

Research Article

The preventive impact of theobromine on enamel microhardness in comparison with sodium fluoride solution: A comparative *in-vitro* study

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Abstract: Background: In the realm of preventive dentistry, fluoride-based remineralization techniques have long been the prevailing approach. However, the field is currently experiencing a revolutionary shift as innovative technological advancements offer effective means to facilitate the remineralization of dental surfaces. This study aimed to investigate the effect of theobromine application compared to sodium fluoride and artificial saliva on the microhardness of human tooth enamel. Methods: A sample of 34 extracted sound maxillary first premolars were selected for the research; one of these teeth was used for scanning electron microscope investigation, while the remaining 33 teeth were assigned randomly to three groups: (1) the theobromine group (2) the sodium fluoride group and (3) the artificial saliva group (negative control). Treatment solutions were applied during a 28-day pH cycle followed by subjecting the samples to demineralizing solution to form artificial white spot lesions. The enamel structure of the study sample was evaluated quantitatively using Vickers's microhardness test (Jinan Kason Testing Equipment Co., China) conducted with a diamond indenter that applied a 300 g load for 15 seconds. Three indentations were made on the buccal surfaces with a distance of 500 μ m and qualitatively by scanning electron microscope (representative samples not included in statistical analysis). Data analyses were performed by Levene test and General Linear Model Repeated Measure Factorial ANOVA with Tukey HSD, the accepted level of significance was 0.05. Results: The present study result showed that teeth treated with theobromine had a higher mean of surface microhardness in the treatment and the demineralization stages than that of the teeth treated with sodium fluoride, with a statistically significant difference ($p < 0.05$). Conclusions: Theobromine could preserve enamel microhardness more than sodium fluoride after the acid challenge.

Keywords: Enamel remineralization, microhardness, sodium fluoride, scanning electron microscopy, theobromine.

Introduction

Dental caries is a chronic and irreversible infection that has been considered the most prevalent oral disease among children ⁽¹⁾. It affects a large portion of the world's population by damaging the mineralized dental structures through a dynamic, multifactorial process ^(2,3). High sugar ingestion, poor oral hygiene, and enamel anomaly were the main predisposing factors responsible for developing dental caries ⁽⁴⁾. An important area of interest in preventive dentistry is the white spot lesion because it is reversible. Many

researchers, using different remineralizing agents, had investigated the management of white spot lesions. The progress in minimally invasive dentistry has highlighted the ongoing requirements for new remineralizing agents, innovative techniques for remineralization, and new combinations of new agents^(2,5). Fluoride is a substance used for dental caries prevention. Using fluoridated toothpaste was an effective manner for children to protect their teeth from dental caries and had an ideal effect on decreasing caries progression⁽⁶⁾. Fluoride helped to strengthen the enamel, but excessive fluoride use had several side effects, including fluorosis^(7,8). The public has exhibited an increasing interest in natural or herbal-based healthcare products, specifically in diverse forms of toothpaste containing theobromine⁽⁹⁾.

Cacao extracts (theobromine) had an effective dental benefit and fewer side effects when compared with fluoride. It is a crystalline powder bitter taste alkaloid belonging to the methylxanthine class of compounds (3,7-dimethylxanthine) and differs from caffeine (1,3,7-dimethylxanthine) in only one methyl group⁽⁹⁻¹¹⁾. Theobromine increased the microhardness of the enamel surface, making teeth less susceptible to decay⁽¹²⁾. Studies conferred that theobromine increased apatite crystal size and improved mineral gain, strengthening enamel against future acid or erosion^(13,14). Mahardhika et al. (2017) reported that theobromine and fluoride exhibited comparable impacts on the surface of enamel and its ability to undergo remineralization. Theobromine is regarded as a more favorable choice because it exhibited lower toxicity when compared to fluoride⁽¹⁵⁾. However, several studies have revealed that theobromine lacks remineralizing potential or a cariostatic effect^(16,17). Given the existence of conflicting findings and the absence of prior research on the preventive impact of theobromine on the enamel tooth surface, further studies are necessary to investigate its preventive efficacy. The objective of this study was to compare the effect of cacao extract (theobromine) and sodium fluoride solution on the microhardness of the intact enamel surface.

