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Effect of dentin pretreatment with hesperidin, cranberry, or grape seed extracts on microshear bond strength of conventional flowable composite bonded with universal adhesive: In-vitro study

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ORIGINAL STUDY

Effect of Dentin Pretreatment with Hesperidin, Cranberry, or Grape Seed Extracts on Microshear Bond Strength of Conventional Flowable Composite Bonded with Universal Adhesive: An In-vitro Study

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Abstract

Purpose: Improving dentin bond strength to universal adhesives could be a controversial issue due to unavoidable hydrolytic and enzymatic degradation potentials. Therefore, novel natural remedies are needed to increase the ability of dentin collagen to resist degradation which could enhance resin composite/dentin bond strength. This study aims to test the microshear bond strength (μSBS) of conventional flowable composite material adhered to dentin with universal adhesive after pretreatment with hesperidin (HPN), cranberry, or grape seed extract. **Patients and methods:** Forty permanent molars were selected for the current study divided into four groups ($n = 10$) considering the type of dentin pretreatment used where; group A1; dentin pretreatment was done with a 5% HPN extract. While group A2; dentin was treated with 6.5% cranberry extract. Moreover, in group A3; dentin pretreatment was done with 6.5% grape seed extract. Group A4; no pretreatment (control) was done. Afterward, Universal light cure dental adhesive was applied in self-etch mode, and cylinder samples of conventional flowable resin composite were made using a polyethylene tube. All samples were then subjected to thermocycling and then tested the μSBS. **Results:** The bond strengths were statistically analyzed using one-way analysis of variance and Tukey's post hoc tests. Results recorded a statistically significant difference between different pretreatment options, where the highest μSBS men value was recorded for HPN while the lowest μSBS men value was for the cranberry group. **Conclusion:** Natural dentin bio-modifiers could be a substitutional therapy to strengthen flowable composite adhesion with universal adhesive to dentin.

Keywords: Cranberry, Flowable resin composite, Grape seed extract, Hesperidin, Microshear bond strength

1. Introduction

Dental tissues mainly comprise an organic matrix of collagen type I and inorganic minerals saturated with hydroxyapatite crystals, so dentin is considered a complicated hydrated tissue. Dentin behaviours vary especially with the different depths of cavity preparation [1]. Efficient dentin bonding depends on the proper resin infiltration into the microporous demineralized collagen network with the production of a stable hybrid layer between resin and collagen microfibers which assures a long-standing bond over different oral environmental conditions [2].

Current clinical assessments confirm that progressive degradation of the dentin-resin bond is an unavoidable event that increases the failure rates of restorations for different adhesive protocols [3]. The interface between adhesive and dentin acts as a permeable membrane that permits the seepage of unreacted monomers. Also, it shows water sorption, polymer swelling, resin hydrolysis, and enzymatic

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activity causing the exposed collagen fibrils to degrade [4]. Degradation of this layer primarily involves the loss of resinous material out of the interfibrillar network together with the disorganization of collagen fibers. This highlights the demand for new therapies that focus on stabilizing the resin components as well as dentin matrix during reparative treatment [5].

Nowadays, using natural remedies in restorative dentistry has become more common where investigators claimed that they can improve resistance to collagen biodegradation at the interface and can increase bond strengths eventually [6]. Glutaraldehyde and proanthocyanidin (PA) are cross-linking agents showing promising outcomes for reparative dentistry. Glutaraldehyde could have collagen stabilization properties but its disadvantages like toxicity restrict its use. On the other side, PA is a natural herbal flavonoid found in fruits, flowers, and nuts with reduced cytotoxicity when compared with synthetic agents [7]. One of the many PA-based medicines is grape seed extract (GSE), which contains over 97% PA and improves cross-linking. This extract strengthens dentin and inhibits matrix metalloproteinase enzymes [8,9].

Another alternative to GSE is cranberry (Vaccinium macrocarpon) which contains a unique A-linkage structure [10]. It contains polyphenols, mainly PAs [11]. Many researches have shown that cranberry polyphenols can treat and prevent caries and periodontal diseases [12] where these properties regarding dental caries are associated with reducing extracellular polysaccharide production, inhibiting acid production, and the functions of glucan-binding proteins. Furthermore, it suppresses the development and activity of matrix metalloproteinase, a key enzyme in dentin and saliva [13].

Hesperidin (HPN), a flavonoid derived from citrus fruit, has several advantages including antimicrobial, collagen cross-linking, caries prevention, improved remineralization, and antioxidant properties [14–16]. There is limited research on how HPN affects the stability of the dentin/resin hybrid layers.

