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Incorporation of MMP inhibitors into dental adhesive systems and bond strength of coronal composite restorations: A systematic review and meta-analysis of *in vitro* studies

Rayan B. Yaghmoor [a,b,c,*], Hasan Jamal [d], Hassan Abed [e], Elaine Allan [c], Paul Ashley [d], Anne Young [b]

[a] Department of Restorative Dentistry, Faculty of Dentistry, Umm Al-Qura University, Makkah 24381, Saudi Arabia
[b] Department of Biomaterials and Tissue Engineering, UCL Eastman Dental Institute, Royal Free Hospital London, NW3 2PF, UK
[c] Department of Microbial Diseases, UCL Eastman Dental Institute, Royal Free Hospital, London NW3 2PF, UK
[d] Unit of Paediatric Dentistry, UCL Eastman Dental Institute, London WC1E 6DE, UK
[e] Department of Basic and Clinical Oral Sciences, Umm Al-Qura University, Faculty of Dentistry, Makkah 24381, Saudi Arabia

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ABSTRACT

Purpose: To systematically review *in vitro* studies that incorporated MMP inhibitors into adhesive systems in terms of the effect on immediate and aged bond strength of dental composite to dentine.
Materials and methods: Independently, two reviewers conducted an electronic search in three databases (MEDLINE, EMBASE, and Google Scholar) following the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P), up to 6 March 2022.
Results: The search resulted in 894 papers, 33 of which were eligible to be included in the review; of those, 13 fulfilled the meta-analysis eligibility criteria. Nineteen inhibitors were used among the studies, and those included in the meta-analysis were 2%, 0.2% chlorhexidine (CHX), 5 μM GM1489, and 0.5%, 1% benzalkonium chloride (BAC). In the meta-analysis, while above inhibitors showed no adverse effect on bond strength, 0.2% CHX and 5 μM GM1489 caused a significant increase in immediate and 12-months bond strength. All other inhibitors resulted in a significant increase in bond strength at six months of ageing.
Conclusions: Incorporation of MMP inhibitors into the adhesive system has no unfavourable effect on immediate bond strength but a favourable effect on longer-term bond strength. Additionally, inhibitors other than CHX could have similar or better effects on bond strength.

Contents

* Corresponding author at: Department of Restorative Dentistry, Faculty of Dentistry, Umm Al-Qura University, Makkah 24381, Saudi Arabia.
E-mail address: rbyaghmoor@uqu.edu.sa (R.B. Yaghmoor).

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1. Introduction

Resin composite is the most widely used direct dental restorative material [1,2]. Typically, bonding of this material can be accomplished by using a resin adhesive. Importantly, the integrity and success rate of composite restorations depend primarily on bond strength to the tooth structure. However, studies showed decreases in adhesive-dentine bond strength with time [3], due to degradation in collagen fibrils of the hybrid layer [4,5].

It is well established that the dentine structure has a considerable amount of organic content (20 wt%) which is composed of 90 wt % collagen, mainly type I [6]. Through the restorative procedure, the hybrid layer is formed, which consists mainly of a demineralised collagen matrix infiltrated by resin adhesive. The integrity of these two parts is crucial in the bond strength/stability, and hence the longevity of resin composite restoration [5,7,8]. It was found that the drop in the bond strength is associated with degradation in the two parts of the hybrid layer [9]. Focusing on the collagen part, studies showed that the endogenous host-derived collagenolytic enzymes, mainly matrix metalloproteinases (MMPs), are responsible for collagen fibrils degradation [5].

MMPs are host enzymes belonging to the family of calcium and zinc-dependent enzymes, which have a role in degrading the extracellular matrix [10]. During teeth development and after mineralisation of the collagen matrix, MMPs become inactive and entrapped in the calcified matrix. Potentially, the silenced MMPs can be reactivated again by exposure to an acidic environment either from the metabolic activity of cariogenic bacteria or by an acidic agent during restorative procedures; acidic monomer in case of the self-etch (SE) adhesive or acid etchant with etch-and-rinse (E&R) adhesive [11–14]. Active MMPs are responsible for degrading exposed collagen fibrils within the hybrid layer and harm the bond stability at the tooth-restoration interface [15]. This indicates that inhibiting MMPs is beneficial to protect the hybrid layer which ultimately, improves the bond stability.

Numerous substances were proven to inhibit/decrease the activity of MMPs and other enzymes (*e.g.*, cysteine and cathepsin) in dentine [16,17]. The most studied among those inhibitors are chlorhexidine (CHX) and benzalkonium chloride (BAC). Typically, MMPs inhibitors can either be incorporated into the adhesive system or through dentine surface application prior to adhesive treatment [18,19].

Previously, two systematic reviews were conducted to evaluate the effect of CHX as dentine pre-treatment [18,19], and one when CHX was added in adhesive systems [20], on the bond strength. Consistently, all reviews present the same results, where no negative effect of CHX on the immediate bond strength and a significant increase in bond strength after ageing was reported. These findings suggested that using or adding CHX prior to or into the adhesive system may maintain the integrity of the collagen part in the hybrid layer over a long period of time [21]. Notably, all previous reviews were focused mainly on CHX and solely meta-analyses its data, while other inhibitors have emerged recently in the literature. Therefore, the aim of this study was to systematically review the literature for *in vitro* studies that evaluated the effect of incorporating MMP inhibitors into the adhesive system on the short- and long-term bond strength of the resin-dentine interface, in order to provide clinicians with a scientific base result on the effect of adding MMP inhibitors in the adhesive systems on resin-dentine bond strength. The null hypothesis stated that whether MMP inhibitors were incorporated into adhesive systems or not, no significant difference in bond strength values would be detected over time.

2. Materials and methods

2.1. Data sources and search strategies

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) guidelines [22,23]. A systematic electronic search was conducted in three databases: MEDLINE, EMBASE, and Google Scholar. The search terms and strategies were formulated to answer the following question: Does incorporating MMP inhibitor into a dental adhesive system compared to the corresponding dental adhesive system with no MMP inhibitor, preserve/increase the bond strength of coronal composite restoration?. The last search was conducted on 6 March 2022 with no lower publication year limit. The search terms used during the searching process in the databases are listed in Table 1. Also, an additional manual search was conducted in the bibliographies of the included studies.

2.2. Eligibility criteria

- Inclusion criteria were:

o Peer-reviewed published studies in the English language.

Table 1
Search terms used during the searching process.

1	extracted human teeth.mp.
2	human teeth.mp.
3	dentin/ or sound dentine.mp.
4	dentin/ or healthy dentine.mp.
5	dentin/ or carious affected dentine.mp.
6	dentin/ or caries affected dentine.mp.
7	dentin/ or affected dentine.mp.
8	dentine.mp. or dentin/
9	matrix metalloproteinase inhibitors.mp. or matrix metalloproteinase inhibitor/
10	MMP inhibitors.mp.
11	no matrix metalloproteinase inhibitors.mp.
12	no MMP inhibitors.mp.
13	bond strength.mp.
14	bond stability.mp.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
16	9 or 10
17	11 or 12
18	13 or 14
19	15 and 16 and 17 and 18

- o *In vitro* randomised controlled trials evaluating the effect of MMP inhibitor/s incorporated into an adhesive system on dentine bond strength.
- o Studies evaluating the micro-bond strength (μ-bond strength) *i.e.*, μ-tensile, and μ-shear of direct coronal composite restoration.
- o Studies reporting the results (means and standard deviation (SD) of bond strength) quantitatively and numerically in mega-pascals (MPa).
- o Studies using coronal dentine of extracted permanent human teeth whether it was sound, caries-free, or caries affected.
- o Studies including control group/s (adhesive system with no MMP inhibitors) corresponding to the experimental group/s.
- o Studies ageing the samples in water or artificial saliva for 24 h (h) and at least one more time point.

- Exclusion criteria were:

- o Studies where numerical data was not reported.
- o Studies using radicular dentine or enamel substrate.
- o Studies incorporating the MMP inhibitor into a luting agent or cement.
- o Antibiotic (*e.g.*, tetracycline) MMP inhibitors or other agents not proven to be an inhibitor for MMP enzymes.
- o MMP inhibitor not incorporated into an adhesive system, *e.g.*, surface pre-treatment.
- o Studies without control or control with no similar composition to the experimental adhesive system.
- o Studies evaluating the macro-bond strength.
- o Studies ageing the samples for 24 h only and/or using ageing solutions other than water or artificial saliva.

2.3. Search and screening

Full texts of all studies resulting from the electronic search were uploaded to reference manager software EndNote X9.3.3TM (Thomson Reuters, New York, NY, USA). Duplicated studies were removed by the same software and an additional check for duplications was performed manually. Then two independent reviewers (R.Y. and H.J.) screened the titles and abstracts. Afterwards, the full texts of the eligible studies were screened by the same reviewers, independently, to evaluate the eligibility of the studies. In case of disagreement between the two reviewers, a third evaluator was involved (P.A. or H.A.). Additionally, the bibliographies of the included studies were screened for any further potential that warranted inclusion.

2.4. Data extraction

A data extraction spreadsheet was designed and used, which included the following elements: Authors' name, year of publication, type of MMP inhibitor, type of ageing solution, type of incorporation, name of the adhesive system and mode of application (E&R or SE), sample size, ageing periods, means and SD of bond strength for each included group. These data were extracted independently by two reviewers (R.Y. and H.J.). A third reviewer (P.A.), independently, extracted data on 10% of studies to check the consistency between reviewers. Conflicts of opinion were resolved through consensus by consulting a further reviewer (H.A. or E.A.).

