

Impact of Dentine Pretreatment with Matrix Metalloproteinase Inhibitors on Bond Strength of Coronal Composite Restorations: A Systematic Review and Meta-analysis of *In Vitro* Studies

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Abstract

Matrix metalloproteinase (MMP) enzymes participate in collagen matrix degradation, including in dentine, potentially compromising bond strength. Therefore, MMP inhibitors have been hypothesized to improve restoration bond strength and stability. This systematic review aimed to evaluate the influence of different MMP inhibitors applied as dentine surface pretreatments on the immediate (24 hours) and longer term (months) bond strength of direct coronal composite restorations. This systematic literature review followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement. A systematic literature search of three databases (Ovid MEDLINE, Ovid Embase, and Google Scholar) was conducted independently by two reviewers from inception to April 2022. An adapted quality assessment tool was independently applied by two reviewers for risk of bias assessment. RevMan v5.4 software was used for meta-analyses. A random effects model was used to generate mean differences with 95% confidence intervals for treatment and control comparisons. The Q-test and I²-test were used to test for heterogeneity. The proportion of total variance across studies attributable to heterogeneity rather than chance was calculated. Overall effects were tested using the Z-test, while subgroup differences were tested using Chi-squared tests. Of 934 studies, 64 studies were included in the systematic review and 42 in the meta-analysis. Thirty-one MMP inhibitors were reported, three of which were included in the meta-analysis: 2% chlorhexidine (CHX), 0.3M carbodiimide (EDC), and 0.1% riboflavin (RIBO). Pretreatment with 2% CHX for 30 and 60 seconds did not significantly improve bond strength compared with

Keywords

- restorations
- bond strength
- matrix metalloproteinase inhibitors
- enzymes
- caries
- dentine.

controls either immediately or after long-term ageing. However, pretreatment with 0.3MEDC and 0.1% RIBO (but not CHX) significantly improved bond strength compared with control groups both immediately and over time. Most studies showed a medium risk of bias. These *in vitro* findings pave the way for rationale clinical trialing of dentine surface pretreatment with MMP inhibitors to improve clinical outcomes.

Introduction

Since their introduction around six decades ago, restorative adhesives have undergone numerous improvements.^{1,2} Despite these advances, adhesive restorations often lose their bond strength over time, leading to their failure.^{3,4} Adhesive restorations critically rely on their bond with the tooth structures for strength, with the interface—the hybrid layer—crucial in determining the bond's longevity and stability.^{5,6} The collagen fibrils in dentine (mainly type 1 collagen) are key to establishing a strong bond, and their deterioration is thought to be the main reason underlying bond failure to dentine.⁷

Recent studies have examined the role of endogenous enzymes present within the dentine extracellular matrix (ECM) and their effect on bond stability. Among these enzymes, matrix metalloproteinases (MMPs) represent a group of calcium- and zinc-dependent host-derived enzymes.⁸ MMPs are divided into six subgroups: collagenases (MMP-1 and MMP-8), stromelysins (MMP-3, MMP-10, MMP-11, and MMP-20), gelatinases or type-IV collagenases (MMP-2 and MMP-9), matrilysin (MMP-7), metalloelastase (MMP-12), and membrane-type metalloproteinases (MMP-14, MMP-15, MMP-16, and MMP-17).⁹ Of these, four MMPs have been identified within the dentine extracellular matrix: MMPs-2, -8, -9, and -20, with MMP-2 and -9 as the most abundant.^{10,11} These enzymes are secreted by odontoblasts during odontogenesis and remain silenced and inactive within the dentine ECM.¹² However, these MMPs are activated either by biological acids produced by cariogenic bacteria¹³ or acids introduced during acid etching.^{14,15} When activated, they start to degrade the exposed collagen fibrils within the dentine.¹⁶ Therefore, inhibiting MMPs could help to preserve the hybrid layer and, therefore, bond stability.

Several types of MMP inhibitor (synthetic and natural) have been described including benzalkonium chloride,^{17,18} chlorhexidine,^{18–21} galardin,²² green tea extract,^{23,24} and zinc.²⁵ MMP inhibitors can be administered either as dentine surface pretreatments or those incorporated into the adhesive. The current systematic review and meta-analysis aimed to collect and analyze the available *in vitro* evidence on the influence of different MMP inhibitors applied as dentine surface pretreatments on the immediate and long-term bonding strength of coronal composite restorations. The null hypothesis was that there would be no difference in bond strength after MMP inhibitor use compared with controls.

Methods

Eligibility Criteria

The systematic review was developed according to the PICO scheme (►Table 1)²⁶ and was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines²⁷:

Population: all studies examining extracted human teeth, caries-free dentine, healthy dentine, sound dentine, carious-affected dentine, or affected dentin.

Interventions: all studies examining MMP inhibitors as dentine surface pretreatments prior to direct coronal composite restoration placement. Therefore, studies that used luting cements and glass ionomer cements were excluded.

Comparator(s)/control(s): teeth without intervention (i.e., without the addition of MMP inhibitor). Studies that included no comparator were excluded.

Outcome: the main outcome was bond strength or bond stability at the microscale (by microtensile and microshear testing). Studies that tested bond strength at the macroscale were excluded. Included studies needed to have aged the samples for at least 24 hours in water or artificial saliva. Thus, studies with ageing up to 24 hours only and/or studies that used ageing solutions other than water or artificial saliva were excluded.

Search Strategy

Types of Searched Studies

The search included published, peer-reviewed *in vitro* studies presenting the results (means and standard deviations [SDs]) quantitatively and numerically in the English language. Thus, studies that reported the results in graphs or figures only were excluded. Non-peer reviewed studies, conference posters, letters, theses, reviews, and editorials were excluded.

Period of Reviews (Timing) and Databases

A systematic literature search was conducted in three databases: Ovid MEDLINE (1946–April 2022), Embase (1974–April 2022; see ►Table 1), and Google Scholar (up to April 2022).

With respect to the search strategy for Google Scholar, the following terms were used: “Extracted human teeth” OR “human teeth” OR “Sound dentine” OR “healthy dentine” OR “affected dentine” OR “Carious affected dentine” OR “Caries affected dentine” OR “Dentine” AND “Matrix metalloproteinase inhibitors” OR “MMP inhibitors” AND “Bond strength” OR “Bond stability.”

Table 1 Keywords and the strategy used in MEDLINE and Embase

	Medline (Ovid)	Embase
P	1. Extracted human teeth.mp./OR Human teeth.mp. 2. Sound dentine.mp./OR healthy dentine.mp. 3. Carious affected dentine.mp./OR Caries affected dentine.mp./OR affected dentine.mp. 4. Dentine\$.mp. 5. 1 OR 2 OR 3 OR 4	1. Extracted human teeth.mp./OR Human teeth.mp. 2. Sound dentine.mp./OR healthy dentine.mp. 3. Carious affected dentine.mp./OR Caries affected dentine.mp./OR affected dentine.mp. 4. Dentine\$.mp. 5. 1 OR 2 OR 3 OR 4
I	6. Matrix metalloproteinase inhibitors/OR MMP inhibitors.mp.	6. Matrix metalloproteinase inhibitors/OR MMP inhibitors.mp.
C	7. No matrix metalloproteinase inhibitors/OR No MMP inhibitors	7. No matrix metalloproteinase inhibitors/OR No MMP inhibitors
O	8. Bond strength/OR Bond stability	8. Bond strength/OR Bond stability
Combined	1 OR 2 OR 3 OR 4 AND 6 AND 7 AND 8)	1 OR 2 OR 3 OR 4 AND 6 AND 7 AND 8)

Abbreviation: MMP, matrix metalloproteinase.

Data Selection and Collection Processes

Full texts of all eligible studies were uploaded to reference management software (EndNote X9.3.1) and duplicate publications were removed automatically. Two authors (H.J. and R.Y.) screened the titles and abstracts, and the full text of studies meeting the inclusion criteria was read. Two evaluators (H.J. and R.Y.) independently screened each full-text paper based on the eligibility criteria. In case of discrepancies about study eligibility between the two reviewers, a further evaluator was involved (H.A. or P.A.). A data extraction form included the following: authors' names, year of publication, type of MMP inhibitor used, duration of MMP inhibitor used as dentine pretreatment, substrate condition, type of bonding agent, type of ageing solution, period of ageing, type of bond strength test, and bond strength means. Two reviewers (H.J. and R.Y.) were independently involved in data collection. An experienced third reviewer (P.A.) independently extracted data from 10% of studies to check process consistency. Conflicts of opinion were resolved through consensus by consulting a further reviewer (H.A. or A.Y.).

Risks of Bias and Quality Assessment

A quality assessment tool adapted from a previous study²⁸ was independently used by two reviewers (H.J. and R.Y.). The tool evaluated bias in terms of sample randomization, substrate condition, duration of dentine pretreatment, the use of materials according to the manufacturer's instructions, storage medium, interface surface area, restorative and bond tests performed by a single operator, sample size calculation (power analysis), and blinding of the operator during bond strength testing. Minor modifications were added to the risk of bias evaluation tool, which are "dentine pretreatment duration" and "storage medium". For each component of the tool, the letter "Y (yes)" was assigned if the author reported the item and "N (no)" if it was not reported. The grading judgement of "low," "medium," or "high" for the study was based on the total number of "Ys" as follows: one to five (high), six, or seven (medium), and eight or nine (low).

Data Synthesis

Findings were summarized narratively using text and tables. For example, findings were summarized according to type of MMP inhibitor used, duration of dentine pretreatment, substrate condition (caries-free or caries-affected), type/mode of bonding agent, type of ageing solution, period of ageing, type of bond strength test, and mean bond strength.

Meta-analysis

Review Manager (RevMan) version 5.4 software from the Cochrane Collaboration was used for meta-analyses using the following information: the average difference in outcome measures between the intervention and control groups, the number of teeth in each treatment group, and the standard deviations. These data were categorized into three time periods: 24 hours, 6 months, and 12 months, where applicable, and further divided into the type of MMP inhibitor, the adhesive application method used (self-etching or etch and rinse), and the pretreatment duration. Only MMP inhibitors applied for 30 and 60 seconds were included as they contained enough data for the meta-analysis.

The mean differences (MDs) and their 95% confidence intervals (CIs) were calculated. Findings from all comparisons were generally pooled according to the three time periods (24 hours, 6 months, and 12 months). After establishing the pooled MDs according to time, additional pooling was carried out depending on the various parameters indicated. A positive MD supports the experimental group, whereas a negative MD favors the control group. A random-effects model was used to generate MDs with 95% CIs for treatment and control comparisons.

The Q-test and I^2 -test were used to test for heterogeneity. The I^2 statistics was interpreted according to the Cochrane guidelines, with 0 to 29% as being low, 30 to 50% as moderate, and 50 to 90% as considerable heterogeneity.²⁹ The proportion of total variance across studies attributable to heterogeneity rather than chance was calculated.

Finally, the overall effects were tested using the Z-test, while subgroup differences were tested using Chi-squared tests.

The following analyses were carried out:

1. 2% chlorhexidine (CHX) versus control at baseline (24 hours).
2. 2% CHX versus control at 6 months.
3. 2% CHX versus control at 12 months.
4. 0.3 M 1-Ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) versus control at baseline.
5. 0.3 M EDC versus control at 12 months.
6. 0.1% riboflavin (RIBO) versus control at baseline.
7. 0.1% RIBO versus control at 6 months.
8. 2% CHX versus control at baseline (according to pretreatment duration of 30 seconds).
9. 2% CHX versus control at 6 months (according to pretreatment duration of 30 seconds).
10. 2% CHX versus control at baseline (according to pretreatment duration of 60 seconds).
11. 2% CHX versus control at 6 months (according to pretreatment duration of 60 seconds).

Results

Study Selection

A flowchart summarizing the selection process according to the PRISMA statement is shown in ►Fig. 1.²⁷ During the initial search, 934 potentially eligible studies were retrieved. After removal of duplicates, 763 studies remained of which 193 remained after reviewing the titles and 163 after reviewing the abstracts. Following reading the full texts,

64 studies were included in the study and 42 were included in the meta-analysis.

Study Characteristics

The data obtained from the included publications are listed in ►Table 2. The 64 included *in vitro* studies were published between 2009 and 2022.

Thirty-one different types of MMP inhibitors were used, 14 synthetically derived and 17 naturally derived. The micro-tensile bond strength test was used in all included studies except for five studies that used microshear bond strength testing. Most studies ($n = 53$) used caries-free dentine substrate, 13 used caries-affected dentine, two studies used eroded dentine, and one study used dentine without mentioning its condition. All studies used permanent teeth except for one study that used primary teeth.

With respect to storage medium, the majority of studies used distilled water (40 studies) and 22 used artificial saliva. Two studies used both distilled and deionized water. The majority of the studies applied MMP inhibitor for 60 s ($n = 47$), six studies applied it for 30 seconds, four for 120 seconds, three for 5 seconds, two for 15 seconds, and one each for 20 and 180 seconds. One study did not report the application duration. Only MMP inhibitors applied for 30 and 60 seconds were included in the meta-analysis, as they contained enough data.