Several types of composites available in the market, including flowable fissure sealant resins, flowable, hybrid and microfilled, highly viscous, and packable resin composites, each having unique benefits and drawbacks [17]. The flowable category is used to restore tiny lesions in non-stress locations, including cervical lesions and preventative resin restorations [18]. Also, flowable composite is used under more packable composite to act as cushion absorbing stresses produced during mastication or that accompanied the polymerization shrinkage due to its well-documented resiliency properties [19].

There are three main systems of dental adhesives based on the mode of application; the 'Etch-and-rinse' system [20], the 'Self-etching' primer system, and the 'all-in-one' or one-step self-etching system [21]. New systems are being introduced for simplicity, better composition, and bonding [22]. The latest sundries in dental adhesives are the preface of 'universal' or 'multi-mode' adhesives [23], where both hydrophobic and hydrophilic components are presentinone bottle [24,25]. Therefore, it is always questionable how stable, and durable is the bond produced by these contemporary multimode adhesive systems [26], where the major enterprises were related to increasing nanoleakage with aging, limiting the durability of the bond [27]. There is a lack of evidence on the exact strategy for creating reliable and strong bonding between universal adhesives and dentin.

Likewise, enhancing bonding may be achieved through utilizing multitudinous strategies. Thus, the study aimed to test the effects of various dentin biomodifiers upon microshear bond strength (μSBS) of conventional flowable composite bonded with universal adhesive. The null hypothesis stated no statistically significant difference between different dentin biomodifiers compared with no pretreatment.

2. Patients and methods

2.1. Teeth selection

Forty human permanent molars were obtained from an outpatient hospital, at the Faculty of Dentistry, Ahram Canadian University (ACU). Ethical approval from the ethics commission of Ahram Canadian University's Faculty of Dentistry (IRB00012891#19). Extraction was carried out because of periodontal reasons and was inspected to be caries-free, any noncarious lesions, cracks, or any restorations, and were chosen from patients of the age range 25–45. For sterilization, teeth were rinsed with stream water, cleaned with an ultrasonic scaler (Cavitron, Dentsply, USA), then submerged in a 0.5% chloramine T solution for one week. Afterward, nonfluoridated pumice and rubber cups were used for teeth polishing. Teeth were maintained in isotonic saline at an indoor temperature (37 °C), changed weekly, and utilized within three months to prevent alteration in the permeability that can negatively affect the bond strength tests [28].

2.2. Sample size calculation

For the evaluation of the effect of dentin pretreatment for 5 min on μSBS and 500 cycles of

thermocycling, ANOVA test or an equivalent nonparametric test will be used to compare between groups. Based on a study by Haralur *et al*. [29], The mean value varied from 122.92 ± 61.97 and 120.21 ± 77.64 to 197.31 ± 12.85 (according to pre-treatment). Following Haralur *et al*. (2022) [29] and Using G power statistical power Analysis program (version 3.1.9.4) for sample size determination [30], the Overall samplesize ($n = 40$; subdivided into 10 per group) will be enough to detect a large effect size (f) = 0.58, with an actual power (1-β error) of 0.8 (80%) and a significance level (α error) 0.05 (5%) for two-sided hypothesis test.

2.3. Acrylic moulds preparation

A special two halves split Teflon mold was used to produce blocks made from acrylic resin. Each tooth was fixed into self-cure acrylic resin (Acrostone Dental Factory, Egypt) in a vertical direction till the cervical line. After the complete polymerization, the Teflon cylinder was removed, and storage of the blocks in isotonic solution at room temperature was carried out.

2.4. Sample preparation

The dentin surface was exposed by removing enamel, at a standardized depth. Cutting and flattened teeth has been done in presence of coolant toward the horizontal direction using a low-speed hand-piece (Komet, Germany) and round bur to made an indentation of 1 mm guided by a rubber stopper glued to the shaft of the bur. Then the final depth was reached by grinding using a rotary grinding device #180-grit silicon carbide papers under coolant to create a uniform smear layer, and to make sure that there was no enamel and/or pulp chamber, the surface was inspected using a laboratory macro-lens at 4X magnification. Finishing of the surface was done using 600-grit silicon carbide paper for 20 s. All the samples preparations were done by the same operator [28].

2.5. GSE solution

6.5 g of GSE powder (MegaNatural, Polyphenolics, Madera, California, USA) was collected from the capsules with a sensitive balance and liquified in 100 ml of distilled water to produce a concentration of 6.5% w/v. The solution's pH was changed up to 7.2 using 100 mg of $NaHCO_3$ before usage. The mixture was freshly prepared immediately before its use [31].

