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Collagen Cross-Linkers for Dentin Bonding: A Systematic Review and Meta-Analysis of In Vitro Studies

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ABSTRACT: Background: The durability of the resin-dentin bond remains a major challenge in adhesive dentistry. Collagen cross-linking agents are promising biomodification strategies that improve bond durability by stabilizing the collagen matrix and inhibiting enzymatic degradation.

Objectives: To systematically evaluate the effect of collagen cross-linking agents on resin-dentin bond strength, nanoleakage, and failure modes, with emphasis on natural versus synthetic agents.

Methods: PubMed, Web of Science, Scopus, and Cochrane Library were searched from 2015 to 2026. In vitro studies evaluating collagen cross-linkers for dentin bonding were included. Random-effects meta-analysis was performed using standardized mean differences (SMD) with 95% confidence intervals (CI).

Results: Twenty-eight studies were included in the qualitative synthesis, of which 22 provided sufficient data for meta-analysis. Collagen cross-linker pretreatment significantly improved immediate bond strength (SMD = 0.82, 95% CI: 0.54–1.10, $P < 0.001$) and long-term bond strength after aging (SMD = 0.68, 95% CI: 0.41–0.95, $P < 0.001$). Nanoleakage was significantly reduced in cross-linker groups (SMD = -0.75, 95% CI: -1.12 to -0.38, $P < 0.001$). Propolis showed relatively large estimated effects across several evaluated outcomes, although direct superiority between cross-linker types could not be established.

Conclusions: Collagen cross-linking agents effectively improve resin-dentin bond performance. Natural agents, particularly propolis, show promising results comparable to synthetic alternatives. Standardization of application protocols is necessary for clinical translation.

INTRODUCTION

The durability of resin-dentin bonds is an ongoing challenge in restorative dentistry. Despite the significant improvements of adhesive systems, the hybrid layer remains the weakest link of the bonded interface and is susceptible to hydrolytic degradation,

enzymatic activity and mechanical fatigue [1,2]. The endogenous degradation of exposed collagen fibrils is mediated by matrix metalloproteinases (MMPs) and cysteine cathepsins released during acid etching and activated by the acidic environment [3,4].

One potential solution to this problem is the use of collagen cross-linking agents. These agents increase extra inter- and intra-molecular cross-links in the collagen matrix, increasing the mechanical properties and enzymatic resistance of the demineralized dentin [5,6]. Cross-linkers are classified into synthetic (glutaraldehyde, carbodiimide, genipin) and natural (proanthocyanidins, flavonoids, propolis).

Natural crosslinkers are of special interest because of their biocompatibility and clinical translation potential. Propolis is a resinous substance produced by honeybees. It contains flavonoids and phenolic compounds which can interact with collagen via multiple mechanisms such as covalent bonding, ionic interactions, hydrogen bonding and hydrophobic interactions [7,8]. Hesperidin, a flavonoid found in citrus fruits, stabilizes collagen by means of hydrophobic interactions and inhibits the action of MMPs [9,10].

The collagen cross-linkers for dentin bonding were systematically reviewed before [10,11], but there are few reports quantifying the comparative efficacy of natural agents or evaluating the effect on failure modes. The aim of this systematic review and meta-analysis was to evaluate the effect of collagen cross-linking agents on resin-dentin bond strength, nanoleakage and failure modes, with special focus on natural agents.

MATERIAL AND METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42026123456).

Inclusion Criteria:

- Studies in vitro of human dentine
- Evaluation of collagen cross linkers for dentin pretreatment - Quantitative reporting of bond strength, nanoleakage or failure modes - English - Publication 2015-2025

Exclusion Criteria:

- Clinical Studies - Studies without a control group
- Cross-linkers were added in adhesive (not used as pre-treatment) - Studies in animals - Case reports, reviews, editorials

Strategy of recherche

The following databases were searched: PubMed/MEDLINE, Web of Science, Scopus and Cochrane Library. The search strategy combined terms relating to collagen cross-linkers, dentin bonding and in vitro studies:

("collagen cross-linker" OR "crosslinking agent" OR "propolis" OR "hesperidin" OR "proanthocyanidin" OR "grape seed extract" OR "glutaraldehyde" OR "genipin" OR "carbodiimide") AND ("dentin bonding" OR "resin-dentin interface" OR "bond strength" OR "nanoleakage" OR "hybrid layer") AND ("in vitro")

Selection of studies and data extraction

Data were collected using a standardized form that included author, year of publication, type and concentration of cross-linker, application protocol, adhesive system, sample size, aging conditions, outcome measurements, and numerical data for the meta-analysis (means and standard deviations for each intervention and control group). Where studies reported multiple aging periods, concentrations or experimental groups, a pre-defined data selection procedure was used to avoid double-counting of participants or specimens within a synthesis. If the numerical information required for the meta-analysis was unclear or incomplete, the reported information was assessed and handled according to the data available.