Ageing periods ranged from 24 hours to 5 years, and various thermocycling ageing protocols were also used. The majority of studies ($n = 62$) aged samples for 24 hours as an immediate ageing period. With respect to long-term ageing, 31 studies aged the samples for 6 months, 19 aged them for 12 months, five aged them for 3 months, three for 2 years, three for 18 months, two for 9 months, and one study each for 3 days, 1 week, 15 days, 15 months, and 5 years. Eleven studies used thermocycling for ageing: four used 1,000 cycles, two used 5,000 cycles, and one study each used 2,500, 3,000, 10,000, and 25,000 cycles.

Risk of Bias Evaluation

►Table 3 shows the evaluated risk of bias of the included studies. Overall, almost half of included studies showed a medium risk of bias (33 of 64), 17 of 64 studies showed a high risk of bias, and 14 studies were classified as a low risk of bias.

Meta-Analysis

Of the 64 studies, data from 42 studies were subjected to further evaluation in meta-analyses (►Figs. 2–6). In the first analysis (2% CHX vs. control in the baseline, immediate bond strength values), 16 etch-and-rinse studies were included, representing 28 datasets considered. There was no statistically significant difference between groups ($Z\text{-test} = 1.26$, $p = 0.21$), and there was considerable heterogeneity ($I^2 = 54\%$). Eight self-etching studies were included, with 11 datasets considered. There was no significant difference between groups ($Z\text{-test} = 0.76$, $p = 0.45$), and there was moderate heterogeneity ($I^2 = 35\%$). Overall (self-etching and etch-and-rinse), there was no statistically significant difference

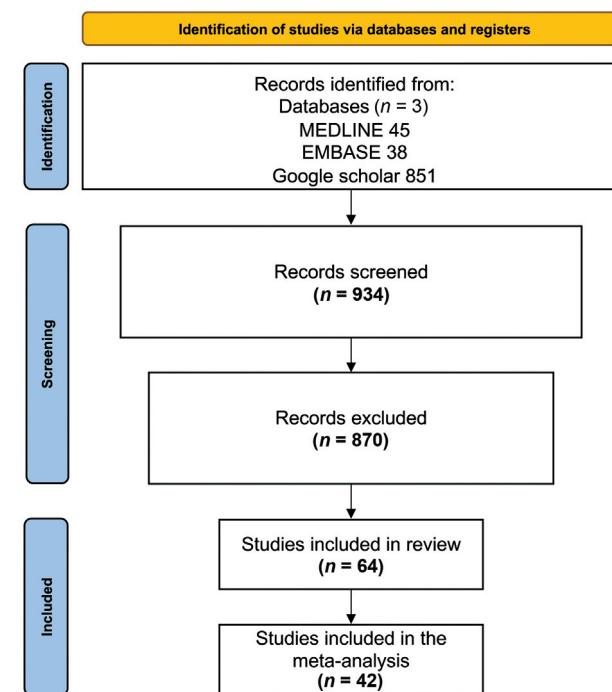


Fig. 1 PRISMA 2020 flowchart diagram of study selection.²⁷ PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses.

Table 2 Characteristics of the included studies

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Baena et al/2020 ³⁰	CS	60	Caries-free	Optibond FL (Kerr; etch-and-rinse; OFL) Scotchbond Universal (3M; self-etch; SBU)	Artificial saliva	24 hours	CS 0.1% + OFL Control (OFL) CS 0.1% + SBU Control (SBU)	38.0 (7.7) 41.3 (14.5) 28.1 (14.3) 25.0 (16.5)
Balloni et al/2017 ³¹	CHX	60	Caries-free	Clearfil SE bond (self-etch)	Water	24 hours	CS 0.1% + OFL Control (OFL) CS 0.1% + SBU Control (SBU)	29.2 (14.1) 32.2 (12.9) 33.1 (17.0) 30.4 (11.8)
Bravo et al/2017 ³²	CHX	20	Caries-free	Adper Scotchbond 1XT (etch-and-rinse; ASB) Adper Prompt (self-etch; AP) Single Bond Universal (self-etch; SBU)	Water	3 days	CHX 2% + ASB Control (ASB) CHX 2% + AP Control (AP) CHX 2% + SBU Control (SBU)	26.28 (9.29) 28.56 (5.83) 24.21 (7.52) 20.14 (4.87) 28.43 (9.78) 29.24 (7.90)
de Faria Teixeira et al/2015 ³³	CHX	60	Not mentioned	Clearfil SE bond (self-etch)	Water	24 hours	CHX 2% + ASB Control (ASB) CHX 2% + AP Control (AP) CHX 2% + SBU Control (SBU)	32.26 (10.33) 19.82 (7.65) 28.51 (13.18) 44.11 (12.09) 23.54 (12.09)
Comba et al/2020 ³⁴	DCC	60	Caries-free	Scotch bond universal (SBU) (self-etch) and etch and rinse	Artificial saliva	24 hours	CHX 2% + ASB Control (ASB) CHX 2% + AP Control (AP) CHX 2% + (SBU) Control (SBU)	31.73 (5.18) 23.39 (5.69) 27.37 (4.40) 20.51 (5.66) 36.88 (6.65) 23.62 (7.07)
Czech et al/2019 ²⁴	CHX EGCG	60	Caries-affected	Adper Single Bond 2 (etch and rinse)	Water	24 hours	CHX 2% Control	28.0 (8.4) 24.2 (7.2)
						6 months	CHX 2% Control	33.4 (9.3) 21.8 (7.3)
						12 months	0.5M DCC SBU (ER) Control SBU (ER) 0.5M DCC SBU (SE) Control SBU (SE)	46.0 (5.3) 37.1 (12.5) 39.4 (11.1) 26.3 (11.4)
							0.5M DCC SBU (ER) Control SBU (ER) 0.5M DCC SBU (SE) Control SBU (SE)	33.5 (13.9) 31.0 (11.0) 35.3 (13.9) 13.4 (9.1)
						6 months	EGCG 200 µg/mL CHX 2% Control	24.08 (7.20) 14.64 (7.74) 23.43 (7.73)
						12 months		18.67 (8.51) 11.20 (4.79) 16.28 (9.58)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Dávila-Sánchez et al/ 2020 ³⁵	QUE HES RUT NAR PAC	60	Caries-affected	Scotchbond Universal (3M; etch and rinse)	Water	24 hours	HES 6.5% PAC 6.5% QUE 6.5% NAR 6.5% RUT 6.5% Control	16.77 (5.50) 10.17 (3.02) 14.91 (6.92)
Costa et al/2019 ³⁶	CHX EGCG	60	Eroded (ERO) and non-eroded (non-ERO)	Clearfil SE bond (self-etch)	Water	24 hours	CHX 2% (non-ERO) CHX 2% (ERO) EGCG 0.1% (non-ERO) EGCG 0.1% (ERO) Control (non-ERO) Control (ERO)	18.41 (5.30) 20.66 (3.92) 24.58 (4.90) 24.64 (3.70) 26.00 (5.51) 14.42 (4.43)
El Baz and Aboulenien/ 2018 ³⁷	EGCG	60	Caries-free	Primer and Bond one (Dentsply; etch and rinse)	Water	6 months	CHX 2% (non-ERO) CHX 2% (ERO) EGCG 0.1% (non-ERO) EGCG 0.1% (ERO) Control (non-ERO) Control (ERO)	40.87 (10.23) 49.30 (9.42) 53.67 (6.10) 61.61 (3.17) 52.44 (8.47) 59.25 (5.91)
Fang et al/2017 ³⁸	MAP GM6001	60	Caries-free	Gluma Comfort Bond (etch and rinse)	Water	24 hours	MAP 1 mg/mL GM6001 10 μM	32.77 (10.67) 36.91 (9.88) 50.02 (3.42) 44.63 (3.26) 47.64 (11.67) 45.16 (11.87)
Fernandes et al/2021 ³⁹	CHX EGCG	60	Caries-free	Clearfil SE Bond Primer (self-etch)	Artificial saliva	6 months	EGCG 0.1% Control	18.8 (0.2) 15.4 (0.7)
Fialho et al/2019 ⁴⁰	CHX EGCG	60	Caries-affected	Adper Single Bond 2 (3M; etch and rinse)	Water	24 hours	CHX 2% EGCG 0.01% Control	19.31 (4.48) 18.86 (4.2) 19.25 (4.21)
						12 months	CHX 2% EGCG 0.01% Control	12.22 (4.49) 10.87 (4.27) 6.08 (3.12)
							CHX 2% EGCG 0.01% Control	44.16 (6.81) 42.76 (7.36) 40.65 (6.51)
							CHX 2% EGCG 0.01% Control	33.58 (10.49) 34.91 (7.84) 33.85 (9.27)
							EGCG 0.2% EGCG 2% EGCG 0.5% CHX 2% Control	32.65 (9.97) 29.16 (11.32) 28.57 (6.30) 33.33 (11.26) 35.81 (8.25)
						12 months	EGCG 0.2% EGCG 2% EGCG 0.5%	22.75 (9.38) 17.15 (10.61) 23.65 (7.19)

(continued)

Table 2 (continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Gerhardt et al./2016 ⁴¹	CHX EGCG GT	60	Caries-free	Clearfil SE Bond (self-etch)	Water	24 hours	CHX 2% Control	19.98 (7.01) 26.17 (12.28)
							CHX 2% EGCG 2% GT 2% Control	13.31 (3.36) 6.93 (3.43) 10.60 (4.69) 8.64 (5.52)
Campos et al./2019 ⁴²	CHX	Not mentioned	Caries-affected	Clearfil SE Bond (self-etch)	Water	24 hours	CHX 2% Control	11.09 (4.98) 15.96 (5.32) 17.82 (12.20) 16.69 (7.20)
							CHX 2% Control	19.84 (8.11) 24.89 (9.44)
Giacomini et al./2020 ⁴³	CHX	30	Caries-free	Adper Single Bond 2 (etch and rinse) Adper Single Bond Universal (etch and rinse) Adper Single Bond Universal self-etch (self-etch)	Artificial saliva	24 hours	CHX 2% (ASB) Control	17.59 (8.85) 28.30 (11.54)
							CHX 2% (ASU-ER) Control	28.41 (7.64) 33.35 (9.01) 33.66 (7.79) 31.62 (8.20) 37.47 (10.68) 45.62 (12.39)
Grandizoli and Pinheiro/2018 ⁴⁴	CHX	60	Caries-affected	Clearfil SE bond (self-etch)	Water	24 hours	CHX 2% (ASB) Control	31.55 (6.15) 32.59 (9.44) 33.79 (6.24) 32.05 (7.04) 34.25 (11.21) 40.15 (14.77)
							CHX 2% (ASU-ER) Control	21.7 (16.3) 19.3 (11.9)
Kairabi and Danesh Kazemi/2016 ⁴⁵	CHX	120	Caries-free	Adper Single Bond (etch and rinse)	Artificial saliva	6 months	CHX 2% Control	1.9 (1.8) 2.5 (1.2)
							CHX 2% Control	52.67 (6.86) 28.84 (6.23)
Kasraei et al./2017 ⁴⁶	RIBO	120	Caries-free	Adper Single Bond (etch and rinse)	Water	5,000 thermocycles	RIBO 0.1% Control	12.79 (3.64) 12.64 (2.35)
							CHX 2% Control	32.8 (3.8) 30.7 (2.2) 25.1 (4.0) 24.3 (3.8)
Lenzi et al./2014 ⁴⁷	CHX	60	Caries-free and caries-affected	Adper Single Bond (etch and rinse)	Water	24 hours	CHX 2% Control	31.3 (2.6) 24.2 (3.6) 23.2 (5.2) 14.3 (5.8)
							CHX 2% (CA) Control	58.86 (4.29) 58.32 (3.95) 41.89 (5.18)
Li et al./2018 ⁴⁸	BAI GD	120	Caries-free	Adper Single Bond 2 (etch and rinse)	Artificial saliva	24 hours	GD 5% BAI 2.5 µg/ml Control	56.10 (5.89) 52.43 (5.43) 34.46 (6.22)
							GD 5% BAI 2.5 µg/ml Control	
							6 months	

