Original

Effect of *Zanthoxylum Zanthoxyloides* Root on Quantity and Quality of Saliva Secretion in Healthy Adults

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Abstract

Background: Zanthoxylum zanthoxyloides (fagara) root is a popular chewing stick reputed to increase saliva production. However, there is no report on the characteristics of the saliva it stimulated. The effect of fagara on the quality and quantity of saliva secretion in healthy adults was therefore studied.

Methods: The Large sample approximate method was used to determine the 24 Healthy adults (12 males and 12 females) included in the study. Sample collections were done in two visits. On day 1, basal saliva was collected before chewing sugarless gum for 2 minutes, the mouth was rinsed with water and another sample was collected as stimulated. The procedure was repeated at the second visit with fagara chewing stick substituting the sugarless gum. Volume, flow rate, pH, amylase activity, total protein, electrolytes, and oxidative stress biomarkers were determined in the saliva samples.

Results: Saliva production was increased by sugarless gum (29.84%) and fagara (584.98%) compared with basal. The increase produced by fagara was about 20 times higher than that of sugarless gum. Salivary flow rate also increased in similar pattern. Sugarless gum and fagara increased saliva pH while total protein was not different. Markers of oxidative were not affected while salivary amylase activities were significantly reduced after chewing fagara. Sodium and chloride levels increased while calcium and potassium were not different following fagara exposure.

Conclusion: Zanthoxylum zanthoxyloides increases saliva volume, flow rate and pH, reduces salivary amylase activity and altered electrolytes through mechanism that is beyond the mechanical stimulatory effect of chewing.

Keywords: *Zanthoxylum zanthoxyloides*, Chewing stick, Saliva, Healthy adults

How to cite this article

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Introduction

Plants as cleansing agents are well documented and the presence of saponin has been ascribed to their detergent-like behavior such that the extent of their foaming property depends on the amount of saponin contained.[1,2] This property along with antimicrobial and anti-inflammatory activities has found usefulness in oral hygiene thus, the World Health Organization in 1987 encouraged the use of chewing sticks obtained from plant roots or stems and this was reaffirmed in the year 2000 Consensus Report on Oral Hygiene.[3] Volatile oils, tannic acid, sulphur, and sterols found in some of the chewing sticks are linked with antiseptic, astringent, and bactericidal properties that help to reduce plaque formation, provide anti-carious effects, eliminate bad odor, enhance taste perception, and provide cure for many systemic diseases.[4] The perception of being natural, less toxic, readily available, and affordable makes them safer alternatives to chemical-based toothpaste among low-income populations.[5] Recent randomized clinical trials have documented effective [6] and somewhat greater mechanical and chemical cleansing of oral tissues [7] by chewing stick in comparison with toothbrush.

Zanthoxylum zanthoxyloides (formerly, *Fagara zanthoxyloides*) called Candlewood in English and '*Orin ata*' in Yoruba belongs to the family Rutaceae. It occurs more abundantly in the savannah and dry forest vegetations and is commonly found in the drier parts of South Western Nigeria extending to Niger States.[8,9] The roots usually give a warm, pungent and benumbing effect on the oral tissues when chewed, and this aromatic warm taste with attendant profuse salivation is believed to be beneficial to the elderly and those with sore gums and other oral disease conditions, it is, therefore, popularly used as a chewing stick.[9,10] Its antimicrobial activity has been shown to be due to the alkaloids (berberine, chelerythrine and canthin-6-one) which are most active at pH 7.5 (or during tooth decay) and simple benzoic acid derivatives which are most active at pH 5.[11] Extract from its root exhibited significant antibacterial activity against a wide spectrum of both gram-positive and gram-negative microorganisms implicated in the pathogenesis of respiratory tract, gastrointestinal tract and urinary tract infections and thus could be used to treat oro-dental infections in view of the ever-increasing resistance to antibiotics.[12] It has a high fluoride content compared to 9 other common chewing sticks [13] and was demonstrated among secondary school students that its usage is associated with high fluoride retention ability when compared with 3 other chewing sticks and a non-herbal fluoridated toothpaste.[14]

Despite the several reports on the beneficial effect of *Zanthoxylum zanthoxyloides* on oral health hygiene and its numerous *in vitro* antimicrobial effects on microbial isolates of oral origin, there is paucity of data on the characteristics of the saliva produced following its use. This study was therefore, designed to investigate the effect of *Zanthoxylum Zanthoxyloides* chewing stick on the quality and quantity of saliva secretion in healthy adults.

