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ORIGINAL ARTICLE

The improvement of biocompatibility of adhesives

The effects of resveratrol on biocompatibility and dentin micro-tensile bond strengths of self-etch adhesives

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Abstract

Objective The aim of this in vitro study is to evaluate the effects of resveratrol (RES) addition on the cytotoxicity and microtensile bond strength (μTBS) of different adhesives.

Materials and methods Five self-etching adhesives (G-aenial Bond-GC, Optibond All in One-Kerr, Gluma Self Etch-Kulzer, Clearfil S^3 Bond-Kuraray, and Nova Compo-B Plus-Imicryl) were tested. They were applied to L-929 cell culture by the extract method. In the test groups, 0.5 μM RES (Sigma-Aldrich) was added into the medium. Cell viability was assessed by MTT assay after 24 h. Human extracted third molars were used for μTBS test ($n = 7$). The adhesives with or without 0.5 μM RES addition were applied on dentin surfaces. A composite build-up was constructed. Then, the specimens were sectioned into multiple beams with the non-trimming version of the microtensile test and subjected to microtensile forces. Statistical analysis was performed using ANOVA and post hoc Tukey test ($p < 0.05$).

Results The extracts of all adhesives decreased the cell viability. However, RES addition increased the cell viability in all groups ($p < 0.05$). RES addition did not cause any decrease in μTBS values of the adhesives compared to baseline. Optibond All in One showed the highest μTBS after RES addition. It was followed by Clerafil S^3 Bond and Nova Compo-B Plus. No difference was determined between the Optibond All in One and Clearfil S^3 Bond. There was difference between Optibond All in One and Nova Compo-B Plus ($p < 0.05$).

Conclusion RES addition may improve the biocompatibility without causing negative influence on μTBS of the adhesives.

Clinical relevance RES addition has clinical applicable potential to overcome the adverse biocompatibility of adhesives.

Keywords Adhesive · Antioxidant · Cell viability · Microtensile bond strength · Resveratrol

Introduction

The clinical success of adhesives are related with their physical and chemical properties and the biocompatibility [1]. Antioxidant addition to adhesives has been known to decrease the hydrolysis and degradation caused by free radicals [2]. Thus, the effect of different antioxidants was investigated to protect cells from the cytotoxicity of resin-based materials. Resveratrol (RES) is a polyphenolic antioxidant found in a large variety of foods such as grapes and berries. RES has protective potential against oxidative damage at lower dose wheras it has apoptotic actions at higher dose. Therefore, the dose-dependent profile is a crucial point for the effects of RES in health benefits [3]. RES has been reported to protect oral fibroblasts from reactive oxygen species (ROS)-inducing

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agents [4]. In a previous study that investigated the cytotoxicity induced by adhesives, RES was found to have generally positive effects on cell viability and reduced oxidative stress, ROS production, and DNA damage [5]. The results of the study depicted that RES addition might contribute to the biocompatibility of the adhesives. However, the protective effect of RES against cytotoxicity varied according to the content of the adhesives. This has been attributed to the interaction between RES and the structural components of the adhesives. The effectiveness of adhesive systems is crucial for the clinical success in adhesive dentistry. Therefore, the critical point to achieve clinical applicable potential is to improve the biocompatibility without causing a negative influence on the adhesion properties of the agents. Bond strength tests are known as useful methods to investigate the effect of an experimental procedure on a product or analyze a new product [6]. In addition, microtensile bond strength (μTBS) test is one of the most preferred and advantageous method to examine the strength of dentin adhesive sytems [7].

From this point of view, the aim of this in vitro study is to investigate the effect of RES addition on the cytotoxicity and μTBS of five different one-step, self-etching adhesives. The hypothesis to be tested was that RES addition does not negatively affect the bonding performance of the adhesives.

