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Effects of resveratrol-enriched endodontic sealants on pulp stem cell viability and collagen production

Pedro Antunes Teixeira[1], Cláudia Fernandes de Magalhães Silveira[1], Alexandre Sigrist de Martin[1], Carlos E Bueno[1], João P Rangel-Coelho[2], Elizabeth Ferreira Martinez[2]

1. Departamento de Endodontia, Faculdade São Leopoldo Mandic, Campinas, SP, Brasil
2. Departamento de Biologia Celular, Faculdade São Leopoldo Mandic, Campinas, SP, Brasil

ABSTRACT

Root canal sealers should provide effective sealing while remaining biocompatible with periapical tissues. Strategies to further improve their biological performance are desirable. Resveratrol, a bioactive polyphenol with antioxidant and regenerative properties, may enhance cellular responses and tissue repair, representing a promising adjunct for endodontic materials. ***Aim:*** *The aim of this study was to evaluate cell viability and type I collagen expression in undifferentiated mesenchymal stem cell cultures exposed to EndoSequence BC bioceramic or AH Plus resin-based endodontic cements, with or without the addition of resveratrol.* ***Materials and Method:*** *Cement specimens were prepared in standardized molds (5 mm × 2 mm), allowed to set for 48 hours, sterilized, and conditioned in culture medium at a concentration of 0.2 g/mL at 37 °C. Resveratrol was added to the culture media at concentrations of 0.25 µM and 0.5 µM. The mesenchymal cell cultures were exposed to the different experimental conditions for 24, 48 and 72 hours, after which viability was assessed by MTT assay, and type I collagen secretion was quantified using the enzyme-linked immunosorbent assay (ELISA).* ***Results:*** *EndoSequence BC demonstrated significantly greater cell viability than AH Plus ($p<0.05$). At 48 hours, AH Plus combined with 0.5 µM resveratrol showed significantly greater cell viability than the cement alone and the 0.25 µM resveratrol group ($p<0.05$). In addition, supplementation with 0.5 µM resveratrol significantly increased type I collagen secretion for both cements compared to the corresponding groups without resveratrol ($p<0.05$), indicating a positive effect on extracellular matrix production.* ***Conclusions:*** *These findings suggest that resveratrol is a promising additive for improving the bioactivity of endodontic cements, enhancing collagen production and potentially contributing to tissue regeneration and bone repair.*

Keywords: *bioceramic cement - resveratrol - mesenchymal stem cells - collagen*

Efeitos de selantes endodônticos enriquecidos com resveratrol sobre a viabilidade de células-tronco pulpares e a produção de colágeno

RESUMO

Os cimentos endodônticos devem proporcionar um selamento eficaz, mantendo a biocompatibilidade com os tecidos periapicais. Estratégias para melhorar ainda mais seu desempenho biológico são desejáveis. O resveratrol, um polifenol bioativo com propriedades antioxidantes e regenerativas, pode potencializar as respostas celulares e o reparo tecidual, representando um adjuvante promissor para materiais endodônticos. ***Objetivo:*** *Este estudo teve como objetivo avaliar a viabilidade celular e a expressão de colágeno tipo I em culturas de células-tronco mesenquimais indiferenciadas expostas aos cimentos endodônticos biocerâmico EndoSequence BC e resinoso AH Plus, com ou sem a adição de resveratrol.* ***Materiais e Método:*** *Os cimentos foram preparados em moldes padronizados (5 mm × 2 mm), mantidos para presa por 48 horas, esterilizados e condicionados em meio de cultura na concentração de 0,2 g/mL a 37°C. O resveratrol foi adicionado ao meio de cultura nas concentrações de 0,25 µM e 0,5 µM. A viabilidade celular foi avaliada pelo ensaio de MTT após a exposição às diferentes condições experimentais, e a secreção de colágeno tipo I foi quantificada por meio do ensaio imunoenzimático (ELISA).* ***Resultados:*** *O EndoSequence BC apresentou viabilidade celular significativamente maior que o AH Plus ($p<0,05$). Em 48 horas, o AH Plus combinado com 0,5 µM de resveratrol apresentou viabilidade celular significativamente maior do que o cimento isolado e do que o grupo com 0,25 µM de resveratrol ($p<0,05$). Além disso, a suplementação com 0,5 µM de resveratrol aumentou significativamente a secreção de colágeno tipo I para ambos os cimentos em comparação com os respectivos grupos sem resveratrol ($p<0,05$), indicando um efeito positivo na produção da matriz extracelular.* ***Conclusões:*** *Esses achados sugerem que o resveratrol é um aditivo promissor para melhorar a bioatividade dos cimentos endodônticos, aumentando a produção de colágeno e potencialmente contribuindo para a regeneração tecidual e o reparo ósseo.*