2.6. Cranberry extract solution

Total amount of 500 g of cranberry fruit was freeze-dried using Christ Lab freeze dryer and ground into fine reddish powder. The powder was placed in Kimax glass tubes and mixed with 1.75 l solvent which is composed of 99% methanol and 1% HCL. Sonication of the mixture was done for 30 min for 3 times using an Ultrasonic Probe system. The extract was then concentrated under vacuum at 50 °C and the remaining liquor was subjected to freeze drying producing red powder. The total phenolics (Gallic Acid Equivalent) of the extract was 11.40 mg/g extract. It was quantified with the microtitre plate Folin-Ciocalteu method using a Gallic acid solution of 1 mg/ml in methanol [32].

The cranberry extract solution preparation was done by measuring 6.5 g of ground cranberry extract powder with a sensitive balance. Then they were liquified in 100 ml of distilled water to reach a concentration of 6.5% w/v. The primary solution pH was recorded as pH = 3 using a pH meter, then pH adjustment was done similarly as mentioned above. Solution was freshly prepared before its use [11,33].

2.7. Hesperidin extract solution

The amount of 5 g of HPN powder (SEDICO Pharmaceutical Company, 6th October City, Egypt) was liquified in 100 ml of distilled water to reach a concentration of 5% w/v. The pH adjustment was done similarly as mentioned above [33].

2.8. Pre-treatment procedures (sample grouping)

Based on the type of pre-treatment used, four groups were created: group A1; pre-treatment with 5% HPN extract solution. Group A2; dentin treated with 6.5% cranberry extract solution. Group A3; dentin treated with 6.5% GSE solution, and group A4; no surface treatment (control group). Where the pre-treatment solutions were applied for 5 min and rinsed with water, gentle air dryness, and then the bonding/buildup procedure was done [34,35].

2.9. Bonding for composite resin build-up

Universal light cure dental adhesive (All-bond universal, BISCO Inc., USA) was used as a self-etch adhesive. The application of the adhesive was done according to the manufacturer's instructions. The adhesive was applied in two coats, with gentle rubbing for 15 s, using a disposable micro brush. After that, there was a 5 s mild air-drying period [28]. Then, four clear cylindrical plastic tubes,

0.9 mm inner diameter × 2.0 mm height (Tygon tubing; Norton Performance Plastic Co, Cleveland, OH, USA), were stabilized on the dentin surface and light cured for 20 s [36] using a LED light-curing unit of 470 wavelengths (Elipar S10, 3 M, ESPE) with a light intensity of 1000 mW/cm^2. No light cure was applied between coats.

2.10. Composite resin build-up

Afterward, flowable resin composite (Nexocomp Flow, Meta Biomed Co. LTD) was used to fill the tubes, followed by light curing for 40 s, at zero distance. To remove the tubes, a medical scalpel blade with the number 11 was used to carefully cut each tube. Finally, there was a total of four cylinders on each tooth. Storage of the samples in distilled water was done at 37 °C for 48 h [35].

2.11. Thermocycling

Following the storage period, specimens were placed in normal water at 37 °C for 24 h and then thermocycled (SD Mechatronik thermocycler Feldkirchen- Westerham, Germany) for 500 cycles with temperature range between 5 °C and 55 °C. The thermocycling was done as follows, 20 s of hot water bath at 55 °C, followed by 20 s of cold-water bath at 5 °C, with 10 s resting period (Fig. 1).

2.12. Microshear bond strength test

Testing was done using a universal testing machine (Instorn model 3345, Instron England), using the software BlueHill universal Instron England (Fig. 2). The compression mode of force was applied at a crosshead speed of 1 mm/min up to specimen failure. μSBS was calculated as the ratio of fracture load and bonding area, expressed in megapascals (MPa) [34].

Fig. 1. Thermocycling of the samples.

Fig. 2. Microshear bond testing.

The following equation was used for calculating the shear bond strength:

$\sigma = F/A$, where: σ is the micro shear bond strength in Mega Pascals (MPa). Where F is the failure load expressed in Newtons (N), and A is the surface area in square millimetres (mm^2), where: $A = \pi r^2$ and $\pi = 3.14$. r = radius of each composite cylinder = 0.9 mm.

2.13. Statistical analysis

Checking data for normality through data distribution tested by mean of normality (Kolmogorov–Smirnov and Shapiro–Wilk tests). All data showed parametric distribution. Data were presented as mean, standard deviation, and confidence interval values. One-way analysis of variance (ANOVA) and Tukey's post hoc tests were used for comparison between groups. The level of significance was set at P less than or equal to 0.05. Data were statistically analyzed with IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

3. Results

One-way analysis of variance (ANOVA) and Tukey's post hoc tests represent statistically significant differences between the four groups ($P = 0.033$) (Table 1, Fig. 3), as following:

3.1. Hesperidin group

Statistical differences were recorded among the samples pretreated with HPN and other groups either no pretreatment or Cranberry groups where; the highest mean value was recorded for HPN group (27.05 ± 3.26) where P value = 0.034 and 0.017, respectively. Meanwhile, there was no significant difference recorded with the Grape seed group where P value = 0.74.

