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# A Randomized Controlled Trial of Aloe Vera versus Thyme Honey Oral Rinse in the Management of Xerostomia in Type 2 Diabetes

## ABSTRACT

**Objective: Comparing the clinical efficacy of aloe vera versus thyme honey mouthwash in people with type 2 diabetes (T2D) with xerostomia.**

**Materials and methods: A single-blinded randomized trial, including 45 T2D patients, was divided into 3 equal groups. The first group was given aloe vera mouthwash, the second group used thyme honey mouthwash, and the control group was given saline. All followed the same protocol (3 times daily for 4 weeks). These parameters [subjective xerostomia scores, unstimulated salivary flow rate, salivary nitric oxide (NO) levels, and xerostomia-related quality of life questionnaire (XeQoLS)] were evaluated for all groups at different intervals.**

**Results: Subjective xerostomia scores showed significant differences between all groups ($p < 0.001$). After 4 weeks, the highest value was in saline (2.80 ± 0.86), followed by aloe vera (1.47 ± 1.06), while the lowest value was in thyme honey (1.27 ± 1.03). After 4 weeks there was a significant difference between groups regarding the salivary flow rate ($p < 0.001$): the highest value was in thyme honey (0.18 ± 0.16), followed by aloe vera (0.17 ± 0.14), while the lowest value was in saline (0.04 ± 0.02). Salivary NO levels had the highest value in thyme honey (96908.67 ± 21115.55), followed by aloe vera (87821.33 ± 34606.48), while the lowest value was in saline (16396.47 ± 4091.94). There was a significant increase in XeQoLS after 4 weeks ($p < 0.001$) for aloe vera and thyme honey while saline showed moderate satisfaction levels ($p = 0.003$).**

**Conclusions: Thyme honey's effectiveness proved noteworthy compared to aloe vera and saline in managing xerostomia in T2D patients.**

**Trial registration: Registered in clinicaltrials.gov in May 2023 with the identifier NCT05885906.**

**Keywords: xerostomia, aloe vera, thyme honey, type 2 diabetes**

## Introduction

Xerostomia (dry mouth) is sometimes accompanied by a burning sensation and usually occurs when saliva production is diminished by 40% to 50%. However, some patients may have xerostomia with no measurable reduction in saliva [1]. Xerostomia prevalence was estimated to be 45% in an Egyptian population sample of people with type 2 diabetes (T2D) [2].

Xerostomia results in discomfort, impaired speech, increased periodontitis, atrophic changes in the oral mucosa, and taste change, which may lead to an unbalanced diet, weight loss, malnourishment, and depression [3]. Treatment modalities for xerostomia

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are classified into drug-dependent therapy and non-drug-dependent including acupuncture, electrostimulation, and low-level laser therapy [4]. Tiny bruises, tiredness, and minimal increase in unstimulated whole saliva were reported with acupuncture. Daily intraoral electrostimulation devices or low-level therapy use are not practical [3].

Drug-dependent treatments (pilocarpine/cevimeline) cannot provide long-term management because they have many side-effects due to their cholinergic effects, so they cannot be used with any underlying systemic disease. It appears that the available therapies do not offer long-term and safe xerostomia management, so searching for an alternative treatment with no or fewer side effects is necessary [5].

Aloe vera is an over-the-counter ingredient used in different preparations. Water represents approximately 99% of the gel in aloe vera leaves, so it has a strong moisturizing effect. It is characterized by strong antioxidant, antimicrobial, and wound-healing properties [6]. Because oxidative stress contributes to the underlying tissue damage in xerostomia, antioxidant activity is a valuable characteristic [7].

Thyme honey is a propolis gel product with strong antioxidant, antibacterial, and antifungal effects that was accepted for managing xerostomia in previous studies [4, 8]. According to Charalambous et al. [4], thyme honey is thought to have a sialagogue effect in the oral cavity encouraging the salivary glands to function. Thyme honey exhibits hypoglycemic properties by considerably lowering blood glucose levels and protecting against metabolic alterations and diabetes-related problems due to its different phenolic components [9].

