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Clinical trial

The efficacy of asafoetida (*Ferula assa-foetida* oleo-gum resin) versus chlorhexidine gluconate mouthwash on dental plaque and gingivitis: A randomized double-blind controlled trial

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ABSTRACT

Introduction: Microbial plaque is known to be the most important causative agent of periodontal disease. Since plaque control by mechanical methods is not enough to keep the gingival health in many people, attention has been brought to medicinal treatments, including mouthwashes. The purpose of this study was to investigate the efficacy of asafoetida versus chlorhexidine gluconate (CHG) mouthwash.

Methods: This study was a double-blind randomized active-controlled clinical trial. One hundred and twenty six patients were randomly assigned into two groups of asafoetida and CHG mouthwashes. They were advised to use 15 ml of their prescribed mouthwash twice daily for a period of 7 days. Before enrollment and then at the end of the 7th day of intervention, the plaque index (PI) and modified gingival index (MGI) were measured. Moreover, safety measures were monitored during this period.

Results: After the intervention period, improvement of MGI mean difference was observed in both of the asafoetida and CHG groups (0.9 ± 0.7 vs. 0.4 ± 0.5, respectively). Also, there was an improvement regarding PI mean difference in both of the asafoetida and CHG groups (1.8 ± 0.6 vs. 0.9 ± 0.6, respectively). However, mean differences of MGI and PI in the asafoetida group showed a significant reduction, compared to the CHG group ($P < 0.0001$). It should be noted that no serious side effects were observed.

Conclusion: Considering the results, it seems that asafoetida mouthwash can be recommended as an efficient herbal mouthwash for improving the indices of gingival health. However, future studies on larger cohorts with longer intervention periods are necessitated.

1. Introduction

Periodontal disease (PD) is one of the general health problems which leads to loss of teeth [1]. It is one of the most prevalent chronic oral diseases worldwide, as well [2]. Microbial plaque is known to be the most important causative agent of PD [3]. Therefore, its control or elimination should be considered as the most important principle during the prevention and treatment stages. According to the current evidence, plaque control by mechanical instruments (e.g. toothbrush and dental floss) is not sufficient and has some limitations [4]. Therefore, attention has been brought to medical treatments, including mouthwashes [5,6].

Nowadays, there is an increasing interest toward medicinal plants [7–9]. Interestingly, different medicinal plants have been used to disinfect the oral cavity and reduce the plaque of the teeth, in the field of periodontology [10–12].

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Ferula assa-foetida L. (F. assa-foetida) is a large herbaceous perennial plant from the Apiaceae family [13]. F. assa-foetida' stem is somewhat thick with a coarse surface. Its height may reach up to 2.5 m. Also, its 60 cm thick leaves are divided into many pieces with serrated edge. An umbilical inflorescences make a pretty view with its yellowish flowers which are located at the stem's end. Additionally, its dark brown nearly flat fruits are elliptical in shape and in five lines [14]. Blade-cutting the base of the stem and the thick root of the plant makes the plant discharge a milky juice as oleo-gum resin, which is known in traditional Persian medicine (TPM) as Heltit, Anghouzeh, Khorakoma, and Anguzakoma [15] or asafoetida in English. Its temperament (mɛzɑǰ) is warm and dry. Its properties according to TPM resources suggest as a mouthwash it is effective for dental decay and relieving toothache [16].

Different parts of F. assa-foetida have a wide variety of medicinal applications:including antifungal, anti-diabetic, anti-inflammatory, anti-mutagenic and anti-microbial effects (5). The antibacterial effects of the plant have been shown in various studies carried out by researchers in different countries. For instance, Kavousi et al. in 2013 have demonstrated its antioxidant and anti-microbial effects against different aerobic and non-aerobic bacteria [17]. Also, in a review study by Iranshahi et al. in 2011, the authors pointed out the anti-inflammatory and anti-microbial effects of F. assa-foetida [18].

Despite traditional uses of asafoetida for oral and dental diseases, besides its known pharmacological properties, there is trace data about its efficacy for plaque control and ginigival health. Therefore, the present study aimed to evaluate the effectiveness of asafoetida versus chlorhexidine gluconate (CHG) mouthwash.

2. Materials and methods

2.1. Type and methods of study

This study was a randomized double-blind active-controlled clinical trial which had two parallel arms. Patients were randomly assigned into the study groups by a 1:1 allocation ratio. The methods were not modified after the final approval of the proposal.