Methodology

Cell viability test

Five different one-step, self-etching adhesives [G-aenial-Bond (GC), Optibond All in One (Kerr), Gluma Self Etch (Kulzer), Clearfil S^3 Bond (Kuraray), and Nova Compo-B Plus (Imicryl)] were used in the study (Table 1). The adhesives were applied to L-929 mouse fibroblast cells (HUKUK, Foot and Mouth Disease Institute, Animal Cell Culture Collection, Ankara, Turkey) by extract method applied in previous studies [5, 8]. The cells (5×10^3 cells/well) were cultured in medium containing RPMI 1640 (Sigma-Aldrich), 10% fetal bovine serum (Gibco Invitrogen), 1% L-glutamine (Sigma-Aldrich), and 100 units/mL penicillin/streptomycin (Gibco Invitrogen) at 37 °C in 5% CO_2. Then, the cells were exposed to extracts of the adhesives with and without RES addition. For the preparation of the extracts; 5 μL adhesive was dropped in 10 mL vial and shaked gently to provide the diffusion of the drop at the base of the vial (2 cm diameter). Then the light source was kept 2 mm away from the base of vial during curing to simulate the clinical application. The extended polymerization time is assumed for high degree conversion of resin structures [9, 10]; therefore, the adhesive was light cured by LED (Elipar Freelight, 3M ESPE) for 20 s. Then 5 mL medium was added per vial and incubated at 37 °C in 5% CO_2 for 24 h. The incubated extract medium was filtered through a sterile 0.22 μm syringe filter. The extract medium was added to the wells with 1:10 concentration (100 μL extract medium in 1 mL medium). In the experimental groups, RES was added into the medium prior to the adhesive extract exposure. Considering the dose-dependent effect of RES [3] the most effective dose of RES that significantly increased the cell viability [5], 0.5 μM was added. The fresh medium and medium with 0.1 mM H_2O_2 was used as control groups. The layout of the well-plates were constituted randomly. The cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay after 24 h. The absorbance was measured at 570 nm and 630 nm using a microplate reader (VersaMax, Molecular Devices, USA).

μTBS test

The study protocol was approved by the Human Ethical Committee of Ege University (Research no: 16-10.1/1) and

Table 1 The adhesives and product details. Data were provided from manufacturers as declared

Adhesives and Manufacturers	Compositions of Adhesives
G-aenial Bond (GC, Tokyo, Japan)	Distilled water, aceton, dimethacrylate monomers, 4-Methacryloxyethyltrimellitate anhydride (4-MET), phosphoric acid, ester monomer, silicon dioxide, photo initiator
Optibond All in One (Kerr, Scafati, Italy)	Glycerol phosphate dimethacrylate (GPDM), co-monomers including mono- and di-functional methacrylate monomers, HydroxyEthylMethAcrylate (HEMA), water, acetone, ethanol, camphorquinone, silica filler, sodium hexafluorosilicate
Gluma Self Etch (Heraeus Kulzer, Hanau, Germany)	Urethane dimethacrylate (UDMA), 4-META/Acidic monomer, acetone, water, fillers, photoinitiators, stabilizers
Clearfil S^3 Bond (Kuraray, Okayama, Japan)	Bisphenol A diglycidylmethacrylate (bis-GMA), 10-Methacryloyloxydecyl dihydrogen phosphate (MDP), HEMA, dl-Camphorquinone, ethanol, water, colloidal silica
Nova Compo-B Plus (Imicryl, Konya, Turkey)	Hydrophilic aliphatic dimethacrylate, hydrophobic aliphatic dimethacrylates, 2 hydroxyethyl methacrylate, UDMA (urethane dimethactylate), Bis-GMA, MDP monomer (10-Methacryloyloxydecyl dihydrogen phosphate), carboxylated methacrylate polymer, silane, ethanol, water, highly dispersed silicon dioxide (10%), initiators and stabilizers

informed consent was obtained from patients before tooth extraction. Human extracted third molar teeth stored in 0.1% thymol and distiled water were used for the study. The roots of all teeth were removed 2 mm beneath the cemento-enamel junction. Than the occlusal enamel were cut 2 mm above the cemento-enamel junction using a slow-speed water-cooled diamond saw and exposing a flat surface of dentin (Isomet, Buehler; Lake Bluff, IL, USA). The pulpal tissue was removed. The exposed dentin surface was abraded with a 600-grit SiC paper for 60 s under running water to obtain a purely dentin surface and create a standardized smear layer. Prepared teeth were randomly divided into ten groups ($n = 7$).