Null hypothesis: Theobromine does not prevent the deterioration of enamel tooth surface microhardness to the same extent as sodium fluoride.

Materials and Methods

This study was carried out between April 2022 and December 2022. The ethical committee approved the study protocol at the College of Dentistry/ University of Baghdad (reference number 549 on 17 April 2022).

The sample consisted of a group of maxillary premolars extracted from patients aged 11 to 14 years for orthodontic demand after gaining signed consent from their parents. The teeth were collected from various dental clinics, (private and public), in the city of Basra. Teeth exhibiting hypoplasia, cracks, incipient carious lesions/white spots, and fillings were excluded from the study^(2,18). Using G*Power 3.1.9.7, Franz Faul (G*Power Team, University of Kiel) With the power of study =80%, alpha error of probability =0.05, a correlation between time points is 0.7, and partial eta square is 0.14 (large effect size) thus effect size of F is 0.402 (Large effect size), with 3 groups and 3-time points, with all these conditions the definite effect size is 10 samples for each group. Effect size F are Small =0.1, medium =0.25, large =0.4. Partial eta square Effect sizes are small (0.01-0.059), medium (0.06- 0.139), Large $\geq$ 0.14. Another four teeth were added for SEM analysis (representative samples not included in the statistical analysis comprised one sound sample and one sample from each study group). A non-fluoridated pumice slurry (Pell-ex, Hawe-Neos Dental, Bioggio, Switzerland) was used to remove residual debris and stain. Following this, the teeth were kept

in a 0.05% thymol solution for one week, an antimicrobial agent that effectively inhibits bacterial growth until the time of the experiment ⁽¹⁸⁾. Subsequently, a diamond bur with water coolant was used to cut the root 2 mm below the cemento-enamel junction and just the crown was used in this experiment ^(19, 20). The dimension of the crown after sectioning was about (6.5-7.5)mm mesiodistally and (9.5-10.5)mm buccopal-
atally.

Every prepared tooth specimen was centrally positioned and secured with the buccal surface directed upward within a plastic ring, (18 mm in diameter, and 14 mm in depth). The plastic ring was then filled with cold cure acrylic resin (Akrodent, Ankara, Turkey). Then, a manual tool held grit paper size 400;800;1000;1200 respectively (Whatman 1003110-DS Qualitative Filter Paper, U.S.A) was utilized to ground and polish the buccal surface of each tooth 10 times in one direction ⁽²⁾. This method only flattened the teeth's surface for microhardness testing ⁽²⁰⁾. The crown surface was then painted with acid-resistant nail varnish after sticking down a 4 mm x 2 mm strip of tape on the middle third of the crown. Once the varnish was thoroughly dried, the tape was carefully removed to expose the enamel surface ^(18, 19). After the sample preparation, each tooth received a special number used for identification, stored in a separate labeled container with the group's name, and the first microhardness reading was assessed.

Study solutions concentrations

The following dilutions were chosen depending on previous studies as follows:

Theobromine solution: 200 mg/L of theobromine-infused deionized water (Carl Roth GmbH, Schoemperlenstrasse 1-5, 76185 Karlsruhe, Germany) ^(21, 22).

Sodium fluoride solution: 0.05% sodium fluoride powder was dissolved in deionized water (sodium fluoride powder, Honeywell Riedel-de Haen, Wunstorfer Str. 40, 30926 Seelze, Germany) ^(21, 22).

