

6 - Potential of Epigallocatechin-3-gallate as Chelating Agent against Matrix Metalloproteinase Expression and as Cross-Linking Agent Towards Hybrid Layer in Dentin Collagen: A Review

By Kun Ismiyatin

REVIEW ARTICLE

Potential of Epigallocatechin-3-gallate as Chelating Agent against Matrix Metalloproteinase Expression and as Cross-Linking Agent Towards Hybrid Layer in Dentin Collagen: A Review

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ABSTRACT

Adhesive dentistry's main assumption is to create a strong chemical bond between dental hard tissues and restorative composite material. One of the most important aspects of this interface is the hybrid layer. Unfortunately, due to physical and chemical causes, the hybrid layer wears away with time. Epigallocatechin-3-gallate (EGCG), a component extracted from green tea, has several roles in the medical and dentistry field including as a crosslinking agent and as a chelating agent. Although there are several negative results, EGCG was proven to be able to preserve resin-dentin bonds without harming the restoration. As a crosslinking agent and chelating agent, EGCG has the potential to enhance the physical properties of dentin collagen and resin-dentin adhesion. The purpose of this study was to see how EGCG, as a cross-linking agent, affected dentinal collagen and hybrid layers, as well as how chelating chemicals affected Matrix metalloproteinase (MMPs).

Keywords: Epigallocatechin-3-gallate (EGCG), Matrix metalloproteinase (MMPs), Crosslink, Chelating, Collagen

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INTRODUCTION

The adhesive system is one of the most revolutionary breakthroughs in the field of conservative dentistry. This system creates minimally invasive restorations that require minimal preparation (1). Du (2) reported that resin adhesion to dentin had high bond strength immediately after application, but decreased by 50-60% after 1-2 years. To avoid the decrease of bond strength, a hybrid layer that is strong, stable, and has high durability is required. A hybrid layer is a layer formed from resin monomers that infiltrate demineralized intratubular, intertubular, and extra tubular collagen fibrils (3,4). Several factors that affect the quality of the hybrid layer, one of which is enzyme that involve in the demineralization of dentin collagen is Matrix metalloproteinase (MMP) on odontoblasts (1,3). MMP must be prevented for increasing the resin-dentin adhesion. The dentine resin attachment mechanism is a physical-mechanical attachment and a chemical reaction between the dentin bonding material and the collagen on the dentin surface. A stable bond can be achieved between the restorative material and the

teeth (5). Dentin also contains water which can cause degradation of resin components, to increase resin-dentin adhesion, prevent water molecular retention are needed, thereby increasing collagen integrity, preventing resin degradation, and strengthening hybrid layer formation (6).

Epigallocatechin-3-gallate (EGCG) is one of the catechins with the highest percentage in green tea extract (49%), has a high affinity for metal ions which can inhibit the action of the enzyme (MMP) through the chelating process and increase the integrity and stability of collagen so it can increase the adhesion strength of the hybrid layer (2). Another research stated by Albuquerque (7) that the application of EGCG can increase the resistance of dentin-bonding attachments within 2 years. As a cross-linking agent, EGCG is also able to replace water molecules in the collagen bond chain by hydrogen bonding with the collagen peptide chain which can reduce collagen interaction with water so that collagen becomes more hydrophobic (8). Thus the monomer can better infiltrate the collagen fibrils and prevent water absorption to increase the monomer-dentin bond (9).

EGCG can also have a negative effect when mixed with adhesives at a certain concentration. Yu (10) stated that

the antioxidant effect of EGCG can change the degree of adhesive conversion. From the research results, it appears that the higher the concentration of EGCG used in the mixture, the lower the degree of conversion of the adhesive. This was confirmed by Du (2) who reported that giving 100-300 µg / mL of EGCG into the adhesive can cause EGCG to be trapped in the polymer linear chain after the irradiation process which causes the adhesive polymerization to be inadequate. This is because the anti-free radical properties of EGCG can interfere with the free radical polymerization process of the adhesive so that research is needed to find the right EGCG concentration.