The adhesives were applied on the flattened dentin surfaces with and without RES addition. The most effective dose of RES (0.5 μM) that significantly increased the cell viability [5] was added into the adhesives before bonding procedure. RES (Sigma-Aldrich, Saint Louis, USA) was added into the bottle of the adhesive at the specified concentration and then homogenized by shaking. RES addition was performed just prior to bonding application in order to prevent the inactivation of the antioxidant. The adhesives were applied according to the manufacturer's instructions and then polymerized with LED light source for 20 s (Elipar Freelight, 3M ESPE, USA).

A composite build up in two layers (each layer 2 mm thick) was constructed with Filtek Z250 (3M ESPE, St. Paul, USA) for each tooth and then each layer polymerized with LED light source for 40 s. The teeth were stored in distiled water for 24 h at 37 °C. Matchsticks ($1.00 \pm 0.003 \times 1.00 \pm 0.003$ mm^2) were obtained from each tooth by sectioning the bonded teeth. The central matchsticks were evaluated and periphery matchsticks including enamel were eliminated. Twenty central matchsticks selected randomly were tested for each group. The matchsticks were fixed to a jig using a cyanoacrylate adhesive and tested to microtensile forces in a microtensile testing machine (Microtensile Tester, BISCO, Inc., Schaumburg, IL, USA) at 1.0 mm/min. The exact cross-sectional area was measured after failure with a digital caliper. The microtensile bond strengths (μTBS) of the sticks from the same bonded tooth were averaged and used for the statistical analysis. Means and standard deviations were calculated and expressed in MPa.

The specimen surfaces were evaluated under a stereomicroscope (LG-P52, Olympus Co, Tokyo, Japan) at × 50 magnification to determine the apparent failure modes. The failures were classified as adhesive (interfacial failure), cohesive in dentin, cohesive in resin, and mix.

IBM SPSS was used for the statistical analysis. The variables were summarized by means of mean ± standard deviation. Statistical analysis was performed by analysis of variance (ANOVA) and followed by post hoc Tukey test for the comparison between the groups ($p < 0.05$).

Results

The MTT assay results are presented in Table 2. The tested adhesives caused reduction in cell viability, although not as much as hydrogen peroxide. The lowest cell viability was observed in the G-aenial Bond and Optibond All in One groups and the highest cell viability was observed in the Gluma Self Etch, Nova Compo-B Plus, and Clerafil S^3 Bond groups. After the RES addition, cell viability was increased in all groups.

The mean μTBS values of the groups are presented in Table 3. Among the groups without RES addition, the highest μTBS values were determined in Optibond All in One Clearfil S^3 Bond and Nova Compo-B Plus, while the lowest values were obtained in G-aenial Bond and Gluma Self Etch. No significant differences were found between the μTBS values of G-aenial Bond and Gluma Self Etch. RES addition did not cause reduction in the μTBS values of adhesives. The highest μTBS values were also determined in Optibond All in One, Clearfil S^3 Bond, and Nova Compo-B Plus after RES addition.

The fracture modes of the groups are shown in Fig. 1. The adhesive failure was the most frequent pattern of failure for all test groups.

Discussion

In this in vitro study, the effect of RES addition on the cytotoxicity and μTBS of the adhesives was investigated. RES is a food-derived antioxidant existing in grapes, berries, nuts, and red wine [11, 12]. This polyphenolic compound has been reported to have chemopreventive, cardioprotective, and

Table 2 Cell viability (%) (mean ± SD). The different superscripts indicate statistical difference ($p < 0.05$)

	RES addition	Mean ± SD
Control	(−)	99.92 ± 8.78^{a}
	(+)	131.75 ± 16.69^{d}
H_2O_2	(−)	58.69 ± 7.52^{b}
	(+)	128.49 ± 14.82^{d}
G-aenial Bond	(−)	78.11 ± 0.88^{c}
	(+)	124.12 ± 17.07^{d}
Optibond All in One	(−)	79.38 ± 4.30^{c}
	(+)	116.56 ± 12.70^{d}
Gluma Self Etch	(−)	$84.60 \pm 5.06^{a,c}$
	(+)	120.91 ± 12.47^{d}
Cleafil S^3 Bond	(−)	$88.58 \pm 5.31^{a,c}$
	(+)	116.64 ± 13.53^{d}
Nova Compo-B Plus	(−)	$87.78 \pm 7.66^{a,c}$
	(+)	118.32 ± 11.98^{d}