Artificial saliva solution: consists of (MgCl₂ ·6 H₂O (0.148 mmol/L), K₂HPO₄ (4.59 mmol/L), KH₂PO₄ (2.38 mmol/L), KCl (8.39 mmol/L), calcium lactate (1.76 mmol/L), fluoride (0.05 ppm), sodium carboxymethyl cellulose (2.25 mmol/L) and methyl-4-hydroxybenzoate (13.14 mmol/L), where pH adjusted to 7.2 using KOH.

pH cycle

The treatment solutions were applied in a 28-day pH cycle consisting of 1- h. demineralization is repeated three times per day, followed by 21- h. of remineralization in artificial saliva. The demineralizing solution comprised KH₂PO₄ (2.2 mmol/L), CaCl₂ (2.2 mmol/L in a 1,000 mmol/L solution), acetic acid (50 mmol/L); the pH of the solution was adjusted to 4.5 using KOH. This cyclic process aimed to replicate the conditions of the oral environment. Before treatment, the pH of both the demineralizing solution and artificial saliva was monitored once a day. All teeth were subjected to treatment solution by being fully immersed in 20 ml of treatment solution for 2 min then the teeth were rinsed with deionized water and dried with disposable tissue. After completing pH cycles for 28 days, the second microhardness reading was recorded ⁽²¹⁾. After being exposed to either demineralizing solution or remineralizing solution, the samples were washed in flowing deionized water. They were then dried using a paper towel before being immersed in the subsequent solution. The pH cycle for a single day was repeated continuously for 28 consecutive days

⁽²¹⁾. After being treated with one of the study solutions, each tooth was kept in 20 ml of artificial saliva in a labeled container in an incubator at 37 °C ⁽²¹⁾. The event of the pH cycle for 1 day is seen in Table 1.

Table 1: Everyday experimental steps(ph cycling for prevention)

Daily events	Treatment
Day 1 is all-day storage in an artificial saliva	
Subsequent day treatments are as follows:	
1 hour (start at 8:00 am)	acid challenge –all groups
1-hour storage in artificial saliva	
2 min	all in its treatment groups
1 hour storage in artificial saliva.	
1 hour (11: 00 am)	acid challenge _all groups
2 min	all in its treatment groups
1 hour storage in artificial saliva.	
1 hour (2:00 pm)	acid challenge _all groups
2 min	all in its treatment groups
Till 8:00 am, the next day, storage in the artificial saliva was in a labeled container in an incubator at 37o	
This pH cycle continues for 28 days and the teeth kept in the incubator	

Artificial white spot lesion formation

To create an artificial enamel lesion, the teeth were soaked individually in a demineralization solution for 7 days. The demineralization solution consists of 0.2% carbopol (BF Goodrich, Cleveland, OH, USA) and 0.1% lactic acid (Sigma-Aldrich chemical, St. Louis, MO, USA) saturated with calcium phosphate tribasic acid. The pH was adjusted to 5 ^(21,23, 25). After seven days, a third microhardness assessment was recorded.

Microhardness examination

It was done using Vickers's microhardness test (Jinan Kason Testing Equipment Co., Ltd. in China) conducted with a diamond indenter that applied a 300 g load for 15 seconds. Three indentations were made on the buccal surfaces and the average of the three indentations was obtained. ^(18, 26, 27)

Scanning Electron Microscope

Surface morphology was qualitatively analyzed using a scanning electron microscope at magnifications 5000x, and 10000x. A representative specimen from each treatment group was chosen after the application of the treatment solution with pH cycles before white spot lesion formation in addition to one sound tooth. The chosen teeth were gold coated by putting them in a vacuum system coating equipment to help or improve the imaging of samples (ion sputter) ^(5, 20, 28).

Statistical analysis

Data description, analysis, and presentation were performed using Statistical Package for Social Science (SPSS version -22, Chicago, Illinois, USA). Shapiro-Wilk statistic was utilized to determine the distributional shape of data. When the data showed a normal distribution, repeated measure two-way ANOVA

and Tukey's HSD were used to evaluate if the groups had statistically significant differences. If the p-value was less than 0.05, it was considered statistically significant.

