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Effect of *Punica granatum* Peel Extract Mouthwash on Gag Reflex During Dental Impression: A crossover Clinical Trial

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Abstract

Introduction: The primary aim was to diminish the gag reflex, quantified by the Gagging Severity Index (GSI), during orthodontic impression procedures. The goal was to enhance patient compliance by incorporating *Punica granatum* peel aqueous extract (*P. granatum* PAE) into a mouthwash solution used during the process.

Methods: This double-blind, longitudinal, controlled clinical trial was conducted on patients at a dental clinic. A total of 40 patients—21 females and 19 males, with average age of 29.3 ± 6.0 years—and GSI scores of 2 and 3 were included. The *P. granatum* PAE was prepared via freeze-drying and enriched with ascorbic acid, potassium sorbate, glycerin, and food coloring. A placebo mouthwash, devoid of *P. granatum* PAE, was also created. These mouthwashes, labeled 'A' and 'B', were administered randomly across two sessions, ensuring each patient received both types. The GSI was assessed before and after administration during the impression procedure.

Results: Statistical analysis using the Chi-squared test revealed that both mouthwash variants generally decreased GSI scores. However, the *P. granatum* PAE was notably more effective in reducing these scores ($P < 0.005$).

Conclusion: The study confirms that *P. granatum* PAE is a powerful antiemetic. Its inclusion in mouthwash formulations can significantly reduce GSI scores, thereby improving patient compliance with orthodontic procedures.

Keywords: Pomegranate, Antiemetics, Gagging, Dental clinics, Patient compliance

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Introduction

The gag reflex presents a significant challenge during orthodontic impression procedures, acting as an involuntary response that disrupts dental operations and leads to patient noncompliance (1). Dentists employ a variety of strategies to mitigate gagging and nausea during these procedures, including the use of antiemetic medications (2, 3), analgesic sprays applied to the distal soft palate and uvula (4), and even acupuncture (1, 5).

Despite the availability of pharmacological and procedural interventions, there remains a lack of accessible, well-tolerated, and natural alternatives that can be easily integrated into routine dental practice. Analgesics offer only temporary relief and may need to be reapplied throughout the dental session (4). Antiemetic drugs do not completely eradicate the intensity of nausea and are not uniformly effective across all patients, although they may lessen the symptoms (6).

In light of the burgeoning interest in natural remedies, many patients are inclined to embrace herbal products (7). In the context of gag reflex management, Punica granatum (pomegranate) enjoys widespread popularity and acceptance as an herbal remedy. Research indicates that pomegranate peel is abundant in antioxidants and bacteriostatic compounds (8, 9), and possesses significant analgesic properties owing to its high tannic acid content (10). Given its analgesic and antimicrobial properties, pomegranate peel extract may offer a dual benefit: reducing discomfort while minimizing microbial contamination during impression procedures.

Developing a natural, effective mouthwash could enhance patient comfort, improve procedural compliance, and reduce reliance on synthetic medications with potential side effects. This study aimed to evaluate the effectiveness of a pomegranate peel extract mouthwash in minimizing gag reflex intensity during orthodontic impression procedures, with a focus on patient tolerability and clinical feasibility.

Methods

Study Design

This study was designed as a double-blind, longitudinal,

randomized crossover trial on participants with moderate to severe gag reflex. Each participant received both the placebo and the *P. granatum* peel aqueous extract (*P. granatum PAE*) mouthwash solution in a crossover sequence, with the intervention alternated between the first and second sessions with a washout period of one week. To maintain the integrity of the double-blind protocol, the mouthwash formulations were labeled as 'A' and 'B', ensuring that neither the investigators nor the dental practitioners administering the treatments were aware of the solution identities. This blinding strategy was implemented to minimize bias and uphold the objectivity of the study outcomes.

Inclusion and Exclusion Criteria

Participants were recruited from the Dentistry Clinics affiliated with the North Khorasan University of Medical Sciences, Bojnurd, Iran, between 2021 and 2022. Eligible individuals were adults aged 15-45 years who exhibited moderate to severe gag reflexes, defined by a Gagging Severity Index (GSI) score of 3 or 4 (1, 11). GSI was assessed during a standardized pre-screening procedure using an abslang examination stick, gently applied to the soft palate and uvula by trained clinicians.