Methodology

Study Area and Ethical Approval

The study was carried out at the Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria. The protocol was approved by the University of Ibadan/University College Hospital Ibadan Nigeria Ethical Review Board (UI/EC/23/0332).

Plant materials, identification and preparation of plant roots

Fresh branch of *Zanthoxylum zanthoxyloides* were collected at Ibadan, Nigeria in the month of April 2023, at about noon. The plant was identified and authenticated by Mr. D.O.E of the Department of Botany, University of Ibadan, by comparison with the herbarium specimen, voucher no UIH - 23247, in the University herbarium. A voucher specimen was deposited in the Faculty of Science herbarium; this was done solely for plant identification. The roots of *Zanthoxylum zanthoxyloides* were obtained from a local market in Ibadan. The roots were washed clean of soil, chopped into smaller sticks and air-dried for two weeks, then stored in an airtight plastic container at room temperature until needed. These roots were used for the experimental study.

Experimental Design

Study design: A cross over experimental study

Sample size determination: The sample size was determined for a crossover study as described by Siyasinghe and Sooriyarachchi [15] using the large sample approximate method. The study involved a 2 x 2 crossover trials, which consider only two treatments and two periods.

Thus, the sample size calculation is as shown below:

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$$n = \frac{\left[Z^{-1}\left(1-\alpha/2\right) + Z^{-1}\left(1-\beta\right)\right]^2}{2\varepsilon_R^2}$$

$Z^{-1}(a)$ indicates the ath ordinate of the standard normal distribution

When using the large sample approximation method based on the z statistic, it has been observed that when the sample size is less than or equal to 10 in most of the cases the test is underpowered, it is worse when the sample size gets smaller. However, when the sample size is approximately greater than or equal to 12, the power is generally well maintained.
Thus, a total of 24 adults, consisting of 12 males and 12 females, aged between 18 and 25 years, recruited from various departments in the University of Ibadan participated in the study. Informed consent forms were duly signed by the participants.

Inclusion criteria: healthy individuals
Exclusion criteria: history of smoking, history of allergy, history of oral disease and current or recent (less than one month) use of medication.
In preparation for the study, the participants were asked to brush in the night preceding the day of sample collection. Then they were asked not to brush or eat in the morning of sample collection as that may alter the saliva.

Sample collections
Salivary samples of the participants were collected in batches over a period of 9 days, between 8:00am-10:00am. Each participant visited twice for sample collection. Upon arrival for the first day collection, the participants were instructed to relax before they proceeded to rinse their mouths with distilled water. The basal saliva was then collected into sample bottles for 5 minutes. They then chewed sugarless gum for 2 minutes, rinsed their mouth with water for 10 seconds and stimulated saliva was collected for another 5 minutes. The pH and volume of saliva were determined immediately and aliquots were taken and stored at 20^0C for biochemical analysis. The procedure was repeated on the second visit except that *Zanthoxylum zanthoxyloides* was chewed instead of sugarless gum to stimulate saliva production.

Determination of salivary flow rate
The flow rate of the salivary samples was calculated as follows:

$$flow\ rate\ (ml/min) = \frac{Volume\ of\ salivary\ secretion\ (ml)}{Time\ of\ collection\ (\text{min})}$$

Determination of saliva pH
Salivary pH was measured within 5 minutes of sample collection using a digital pH meter (HSC® pH meter). The pH meter was rinsed thoroughly after each consecutive reading to ensure it is properly rid of saliva.

Determination of alpha amylase activity
Salivary amylase activity was determined using the Bernfeld [16] method. The method relies on the ability of amylase to hydrolyse starch into maltose which forms colour complex with 3,5-dinitrosalicylic acid (DNS) that can be quantified spectrophotometrically. Briefly, 500µL of cooked (1% w/v in phosphate buffer, pH 6.9) was pipette into a tube, 500µL of saliva was added and incubated for 5 minutes at 37 ^{0}C. After the incubation, the reaction was stopped by addition of 500µL of DNS reagent (containing 3,5-dinitrosalicylic acid and sodium potassium tartrate in a strong alkaline solution). The tube was then placed in boiling water for 15 minutes for colour development, it was cooled over ice and 4500 µL of distilled water was added. The absorbance of the solution was read at 540 nm against a reagent blank. The amylase activity was then obtained from a standard curve plotted by serial dilution of 0.2 % maltose treated with DNS reagent.