Even though it has quite a lot of therapeutic effects, until now EGCG materials in the field of dentistry are still minimal. This literature study discusses the potential of EGCG as a cross-linking agent against dentine collagen and hybrid layer and chelating agent against MMPs.

DENTIN

Dentin is a layer of tooth structure underneath the enamel. This layer consists of 65% inorganic components in the form of hydroxyapatite crystals, 30% organic components in the form of collagen, and 5% water (11). The extracellular matrix of the dentin is made up of a complex three-dimensional network of collagen fibrils calcified by nanoapatite crystals. A central triple-helix area, a non-helical aminoterminal area (N-telopeptide), and a carboxy-terminal area make up the collagen chain (C-telopeptide). The length of the collagen fibrils looks to have a hollow of 15-20 nm, which the resin monomer will penetrate and polymerize under 150,000-fold magnification. The mechanical retention of dentin adhering to collagen is the result of this situation (3,12). Collagen chains in the dentin are the most stable collagen compared to collagen in the body system (13). This is due to intramolecular and intermolecular cross-links formed by covalent connections between the C terminal on one collagen molecule and the N terminal on the collagen molecule next to it. By linking the spaces between collagen molecules that are filled with water, hydrogen bonds help to stabilize the triple-helical chain (4). This crosslink plays a role in the acid etching process during the bonding procedure and prevents collagen denaturation so that a hybrid layer can be formed (3).

Elasticity, hardness, visco-elasticity, and fracture coefficient are all mechanical properties of teeth. When exposed to external forces, visco-elasticity is used to measure materials with viscous and elastic properties. The storage modulus and loss modulus are the measuring indices employed (11,14).

MATRIX METALLOPROTEINASE (MMP)

The MMP enzyme is an enzyme that basically can degrade all components of the dentin extracellular matrix. Almost all MMPs are secreted as enzyme

precursors, namely zymogens, in which cysteine propeptide binds to its sulfhydryl groups until the active zinc ion region as the fourth ligand undergoes "cysteine change". In vitro the change from a form to an active form can be achieved by proteolytic elimination of the propeptide, randomizing the cysteine-zinc interactions, or modifying the sulfhydryl groups, allowing the interaction between the zinc active region and the water molecule and contact with the active site. In many cases, the activation process occurs gradually including the autocatalytic process. In vitro proMMPs can be activated by various chemical compounds and reactions, including thiol-modified compounds, denaturation, chaotropic compounds, reactive oxygen, and heating. MMP-2, MMP-8, and MMP-9 can also be activated by acidic pH followed by neutralization (12).

HYBRID LAYER

The hybrid layer is the most vital part of the adhesive-based restoration. The quality of the hybrid layer determines the strength and durability of a restoration. The hybrid layer can be interpreted as a layer formed due to resin infiltration between collagen and hydroxyapatite fibers which functions as micromechanical retention of composite resin restorations to the dentin tissue. This layer consists of 50% collagen matrix and 50% resin. The hybrid layer serves to combine 2 different elements, namely hydrophilic dentin, and hydrophobic composite material, protecting the dentin surface from micro-leakage and increasing dentin resistance to acid. The ideal hybrid layer is characterized by the presence of a collagen network that is bonded and reinforced with polymers (3,15).

Hybrid Layer Degradation

The adhesive is now starting to use hydrophilic monomers such as Hydroxyethyl methacrylate (HEMA) as a hydrophobic monomer solvent to increase the wetting ability of the adhesive and prevent phase changes that occur when the diacrylate-based adhesive is applied to the dentin matrix which tends to be moist. Resin monomers which are hydrophilic in nature are very susceptible to hydrolysis due to the presence of ester bonds in the HEMA component. In addition, the increase in the HEMA component in the adhesive has been shown to increase water absorption in polymerized polymers, which causes a decrease in the mechanical properties of the hybrid layer. HEMA can provide good adhesions and is not easily degraded so that it can produce long-lasting restoration (16).