Inclusion required clinical stability and the ability to provide written informed consent. Exclusion criteria included conditions known to influence gag reflex or interfere with oral procedures: nasal obstruction, sinusitis, post-nasal drip, xerostomia, nasal polyps, alcohol dependency, gastrointestinal malignancies, chronic peptic ulcers, cholecystitis, habitual smoking, mucosal congestion of the upper respiratory tract, use of emetogenic chemotherapy agents, and psychological disorders such as anxiety or paranoia.

Participants were screened consecutively and enrolled only if they met all criteria and agreed to participate in both phases of the crossover design. Subsequently, a total of 40 participants were enrolled in the study, all of whom completed both phases without any withdrawals.

Sample Size and Sampling Procedure

The sample size was determined through a specific statistical formula (eq. 1). The values for p and p_0 were set at 0.8 and 0.5, respectively. Additionally, the risks of Type I and Type II errors, denoted by alpha and beta, were established at 0.05 and 0.2, respectively. The formula used is as follows:

$$n = \frac{(\frac{Z\alpha}{2} + Z_\beta)^2 \, pq}{(p - p_0)^2} \qquad \text{eq. 1}$$

Sampling was conducted randomly from the patients admitted at the dentistry clinic. Those patients met the inclusion and exclusion criteria were enrolled in the study after written consent.

Preparing P. Granatum PAE

To prepare the ***P. granatum*** PAE, the outer layer was first carefully removed and allowed to air dry at ambient room temperature. Once dried, the peel was finely ground into a powder. This powder was then steeped in deionized water for a period of 48 hours. Following the steeping process, the clear liquid (supernatant) was carefully filtered through a porcelain Buchner funnel lined with a double layer of Whatman filter paper. The filtrate was then aliquoted and subjected to freeze-drying, resulting in a fine, dry powder.

Preparation of P. Granatum PAE-Based Mouthwash

To prepare a **100-ml *P. granatum* PAE-based mouthwash**, **30 g** of the dried *P. granatum* PAE powder, **0.1 g** of ascorbic acid, **0.1 g** of potassium sorbate, and **10 ml** of glycerin were dissolved in boiling deionized water. Additionally, a suitable quantity of flavoring agents was incorporated to enhance taste. To standardize the color of both the placebo and the active *P. granatum* PAE mouthwash solutions, a blend of Red 10-Carmoisine and orange food colorings is added until a consistent brownish hue is achieved. After preparation, the placebo and ***P. granatum*** PAE mouthwash solutions were carefully dispensed into sterile, empty bottles.

Orthodontic Molding

Orthodontic impressions were taken using trays sized to fit the patient's mouth, employing Marlic-Chromogel Chromatic Alginate for molding. The alginate powder was measured and mixed with water in the following proportions: 1.5 cups of powder to 20 ml of water for small trays, 2 cups to 35 ml for medium trays, and 3 cups to 50 ml for large trays. The tray's distal ends were sealed with wax to prevent leakage. During the initial session, patients were randomly assigned to rinse with either the A-labeled or B-labeled mouthwash solution. In the subsequent (one week later) assignments were switched, ensuring that each patient experienced both solutions. For each session, patients rinsed their mouth with 40 ml of the mouthwash for 20 minutes.

GSI Measurement

Measurements of the gag reflex were conducted both before and after mouthwash administration. Following these procedures, patients completed the Fiske and Dickinson GSI questionnaire to evaluate their gag reflex intensity after each session (11). Gag reflex intensity was scored according to the GSI scale as follows:

- A GSI score of 0 indicates no gag reflex observed.
- A score of 1 reflects mild gagging that is tolerable and manageable without intervention.
- A score of 2 denotes moderate gagging that may require behavioral or clinical management.
- A score of 3 represents severe gagging that interferes with treatment and necessitates active intervention.
- A score of 4 corresponds to very severe gagging, where treatment is typically not feasible without specialized techniques or sedation.