Nitric oxide (NO) is a free radical that is actively produced by the body, can be used as a biochemical marker, and is involved in the physiological and pathological salivary gland functions [10, 11]. The salivary NO level became a xerostomia predictor in people with diabetes when a recent study showed that its level in people with diabetes suffering from xerostomia is much lower than in those without xerostomia [10].

The oral health status of T2D patients suffering from xerostomia is important; thus, this study aimed to compare the efficiency of novel natural agents such as thyme honey (20%) and aloe vera (50%) rinses for xerostomia in T2D patients.

## Subjects and methods

### Study design

A single-blinded randomized controlled clinical trial with biochemical assessment. Patients were randomly distributed into 3 groups using a computer-generated randomization table with a ratio of 1:1:1. A third party oversaw participant randomization and allocation.

### Subjects

Patients were recruited from the Oral Medicine and Periodontology Department outpatient clinic at the Faculty of Dentistry Ain Shams University. Both genders, aged above 18 years, with T2D only having optimal glycemic control (HbA1c < 7%, or fasting blood glucose [FBG] level 70–130 mm/dL, or postprandial blood glucose level < 180 mm/dL) and on an oral hypoglycemic, complaining of xerostomia, and willing to follow all the instructions and attend all the study-associated visits were included [12, 13]. Patients who had received radiation therapy to the head and neck region or with other systemic diseases known to cause xerostomia or patients using any other medication for their xerostomia condition or requiring hospitalization for any medical problem were excluded [12].

### Ethical approval

Approval number FDASU-REC IM122208 was obtained from the research Ethical Committee of the Faculty of Dentistry, Ain Shams University. Informed written consent was obtained from all individual participants in the study.

### Data collection

Severity of subjective xerostomia symptoms was assessed before recruitment using a questionnaire with 4 questions. Patients answered these questions with yes or no. Patients were recruited after giving a positive response indicating a reduced unstimulated salivary flow rate [14].

### Outcomes evaluation

The assessment of subjective xerostomia score and salivary flow rate was carried out at baseline, 2 weeks, and 4 weeks after starting the treatment [4]. In comparison, salivary NO levels and XeQoLS were measured at baseline and after 4 weeks of treatment [10].

#### Primary outcome

Subjective xerostomia score [14]: All patients were interviewed for their symptoms of xerostomia using a questionnaire as previously mentioned.

#### Secondary outcomes

— Unstimulated salivary flow rate: To eliminate any circadian changes obtaining samples was between 9:00 to 11:00 a.m. Before collection, participants were requested to wait at least

**Table 1. Intergroup Comparisons for Demographic Data**

| Parameter | | Aloe vera | Thyme honey | Saline | P-value |
|---|---|---|---|---|---|
| Gender [n (%)] | Male | 9 (60.00%) | 7 (46.67%) | 8 (53.33%) | 0.765 |
| | Female | 6 (40.00%) | 8 (53.33%) | 7 (46.67%) | |
| Age (mean ± SD) [years] | | 51.27 ± 8.37 | 54.87 ± 8.90 | 53.80 ± 7.15 | 0.471 |
| Diabetes duration (mean ± SD) [years] | | 6.1 ± 2.8 | 5.7± 3.1 | 6.7 ± 2.2 | 0.611 |
| HbA1c [%] | | 6.3 ± 0.42 | 6.5 ± 0.15 | 6.4 ± 0.30 | 0.413 |
| Medications | | | sulfonylureas | | |
| Oral complications | | | xerostomia in 100% of patients | | |

*Significant ($p < 0.05$); HbA1c — glycated hemoglobin; Ns — non-significant ($p > 0.05$); SD — standard deviation

two hours without eating, drinking, or brushing. Then, after swallowing all the saliva in their mouth, unstimulated whole saliva was collected using the spitting method every 60 seconds for 5 min in a sterile tube [15]. The tubes were frozen at –20°C to avoid changes in saliva composition before sending them to the lab [10].

If the unstimulated flow rate was less than 0.2 mL/min, which was considered to represent hyposalivation, the patient was included in the study [16].

— Salivary NO levels: Using the Biodiagnostic Nitrite Assay Kit (colorimetric) utilizing the Griess reaction measured at baseline and after 4 weeks in the lab after saliva collection and preservation in a refrigerator (at –20°C) for pre-assay preparation and operating steps following the manufacturer's instructions [10].

