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Effect of the cranberry (*Vaccinium macrocarpon*) juice on reducing dentin erosion: an *in vitro* study

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Abstract: Vaccinium macrocarpon (cranberry) is a fruit that has an inhibitory effect on matrix metalloproteinases (MMPs) present in dentin and saliva. The inhibition of MMPs has been shown to prevent dentin erosion. The aim of this study was to analyze the effect of cranberry juice on the reduction of dentin erosion in vitro. Specimens of bovine dentin (4×4×2 mm) were randomized and divided into 4 groups (n = 17/group): distilled water (C-control, pH 7.2); green tea extract solution containing 400 µm epigallo-catechin-gallate (EGCg, positive control, pH 4.5); 10% cranberry extract (CrE, pH 3.9), and cranberry juice (CrJ, Cranberry JuxxTM, pH 2.8). Specimens were submitted to erosive pH cycles for 5 days. Each day, four demineralizations were carried out with 0.1% citric acid (90 s). After the acid challenges, specimens were rinsed and kept in treatment solutions for 1 min; afterwards, they were rinsed and stored in artificial saliva for 1 h at 37°C (or overnight at the end of each day). After the experimental period of 5 days, dentin loss was evaluated by contact profilometry. Data were analyzed by ANOVA and Tukey's test ($p < 0.05$). Dentin loss (µm ± SD) was significantly lower for all treatments (EGCg = 9.93 ± 2.90; CrE = 12.10 ± 5.44; CrJ = 11.04 ± 5.70) compared to control (21.23 ± 11.96), but it did not significantly differ from each other. These results indicate that the commercial cranberry juice, despite its low pH, is able to reduce dentin erosion, which might be due to the ability of cranberry components to inhibit MMPs.

Keywords: Vaccinium macrocarpon; Dentin; Tooth Erosion.

Introduction

In recent decades, a reduction in the incidence of caries lesions has been observed in developed countries,[1] leading people to maintain their teeth into old age. Thus, other types of lesions that affect both the young and the elderly population, such as erosive tooth wear (ETW), are gaining clinical relevance.[2,3] Erosive demineralization in dentin results in the exposure of an outer layer of fully demineralized organic matrix, followed by a partially demineralized zone until reaching the inner dentin.[4] The dentin demineralization rate decreases as the amount of degradable collagen increases. Therefore, the demineralized matrix

is believed to hinder the ion diffusion into and out of the demineralization zone.[5,6] The organic matrix of dentin can be degraded by the action of collagenase. The dentin matrix contains mainly type I collagen, which can be degraded by collagenases after demineralization.[7] The intact human dentin also contains latent mammalian collagenase,[8] besides the matrix metalloproteinases (MMPs) MMP-2 and MMP-9,[9-11] which can degrade the dentin matrix. Van Strijp[12] investigated the presence and activity of MMP-1, -2, and -9 in saliva and in specimens of fully demineralized dentin and found a correlation between these enzymes and the levels of collagen degradation. Furthermore, the use of gels, toothpastes, and mouthwash with MMP inhibitors (green tea extract and chlorhexidine), are able to reduce dentin wear after erosive challenges.[13-15]

Green tea was effective in reducing the wear of dentin subjected to erosion associated or not with abrasion.[16] Moreover, in another study, the addition of the active ingredient of green tea, epigallocatechin-gallate polyphenol (EGCg), to a topical gel was effective in preventing the wear of dental erosion.[14,17] The hypothesis was that the active ingredient of green tea effectively decrease dentin wear because EGCg is a polyphenol, a natural inhibitor of MMPs.[18,19] MMPs present in saliva or dentin hydrolyze the extracellular matrix components, such as the organic components present in the dentin matrix. Dentin contains about 18-20% of collagen, which can play an important role in the diffusion of acids.[20]

