

Baicalein: Role in Resin-Dentin Adhesion

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Received: January 23, 2021; **Published:** March 30, 2021

Abstract

Baicalein, a natural MMP inhibitor and collagen cross linker can silence the activity of dentinal collagenases and gelatinases and cross-link the collagen matrix which would increase the biostability of resin-dentin interface and is essential for promising adhesive dentistry the review provides and overview of the structure, properties of baicalein and its effect on dentinal MMPs and durability of resin-dentin bond.

Keywords: Baicalein; MMP Inhibitor; Resin-Dentin Bond; Cross Linker

Abbreviations

MMPs: Matrix Metalloproteinases; EDTA: Ethylenediamine Tetraacetic Acid; BAI: Baicalein

Introduction

Bonding of resinous materials to dentin requires prior application of acid conditioners to attain a demineralized surface and expose the organic dentin matrix [1,2]. In addition, the exposed collagen network has to be fully infiltrated by monomers from the adhesive system, which will be polymerized to form a tooth-restoration interface called the hybrid layer [3]. However, during this process, and collagen fibrils remain unprotected in some areas at the base of the hybrid where monomer infiltration is deficient and are susceptible to the activity of MMPs [4]. The hydrolytic and enzymatic degradation of resin-dentin interfaces challenges the durability of resin-bonded restorations. Although the immediate resin-dentin bond strength of contemporary adhesives is good but it gradually falls due to the hydrolytic degradation of collagen and adhesive resin leading to dentin hypersensitivity or secondary caries besides decreasing the longevity of the restoration [5]. Recent strategies to prevent the degradation of collagen matrix in demineralized dentin focus on improving the cross-link density of collagen and preventing collagen degradation by inhibition of proteases through the use of MMP inhibitors and collagen cross linkers such as chlorhexidine, carbodiimide, ethylenediamine tetraacetic acid (EDTA), doxycycline, proanthocyanidins [6]. Recently, Baicalein has been investigated in various studies as a candidate preconditioning agent for improving the resin-dentin bond durability. This review aims to discuss the role of baicalein in preservation of resin-dentin bond durability.

Baicalein

Structure, chemistry and properties: Baicalein (BAI) is one of the major flavonoids in *Scutellaria baicalensis* [7]. BAI can inhibit the activity and expression of MMP-2 and MMP-9 via PI3K/AKT, p38-MAPK-NF- κ B and MAPK-ERK1/2 signal pathways in various tumor cells.

It has many biological properties including antioxidative, antimicrobial, anti-tumor and anti-enzymatic effects [8-12]. As a protease inhibitor, BAI reduced the expression of MMP2, MMP-9 and cathepsin-B in a swiss albino mouse model of lung cancer. In addition, BAI was found to inhibit the expression of MMPs and cathepsin in osteoarthritic chondrocytes [13]. BAI and proanthocyanidins are natural plant polyphenols that share a similar molecular structure with phenolic hydroxyl functional groups suggesting they share comparable cross-linking properties [14,15].

Effect on dentin dentinal MMPs and collagen cross linking

The MMP inhibitory mechanism of BAI in endogenous dentin-bond MMPs might be as follows: Firstly, BAI could compete with the active center of the enzyme through a metal chelating effect, grabbing metal ions such as Zn^{+2} to suppress the activity of MMPs. Secondly, BAI might cross-link and alter the three-dimensional structure or molecular mobility of MMPs, resulting in the loss of the collagen enzymolysis ability of the latter. Thirdly, BAI might cross-link with dentin collagen fibers through hydrogen bonds, changing or covering the recognition sites of MMPs in collagen to interfere with enzymatic coordination and complexation, thereby protecting noncoated collagen from degradation [7]. The stronger hydrophobic performance of BAI might also decrease water absorption and the swelling of collagen, thereby minimizing sensitivity to hydrolysis and protecting collagen from degradation. The enzyme inhibition ability of baicalein is also closely related to its oxidation resistance ability. It has been shown that BAI can directly scavenge free radicals due to its polyphenolic structure. BAI can significantly protect human retinal pigment epithelial cells from oxidative stress by scavenging reactive oxygen species and downregulating the expression of MMP-9 [16]. Baicalein can act as a potential cross-linker since its hydroxyl groups can form hydrogen bonds with the amide carbonyl of proteins. Moreover, it is well established that cross-linkers can cross-link not only proteins but also proteases. This may directly interfere with the molecular mobility of proteases or inactivate C-terminal telopeptidases, maintaining telopeptides ability and sterically blocking collagenase binding to the critical peptide bond [17,18]. Therefore, it may be assumed that due to its potential MMP inhibition and cross-linking abilities, BAI could stabilize collagen fibrils and protect the integrity of the hybrid layer in dentin bonding.

Effect of Baicalein on Resin-dentin bond Li., *et al.* [7] evaluated the effects of baicalein as a preconditioner on matrix metalloproteinases and adhesive durability. Different concentrations of baicalein (0.1, 0.5, 2.5, 5.0 $\mu\text{g/ml}$) on dentin powder were used to detect the MMP inhibitory effect. Acid etched dentin surfaces on sound third molars were preconditioned with 2.5 $\mu\text{g/ml}$ baicalein followed by adhesive process and build up of resin composite. Microtensile bond strength was evaluated immediately and after storage in artificial saliva for 6 months. The activity of dentin-bond gelatinase and collagenase were inhibited and increased microtensile bonding strength was seen at the concentration of 2.5 $\mu\text{g/ml}$ both immediately and after 6 months aging.

Zheng., *et al.* [19] showed that BAI improved enzymatic resistance of the dentin collagen matrix better than proanthocyanidins and quercetin at a concentration of 50 g/L . Yi., *et al.* [20] validated that the combination of ethanol wet bonding strategy and baicalein could efficiently enhance the quality and durability of dentin bonding by simultaneously inhibiting the hydrolysis of hybrid layer and enzymatic hydrolysis of collagen fiber. Baicalein could also inhibit the formation of *S. mutans* biofilm, thereby preventing restoration failure caused by secondary caries. Moreover, baicalein exhibited high biological safety and bioactivity, with lower toxicity and drug-resistance compared with modifiers such as chlorhexidine and glutaraldehyde. Chu., *et al.* [21] evaluated the effect of baicalein on the expression of MMPs and cathepsins in human dental pulp cells. The results showed that baicalein significantly suppress the expression of MMP-2, MMP-9, Cathepsin-B, Cathepsin-K, in human dental pulp cell at concentrations that did not affect cell viability. They used baicalein in three different concentrations with 12.5 $\mu\text{mol/l}$ showing the highest resin-dentin bond strength and reported that baicalein effectively improved resin- dentin bonding durability *in vitro*.

Conclusion

Due to the versatile performance of baicalein, it has greater potential in dental application. It appears that baicalein may be a promising preconditioner for improving the durability of resin-dentin bonding by protecting against collagen degradation via the inhibition of MMPs and cathepsins. However further research is required to analyze its potential value in clinical bonding procedures, including optimum concentration and duration of application required to preserve the integrity of resin-dentin bond interface.

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Volume 20 Issue 4 April 2021

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