L. (Asteraceae)
4. Fruits of *Pimpinella anisum* L. (Apiaceae)
5. Seeds of *Portulaca oleracea* L. (Portulacaceae)
6. Fruits of *Tribulus terrestris* L. (Zygophyllaceae)

The results also indicated that saliva secretion increased after injection of other herbal extracts when compared with the negative control group. However, the difference was not statistically significant. Since the saliva secretion after injection of pilocarpine (positive control) was much higher than extracts of seven herbs, pilocarpine result has not shown in Figure 1. The investigators believe that in order to compare the effect of ginger on salivation with pilocarpine, the dose of pilocarpine should be adjusted in future studies.

Discussion

Although most clinicians trained in the Western education system are unfamiliar with herbal medications and other forms of alternative medicine (4), alternative medicines are gaining popularity and recognition within the professional community. The results of the present study showed that the rate of salivation increased significantly in response to the injection of *Zingiber officianale* (ginger) extract.

Ginger is one of the most commonly used herbal supplements and its substantial use in folk remedies for different medical conditions has been documented (9). Based on phytochemical studies, ginger is rich in a large number of substances including gingerols and shogaols (10,11). Some of the main pharmacological actions of these compounds include anti-inflammatory, antioxidant and anticarcinogenic activities (10,12,13).

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been used for a wide array of unrelated ailments that include vomiting, stomachaches, abdominal spasm, nausea, motion sickness, arthritis, rheumatism, hypertension, ulcerative colitis, fever and infectious diseases (14-20). Extracts and fractions of *Zingiber officinale* have been shown to protect against chemically-induced tissue damage (21). The radio protective effect of ginger extract has also been confirmed (22-24).

As mentioned earlier, ginger (rhizome of *Zingiber officinale*) has been widely used for centuries in gastrointestinal disorders, particularly dyspepsia, but its precise mode of action was to be elucidated. Ghayur and colleagues showed that aqueous-methanolic extract of ginger 70% (Zo.Cr) exhibits prokinetic activity in rats via activation of post-synaptic muscarinic M3 receptor in rat stomach fundus (25). Prokinetic activity of ginger extract (Zo.Cr) was also confirmed in an *in vivo* test. This study showed that Zo.Cr contains a cholinergic, spasmogenic component evident in stomach fundus preparations which provides a sound mechanistic insight for the prokinetic action of ginger (26).

Although research studies have widely been performed about different pharmacological properties of *Zingiber officianale*, there is little evidence about its effect(s) on saliva secretion in the literature (27). It has been determined that parasympathetic stimulation causes a copious flow of saliva with low outputs of protein and

sympathetic nerve stimulation which *per se* causes less fluid secretion, but exocytosis of secretory granules occurs from both acini and granular tubules (28). Since the prokinetic activity of ginger has been confirmed (25, 26), the authors believe that ginger effect on salivation can be attributed to some kind of cholinergic action. However, the exact mechanism is not fully understood and more researches using atropine may help to clear the mechanism of action. Further investigations on different constituents of *Zingiber officinale* in different doses also seem to be essential to identify the responsible constituent and the optimum effective dose for saliva secretion.

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Effects of zingiber officinalis on salivation in rats

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