2.5. Risks of bias and quality assessment

The quality assessment tool employed was modified from a previous study [24]. The assessment was performed independently by two reviewers (R.Y. and H.J.). The following parameters were assessed: sample randomisation, substrate condition, adhesive system and incorporation type, following the manufacturer's instructions in material application, storage medium, bonded area, sample size calculation (power analysis), restoration and bond test performed by a single operator, and blinding of the operator during bond strength testing. Under each component of the tool, the letter 'Y' (yes) was added if the study reported the component and 'N' (no) if it was not reported. The grading judgement of "low", "medium", or "high" risk of bias was based on the total number of 'Y' in each study according to the following grading system: one to five (high), six or seven (medium) and eight or nine (low).

2.6. Data synthesis

Narrative analysis for the findings was summarised using text and tables. It included type of MMP inhibitor, type of incorporation, mode of adhesive system application, type of ageing solution, ageing period, substrate condition, type of μ-bond strength test, means of bond strength, and SD.

2.7. Meta-analysis

Review Manager software (RevMan) [The Cochrane Collaboration, Version 5.4, 2020] was used to meta-analyse the data. The following information was entered into RevMan: mean bond strength and SD (outcome measures) of MMP Inhibitor and control groups, and number of teeth in each group. A random-effects meta-analysis model was used to generate the mean differences (MD) in bond strength and their 95% confidence intervals (95% CI). The findings of all comparisons were pooled. Subsequently, the pooled data were categorised into three time periods to decrease the heterogenicity: 24 h, 6 m, and 12 m. These time periods were selected based on the common time periods used in the included studies. Following the establishment of the pooled MD in relation to time, additional pooling was done based on the MMP inhibitor kind/concentration and the adhesive application mode (E&R or SE). Additional grouping was considered, when possible, by pooling data based on the part of incorporation into the adhesive system (adhesive, etchant, or primer). A positive MD supports the MMP inhibitors group, whereas a negative MD favours the control group. The overall effects were tested using a Z test, whereas a *P-value* of < 0.05 was considered significant.

To check the statistical heterogeneity, the Q test was utilised, with a significant level of 0.1, to clarify the proportion of total variance across studies that can be attributable to heterogeneity rather than chance. In addition, the inconsistency (I^2) test was performed to indicate the degree of discrepancy between the included data. The I^2 *value* of heterogeneity can be interpreted as (0–40) % insignificant, (30–60) % moderate, (50–90) % substantial, and (75–100) % considerable [25].

MMP inhibitors with the same concentration but which did not have enough data sets (less than three) to analyse were not included in the meta-analysis. Also, the MMP inhibitor with the same concentration that had enough data sets at 24 h time period only was excluded from the meta-analyses. Based on the above meta-analysis protocol, the included MMP inhibitors were 2% CHX, 0.2% CHX, 5 μM GM1489, 0.5% BAC, and 1% BAC when the adhesive was applied in E&R mode. The bond strength effects of these inhibitors were analysed as follows:

- 2% CHX *vs.* control at 24 h, 6 m, and 12 m.
- 0.2% CHX *vs.* control at 24 h and 12 m.
- 5 μM GM1489 *vs.* control at 24 h and 12 m.
- 0.5% BAC *vs.* control at 24 h, 6 m, and 12 m.
- 1% BAC *vs.* control at 24 h, 6 m, and 12 m.
- 1% BAC *vs.* control at 24 h, 6 m, and 12 m (when incorporated into adhesive part).

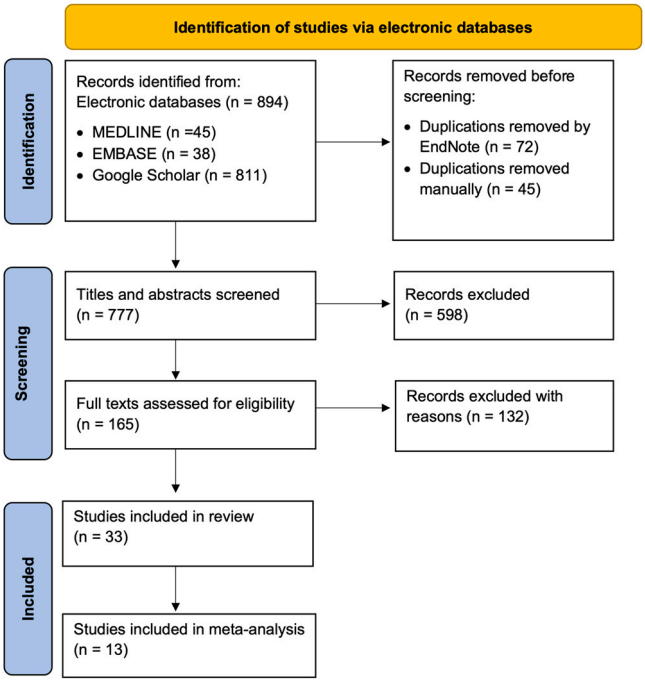

Fig. 1. PRISMA flow diagram of study selection.

- 1% BAC *vs.* control at 24 h and 12 m (when incorporated into etchant part).

3. Results

3.1. Narrative analysis

Initially, the electronic databases search resulted in 894 papers, then duplicated papers were removed which resulted in 777 papers. These were subjected to title and abstract screening, then 165 papers remained. In the end, based on the eligibility criteria and the full text reviewing of the remaining papers, a total of 33 papers were included in the systematic review (Fig. 1).

The extracted data from the included studies were summarised in Table 2. In summary, 33 studies were published between 2003 and 2022 with the dominant year of publication in 2020, with six studies. A total of 19 different MMP inhibitors were used and the most used was CHX, in nine studies. Followed by Epigallocatechin gallate (EGCG) in seven studies, and BAC in six studies. Also, Proanthocyanidins (PAC) in four studies and GM1489 in three studies. In terms of incorporation into adhesive systems, the majority of the studies (25 studies) incorporated the inhibitors into the adhesive part of the system followed by incorporation into etchant in seven studies, and into primer in four studies only. Additionally, most of the studies used the adhesive in E&R mode (27 studies). As included studies used only water or artificial saliva as an ageing solution, 23 of them used water. All included studies aged the samples for 24 h; from those, 15 and 13 studies aged samples for 12 months (m) and 6 m, respectively. Interestingly, one study reported 2 y and another one reported 5 y of *in vitro* ageing. Considering the substrate condition, all studies used caries-free dentine of permanent teeth, except Campos 2019 [26], Czech 2019 [27], and Rolim 2022 [28] which used caries affected dentine of permanent teeth. Regarding the μ-bond strength tests, all studies measured the bond strength by μ-tensile test except Simmer 2019 [29] study which used a μ-shear test; also, it is the only study that classified the substrate into superficial and deep dentine.

3.2. Risk of bias

Of the 33 included studies, the majority indicated a medium risk of bias (n = 20, 60.6%), while 39.4% (13 studies) indicated a high risk of bias and no study showed a low risk of bias. Additionally, of the 13 studies included in the meta-analysis, the majority indicated a medium risk of bias (n = 10, 77%), and 23% (three studies) indicated a high risk of bias and no study showed a low risk of bias. These results are based on the selected parameters in the quality assessment tool (Table 3).

3.3. Meta-analysis

A total of 60 data sets from 13 papers were included in the meta-analysis. In general, the analysis showed that different MMP inhibitors have different effects on the bond strength at different time periods.

Regarding the 2% CHX *vs.* control, the following analyses were conducted (Fig. 2). For the 24 h analysis, eight data sets from five papers were included. The MD was not significantly different between groups ($Z = 0.43$, $P = 0.67$) and the heterogeneity between the data was moderate and not significant ($I^2 = 41\%$, $P = 0.10$) (Fig. 2A). For 6 m, three data sets from two papers were included. The MD significantly favoured the 2% CHX group ($Z = 2.43$, $P = 0.02$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 89\%$, $P = 0.0001$) (Fig. 2B). For the 12 m analysis, three data sets from two papers were included. The MD was not significantly different between groups ($Z = 0.14$, $P = 0.89$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 88\%$, $P = 0.0003$) (Fig. 2C).

Regarding the 0.2% CHX *vs.* control, the following analyses were conducted (Fig. 3). For the 24 h analysis, five data sets from three papers were included. The MD significantly favoured the 0.2% CHX group ($Z = 3.4$, P = 0.0007) and the heterogeneity between the data was moderately to substantially significant ($I^2 = 56\%$, $P = 0.06$) (Fig. 3A). For the 12 m analysis, three data sets from two papers were included. The MD significantly favoured the 0.2% CHX group ($Z = 11.97$, $P = 0.00001$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.83$) (Fig. 3B).

Regarding the 5 μM GM1489 *vs.* control, the following analyses were conducted (Fig. 4). For the 24 h analysis, five data sets from three papers were included. The MD significantly favoured the 5 μM GM1489 group ($Z = 2.35$, $P = 0.02$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.82$) (Fig. 4A). For the 12 m analysis, five data sets from three papers were included. The MD significantly favoured the 5 μM GM1489 group ($Z = 5.77$, $P < 0.00001$) and the heterogeneity between the data was insignificant ($I^2 = 38\%$, $P = 0.17$) (Fig. 4B).

Regarding the 0.5% BAC *vs.* control, the following analyses were conducted (Fig. 5). For the 24 h analysis, four data sets from three papers were included. The MD was not significantly different between groups ($Z = 0.78$, $P = 0.43$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.62$) (Fig. 5A). For 6 m, three data sets from two papers were included. The MD significantly favoured the 0.5% BAC group ($Z = 6.64$, $P < 0.00001$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.46$) (Fig. 5B). For the 12 m analysis, three data sets from two papers were included. The MD was not significantly different between groups ($Z = 1.59$, $P = 0.11$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 87\%$, $P = 0.0005$) (Fig. 5C).