Determination of Oxidative stress markers
Malondialdehyde (MDA) level, Superoxide Dismutase (SOD) activity and Catalase activity were determined by the methods described by Hagege *et al.*, [17] Misra and Fridovich [18] and Goth et al., [19] respectively.

Determination of total protein and electrolytes
Total protein, Sodium, Potassium, Calcium and Chloride concentrations in the saliva were determined using commercially available kits (Fortress Diagnostics, United Kingdom). The procedures were carried out according to the manufacturers' description.

Statistical Analysis
Data were expressed as Mean ± Standard Error of Mean (SEM) and percentage. Inferential statistics was carried out using one-way analysis of variance for all the groups

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while paired t test was used to determine differences between basal and stimulated variables at $P < 0.05$. The analysis were done with the aid of GraphPad Prism® version 9.

Results

Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary volume and flow rate in healthy adults

As shown in figure 1A-C, chewing sugarless gum and fagara significantly ($P< 0.05$) increased saliva volume (A) and flow rate (B) when compared with their respective basal values. While sugarless gum produced a 29.84% increase in saliva, fagara produced 584.98% (C). The increase in saliva volume produced by Fagara was about 20 times higher than that produced by sugarless gum.

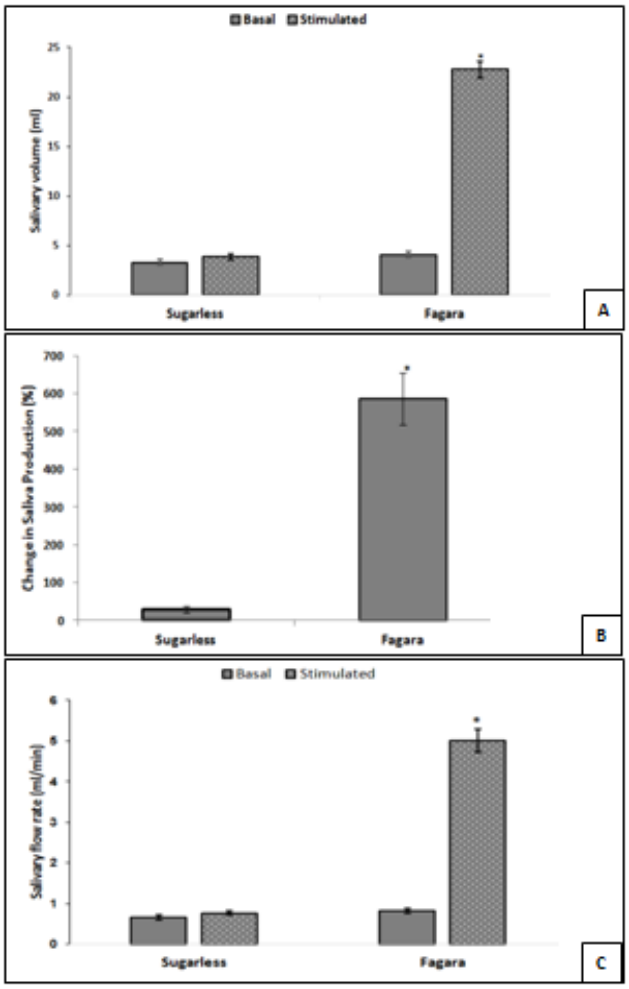

Figure 1. Comparison of the effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary volume (A), percentage change in saliva volume (B) and flow rate (C) in healthy adults*P<0.01

Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary pH in healthy adults

As shown in figure 2, saliva pH was significantly ($P< 0.05$) increased by chewing sugarless gum (7.36 ± 0.04 vs 7.23 ± 0.04) and *Zanthoxylum zanthoxyloides* (7.32 ± 0.03 vs 7.18 ± 0.05) when compared to their basal values. The pH after chewing sugarless gum (7.36 ± 0.04) was not statistically different ($P> 0.05$) from the one obtained after chewing *Zanthoxylum zanthoxyloides* (7.32 ± 0.03).