2.2. Ethics

The trial was in compliance with the Declaration of Helsinki (1989 revision) and was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (SSUMS) in Yazd (ID No. IR.SSU.REC.1395.182). The aim and methods of the research were initially explained to patients. Then, written informed consent forms were signed before the patients' enrollment. The trial protocol was registered in Iranian Registry of Clinical Trials database (registration ID: IRCT2017012532171N1).

2.3. Preparation of asafoetida mouthwash

Asafoetida was bought from a local herbal market in Yazd. It was identified and approved by Professor Hakimiand a sample was deposited at the Herbarium Center of Natural Resources Faculty of Yazd University (voucher specimen: 888).

To prepare the aqueous extract of the asafoetida, we prepared its powder by an electric grinder. The powder (10 g) was dissolved in 100cc of water and then mixed in a 250 ml Erlenmeyer flask. The solution was then placed on a stirrer for 24 h. Then, it was filtered by a vacuum pump and an Atman filter. The solution was then mixed with water by 0.5% w/w and packaged in opaque bottles.

2.4. Inclusion and exclusion criteria

From March 2017 to July 2017, patients (of both genders) who were referred to the dental clinics affiliated to SSUMS were asked to participate if they were between 18–35 years of age. While, the patients who had the following criteria were excluded from the study: antibiotic use at least one month before the study, periodontal treatment in the last six months, diabetes mellitus and hypertension, mucosal lesions, malocclusion and severe dental crowning, subgingival calculus formation, smoking and alcohol consumption, need for antibiotic prophylaxis, presence of any removable orthodontic appliances, positive history of sensitization to herbs or herbal medicines, pregnancy, or an acute peptic ulcer.

2.5. Intervention

After supra-gingival scaling was followed by brushing, the patients did not use any method of plaque control for 7 days. Patients were asked not to use any other methods for plaque control during this period. They were required to swish 15 ml of the prescribed mouthwashes (i.e. chlorhexidine gluconate 0.2% by Najo Pharmaceutical Company OR asafetida mouthwash 0.5%) around the mouth for 60 s twice daily. In addition, they were also instructed not to eat anything for one hour after mouth washing. They were asked not to rinse their mouth with water afterwards, as well.

2.6. Outcome measures and follow-up

Before the patients' enrollment, the plaque index (PI) and modified gingival index (MGI) were measured by a constant person. To record PI, we checked the presence of dental plaque on the mesial, buccal, distal, and lingual or palatal surfaces. The PI score was recorded as follows: 0 = no plaque, 1 = plaque in the gum and teeth margin, 2 = continuous band of plaque with width < 1 mm in the margin of the gum, 3 = continuous band of the plaque with width ≥ 1 mm, but less than 1/3 of the crown of the teeth, 4 = the plaque covering over 2/3 of the teeth [19,20].

Furthermore, MGI was determined in four areas around the tooth. It ranges from 0 to 3, when zero indicates normal gingival status. Score 1 (mild inflammation) means slight changes in color, mild edema, and no bleeding in the probing. Score 2 (medium inflammation) designated to those patients with redness, edema, and bleeding in the probing. Score 3 (severe inflammation) shows redness, edema, and wound tendency to self-healing [21]. These indices were based on Carranza's clinical periodontology textbook and Ramfjord, Sigurd's paper suggestions [22,23].

The examination was completed, recorded and approved by the periodontologist (F.V.). Besides, at the end of 7 days of intervention, patients were recalled again and the indexes were recorded by the same periodontologist.

2.7. Randomization, allocation concealment and blinding

The bottles were divided into two groups labeled with A and B. Patients were assigned into two groups of 63 subjects according to a block-randomization list. Moreover, allocation concealment performed based on the sequential numbered sealed opaque envelops.

Since the basis of the study was a double-blind clinical trial, the mouthwashes were packaged in opaque bottles of the same shape and size by a person who was not involved in the study. The physician and the patient were not informed about the content of the bottles.

2.8. Sample size

The required sample size was estimated using below formula. Two-sided alpha of 0.05 and beta of 0.2 was considered for the calculation. According to a similar previous study, P_1 was set as 47%. Also, minimum clinical significant difference of 25% between the study groups was considered. Then, P_2 was set 22% [24]. Finally, sample size was set to be 63 persons in each group, by estimating a probable 15 percent drop-out.

$$N = \frac{2 \times \left(Z_{1-\frac{\alpha}{2}} + Z_{\beta}\right)^2 \times \bar{P}(1-\bar{P})}{(P_1 - P_2)^2}$$

2.9. Data analysis

The data are presented as mean ± standard deviation (SD), 95% confidence interval, percentage and proportion. Different statistical tests, including Chi-square, Mann Whitney U, Wilcoxon, and *t*-test were applied. Statistical Package for the Social Sciences (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) was used for data analysis. Moreover, *P* values less than 0.05 were taken to be statistically significant.