Regarding the 1% BAC *vs.* control, the following analyses were conducted (Fig. 6). For the 24 h analysis, eight data sets from five papers were included. The MD was not significantly different between groups ($Z = 0.89$, $P = 0.38$) and the heterogeneity between the data was substantially significant ($I^2 = 65\%$, $P = 0.006$) (Fig. 6A). For 6 m, four data sets from two papers were included. The MD

Table 2
Extracted data from the included studies.

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
Almahdy 2012[30]	Distilled water	Primer	Optibond FL (E&R)	5 μM GM6001	24 h	42.0 (18.7)
					3 m	30.9 (15.7)
				5 μM BB94	24 h	48.0 (20.3)
					3 m	34.2 (17.0)
				Control	24 h	34.7 (18.7)
					3 m	36.8 (17.0)
			Prime&Bond NT(E&R)	5 μM GM6001	24 h	41.9 (15.8)
					3 m	31.4 (16.0)
				5 μM BB94	24 h	43.2 (18.4)
					3 m	46.4 (14.5)
				Control	24 h	48.2 (20.4)
					3 m	42.7 (17.5)
			G-Bond (SE)	5 μM GM6001	24 h	41.7 (17.7)
					3 m	17.0 (13.2)
				5 μM BB94	24 h	34.8 (19.2)
					3 m	18.4 (16.1)
				Control	24 h	25.3 (15.7)
					3 m	12.2 (10.0)
Almeida 2017[31]	Distilled water	Adhesive	Experimental (E&R)	2% $ZnCl_2$	24 h	32.3 (2.1)
					12 m	31.4 (2.1)
				3.5% $ZnCl_2$	24 h	28.4 (0.6)
					12 m	27.1 (0.7)
				5% $ZnCl_2$	24 h	26.7 (0.8)
					12 m	24.1 (1.1)
				Control	24 h	34.6 (2.5)
					12 m	31.5 (2.4)
Barcellos 2016[32]	Distilled water	Adhesive	Experimental (E&R)	1% Zn-methacrylate	24 h	26.4 (6.1)
					6 m	14.2 (3.6)
				1% ZnO	24 h	28.7 (6.1)
					6 m	27.8 (4.0)
				Control	24 h	24.8 (8.0)
					6 m	13.8 (4.3)
Campos 2019[26]	Distilled and deionised water	Primer	Clearfil SE Bond (SE)	2% $ZnCl_2$	24 h	22.6 (10.4)
					12 m	19.5 (11.5)
				Control	24 h	24.9 (9.4)
					12 m	28.3 (11.5)
Choi 2020[33]	Water	Adhesive	All-Bond Universal (E&R)	0.1% (Zn)-doped MBN	24 h	36.3 (7.5)
					After 5000 thc	35.6 (10.0)
				0.5% (Zn)-doped MBN	24 h	37.0 (8.9)
					After 5000 thc	35.8 (11.4)
				1% (Zn)-doped MBN	24 h	38.4 (8.1)
					After 5000 thc	37.9 (7.1)
				0.1% MBN Control	24 h	36.8 (10.2)
					After 5000 thc	35.7 (4.6)
				0.5% MBN Control	24 h	37.6 (11.3)
					After 5000 thc	37.0 (5.3)
				1% MBN Control	24 h	37.6 (8.1)
					After 5000 thc	37.6 (10.3)
Comba 2019[34]	Artificial saliva	Adhesive	All-Bond Universal (SE)	0.5% BAC	24 h	40.5 (13.1)
					12 m	30.2 (12.5)
				1% BAC	24 h	40.8 (12.4)
					12 m	21.8 (11.6)
				Control	24 h	42.2 (16.8)
					12 m	35.8 (17.5)
			All-Bond Universal (E&R)	0.5% BAC	24 h	39.7 (9.4)
					12 m	29.0 (7.8)
				1% BAC	24 h	36.2 (8.7)
					12 m	17.4 (10.5)
				Control	24 h	44.1 (13.9)
					12 m	31.6 (14.8)
Czech 2019[27]	Distilled water	Adhesive	Adper Single Bond 2 (E&R)	200 μg/ml EGCG	24 h	23.3 (6.6)
					6 m	16.1 (6.9)
					12 m	16.2 (9.0)
				Control	24 h	23.4 (7.7)
					6 m	16.3 (9.6)
					12 m	14.9 (6.9)

(*continued on next page*)

Table 2 (*continued*)

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
da Silva 2015[35]	Distilled water	Adhesive	Experimental (E&R)	5 μM GAL	24 h	38.2 (3.9)
					6 m	33.2 (2.6)
					12 m	31.5 (1.9)
				5 μM BAT	24 h	37.7 (3.6)
					6 m	33.6 (2.9)
					12 m	31.9 (2.7)
				5 μM GM1489	24 h	37.9 (3.3)
					6 m	33.5 (1.4)
					12 m	32.2 (2.8)
				2% CHX	24 h	38.3 (2.0)
					6 m	33.5 (1.1)
					12 m	33.0 (1.2)
				Control	24 h	33.3 (5.7)
					6 m	33.3 (2.7)
					12 m	25.5 (2.9)
Daood 2020[36]	Artificial saliva	Adhesive	Experimental (SE)	0.125% RF	24 h	30.5 (3.2)
					12 m	27.3 (5.1)
				Control	24 h	29.2 (6.0)
					12 m	21.9 (4.6)
de Macedo 2019[37]	Distilled water	Adhesive	Experimental (SE)	0.1% EGCG	24 h	47.9 (3.4)
					6 m	38.4 (3.7)
				0.5% EGCG	24 h	30.7 (2.9)
					6 m	17.6 (3.9)
				Control	24 h	39.0 (9.5)
					6 m	43.9 (8.7)
			Experimental (E&R)	0.1% EGCG	24 h	25.5 (6.1)
					6 m	22.8 (4)
				0.5% EGCG	24 h	22 (2.6)
					6 m	44.3 (8.0)
				Control	24 h	36 (7.3)
					6 m	22.3 (4.1)
Dias 2020[38]	Distilled water	Adhesive	Experimental (E&R)	1% PAC	24 h	27.6 (9.8)
					12 m	13.6 (4.6)
				2% PAC	24 h	27.9 (8.6)
					12 m	18.1 (5.4)
				4.5% PAC	24 h	26.5 (7.4)
					12 m	26.4 (5.9)
				6% PAC	24 h	25.2 (6.9)
					12 m	15.5 (2.1)
				Control	24 h	29.9 (9.1)
					12 m	12.4 (3.9)
Du 2012[39]	Distilled water	Adhesive	Adper Single Bond 2 (E&R)	100 μg/ml EGCG	24 h	43.6 (6.5)
					6 m	42.2 (9.0)
				200 μg/ml EGCG	24 h	48.2 (6.6)
					6 m	46.5 (8.5)
				300 μg/ml EGCG	24 h	41.8 (8.0)
					6 m	39.1 (9.7)
				Control	24 h	36.8 (6.3)
					6 m	28.1 (6.7)
El Gezawi 2018[40]	Distilled water	Adhesive	Clearfil SE protect (SE)	MDPB	24 h	24.6 (7.3)
					6 m	17.1 (8.8)
		Etchant	Prime&Bond One (E&R)	BAC	24 h	33.4 (9.9)
					6 m	13.9 (8.1)
		Control			24 h	39.5 (10.5)
					6 m	14.1 (8.7)
Fernandes 2020[41]	Artificial saliva	Primer	Clearfil SE Bond (SE)	0.01% EGCG	24 h	36.33 (6.1)
					12 m	29.2 (7.6)
				Control	24 h	40.7 (6.5)
					12 m	33.9 (9.3)
Ghorab and Ibraheim 2018[42]	Distilled water	Adhesive	Optibond solo plus (E&R)	0.2% HES	24 h	35.5 (5.3)
					After 10,000 thc	24.3 (3.2)
				0.5% HES	24 h	37.5 (3.1)
					After 10,000 thc	28.7 (2.3)
				1% HES	24 h	31.4 (2.3)
					After 10,000 thc	23.1 (4.6)
				Control	24 h	29.6 (5.3)
					After 10,000 thc	22.9 (5.3)
Hass 2016[43]	Distilled water	Etchant	Adper Single Bond Plus (E &R)	2% PAC	24 h	47.4 (2.9)
					6 m	48.7 (4.8)
				Control	24 h	41.5 (2.1)
					6 m	21.9 (1.0)

(*continued on next page*)

Table 2 (*continued*)

