



Theobromine: A Non-Invasive Treatment Approach of Demineralized Tooth Structure

Manar S. Mohammad ⁽¹⁾
Rasha H. Jihad ⁽²⁾ *

^(1,2) Department of Restorative and Aesthetic Dentistry, College of Dentistry, University of Baghdad.,
Iraq.

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***Corresponding Author:**

Email:

[rasha.h.jihad@codental
.uobaghdad.edu.iq](mailto:rasha.h.jihad@codental.uobaghdad.edu.iq)

Department of Restorative
and Aesthetic Dentistry,
College of Dentistry,
University of Baghdad., Iraq.

Abstract

Background: Theobromine is a natural alkaloid of cocoa beans of plant origin. Theobromine found in chocolate and a number of other foods, such as tea leaves. Aims: Give summary of theobromine effects on tooth structure, describe the studies looking into how they affect the surfaces of enamel and dentin, and point out areas that need more research. Data: By using Pub Med, Google Scholar, and Research Gate databases. Keywords: "Theobromine", "cocoa extract", and "remineralization". Study selection: 48 papers were selected between 1983 to December 2023. Conclusions: Theobromine is a nontoxic, organic, and an effective agent on tooth structure that could be right for daily use. Theobromine attracts calcium and phosphorus from saliva and promotes the growth of four times larger unit hydroxyapatite crystals. Theobromine can increase the micro-hardness of surface of enamel. It improved the protection of tooth enamel against acid. The use of theobromine containing toothpaste may cause occlusion of dentinal tubules and their capacity for treatment of dentin hypersensitivity.

Introduction:

Theobromine is a naturally occurring alkaloid of cocoa bean of plant source of the methylxanthine family, which also contains caffeine and theophylline, two related chemicals. The chemical compound of theobromine exhibiting structural resemblances to that of the caffeine and theophylline has been detected in a range of food sources, including chocolate, cocoa, and tea leaves. The molecular diagrams of theophylline, theobromine, and caffeine, where theophylline is represented as 1,3 - dimethylxanthine, theobromine as 3-7dimethylxanthine, and caffeine as 1,3,7-trimethyl-xanthine (1, 2) Figure (1). 'Xantheose' is another name for Theobromine, with the chemical formula $C_7H_8N_4O_2$. Theobromine is an odorless white water-soluble, crystalline bitter luminous colored powder and a pH (5.5_7) of saturated solution (4). Methylxanthines families are alkaloids that can be found in high concentrations in tea, coffee, and chocolate. Theophylline, theobromine, and caffeine are the most popular (5).

High concentrations of theobromine are present in cocoa; theobromine content in the powder of cocoa in the range (1.2% _ 2.4%). Theobromine can be found in chocolate and a variety of other foods, include tea leaves and cola. There is naturally 1%–4% theobromine in cocoa beans. Many believed that cocoa was a beneficial nutrient and possibly a medication. The health benefits of cocoa have always been associated with the elevated antioxidant content of Theobroma cocoa beans. Parts of cacao contain theobromine and caffeine. Several effects linked to cocoa consumption are caused by theobromine (4). The aims of this review is to give a summary of theobromine effects on tooth structure, describe the studies looking into how they affect the surfaces of enamel and dentin, and point out areas that need more research.

Methods

A comprehensive search has been performed in the English language on published resources using Pub Med,

Google Scholar, and Research Gate databases from 1983 to Dec 2023 by using the keywords: "Theobromine", "cocoa extract", and "remineralization". Forty-Eight papers in this review. Social media sources were excluded from the review. Data selection was completed by one reviewer and checked for accuracy and consistency by a second reviewer. Endnote reference management software was used for organization of citations.