Table 1. Descriptive statistics and comparison of microshear bond strength (MPa) between different groups (analysis of variance test).

	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum	F	Sig
				Lower bound	Upper bound				
Hesperidin	27.05^{A}	3.26	1.33	23.62	30.47	22.40	30.19	3.545	0.033*
Cranberry	19.21^{C}	5.18	2.11	13.77	24.64	13.32	25.65		
Grape seed	26.07^{AB}	7.53	3.08	18.16	33.97	19.21	35.75		
No pretreatment	20.19^{BC}	3.75	1.53	16.25	24.13	16.03	25.38		

Superscripts with different capital letters demonstrate statistically significant differences within the same column.
*Significant ($P \leq 0.05$) ns; nonsignificant ($P > 0.05$).

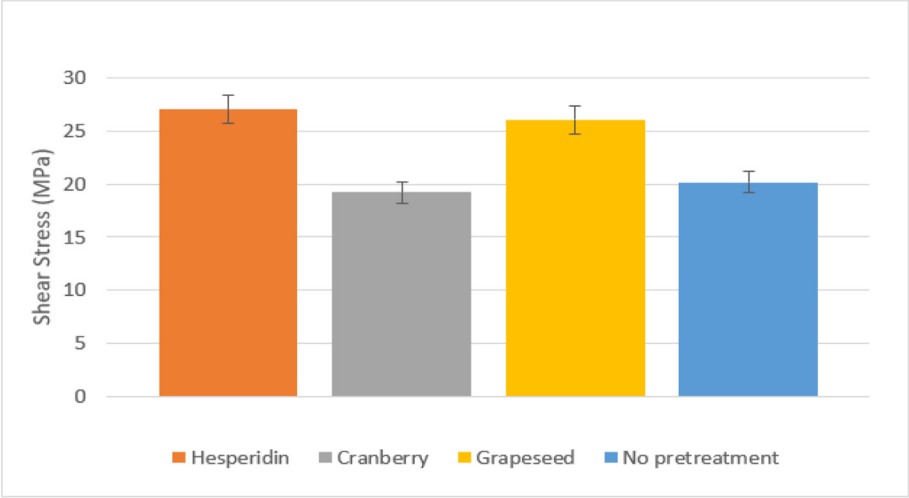

Fig. 3. The mean value of microshear bond strength (MPa) in different groups.

3.2. Cranberry group

Statistically significant differences were recorded between the Cranberry and other groups either HPN nor Grape seed groups with the highest mean value was recorded for HPN (27.05 ± 3.26) where *P* value = 0.017 and 0.033, respectively. However, there was no statistically significant difference recorded for the no pretreatment group (control group) where *P* value = 0.74.

3.3. Grape seed group

A statistically significant difference was recorded between the Grape seed and the Cranberry group with the highest mean value recorded for grape seed (26.07 ± 7.53) where *P* value = 0.033. However, no statistically significant difference was recorded with other groups (no pretreatment and HPN) where *P* value = 0.065 and 0.74, respectively.

3.4. No pre-treatment group

A statistically significant difference (*P* value = 0.034) was recorded between the pretreatment group and the HPN group where the greatest mean value was recorded for the hesperidin group (27.05 ± 3.26). However, no statistically significant difference was recorded with other groups (Grape seed and Cranberry) where *P* value = 0.065 and 0.74, respectively.

4. Discussion

The inter-along with intramolecular cross-links that make up collagen in dentin can increase elasticity and tensile strength. Covalent intermolecular cross-links occur extracellularly and give type I collagen its natural rigidity [37]. So, bonding to dentin can be considered a sort of tissue engineering that strengthens the connection and makes the resin/dentin interface more resistant to hydrolytic and/or enzymatic degradation over time.

Extrinsic cross-linking agents can be used to improve the biomechanical characteristics of dentin. Naturally derived compounds have gained more attention recently in dentistry. Commonly used cross-linkers in dentistry are PAs, glutaraldehyde, genipin, and carbodiimide. The primary mechanism of collagen stabilization with PAs is hydrogen bond formation [38].