3. Results

3.1. Study flow

Participants in this study included 126 patients (65 men and 61 women) who referred to periodontics department of SSUMS from March to July 2017. Details on patients' screening, allocation, drop-out and those included for analysis are presented in Fig. 1.

3.2. Baseline characteristics

According to the results shown in Table 1, the mean age and gender of subjects was not significantly different between the two groups.

3.3. Clinical response

After the intervention period, there was a significant difference of MGI score in two groups of the study. However, patients in asafoetida group compared to those in CHG group experienced significant improvement regarding MGI mean difference ($P < 0.0001$) (Table 2).

Moreover, according to the results shown in Table 3, it was determined that the effect of asafoetida mouthwash on reduction of the PI was more than CHG mouthwash ($P < 0.0001$). There was an improvement regarding PI mean difference in both asafoetida and CHG groups (1.8 ± 0.6 vs. 0.9 ± 0.6, respectively).

Table 1
Demographic characteristics of patients in the two groups of asafoetida and chlorhexidine gluconate.

	Asafoetida (n = 63)	CHG (n = 63)	*P* value
Age (years), Mean ± SD	27.3 ± 5.8	26.2 ± 6.04	0.2*
Male/female (n)	33/30	28/35	0.4**

CHG: chlorhexidine gluconate; SD: standard deviation.
* *t*-test.
** Fishers exact test.

3.4. Safety

There were not any important harms or adverse effects in both groups. Only, few people complained about the smell of asafoetida (3 persons) and taste of CHG (4 persons).

4. Discussion

According to the results of this randomized double-blind active-controlled clinical trial, patients in both of the trial's arms experienced amelioration regarding PI and MGI. However, the efficacy of asafoetida mouthwash was superior compared to CHG mouthwash at the end of the intervention.

Among the antibacterial agents that are topically used for the prevention and treatment of periodontal diseases, antiseptics, including CHG, are the most commonly used agents. Among them, CHG mouthwash has wide and potent anti-microbial effects. Hence, CHG is the most popular mouthwash today [25,26]. Nonetheless, CHG has several known adverse effects. These effects include dryness of the mouth, taste alteration, mucus sensitivity, tooth discolorization, and some of systemic side effects followed by its accidental swallowing [27]. Therefore, there are several studies to find an alternative, including herbal mouthwashes.

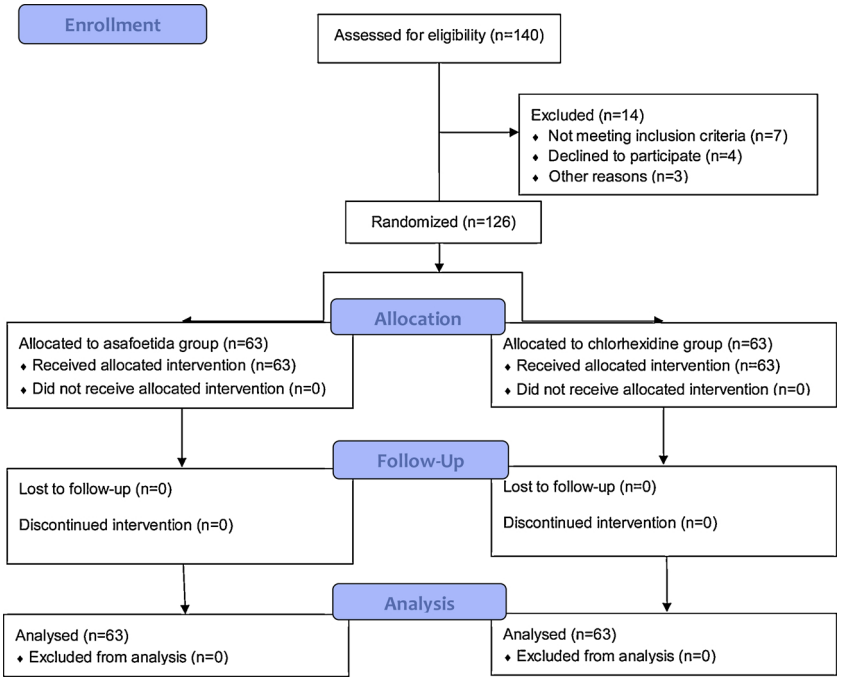

Fig. 1. The CONSORT flowchart of trial.