Action of theobromine on tooth

The Mechanism of action of theobromine by higher electronegativity of the oxygen and nitrogen in the theobromine molecule ($C_7H_8N_4O_2$) attracts the lower electronegativity ions (phosphate and calcium), which leads to the creation of new theobromine apatite crystals with increased calcium deposition. It has been shown that theobromine increases the medium's capacity for remineralization such ability to re-mineralize the demineralized tissue of the tooth in an apatite-forming media. Theobromine attracts calcium and phosphorus from saliva and promotes the formation of bigger unit hydroxyapatite crystals four times larger (2 μm) than HA (0.5 μm) (6-8). The effect of theobromine on enamel is to increase the resistance of tooth enamel to bacterial acid erosion due to the formation of large crystals thereby influence the enamel surface hardness. The surface hardness of the enamel can be affected by minerals exchange on the surface of the enamel. When the theobromine 200 mg/L applied to the surface of tooth enamel remineralization effect occurring leads to increase in the hardness of enamel surface (7, 9-12)

- The enamel surface becomes rough and rugged when it comes into contact with acid during demineralization so, application of theobromine containing agent to the enamel surfaces can decrease enamel permeability causing smaller pores in enamel, which reduced absorption of staining materials, which should allow to prevent or to decrease discoloration. Nakamoto, Falster and Simmons (2016) investigated theobromine's ability to repair enamel surface by scraping it using an

edged instrument (2). The teeth were soaked in an acceptable solution of theobromine to cover them for thirty minutes. The results returned the smooth surface of enamel by adding a layer of theobromine and generated a remarkably smooth surface Figure (2) (13, 14).

The effect of Theobromine on Dentin, Utilizing an apatite-forming method with an effective theobromine concentration, hydroxyapatite was grown to increase crystallite size and improve the crystallinity of teeth. These investigations provided the basis for the development of Theodent classic®, a commercially available toothpaste (theobromine containing agent) fluoride-free that used to treat and prevent dental cavities. The use of theobromine toothpaste can stimulate occlusion of dentinal tubules by crystallite precipitation, which has potential to treat dentin hypersensitivity by blockage the pathway of fluid movement within the dentinal tubules of the dentin that contain sensitive nerve receptors which is stimulated by this fluid (3, 15, 16). Fluorides are relatively cheap and may be delivered in a number of ways that are both cost-effective and efficient; they are frequently employed as chemotherapeutic agents for dentinal hypersensitivity. For many years, toothpaste with a fluoride base has been the standard norm. The commercially available fluoride containing toothpastes were being a standard in oral care, they have many adverse effects. Dental fluorosis can be brought on by excessive fluoride exposure when teeth are still growing. It is also advised that mouthwash containing fluoride not be used on children younger than six years old. When teeth are still forming, there is a chance of irreversible discoloration if too much fluoride is consumed. Consequently, theobromine and other naturally occurring and biocompatible substitutes for fluoride are becoming increasingly prominent in contemporary dental hygiene products (17). Skeletal fluorosis is another detrimental impact of excessive fluoride consumption on bones. According to a recent investigation, thyroid gland disorders and fluoride intake are related. Excessive fluoride can cause damage to

the parathyroid gland which may lead to hyperparathyroidism disease (18, 19).

Action of theobromine as an antimicrobial activity

Theobromine has shown a antimicrobial effect and reduced *Streptococcus mutans* biofilm deposition. The anti-caries potential of theobromine is proved in many studies (4). The kind of toothpaste and its ingredients become more crucial because caries prevention is based on plaque reduction. Any toothpaste's effectiveness partially depends on its capacity to eradicate harmful oral microorganisms. Study has shown that cocoa bean extract is highly effective in reducing *mutans streptococci* counts and plaque deposition when used as a mouth rinse by children (20). According to Srikanth et al. (2008), there is a component of the cocoa that may be able to stop tooth cavities and decay (20). In its natural state, cocoa contains the husk of the cocoa bean, even though we cannot see it. Moreover, one benefit of chocolate made from cocoa beans is that they contain compounds that have anti-cariogenic properties. A byproduct of the chocolate business, the cocoa bean is recognized for having a high concentration of dietary fibers (21). Theobroma cacao beans that have been perorated are separated from the cocoa bean. Two kinds of cariostatic compounds have been found in the husk of cocoa beans; one of them has antiglucosyltransferase activity (22).