— XeQoLS: Included 15 questions regarding how xerostomia affects a person's quality of life [17].

Xerostomia's consequences on the 4 primary categories of oral health-related quality of life: physical (1, 6, 10, 12), pain (2, 3, 7, 9), personal (8, 13, 14, 15), and social (4, 5, 11) were measured by the XeQoLS questionnaire. The 15 items in the questionnaire were each rated on a Likert scale from 0 to 4, with higher scores denoting a more severe symptom burden for each available time point. The average of the 15 individual items, each scored on a 0-to-4 scale, was used to calculate the mean XeQoLS scores for the global and individual subdomains.

## Interventions

**Group 1:** (Aloe vera group) received aloe vera mouthwash based on a previously developed protocol [7] (20 mL aloe vera 50%).

*Aloe vera mouthwash preparation [18]: aloe vera gel 50%, distilled water 1000 mL, and 10 drops of a flavoring material.

**Group 2:** (Thyme honey group) received thyme honey mouthwash based on a previously developed protocol [4] (20 mL thyme honey diluted in 100 mL distilled water).

*Thyme honey mouthwash preparation [19]: Distilled water was collected from the distillation unit, and then the thyme honey was diluted using sterile water with a ratio of 1:5 and distributed in sterile bottles.

**Group 3:** (Saline control group) received saline mouthwash as a control group (20 mL saline) [12].

## Statistical analysis

Power analysis was performed to have adequate power to apply a 2-sided statistical test of the null hypothesis that there was no difference between tested groups regarding salivary flow rate. By adopting an alpha level of 0.05, a beta of 0.2, i.e., power = 80%, and an effect size (f) of 0.518, the predicted total sample size (n) was found to be 39 cases (13 cases per group), which was calculated based on a previous study result.[12] Ordinal and categorical data are presented as frequency and percentage values. The chi-square test was used for categorical data. Numerical data were presented as mean and standard deviation values and analyzed for normality using the Shapiro-Wilk test. Parametric data (age) were analyzed using an independent t-test for intergroup comparisons. Non-parametric data and ordinal data were analyzed using the Mann-Whitney U test for intergroup comparisons and Friedman's test followed by the Nemenyi post hoc test for intragroup comparisons. The significance level was set at $p < 0.05$ within all tests. Statistical analysis was performed with R statistical analysis software version 4.3.2 for Windows.

## Results

The study was conducted on 45 patients randomly and equally allocated to the studied groups. There was no significant difference between tested groups regarding different demographic characteristics ($p > 0.05$), as shown in Table 1.

**Table 2. Inter- and Intragroup Comparisons, Mean and Standard Deviation Values for Subjective Dry Mouth Score, Unstimulated Salivary Flow (mL/min), and Nitric Oxide (μmol/L)**

| Time | Subjective dry mouth score (Mean ± SD) | | | P-value |
|---|---|---|---|---|
| | Aloe vera | Thyme honey | Saline | |
| Baseline | 3.60 ± 0.63$^{Aa}$ | 3.47 ± 0.74$^{Aa}$ | 3.40 ± 0.74$^{Aa}$ | 0.734 |
| 4 weeks | 1.47 ± 1.06$^{Bc}$ | 1.27 ± 1.03$^{Bc}$ | 2.80 ± 0.86$^{Ab}$ | < 0.001* |
| P-value | < 0.001* | < 0.001* | 0.008* | |
| | Unstimulated salivary flow (mL/min) (Mean ± SD) | | | P-value |
| | Aloe vera | Thyme honey | Aloe vera | |
| Baseline | 0.05 ± 0.04$^{Ac}$ | 0.07 ± 0.05$^{Ab}$ | 0.07 ± 0.04$^{Ac}$ | 0.106 |
| 4 weeks | 0.22 ± 0.16$^{Aa}$ | 0.25 ± 0.16$^{Aa}$ | 0.11 ± 0.03$^{Ba}$ | < 0.001* |
| P-value | < 0.001* | < 0.001* | 0.001* | |
| | Nitric oxide (μmol/L) (Mean ± SD) | | | P-value |
| | Aloe vera | Thyme honey | Saline | |
| Before | 101.60 ± 47.68$^{A}$ | 128.40 ± 33.43$^{A}$ | 97.47 ± 49.76$^{A}$ | 0.079 |
| After | 87821.33 ± 34606.48$^{A}$ | 96908.67 ± 21115.55$^{A}$ | 16396.47 ± 4091.94$^{B}$ | < 0.001* |
| P-value | < 0.001* | < 0.001* | < 0.001* | |