Statistical Analysis

Statistical analyses were conducted using a significance threshold of 0.05. Descriptive statistics included frequency

counts, percentages, medians, and interquartile ranges (IQR). The nonparametric Wilcoxon matched-pairs signed-rank test was employed to assess sequence effect differences. For sequence effect comparisons, change scores were computed by subtracting pre-intervention values from post-intervention values. The Chi-square test was applied to examine the distribution of GSI scores across the sample. Furthermore, Spearman's rank-order correlation was calculated within and between groups to evaluate the strength and significance of associations, and to determine whether pairing was statistically significant.

Results

Figure 1 displays the age range of the participants. The mean age of the subjects was 29.3 years with a standard deviation of ± 6.0 years. Of the total, 52.5% (21 patients) were female, while the remainder was male.

Table 1 presents the GSI scores for both the P. granatum PAE and placebo conditions, measured before and after each intervention. Overall, the use of the mouthwash was associated with a reduction in GSI scores, with a more pronounced effect observed in the treatment condition.

Descriptive statistics indicated a decrease in the median GSI score from 3 (IQR = 1) to 2 (IQR = 1) following administration of the *P. granatum* PAE mouthwash. A Chi-square test revealed a significant difference in the proportion of participants with a GSI score of 3 (patients experiencing severe gagging reflex) between the *P. granatum* PAE and placebo conditions ($P = 0.005$).

Change scores (= post – pre) also yielded a Wilcoxon signed-rank statistic of W = –595 ($P = 0.0001$) significantly favoring the *P. granatum* PAE condition. Moreover, the Spearman correlation of change scores across the placebo and treatment conditions was low and non-significant (r = 0.17, $P = 0.15$), suggesting that the reduction in GSI scores observed under placebo was not significantly associated with the reduction observed under *P. granatum PAE*. This finding supports the independence of treatment effects from placebo responsiveness.

Moreover, additional control analyses were conducted to ensure that changes in GSI scores could be attributed specifically to the *P. granatum* PAE mouthwash. A Wilcoxon matched-pairs signed-rank test revealed no significant difference between baseline (pre-treatment) scores across Session 1 and Session 2 ($P > 0.999$, W = 1.000), indicating that baseline GSI values from the preceding session did not influence subsequent baseline measurements. To further evaluate washout efficiency, a Mann–Whitney test demonstrated no significant difference between baseline scores for the pre-placebo and pre-*P. granatum* PAE conditions in Session 2 ($P > 0.999$, U = 200). Finally, a Mann–Whitney test comparing post-treatment scores for placebo and *P. granatum* PAE mouthwash in Session 2 also showed no significant difference ($P = 0.172$, U = 152), suggesting the absence of any carryover effect from treatments administered in the first session.

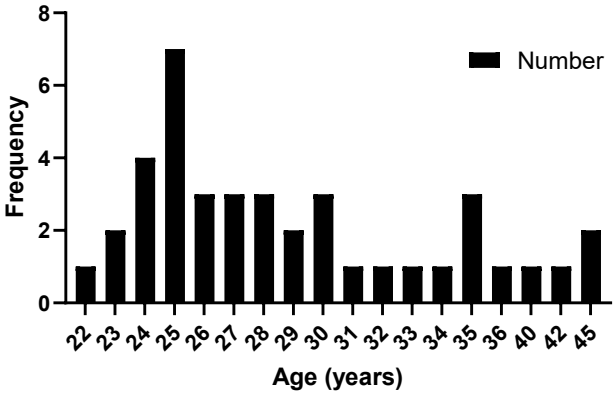

Figure 1. The frequency of age among the participants

Discussion

Our research has demonstrated that *P. granatum* (pomegranate) PAE, as a promising antiemetic agent, can significantly attenuate gag reflex responses and reduce GSI scores. This suggests that *P. granatum* PAE is an effective antiemetic agent that can be exploited in mouthwashes used during orthodontic impression procedures.