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Loguercio et al/2016 ⁴⁹	CHX	60	Caries-free	Primer & Bond NT (etch-and-rinse; PB) Adper Single Bond 2 (etch and rinse)	Water	24 hours	GD 5% BAI 2.5 µg/ml Control	51.86 (6.42) 52.43 (5.43) 26.82 (5.30)
Loguercio et al/2009 ⁵⁰	CHX	15/60	Caries-free	Primer & Bond (etch and rinse) Adper Single Bond (SB; etch and rinse)	Water	24 hours	CHX 2% (PB) Control CHX 2% (ASB) Control	33.1 (2.8) 35.1 (3.1) 43.5 (3.5) 40.2 (3.3)
Maravic et al/2018 ⁵¹	ACR	60	Caries-free	Adper Scotchbond 1XT (etch and rinse)	Artificial saliva	24 hours	CHX 2% (PB) Control CHX 2% (SB) Control	22.1 (2.2) 11.0 (2.7) 31.3 (2.7) 16.1 (2.1)
Mazzoni et al/2013 ⁵²	EDC	60	Caries-free	Optibond (OB) FL (etch and rinse) Scotchbond (SB) 1XT (etch and rinse)	Artificial saliva	24 hours	CHX 2% (PB) Control CHX 2% (ASB) Control	41.2 (4.8) 39.2 (5.4) 31.3 (5.1) 29.2 (3.4)
Mazzoni et al/2018 ⁵³	EDC	60	Caries-free	Clearfil SE primer (self-etch) Xp Bond (etch and rinse)	Artificial saliva	24 hours	CHX 2% (PB) Control CHX 0.002% (PB) Control CHX 2% (SB) Control CHX 0.002% (SB) Control	32.4 (5.4) 32.4 (5.4) 41.2 (4.2) 43.2 (6.1) 41.5 (6.4)
						6 months	CHX 2% (PB) Control CHX 2% (SB) Control CHX 2% (ASB) Control	27.3 (4.2) 23.2 (4.1) 20.1 (4.2)
						12 months	CHX 2% (PB) Control CHX 2% (SB) Control CHX 2% (ASB) Control	40.1 (5.7) 37.2 (6.1) 27.9 (6.2)
							EDC 0.3M + OB Control EDC 0.3M + SB Control	28.1 (4.4) 27.0 (3.6) 21.2 (3.8) 37.6 (3.3) 40.1 (3.7) 25.4 (4.1)
							EDC 0.3M + OB Control EDC 0.3M + SB Control	41.2 (10.1) 33.1 (7.9) 32.5 (9.6) 24.8 (8.8)
							EDC 0.3M + (Clearfil) Control EDC 0.3M + (XP bond) Control	30.1 (6.3) 32.8 (4.4) 36.5 (7.1) 37.6 (5.9)
						12 months		

(Continued)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Mohamed et al/2020 ⁵⁴	CS	60	Caries-free	Universal Single Bond adhesive (self-etch)	Water	24 hours	CS 0.2% CS 2.5% Control	39.16 (38.62) 15.63 (14.64) 20.83 (21.43)
Mosallam et al/2018 ⁵⁵	GT MA MN	60	Caries-free	Tetric N-Bond Universal (etch and rinse)	Water	24 hours 3 months 6 months	CS 0.2% CS 2.5% Control	23.95 (25.08) 16.89 (17.79) 21.1 (21.03)
Mosallam et al/2019 ⁵⁶	MA MN	60	Caries-free	Scotch Bond Universal (etch and rinse)	Water	24 hours	GT 20mg/mL (WE) GT 5mg/mL (AE) MA 20mg/mL (WE) MA 5mg/mL (AE) MN 20mg/mL (WE) MN 5mg/mL (AE) Control	29.22 (6.29) 16.70 (5.39) 4.01 (1.92) 26.68 (5.81) 24.90 (6.74) 26.68 (5.81) 28.38 (6.68)
Ou et al/2018 ⁵⁷	CHX MMP8-I inhibitor	30	Caries-free	Adper Single Bond 2 (etch and rinse)	Water	24 hours 6 months 12 months	GT 20mg/mL (WE) GT 5mg/mL (AE) MA 20mg/mL (WE) MA 5mg/mL (AE) MN 20mg/mL (WE) MN 5mg/mL (AE) Control	18.97 (6.66) 12.73 (6.63) 2.64 (2.27) 17.93 (4.82) 17.83 (6.57) 17.93 (4.82) 17.39 (1.71)
Paulose and Fawzy/ 2018 ⁵⁸	EDC	60	Caries-free	Adper Scotchbond multipurpose (etch-and-rinse: SBM) Single bond Universal adhesive (etch and rinse)	Water	24 hours	EDC 0.3M + SBM Control EDC 0.3M -dry + SBU Control EDC 0.3M -wet + SBU Control	40.7 (9.3) 43.2 (8.1) 39.7 (5.3) 36.9 (8.7) 30.9 (5.7) 33.6 (6.1)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Pedrosa et al/2018 ⁵⁹	CA	60	Caries-free	Adper Scotchbond multipurpose (etch-and-rinse) Clearfil SE bond (self-etch)	Water	24 hours	CA 0.05% (ASB) CA 0.1% (ASB) Control CA 0.05% (CSE) CA 0.1% (CSE) Control	34.40 (7.75) 22.38 (6.16) 40.67 (3.90) 23.47 (6.91) 25.73 (5.55) 31.74 (8.05)
Perote et al/2015 ⁶⁰	CHX EPE APE	60	Caries-free	Adper Single Bond 2 (etch and rinse)	Artificial saliva	24 hours	CHX 0.2% EPE 10% APE 10% Control	31.6 (7.0) 29.1 (6.9) 33.0 (6.7) 28.6 (5.3)
Porto et al/2018 ⁶¹	CHX QfE Res	60	Caries-free	Single Bond Universal (etch and rinse)	Water	24 hours	CHX 2% QfE ($\mu\text{g mL}^{-1}$) 100 250 500 1,000 Res ($\mu\text{g mL}^{-1}$) 100 250 500 1,000 QfE + Res ($\mu\text{g mL}^{-1}$) 3:1 100 250 500 1,000 QfE + Res 1:1 100 250 500 1,000 Control	27.78 (6.88) 32.06 (8.90) 27.51 (3.70) 31.21 (9.93) 31.30 (10.33) 18.81 (6.07) 23.90 (7.46) 23.74 (5.98) 20.11 (5.31) 27.40 (7.19) 19.33 (6.02) 28.44 (7.07) 31.38 (8.45) 18.78 (3.63) 23.93 (7.20) 23.29 (5.23) 19.10 (5.49) 22.73 (6.37) 20.83 (6.61) 25.99 (7.89) 23.76 (5.76) 23.62 (6.71)
						3 months	CHX 2% QfE ($\mu\text{g mL}^{-1}$) 100 250 500 1,000 Res ($\mu\text{g mL}^{-1}$) 100 250	30.68 (8.71) 25.29 (8.01) 34.68 (16.17) 42.37 (13.59) 37.40 (11.37) 31.03 (11.25) 37.90 (10.11)

(Continued)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Prasansuttiporn et al/ 2020 ⁶²	RA	5	Caries-affected	Clearfil SE Bond (self-etch)	Artificial saliva	24 hours	RA 100 µM Control	35.4 (5.5) 35.1 (5.3)
Prasansuttiporn et al/ 2017 ⁶³	RA	5	Caries-free	Clearfil SE Bond (self-etch)	Artificial saliva	12 months	RA 100 µM Control	34.2 (4.3) 30.3 (4.2)
Ruksaphon and Pisol/ 2017 ⁶⁴	CHX RA	60	Caries-free	OptiBond FL (etch and rinse) OptiBond Solo (solo) (etch and rinse)	Artificial saliva	24 hours	RA 100 µM Control	54.8 (3.9) 55.2 (4.1)
						12 months	RA 100 µM Control	52.6 (4.7) 45.8 (4.0)
							CHX 2% + (solo) CHX 2% + (FL) RA 100 µM + (solo) RA 100 µM + (FL) Control (solo) Control (FL)	38.42 (3.04) 38.46 (7.82) 36.00 (8.04) 41.27 (6.76) 39.60 (7.50) 37.27 (8.45)
						3 months	CHX 2% + (solo) CHX 2% + (FL) RA 100 µM + (solo) RA 100 µM + (FL) Control (solo) Control (FL)	40.75 (7.12) 41.26 (5.51) 39.43 (10.12) 41.27 (6.76) 32.13 (7.32) 29.45 (8.12)
						6 months	CHX 2% + (solo) CHX 2% + (FL) RA 100 µM + (solo) RA 100 µM + (FL) Control (solo) Control (FL)	32.83 (6.82) 29.33 (6.66) 31.37 (10.24) 32.79 (7.37) 30.54 (8.05) 26.46 (6.39)
						12 months	CHX 2% + (solo) CHX 2% + (FL) RA 100 µM + (solo) RA 100 µM + (FL) Control (solo) Control (FL)	22.85 (11.72) 27.83 (11.54) 28.98 (7.68) 28.04 (9.09) 31.10 (8.22) 3.91 (9.20)
Sacramento et al/ 2012 ⁶⁵	CHX	60	Caries-affected	Clearfil protect Bond (self-etch) Clearfil SE Bond (self-etch)	Water	24 hours	CHX 2% (SE) CHX 2% (PB) Control (SE) Control (PB)	12.39 (2.37) 14.60 (3.65) 12.28 (2.91) 16.24 (2.71)
						6 months		

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Sadeghi et al/2017 ⁶⁶	CHX	60	Caries-free	Optibond Solo Plus (etch and rinse) Single Bond Universal (SBU; etch and rinse)	Water	1 week	CHX 2% (SE) CHX 2% (PB) Control (SE) Control (PB)	2.88 (1.30) 3.09 (0.92) 2.95 (0.77) 2.32 (0.60)
Santiago et al/2013 ⁶⁷	CHX EGCG	60	Caries-free	Adper Single Bond 2 (etch and rinse)	Water	24 hours	CHX 0.2% + OSP Control CHX 0.2% + SBU Control	1.76 (0.35) 2.34 (0.76) 1.36 (0.22) 1.11 (0.59)
Shen et al/2020 ⁶⁸	CHX	60	Caries-free	Single Bond 2 (etch and rinse)	Water	24 hours	EGCG 0.02% EGCG 0.1% EGCG 0.5% CHX 2% Control	29.84 (5.43) 34.57 (8.22) 35.75 (8.58) 58.17 (10.25)
Venigalla et al/2016 ⁶⁹	RIBO EDC PAC	120	Caries-free	Adper Single Bond water wet bonding (etch and rinse) Ethanol wet bonding (etch and rinse)	Artificial saliva	6 months	EGCG 0.02% EGCG 0.1% EGCG 0.5% CHX 2% Control	20.59 (5.52) 22.51 (3.55) 23.28 (3.90) 33.42 (7.04)
Xu et al/2020 ⁷⁰	BAC PVPA PAC	30	Caries-free	Clearfil SE bond (self-etch)	Water	24 hours	RIBO 0.1% + WWB EDC 1M + WWB PAC 6.5% + WWB Control RIBO 0.1% + EWB EDC 1M + EWB PAC 6.5% + EWB Control	1.74 (0.35) 2.34 (0.76) 1.36 (0.22) 1.11 (0.59)
							RIBO 0.1% + WWB EDC 1M + WWB PAC 6.5% + WWB Control RIBO 0.1% + EWB EDC 1M + EWB PAC 6.5% + EWB Control	29.2 (6.6) 27.9 (4.1) 26.5 (6.9) 26.9 (5.8) 31.7 (4.0) 30.4 (6.7)