Palavras-chave: *cimento biocerâmico - resveratrol - células tronco mesenquimais - colágeno*

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Corresponding Author:
João Pedro Rangel-Coelho
rangelcoelhojp@gmail.com

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INTRODUCTION

During endodontic treatment, the root canal system is disinfected chemically and mechanically, and then filled to ensure adequate seal[1]. Properly performed endodontic treatment effectively reduces the bacterial load, thereby minimizing the risk of periapical lesions[2]. Periapical lesions of endodontic origin arise from an inflammatory response to microorganisms located around the root and within the root canal[3].

The most frequently used materials for root canal obturation are gutta-percha and root canal cements[4,5]. These materials must have dimensional stability, biocompatibility, and favorable handling properties[6]. An ideal root canal filling material should promote periradicular tissue regeneration, including cementogenesis on its surface, ensure an adequate seal, and be well tolerated by periapical tissues[7,8].

During conventional restorative techniques, vertical compression may cause extrusion of small amounts of restorative cement through the apical foramen and/or secondary canals into the surrounding tissues[9], harming periapical tissues and inducing inflammation[10]. Although extrusion generally does not compromise the success of endodontic treatment, it may delay the repair process[9]. Moreover, even in the absence of extrusion, these materials may release soluble substances that can be toxic to periapical tissues, affecting local bone metabolism and the healing process. It is therefore important that these cements should be highly biocompatible and not cause adverse or contact reactions in biological tissues[11].

A wide range of endodontic cement compositions is available for root canal obturation, including zinc oxide-eugenol, epoxy resin, and calcium silicate-based sealants[12-14]. Resin-based or resin-containing sealants and cements are often cytotoxic to various cell subpopulations[15]. In contrast, calcium silicate-based cements are characterized by adequate biocompatibility and bioactive properties, demonstrating non-cytotoxic behavior when in contact with periradicular tissues[16]. These cements promote the formation of a hydroxyapatite layer on their surface[17], which facilitates the creation of a mineral bond with dentin tissue[18].

AH Plus (De Trey-Dentsply, Konstanz, Germany) is an epoxy resin-based cement, widely recognized as the gold standard among endodontic cements due to its excellent physicochemical properties, despite lacking bioactive potential[16]. Endosequence BC Sealer (BCS) cement (Brasseler USA, Savannah, GA, USA) is a ready-to-use, premixed, injectable calcium silicate-based material designed for root canal filling and sealing[19], which has good physicochemical properties and cures in moist environments such as dentin tubules[20]. Resveratrol (trans-3,4,5-trihydroxystilbene) is a dietary antioxidant polyphenol found in various plants, including grapes, red wine, fruits, and peanuts. Over recent decades, it has gained significant attention for its potential to promote health and combat disease[21,22]. Resveratrol prevents ofatherosclerosis[22], and has cardioprotective and neuroprotective effects, as well as anticarcinogenic, antioxidant and photoprotective properties[22–24]. It also enhances collagen production which, in combination with its antioxidant effects, protects cells from oxidative damage caused by free radicals. The aim of this study was to evaluate cell viability and type 1 collagen secretion by adult mesenchymal stem cells exposed to an epoxy resin-based restorative cement and a bioceramic cement, both with and without the addition of resveratrol at different concentrations, at different time points.