Unlike conventional sedatives such as diazepam and nitrous oxide (12-14), which require controlled dosing to avoid adverse effects such as post-procedural drowsiness and dizziness, frequent administration of *P. granatum* PAE mouthwash does not cause these symptoms. As a result, *P. granatum* PAE mouthwash offers a safer alternative that can be employed as frequently as necessary during dental practices.

The antiemetic properties of *P. granatum* peel extract have been rarely investigated, with only two studies

Table 1. GSI score of patients before and after receiving P. granatum PAE and placebo mouthwash.

GSI Score \ Intervention	Placebo		*P. granatum* PAE		*P*-value
	Before	After	Before	After	Chi-squared
Normal (1)	18 (45%)	0	0	0	0.999
Low (2)	14 (35%)	0	7 (17.5%)	0	0.63
Medium (3)	8 (20%)	26 (65%)	31 (77.5%)	27 (67.5%)	0.005
High (4)	0	14 (35%)	2 (5%)	13 (32.5%)	0.58
Median	2	3	3	3	
IQR	1	1	0	1	
Median score change	0		-2		
Sequence effect Wilcoxon signed-rank statistic of W & Spearman's r	-595, $P = 0.0001$ & r = 0.17, $P = 0.15$				

GSI Scors: Gag reflex intensity Score; *P. granatum* PAE: *Punica granatum* peel aqueous extract

currently available on the subject (15, 16). One non-peer-reviewed institutional study assessed the antiemetic potential of a methanolic extract of *P. granatum* peel using the chick emesis model, demonstrating that oral administration of the extract significantly reduced the frequency of emetic episodes (16). The second was a randomized, double-blind, controlled clinical trial involving 84 dental patients, in which participants who received lozenges containing 80% pomegranate peel extract exhibited a marked reduction in gag reflex intensity (15). Both studies attributed the antiemetic effect of *P. granatum* peel extract to the presence of tannic acids and flavonoids; however, this proposed mechanism of action remains to be elucidated through further investigation.

Tannic acids are primarily responsible for the astringent effects—characterized by mucosal tightening and drying—and may also exert mild anesthetic properties through protein precipitation and local desensitization (17). In contrast, flavonoids likely contribute to antiemetic activity through their antioxidant and anti-inflammatory mechanisms (18), although their role appears to be secondary.

The present study demonstrates both methodological strengths and elements of novelty, though it has also some limitations. The crossover design, in which each participant served as their own control, enhanced statistical power and minimized the influence of confounding variables. Furthermore, the use of change scores (pre–post) enabled direct comparison of treatment and placebo effects, aligning with the study's primary objective.

However, the relatively small sample size may constrain external validity and reduce sensitivity to detect nuanced interactions. For instance, stratification based on individual predisposition to gag reflex severity or comorbid conditions such as gastroesophageal reflux or asthma—both of which may modulate gag reflex intensity—was not feasible. Consequently, the findings may not be generalizable to broader populations with diverse gag reflex profiles or clinical backgrounds.

Finally, the study focused exclusively on GSI scores, which limited the scope of inquiry. This narrow focus may partly explain the scarcity of related literature—currently limited to two reports, one clinical trial and one non-peer-reviewed animal study. Future research could benefit from incorporating additional outcome measures, such as patient comfort, treatment adherence, and physiological markers, thereby broadening the relevance and applicability of findings to both scientific and clinical audiences.

Conclusion

Our findings support the potential use of *P. granatum* PAE as a safe and effective antiemetic adjunct in dental mouthwashes, particularly during procedures that commonly provoke the gag reflex. This approach may enhance patient comfort and compliance in orthodontic settings.

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Authors' Contribution

Conceptualization: Sahereh Soltani.
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Visualization: Manouchehr Teymouri.
Writing–original draft: Manouchehr Teymouri.

Competing Interests

The authors declare that they have no conflict of interest.

Data Availability

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

Ethical Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of North Khorasan University of Medical Sciences (Ethical approval code: IR.NKUMS.REC.1400.020 and IRCT20210505051187N2).

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