(Continued)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Kazemi-Yazdi et al/ 2020 ⁷¹	CHX	60	Caries-free	Clearfil SE Bond (self-etch)	Water	24 hours	CHX 2% Control	14.58 (5.04) 18.00 (5.54)
Da Silva et al/ 2015 ⁷²	CHX	60	Caries-free	Single Bond 2 (etch and rinse) Ambar (etch and rinse)	Water	24 hours	CHX 2% (SB) Control CHX 2% (Ambar) Control	14.36 (7.44) 16.71 (8.00)
Zheng et al/ 2015 ⁷³	CHX GT FeSO ₄ Galardin	60	Caries-free	Optibond FL (etch and rinse) Clearfil SE Bond (self-etch)	Artificial saliva	9 months	CHX 2% (FL) GT 0.05% (FL) FeSO ₄ 1 mM (FL) Galardin 0.2 mM (FL) Control CHX 2% (SE) GT 0.05% (SE) FeSO ₄ 1 mM (SE) Galardin 0.2 mM (SE) Control	32.9 (11.3) 33.2 (14.0) 25.3 (10.5) 33.6 (10.5) 25.3 (11.8) 32.9 (11.3) 26.1 (14.2) 25.3 (10.5) 33.6 (14.1) 20.3 (13.6)
Sadek et al/ 2010 ⁷⁴	CHX	60	Not mentioned	Scotchbond multipurpose (self-etch) Single Bond 2 (self-etch) Experimental ethanol wet-bonding adhesive (self-etch)	Artificial saliva	24 hours	CHX 2% + EWB Control CHX 2% + MP Control CHX 2% + SB Control	46.8 (5.1) 45.8 (7.2) 41.3 (8.1) 44.2 (3.5) 42.6 (5.2) 42.3 (7.4)
Breschi et al/ 2010 ²²	Galardin	30	Caries-free	Adper Scotchbond 1XT (etch and rinse)	Artificial saliva	24 hours	CHX 2% + EWB Control CHX 2% + MP Control CHX 2% + SB Control	44.6 (5.6) 44.4 (6.9) 37.4 (5.6) 37.4 (3.5) 38.2 (4.7) 44.4 (4.9)
						9 months	CHX 2% + EWB Control CHX 2% + MP Control CHX 2% + SB Control	43.6 (5.5) 44.2 (7.8) 30.5 (8.0) 32.6 (7.1) 28.8 (8.3) 31.5 (4.3)
						18 months	CHX 2% + EWB Control CHX 2% + MP Control CHX 2% + SB Control	44.1 (7.3) 41.4 (5.9)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Stanislawczuk et al/ 2009 ⁷⁵	CHX	60	Caries-free	Prime & Bond NT (etch and rinse) Single Bond (SB) 2 (etch and rinse)	Water	24 hours	Galardin 0.2 mM Control	32.4 (6.6) 22.6 (5.4)
						12 months	CHX 2% + Prime & Bond Control CHX 2% + (SB) Control	21.9 (4.7) 22.0 (9.7) 23.4 (2.1) 14.6 (3.1)
						6 months	CHX 2% + Prime & Bond Control CHX 2% + (SB) Control	31.1 (3.1) 27.2 (6.1) 31.1 (2.6) 20.4 (2.1)
Firouzmandi et al/ 2020 ⁷⁶	SDF	180	Caries-free and Caries-affected (CA)	Adper single Bond 2 (etch and rinse)	Water	24 hours	SDF 30% Control SDF 30% (CA) Control	17.08 (4.88) 18.37 (4.71) 17.63 (4.19) 12.20 (2.34)
						6 months	SDF 30% Control SDF 30% (CA) Control	15.72 (2.34) 14.72 (3.51) 10.30 (3.78) 11.53 (2.66)
Giacomini et al/2017 ⁷⁷	CHX E-64	60	Caries-free Eroded (ERO) and Caries-affected (CA)	Adper Single Bond Universal (etch and rinse)	Artificial saliva	24 hours	CHX 2% CHX 2% (ERO) CHX 2% (CA) E-64 5 µM E-64 5 µM (ERO) E-64 5 µM (CA) Control Control (ERO/water) Control (CA/water)	28.36 (5.88) 22.53 (4.76) 18.31 (3.50) 28.33 (5.42) 30.23 (6.51) 24.51 (4.41) 35.32 (5.30) 29.85 (4.77) 23.42 (4.95)
						6 months	CHX 2% CHX 2% (ERO) CHX 2% (CA) E-64 5 µM E-64 5 µM (ERO) E-64 5 µM (CA) Control Control (ERO/water) Control (CA/water)	16.50 (3.89) 20.13 (4.62) 16.50 (3.90) 20.80 (3.71) 27.70 (5.32) 20.80 (3.71) 27.45 (5.33) 26.07 (4.96) 20.28 (3.55)
Sabatini et al/2014 ⁷⁸	CHX BAC	60	Caries-free	Adper Single Bond Plus (etch and rinse)	Artificial saliva	24 hours	CHX 2% BAC 0.5% BAC 1.0% Control	38.3 (10.3) 36.4 (8.4) 51.4 (7.9) 34.3 (7.8)
						6 months	CHX 2% BAC 0.5% BAC 1.0% Control	34.3 (5.2) 36.6 (6.2) 53.9 (6.9) 27.4 (6.2)
Carvalho et al/2016 ⁷⁹	CHX EGCG	60	Caries-affected	Adper Single Bond 2 (etch-and-rinse)	Water	24 hours	EGCG 2% CHX 2% Control	23.0 (6.3) 23.3 (6.0) 24.3 (8.6)
						6 months	EGCG 2% CHX 2% Control	35.7 (8.4) 23.0 (7.2) 21.6 (6.4)

(Continued)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Loguerio et al/2016 ⁸⁰	CHX	15	Caries-free	Prime & Bond NT (etch and rinse) Adper Single Bond 2 (etch and rinse)	Water	24 hours	CHX 2% (PB) Control CHX 2% (SB) Control	44.2 (4.3) 42.3 (3.4) 50.3 (5.6) 46.2 (4.7)
							CHX 2% (PB) Control CHX 2% (SB) Control	36.3 (5.1) 23.6 (5.3) 43.3 (3.5) 32.3 (4.5)
Cova et al/2011 ⁹⁹	RIBO	60	Caries-free	XP Bond adhesive (etch and rinse)	Artificial saliva	24 hours 6 months 12 months	RIBO 0.1% Control	44.4 (10.4) 37.3 (10.3)
							RIBO 0.1% Control	35.6 (11.2) 22.0 (7.0)
							RIBO 0.1% Control	30.9 (12.2) 17.7 (9)
Mobarak/2011 ⁸¹	CHX	60	Caries-free Caries-affected (CA)	Self-etch primer adhesive (Clearfil SE Bond; self-etch)	Artificial saliva	24 hours 6 months 12 months	CHX 2% Control CHX 5% Control CHX 2% (CA) Control CHX 5% (CA) Control	23.79 (5.9) 25.94 (6.4) 24.33 (5.1) 20.84 (6.2) 20.59 (5.1) 21.73 (6.0)
							CHX 2% Control CHX 5% Control CHX 2% (CA) Control CHX 5% (CA) Control	8.74 (3.2) 10.98 (3.3) 9.46 (3.4) 9.99 (3.4) 14.67 (4.5) 9.97 (3.5)
							CHX 2% Control CHX 5% Control CHX 2% (CA) Control CHX 5% (CA) Control	8.74 (3.2) 10.98 (3.3) 9.46 (3.4) 9.99 (3.4) 14.67 (4.5) 9.97 (3.5)
Manso et al/2014 ⁴²	CHX	30	Caries-free	All Bond 3 (Bisco) (etch and rinse) Excite (Vivadent) (etch and rinse)	Water	24 hours	CHX 2%/water (Bisco) Control CHX 2%/ethanol (Bisco) Control CHX 2%/water (Excite) Control CHX 2%/ethanol (Excite) Control	46.96 (3.6) 51.07 (3.6) 54.67 (3.6) 59.41 (3.6) 40.05 (5.4) 49.51 (5.4) 53.37 (5.4) 49.67 (5.4)
							CHX 2%/water (Bisco) Control CHX 2%/ethanol (Bisco) Control CHX 2%/water (Excite) Control CHX 2%/ethanol (Excite) Control	50.69 (3.6) 57.13 (3.6) 52.17 (3.6) 56.41 (3.6) 36.78 (5.4) 42.10 (5.4) 57.47 (5.4) 44.56 (5.4)
							CHX 2%/water (Bisco) Control CHX 2%/ethanol (Bisco) Control CHX 2%/water (Excite) Control CHX 2%/ethanol (Excite) Control	46.07 (4.4) 47.29 (4.4) 39.58 (4.4) 44.41 (4.4) 40.87 (6.6) 45.51 (6.6) 49.55 (6.6) 42.48 (5.4)
Breschi et al/2010 ¹⁹	CHX	30	Caries-free	Adper Scotchbond 1XT (etch and rinse)	Artificial saliva	24 hours	CHX 2% Control CHX 0.2% Control	41.2 (9.6) 39.2 (9.3) 40.8 (8.7)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Montagner et al/ 2015 ⁸⁵	CHX	60	Caries-free	Adper Single Bond 2 (etch and rinse)	Water	24 hours 18 months	CHX 2% CHX 0.2% Control CHX 2% Control	28.5 (7.2) 32.6 (8.3) 13.4 (4.9) 25.3 (6.2) 26.7 (10.0) 20.1 (10.3) 14.8 (9.4)
Li et al/2020 ⁸⁴	DMA	60	Caries-free	Adper Single Bond 2 (etch and rinse)	Water	24 hours 1,000 thermocycles	DMA 0.1 mM DMA 1.0 mM DMA 10 mM Control DMA 0.1 mM DMA 1.0 mM DMA 10 mM Control	28.73 (5.19) 30.76 (7.57) 27.06 (7.53) 29.96 (6.43) 23.84 (7.06) 29.19 (6.58) 23.34 (7.26) 16.24 (6.90)
Hass et al/2016 ⁸⁸	PAC RIBO GD	60	Caries-free	Adper Single Bond 2 (etch and rinse) Tetric N-Bond (etch and rinse)	Water	24 hours	PAC 6.5% (SB) RIBO 0.1% (SB) GD 5% (SB) Control PAC 6.5% (TN) RIBO 0.1% (TN) GD 5% (TN) Control	36.2 (5.5) 37.1 (9.7) 38.5 (2.4) 39.5 (7.9) 29.2 (1.2) 31.5 (6.9) 35.7 (1.9) 36.8 (4.7)
Kalagi et al/2020 ⁸⁵	CHX	5	Caries-free	Adper Scotchbond multipurpose (etch and rinse)	Water	18 months	PAC 6.5% (SB) RIBO 0.1% (SB) GD 5% (SB) Control PAC 6.5% (TN) RIBO 0.1% (TN) GD 5% (TN) Control	31.9 (4.3) 31.6 (3.5) 29.7 (2.6) 13.9 (1.8) 27.6 (6.3) 25.1 (1.3) 24.2 (1.4) 13.9 (1.8)
Tekçe et al/2016 ⁸⁶	CHX	60	Caries-free	Single Bond Universal (self-etch) All Bond Universal (self-etch)	Water	24 hours 6 months	CHX 2% (SBU) CHX 2% (ABU) Control CHX 2% (SBU) CHX 2% (ABU) Control	45.22 (6.32) 43.33 (3.41) 38.92 (4.01) 43.81 (3.61) 41.19 (3.98) 37.67 (3.40) 31.37 (5.97) 38.54 (6.19)
de Moura et al/2021 ⁸⁷	GT	60	Caries-affected	Adper Single Bond 2 (etch-and-rinse)	Water	24 hours 6 months	GT 0.05% GT 0.2% GT 2% Control GT 0.05% GT 0.2% GT 2% Control	14.42 (6.20) 17.80 (6.49) 11.04 (2.94) 11.29 (4.78) 9.53 (4.83) 13.25 (5.82) 7.09 (4.14) 8.82 (6.23)

(Continued)

Table 2 (Continued)

Study/year	MMP inhibitor type	Pretreatment duration (s)	Substrate condition	Adhesive system (mode of application)	Ageing solution	Period of ageing	Groups	Bond strength means (SD)
Li et al/2021 ⁸⁸	DMA	60	Caries-free	Adper Single Bond 2 (etch-and-rinse)	Water	24 hours	DMA 1 mM DMA 5 mM DMA 10 mM Control	33.16 (8.41) 32.59 (8.70) 32.73 (7.39) 30.08 (7.55)

Abbreviations: ACR, acrolein; AE, alcohol extract; APE, aqueous propolis extract; BA1, baicalein; BAC, benzalkonium chloride; CA, caffeic acid; CS, chitosan; CHX, chlorhexidine; DCC, N,N'-dicyclohexylcarbodiimide; DMA, dopamine methacrylamide; EDC, carbodiimide; EGCG, epigallocatechin gallate; EPE, ethanolic propolis extract; FeSO₄, ferrous sulfate; GD, 5% glutaraldehyde; GT, green tea; HES, hesperidin; MA, *Morus alba* leaves; MAP, mussel adhesive protein; MN, *Morus nigra* leaves; NAR, naringin; PAC, proanthocyanidin; PVPA, polyvinylphosphonic acid; QUE, quercetin; RA, rosmarinic acid; Res, resveratrol; RBO, riboflavin; RUT, rutin; SDF, silver diamine fluoride; WE, water extract.

between groups ($Z\text{-test} = 1.51$, $p = 0.13$), with moderate heterogeneity observed between subgroups ($I^2 = 49\%$; ▶Fig. 2A).

The second analysis (2% CHX vs. control at 6 months of ageing) included 14 etch-and-rinse studies, representing 25 datasets. There was overall a higher bond strength for the experimental group compared with controls, but this was not statistically significant ($Z\text{-test} = 1.81$, $p = 0.07$) and heterogeneity was considerable ($I^2 = 88\%$). Six self-etching studies were included, with nine datasets considered. There was no statistically significant difference between groups ($Z\text{-test} = 0.86$, $p = 0.39$), and again there was considerable heterogeneity ($I^2 = 73\%$). Tests for overall effect showed significantly higher bond strength in the experimental group compared with controls ($Z\text{-test} = 2.33$, $p = 0.02$), with considerable heterogeneity between subgroups ($I^2 = 86\%$; ▶Fig. 2B).

The third analysis (2% CHX vs. control at 12 months of ageing) included five etch-and-rinse studies with seven datasets. There were overall higher bond strength values in the experimental group compared with the control group, but this was not statistically significant ($Z\text{-test} = 1.09$, $p = 0.28$) and heterogeneity was considerable ($I^2 = 91\%$). For self-etching, three studies were included with four datasets considered, and there was no statistically significant difference between groups ($Z\text{-test} = 0.18$, $p = 0.86$) but with considerable heterogeneity ($I^2 = 84\%$). Tests for overall effect favored the experimental group over the control group but without statistical significance ($Z\text{-test} = 1.66$, $p = 0.10$) and with considerable heterogeneity between subgroups ($I^2 = 90\%$; ▶Fig. 2C).

For the fourth analysis (0.3 EDC vs. control at baseline), only etch-and-rinse studies met the inclusion criteria. Three studies were included, representing six datasets. Overall, the effect was not statistically significant ($Z\text{-test} = 0.33$, $p = 0.74$). Heterogeneity between groups was low ($I^2 = 0\%$; ▶Fig. 3A).

For the fifth analysis (0.3 EDC vs. control at 12 months), again, three etch-and-rinse studies representing six datasets were included. Overall, there were significantly higher bond strength values in the experimental group compared with the control group ($Z\text{-test} = 2.58$, $p = 0.01$) but with considerable heterogeneity ($I^2 = 66\%$; ▶Fig. 3B).