EPIGALLOCATECHIN GALLATE (EGCG)

EGCG is a polyphenol that belongs to the catechin group, which able to inhibit the opening of sodium ion channels so that it has the potential to be anti-inflammatory. In addition, EGCG also has antioxidant properties that can reduce ROS by binding to ROS

(17,18). EGCG is composed of 2- phenylchromane framework which is substituted in chain number 17,31,41 with a hydroxyl group (Figure 1). During biosynthesis, if the B-ring comes from sinton gallic acid, the catechin will be substituted with the 51st position of the hydroxyl group, namely "gallo" catechins which will esterify with gallic acid to form "gallate". Levorotatory compounds (2R, 3R) are called "epi" while dextrorotatory compounds (2S, 3R) are called "catechin" so that when combined, they will become epigallocatechin gallate (EGCG). EGCG compound has the chemical formula (2R, 3R) -5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl) -3,4-dihydro-2H-chromen-3-yl-3,4,5-trihydroxybenzoate (19) (Figure 2). Judging from its chemical structure, EGCG is said to have the most potent antioxidative properties.

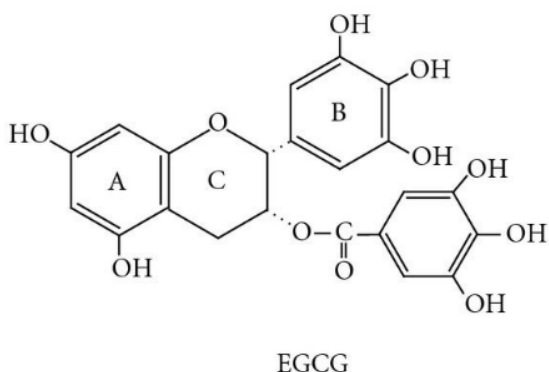


Figure 1: EGCG

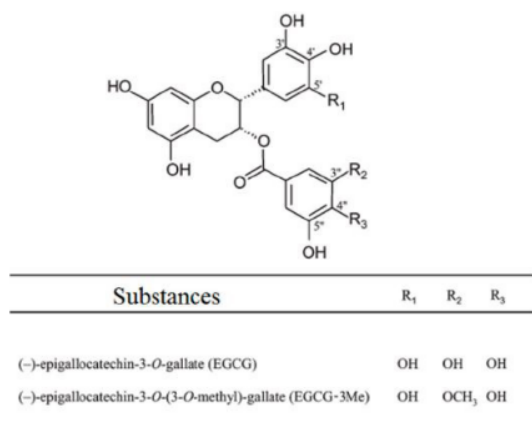


Figure 2: The Chemical Structure of EGCG and EGCG-3Me

EGCG can close TLR4 which can increase the production of TNF-α and hydroxyl and gallate groups that will bind to free radical ions so that it can prevent oxidation reactions that can cause tissue damage (9,20). EGCG can also carry out an antioxidant activity, EGCG will bind free metal ions such as Fe²⁺ and Zn²⁺ ions and make them more stable so that the catalyzed reactions

can be inhibited (1).

Deminerlization in the caries process has been shown not only to be caused by contact with acids from bacteria but also due to the collagenolytic and gelatinolytic activity of the proteases present in the dentin organic matrix. The enzymes that play a role in this are MMP and cysteine cathepsin (21). Table 1 shows a summary of studies done on the efficacy of EGEC.

EGCG as Cross-Linking Agent Towards Hybrid Layer in Dentin Collagen

The technology regarding adhesive materials is still developing, one of the weaknesses is the decrease in the resin-dentin bond which is often associated with an unstable hybrid layer. On the other hand, dentin also has MMP proenzymes and cysteine cathepsin which play a role in the destruction of collagen fibrils in the hybrid layer.

Collagen fibrils' stability, tensile strength, and viscoelasticity depend on the intermolecular cross-links from a translation of collagen. This is indicated by an increase in the degree of cross-link which is accompanied by an increase in the elastic tension of collagen fibrils. Chu (9), reported that applying EGCG solution to the collagen surface resulted in more regular collagen fibrils with a larger diameter and smaller interfibrillar space. The higher the concentration used, the greater the diameter of the collagen fibrils formed.

The cross-linking between EGCG and collagen chains can also affect the permeability of the hybrid layer to water molecules. This is evidenced by the research of Sun (8), which shows that the application of 0.1% EGCG to dentin after acid etching can increase the contact angle of the dentine surface to water.