Cranberry juice is known to have a preventive effect against urinary tract infections,[21] interrupt the critical stage of gastric ulcers,[22] inhibit the influenza virus adhesion and infectivity,[23] a potential cardiovascular benefit,[24] and inhibit the proliferation of cancer cells in the mouth, colon and prostate.[25] Regarding oral health, several studies have shown that cranberry polyphenols have beneficial properties in the treatment and prevention of caries and periodontal diseases.[26-28] In caries, these properties are associated with the reduction of extracellular polysaccharides production, inhibition of acid production of acids by cariogenic bacteria, inhibition of the functions of glucan-binding proteins, and reduction in biofilm formation. In periodontal disease, the benefits are due to inhibition of biofilm formation and adhesion of periodontal pathogens, proteolytic activity of bacteria and tissue, and cytokine production by immune cells. More importantly, it inhibits MMP production and activity,[29,30] main enzymes in dentin and saliva. Although cranberry juice has an acidic pH (pH 2.8) and can be considered potentially erosive, no study has yet tested cranberry juice to reduce dental erosion.

Due to the preservation of the collagen layer, we can expect a good protective potential of this polyphenol against erosive challenges. In patients at risk of dental erosion, the inhibition of MMPs by cranberry could reduce the degradation of the collagen-rich demineralized dentin surface, which would have a positive effect on the prevention of the disease. However, these effects have mostly been demonstrated in laboratory studies, and well-designed clinical trials are needed to evaluate whether the proposed protective potential of this polyphenol against erosive challenges can actually lead to prevention in high-risk individuals and population groups. A combination of cranberry juice and remineralizing agents in a single oral care product for clinical use that could be used by patients at home would be conceivable.

Objective

In view of the above, the aim of this study was to analyze the effect of cranberry juice on dentin erosion in an in vitro study. The null hypothesis tested was that the pretreatment with cranberry juice does not influence dental erosion.

Methodology

Specimen preparation

Thirty incisors were obtained from bovines with an average age of 36 months at the meat processing facility (Frigorífico Vangélio Mondelli Ltda., Bauru, Brazil). The incisors were cleaned of periodontal tissues with periodontal curettes to remove any residues and stored in a solution of 0.02% sodium azide and 0.9% sodium chloride. The teeth were fixed with thermoplastic Godiva (Kerr Corporation,

USA) on the bottom right corner of a small clear acrylic plaque (40mm x 40mm x 5mm) to facilitate the adaptation in the cutting machine. The acrylic plaque was coupled to a precision cutting machine (ISOMET Low Speed Saw, Bulher Ltda., Lake Bluff, USA), and 100 dentin specimens (4 x 4 mm) of the crown's flattest portion (medium third) were obtained using two double-sided diamond discs – XLI 2205, "height concentration", 102 x 0.3 x 12.7 mm (Extec Corp., Enfield, USA / Ref: 12.205) and a stainless steel spacer (7 cm diameter, 4 mm thick, and 1.3 cm of central opening) between the discs, at 300 rpm speed with deionized water cooling. A double cut was performed in the cervical-incisal direction and another one in the mesial-distal direction. Dentin blocks were fixed with Kota sticky wax (Kota Ind. and Com. Ltda., São Paulo, Brazil) on the center of a clear acrylic disc (30 mm diameter and 8 mm thickness) with the enamel facing the disc in order to flatten the dentin. The set (disc/tooth) was adapted into a Metallographic Polishing Machine (APL 4, Arotec, Cotia, Brazil) with a multiple polishing system for the automatic polishing of 6 test specimens, allowing parallelism between the polished surfaces and the acrylic support. Silicon carbide sandpapers of 320 grit (Extec Corp., Enfield, USA), were used under cooling with 2 pattern weights of 6 g, and blocks were polished for 30 s to 7 min until the desired thickness was achieved. Finally, 80 dentin blocks with a thickness of 4 x 4 mm were obtained.