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
Kalagi 2020[44]	Water	Primer	Adper Scotchbond Multipurpose (E&R)	10% CHX	24 h	57.4 (11.2)
					6 m	67 (10.6)
				20% CHX	24 h	52.4 (11.2)
					6 m	62.9 (15.7)
		Adhesive		10% CHX	24 h	56.4 (10.9)
					6 m	52.7 (13.1)
				20% CHX	24 h	60.6 (6.4)
					6 m	52.1 (8.0)
		Control			24 h	60.8 (12.7)
					6 m	47.1 (7.5)
Khamverdi 2015[45]	Distilled water	Adhesive	Clearfil SE Bond (SE)	25 μM EGCG	24 h	28.1 (5.3)
					After 2500 thc and 6 m	24.3 (6.6)
				50 μM EGCG	24 h	29.5 (3.3)
					After 2500 thc and 6 m	28.2 (6.7)
				100 μM EGCG	24 h	28.7 (6.4)
					After 2500 thc and 6 m	30.3 (3.9)
				Control	24 h	29.6 (4.1)
					After 2500 thc and 6 m	25.9 (2.8)
			Filtek Silorane (SE)	25 μM EGCG	24 h	21.3 (2.3)
					After 2500 thc and 6 m	21.0 (2.6)
				50 μM EGCG	24 h	18.2 (1.4)
					After 2500 thc and 6 m	17.8 (1.6)
				100 μM EGCG	24 h	17.6 (1.7)
					After 2500 thc and 6 m	17.3 (2.2)
				Control	24 h	23.4 (2.1)
					After 2500 thc and 6 m	22.1 (2.7)
Loguercio 2016[46]	Distilled water	Etchant	Adper Single Bond 2 (E&R)	2% CHX	24 h	39.5 (4.1)
					5 y	26.9 (2.3)
				Control	24 h	40.2 (3.3)
					5 y	16.1 (2.1)
			Prime&Bond NT (E&R)	2% CHX	24 h	36.2 (3.9)
					5 y	21.3 (2.9)
				Control	24 h	35.1 (3.1)
					5 y	11 (2.7)
Loguercio 2017[47]	Distilled water	Etchant	Adper Single Bond 2 (E&R)	2% CHX	24 h	42.1 (3.8)
					12 m	37.1 (3.9)
				1% BAC	24 h	38.1 (5.1)
					12 m	39.4 (4.6)
				2% PAC	24 h	43.2 (3.2)
					12 m	38.8 (4.7)
				Control	24 h	38.7 (5.4)
					12 m	30.1 (4.3)
Malaquias 2018[48]	Distilled water	Adhesive	Ambar (E&R)	0.01% CHX	24 h	53.8 (4.0)
					2 y	44.8 (2.3)
				0.05% CHX	24 h	50.0 (4.7)
					2 y	41.5 (4.0)
				0.1% CHX	24 h	52.7 (3.5)
					2 y	47.4 (3.4)
				0.2% CHX	24 h	55.6 (3.3)
					2 y	49.8 (3.1)
				Control	24 h	50.3 (4.1)
					2 y	30.1 (4.3)
			XP Bond (E&R)	0.01% CHX	24 h	63.3 (4.7)
					2 y	41.9 (3.9)
				0.05% CHX	24 h	59.4 (4.0)
					2 y	40.3 (3.9)
				0.1% CHX	24 h	64.1 (4.0)
					2 y	45.5 (3.9)
				0.2% CHX	24 h	63.2 (3.1)
					2 y	44.7 (3.9)
				Control	24 h	60.2 (3.1)
					2 y	28.1 (3.9)

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Table 2 (*continued*)

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
Maravic 2019[49]	Artificial saliva	Adhesive	Peak Universal Bond (E&R)	0.2% CHX	24 h	50.1 (11)
					12 m	40.7 (8.6)
				Control	24 h	38.9 (12.8)
					12 m	21.6 (7.7)
			Peak Universal Bond (SE)	0.2% CHX	24 h	53 (11.3)
					12 m	43.9 (11.7)
				Control	24 h	35.8 (13)
					12 m	33.6 (11.1)
Miranda 2020[50]	Distilled water	Adhesive	Experimental (E&R)	1 μM GM1489	24 h	21.4 (4.2)
					12 m	22.2 (2.6)
				5 μM GM1489	24 h	31.0 (7.2)
					12 m	29.4 (8.2)
				10 μM GM1489	24 h	43.4 (4.1)
					12 m	36.2 (3.3)
				Control	24 h	27.4 (4.3)
					12 m	21.2 (4.8)
			Adper Single Bond 2 (E&R)	1 μM GM1489	24 h	35.0 (4.5)
					12 m	28.0 (7.0)
				5 μM GM1489	24 h	30.9 (5.9)
					12 m	40.2 (6.0)
				10 μM GM1489	24 h	27.1 (8.3)
					12 m	31.1 (7.4)
				Control	24 h	31.5 (9.9)
					12 m	26.3 (7.8)
Nakajima 2003[51]	Water	Adhesive	Experimental (SE)	NaF	24 h	39.8 (8.0)
					3 m	32.4 (6.1)
					6 m	36.8 (12.3)
				Control	24 h	44.6 (11.2)
					3 m	26.3 (8.8)
					6 m	23.6 (10.7)
Rolim 2022[28]	Distilled water	Adhesive	Ambar Universal (SE)	1% PAC	24 h	22.1 (5.8)†
						23.9 (7.5)‡
					12 m	28.5 (8.8)†
						21.9 (10.0)‡
				1% EGCG	24 h	29.0 (13.4)†
						21.6 (7.7)‡
					12 m	40.1 (9.3)†
						23.1 (4.1)‡
				Control	24 h	15.6 (10.0)†
						21.2 (4.9)‡
					12 m	23.9 (6.1)†
						27.4 (4.2)‡
			Clearfil SE Bond (SE)	1% PAC	24 h	35.3 (11.2)†
						27.1 (5.1)‡
					12 m	50.9 (15.5)†
						26.7 (6.5)‡
				1% EGCG	24 h	31.6 (13.1)†
						32.8 (10.1)‡
					12 m	39.7 (14.2)†
						23.4 (4.2)‡
				Control	24 h	32.8 (13.2)†
						22.5 (9.9)‡
					12 m	40.7 (12.3)†
						31.4 (7.9)‡
Sabatini 2014[52]	Artificial saliva	Etchant	Adper Single Bond Plus (E &R)	1% BAC	24 h	43.0 (11.8)
					6 m	35.1 (6.5)
		Adhesive		0.5% BAC	24 h	51.4 (7.9)
					6 m	53.9 (6.9)
		Control			24 h	34.3 (7.8)
					6 m	27.4 (6.2)

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Table 2 (*continued*)

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
Sabatini and Pashley 2015[53]	Artificial saliva	Adhesive	All-Bond Universal (E&R)	0.5% BAC	24 h	30.6 (7.4)
					6 m	31.4 (3.9)
					12 m	30.1 (9.8)
				1% BAC	24 h	31.3 (6.9)
					6 m	29.9 (5.2)
					12 m	33.5 (10.6)
				2% BAC	24 h	29.1 (8.5)
					6 m	27.5 (4.0)
					12 m	25.2 (8.4)
				0.5% BAC	24 h	25.8 (6.0)
					6 m	28.7 (9.0)
					12 m	32.6 (4.6)
				1% BAC	24 h	26.0 (4.3)
					6 m	27.4 (4.0)
					12 m	32.0 (4.8)
				2% BAC	24 h	30.5 (5.4)
					6 m	28.8 (6.4)
					12 m	30.2 (4.8)
				Control	24 h	29.4 (4.7)
					6 m	16.4 (4.4)
					12 m	15.3 (4.6)
Samani 2018[54]	Distilled water	Adhesive	Solobond M (E&R)	5 mg/ml NaF	24 h	13.9 (6.8)
					3 m	14.2 (5.5)
				10 mg/ml NaF	24 h	15.8 (6.9)
					3 m	16.8 (5.7)
				Control	24 h	10.2 (6.0)
					3 m	9.7 (4.2)
Simmer 2019[29]	Distilled water	Adhesive	Adper Single Bond 2 (E&R)	5 µM BAT	24 h	33.3 (4)*
						29.5 (1.8)**
					12 m	29.3 (6.3)*
						21.5 (8.7)**
				5 µM GM1489	24 h	34.1 (6.0)*
						28.8 (1.8)**
					12 m	36.0 (4.3)*
						25.9 (5.7)**
				2% CHX	24 h	24.9 (5.2)*
						19.7 (4.7)**
					12 m	17.8 (2.7)*
						10.2 (2.1)**
				Control	24 h	32.2 (4.2)*
						22.5 (5.2)**
					12 m	20.2 (2.4)*
						13.6 (3)**
Stanislawczuk 2009[55]	Distilled water	Etchant	Prime&Bond NT (E&R)	2% CHX	24 h	30.6 (9.0)
					6 m	25.7 (2.5)
				Control	24 h	22.0 (9.7)
					6 m	14.6 (3.1)
			Adper Single Bond 2 (E&R)	2% CHX	24 h	28.4 (4.4)
					6 m	27.1 (1.4)
				Control	24 h	27.2 (6.1)
					6 m	20.4 (2.1)
Stanislawczuk 2014[56]	Distilled water	Adhesive	Ambar (E&R)	0.01% CHX	24 h	56.2 (4.3)
					12 m	50.8 (2.5)
				0.05% CHX	24 h	51.2 (4.1)
					12 m	49.6 (4.2)
				0.1% CHX	24 h	55.3 (3.2)
					12 m	53.4 (4.5)
				0.2% CHX	24 h	54.1 (3.8)
					12 m	52.9 (7.6)
				Control	24 h	54.5 (3.9)
					12 m	34.8 (4.1)
			XP Bond (E&R)	0.01% CHX	24 h	61.9 (5.8)
					12 m	47.4 (3.2)
				0.05% CHX	24 h	56.7 (3.1)
					12 m	45.2 (5.0)
				0.1% CHX	24 h	66.9 (4.2)
					12 m	54.2 (4.3)
				0.2% CHX	24 h	67.3 (2.6)
					12 m	56.5 (4.3)
				Control	24 h	64.5 (2.7)
					12 m	35.9 (2.8)

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Table 2 (*continued*)

Authors year	Ageing solution	MMP inhibitor Incorporated into	Adhesive system (mode of application)	MMP inhibitor/ control groups	Ageing period	Bond strength means (MPa) (SD)
Tekçe 2016[57]	Distilled water	Etchant	Adper Single Bond Universal (E&R)	1% BAC	24 h	45.6 (2.1)
					12 m	35.1 (3.6)
				Control	24 h	43.3 (3.4)
					12 m	37.7 (3.4)
			All-Bond Universal (E&R)	1% BAC	24 h	46.6 (5.0)
					12 m	39.5 (6.7)
				Control	24 h	43.8 (3.6)
					12 m	38.5 (6.2)
Yu 2017[58]	Deionized water	Adhesive	Adper Single Bond 2 (E&R)	200 µg/ml EGCG	24 h	32.6 (5.3)
					After 5000 thc	27.1 (3.0)
				200 µg/ml EGCG-3Me	24 h	30.4 (5.2)
					After 5000 thc	27.8 (2.4)
				400 µg/ml EGCG	24 h	30.4 (3.6)
					After 5000 thc	27.6 (1.4)
				400 µg/ml EGCG-3Me	24 h	31.2 (4.2)
					After 5000 thc	29.6 (2.0)
				600 µg/ml EGCG	24 h	30.2 (4.8)
					After 5000 thc	27.8 (1.8)
				600 µg/ml EGCG-3Me	24 h	31.5 (3.1)
					After 5000 thc	30.0 (2.3)
				Control	24 h	33.4 (6.4)
					After 5000 thc	20.8 (2.2)