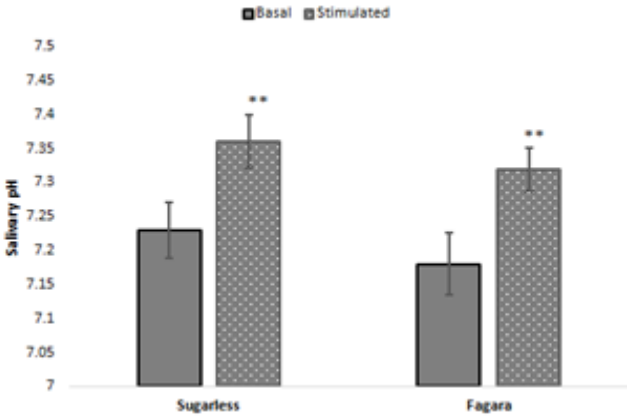

Figure 2. Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary pH in healthy adults. *P<0.01

Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary amylase activity in healthy adults

As shown in figure 3, the basal salivary amylase activity for the sugarless group (1.67 ± 0.08 activity/mg.pr) and the *Zanthoxylum zanthoxyloides* group (1.74 ± 0.12 activity/mg.pr) were not significantly different ($P> 0.05$). Also, there was no significant difference in the amylase activity following sugarless gum stimulation (1.67 ± 0.08 vs 1.68 ± 0.06 activity/mg.pr), $P> 0.05$. However, amylase activity (1.35 ± 0.07 activity/mg.pr) was significantly decreased ($P< 0.05$) after chewing *Zanthoxylum zanthoxyloides*.

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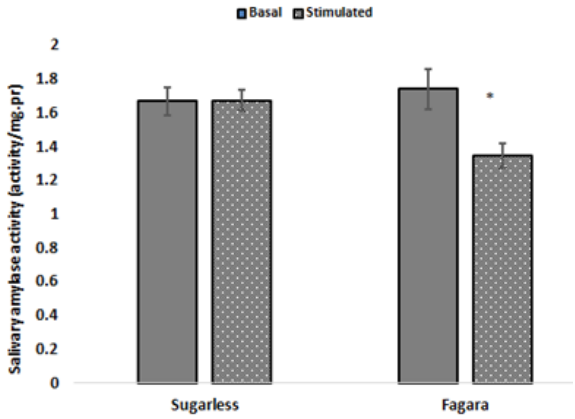

Figure 3. Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary amylase activity in healthy adults *P<0.01

Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on markers of oxidative stress in healthy adults

There was no significant difference (P> 0.05) in the markers of oxidative stress after chewing sugarless gum or fagara as shown in table 1

Table 1. Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on markers of oxidative stress in saliva of healthy adults

	Sugarless gum		***Zanthoxylum zanthoxyloides***	
	Basal	Stimulated	Basal	Stimulated
MDA (x10^{-3} nMol/ml)	2.26 ± 0.72	2.27 ± 0.98	1.95 ± 1.01	2.34 ± 0.87
SOD (x10^{-3} Activity/ml)	133.71 ± 10.26	122.80 ± 12.92	126.50 ± 20.18	140.33 ± 16.31
Catalase (KU/L)	78.90 ± 1.47	77.79 ± 1.23	73.59 ± 1.87	75.97 ± 1.00

Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary protein and electrolytes levels in healthy adults

As shown in table 2, sodium and chloride concentrations were significantly increased (P < 0.05) after chewing fagara when compared with their basal values. There was however, no significant difference in the total protein, potassium, and calcium levels after chewing fagara or sugarless gum.

Table 2. Effect of sugarless gum and *Zanthoxylum zanthoxyloides* on salivary protein and electrolytes levels in saliva of healthy adults

	Sugarless gum		***Zanthoxylum zanthoxyloides***	
	Basal	Stimulated	Basal	Stimulated
Total Protein (mg/ml)	0.23±0.011	0.23±0.023	0.24±0.016	0.25±1.13
Sodium (mmol/L)	17.37±4.93	24.62±3.91	26.01±8.26	40.43±2.85*
Potassium (mmol/L)	9.89±2.88	5.40±1.84	7.75±2.59	10.01±0.64
Calcium (mg/dL)	7.90±0.35	5.69±0.90	5.92±1.20	8.79±1.05
Chloride (mg/dL)	19.62±3.69	12.32±3.08	9.36±2.82	24.50±3.01*

*P<0.01

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Discussion

This study was designed to determine the effect of *Zanthoxylum zanthoxyloides* chewing stick on the salivary flow rate, pH, amylase activity, protein and electrolyte concentration, and oxidative biomarkers in healthy adults.