Table 3 μTBS values (mean ± SD) in MPa. The different superscripts indicate statistical difference ($p < 0.05$)

	RES Addition	Mean ± SD
G-aenial Bond	(−)	13.42 ± 3.41[a]
	(+)	17.18 ± 6.31[a]
Optibond All in One	(−)	31.90 ± 9.33[b]
	(+)	33.85 ± 11.25[b]
Gluma Self Etch	(−)	16.68 ± 4.85[a]
	(+)	14.90 ± 5.76[a]
Cleafil S^3 Bond	(−)	30.23 ± 11.00[b,c]
	(+)	27.41 ± 7.22[b,c]
Nova Compo B-Plus	(−)	23.47 ± 8.37[c]
	(+)	26.11 ± 5.78[c]

neuroprotective effects [13–15]. RES is an antioxidant which has also potential positive effects on adhesive biocompatibility [5]. In the current study, based on the previous findings, RES was added into different self-etching adhesives in order to improve their biocompatibility without causing any negative effect on their adhesive potentials. The results indicated that RES addition increased cell viability in L929 cell culture exposed to adhesive extracts and furthermore RES addition did not cause any negative influence on the μTBS of the tested adhesives.

The monomers such as Bis-GMA and UDMA have been reported to have more cytotoxicity compared to TEG-DMA and HEMA [16–18]. In this in vitro study, the cytotoxicity of adhesives including different monomer combinations was investigated instead of the analysis of a single monomer. The least cytotoxic effect was depicted in Bis-GMA and UDMA incorporated adhesives. The adhesives including HEMA showed different cell viabilty rates in different monomer combinations. These results suggest that adhesives may exhibit cytotoxic effects more or less than the monomer alone, consistent with the previous report [19].

The antioxidants have been reported to protect cells against cytotoxicity caused by resin-based materials [20, 21]. In accordance with previous reports, in this study, it was determined that RES, a strong antioxidant increased the cell viability. On the other hand, the innovative aspect of this study is that the analysis was not limited to cytotoxicity test alone, and μTBS test was also applied to determine the effect of RES addition on the bonding performance of the materials.

The μTBS values obtained in this study were consistent with the previous reports [22–25]. However, there were differences between the groups considering the adhesive type as variable. The variability between the performances of the different self-etch adhesives may be attributed to their different functional monomers (Table 1). Optibond All in One, Clearfil S^3 Bond, and Nova Compo-B Plus including hydroxyethyl methacrylate (HEMA) had the highest μTBS values with or without RES addition among the all groups. The remarkably lower μTBS values were depicted in G-aenial Bond including HEMA-free formulation and Gluma Self Etch including urethane dimethacrylate (UDMA). These findings support that the absence of HEMA leads to the contact of water with hydrophobic groups and creates unfavorable condition causing water separation [25].

The monomer 10-methacryloxydecyl dihydrogen phosphate (10-MDP) has been reported to be stable due to the adherence to hydroxyapatite [25, 26]. The higher μTBS values of Clearfil S^3 Bond and Nova Compo-B Plus in this study may be correlated with 10-MDP content of the materials consistent with a previous report [25]. On the other hand, the bonding potential of 4-methacryloxyethyl trimellitic acid (4-MET) was noticed to be lower [26]. In accordance with the previous findings, G-aenial Bond including 4-MET showed lower μTBS values. Furthermore, the rapid convertion potential of 4-META to 4-MET has been reported [27]. Thus, the lower μTBS values of Gluma Self Etch may also related with 4-META content.