The *Streptococcus mutans* microbe creates three different kinds of GTF and uses sucrose to create an adherent, water-insoluble glycan that makes the organisms stick securely to the tooth surface. Additionally, the adhering glycan has a role in the development of dental plaque, which is characterized by the buildup of acids that cause localized decalcification of the enamel surface. It is claimed that the extract from cocoa bean husks contains a strong (GTF) polyphenolic component with a higher molecular weight. In addition, it includes unsaturated free fatty acids that have antibacterial activity against *S. mutans*, such as oleic and linoleic (22).

Chocolates, chewing gum, drinks, mouthwash, and toothpaste all contain theobromine, which can help prevent dental cavities (23). Regrettably, the zone of inhibition was least with *C. albicans* and largest with *S. mutans* numbers, *L. acidophilus*, and *E. faecalis*. These results demonstrate that theobromine prevents caries and dramatically reduces plaque formation since *C. albicans* is not a prominent factor in the carious process (24). Theobromine's capacity to promote the remineralization of enamel lesions (anti-cariogenic action) means that theobromine-forming media can increase the tooth's capacity for remineralization (7, 25). To enhance enamel remineralization, a subtle combination of theobromine calcium and phosphate was applied. More so than fluoride, theobromine keeps teeth free from decay. While fluoride is an efficient way to strengthen enamel, large dosages can cause gastrointestinal irritation and dental fluorosis, or discolored teeth. In contrast, theobromine was discovered to be easily absorbed by the stomach and to be completely digested and eliminated by humans (26).

Safety of the theobromine

Theobromine can be considered a safe alternative to sodium fluoride as a dental suspension substitute for the prevention and treatment of dental caries (8, 27). Theobromine, derived from cacao, is a natural substance and is currently recognized as a dietary supplement for individuals and it's highly safe for human consumption, even at high concentrations. Despite decades of popular use of chocolate treats, there have never been any reported cases of theobromine poisoning in humans (17). Earlier findings from animal studies that claimed theobromine could have negative effects. It has been observed that certain animal species, such as dogs and horses, are more susceptible to the negative effects of methyl xanthine (theobromine) compared to others. The variation is probably due to differences between how theobromine is metabolized by people and animals. Theobromine is easily absorbed and metabolized in the human body; thus, it

does not have the adverse effects. Theobromine can be added to various dental products to treat the enamel and prevent caries, such as natural remineralizing candies or gum and tooth paste, the pleasant chocolate flavor would make the children relish it (28).

Theobromine seems to be safe when taken as prescribed. Daily dosages of up to 1,500 mg over an extended period of time may cause side effects such headaches, nausea, and appetite loss. Throughout decades of chocolate confection consumption, no human instances of theobromine poisoning have been documented. Theobromine is now considered a dietary supplement for people (29).

Although, fluoride is an excellent remineralizing agent, however is associated with potential toxic side-effects. On the other hand, the natural compound, Theobromine is safe and does not produce chemical dependent. This FDA approved non-fluoride prototype (Theodent classic™ toothpaste can be used has a major step forward in oral health maintenance and prevention of dental caries. Methylxanthines primary pharmacological effects include diuresis, increased stomach acid secretion, relaxing of the bronchi, impact on the cardiovascular system, and metabolism. These drugs do not lead to chemical dependence despite their core activities. Theobromine is a very weak central nervous system stimulant, unlike caffeine (29-31). A study of Lippert in (2017) that comparing various doses of theobromine (ranging from 250 mg to 1 g) with a single dose of caffeine (200 mg) found that moderate consumption of theobromine might enhance the positive effects associated with chocolate, however, at higher doses, these effects could turn negative (32). There remains a significant need for further research to explore the mechanisms through which theobromine promotes mineral deposition and crystal growth. Additionally, studies should compare its benefits to the enamel structure, examine its effects on salivary composition and buffering capacity, and assess the implications of long-term use.