MATERIALS AND METHOD

Undifferentiated mesenchymal cell culture

Immortalized stem cells derived from dental pulp were obtained from Lonza (USA, catalog #PT-5025). The cells were thawed and cultured in a growth medium composed of α-MEM supplemented with 10% fetal bovine serum (Gibco, USA), 50 µg/mL gentamicin, and 0.3 µg/mL fungizone. Cultures were maintained at 37 °C in a humidified atmosphere with 5% CO_2 and 95% atmospheric air. The medium was replaced three times per week. Upon reaching subconfluence, the culture medium was removed, and a solution containing 0.25% trypsin (Gibco, USA), 1.3 mg/mL type II collagenase (Gibco, USA), and 1 mM EDTA (Gibco, USA) was added to obtain a cell suspension for the subsequent experiments.

Experimental groups

The materials tested in this study were: EndoSequence BC Sealer (Brasseler, Savannah, Georgia, USA), AH Plus (De trey- Dentsply, Konstanz, Germany) and Resveratrol ≥ 99% (Sigma-Aldrich, St. Louis, MO, USA).

Cement specimens were prepared under aseptic conditions according to the manufacturer's instructions in compliance with ISO 10993-12 standards in inert silicone molds measuring 5 mm in diameter and 2 mm in height. They were placed in an oven for 48 hours to set, sterilized with ultraviolet light for 15 minutes[15], and stored in the culture medium to obtain eluates for the subsequent experiments.

Eluates were prepared following the ISO 10993-12 (International Organization for Standardization) guidelines, using a proportion of 0.2 g/mL by placing each cement specimen in a polypropylene tube (Eppendorf, Hauppauge, NY, USA) containing 1 mL of Dulbecco's Modified Eagle's Medium (DMEM, Nutricell Nutrientes Celulares, Campinas, SP, Brazil), and inclubating at 37°C for 24 hours in a humidified atmosphere with 5% CO_2 and 95% atmospheric air. After incubation, the culture medium was collected, filtered through a 0.22 µm filter, aliquoted, and stored at 4 °C. All experiments were performed in three independent biological replicates, with each condition analyzed in technical triplicate.

Resveratrol was dissolved in 1% dimethyl sulfoxide (DMSO) and added to the eluate at concentrations of 0.25 µM and 0.5 µM. The experimental groups consisted of eluates obtained from:

- EndoSequence BC Sealer (ES),
- EndoSequence BC Sealer supplemented with 0.25 µM resveratrol (ES+R0.25 µM),
- EndoSequence BC Sealer supplemented with 0.5 µM resveratrol (ES+R0.50 µM),
- AH Plus (AH),
- AH Plus supplemented with 0.25 µM resveratrol (AH+R0.25 µM), and
- AH Plus supplemented with 0.5 µM resveratrol (AH+R0.50 µM).

All groups were compared to a negative control group, which consisted of culture medium without the addition of resveratrol or cement eluates.

Cell viability assay

Cell cultures were seeded in 96-well polystyrene plates at a density of 110 cells/mm² and exposed to the prepared eluates. An MTT assay was conducted at 24, 48 and 72 hours after cell plating. Briefly, 10 µL of MTT solution (5 mg/mL; Sigma, USA) diluted in serum-free DMEM culture medium was added to the treated cultures, and incubated at 37 ºC for 3 hours. Following incubation, 100 µL of a 10% dimethyl sulfoxide (DMSO; LGC, São Paulo, Brazil) solution was added to solubilize the formazan crystals. Quantification was performed using an ELX800 microplate reader (Epoch Biotek Instruments, Inc.) at a wavelength of 590 nm to determine the optical density (OD) values.