MMP, matrix metalloproteinase; $ZnCl_2$, zinc chloride; ZnO, zinc oxide; MBN, mesoporous bioactive glass nanoparticles; BAC, Benzalkonium chloride; EGCG, Epigallocatechin gallate; GAL, Galardine; BAT, Batimastatin; CHX, Chlorhexidine; RF, Riboflavin; PAC, Proanthocyanidins; MDPB, methacryloyloxydodecylpyridinium bromide; HES, hesperidin; EGCG-3Me, Epigallocatechin-3- gallate; E&R, etch-and-rinse; SE, self-etch; SD, standard deviation; MPa, megapascal; h, hours; m, months; y, years; thc, thermocycles. † Sound dentine, ‡Caries affected dentine, * Superficial dentine substrate, ** Deep dentine substrate.

significantly favoured the 1% BAC group ($Z = 4.11$, $P < 0.0001$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 77\%$, $P = 0.005$) (Fig. 6B). For the 12 m analysis, six data sets from four papers were included. The MD was not significantly different between groups ($Z = 1.09$, $P = 0.28$) and the heterogeneity between the data was considerably significant ($I^2 = 91\%$, $P < 0.00001$) (Fig. 6C).

Regarding the 1% BAC *vs.* control only when incorporated into the adhesive part, the following analyses were conducted (Fig. 7). For the 24 h analysis, four data sets from three papers were included. The MD was not significantly different between groups ($Z = 0.33$, $P = 0.75$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 82\%$, $P = 0.0007$) (Fig. 7A). For 6 m, three data sets from two papers were included. The MD significantly favoured the 1% BAC group ($Z = 3.91$, $P < 0.0001$) and the heterogeneity between the data was substantially to considerably significant ($I^2 = 80\%$, $P = 0.006$) (Fig. 7B). For the 12 m analysis, three data sets from two papers were included. The MD was not significantly different between groups ($Z = 0.69$, $P = 0.49$) and the heterogeneity between the data was considerably significant ($I^2 = 94\%$, $P < 0.00001$) (Fig. 7C).

Regarding the 1% BAC *vs.* control only when incorporated into the etchant part, the following analyses were conducted (Fig. 8). For the 24 h analysis, four data sets from three papers were included. The MD was not significantly different between groups ($Z = 1.55$, $P = 0.12$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.52$) (Fig. 8A). For the 12 m analysis, three data sets from two papers were included. The MD was not significantly different between groups ($Z = 1.30$, $P = 0.19$) and the heterogeneity between the data was insignificant ($I^2 = 0\%$, $P = 0.59$) (Fig. 8B).

4. Discussion

The MMP inhibitors were proposed to be used clinically to preserve the bond strength of the dental restoration to tooth substrate, hence increasing the longevity of restorations. This can be achieved by inhibiting the MMPs to maintain the integrity of the collagen part in the hybrid layer.

The current review showed that the effect of MMP inhibitors incorporated into the adhesive system on the bond strength not only depends on the type and concentration of MMP inhibitor but also on the ageing period. Attempting to understand the effect of different MMP inhibitors in different ageing periods and to test the null hypothesis of this review, a statistical meta-analysis was conducted. Based on the meta-analysis results, the null hypothesis was rejected for all included MMP inhibitors except for 1% BAC only when incorporated into the etchant part, whereas there were no significant differences in bond strength between 1% BAC *vs.* control group.

In the 24 h and 12 m time periods, the only two inhibitors that showed a significant increase in bond strength compared to the control group are 0.2% CHX and 5 µM GM1489. While in 6 m time period, all included MMP inhibitors, 2% CHX, 0.5%, and 1% BAC, revealed a significant increase in bond strength. Of note, none of the included MMP inhibitors had a significant negative effect on the bond strength at any of the included time periods. The results of 0.2% CHX are consistent with Zhang 2020 [20], however, unlike the current review, their results for the 2% CHX at 24 h showed a significant increase in bond strength. Noticeably, although they analysed three data sets for 2% CHX at 24 h when E&R was used, all these data were pooled from a single study. Moreover, the results of the other previous two meta-analyses showed that 0.2% and 2% of CHX had a significant positive effect on bond strength after 6 m and 12 m of ageing. These two studies included CHX when used as dentine pretreatment only [18,19]. To the best of our knowledge, no previous study meta-analysed the effect of MMP inhibitors, other than CHX, on the bond strength of composite coronal restoration.

The effect of MMP inhibitors concentration on the bond strength over time is not fully clear in our results; however, previous studies had the same vague results. A meta-regression analysis reported no linear relationship between CHX concentration and bond strength [59]. It is worth mentioning that a low concentration of CHX has an inhibitory effect on MMPs (Gendron et al., 1999); this inhibitory effect is supported by the results of a recent and current meta-analysis. The results of the recent one showed both 0.1% and 0.2% CHX incorporated into the adhesive system increase the bond strength over time [20], and the same results are noted in the present meta-analysis with 0.2% CHX. Moreover, one included study in

Table 3
Quality assessment of included studies.

Authors year	Randomisation	Substrate condition	Adhesive system and incorporation	Manufacturer instruction	Storage medium	Bonded area	Single operator	Sample size calculation	Blinding of operator	Risk of bias
Almahdy 2012[30]	N	Y	Y	Y	Y	Y	N	N	N	High
Almeida 2017[31]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Barcellos 2016[32]	N	Y	Y	N	Y	Y	N	N	N	High
Campos 2019[26]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Choi 2020[33]	Y	Y	Y	N	Y	Y	N	N	N	High
Comba 2019[34]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Czech 2019[27]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
da Silva 2015[35]	N	Y	Y	N	Y	Y	N	N	N	High
Daood 2020[36]	Y	Y	Y	N	Y	Y	N	N	N	High
de Macedo 2019[37]	Y	Y	Y	N	Y	Y	N	N	N	High
Dias 2020[38]	N	Y	Y	N	Y	Y	N	N	N	High
Du 2012[39]	Y	Y	Y	N	Y	Y	N	N	N	High
El Gezawi 2018[40]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Fernandes 2020[41]	Y	Y	Y	Y	Y	Y	N	Y	N	Medium
Ghorab and Ibraheim 2018[42]	N	Y	Y	N	Y	Y	N	N	N	High
Hass 2016[43]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Kalagi 2020[44]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Khamverdi 2015[45]	Y	Y	Y	N	Y	Y	N	N	N	High
Loguercio 2016[46]	Y	Y	Y	N	Y	Y	Y	N	N	Medium
Loguercio 2017[47]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Malaquias 2018[48]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Maravic 2019[49]	N	Y	Y	Y	Y	Y	N	N	N	High
Miranda 2020[50]	N	Y	Y	N	Y	Y	N	N	N	High
Nakajima 2003[51]	Y	Y	Y	N	Y	Y	N	N	N	High
Rolim 2022[28]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Sabatini 2014[52]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Sabatini and Pashley 2015[53]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Samani 2018[54]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Simmer 2019[29]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Stanislawczuk 2009[55]	Y	Y	Y	N	Y	Y	Y	N	N	Medium
Stanislawczuk 2014[56]	Y	Y	Y	Y	Y	Y	Y	N	N	Medium
Tekçe 2016[57]	Y	Y	Y	Y	Y	Y	N	N	N	Medium
Yu 2017[58]	Y	Y	Y	N	Y	Y	N	Y	N	Medium

Y: Yes; N: No

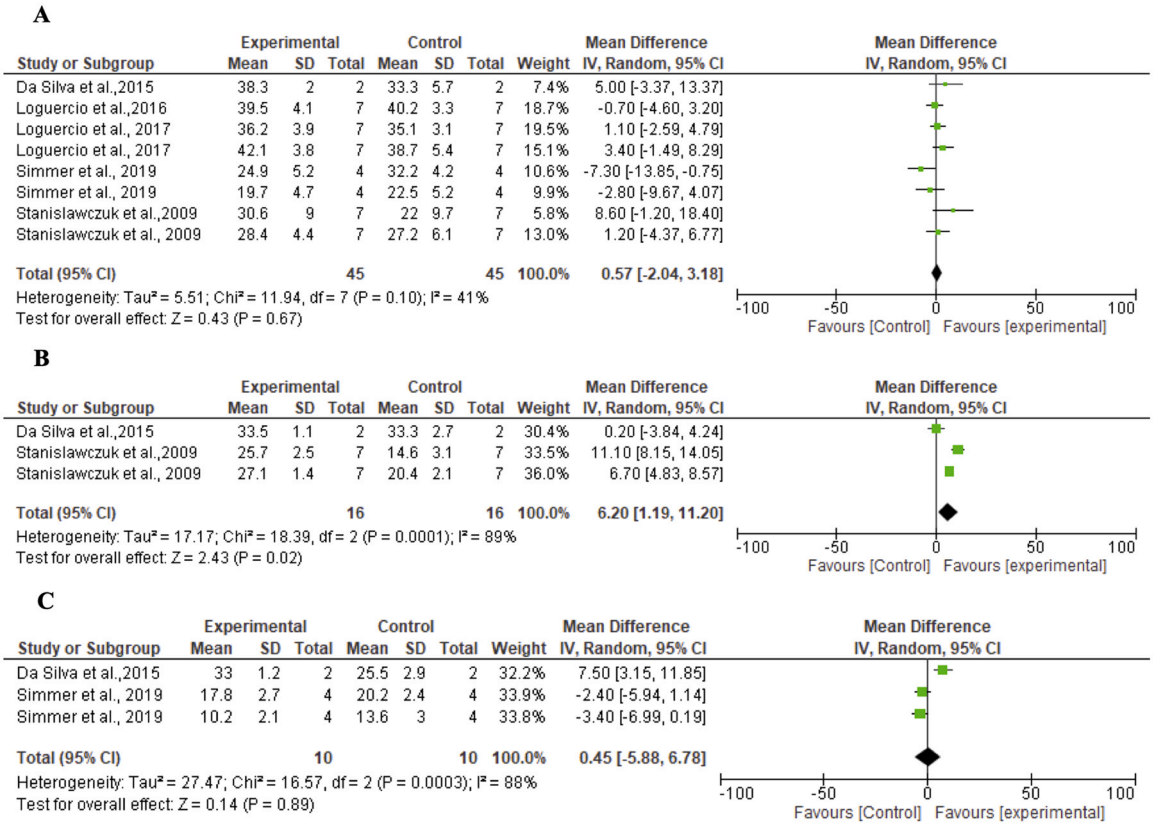

Fig. 2. Forest plots for analysis of bond strength means with 2% CHX *vs.* control at: (A) 24 h, (B) 6 m, and (C) 12 m.