Table 2
Modified gingival index score, comparing mean values before and after trial within groups, and mean differences between asafoetida and chlorhexidine gluconate groups.

	Before intervention		After intervention		Difference		*P* value	
	Mean ± SD (CI 95%)	Median (IQR)	Mean ± SD (CI 95%)	Median (IQR)	Mean ± SD (CI 95%)	Median (IQR)	Within group*	Between group**
Asafoetida (n = 63)	1.06 ± 0.75 (0.8–1.2)	1 (2)	0.1 ± 0.4 (0.05–0.2)	0 (0)	0.9 ± 0.7 (0.8–1)	1 (1)	< 0.0001	< 0.0001
CHG (n = 63)	0.6 ± 0.58 (0.4–0.7)	1 (1)	0.15 ± 0.3 (0.06–0.2)	0 (0)	0.4 ± 0.5 (0.3–0.5)	0 (1)	< 0.0001	
P value	0.001**		0.8**					

CHG: chlorhexidine gluconate; IQR: interquartile range; CI 95%: 95% Confidence Interval; SD: standard deviation.
* Wilcoxon test.
** Mann-whitney U test.

Table 3
Plaque Index score, comparing mean values before and after trial within groups, and mean differences between asafoetida and chlorhexidine gluconate groups.

	Before intervention		After intervention		Difference		*P* value	
	Mean ± SD (CI 95%)	Median (IQR)	Mean ± SD (CI 95%)	Median (IQR)	Mean ± SD (CI 95%)	Median (IQR)	Within group*	Between group**
Asafoetida (n = 63)	2.4 ± 0.8 (2.2–2.6)	3 (1)	0.5 ± 0.6 (0.4–0.7)	1 (1)	1.8 ± 0.6 (1.7–2)	2 (0)	< 0.0001	< 0.0001
CHG (n = 63)	2.4 ± 0.7 (2.3–2.6)	3 (1)	1.5 ± 0.7 (1.3–1.7)	2 (1)	0.9 ± 0.6 (0.7–1)	1 (1)	< 0.0001	
P value	0.9**		< 0.0001**					

CHG: chlorhexidine gluconate; IQR: interquartile range; CI 95%: 95% Confidence Interval; SD: standard deviation.
* Wilcoxon test.
** Mann-whitney *U* test.

For instance, Darwishi Khezri and colleagues compared the antibacterial effects of chamomile, persica and CHG mouthwashes in ICU patients with mechanical ventilation. The results of this study showed that persica and chamomile mouthwashes have an acceptable effect on *Streptococcus pneumoniae* and *Staphylococcus aureus* of the patients' oropharyngeal region [28]. Another study by Araqi Zadeh et al. showed the inhibitory effect of green tea on cariogenic and periodontic bacteria [29].

To the best of our knowledge, there is no clinical study on the efficacy of asafoetida mouthwash. However, there is numerous preclinical research on the activity of asafetida against different microbial agents, which had an important role in dental plaque control [30–32]. "The antimicrobial activity of *Ferula assa-foetida* may be due to biologically active compounds, such as sesquiterpenes, terpenoid coumarins, and sulfur containing compounds" [33]. Also, asafetida possesses anti-inflammatory property which is a favorable characteristic for treatment of different dental and gingival disorders [34]. Moreover, the aqueous extract of the asafoetida is effective in increasing the proliferation of epithelial cells and speeding up blood flow in the inflammatory processes [35].

4.1. Limitations

Our study had some limitations. First, the short period of intervention and the small sample population ought to be stated as a major concern. Our study was the first clinical trial on asafoetida mouthwash. Therefore, we selected an intervention period of one week as a standard in previous researches [4,6,27,36–38]. Subsequent clinical trials of larger sample size and longer intervention period are necessary for assessment of its efficacy and safety. Second, there are several other dental health instruments which could be used for more reliable judgment. Specially, bleeding on probing was not assessed. This could make results clearer and provide better understanding about its efficacy. However, due to the importance of plaque control in periodontal diseases, we used two indices of PI and MGI considering their non-invasive nature. Lack of placebo comparison group is another methodological problem in the current study.

5. Conclusion

Considering the greater effect of the asafoetida mouthwash on the improvement of the measured indices (i.e. PI and MGI), as compared to CHG mouthwash, this herbal mouthwash can be used in addition to mechanical methods for plaque control and gingival health. However, further preclinical and clinical studies which overcome our limitations are required for better scientific understanding about asafoetida mouthwash. Specifically, community-based trials are encouraged for assessment of its effectiveness and safety. Finally, it is suggested that future studies should evaluate its efficacy on patients with periodontal diseases.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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