For the sixth analysis (0.1% RIBO vs. control at baseline), only two etch-and-rinse studies met the criteria, representing three datasets. There was overall a significant difference favoring the experimental group over the control group ($Z\text{-test} = 3.12$, $p = 0.002$), with considerable heterogeneity ($I^2 = 99\%$; ▶Fig. 4A).

For the seventh analysis (0.1% RIBO vs. control at 6 months), two studies representing three datasets showed significantly higher bond strengths in the experimental group than the control group ($Z\text{-test} = 5.78$, $p < 0.00001$) but with considerable heterogeneity ($I^2 = 98\%$; ▶Fig. 4B).

For the eighth analysis of pretreatment for 30 seconds (2% CHX vs. control at baseline), only four etch-and-rinse studies were included, representing seven datasets. There was overall a statistically significant difference favoring the control

Table 3 Quality assessment and risk of bias

Study/year	Randomization	Substrate condition	Dentine pretreatment duration	Manufacturer instruction	Storage medium	Interface surface area	Single operator	Sample size calculation	Blinding of operator	Risk of bias
Baena et al/2020 ³⁰	N	Y	Y	Y	Y	Y	N	N	N	High
Balloni et al/2017 ³¹	Y	Y	Y	Y	Y	Y	N	N	Y	Medium
Bravo et al/2017 ³²	Y	Y	Y	Y	Y	Y	N	N	N	Medium
de Faria Teixeira et al/2015 ³³	Y	N	Y	Y	Y	Y	N	N	N	High
Comba et al/2020 ³⁴	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Czech et al/2019 ²⁴	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Dávila-Sánchez et al/2020 ³⁵	Y	Y	Y	Y	Y	Y	Y	N	N	Low
Costa et al/2019 ³⁶	Y	Y	Y	Y	Y	Y	N	N	N	Medium
El Baz, and Aboulenien/2018 ³⁷	N	Y	Y	Y	Y	Y	Y	N	N	Medium
Fang et al/2017 ³⁸	N	Y	Y	Y	Y	Y	Y	N	N	High
Fernandes et al/2021 ³⁹	Y	Y	Y	Y	Y	Y	Y	Y	N	Medium
Fialho et al/2019 ⁴⁰	Y	Y	Y	Y	Y	Y	Y	Y	N	Low
Gerhardt et al/2016 ⁴¹	Y	Y	Y	Y	Y	Y	N	N	N	High
Campos et al/2019 ⁴²	Y	Y	N	Y	Y	Y	Y	N	N	Medium
Giacomini et al/2020 ⁴³	Y	Y	Y	Y	Y	Y	N	Y	N	Medium
Grandizoli and Pinheiro/2018 ⁴⁴	Y	Y	Y	Y	Y	Y	Y	Y	N	Medium
Karrabi and Danesh Kazemi/2016 ⁴⁵	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Kasraei et al/2017 ⁴⁶	Y	Y	N	Y	Y	Y	N	N	N	High
Lenzi et al/2014 ⁴⁷	Y	Y	Y	Y	Y	Y	N	N	N	High
Li et al/2018 ⁴⁸	Y	Y	Y	Y	Y	Y	Y	N	N	High
Loguerio et al/2016 ⁴⁹	Y	Y	N	Y	Y	Y	N	N	N	High
Loguerio et al/2009 ⁵⁰	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Maravic et al/2018 ⁵¹	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Mazzoni et al/2013 ⁵²	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Mazzoni et al/2018 ⁵³	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Mohamed et al/2020 ⁵⁴	N	Y	Y	Y	Y	Y	Y	N	N	High
Mosallam et al/2018 ⁵⁵	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Mosallam et al/2019 ⁵⁶	Y	Y	Y	Y	Y	Y	N	N	N	High
Ou et al/2018 ⁵⁷	Y	Y	Y	Y	Y	Y	N	N	N	High
Paulose and Fawzy/2018 ⁵⁸	Y	Y	Y	Y	Y	Y	Y	N	N	High
Pedrosa et al/2018 ⁵⁹	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Perote et al/2015 ⁶⁰	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Porto et al/2018 ⁶¹	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Prasansuttiporn et al/2020 ⁶²	Y	Y	Y	Y	Y	Y	Y	N	N	Medium

(Continued)

Table 3 (Continued)

Study/year	Randomization	Substrate condition	Dentine pretreatment duration	Manufacturer instruction	Storage medium	Interface surface area	Single operator	Sample size calculation	Blinding of operator	Risk of bias
Prasansuttiporn et al/2017 ⁶³	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Ruksaphon and Pisol/2017 ⁶⁴	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Sacramento et al/2012 ⁵⁵	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Sadeghi et al/2017 ⁶⁶	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Santiago et al/2013 ⁶⁷	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Shen et al/2020 ⁶⁸	Y	Y	Y	N	Y	Y	N	N	N	High
Venigalla et al/2016 ⁶⁹	Y	Y	Y	Y	Y	N	N	N	N	High
Xu et al/2020 ⁷⁰	Y	Y	Y	N	Y	Y	N	N	N	High
Kazemi-Yazdi et al/2020 ⁷¹	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Da Silva et al/2015 ⁷²	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Zheng et al/2015 ⁷³	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Sadek et al/2010 ⁷⁴	Y	N	Y	Y	Y	Y	N	N	N	High
Breschi et al/2010 ²²	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Stanislawczuk et al/2009 ⁷⁵	Y	Y	Y	N	Y	Y	Y	N	N	Medium
Firouzmandi et al/2020 ⁷⁶	N	Y	Y	Y	N	N	N	N	N	High
Giacomini et al/2017 ⁷⁷	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Sabatini et al/2014 ⁷⁸	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Carvalho et al/2016 ⁷⁹	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Loguercio et al/2016 ⁸⁰	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Cova et al/2011 ⁹⁹	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Mobarak/2011 ⁸¹	N	Y	Y	Y	Y	N	N	N	N	High
Manso et al/2014 ⁸²	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Breschi et al/2010 ¹⁹	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Montagner et al/2015 ⁸³	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Li et al/2020 ⁸⁴	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Hass et al/2016 ⁹⁸	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Kalagi et al/2020 ⁸⁵	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Tekce et al/2016 ⁸⁶	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
de Moura et al/2021 ⁸⁷	Y	Y	Y	Y	Y	Y	Y	Y	N	Low
Li et al/2021 ⁸⁸	Y	Y	Y	Y	Y	Y	Y	N	N	Medium

Abbreviations: N, no; Y, yes.

Note: This table demonstrates the quality assessment and risk of bias as reported in the materials and methods section.

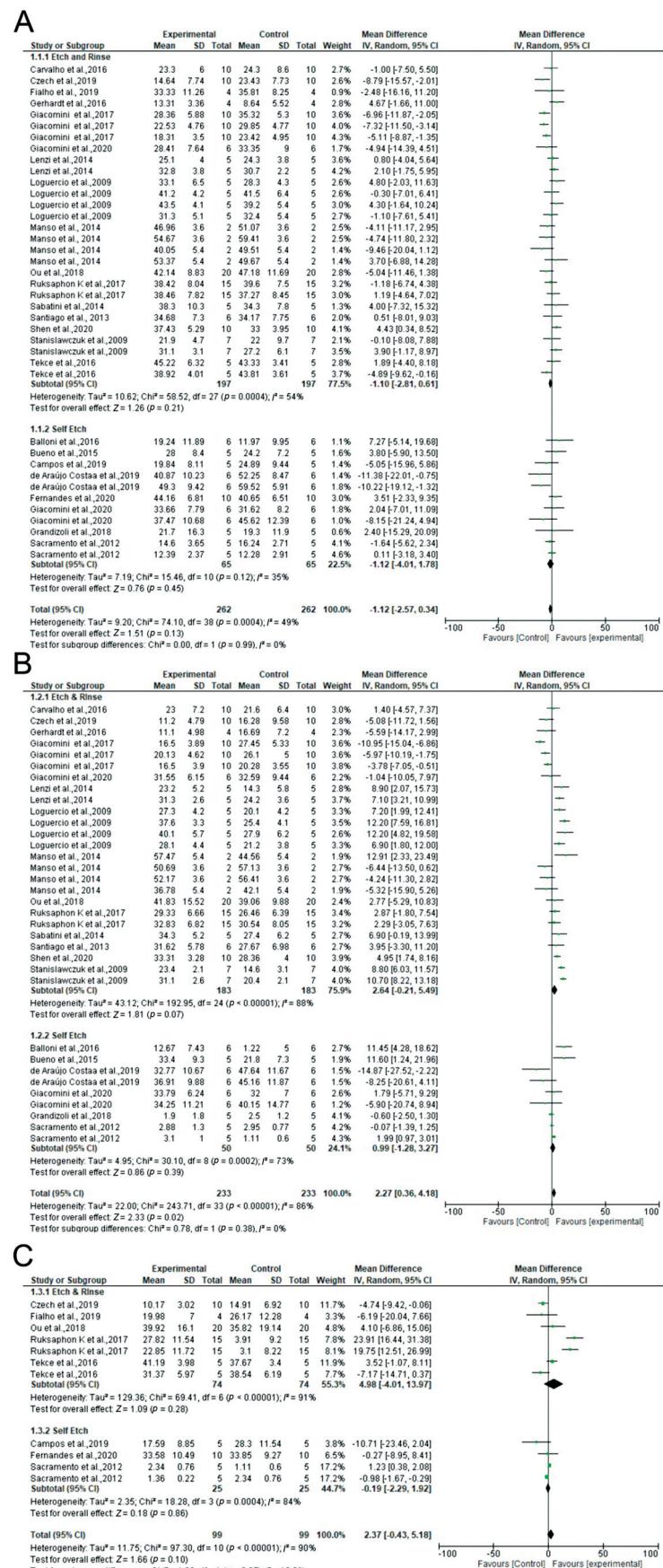


Fig. 2 Forest plots according to MMP inhibitor type. 2% CHX vs. control at 24 hours (A), 6 months (B), and 12 months (C). CHX, chlorhexidine; CI, confidence interval; MMP, matrix metalloproteinase; SD, standard deviation.

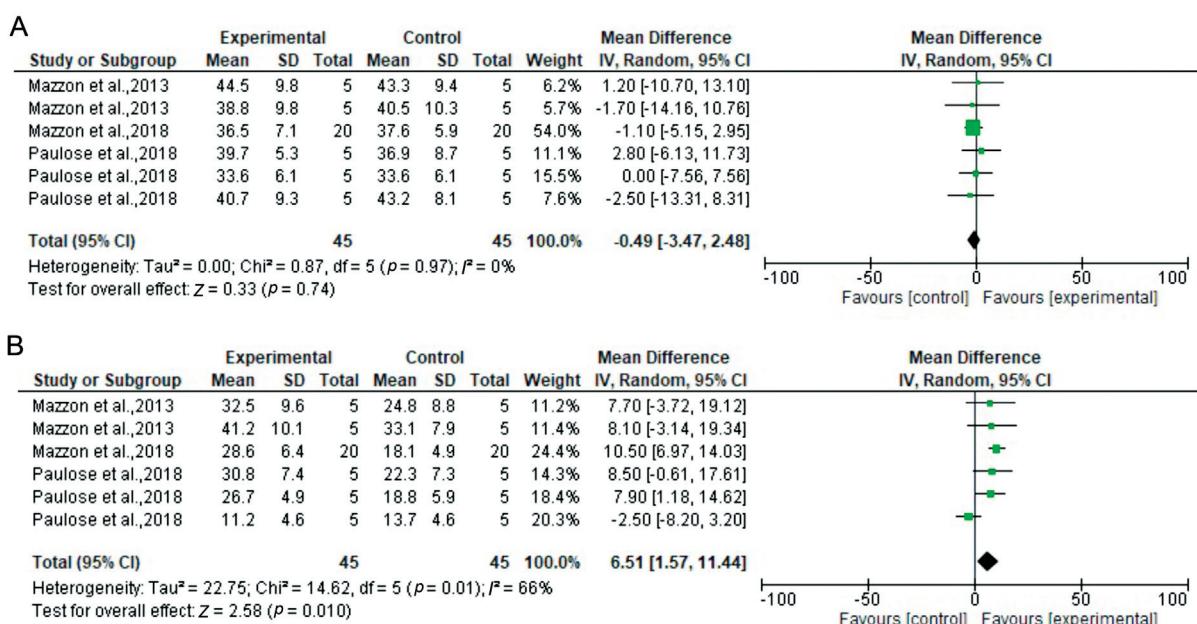


Fig. 3 Forest plots according to MMP inhibitor type. 0.3 M EDC vs. control at 24 hours (A) and 12 months (B). CI, confidence interval; EDC, carbodiimide; MMP, matrix metalloproteinase; SD, standard deviation.