the present review showed that CHX concentration ranged from 0.01% to 0.2% had a significant positive effect on bond strength up to 2 y [48]. On the contrary, another included study in the current review revealed that 2% CHX significantly preserves high bond strength over a 5 y period [46]. Therefore, future studies needed to evidentially clear the vague about the association between MMP inhibitors concentration and the effect on bond strength.

CHX is a cationic antimicrobial agent and broad-spectrum MMPs inhibitor [60,61]. Its anti-proteolytic potency was markedly tested on the collagen fibrils preservation in the hybrid layer [60,62], and it was suggested that the inhibitory mechanism is based on cation chelation of calcium and zinc ions present in MMPs [60]. A previous study demonstrated that CHX had bonding ability to demineralised dentine [63] by electrostatic forces, which indicated that this agent can bind to collagen fibrils for future release after filling the binding sites of MMP enzymes [64]. This was evidentially supported by an *in vitro* study that reported the presence of CHX in resin/dentine interface after 5 y of water storage, particularly when CHX was used as an aqueous dentine pre-treatment or incorporated into etchant, and this was evaluated by micro-Raman spectroscopy [46]. In contrast, Sabatini 2014 [52] claimed that the high water solubility of the large size CHX molecules allow for easy leach-out, in a short time, from the hybrid layer which may decrease the long-term inhibitory effect and consequently, decrease the resin-dentine bond strength. This

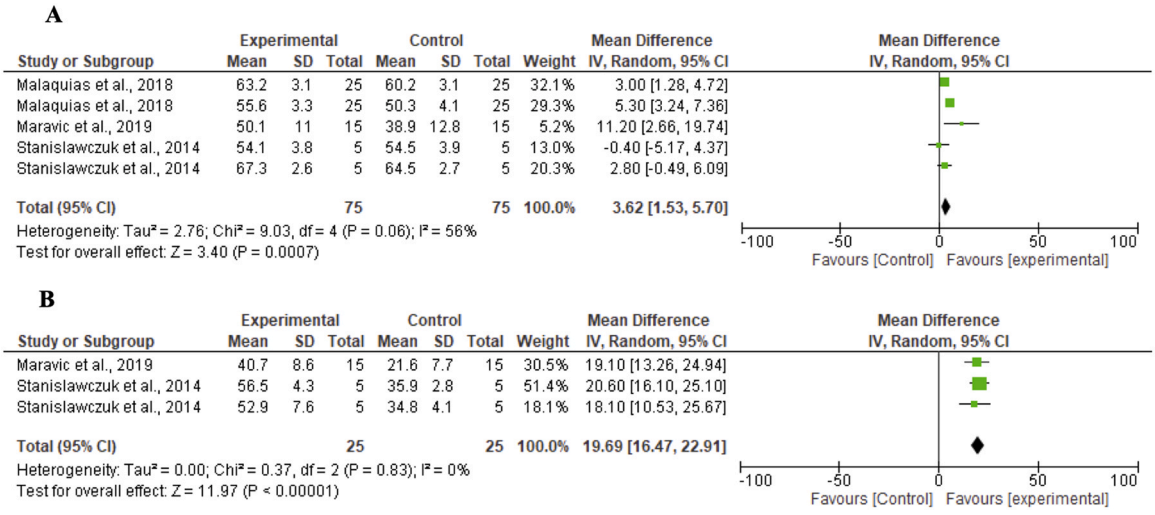

Fig. 3. Forest plots for analysis of bond strength means with 0.2% CHX *vs.* control at: (A) 24 h, (B) 12 m.

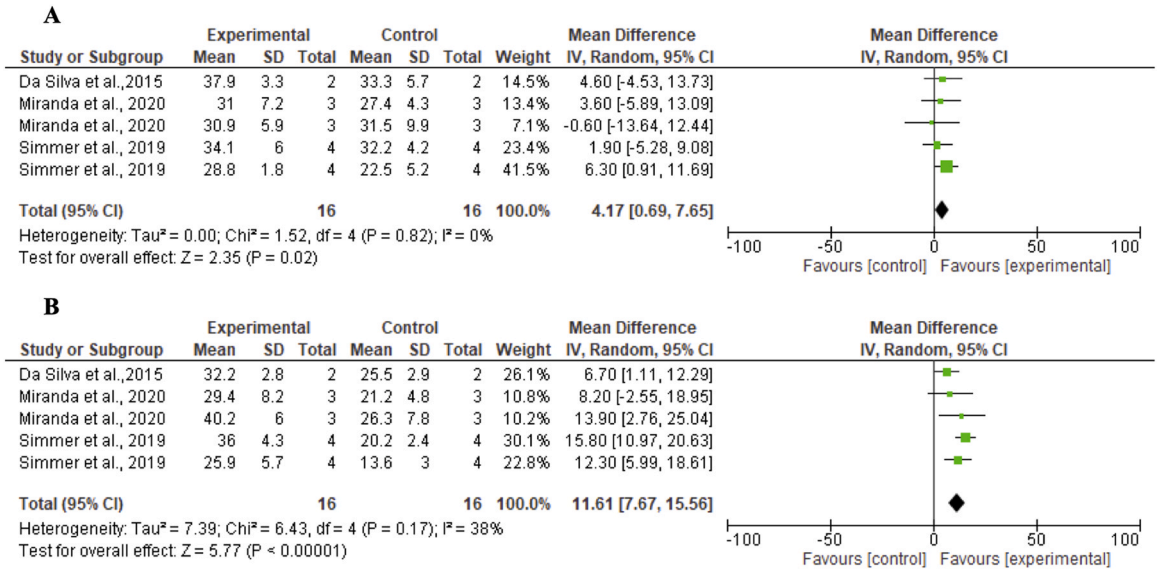

Fig. 4. Forest plots for analysis of bond strength means with 5 μM GM1489 *vs.* control at: (A) 24 h, (B) 12 m.

claim supports the results of the current meta-analysis for 2% CHX at 12 m time.

The second MMP inhibitor included in the meta-analysis is GM1489, which has been used in the medical field. It is synthetic and potent on a broad range of collagenase enzymes. Also, its inhibition effects were tested against MMP 1, 2, 3, 8, and 9 [65,66]. GM1489 is an acetohydroxamic acid that has a heterocyclic complex structure, and it also contains a functional metal-ligand group. The unique structure and the functional group of this inhibitor might be the reason behind the potent inhibitory effect, which enhances binding to MMPs' active site and chelating the zinc ions [29,35]. The current meta-analysis showed very promising results when 5 μM GM1489 was incorporated into adhesive systems, there was a significant increase in bond strength compared to the control group up to 12 m of ageing. Beneficially, adding a small amount of GM 1489 into the adhesive not only shows a positive effect on bond strength but also does not jeopardise other properties such as the degree of conversion, water sorption, and solubility [29,35,50].

Another antimicrobial and broad-spectrum MMPs inhibitor agent is BAC. It is a potent basic agent, containing a quaternary ammonium group, with nitrogenous cationic properties when ionised in solvent, *e.g.*, water [67]. Studies revealed an inhibitory effect of 0.5% and 1% BAC against MMP within the hybrid layer which led to a uniform and continuous adhesive layer with less degradation compared to the control group [53,57,64,68]. Chemically, BAC molecules, particularly the positive charge part, can bind to negative charges in