Assessment of risk of bias

Two reviewers independently assessed the risk of bias using the Quality Assessment Tool for In Vitro Studies (QUIN) (13). The assessment comprised the prespecified domains of sample size calculation, randomization, blinding, control group and reporting of outcomes. Disagreements among reviewers were discussed and, if consensus could not be reached, a third reviewer was consulted. The criteria used to make an overall risk-of-bias judgment for each study are shown in Supplementary Table S2.

Statistical Analyzes

Meta-analyses were conducted using RevMan 5.4 (Cochrane Collaboration, Copenhagen, Denmark) and Stata 17.0 (StataCorp, College Station, TX, USA). For continuous outcomes we calculated standardized mean differences (SMD) with 95% confidence intervals using random-effects models (DerSimonian-Laird). Heterogeneity was evaluated using the I^2 statistic. Subgroup analyzes by cross-linker type were performed. Publication bias was assessed using funnel plots and Egger's test.

RESULTS

Selection of studies

The search retrieved 1,247 records initially. After removal of duplicates, 892 records were retained. After title and abstract review, 68 articles were eligible for full text review. Finally, 28 studies met the inclusion criteria and were included in the qualitative synthesis. 22 studies provided adequate data for meta-analysis.

Characteristics of Studies

The studies included were published between 2015 and 2025. The cross-linkers used were: propolis (n=8), hesperidin (n=5), proanthocyanidins/grape seed extract (n=7), epigallocatechin-3-gallate (n=4), glutaraldehyde (n=2) and other agents (n=2). Adhesive systems were etch-and-rinse (n = 16) and self-etch (n = 12) systems. Aging conditions were 24 hours to 12 months in water storage, artificial saliva or thermocycling [14–16].

Risk of Bias

Most studies (71.4%) were classified as moderate risk of bias. Common limitations included: lack of sample size calculation (82%), unclear randomization (57%), and absence of blinding (64%). Four studies (14.3%) were rated as low risk of bias (Table 1).

Table 1. Risk of bias assessment of included studies

Domain	Low Risk (%)	Moderate Risk (%)	High Risk (%)
Sample size calculation	18%	0%	82%
Randomization	43%	0%	57%
Blinding	36%	0%	64%
Control group	100%	0%	0%
Outcome reporting	86%	14%	0%

Meta-analysis results

Immediate bond strength Twenty-two studies were included. Compared with controls, there was a significant increase in immediate bond strength following collagen cross-linker pretreatment (SMD = 0.82, 95% CI: 0.54–1.10, $P < 0.001$) with moderate heterogeneity ($I^2 = 58\%$). Subgroup analysis revealed that the highest effect was observed in propolis (SMD = 1.24, 95% CI: 0.76–1.72), followed by glutaraldehyde (SMD = 0.96, 95% CI: 0.52–1.40) and proanthocyanidins (SMD = 0.71, 95% CI: 0.38–1.04). Hesperidin was close to significance (SMD = 0.48, 95% CI: –0.02 to 0.98, $P = 0.06$) but did not reach statistical significance.

Long-term bond strength (≥ 6 months of aging): Twelve studies were included in the review. Cross-linker groups had significantly higher bond strength retention than controls (SMD = 0.68, 95% CI: 0.41–0.95, $P < 0.001$) with high heterogeneity

($I^2 = 72\%$). Propolis (SMD=0.91) and carbodiimide (SMD=0.84) provided the most protection in the long term. Silver nitrate staining was used to evaluate nanoleakage in eight studies. Cross-linker pretreatment significantly reduced silver deposition (SMD = -0.75, 95% CI: -1.12 to -0.38, $P < 0.001$) with moderate heterogeneity ($I^2 = 63\%$). The highest decrease of nanoleakage was found for Propolis (SMD = -1.05).

Failure Modes: Six studies reported data on failure modes. Cross-linker groups showed higher incidences of cohesive failure and lower adhesive failure compared to controls, suggesting improved interfacial bond strength. In the study of Elmogher et al. [17], the propolis treatment presented 40.0% cohesive-in-dentin failure, while the control group showed 10.0% .

Bias of Publication

Inspection of the funnel plot showed mild asymmetry, but Egger's test was not statistically significant ($P = 0.08$), indicating low likelihood of publication bias.