Stimulation of mechanoreceptors in the periodontal ligament and gingival tissue referred to as masticatory-salivary reflex, activates parasympathetic nerves results in increased saliva secretion particularly from the parotid glands [20] thus, chewing gum increased salivary flow rate [21] as observed in this study when participants chewed sugarless gum. However, the increased in saliva produced by chewing sugarless gum during this study was much lower than that produced after chewing *Zanthoxylum Zanthoxyloides*, which implies that other than mechanical stimulation, some constituents of *Zanthoxylum zanthoxyloides* may account for the increased saliva production.

The observed wide margin between the volumes of saliva produced by *Zanthoxylum zanthoxyloides* exposure and by chewing sugarless gum suggests that *Zanthoxylum zanthoxyloides* may have a stimulatory effect on saliva that is beyond mechanical stimulation. Pilocarpine, a muscarinic type 2 agonist was observed to stimulate saliva production by activating the parasympathetic neurons innervating salivary glands. While pilocarpine increases saliva production ranged from 64.5% [22] to 100 %, [23] the almost 600 % increase observed in this study is a pointer that the signal transduction involved in the *Zanthoxylum zanthoxyloides* stimulation of saliva production requires further elucidation.

The observed increase in salivary pH following stimulation from *Zanthoxylum zanthoxyloides* gave credence to its earlier reported antimicrobial property. Its antimicrobial activity is observed to be due to alkaloids such as berberines, chelerythrine and canthine-6-one which are most active at an alkaline pH. [10] These findings suggest that intervention from *Zanthoxylum zanthoxyloides* can increase salivary pH which favors antimicrobial activities of saliva. Such antimicrobial activity of *Zanthoxylum zanthoxyloides* had been reported *in vitro.* [12,24] Increased saliva pH following mechanical stimulation had been suggested to be beneficial to oral and dental health [25] thus; chewing gum has been suggested as alternative to improve oral cavity humidification in patients with water restriction without predisposing them to bronchoaspiration risk [26] which could be worsened by acidic pH. [27]

Increased salivary amylase concentration is reported in diabetic patients [28] and following stress-induced inflammation caused by disorders such as parotitis. [29] It is therefore surprising that despite an increase in salivary pH which should have favored an increase in amylase activity, *Zanthoxylum zanthoxyloides* caused a decrease in salivary amylase, which has further given credence to its anti-diabetic [30,31] and anti-inflammatory property. [32] The anti-diabetic property of *Zanthoxylum zanthoxyloides* could potentially alter carbohydrate breakdown and absorption in the oral cavity which helps in regulating food-induced hyperglycemia. Other members of the Zanthoxylum species have been documented to inhibit α amylase and α glucosidase activities in a manner comparable to standard drug, acarbose. [33,34]

Salivary protein levels and oxidative biomarkers activity were not affected by stimulation from *Zanthoxylum zanthoxyloides*. Other sialagogue such as pilocarpine was also observed to have no effect on protein level when administered intraperitoneally [35] or orally. [36] The increased sodium and chloride level observed in this study matched the increased saliva flow rate which aligns with earlier reports that increased salivary flow rate following mastication is associated with increased electrolyte concentration. [37]

Strengths and limitations of the study

This study is the first to quantitatively and qualitatively document the effect of *Zanthoxylum zanthoxyloides* chewing stick on salivation in human or animal. However, further research is needed to fully understand the underlying mechanisms and clinical implications of these effects. Such data will assist in determining the candidacy of *Zanthoxylum zanthoxyloides* chewing stick or its identified bioactive component in ameliorating the dry mouth associated with Sjögren's disease or radiation and drug-induced hyposalivation.

Conclusion

Zanthoxylum zanthoxyloides increases salivary volume, flow rate and pH and reduces salivary amylase activity through mechanism(s) that is beyond the mechanical stimulatory effect of chewing.

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Conflicting Interest: None

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