Results

Shapiro Wilk test showed that surface microhardness was distributed normally among groups and stages at $p > 0.05$, with the minimum p-value being 0.057 and the maximum being 0.995.

Table 2 showed that the microhardness values at baseline did not vary significantly ($p = 0.516$) across the study groups. However, after treatment, the control group had the least microhardness value while the theobromine group had the greatest microhardness value with a statistically significant difference ($p < 0.001$). After demineralization, the control group showed the lowest mean value of microhardness, followed by the group using fluoride solution, while, the group of theobromine solution had the highest score of the microhardness value, with a statistically significant difference between groups.

Table 2: Descriptive and statistical test of microhardness(Kg/mm²) among groups and stages using repeated measure ANOVA.

Groups	Baseline		Treatment (pH cycles)		Demineralization		F	P-value	Effect size
	Mean	±SD	Mean	±SD	Mean	±SD			
Theobromine	350.255	20.199	320.623	15.331	171.407	15.845	3033.050	<0.001	0.995
Sodium fluoride	344.799	25.744	271.822	26.269	114.738	23.362	1755.959	<0.001	0.992
Control	352.043	28.694	215.934	19.929	54.616	5.027	1609.029	<0.001	0.991
F	0.826		31.480		50.050				
P-value	0.516		0.000		0.000				
Effect size	0.068		0.737		0.816				

The surface microhardness of each phase within the groups was compared using the Tukey HSD test, as depicted in Table 3. The results indicated a statistically significant difference among phases (baseline, treatment, demineralization) for all groups.

Table 3: Multiple pairwise comparisons of microhardness(Kg/mm²) among stages in each group using Tukey HSD

Groups	(I) Stages	(J) Stages			
		Treatment		Demineralization	
		Mean Difference	p-value	Mean Difference	p-value
Theobromine	Baseline	29.632	<0.001	178.848	<0.001
	treatment			149.216	<0.001
Sodium fluoride	Baseline	72.977	<0.001	230.061	<0.001
	treatment			157.084	<0.001
Control	Baseline	136.109	<0.001	297.427	<0.001
	treatment			161.318	<0.001

Table 4 reveals a significant difference between the control group and the groups treated with theobromine and sodium fluoride in both the treatment and demineralization stages. Furthermore, there is a statistically significant difference between theobromine group and the sodium fluoride one in both the treatment and demineralization stages .

Table 4: Comparisons of surface microhardness(Kg/mm²) between the groups after the treatment and the demineralization phase.

Stages	(I) Groups	(J) Groups	Mean Difference	p-value
Treatment	Control	Theobromine	-104.689	<0.001
		Sodium fluoride	-55.888	<0.001
	Theobromine	Sodium fluoride	48.801	<0.001
Demin.	Control	Theobromine	-116.791	<0.001
		Sodium fluoride	-60.122	<0.001
	Theobromine	Sodium fluoride	56.669	<0.001

Evaluation of surface morphology using SEM

Sound enamel: scanning electron microscope revealed a smooth and flattened surface with many enamel prism and the absence of surface deposits and cracks, as depicted in Figure 1 A1 and A2. Control: The SEM image of the enamel surface treated with artificial saliva exhibited a microscopic modification of the enamel surface, characterized by the merging of enamel rods with a deteriorative appearance, accompanied by irregularities and porous regions throughout the enamel surface. Figure 1 B1.B2. Theobromine: SEM showed surface changes in the deposition of particles over the demineralized enamel surface that made it smooth and uniform, almost closed the micropores, and decreased surface roughness compared with the control group sample and small pores that occur due to demineralization as shown in Figure 1 C1 and C2. Sodium fluoride: showed partial dissolution of enamel, globular deposits of fluoride on the enamel surface that could be CaF₂ deposits with surface roughness Figure 1 D1, D2.