Systematics effect

Theobromine is a vasodilator, diuretic, a cardiovascular stimulant that also widens blood vessels and promotes urination, and this helps reduce the risk of developing kidney stones (33). The potential capacity of theobromine to widen blood vessels and provide a diuretic effect makes it useful in the treatment of high blood pressure. Theobromine has an extended history of usage as a therapy for various circulatory disorders (7, 34). Theobromine acts as a bronchodilator and may help to increase the lung capacity. Make it easier to treat a variety of respiratory conditions. The anti-inflammatory effects of theobromine are likely responsible for this impact. It can reduce the levels of inflammatory cytokines (35). It has been demonstrated that theobromine raises HDL cholesterol levels while decreasing LDL cholesterol levels (36). Theobromine may be safely eaten if it is done so in the appropriate amounts. Negative side effects, including nausea, loss of appetite, headaches, and others, have been linked to daily dosages of up to 1,500 mg over an extended period; therefore, many new studies suggested theobromine as anticancer material (37, 38).

Commercially available product form

Theobromine can be introduced into toothpastes and oral washes aimed at strengthening teeth and preventing decay. It can also be used in teeth whitening products that rely on strengthening tooth enamel instead of relying on whitening chemicals that may be harsh on enamel. In this way, theobromine can provide preventive and therapeutic benefits for teeth within daily care products.

1-Theobromine-containing toothpaste is used extensively in the US, although its use is rather uncommon compared to other remineralizing agents that are accessible globally. Furthermore, little is known about how theobromine stacks up against other common remineralizing agents, and there is little data to support claims made by manufacturers regarding the theobromine-containing dentifrices' ability

to remineralize teeth. Theodent toothpaste uses chocolate's strength. The word "rennou" refers to the primary ingredient of Theodent, which is a unique mixture of theobromine, calcium, and phosphate. This toothpaste works well to restore tooth enamel's mineral content and lessen hypersensitivity without using fluoride. Toothpastes that contain new remineralization agents may be utilized because of their low cost, easy application, and capability of preventing the formation of the dental caries with their remineralizing characteristics. Theobromine toothpaste is generally considered safe, but potential side effects may include allergic reactions (such as skin irritation), gastrointestinal issues if ingested in large amounts, it could cause stomach upset or nausea, sensitivity to caffeine (Theobromine is related to caffeine), so those sensitive to caffeine might experience increased heart rate, some formulations may cause staining of teeth over time (39, 40). Three phenotype of toothpaste are available commercially: Theodent, Theodent 300, Theodent kids.

2- Theobromine varnish increases surface micro-hardness and mineral gain by promoting calcium deposition on the demineralized enamel surface. The new varnish will offer a viable substitute for fluoride in the remineralization of enamel (8).

3- Theobromine gels are not yet commercially available. Gel is a partially dissolved material that is in the form of a colloid solution. Gel has a number of benefits over mouthwash, such as less usage, stability, and stickiness to extend the duration of the active ingredient (41).

Theobromine uptake, metabolism and pharmacokinetics

Theobromine is absorbed from the digestive system more slowly after oral consumption than caffeine, with an estimated peak-plasma time of 2.5 hours as compared to 0.5 hours for caffeine. The concept posits that decrease in the duration of theobromine's peak plasma concentration following the consumption of chocolate could be linked to the

activation of bile production. Previous study has shown that increased bile production can enhance the absorption of drugs. Methylxanthines are metabolized in human bodies through the process of demethylation, which refers to the elimination of methyl side groups. The process is executed by the enzyme known as cytochrome P450 (CYP). Consequently, CYP will break down theobromine, which is composed of 3, 7 dimethylxanthine, into 3-methylxanthine and 7-methylxanthine. The metabolism of 7-Methylxanthine involves its conversion into 7-methyluric acid through the action of xanthine oxidase (42).

Theobromine catabolism

The breakdown of theobromine into its parts may occur in biological organisms through several different pathways. Theobromine has the potential to undergo direct oxidation to yield 3, 7-dimethyl uric acid. This reaction can be facilitated by theobromine oxidase, theobromine dehydrogenase, or a xanthine oxidase with broad substrate specificity. This product can then be further metabolized to uric acid. Several enzymes are involved in the mechanism of degradation (43). The plasma half-lives of theobromine for humans are estimated to be between 7 and 12 hours, following the catabolic route to theobromine. The rapid rate of degradation is responsible for theobromine's reduced adverse impacts on humans (40). According to a pathway of theobromine (cacao extract) in the human that is safe for humans to consume in large quantities. Theobromine was more favorable when compared to fluoride because of its low toxicity (28, 44)

Clinical applications of theobromine-containing products

1. Strengthening tooth enamel:

Theobromine enhances tooth enamel remineralization, making the teeth more resistant to the acid. It increase the hardness of enamel.