A different point was stated by Chu (9), who reported that administering EGCG 0.64% could reduce the contact angle of the dentin surface against water and allow maximum surface wetting. From the research method used, the two studies with different results used different methods. A dentin collagen membrane was immersed in EGCG solution for 1 hour at room temperature. Meanwhile, Sun (8), used pieces of dentin that had been polished and demineralized using acid etching and applied EGCG for 120 seconds. This difference in the material used allows for differences in research results even though they both use water droplets.

To determine the degree of attachment between the adhesive and dentin, most studies (n = 23) used a tensile bond strength test (TBS), and 4 journals evaluated nanoleakage analysis. Among the 17 studies that tested TBS with positive results, 10 of them use EGCG solution with varying concentrations on dentin before bonding application. According to Yu (10), EGCG can maintain adhesion stability through the inhibitory

Table 1: Studies on the efficacy of EGCG

| 10 | Title | Findings | Reference |
|----|--|--|-----------|
| | Evaluation of epigallocatechin-3-gallate (EGCG) cross-linked collagen membranes and concerns on osteoblasts | Immersion of collagen membranes in 0.64%, 0.064%, and 0.0064% (w/v) EGCG solutions for 1 hour resulted in collagen that looks more compact, fibrils are more organized, increases fibril diameter, and narrows the space between fibrils. The higher the concentration of EGCG used, the more hydrophilic the dentinal collagen is. EGCG can also increase the modulus of elasticity and strength of collagen. | 9 |
| 11 | Epigallocatechin-3-gallate enhance dentin biomodification and bond stability of etch-and-rinse adhesive sistem | Application of EGCG 0.1% for 120 seconds before bonding can increase Tensile Bond Strength (TBS) significantly compared to no treatment. EGCG can increase the contact angle by increasing the degree of hydrophobicity. | 8 |
| | Effect of epigallocatechin-3- gallate solutions on bond durability at the adhesive interface in caries-affected dentin | Application 20µl of 0.02%, 0.2%, 0.5% EGCG for 60 seconds did not show a significant difference in FFB. Both the CHX and EGCG groups had lower TBS than the control. The application of 0.02% EGCG had the lowest degree of nanoleakage compared to other concentrations, CHX, and control although not significant. | 6 |
| | Effect of adjunctive application of epigallocatechin-3-gallate and ethanol-wet bonding on adhesive-dentin bonds | Administration of 0.02% w/v EGCG for 60 seconds before bonding application showed higher TBS than other groups and control. Most fractures are adhesive failures. EGCG+ethanol also showed the lowest degree of nanoleakage compared to the other groups. | 32 |
| 12 | functionalized epigallocatechin gallate copolymer inhibit dentin matrices degradation: Mechanical, solubilized peptide and proteomic assays | Application Adhesives containing 1%w/w EGCG showed the highest tensile strength compared to adhesives containing CHX and negative control. EGCG can also inhibit proteolytic enzymes (mmp and CT) (shown in soluble telopeptide analysis) and collagen biomodification. | 22 |
| 5 | Influence of dentin biomodification with epigallocatechin-3-gallate on the bond strength of self-etch adhesive: Twelve-month results | The use of 0.1 % EGCG for 60 seconds before bonding resulted in reduced microtensil bond strength on the first day compared to the control, but higher bond strength at 6 and 12 months. Adhesion failure was similarly higher in the EGCG group on day 1 compared to the control and CHX groups, but it increased after 6 and 12 months. | 23 |
| 2 | Effect of polymeric microparticles loaded with catechin on the physicochemical properties of an adhesive sistem | Addition of PLGA (poly(D-L lactide-coglycolide) Acid) containing EGCG in the form of microparticles into bonding as much as 0.5%, 1.0%, and 2.0% w/w manually and the description of the application of 0.1% and 1% EGCG solutions before the bonding application showed an increase in TBS after 12 months is characterized by decreased degradation of collagen fibrils | 7 |
| 3 | Epigallocatechin-3-gallate and epigallocatechin-3-O-(3-O-methyl)-gallate enhance the bonding stability of an etch-and-rinse adhesive to dentin | The addition of EGCG-Me 600 µg/mL to the adhesive applied to teeth that had been etched in 2 layers showed the highest TBS. | 10 |
| | Effect of epigallocatechin gallate, green tea extract and chlorhexidine application on long-term bond strength of self-etch adhesive to dentin | There is no significant difference in tensile bond strength. Administration of 2% EGCG for 60 seconds did not increase the tensile bond strength. EGCG had the lowest bond strength compared to green tea extract, chlorhexidine, and control. | 28 |
| 2 | Epigallocatechin-3-gallate (EGCG) enhances the therapeutic activity of a dental adhesive | The application of a bonding agent that had been mixed with 200 g/ml EGCG on the etched teeth showed significantly higher TBS than the control and other concentrations. There was no significant difference in the degree of conversion in bonding after being given EGCG solution against the control. | 2 |
| 2 | Galloyl moieties enhance the dentin biomodification potential of plant-derived adhesives | Dentin incubation in 0.65w/v percent EGCG solution for 1 hour resulted in a considerable increase in modulus of elasticity, a decrease in the degree of dentin biodegradation, a decrease in MMP-9 and CT-B. | 24 |
| 15 | Durability of resin on bleached dentin treated with antioxidant solutions | Application of 1mL 0.5% EGCG for 10m after bleaching before the filling procedure resulted in the highest shearbond strength compared to laser and control after 12 months. | 25 |
| 7 | Influence of protease inhibitors on the degradation of sound, sclerotic and caries-affected demineralized dentin | Before enzyme administration, dentin incubation in a 0.5% EGCG solution for 1 hour at 37°C had a beneficial effect on nanohardness and modulus of elasticity in the afflicted dentin. Tensile strength was likewise higher in the EGCG group than in the CHX group, but lower than in the control group. | 26 |
| | Antioxidants and Collagen-Crosslinking: Benefit on Bond Strength and Clinical Applicability | The administration of primers that had been mixed with EGCG 100 M (wt./vol) for 20 seconds and dried for 5 seconds before bonding showed inferior shear bond strength and Weibull modulus performance compared to proantocyanin, hesperidin, and control, although no loss of shear bond strength was found. | 27 |