It is known that some special antioxidants are added into dental adhesives to eliminate the free radicals and inhibit spontaneous polymerization [28]. Antioxidants have also been reported to reduce hydrolysis [2]. In a previous study, the antioxidants vitamin C, vitamin E and quercetin were

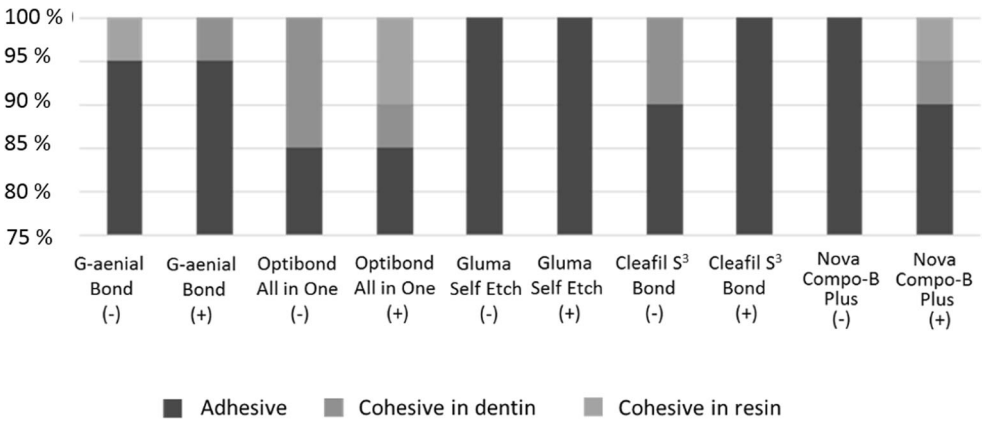

Fig. 1 The fracture modes of the tested groups

added into dentin adhesives and the bond strengths of the antioxidant-doped adhesives were determined to be maintained or increased over the time [29]. It has been reported that ascorbic acid and ferric chloride might improve the microtensile bond strength between resin and dentin [30]. In the present study, RES a potential protective agent against cytotoxicity, was used as antioxidant. RES addition did not cause any adverse effect on μTBS of the adhesives and adhesive performances were determined to be maintained after antioxidant addition, where this finding was consistent with the previous antioxidant reports. Although RES addition into the adhesives did not cause statistically significant differences regarding the μTBS values, it caused an upward trend in μTBS values of G-aenial Bond, Optibond All in One, and Nova Compo-B Plus. On the contrary, it induced tendency to decrease in μTBS values of Gluma Self Etch and Clearfil S^3 Bond. Although Optibond All in One, Clearfil S^3 Bond, and Nova Compo-B Plus include HEMA, the tendency to decrease in μTBS values was remarkable in Clearfil S^3 Bond after RES addition. This finding suggests that the interaction of RES with different combinations of monomers may cause diverse effects. On the other hand, it is also noteworthy that despite the tendency to decrease, the bonding strength of Clearfil S^3 Bond after RES addition was higher compared to the G-aenial Bond and Gluma Self Etch.

In this study, the μTBS of the specimens were investigated 24 h later without any aging procedure, as we could not predict how RES addition would affect the performance of the adhesives. However, it has been reported that aging procedure is of great importance since it may affect the initial bond strength in the long term [29]. Therefore, further studies are necessary to determine the long-term effect of RES addition on μTBS of adhesives. The diffusion of monomers into the dentin and polymerization of the diffused monomer are the key points for adhesion. The antioxidants may display further reaction with degradation products after the initial polymerization and this reaction has the potential to increase the bond strength in long term [29]. But the realization of this potential needs to be investigated for RES addition.

Different antioxidants were tested to restore dentin bond strength after dental bleaching in previous studies. Vitamins C and E have been reported to improve dentin bond strength after dental bleaching, as they reduce oxidative compounds and free radicals [31, 32]. Considering the results of this study, the investigation of the effect of RES on bleached enamel may be recommended for further studies. The adhesives included in this study have different monomers with different diffusion properties. The bond strength of adhesives might be dependent on both chemical composition and pH of adhesives [22]. Therefore, pH measurement may be included in further studies to obtain more evidence about the effect of RES addition on adhesive durability.

Conclusion

Within the limitation of this in vitro study, it can be concluded that the addition of RES, a polyphenolic antioxidant, to adhesives increases the cell viability and it does not adversely affect the dentin μTBS strength. Thus, RES seems to have a potential to improve the biocompatibility without causing any adverse effect on the adhesive properties of the material. But, further studies are necessary to investigate the stability of adhesives after RES addition for further understanding.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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