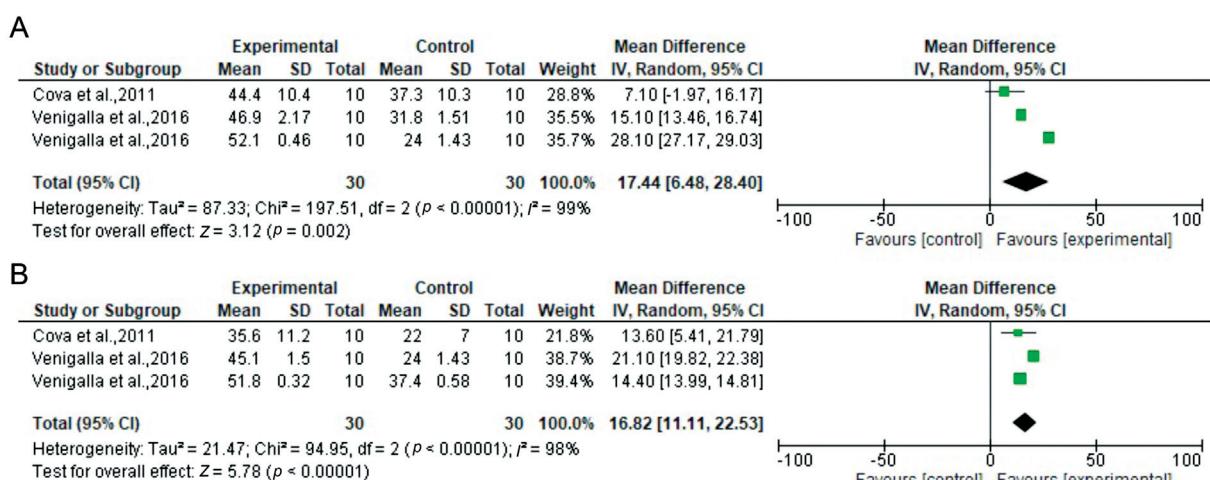


Fig. 4 Forest plots according to MMP inhibitor type: 0.1% RIBO vs. control at 24 hours (A) and 6 months (B). CI, confidence interval; MMP, matrix metalloproteinase; RIBO, riboflavin; SD, standard deviation.

group over the experimental group ($Z = 2.42$, $p = 0.02$), and heterogeneity was low ($I^2 = 0\%$; ▶ Fig. 5A).

For the ninth analysis of pretreatment for 30 seconds (2% CHX vs. control at 6 months), only three etch-and-rinse studies met the criteria, representing six datasets. There was overall no statistically significant difference between groups ($Z = 0.28$, $p = 0.78$), and heterogeneity was considerable ($I^2 = 55\%$; ▶ Fig. 5B).

For the 10th analysis of pretreatment for 60 seconds (2% CHX vs. control at baseline), 14 etch-and-rinse studies were included, representing 19 datasets. There was overall no statistically significant difference between groups (Z -test = 0.07, $p = 0.95$), but there was considerable heterogeneity between groups ($I^2 = 63\%$). For self-etching, six studies were

included with six datasets. Again, there was no statistically significant difference between groups (Z -test = 0.01, $p = 0.89$) and moderate heterogeneity ($I^2 = 41\%$). Tests for overall effect showed no statistically significant difference between groups (Z -test = 0.01, $p = 0.99$) and considerable heterogeneity between subgroups ($I^2 = 58\%$; ▶ Fig. 6A).

For the 11th and final analysis of pretreatment for 60 seconds (2% CHX vs. control at 6 months), 11 etch-and-rinse studies were included, representing 16 datasets. Overall, the experimental group was slightly, but not significantly, favored over the control group (Z -test = 1.73, $p = 0.08$), with considerable heterogeneity ($I^2 = 91\%$). Five self-etching studies were included representing five datasets. Overall, the experimental group was slightly, but not significantly,

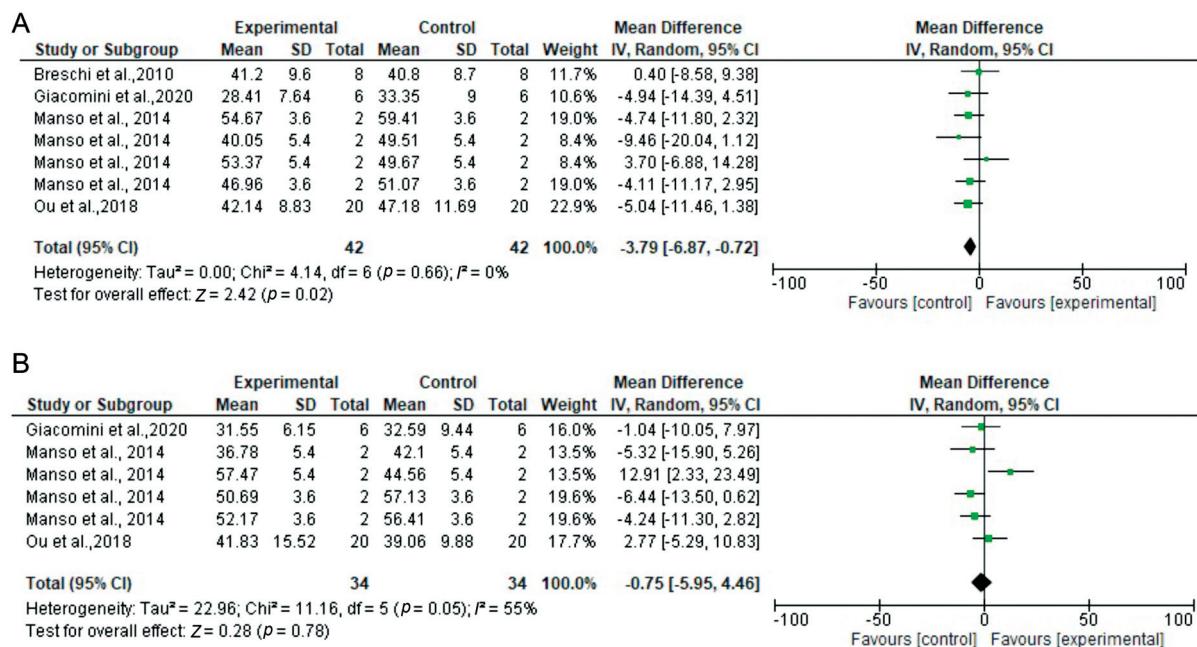


Fig. 5 Forest plots according to pretreatment duration for 30 seconds: pretreatment with 2% CHX vs. control group at 24 hours (A) and 6 months (B). CHX, chlorhexidine; CI, confidence interval; SD, standard deviation.

favored over the control group (Z -test = 1.22, $p = 0.22$), with considerable heterogeneity ($I^2 = 83\%$). The tests for overall effect favored the experimental group but this was not statistically significant (Z -test = 2.35, $p = 0.73$). Heterogeneity between subgroups was considerable ($I^2 = 90\%$; ►Fig. 6B).

Discussion

This meta-analysis revealed that at least some MMP inhibitors significantly alter bond strength, both immediately and over the longer term. Accordingly, the null hypothesis was rejected.

Of all MMP inhibitors considered for meta-analysis, two MMP inhibitors improved bond strength: 0.3 M EDC and 0.1% RIBO. The 0.3 M EDC did not improve bond strength immediately (24 hours) but showed benefit after ageing for 12 months, while 0.1% RIBO showed statistically significant increases in bond strength both immediately (24 hours) and over the long term (6 months) compared with controls. Conversely, 2% CHX showed a slight but nonsignificant improvement in bond strength after 6 months of ageing but not immediately (24 hours) or after 12 months. The lack of immediate benefit with 2% CHX is consistent with two previous meta-analyses,^{28,89} but the long-term results differ, possibly due to the different concentration of CHX used in previous studies. It has been suggested but not consistently proven that MMP inhibition by CHX is dose dependent.^{90,91} It is worth noting that, of the few clinical trials evaluating pretreatment with CHX, no improvement in bond strength was observed over time.^{92–97} With respect to adhesive systems, a previous systematic review²⁸ found that both types of adhesive system (self-etching and etch and rinse) benefited from 2% CHX *in vitro*. This, however, was also not

consistent with the current meta-analysis results, since we found no significant difference according to the adhesive system used.

EDC and RIBO have a different mechanism of MMP inhibition to CHX through their cross-linking action. Generally, collagen cross-linkers protect collagen fibrils from further degradation by enhancing both the chemical and mechanical properties of collagen.^{98–100} These additional functions could explain their superiority in maintaining adhesive interface integrity.

Pretreatments of 30 and 60 seconds with 2% CHX met the inclusion criteria for meta-analysis. Generally, neither pretreatment protocol significantly improved bond strength either immediately (24 hours) or over the long term (6 months). Indeed, when 2% CHX was applied for 30 seconds, there was a significant negative effect on bond strength over 24 hours. After 6 months of aging, there was a slight improvement in bond strength, still favoring the control group. With pretreatments of 60 seconds, 2% CHX showed no effect on bond strength and was similar to controls and, while slightly improved bond strength was observed with CHX after 6 months, it was nevertheless not statistically significant.

Our results show some inconsistencies with previous systematic reviews which might be due to differences in the inclusion criteria. For example, Montagner et al.²⁸ and Kiuru et al.⁸⁹ included different concentrations of CHX other than 2%, as well as various bond strength tests other than microtensile bond strength testing.

Limitations

There are a few limitations to our study. This review only included *in vitro* studies since there have been very few *in*

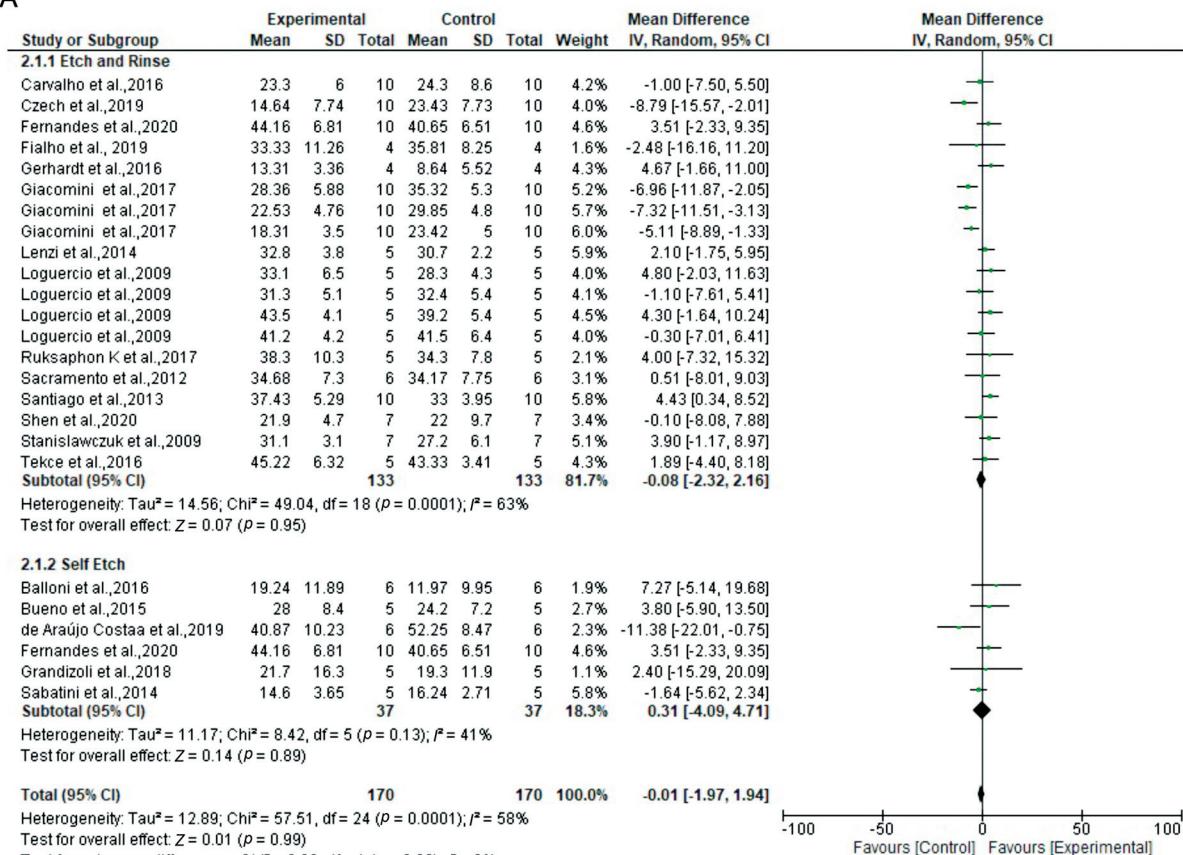
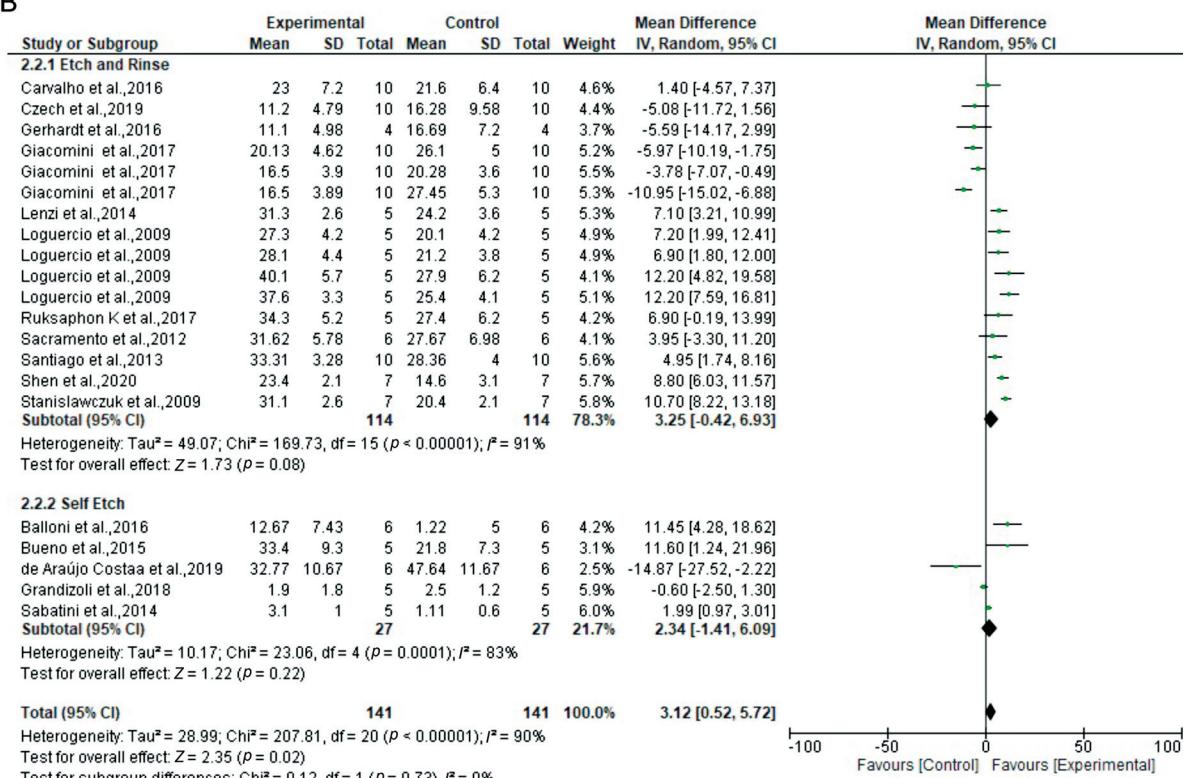
A**B**