activity of MMPs. Meanwhile, Maria Fonesca (14), EGCG has hydrophobic properties through aromatic groups and hydrophilic through polar hydroxyl groups. The hydrophobic group can induce Van der Waals bonds with hydrophobic molecules in the resin. While the hydrophilic group hydrogen bonds with proteins in the collagen chain. Gerhardt (28), reported that the administration of EGCG solution with a concentration of 2% before the bonding application showed lower TBS rates than controls both immediately after application and 6 months later. Gerhardt added that these results could be due to the formation of a precipitate in the EGCG solution.

Application of EGCG gel containing 400 µM for 5 minutes 5 days before the filling procedure showed the same Tensile Bond Strength (TBS) as the control in both normal and erosion dentin (29). The addition of PLGA (poly (D-L lactide-coglycolide) Acid) containing EGCG in the form of microparticles into bonding as much as 0.5%, 1.0%, and 2.0% w/w manually and the application of 0.1% EGCG solution and 1% before the bonding showed an increase in TBS after 12 months, which was marked by a decrease in the degradation of collagen fibrils (7). Addition of 200 g/mL EGCG solution before bonding application using the etch and rinse method had the highest TBS when compared to

mixing the bonding material with EGCG solution with the same concentration, pretreatment with CHX and control. Flexural strength of bonding materials that have been mixed with EGCG is lower than bonding materials without EGCG (30).

Yang (31), reported that giving EGCG in ethanol and water solvents with a concentration of 0.02% showed a lower degree of nanoleakage than the 0.1% concentration, this research is in line with another research that stated EGCG with the smallest concentration (0.0065%) can inhibit protease activity but its effectiveness drops significantly when it reaches a certain concentration. This raises the theory that the EGCG used in the treatment is highly dependent on the concentration used. Regarding this, Du (2), explained that giving EGCG in high concentrations can reduce the degree of adhesive conversion, because, during the polymerization period, EGCG trapped in the adhesive can interfere with the formation of polymer linear chains.