Enzymatic immunoassay for type I collagen quantification (ELISA)

Cell cultures were seeded in 96-well polystyrene plates at a density of 110 cells/mm² and exposed to the prepared eluates. At 24, 48, and 72 hours, the culture supernatant was aspirated and centrifuged at 5000 × g for 15 minutes at 4 °C. Aliquots of each supernatant were analyzed according to the manufacturer's protocol (R&D Systems, USA) to determine type I collagen secretion by cells cultured under different conditions.

The reaction was finalized by adding 50 µL of 2N sulfuric acid (H_2SO_4) to the substrate solution in each well, and the resulting color intensity was measured using a spectrophotometer (Epoch, Biotek, Winooski, VT, USA) at a wavelength of 450 nm. Protein concentrations were expressed in picograms per milliliter (pg/mL).

Statistical analysis

Descriptive and exploratory analyses were initially conducted on the dataset. Variables were summarized using means, standard deviations, medians, and minimum and maximum values. Since the data did not satisfy the assumptions required for classical analysis of variance (ANOVA), generalized linear mixed models were employed to account for repeated measures over time. All statistical analyses were performed using R software, with significance level set at 5%.

RESULTS

The results of cell viability after exposure to the different eluates are presented in Table 1. When comparing the cements alone, EndoSequence cement displayed significantly higher cell viability than AH Plus at all evaluated time points (p<0.05). For EndoSequence cement, no significant increase in cell viability was observed when associated with resveratrol at either concentration compared to the cement alone (p<0.05).

In contrast, for AH Plus cement, no significant

Table 1. Quantification of cell viability (MTT) at different conditions. Data presented as mean (standard deviation) and median (minimum and maximum value) expressed in Arbitrary Units (AU).

Group	Time (hours)					
	24		48		72	
	Mean (standard deviation)	Median (minimum and maximum value)	Mean (standard deviation)	Median (minimum and maximum value)	Mean (standard deviation)	Median (minimum and maximum value)
Control	0.633 (0.052) Ba	0.608 (0.599; 0.693)	0.629 (0.070) Ba	0.662 (0.549; 0.677)	0.846 (0.042) Aa	0.836 (0.810; 0.892)
ES	0.600 (0.087) Aa	0.572 (0.530; 0.698)	0.528 (0.100) Aa	0.567 (0.414; 0.602)	0.569 (0.077) Ab	0.596 (0.483; 0.629)
ES+R0.25μM	0.457 (0.033) Bb	0.474 (0.419; 0,477)	0.588 (0.054) Aa	0.599 (0.529; 0.635)	0.628 (0.057) Ab	0.656 (0.562; 0.665)
ES+R0.5μM	0.434 (0.029) Bbc	0.425 (0.41; 0.466)	0.599 (0.012) Aa	0.594 (0.590; 0.612)	0.523 (0.015) ABb	0.517 (0.513; 0.540)
AH	0.365 (0.035) Ac	0.377 (0.325; 0.392)	0.364 (0.070) Ab	0.334 (0.314; 0.444)	0.395 (0.066) Ac	0.365 (0.350; 0.471)
AH+R0.25μM	0.434 (0.082) Abc	0.480 (0.340; 0.483)	0.345 (0.019) Bb	0.347 (0.326; 0.363)	0.281 (0.022) Cd	0.272 (0.266; 0.306)
AH+R0.5μM	0.611 (0.063) Aa	0.586 (0.564; 0.683)	0.627 (0.067) Aa	0.643 (0.554; 0.685)	0.534 (0.082) Ab	0.537 (0.451; 0.615)

Caption: p(group) < 0.0001; p(time)= 0.7913; p(interaction) < 0.0001. Different letters (uppercase horizontally and lowercase vertically) indicate statistically significant differences ($p < 0.05$); ES: Endo Sequence; AH: AH Plus; R: Resveratrol; Control: culture medium without resveratrol or cement eluates.

increase in cell viability was observed at 24 hours when associated with resveratrol at either concentration compared to the cement alone. At 72 hours, the AH+R0.25 μM group showed lower cell viability than the cement-only group. At 48 hours, however, a significant increase in cell viability was observed when AH Plus was combined with resveratrol at a concentration of 0.5 μM, compared to either the cement alone or the lower concentration of resveratrol.