2. Prevention of caries: Through its ability to increase the enamel hardness, theobromine helps to prevent caries. It also has an antibacterial effect, which

reduces the buildup of plaque that can cause tooth decay.

3. Improve tooth whiteness: Enhancing the hardness of the enamel helps to make the teeth roughness decreased and less likely to catch stains, which helps improve the appearance of the teeth and increases their natural whiteness.

4. Prevention of dentin hypersensitivity: Theobromine may contribute to reducing tooth sensitivity by blockage of opened dentinal tubules.

Previous researches on theobromine

Theobromine had the higher preventive capability when applying to the sound enamel tooth structure because it increased the enamel resistance to acid attacks resulted in a minor percentage of loss in surface microhardness when compared with sodium fluoride that result in a higher percentage loss in surface microhardness (45). These results might be attributed to the ability of theobromine to the attraction of calcium and phosphate and retain them to demineralize teeth due to its chemical structure, theobromine work as a carrier for mineral leading to the treatment of the demineralize teeth better than other solutions (46). When Amaechi BT. et al testing the surface microhardness of enamel structure to investigated the effects of theobromine and sodium flouride containing toothpastes, which found that theobromine, has a remineralization enhancing effect in comparison with the sodium fluoride containing toothpastes. Notably, the concentration of theobromine required to achieve a cariostatic effect (0.0011 mol/L) is 71 times lower than that of fluoride (0.0789 mol/L) for a comparable effect. This indicates that a smaller amount of theobromine is needed to achieve similar remineralizing benefits (7). Amaechi et al. (2015) investigated the ability of theobromine-containing toothpaste (Theodent Classic™) to physically occlude dentin tubules as a measure of its potential to relieve dentin hypersensitivity. Their study assessed how effectively this toothpaste could reduce sensitivity by blocking the tubules. They found that there is a steady increase in the occlusion of dentinal tubules after 2, 4, 6, and 14 times usage of the toothpaste.

Almost the entire dentin surface was covered by precipitate layer deposition with only two times usage of theodent classic toothpaste. The addition of 1,500 ppm fluoride to this dentifrice did not result in a significant change in its ability to occlude tubules or form a precipitate layer. The SEM images Figure (3) further confirmed the results. The authors stated that by growing HA in a medium that can yield apatite with a sufficient theobromine content, this enhanced the size of crystallites and the crystallinity of the teeth. Theobromine was thought to stimulate phosphorous and calcium to form a crystal that is Four times greater in size (2 μm) compared to HA (0.5 μm) (3). Previous study conducted by Farooq et al., it was proposed that theobromine could have permeated the micro-tunnels of hydroxyapatite (HA), inducing internal stress that resulted in increased resistance to indentation and, consequently, higher microhardness (11), this agree with the result of a study done on enamel which conclude that following exposure to 200 mg/L theobromine gel, there was an increase in hardness observed in the demineralized enamel surfaces (47).

Study of Yu CL et al. in 2009 has compared toothpastes containing theobromine and hydroxyapatite effects on enamel microhardness. This study found a significant increase in enamel microhardness after using both Theodent (which contains theobromine) and Pepsodent (which contains hydroxyapatite) (48). Contrary to these finding, the report by Golfeshan, Mosaddad et al. in 2021 indicate that there is no significant difference in microhardness between the fluoride and theobromine groups, both of which showed significantly higher values compared to the caffeine and distilled

water groups. This suggests that theobromine may serve as a suitable alternative to fluoride, helping to overcome the side effects associated with high concentrations of fluoride (27). The potential for theobromine to influence the mineralization behavior depends on the characteristic of the lesion as well as the methodology used. Lippert reported no added effect for theobromine in re-hardening established lesions when combined with fluoride and strontium (49). Elmalawany et al. in 2023 evaluate the values of the Ca/P ratio for demineralized dentin that pre-treated with theobromine for 5 min or 1 month, they found that increased in the microhardness values but still lower than sound dentin. Regarding the effect of time of theobromine, no significant difference was found between the 5 min and 1 month (50).