Afterwards, the blocks were detached from the acrylic disc and cleaned with xylene (MERCK, Darmstadt, Germany). Then, the blocks were fixed again with sticky wax in the center of the acrylic plaque with the dentin against the plaque. The enamel was worn with 320 grit silicon carbide sandpaper (Extec Corp., Enfield, USA) under cooling for 5 minutes at high speed until reaching dentin. The surface was polished with 600 grit silicon carbide sandpaper (Extec Corp., Enfield, USA) under cooling for 1 minute at low speed and than with 1,200 grit silicon carbide sandpapers (Extec Corp., Enfield, USA) under cooling for 2 minutes and 30 seconds at high speed. To finish the polishing, a moistened felt (Extec. Corp., Enfield, USA) with a 1 µm (Buehler) diamond suspension was used for 3 minutes at high speed to smooth the dentin blocks and allow a precise profilometry analysis. Between changes of sandpapers, we used a T7 Thornton (Electronic Products Unique Ind. and Com. Ltda., São Paulo, Brazil) ultrasound device with a frequency of 40 KHz for 2 minutes with deionized distilled water to remove the residues from the sandpaper. After the final polishing, two 10-minute-washes were performed in the ultrasound device.

Treatment

One hundred dentin blocks were prepared and randomly divided into 4 groups (n = 25/group) of treatments. Sample losses occurred due to experimental conditions in baseline selection by microhardness and due to complete loss of demineralized organic matrix (DOM) in some specimens after pH cycling, and 68 specimens remained (n = 17/group). The treatment groups were distilled water (C, control, pH 7.2), epigallocatechin-gallate green tea extract (EGCg, positive control, 400 µM, pH 4.5), 10% cranberry extract (ECr, pH 3.9) (Shaanxi M.R Natural Product Co., Ltd, Xi'an, China), and commercial cranberry juice (SCr, Cranberry Juxx®, pH 2.8). Two-thirds of the dentin surface were protected with nail polish (two layers, dried for 24h) to be used as a reference surface for wear determination.

Dentin blocks were subjected to demineralization and remineralization cycles (DES-RE) for 5 days. A total of 4 demineralizations were carried out with 0.1% citric acid for 90 s, every day. After the acid challenge, the blocks were rinsed and kept in treatment solutions for 1 minute, according to group allocation, rinsed again, and then stocked in artificial saliva (20 mmol/L HEPES, 0.70 mmol/L CaCl2, 0.20 mmol/L MgCl2·6H2O, 4 mmol/L KH2PO4, 30 mmol/L KCl, 0.30 mmol/L NaN3)20 overnight at 37°C between the DES-RE challenges or between experiment days.[31] All solutions were renewed daily at the beginning of the experiment.

Dentin loss measurement

At the end of the experimental phase and before wear evaluation, the nail polish was removed carefully from the blocks with a spatula avoiding

contact with the surface to be analyzed. The erosion on the dentin surface was evaluated in the interface control-erosion-control by a topographical analysis using a Profilometer (MarSurf GD 25, Mahr, Göttingen, Germany). The tip of the measuring probe was positioned on the reference section and moved through the eroded section until the second reference section, adding to a course of about 2.5 mm in the X axis and 5 mm in the Y axis. The software MarSurf XT 20 (Mahr, Göttingen, Germany) installed on a computer linked to the Profilometer was used for the topographical analysis of the total area, and the height difference (Z axis) between the control-erosion-control faces was obtained. For the analysis, the topographical graph represented by reading lines (5 reading lines) was aligned without using the filter. Therefore, the average erosion per block represented the average of 10 readings. The experimental design is shown in Figure.

Statistical analysis

The InStat. Software was used. Data were homogeneous and with normal distribution. After this verification, one way analysis of variance (ANOVA) was applied, followed by Tukey's test to identify significant differences among groups. The level of <significance adopted in all tests was of 5%.