Discussion

In this study, fluoride was used as a positive control at a concentration of 0.05%, which is suitable for young children. On the other hand, theobromine was utilized to introduce the required crystal enlargement, which had been previously determined in 200 mg/L studies ⁽²²⁾.

The application of the treatment solution was performed with a pH-cycling protocol to simulate the ongoing cycle of demineralization and remineralization within the oral cavity ⁽²³⁾. Demineralizing solution of pH 5.0 was used to create subsurface lesions ⁽²⁹⁾. Artificial saliva was used as a negative control as well as the storage medium for the samples. Artificial saliva serves a dual purpose: it not only replicates the natural composition of saliva but also creates an artificial oral milieu, effectively preventing bacterial contamination of enamel specimens. ⁽²¹⁾. The microhardness examination can explore the impact of both extrinsic and intrinsic acids on the hard tissues of the teeth. This approach enables the evaluation of the initial stages of enamel and dentin degradation, which are characterized by surface debilitation and softening ^(20, 28). Statistically non-significant differences in microhardness values for sound teeth at the baseline stage were found among different groups, which revealed a standardization among the samples used in the study.

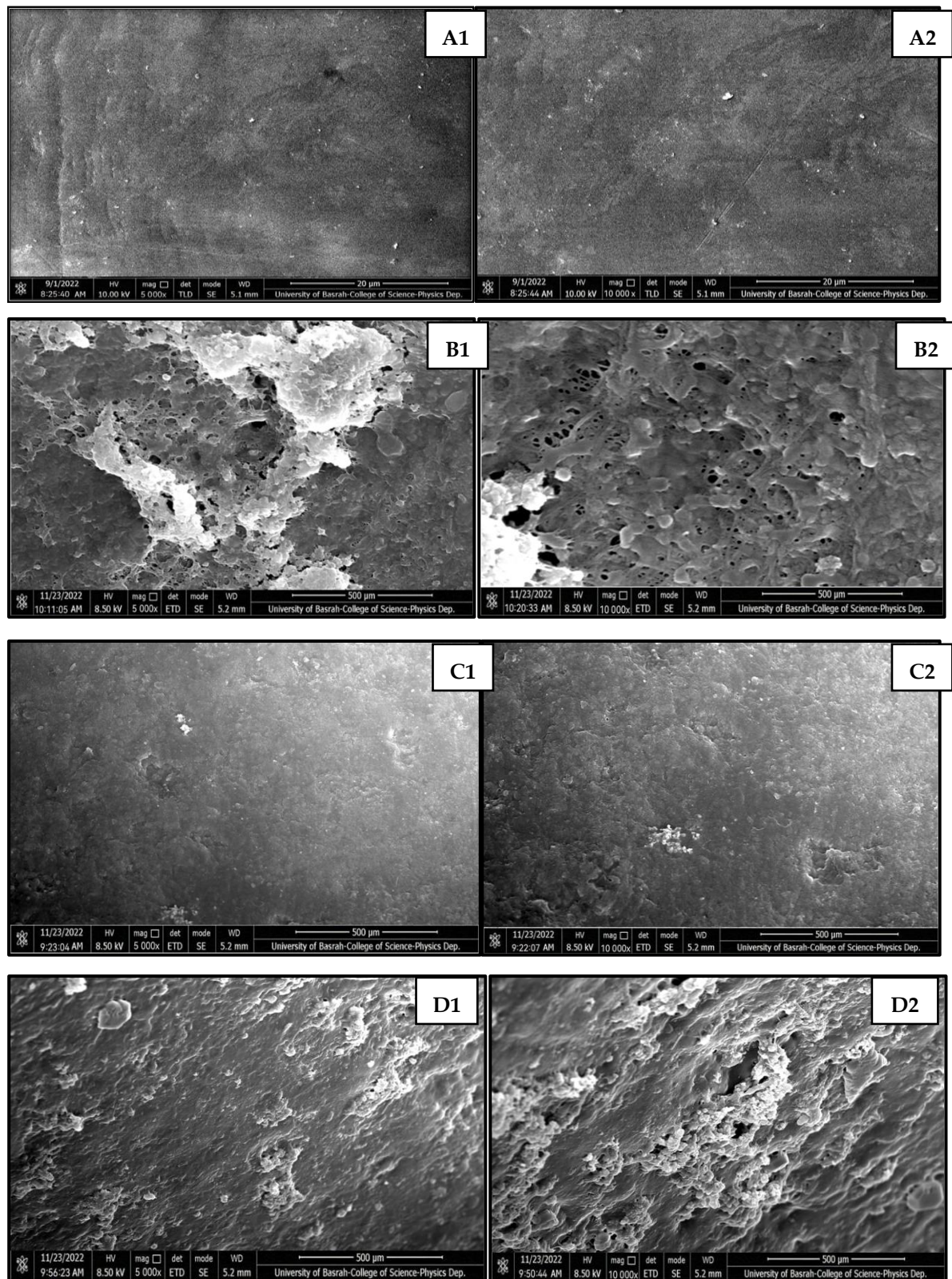


Figure 1: A) SEM image for sound tooth (A1. 5000x, A2. 10000x). B) SEM image for the control group (B1. 5000x, B2. 10000x). C) SEM image for theobromine group (C1. 5000x, C2. 10000x). D) SEM image for sodium fluoride group (D1. 5000x, D2. 10000x).

Nevertheless, the treatment stage significantly improved the enamel's microhardness by using theobromine solution and sodium fluoride solution with the highest score of microhardness value related to the theobromine treated teeth. In the current experiment, theobromine revealed a greater protective potential as it enhanced the resistance of enamel to acid attacks during pH cycles. Following demineralization, a significant decrease in microhardness of the enamel surface was observed in all groups after 7 days in the demineralization solution. This reduction in microhardness is attributed to the acidic environment created when