Supplementary Table S1. Search strategy used for identification of eligible studies

Database	Search concepts	Search terms reported in the manuscript	Limits / eligibility period
PubMed/MEDLINE	Collagen cross-linkers AND dentin bonding AND in vitro	("collagen cross-linker" OR "crosslinking agent" OR "propolis" OR "hesperidin" OR "proanthocyanidin" OR "grape seed extract" OR "glutaraldehyde" OR "genipin" OR "carbodiimide") AND ("dentin bonding" OR "resin-dentin interface" OR "bond strength" OR "nanoleakage" OR "hybrid layer") AND ("in vitro")	Publications from 2015–2025; English
Web of Science	Collagen cross-linkers AND dentin bonding AND in vitro	Same core concepts and keywords, adapted to the database indexing/search syntax	Publications from 2015–2025; English
Scopus	Collagen cross-linkers AND dentin bonding AND in vitro	Same core concepts and keywords, adapted to the database indexing/search syntax	Publications from 2015–2025; English
Cochrane Library	Collagen cross-linkers AND dentin bonding AND in vitro	Same core concepts and keywords, adapted to the database indexing/search syntax	Publications from 2015–2025; English

Core search concepts: collagen cross-linker/crosslinking agent; propolis; hesperidin; proanthocyanidin; grape seed extract; glutaraldehyde; genipin; carbodiimide; dentin bonding; resin-dentin interface; bond strength; nanoleakage; hybrid layer; in vitro.

Supplementary Table S2 — Modified QUIN

Supplementary Table S2. Domains and criteria used for the modified QUIN risk-of-bias assessment

Domain	Assessment criterion	Low risk of bias	Moderate risk of bias	High risk of bias
Sample size calculation	Whether an appropriate sample-size calculation was reported	Sample-size calculation clearly reported and justified	Calculation incompletely described or insufficiently justified	No sample-size calculation reported

Randomization	Whether allocation of specimens to experimental groups was adequately randomized	Appropriate randomization clearly described	Randomization mentioned but method unclear	No randomization reported
Blinding	Whether investigators/outcome assessors were blinded where applicable	Appropriate blinding clearly reported	Blinding incompletely described	No blinding reported
Control group	Whether an appropriate control group was included	Appropriate control group clearly described	—	No appropriate control group
Outcome reporting	Whether predefined outcomes were adequately and completely reported	Outcomes clearly and completely reported with sufficient numerical data	Some outcome information incompletely reported	Major outcome information missing or inadequately reported

Supplementary Table S3 — Characteristics of included studies

Supplementary Table S3. Characteristics of the included studies

Cross-linker / agent	Number of studies	Adhesive system	Reported aging range	Outcomes assessed
Propolis	8	Etch-and-rinse and/or self-etch	24 h to 12 months	Bond strength, nanoleakage, failure mode
Hesperidin	5	Etch-and-rinse and/or self-etch	24 h to 12 months	Bond strength, nanoleakage and/or failure mode
Proanthocyanidins / grape seed extract	7	Etch-and-rinse and/or self-etch	24 h to 12 months	Bond strength, nanoleakage and/or failure mode
Epigallocatechin-3-gallate (EGCG)	4	Etch-and-rinse and/or self-etch	24 h to 12 months	Bond strength, nanoleakage and/or failure mode
Glutaraldehyde	2	Etch-and-rinse and/or self-etch	24 h to 12 months	Bond strength and/or other reported outcomes
Other agents	2	Etch-and-rinse and/or self-etch	24 h to 12 months	Reported outcomes varied
Total	28	Etch-and-rinse: 16; self-etch: 12	24 h–12 months	Bond strength, nanoleakage, failure mode

DISCUSSION

Main Findings

The findings of this systematic review and meta-analysis validated the significant improvement in the immediate and long-term bond performance of resin-dentin by collagen cross-linker pretreatment. These results are consistent with previous systematic reviews reporting the positive effects of collagen cross-linking on dentin bonding [10,11].

The estimated effects of propolis were quite large for several outcomes assessed in this review. However, direct comparisons between agents are limited by differences in study protocols, concentrations, adhesive systems, aging conditions, and the number of studies available for each cross-linker. Thus, the present findings should not be interpreted as propolis being better

than other natural or synthetic cross-linkers [7,18]. In addition, propolis promotes the production of transforming growth factor-beta 1, which increases the synthesis of collagen and the differentiation of odontoblasts [19].

Hesperidin showed a positive estimated effect on the outcomes evaluated, but the pooled effect for immediate bond strength was not statistically significant. The available evidence is restricted by the limited number of studies and variation in experimental protocols. Therefore, hesperidin and other cross-linkers should be compared with care [9,10]. The mechanical properties are improved and the scoping review by Beckman et al. [20] confirmed that collagen is preserved by hesperidin in the hybrid layer. However, the cross-linking efficiency of hesperidin seems to be lower than that of propolis, which could be explained by differences in molecular architecture and reactivity.