Values with different upper and lowercase superscripts within the same horizontal row and vertical column, respectively, are significantly different; *significant ($p < 0.05$); Ns — non-significant ($p > 0.05$); SD — standard deviation

Subjective dry mouth scores showed no significant difference between groups at baseline ($p = 0.734$), but after 4 weeks there was a significant difference between groups ($p < 0.001$), with the highest value found in saline (2.80 ± 0.86), followed by aloe vera (1.47 ± 1.06), and the lowest value in thyme honey (1.27 ± 1.03), as shown in Table 2 and Supplementary Table 1. Within the aloe vera group, a significant difference between values measured at different intervals ($p < 0.001$) was found, with the highest value at baseline (3.60 ± 0.63) and the lowest value at 4 weeks (1.47 ± 1.06). While the thyme honey group showed a significant difference between values measured at different intervals ($p < 0.001$), the highest value was found at baseline (3.47 ± 0.74). In contrast, the lowest value was found at 4 weeks (1.27 ± 1.03). Also, the saline group showed a significant difference between values measured at different intervals ($p = 0.08$): the highest value was at baseline (3.40 ± 0.74), while the lowest value was found at 4 weeks (2.80 ± 0.86).

At baseline, there was no significant difference between groups ($p = 0.106$) regarding the unstimulated salivary flow rates. The highest values were in thyme honey (0.07 ± 0.05) (ml/min) and saline (0.07 ± ± 0.04) (ml/min), while the lowest value was in aloe vera (0.05 ± 0.04) (ml/min). However, after 4 weeks a significant difference between groups started to appear ($p = 0.001$). The highest value was in thyme honey (0.25 ± 0.16) (mL/min), followed by aloe vera (0.22 ± 0.16) (mL/min), while the lowest value was in saline (0.11 ± 0.03) (mL/min), as shown in Table 2 and Supplementary Table 1.

In the present study, regarding (NO) levels, there were no significant differences between groups ($p=0.079$) at baseline. The highest value was in thyme honey (128.40 ± 33.43) (μmol/L), followed by aloe vera (101.60 ± 47.68) (μmol/L), while the lowest value was in saline (97.47 ± 49.76) (μmol/L). After 4 weeks there was a significant difference between groups ($p < 0.001$). The highest value was in thyme honey (96908.67 ± 21115.55) (μmol/L), followed by aloe vera (87821.33 ± 34606.48) (μmol/L), while the lowest value was in saline (16396.47 ± 4091.94) (μmol/L), as shown in Table 2.

Regarding the XeQoLS at baseline, most patients had low satisfaction levels, and there was no significant difference between groups ($p = 0.688$), while after 4 weeks there was a significant difference between groups ($p = 0.002$). There was a significant increase in patients with good satisfaction levels after 4 weeks ($p < 0.001$) for aloe vera and thyme honey, while saline showed a significant increase in the percentage of patients with moderate satisfaction levels ($p = 0.003$), as shown in Supplementary Table 2.

## Discussion

After 4 weeks the intervention groups had significantly lower subjective xerostomia scores than the control group, indicating a reduced perception of xerostomia as per the result of a study conducted using aloe

vera-peppermint moisturizing gel for a short duration, which concluded that the mean score of xerostomia in the intervention group was significantly lower than in the placebo group [20], Similarly, another study reported that after 2 weeks of aloe vera mouthwash use the xerostomia in the interventions was significantly lower than in the controls [12].

Also, Charalambous et al. [4] and Ibrahim et al. [8] reported that after using thyme honey mouthwash, the xerostomia in the intervention arm was significantly lower than in the controls. Another study concluded that daily consumption of royal honey jelly for 12 weeks was effective in alleviating subjective xerostomia sensation with normal saliva function [21].