The results of collagen I secretion are presented in Table 2. Significantly higher levels of collagen I expression were observed when cells were cultured on basal medium without resveratrol or cement eluates (control) compared to all other groups (p<0.05).

For both cements, the incorporation of resveratrol at a concentration of 0.5 μM resulted in significantly higher levels of collagen I secretion compared to the absence of the polyphenol (p<0.05) across all evaluated time points.

Table 2. Quantification of type I collagen secreted by undifferentiated mesenchymal cell culture under different conditions. Data presented as mean (standard deviation) and median (minimum and maximum value) expressed in pg/ml.

Group	Time (hours)					
	24		48		72	
	Mean (standard deviation)	Median (minimum and maximum value)	Mean (standard deviation)	Median (minimum and maximum value)	Mean (standard deviation)	Median (minimum and maximum value)
Control	1532.085 (265.612) Aa	1537.323 (1263.893; 1795.039)	1849.156 (434.385) Aa	2099.897 (1347.572; 2100.000)	1730.348 (276.842) Aa	1573.073 (1567.966; 2050.004)
ES	255.032 (30.296) Bc	271.532 (220.068; 273.496)	166.519 (83.566) Ccd	120.928 (115.664; 262.964)	453.272 (64.915) Ac	428.676 (404.249; 526.89)
ES+R0.25μM	335.306 (43.44) Ac	321.818 (300.211; 383.890)	194.27 (19.287) Bc	188.639 (178.425; 215.746)	415.413 (52.232) Ac	387.425 (383.139; 475.675)
ES+R0.5μM	495.331 (52.217) Ab	504.104 (439.283; 542.605)	509.343 (86.376) Ab	489.569 (434.568; 603.891)	600.617 (109.376) Ab	643.962 (476.212; 681.677)
AH	190.975 (15.517) Ad	182.332 (181.703; 208.889)	193.179 (28.348) Ac	209.086 (160.450; 210.000)	194.836 (10.881) Ad	198.164 (182.68; 203.664)
AH+R0.25μM	124.865 (11.211) Be	124.21 (113.996; 136.389)	143.722 (29.755) Bd	128.139 (124.996; 178.032)	239.27 (32.171) Ad	242.674 (205.532; 269.603)
AH+R0.5μM	443.485 (34.097) Bb	430.64 (417.676; 482.139)	415.413 (47.69) Bb	409.853 (370.746; 465.639)	594.449 (36.233) Ab	578.211 (569.175; 635.961)

Caption: p(group) < 0.0001; p(time) < 0.0001; p(interaction) < 0.0001; Different letters (uppercase horizontally and lowercase vertically) indicate statistically significant differences (p<0.05); ES: Endo Sequence; AH: AH Plus; R: Resveratrol; Control: culture medium without resveratrol or cement eluates.

DISCUSSION

This study investigated the viability and type I collagen expression of undifferentiated mesenchymal cells following exposure to EndoSequence BC bioceramic cement and AH Plus resin-based cement, with and without the incorporation of resveratrol at varying concentrations and exposure times.

The findings revealed that EndoSequence cement consistently promoted greater cell viability than AH Plus across all evaluated time points. For EndoSequence cement, the addition of resveratrol at different concentrations did not enhance cell viability relative to the cement alone. For AH Plus, the addition of resveratrol did not improve cell viability at 24 hours compared with the cement alone. At 72 hours, the lower concentration of resveratrol (0.25 μM) resulted in reduced cell viability, whereas the higher concentration (0.5 μM) improved cell viability. Notably, at 48 hours, the association of AH Plus with 0.5 μM resveratrol resulted in significantly higher cell viability compared to the cement alone or to the lower resveratrol concentration.

The potential toxicity of restorative materials has been a key concern in endodontic research since they were first used in 1962[8]. *In vitro* studies have demonstrated that materials exhibiting high toxicity in cell cultures are likely to exhibit similar toxicity when in contact with living tissues[25]. This makes *in vitro* testing a crucial step in assessing biocompatibility and cytotoxicity, providing essential information before progressing to *in vivo* evaluations.