μSBS test was selected because of the ease of sample preparation, small amount of material, and

fewer number of samples are needed. It is believed that μSBS is highly reliable because the stress distribution is more homogenous on the bonding surface, so statistical analysis would be more accurate. Also, the size of contact surface stress concentration is decreased, as a result, failure modes shift to be adhesive instead of being cohesive and this will minimize methodological errors [39,40].

PAs are naturally existing bioflavonoids in vegetables, fruits, flowers, nuts, barks, and seeds. HPN, cranberries, and GSE are among the most significant sources of PAs. Because PAs may bind to proline-rich proteins like collagen and promote enzymatic activity of proline hydroxylase, which is mandatory for the manufacture of collagen, they are extremely important. Additionally, PAs have merged beneficial crosslinking and anti collagenolytic properties that help stop dentin collagen deterioration in the hybrid layer [41,42].

Many researchers have studied the effect of GSE used as dentin primer with universal adhesive systems, but its effect on flowable composite has not yet been investigated [43]. Adhesive dentistry has been enhanced by universal adhesives. Their primary drawback, though, is that they are too hydrophilic, which weakens the connection [44]. According to Valizadeh *et al*. [45], concluded that the greatest mean μSBS value was observed in the self-etch mode of Scotchbond Universal.

In the current study, the bonding agent used for all the groups was All-bond universal which is an ethanol/water-based dental adhesive. Nie *et al*. [46], stated that the ethanol might be a perfect solvent for PA−based pretreatment since ethanol stimulates PA and collagen interactions rather than acetone by reducing the dielectric constant of the media.

Thermocycling was used to simulate clinically relevant circumstances. Hadan *et al*. [27] demonstrated that using collagen crosslinking as pretreatment strengthens dentinal collagen fibrils and improves bonding durability. Their effect appears over time (aging) to reinforce collagen by maintaining an expanded position that can receive solvents and monomers.

The current study investigated the effect of HPN, cranberry, or GSE as a dentin pretreatment agents on the μSBS of flowable composite adhered with a universal adhesive in self-etch modes compared with no pretreatment. The results found that there was a statistically significant difference between different groups with highest value recorded for values group 1 (HPN) followed by group 3 (Grape seed), and then group 4 (No pretreatment), and the lowest values were recorded for group 2 (Cranberry). Thus, the null hypothesis was rejected.

PAs concentration is a critical point in determining the extract's efficacy. Castellan *et al*. [33] stated that GSE and cocoa seed extract showed higher bond strength, and this could be attributed to high PAs content (95% and 45%, respectively) Therefore, the composition, potency, and PA concentration of the final extract were significantly influenced by the source of the starting material and the production procedure, as the uncooked cranberries, grape and cocoa seeds have total phenol content higher than that of other common fruits including strawberries, apples, blueberries, and red grapes. However, only 56% of the two primary types of phenolics found in it are PAs [47]. The therapeutic effect of two cranberry extracts was strongly affected by PA concentration [48]. Less than 1% of PA was present in the commercial cranberry extract utilized in this investigation, which might contributed to its unexceptional impact and lowest binding strength values.

The results of this study proved that HPN had the highest bond strength among other groups. This was in accordance with Soliman and Ghorab in 2018 [49]. This significant increase could be attributed to improvement in the stability of dentin collagen because PAs and HPN are phenolic flavonoids that have a chroman ring. Moreover, the HPN's action on collagen fibrils might related to the similarity to PAs' cross-linking effect [50].

To prevent collagenase degradation, The application of 0.5% HPN, PA, and epigallocatechin gallate resulted in the largest decrease in collagen breakdown this was in agreement with Hiraishi N *et al*. [51] who investigated the effects of many plant-derived compounds on the integrity of the dentin collagen matrix, including genipin, epigallocatechin gallate, PA, and HPN and found that these natural substances improved the mechanical characteristics of dentin when measured the Ultimate Tensile Strength and Swelling Ratio.

In addition, Abo El-Mal *et al*. in [52] concluded that HPN is a hopeful direct pulp capping agent inducing mild inflammation and a high-quality dentin bridge comparable to MTA [53]. There is another explanation for the higher bond strength of the HPN group as it is slightly acidic since HPN was obtained from slightly acidic citrus fruits, so it might have selective demineralize effect on dentin and activate proper infiltration of universal adhesives in between the collagen networks and enhance bond strength durability.

4.1. Conclusion

Within the limitations of this study, Natural dentin bio-modifiers could be a substitutional

therapy to strengthen flowable composite adhered with universal adhesive to dentin.

4.2. Recommendations

Further in vitro studies are recommended with longer aging periods to mimic the oral cavity conditions. Since HPN showed the best bond strength, further clinical research would be beneficial.

Conflict of interest

There are no conflicts of interest.

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