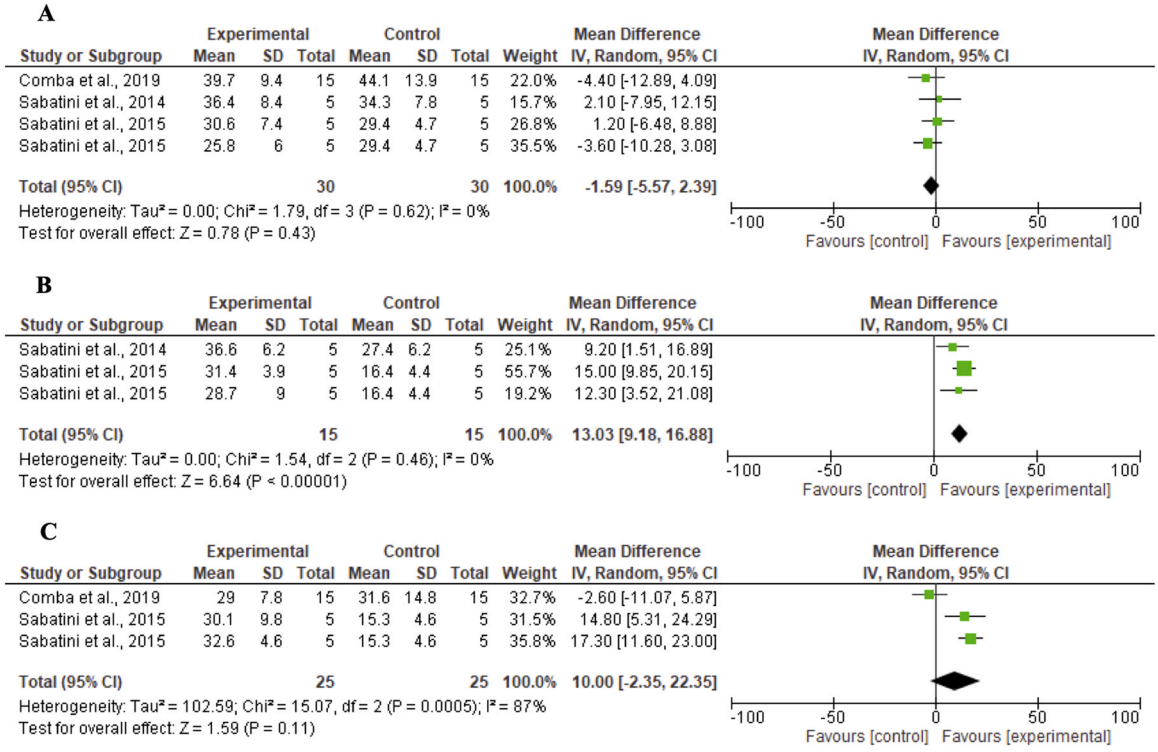

Fig. 5. Forest plots for analysis of bond strength means with 0.5% BAC *vs.* control at: (A) 24 h, (B) 6 m, and (C) 12 m.

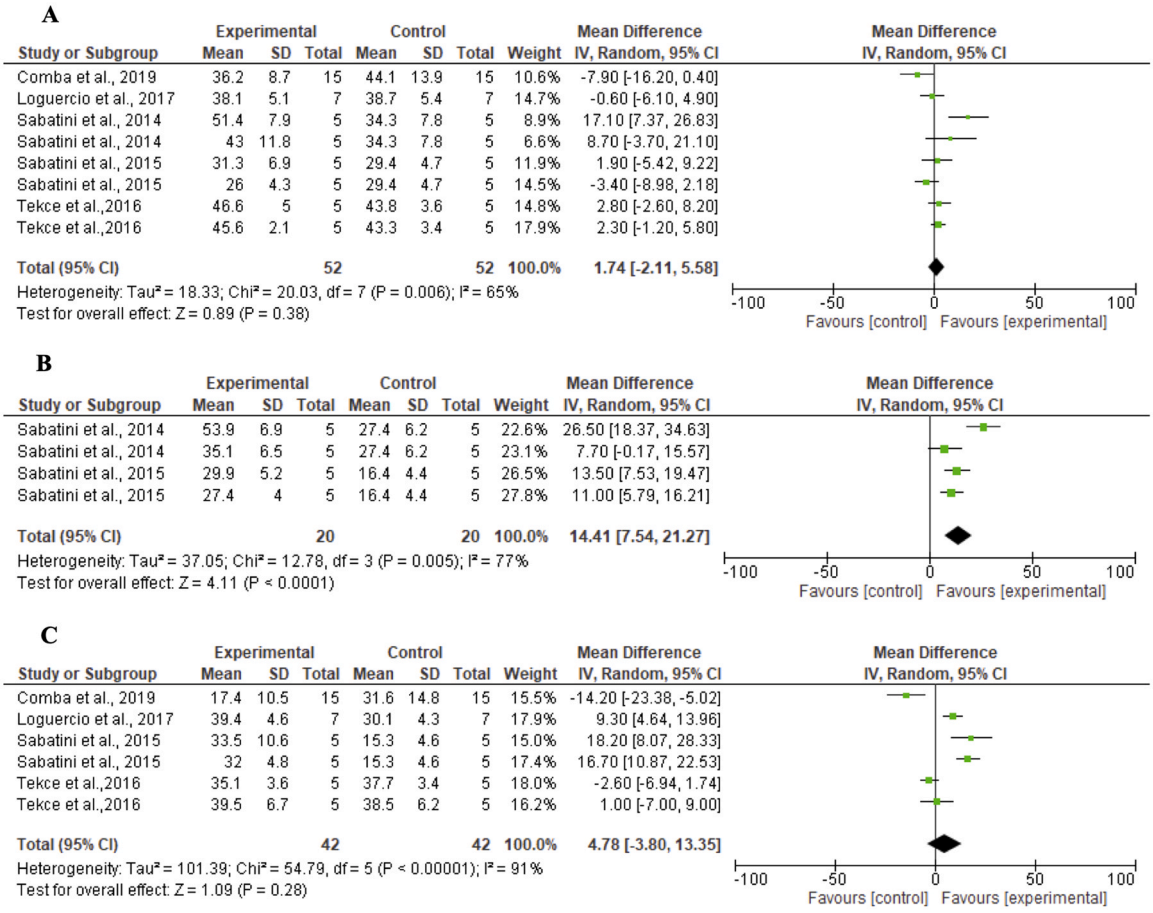

Fig. 6. Forest plots for analysis of bond strength means with 1% BAC *vs.* control at: (A) 24 h, (B) 6 m, and (C) 12 m.

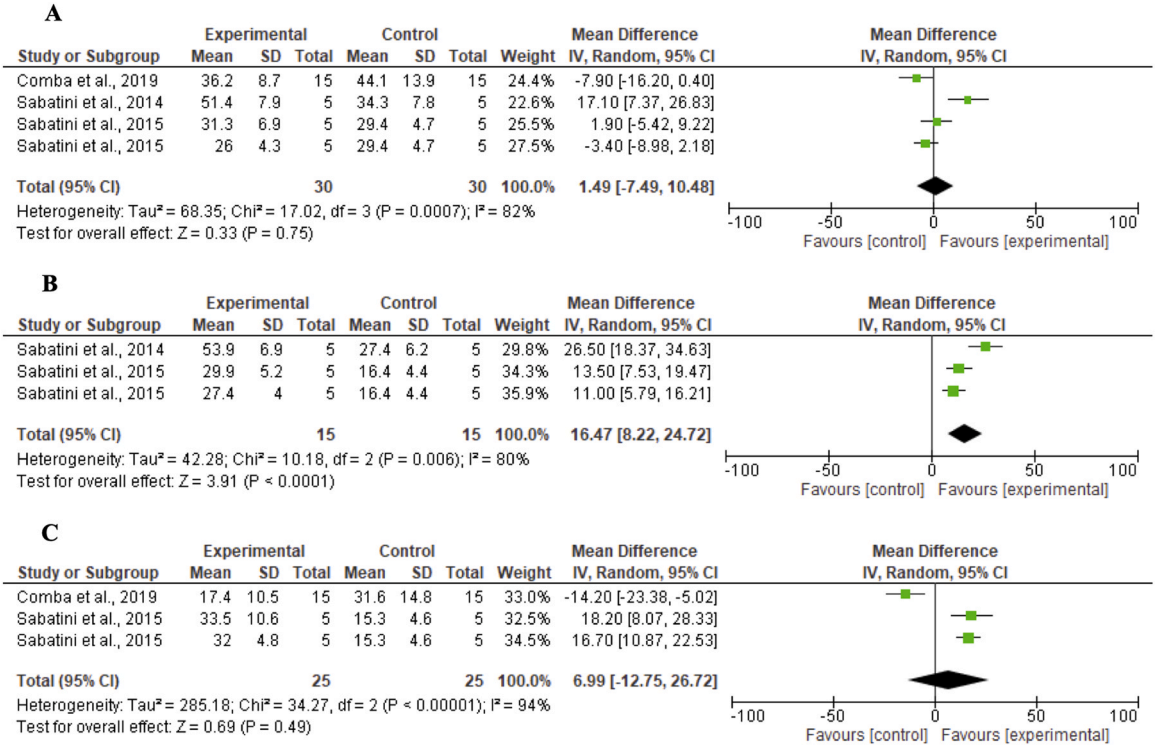

Fig. 7. Forest plots for analysis of bond strength means with 1% BAC *vs.* control only when incorporated into adhesive part at: (A) 24 h, (B) 6 m, and (C) 12 m.