Fig. 6 Forest plots according to pretreatment duration for 60 seconds: pretreatment with 2% CHX vs. control group at 24 hours (A) and 6 months (B). CHX, chlorhexidine; CI, confidence interval; SD, standard deviation..

vivo studies or clinical trials in the literature. More *in vivo* studies will ultimately be crucial for providing high-quality evidence of the safety, toxicity, and efficacy of a given intervention in a complex model. Furthermore, although strict measures were taken during the search of the articles included for meta-analysis, several data demonstrated high heterogeneity. It is worth mentioning that most of the results with high heterogeneity were observed in the long-term ageing periods, unlike the immediate ageing periods which showed lower heterogeneity. Factors that could influence this may include the different brands of adhesive systems used and the ageing methods utilized. Similar findings were observed in the study by Montagner et al²⁸ which found that the aging methods were the greater influencing factor in the high heterogeneity. It is also worth noting that there are no standardized protocols for evaluating bond strength which previously shown will inevitably increase the heterogeneity of results.¹⁰¹ To improve the reliability and quality of future bond strength testing studies, robust and strict guidelines for laboratory testing must be developed and implemented.

Many of the studies carried a risk of bias, and only one study mentioned blinding of the operator testing the bond strength; this parameter will be important to include in future studies to reduce the risk of bias. Moreover, only six studies calculated the sample size and reported a power analysis.

Nevertheless, these *in vitro* findings pave the way for rationale clinical trialing of dentine surface pretreatment with MMP inhibitors to improve clinical outcomes.

Conclusion

The data suggest that using 2% CHX had no significant positive effect on bond strength either immediately or over the longer term. Pretreatments with 2% CHX for either 30 or 60 seconds do not improve the bond strength. Both 0.3 M EDC and 0.1% RIBO improve bond strength immediately and over time. There was considerable heterogeneity between the different adhesive systems used, limiting our meta-analysis. Given the limited clinical evidence available, more research is required to confirm the beneficial use of MMP inhibitors.

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Conflict of Interest

None declared.

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References

- 1 Buonocore MG. A simple method of increasing the adhesion of acrylic filling materials to enamel surfaces. *J Dent Res* 1955;34 (06):849–853
- 2 Van Meerbeek B, Yoshihara K, Van Landuyt K, Yoshida Y, Peumans M. From Buonocore's pioneering acid-etch technique to self-adhering restoratives. a status perspective of rapidly advancing dental adhesive technology. *J Adhes Dent* 2020;22(01): 7–34
- 3 De Munck J, Van Landuyt K, Peumans M, et al. A critical review of the durability of adhesion to tooth tissue: methods and results. *J Dent Res* 2005;84(02):118–132
- 4 Mjör IA, Moorhead JE, Dahl JE. Reasons for replacement of restorations in permanent teeth in general dental practice. *Int Dent J* 2000;50(06):361–366
- 5 Breschi L, Maravic T, Cunha SR, et al. Dentin bonding systems: From dentin collagen structure to bond preservation and clinical applications. *Dent Mater* 2018;34(01):78–96
- 6 Nakabayashi N, Nakamura M, Yasuda N. Hybrid layer as a dentin-bonding mechanism. *J Esthet Dent* 1991;3(04):133–138
- 7 Frassetto A, Breschi L, Turco G, et al. Mechanisms of degradation of the hybrid layer in adhesive dentistry and therapeutic agents to improve bond durability—A literature review. *Dent Mater* 2016;32(02):e41–e53
- 8 Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res* 2003;92(08):827–839
- 9 Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. *Cardiovasc Res* 2006;69(03): 562–573
- 10 Sulkala M, Tervahartiala T, Sorsa T, Larmas M, Salo T, Tjäderhane L. Matrix metalloproteinase-8 (MMP-8) is the major collagenase in human dentin. *Arch Oral Biol* 2007;52(02):121–127
- 11 Mazzoni A, Mannello F, Tay FR, et al. Zymographic analysis and characterization of MMP-2 and -9 forms in human sound dentin. *J Dent Res* 2007;86(05):436–440
- 12 Tjäderhane L, Palosaari H, Wahlgren J, Larmas M, Sorsa T, Salo T. Human odontoblast culture method: the expression of collagen and matrix metalloproteinases (MMPs). *Adv Dent Res* 2001;15 (01):55–58
- 13 Chaussain-Miller C, Fioretti F, Goldberg M, Menashi S. The role of matrix metalloproteinases (MMPs) in human caries. *J Dent Res* 2006;85(01):22–32
- 14 Apolonio FM, Mazzoni A, Angeloni V, et al. Effect of a one-step self-etch adhesive on endogenous dentin matrix metalloproteinases. *Eur J Oral Sci* 2017;125(02):168–172
- 15 DeVito-Moraes AG, Francci C, Vidal CM, et al. Phosphoric acid concentration affects dentinal MMPs activity. *J Dent* 2016; 53:30–37
- 16 Pashley DH, Tay FR, Yiu C, et al. Collagen degradation by host-derived enzymes during aging. *J Dent Res* 2004;83(03): 216–221
- 17 Sabatini C, Pashley DH. Aging of adhesive interfaces treated with benzalkonium chloride and benzalkonium methacrylate. *Eur J Oral Sci* 2015;123(02):102–107
- 18 Sabatini C, Patel SK. Matrix metalloproteinase inhibitory properties of benzalkonium chloride stabilizes adhesive interfaces. *Eur J Oral Sci* 2013;121(06):610–616
- 19 Breschi L, Mazzoni A, Nato F, et al. Chlorhexidine stabilizes the adhesive interface: a 2-year *in vitro* study. *Dent Mater* 2010;26 (04):320–325
- 20 Kim J, Uchiyama T, Carrilho M, et al. Chlorhexidine binding to mineralized versus demineralized dentin powder. *Dent Mater* 2010;26(08):771–778
- 21 Lenzi TL, Tedesco TK, Soares FZM, Loguercio AD, Rocha RdeO. Chlorhexidine does not increase immediate bond strength of etch-and-rinse adhesive to caries-affected dentin of primary and permanent teeth. *Braz Dent J* 2012;23(04):438–442
- 22 Breschi L, Martin P, Mazzoni A, et al. Use of a specific MMP-inhibitor (galardin) for preservation of hybrid layer. *Dent Mater* 2010;26(06):571–578

- 23 Barbosa CS, Kato MT, Buzalaf MA. Effect of supplementation of soft drinks with green tea extract on their erosive potential against dentine. *Aust Dent J* 2011;56(03):317–321
- 24 Czech R, Oliveira C, França F, Basting R, Turssi C, Amaral F. Incorporation of EGCG into an etch-and-rinse adhesive system: mechanical properties and bond strength to caries affected dentin. *J Adhes Sci Technol* 2019;33(22):2430–2442
- 25 Henn S, de Carvalho RV, Ogliari FA, et al. Addition of zinc methacrylate in dental polymers: MMP-2 inhibition and ultimate tensile strength evaluation. *Clin Oral Investig* 2012;16(02): 531–536
- 26 Page MJ, Shamseer L, Altman DG, et al. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. *PLoS Med* 2016;13(05): e1002028
- 27 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71
- 28 Montagner AF, Sarkis-Onofre R, Pereira-Cenci T, Cenci MS. MMP Inhibitors on Dentin Stability: A Systematic Review and Meta-analysis. *J Dent Res* 2014;93(08):733–743
- 29 Green S, Higgins JP. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration. 2011. Accessed September 7, 2022 at: <https://handbook-5-1.cochrane.org/>
- 30 Baena E, Cunha SR, Maravić T, et al. Effect of chitosan as a cross-linker on matrix metalloproteinase activity and bond stability with different adhesive systems. *Mar Drugs* 2020;18(05):263
- 31 Balloni ECP, Amaral FLBd, França FMG, Turssi CP, Basting RT. Influence of chlorhexidine in cavities prepared with ultrasonic or diamond tips on microtensile bond strength. *J Adhes Sci Technol* 2017;31(10):1133–1141
- 32 Bravo C, Sampaio C, Hirata R, Puppin-Rontani RM, Mayoral JR, Giner L. In-vitro comparative study of the use of 2% chlorhexidine on microtensile bond strength of different dentin adhesives: a 6 months evaluation. *Int J Morphol* 2017;35(03):893–900
- 33 de Faria Teixeira M, Basting RT, Turssi CP, França FMG, Amaral FLB. Effect of 2% chlorhexidine digluconate application and water storage on the bond strength to superficial and deep dentin. *J Adhes Sci Technol* 2015;29(12):1258–1267
- 34 Comba A, Maravić T, Villalta V, et al. Effect of an ethanol cross-linker on universal adhesive. *Dent Mater* 2020;36(12): 1645–1654
- 35 Dávila-Sánchez A, Gutierrez MF, Bermudez JP, et al. Influence of flavonoids on long-term bonding stability on caries-affected dentin. *Dent Mater* 2020;36(09):1151–1160
- 36 Costa CAG, Passos VF, Neri JR, Mendonça JS, Santiago SL. Effect of metalloproteinase inhibitors on bond strength of a self-etching adhesive on erosively demineralized dentin. *J Adhes Dent* 2019; 21(04):337–344
- 37 El Baz MA, Aboulenien K. The effect of green tea extract as a matrix metalloproteinase inhibitor on the bond strength of resin composite. *Egypt Dent J* 2018;64:2807–2817
- 38 Fang H, Li QL, Han M, Mei ML, Chu CH. Anti-proteolytic property and bonding durability of mussel adhesive protein-modified dentin adhesive interface. *Dent Mater* 2017;33(10):1075–1083
- 39 Fernandes FP, Adorno CC, da Silva TM, et al. Addition of EGCG to self-etching primer: effect on adhesive properties and bond stability to dentin. *J Adhes Sci Technol* 2021;35:1895–1908
- 40 Fialho MPN, Hass V, Nogueira RP, et al. Effect of epigallocatechin-3-gallate solutions on bond durability at the adhesive interface in caries-affected dentin. *J Mech Behav Biomed Mater* 2019; 91:398–405
- 41 Gerhardt K, Oliveira C, França F, Basting R, Turssi C, Amaral F. Effect of epigallocatechin gallate, green tea extract and chlorhexidine application on long-term bond strength of self-etch adhesive to dentin. *Int J Adhes Adhes* 2016;71:23–27
- 42 Campos R, Oliveira C, Macedo J, et al. Effect of zinc chloride added to self-etching primer on bond strength to caries-affected dentin and chemical-physical-mechanical properties of adhesives. *Int J Adhes Adhes* 2019;95:102412
- 43 Giacomini MC, Scaffa PMC, Gonçalves RS, et al. Profile of a 10-MDP-based universal adhesive system associated with chlorhexidine: dentin bond strength and in situ zymography performance. *J Mech Behav Biomed Mater* 2020;110:103925
- 44 Grandizoli DRP, Pinheiro SL. Influence of protease inhibitors on bond degradation of self-etch adhesive systems to caries-affected dentin: an in vitro study. *Adv Biol Chem* 2018; 8:15–28
- 45 Karrabi M, Danesh Kazemi A. Comparison of chlorhexidine 2 and sodium hypochlorite 5 as rewetting agents on resin-dentin micro tensile bond strength. *J Dent Mater Tech* 2016;5(04): 189–195
- 46 Kasraei S, Malek M, Khamverdi Z, Mojtabedi M. The efficacy of riboflavin for collagen cross-linking and optimizing the bond strength of an etch and rinse adhesive system to dentin. *Avicenna J Dent Res* 2017;9:e13254
- 47 Lenzi TL, Tedesco TK, Soares FZM, Loguercio AD, de Oliveira Rocha R. Chlorhexidine application for bond strength preservation in artificially-created caries-affected primary dentin. *Int J Adhes Adhes* 2014;54:51–56
- 48 Li J, Chen B, Hong N, Wu S, Li Y. Effect of baicalein on matrix metalloproteinases and durability of resin-dentin bonding. *Oper Dent* 2018;43(04):426–436
- 49 Loguercio AD, Hass V, Gutierrez MF, et al. Five-year effects of chlorhexidine on the in vitro durability of resin/dentin interfaces. *J Adhes Dent* 2016;18(01):35–42
- 50 Loguercio AD, Stanislawczuk R, Polli LG, Costa JA, Michel MD, Reis A. Influence of chlorhexidine digluconate concentration and application time on resin-dentin bond strength durability. *Eur J Oral Sci* 2009;117(05):587–596
- 51 Maravic T, Breschi L, Comba A, et al. Experimental use of an acrolein-based primer as collagen cross-linker for dentine bonding. *J Dent* 2018;68:85–90
- 52 Mazzoni A, Angeloni V, Apolonio FM, et al. Effect of carbodiimide (EDC) on the bond stability of etch-and-rinse adhesive systems. *Dent Mater* 2013;29(10):1040–1047
- 53 Mazzoni A, Angeloni V, Comba A, et al. Cross-linking effect on dentin bond strength and MMPs activity. *Dent Mater* 2018;34 (02):288–295
- 54 Mohamed AM, Nabih SM, Wakwak MA. Effect of chitosan nanoparticles on microtensile bond strength of resin composite to dentin: an in vitro study. *Braz Dent Sci* 2020;23(02):10
- 55 Mosallam R, Younis N, Farouk H, Mosallam O. Effect of green tea and two mulberry leaf extracts on micro-tensile bond strength to dentin. *Futur Dent J* 2018;4(02):150–155
- 56 Mosallam R, Younis N, Farouk H, Mosallam O. Effect of matrix metalloproteinase inhibitor from mulberry fruit extract on the microtensile bond strength stability: an in vitro study. *Egypt Dent J* 2019;65(01):541–550
- 57 Ou Q, Hu Y, Yao S, Wang Y, Lin X. Effect of matrix metalloproteinase 8 inhibitor on resin-dentin bonds. *Dent Mater* 2018;34(05):756–763
- 58 Paulose NE, Fawzy AS. Effect of carbodiimide on the bond strength and durability of resin-dentin interface. *J Adhes Sci Technol* 2018;32(09):931–946
- 59 Pedrosa VO, França FMG, Turssi CP, et al. Effects of caffeic acid phenethyl ester application on dentin MMP-2, stability of bond strength and failure mode of total-etch and self-etch adhesive systems. *Arch Oral Biol* 2018;94:16–26
- 60 Perote LC, Kamozaki MB, Gutierrez NC, Tay FR, Pucci CR. Effect of matrix metalloproteinase-inhibiting solutions and aging methods on dentin bond strength. *J Adhes Dent* 2015;17(04):347–352
- 61 Porto ICCM, Nascimento TG, Oliveira JMS, Freitas PH, Haimeur A, França R. Use of polyphenols as a strategy to prevent bond degradation in the dentin-resin interface. *Eur J Oral Sci* 2018; 126(02):146–158