Results

Data referring to dentin wear are shown in Table. EGCg significantly reduced dentin wear compared to distilled water (C-control) ($p < 0.05$). The same happened with commercial cranberry juice (SCr) and cranberry extract (ECr) ($p < 0.05$). This analysis revealed that all treatments significantly reduced dentin wear compared to water (control), and treatments did not differ among each other, although the pH of solutions was acid.

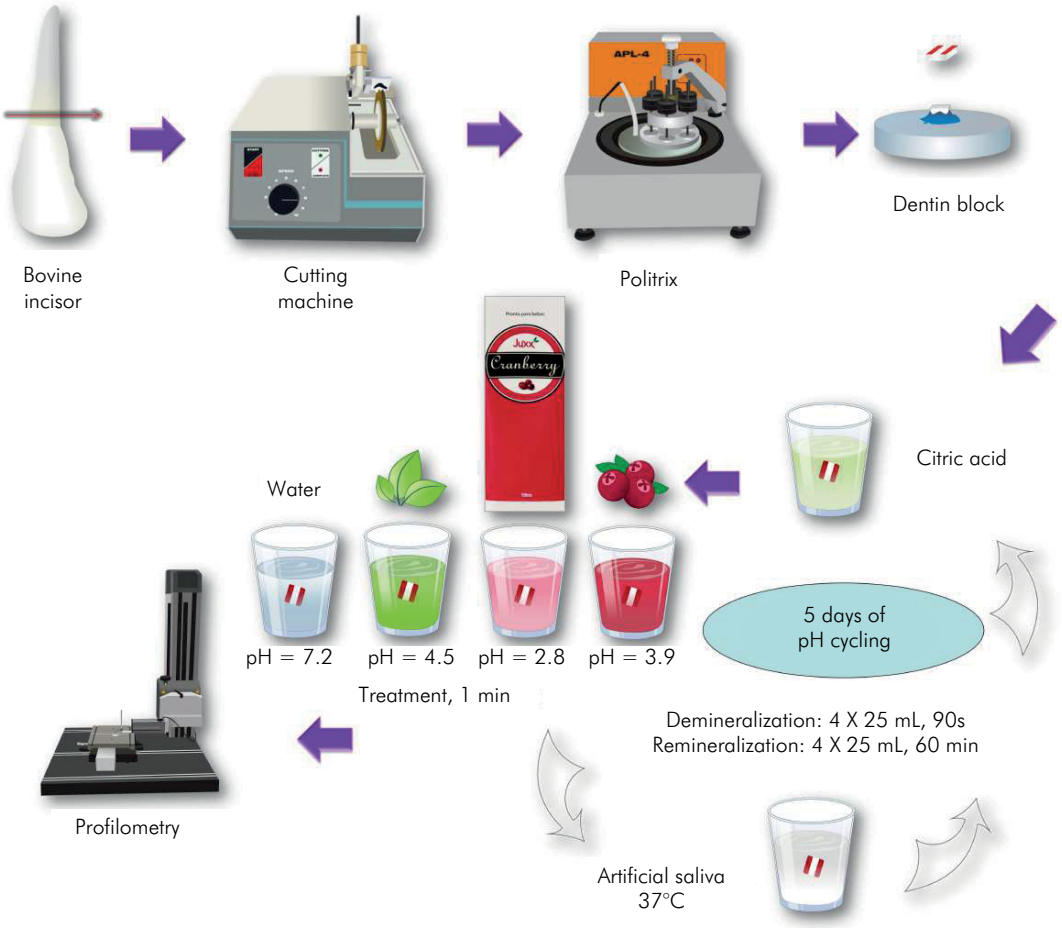

Figure 1. Flowchart of the experimental design.

Table. Wear (mm, medium±DP) of dentin subjected to pH cycling of demineralization in citric acid (90 s) and remineralization in artificial saliva (1 h) and treated with solutions of different pH.