Conclusions

1. Theobromine is a nontoxic, organic, and effective agent on tooth structure that could be right for daily use.
2. Theobromine attracts calcium and phosphorus from saliva and promotes the growth of four times larger unit hydroxyapatite crystals
3. Theobromine can improve the microhardness of the enamel surface. It enhanced the protection of tooth enamel against acid.
4. The use of theobromine containing toothpaste may cause occlusion of dentin tubules and their capacity for treatment pf dentin hypersensitivity.
5. It would be a cost-effective alternative to fluoride without the negative side effects of fluorosis. Due to the availability of theobromine in chocolate and other food sources, it is becoming a superior non-invasive alternative to fluoride.

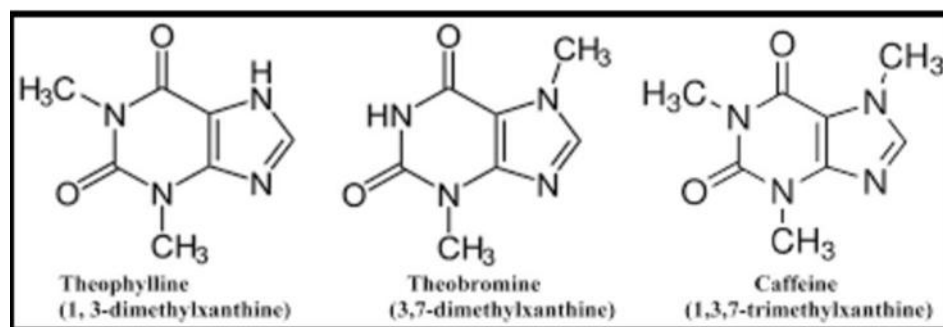


Figure 1 :Molecular formulas of (theophylline, theobromine, and caffeine) (1)

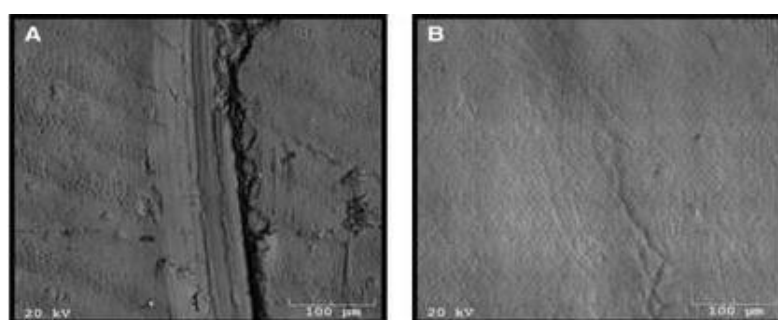


Figure 2: A, shows the enamel surface with scratches before treatment. B, shows the results after applying the theobromine solution (2)

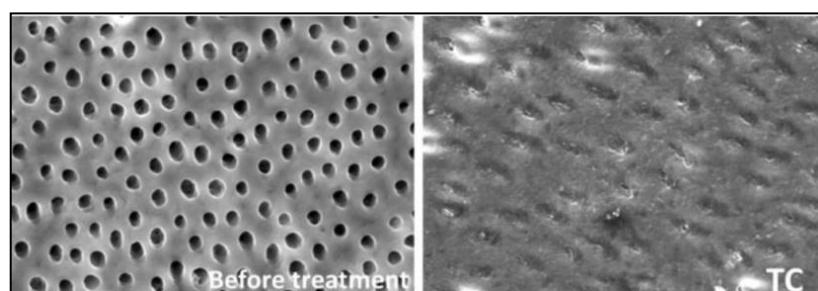


Figure 3: SEM images of dentin blocks; before and after treatment Theodent Classic toothpaste ® (TC) This ability of TC, to occlude the dentinal tubules and deposit layer of precipitate on dentinal surface (3)

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