Regarding the unstimulated salivary flow rate, a significant difference was found after 4 weeks, which was in agreement with previous studies [8, 12, 22]. Another study by Atashi et al. [20] concluded that the aloe vera gel markedly reduced xerostomia and improved oral health.

Aloe vera is similar in its composition to saliva in terms of complexity and high-water ratio. Its moisturizing effect results from its lubrication, ability to cover the mucosal surface, and pleasant foaming action [6]. For its role in xerostomia, the binding of moisture to oral mucosa is through the mucopolysaccharides in the aloe vera, which prolong its contact with the mucosa potentiating efficiency as a salivary substitute [12]. However, certain side effects and contraindications are associated with aloe vera use including diarrhea, hypokalemia, kidney failure, as well as phototoxicity and hypersensitive reactions [23].

An increase in salivary flow rate is associated with topically applying honey because it can stimulate taste sensation [24]. Thyme has a high content of substances that stimulate the neuroactive salivary secretory system such as organic acids that could increase the flow of saliva by stimulating the chemoreceptors in the mouth [9]. However, high doses of thyme can cause side effects due to thymol. Still, it is difficult to find any documentation of side effects related to thyme use. Although uncommon, it is possible to be allergic to thyme [25].

Salivary NO levels showed great results for the intervention groups compared to the control group, in agreement with previous studies that evaluated the salivary NO levels after using honey and thyme honey [8, 26]. It should be noted that there are no earlier reports assessing salivary NO levels after using aloe vera with which we could compare our results; however, this improvement may be attributed to both aloe vera and thyme honey having strong antioxidant properties capable of transforming the free radical of NO into the stable products of nitrate and nitrite by donating their electrons. In addition, the increase of total nitrite in saliva, plasma, and urine by honey solution was established in an earlier study [7].

Xia et al. [27] concluded that changes in nitrite and nitrate levels in the saliva are associated with hypofunction of the salivary glands. Our result is also comparable to other studies that established the ability of honey to decrease prostaglandin levels, thus having strong healing power and anti-bacterial action, elevating NO levels, and exerting prebiotic effects [8, 26]. Several studies showed that aloe vera can activate monocytes and macrophages to generate NO increasing the salivary NO levels, which has several functions whether intra- or inter-cellularly as a messenger [28, 29].

After 4 weeks there was an increase in the life quality of the patients due to an improvement in the salivary flow rate, and this was in agreement with a previous study by Morales-Bozo et al. [22], who used aloe vera, and Charalambous et al. [4], who used thyme honey. This questionnaire was used to evaluate patients' satisfaction regarding the mouthwashes used and to evaluate the effectiveness of the treatment, as per the questionnaire in the studies performed by Charalambous et al. [4] and Badooei et al. [12], but in the latter study, the patients answered the questionnaire self-reportedly, which was a limitation, while in our study the researcher obtained the answers from the patients during their visits. However, this study involved only one center; to further validate our results a larger sample size with a multi-centered approach and longer duration must be conducted. Also, some patients complained about the aloe vera rinse due to its bitter taste, so a different preparation method may be more suitable.

In conclusion, both mouthwashes are safe and cost-effective options for treating xerostomia in people with underlying systemic illnesses, considerably reducing xerostomia symptoms and enhancing patients' quality of life, as well as increasing the salivary flow rate and salivary NO levels.

## Article information

### Supplementary material

Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/103694.

### Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

## Ethics statement

The study received ethical approval (no. FDASU-REC IM122208) from the Faculty of Dentistry's Ethics Committee at Ain Shams University. Informed written consent was obtained from all individual participants in the study, registered in clinicaltrials.gov on May 22, 2023, with the identifier NCT05885906.

## Authors' contributions

All authors contributed substantially to the study's design, D.B.E, R.R.H, and S.S.I conceptualized and designed the study, D.B.E was responsible for data collection, D.B.E and R.R.H were responsible for data analysis and interpretation, and R.R.H and S.S.I revised the draft of the manuscript critically and have given final approval for the version to be published.

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## Conflict of interest

The authors declare no conflict of interest.

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