Treatment	Wear (mm, medium±DP)	pH
C (water)	21.23 ± 11.96[a]	7.2
EGCg	9.93 ± 2.90[b]	4.5
SCr	11.04 ± 5.70[b]	2.8
ECr	12.10 ± 5.44[b]	3.9

Different lowercase letters indicate significant difference among treatments. ANOVA and Turkey test ($p < 0.05$), n = 17 per grup.

Discussion

Among potential MMPs inhibitors, cranberry contains flavonoids and catechins, such as epigallocatechin-3-gallate (EGCg) and proanthocyanidins, respectively. Cranberry flavonoids, particularly EGCg, have been shown to be potent inhibitors of MMPs in cell culture tests.[18,19] EGCg seems be linked to collagenases by hydrogen bonds and hydrophobic interactions, resulting in alterations in their secondary structure and consequent inhibition.33 Proanthocyanidins are also potential inhibitors of MMP production and activity.[29,30]

Cranberry properties against caries and periodontal disease are known;[26,27] however, the effect of cranberry on erosion still needs investigation. Previous data showed that a gel containing cranberry extract used in an in vitro study was able to reduce dentin wear when subjected to erosion by a cola-based beverage.[32] The results showed that the purified proanthocyanidin gel had the best results in reducing the DOM degradation, followed by cranberry extract gel and placebo gel. In this study, we cannot conclude whether the effect was due to the presence of EGCg or proanthocyanidins, since the juice contains both chemicals and showed a significant reduction in dentin wear, similar to the group containing only EGCg. Another study[34] showed that grape seed extract significantly reduced dentin wear compared to cranberry extract and chlorhexidine, which did not differ statistically and both reduced wear compared to NaF and placebo treatments. The authors showed that cranberry extract reduced the dentin wear and collagen degradation, likely due to the proanthocyanidin content and its action.

Other vehicles, such as mouthwash and gel, containing purified proanthocyanidin (PA) were tested in in situ or in vitro. These studies have demonstrated the PA protective effect on dentin erosion.[34,35] The protocol used in the present study does not allow us to conclude that the protective effect of cranberry on reducing dentin wear was due to the inhibitory effect of MMP activity, as this was not tested directly. Further studies focusing on determining the activity of MMPs in the organic layer on etched dentin after erosive challenge could better answer this question. Cranberry extract (CrE) containing proanthocyanidin was used as a positive control due to its reported efficacy in the inhibition of collagen degradation by MMPs and ability to decrease dentin wear.[34]

The acidity of the cranberry extract (pH = 3.9) and cranberry juice (pH = 2.8) and EGCg (pH = 4.5) draws our attention. It is evident that the acidic pH would cause some level of wear under these conditions. However, the cranberry juice, even with the lowest pH, significantly reduced dentin wear compared to the control (water, pH 7.2), and did not significantly differ from the other acidic groups. The properties of polyphenols may vary according to the fruit's cultivation or harvest season, once the concentration of the active ingredients may vary depending on the circumstances. In this case, commercial cranberry juice from the same batch was used so there would be no risk of bias related to the polyphenol concentration in the results.

In spite of study limitations, we can expect a good protective effect of cranberry juice against erosive challenges due to the preservation of the collagen layer. Clinical trials are needed to evaluate whether this effect can actually translate into prevention in high-risk individuals and population groups. It would be interesting to see a combination of cranberry juice and remineralizing agents in a single oral care product for clinical application, which could be used by the patient at home, or even to recommend drinking the juice itself more often as a natural agent to prevent dentin erosion.

Conclusion

Despite its acidic pH, commercial cranberry juice, which contains polyphenols especially in the

form of EGCg and/or proanthocyanidin, reduced the erosive effect on dentin. More studies are needed to understand the effect of cranberry on the demineralized organic matrix degradation and to establish the ideal concentration of the extract or its fractions. Randomized clinical trials are necessary to define protocols for the use of this natural product.

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