This considerable decrease in nanoleakage with cross-linker treatment is of clinical significance. Nanoleakage is the presence of nanometer-sized spaces in the hybrid layer where the collagen is left unprotected because of incomplete resin infiltration [21]. These spaces provide routes for hydrolytic degradation and enzymatic attack. Cross-linkers may enhance the long-term sealing ability of adhesive restorations by reducing nanoleakage [22].

Comparison to previous reviews

Liao et al. [23] conducted a systematic review evaluating the use of different collagen cross-linkers for dentin bonding. The effects of the cross-linkers were dependent on the type of the agent, mode of application and adhesive system. These findings are consistent with the heterogeneity observed in the current review where effect sizes varied across the types of cross-linker and experimental protocols. The network meta-analysis performed by Chen et al. [24] compared the six classes of cross-linkers and found polyphenolic agents to have a good long-term bonding performance. This finding is generally consistent with the present results although differences in study eligibility criteria, experimental protocols and cross-linker classification preclude direct comparison between the two analyzes. This is consistent with the present findings as propolis (rich in polyphenols) exhibited better long-term protection.

Compromised bonding to sodium hypochlorite treated dentin was reversed by natural cross-linkers (grape seed extract, tannic acid, green tea) (Cecchin et al. [25]). This observation supports the concept that cross-linkers can restore bonding to degraded dentin substrates and is especially relevant to clinical situations involving caries-affected or eroded dentin.

Mechanisms of Actions

Cross-linkers improve dentin bonding through mechanisms that act at different levels. At the molecular scale, the exogenous cross-links increase the stiffness and the resistance to enzymatic degradation of collagen fibrils [5,6]. Cross-linking at the interfacial level reduces the amount of exposed unprotected collagen in the hybrid layer, thus reducing the targets for hydrolytic and enzymatic attack [11,21]. At the microscopic level, the cross-linkers may alter the surface characteristics of collagen, promoting the infiltration and polymerization of resin monomers [26].

Propolis may also have some other benefits apart from direct cross-linking. It may have a resinous nature that forms a protective layer in the interface and an antioxidant nature that scavenges free radicals that would otherwise degrade collagen [18,19]. Additionally, propolis showed antibacterial activity which can reduce bacterial collagenase activity at the margins of the restoration [27].

Clinical Implications

The results indicate the possibility of collagen cross-linker pretreatment as an adjuvant method to enhance the durability of resin-dentin bonding. However, all included studies were in vitro studies and the clinical safety and efficacy and the optimal concentration and application protocol of these agents could not be determined based on the current evidence. Therefore, clinical trials are needed before routine clinical use can be recommended [28,29].

However, standardization of natural products remains a concern. The chemical composition of propolis varies by geographic origin, plant source, and harvest season, potentially affecting cross-linking efficacy [30]. Future clinical studies should employ standardized propolis formulations with defined active compound profiles.

Constraints

The results should be understood within the framework of several limitations. There was considerable methodological heterogeneity, especially in cross-linker concentration, application time, adhesive system, dentin preparation and aging protocol.

This was evidenced by the moderate to high statistical heterogeneity among the meta-analyses ($I^2 = 58\text{--}72\%$). Second, most of the included studies (71.4%) were judged to have a moderate risk of bias, with common limitations including sample size calculation, randomization, and blinding, which may have affected the estimation of treatment effects. Third, some subgroup analyzes (e.g., hesperidin and synthetic cross-linkers) were based on a small number of studies, leading to a reduction of the precision and reliability of the subgroup estimates. Fourth, all the studies included were only in vitro. Thus, the generalizability of the findings to clinical practice is limited. Finally, differences in experimental protocols and methods of outcome assessment prevented direct comparisons between individual cross-linkers. Therefore, differences between agents should not be interpreted as evidence of clinical superiority.

CONCLUSION

To date, in vitro evidence suggests that collagen cross-linkers may improve resin-dentin bond performance, including immediate and long-term bond strength and nanoleakage. Propolis demonstrated relatively large estimated effects in some of the outcomes evaluated. However, the existing evidence does not support the superiority of propolis over other natural or synthetic crosslinkers due to heterogeneity in the methodology and differences in study protocols. Hesperidin also had a positive estimated effect, but evidence was still limited. Further well-designed studies with standardized concentrations, application protocols, adhesive systems and aging conditions are needed followed by clinical investigations to determine the clinical effectiveness and long-term safety of these approaches.

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