the pH of the surrounding environment falls below the critical pH of 5.5. The acidic medium leads to the leaching of minerals, primarily calcium and phosphorus, from the tooth structure, resulting in the formation of micropores and a subsequent reduction in the hardness ⁽²⁹⁾. This decrease in surface microhardness values aligns with the finding of previous studies conducted by other researchers ^(2, 24).

Another finding was that the theobromine group had greater mean values when compared with the sodium fluoride group indicating that theobromine had a higher effect to prevent deterioration in microhardness than sodium fluoride. This result was in harmony with that of previous studies, which reported the ability of theobromine to infiltrate the micro spaces within the enamel and serve as a mold during precipitation. This, in turn, facilitates the attraction of a significant quantity of calcium and phosphorus from the remineralizing solution to the enamel surface, thereby occupying the vacated spaces of the enamel crystals and promoting the desired remineralization result ^(12, 13, 21,30).

Several studies either disregarded theobromine's remineralization potential or assigned it an inferior rank compared to fluoride ^(16, 17, 31). These conflicting findings could be due to differences in the remineralization medium's composition, time length, pH range, and pH cycling models.

The current study's SEM images of the sound specimen demonstrated that its surface was homogeneous and smooth. Similar findings were reported by El Moshy et al. in their study ⁽³³⁾. The SEM images of the tooth treated with theobromine revealed a restored smooth texture of the enamel surface, resembling the appearance of healthy teeth with minimal pore size. In contrast, teeth treated with sodium fluoride exhibited rough surfaces. On the other hand, the SEM images of the tooth treated with artificial saliva (control group) showed an extremely rough and uneven surface, with visible tiny pores and cracks throughout. These observations may be attributed to the acidic environment the teeth are exposed to. These findings align with previous studies ^(32, 34). The null hypothesis was rejected as theobromine prevent the deterioration in enamel microhardness more than sodium fluoride.