- 62 Prasansuttiporn T, Thanatvarakorn O, Mamanee T, et al. Effect of antioxidant/reducing agents on the initial and long-term bonding performance of a self-etch adhesive to caries-affected dentin with and without smear layer-deproteinizing. *Int J Adhes Adhes* 2020;102:102648
- 63 Prasansuttiporn T, Thanatvarakorn O, Tagami J, Foxton RM, Nakajima M. Bonding durability of a self-etch adhesive to normal versus smear-layer deproteinized dentin: effect of a reducing agent and plant-extract antioxidant. *J Adhes Dent* 2017;19(03):253–258
- 64 Ruksaphon K, Pisol S. Efficacy of chlorhexidine and rosmarinic acid to prevent resin/dentine interface degradation. *Dent Oral Craniofac Res* 2017;4(02):1–9
- 65 Sacramento PA, de Castilho AR, Banzi EC, Puppi-Rontani RM. Influence of cavity disinfectant and adhesive systems on the bonding procedure in demineralized dentin - a one-year in vitro evaluation. *J Adhes Dent* 2012;14(06):575–583
- 66 Sadeghi M, Salehi A, Roberts MW. Effect of chlorhexidine application on dentin bond strength durability of two etch-and-rinse adhesive versus a universal bond system. *JDOC* 2017;3(02):202
- 67 Santiago SL, Osorio R, Neri JR, Carvalho RM, Toledoano M. Effect of the flavonoid epigallocatechin-3-gallate on resin-dentin bond strength. *J Adhes Dent* 2013;15(06):535–540
- 68 Shen J, Xie H, Wang Q, Wu X, Yang J, Chen C. Evaluation of the interaction of chlorhexidine and MDP and its effects on the durability of dentin bonding. *Dent Mater* 2020;36(12):1624–1634
- 69 Venigalla BS, Jyothi P, Kamishetty S, Reddy S, Cherukupalli RC, Reddy DA. Resin bond strength to water versus ethanol-saturated human dentin pretreated with three different cross-linking agents. *J Conserv Dent* 2016;19(06):555–559
- 70 Xu J, Li M, Wang W, et al. A novel prime-&-rinse mode using MDP and MMPs inhibitors improves the dentin bond durability of self-etch adhesive. *J Mech Behav Biomed Mater* 2020;104:103698
- 71 Kazemi-Yazdi H, Saeed-Nezhad M, Rezaei S. Effect of chlorhexidine on durability of two self-etch adhesive systems. *J Clin Exp Dent* 2020;12(07):e663–e669
- 72 Da Silva EM, Glir DH, Gill AW, Giovanini AF, Furuse AY, Gonzaga CC. Effect of chlorhexidine on dentin bond strength of two adhesive systems after storage in different media. *Braz Dent J* 2015;26(06):642–647
- 73 Zheng P, Zaruba M, Attin T, Wiegand A. Effect of different matrix metalloproteinase inhibitors on microtensile bond strength of an etch-and-rinse and a self-etching adhesive to dentin. *Oper Dent* 2015;40(01):80–86
- 74 Sadek FT, Braga RR, Muench A, Liu Y, Pashley DH, Tay FR. Ethanol wet-bonding challenges current anti-degradation strategy. *J Dent Res* 2010;89(12):1499–1504
- 75 Stanislawczuk R, Amaral RC, Zander-Grande C, Gagler D, Reis A, Loguercio AD. Chlorhexidine-containing acid conditioner preserves the longevity of resin-dentin bonds. *Oper Dent* 2009;34(04):481–490
- 76 Firouzmandi M, Mohaghegh M, Jafarpisheh M. Effect of silver diamine fluoride on the bond durability of normal and carious dentin. *J Clin Exp Dent* 2020;12(05):e468–e473
- 77 Giacomini MC, Scaffa P, Chaves LP, et al. Role of proteolytic enzyme inhibitors on carious and eroded dentin associated with a universal bonding system. *Oper Dent* 2017;42(06):E188–E196
- 78 Sabatini C, Kim JH, Ortiz Alias P. In vitro evaluation of benzalkonium chloride in the preservation of adhesive interfaces. *Oper Dent* 2014;39(03):283–290
- 79 Carvalho C, Fernandes FP, Freitas VdaP, et al. Effect of green tea extract on bonding durability of an etch-and-rinse adhesive system to caries-affected dentin. *J Appl Oral Sci* 2016;24(03):211–217
- 80 Loguercio AD, Stanislawczuk R, Malaquias P, Gutierrez MF, Bauer J, Reis A. Effect of minocycline on the durability of dentin bonding produced with etch-and-rinse adhesives. *Oper Dent* 2016;41(05):511–519
- 81 Mobarak EH. Effect of chlorhexidine pretreatment on bond strength durability of caries-affected dentin over 2-year aging in artificial saliva and under simulated intrapulpal pressure. *Oper Dent* 2011;36(06):649–660
- 82 Manso AP, Grande RHM, Bedran-Russo AK, et al. Can 1% chlorhexidine diacetate and ethanol stabilize resin-dentin bonds? *Dent Mater* 2014;30(07):735–741
- 83 Montagner AF, Pereira-Cenci T, Cenci MS. Influence of cariogenic challenge on bond strength stability of dentin. *Braz Dent J* 2015;26(02):128–134
- 84 Li K, Sun Y, Tsoi JKH, Yiu CKY. The application of mussel-inspired molecule in dentin bonding. *J Dent* 2020;99:103404
- 85 Kalagi S, Feitosa SA, Münchow EA, et al. Chlorhexidine-modified nanotubes and their effects on the polymerization and bonding performance of a dental adhesive. *Dent Mater* 2020;36(05):687–697
- 86 Tekçe N, Tuncer S, Demirci M, Balci S. Do matrix metalloproteinase inhibitors improve the bond durability of universal dental adhesives? *Scanning* 2016;38(06):535–544
- 87 de Moura RR, França FMG, Turssi CP, Basting RT, do Amaral FLB. Effect of different concentrations of green tea extract solutions on bonding durability of etch-and-rinse adhesive system to caries affected dentin. *Braz J Oral Sci* 2021;20:e210328–e210328
- 88 Li K, Yao C, Sun Y, et al. Enhancing resin-dentin bond durability using a novel mussel-inspired monomer. *Mater Today Bio* 2021;12:100174
- 89 Kiuru O, Sinervo J, Vähänikkilä H, Anttonen V, Tjäderhane L. MMP inhibitors and dentin bonding: systematic review and meta-analysis. *Int J Dent* 2021;2021:9949699
- 90 Gendron R, Grenier D, Sorsa T, Mayrand D. Inhibition of the activities of matrix metalloproteinases 2, 8, and 9 by chlorhexidine. *Clin Diagn Lab Immunol* 1999;6(03):437–439
- 91 Collares FM, Rodrigues SB, Leitune VC, Celeste RK, Borba de Araújo F, Samuel SM. Chlorhexidine application in adhesive procedures: a meta-regression analysis. *J Adhes Dent* 2013;15(01):11–18
- 92 Montagner AF, Perroni AP, Corrêa MB, Masotti AS, Pereira-Cenci T, Cenci MS. Effect of pre-treatment with chlorhexidine on the retention of restorations: a randomized controlled trial. *Braz Dent J* 2015;26(03):234–241
- 93 Dutra-Correia M, Saraceni CH, Ciaramicoli MT, Kiyan VH, Queiroz CS. Effect of chlorhexidine on the 18-month clinical performance of two adhesives. *J Adhes Dent* 2013;15(03):287–292
- 94 Favetti M, Schroeder T, Montagner AF, Correa MB, Pereira-Cenci T, Cenci MS. Effectiveness of pre-treatment with chlorhexidine in restoration retention: A 36-month follow-up randomized clinical trial. *J Dent* 2017;60:44–49
- 95 Sartori N, Stolf SC, Silva SB, Lopes GC, Carrilho M. Influence of chlorhexidine digluconate on the clinical performance of adhesive restorations: a 3-year follow-up. *J Dent* 2013;41(12):1188–1195
- 96 Hebling J, Pashley DH, Tjäderhane L, Tay FR. Chlorhexidine arrests subclinical degradation of dentin hybrid layers in vivo. *J Dent Res* 2005;84(08):741–746
- 97 Carrilho MR, Geraldini S, Tay F, et al. In vivo preservation of the hybrid layer by chlorhexidine. *J Dent Res* 2007;86(06):529–533
- 98 Hass V, Luque-Martinez IV, Gutierrez MF, et al. Collagen cross-linkers on dentin bonding: Stability of the adhesive interfaces, degree of conversion of the adhesive, cytotoxicity and in situ MMP inhibition. *Dent Mater* 2016;32(06):732–741
- 99 Cova A, Breschi L, Nato F, et al. Effect of UVA-activated riboflavin on dentin bonding. *J Dent Res* 2011;90(12):1439–1445
- 100 Chiang YS, Chen YL, Chuang SF, et al. Riboflavin-ultraviolet-A-induced collagen cross-linking treatments in improving dentin bonding. *Dent Mater* 2013;29(06):682–692
- 101 Heintze SD, Zimmerli B, Zahnmed SM. Relevance of in vitro tests of adhesive and composite dental materials. A review in 3 parts. Part 3: in vitro tests of adhesive systems [in German]. *Schweiz Monatsschr Zahnmed* 2011;121(11):1024–1040