EGCG as a cross-linking agent and the wetting ability of the bonding material caused by the EGCG solvent, which is water. The use of different solvents can also cause differences in test results, Chemical bonding using acetone solvent can produce a stronger bond between the bonding material and dentin collagen when compared to using ethanol solvent (15). A study conducted by Soetojo (32), compared HEMA water solvent expresses less MDA and has good biocompatibility when compared to HEMA with ethanol or acetone solvent. Water solvents are considered to provide a wetting effect that can act as plasticizers of dentin collagen fibrils and keep collagen from collapsing. Water molecules in collagen make the diffusion of the bonding material with ethanol and acetone solvents into collagen fibrils easier, but the water molecules will also diffuse into the solvent, so the concentration of the adhesive solvent and the concentration of BisGMA decreases which causes the infiltration of BisGMA to be inadequate (33). Yang (31), used ethanol solvent in his EGCG solution. The use of ethanol as a solvent to replace water can increase the TBS of most hydrophobic resins such as BisGMA / TEGDMA by making the total ethanol-matrix cohesive force approaching the ethanol-BisGMA / TEGDMA solution so that the collagen matrix will immediately form interpeptid hydrogen bonds. This evidence showed a high number of TBS and nanoleakage of the EGCG-ethanol group compared to the EGCG-water group. EGCG is able to increase the stability of the hybrid layer, which can be proven by the amount of soluble type I collagen telopeptide, which is lower than the control (22).

EGCG as Chelating Agent against MMPs' Expression

The use of MMP inhibitors is thought to increase the bond strength of the adhesive to dentin. EGCG also functions as a chelating agent, EGCG interacts with

MMP by exploiting the nature of catechins which have a high affinity for metal ions. Yang (23) states that the Zn ion which is the chemical structure of MMP can be bound by EGCG so that MMP is no longer recognized by the collagen matrix so that collagen degradation can be inhibited. But Cheng (34) has a different theory that stated EGCG inhibits the gelatinolytic activity of MMP by binding EGCG with the catalytic area or the area close to the catalytic area where gelatinolytic activity is occurring.

Based on journal search results, most studies (n = 15) regarding the application of EGCG to dentin collagen did show positive results both on TBS, nanoleakage, and the morphology of collagen fibrils. However, there is one randomized clinical trial that showed negative results. Costa (35), reported that administering 0.1% EGCG solution for 60 seconds before application of the bonding to the cervical lesion restoration procedure without caries (NCCL) did not show any difference in terms of retention, margin adaptation, secondary caries, and post-restoration sensitivity after 24 months with or without the procedure. This result explains that although EGCG does not have a positive effect on the restoration results, EGCG also does not have a negative effect that can worsen the restoration. Therefore, further evaluation is needed regarding concentrations, solvents, and application methods that can be used to increase the resin-dentin adhesion in the hybrid layer.

Vidal (24) reported a degree of MMP-9 inhibition that exceeded positive controls after incubation in an EGCG solution. MMP is basically secreted as an inactive proenzyme, but will be active when the pH of the environment drops. This will lead to degradation of the extracellular matrix in both biological and pathological processes. This process usually occurs in affected dentin, where cariogenic bacteria still produce lactic acid which can activate MMP (28). Administration of EGCG-nanohydroxyapatite solution in 100mg/mL distilled water for 30 seconds before bonding application showed significantly higher TBS than the control, either with or without the etching procedure. The EGCG-nanohydroxyapatite group also showed significantly lower nanoleakage rates than the control group. The EGCG group also showed a significant decrease in gelatinolytic activity due to MMPs compared to the control group (36).

CONCLUSION

The application of EGCG can have a positive effect on the morphology of dentinal collagen fibrils, inhibit MMPs activity in dentinal collagen, decrease the hydrophilic properties of dentinal collagen fibrils, increase the tensile bond strength (TBS) of the hybrid layer and reduce the nanoleakage of the hybrid layer in dentin collagen.

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