Ultimately, the results of these studies indicated that while the theobromine group exhibited a higher average microhardness, it did not fully restore the measurements to the baseline level. These findings are agreed with previous studies, which showed that theobromine can enhance the microhardness of demineralization enamel but does not fully recover it to its original hardness level ⁽²⁵⁾.

Nonetheless, further research is required to delve into the specific mechanism by which theobromine promotes crystal enlargement. One potential limitation of this study was the inadequate simulation of biological aspects inherent to caries within an in vitro model. Therefore, additional human clinical trials are necessary to fully explore and harness the potential benefits of theobromine in enhancing oral health and reducing the occurrence of dental caries. However, the initial findings propose that theobromine solution holds promise as a preferred material for the prevention of white spot lesions.

Conclusion

Under simulated oral conditions, theobromine exhibited superior efficacy than sodium fluoride in maintaining enamel microhardness following an acid challenge. These in vitro findings indicated that theobromine may enhance enamel resistance to demineralization, underscoring its potential as a promising non-fluoride anticariogenic agent. Further translational research is warranted to determine optimal concentrations, assess long-term biocompatibility, and confirm its remineralization efficacy under in vivo conditions before clinical application

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

AHMJ; study conception and design. MIA; data collection. AHMJ and NA.; Methodology. AHMJ and MIA; statistical analysis and interpretation of results. MIA; original draft manuscript preparation. AHMJ and AF; Writing & editing. Supervision; AF and AHMJ. All authors reviewed the results and approved the final version of the manuscript to be published.

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Informed consent

Informed consent was obtained from all individuals or their guardians included in this study.

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التأثير الوقائي للثيوبرومين على سطح مينا الأسنان مقارنة بمحلول فلوريد الصوديوم (دراسة مخبرية مقارنة) الباحثون: مريم عيسى عجيل، اسيل حيدر الحيدر، نجم المسعودي، عباس فرماني المستخلص:

خلفية: في مجال طب الأسنان الوقائي، كانت تقنيات إعادة التمعن القائمة على الفلورايد هي النهج السائد منذ فترة طويلة. ومع ذلك، يشهد المجال حالياً تحولاً ثورياً كتطورات تكنولوجية مبتكرة، مما يوفر وسائل فعالة لتسهيل إعادة تمعدن أسطح الأسنان. الهدف: التحقيق في تأثير تطبيق الثيوبرومين مقارنة بفلوريد الصوديوم واللعب الاصطناعي على مينا الأسنان البشرية. تم اختيار عينة من 34 ضواحك أولى للفك العلوي المستخرج للبحث، أحد هذه الأسنان لفحص المجهر الإلكتروني الماسح، بينما تم تعيين الأسنان الـ 33 المتبقية بشكل عشوائي إلى ثلاث مجموعات: (1) مجموعة الثيوبرومين (2) مجموعة فلوريد الصوديوم و (3) مجموعة اللعب الاصطناعي (كعنصر تحكم سلبي). تتكون كل مجموعة من إحدى عشرة عينة، واحدة للمجهر الإلكتروني الماسح وعشرة الأسنان الأخرى لاختبار الصلابة السطحية الدقيقة تم تطبيق محاليل العلاج خلال دورة الأس الهيدروجيني لمدة 28 يوماً تليها تعريض العينات لتحدي الحمض لتشكيل آفة بقعة بيضاء اصطناعية. تم إجراء اختبار فيكرز للصلابة الدقيقة والمجهر الإلكتروني الماسح للأسنان التمثيلية من عينة الدراسة لتقييم بنية المينا كميًا ونوعياً أظهرت نتائج الدراسة الحالية أن الأسنان المعالجة بالثيوبرومين كان لها متوسط صلابة سطحية أعلى

في مراحل المعالجة وإزالة المعادن من الأسنان المعالجة بالفلورايد، مع وجود فرق ذو دلالة إحصائية بينهما. يمكن أن يحافظ الثيوبرومين على صلابة المينا الدقيقة أكثر من فلوريد الصوديوم بعد تحدي الحمض.