Endodontic cements used during the obturation phase have biological properties that can influence their cytotoxicity and potential for leakage through the apical and secondary foramina during root canal treatment. Such leakage can vary in amount and may harm periapical tissues, potentially causing inflammation[10,13]. Therefore, these cements must have adequate biocompatibility, i.e., they should not elicit adverse reactions or undesirable responses from the surrounding biological tissues[14].

In the present study, the comparison between the isolated cements revealed consistently lower cell viability in cells exposed to AH Plus cement compared to EndoSequence BC Sealer at all evaluated time points. These findings are consistent with previous studies reporting greater biocompatibility and bioactivity of EndoSequence BC Sealer than AH Plus[15,26]. This behavior may be related to the calcium ion release and alkaline pH promoted by EndoSequence BC Sealer[20,27], which foster cell viability and mineralization potential[28]. In contrast, the lower cell viability observed for AH Plus may be associated with the release of residual cytotoxic components, including trace amounts of formaldehyde and unreacted resin compounds, even after setting[29].

For EndoSequence cement, different concentrations of resveratrol did not increase cell viability. Although previous studies have found EndoSequence BC Sealer to have lower cytotoxicity and genotoxicity than AH Plus, the present findings suggest that the addition of resveratrol did not further enhance the already favorable biological behavior of the bioceramic sealer under the evaluated conditions[30]. Moreover, other studies have shown that resin-based or resin-containing cements such as AH Plus often exert cytotoxic effects on various cell subpopulations[15]. In contrast, calcium silicate-based cements, including EndoSequence, are generally recognized for their adequate biocompatibility and bioactive properties, with no cytotoxicity when in contact with periradicular tissues. This discrepancy highlights the complex interactions between cement composition, experimental conditions, and cellular responses[16].

The results for AH Plus cement showed that the addition of resveratrol did not increase cell viability at 24 hours compared to the cement alone. At 72 hours, the lower concentration of resveratrol (0.25 μM) resulted in reduced cell viability, whereas the higher concentration (0.5 μM) improved cell viability. Notably, at 48 hours, the addition of 0.5 μM resveratrol significantly enhanced cell viability compared to the cement alone or to the lower resveratrol concentration. These findings suggest that the association of resveratrol with AH Plus may promote cell viability in a concentration-dependent manner, particularly at 0.5 μM.

The expression of type I collagen was also evaluated in undifferentiated mesenchymal cells after exposure to EndoSequence BC bioceramic filling cement and AH Plus resin-based cement. Type I collagen is a key structural protein in the extracellular matrix of bone tissue and serves as a chemotactic agent for critical repair cells. It plays a fundamental role in bone tissue formation and is a significant marker indicating the initiation of the mineralization phase[31,32]. The results showed significantly higher

levels of collagen I expression when cells were cultured on basal medium without resveratrol or cement eluates (control) compared to all other groups. For both cements, the incorporation of 0.5 μM resveratrol consistently resulted in increased collagen I secretion compared to the cements without the polyphenol at all evaluated time points. Resveratrol exhibits an affinity for estrogenic protein receptors found on fibroblasts and macrophages, which are key cells involved in the production of type I and type II collagen[33]. By interacting with these receptors, resveratrol may enhance their activity, thereby promoting the synthesis of these collagen types.

CONCLUSIONS

Based on the findings for cell viability and type I collagen secretion, it can be concluded that incorporating resveratrol into the tested cements enhanced type I collagen production without adversely affecting their cytotoxicity. However, as this is an *in vitro* study, certain limitations must be acknowledged, particularly regarding the extrapolation of these results to clinical practice. Despite being conducted on isolated cells, this study provides promising insights into improving type I collagen production, which may support bone repair in periapical lesions and potentially reduce the cytotoxicity of the evaluated endodontic cements.

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CONFLICT OF INTEREST

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