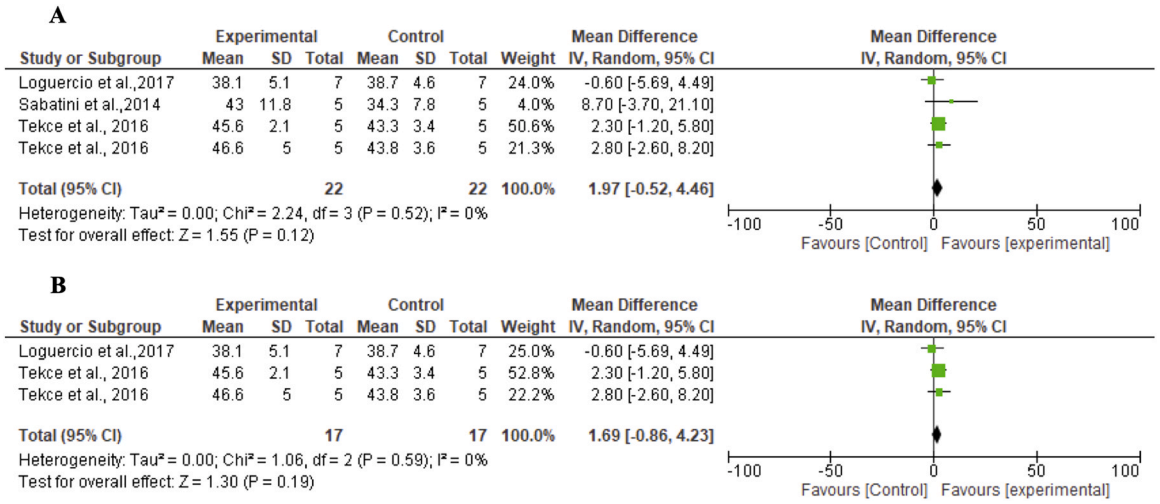

Fig. 8. Forest plots for analysis of bond strength means with 1% BAC *vs.* control only when incorporated into etchant part at: (A) 24 h, (B) 12 m.

hydroxyapatite, collagen, and MMPs, which cause enzyme inactivation by intermolecular interactions [67]. Comparing BAC to CHX, the former has only one positive charge while the latter has two; this fact favours the CHX stability in the hybrid layer over the BAC [69]. In addition to the unstable (weak) electrostatic interaction of BAC, it is water-soluble, which allows for leaching out from the hybrid layer easily [53]. However, the small molecular size of the BAC allows for better stabilisation within the hybrid layer [52]. An etchant containing 1% BAC was commercialised (Bisco) and extensively studied, regarding its antimicrobial and anti-collagenolytic properties. The current review showed neither negative nor positive effect on the immediate and 12 m bond strength when using 1% BAC in the etchant, which is likely due to the weak binding ability of the BAC to collagen, and also the rinsing effect during the E&R process which decreases the amount of BAC in the hybrid layer by up to 50%; hence, MMP inhibition effect and bond strength [67]. To overcome the rinsing effect, studies had investigated the incorporation of BAC into adhesive. Our results showed that the incorporation of 1% BAC into the adhesive has similar results to incorporation of 2% CHX into adhesive system, which shows a significant positive effect on bond strength only in 6 m ageing. Possibly, the low binding ability of BAC eases the leach-out of this agent from the bonding interface after ageing for more than 6 m, which could affect the longer-term anti-proteolytic ability, and this appears clinically in the bond strength measure.

Obviously, incorporation of an MMP inhibitor agent into an adhesive system has positive impacts on the bond strength not only by inhibiting the collagen degradation process, but also it provides less restorative clinical steps and theoretically longer-lasting effects than applying an inhibitor in a separate step as dentine pre-treatment. However, some concerns should be considered when incorporating such agents. The detrimental effects on other properties such as degree of conversion, elastic modulus, water sorption, solubility, and mechanical effects have to be minimised [29,35,70,71]. Additionally, the stability and the sustainability of the additive agents (MMP inhibitors) in the adhesive structure must be prioritised in the incorporation process. For instance, adding non-polymerisable agents with no covalent bond ability to the adhesive resulted in easy leach-out of the inhibitor from the hybrid layer; hence, the MMP inhibition potential of the agent will not be reflected in the bond strength and the only effect that appears is delaying but not preventing the collagen degradation in the adhesive interface [72]. Studies suggested ways to overcome this issue by either using a copolymerisable MMP inhibitor agent that can be covalently bonded in the adhesive monomers, or by using nanotubes as a delivery method, in order to have a more sustainable effect over the long term [44,53,72,73]. Of note, some of the included studies in the current review choose to add the MMP inhibitors into a commercial adhesive, while others added the inhibitors into a standard experimental formulation, attempting to control the adhesive ingredients and to avoid the undesirable effects of the unknown ingredients in the commercial adhesives.

Aiming to decrease the heterogeneity in the current review and meta-analysis, an extensive and restricted search was conducted. This can be noticed in the specific and restricted inclusion and exclusion criteria, such as including only μ-scale bond strength test, water, or artificial saliva ageing solution; also, meta-analysing the data from the same inhibitor, concentration, ageing period, and adhesive application mode. However, many of the present meta-analyses revealed significant heterogeneity and the majority of them were substantial to considerable at 6 m and 12 m ageing analysis, which is expected in bond strength *in vitro* studies [74].

Many methodological factors contributed to the variability of the *in vitro* bond strength tests [75,76], hence, the heterogeneity between studies. These include the type and brand of the adhesive system, ageing method, ageing/storing temperature, tooth type, specimen size, and location in the tooth [3,18,59,74]. Moreover, in particular to the current meta-analysis, we found that incorporation of MMP inhibitor into different parts of the adhesive system has an impact on the heterogeneity of the data of the bond strength. This is evident in 1% BAC analysis when incorporated into etchant part only; the heterogeneity is insignificant, and the inconsistency is 0% at 24 h and 12 m. Conversely, the analysis of 1% BAC in general without grouping shows substantially to considerably significant heterogeneity and inconsistency ranging from 65% to 91%. Nonetheless, the same conclusion could not be drawn with 1% BAC analysis when incorporated into adhesive only; therefore, more extensive, and focused studies are needed to identify the role of MMP inhibitor incorporation in different parts of adhesive systems on bond strength. Another possible explanation of the high heterogeneity is that all the included studies in the meta-analysis are classified as having either medium or high risk of bias. Additionally, a small sample number in the studies, as well as the few numbers of studies included in some of the analyses may affect the heterogeneity of the data [25]. In the end, there is uncertainty in the heterogeneity and the inconsistency measures due to the effect of numerous factors; therefore, the results of these two parameters should be interpreted with caution to avoid misleading conclusions [25].

The main purposes of the risk of bias and quality assessments evaluation are to check the credibility of the findings and to identify

the deficient elements, in order to give an evidence-based statement for future work in this research area. Alongside the previous works, the current review has classified most of the included study as medium risk of bias and the rest as high risk of bias [18,19]. Looking deeply at the results of each parameter, the most neglected two are blinding of the operator and sample size calculation, whereas among all included studies, none of them reported the blinding of the operator and only two stated a sample size calculation. Another parameter that shows a significant impact on the risk of bias is depending on a single operator in performing the bond strength test, which is reported only in eight studies. Also, two parameters that have less influence on the results of bias are following the manufacturer's instructions in material application and reporting sample randomisation. The results of this evaluation reflect the approach of reporting protocols and findings in bond strength studies. To increase the reliability and the quality of future work in bond strength studies, it is recommended to establish a strict, clear, and well-documented guideline for such a laboratory test.

The current review included and analysed only *in vitro* bond strength data, which is considered as an indirect approach to evaluate the efficiency of MMP inhibitors on the MMP activity. Even though a previous review suggested a correlation between *in vitro* bond strength test and clinical performance of restoration [76], bond strength is only a single property that evaluated the restoration adhesion to the tooth structure. Other factors could have an influence, to some extent, on the integrity of the restoration/tooth adhesion, such as mastication force, temperature, pH as well as physical, chemical, and mechanical properties of the adhesive/restoration interface. Importantly, gaps between laboratory and clinical studies should be taken seriously in interpretating the results of the former.

Some of the analyses in the current review included a small number of data/studies, potentially, due to the strict inclusion criteria which were proposed to decrease the degree of heterogeneity between the included studies. More focused meta-analyses are recommended on a single MMP inhibitor but with less strict criteria, to include more data and more studies aiming to have a more generalised conclusion from different research groups. Also, in the present meta-analysis, the effect of the included MMP inhibitors on the bond strength when incorporated into the primer part or SE adhesive system could not be analysed, due to the lack of sufficient data for a single inhibitor with the same concentration. It was suggested by a previous study that the type of adhesive system has a significant effect on the bond strength; hence, a future meta-analysis is needed to address the effect with the self-etch adhesive system in the context of MMP inhibitor incorporation [59]. In another aspect, in order to meta-analyse the long-term effect on bond strength, more *in vitro* studies are in demand as the results of our review showed only two studies with promising results that had evaluated the bond strength after two and five years with CHX incorporation into the adhesive system [46,48].

5. Conclusions

Within the limitations of *in vitro* studies, the present systematic review and meta-analysis indicated that the incorporation of MMP inhibitors into the dental adhesive systems has a beneficial effect on bond strength. Incorporating 0.2% CHX and 5 µM GM1489 in E&R adhesive systems revealed a significant positive effect on the immediate and 12 m bond strength. Other included inhibitors 2% CHX and (0.5 or 1) % BAC have no adverse effect on immediate bond strength and a significantly better bond strength after 6 m, but not at 12 m of ageing. However, incorporating 1% BAC in etchant did not show any effect on either immediate or 12 m bond strength. In addition, MMP inhibitors other than CHX, such as BAC, can serve similarly in terms of bond strength. Further, another synthetic inhibitor *e.g.*, GM1489 could have a superior result compared to CHX. Finally, this review would provide clinicians and researchers with scientific-based results regarding the effect of incorporating MMP inhibitors in the adhesive system on resin-dentine bond strength. Also, this review clarifies possible future paths in using and manufacturing dental adhesive systems containing MMP inhibitors.

Scientific field of dental Science

Restorative Dentistry and Dental Biomaterials.

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Data availability statement

Data are contained within the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Heintze SD, Rousson V. Clinical effectiveness of direct class II restorations - a meta-analysis. J Adhes Dent 2012;14(5):407–31.
[2] Sunnegardh-Gronberg K, van Dijken JW, Funegard U, Lindberg A, Nilsson M. Selection of dental materials and longevity of replaced restorations in Public Dental Health clinics in northern Sweden. J Dent 2009;37(9):673–8.
[3] De Munck J, Van Landuyt K, Peumans M, Poitevin A, Lambrechts P, Braem M, et al. A critical review of the durability of adhesion to tooth tissue: methods and results. J Dent Res 2005;84(2):118–32.
[4] Hashimoto M, Ohno H, Kaga M, Endo K, Sano H, Oguchi H. In vivo degradation of resin-dentin bonds in humans over 1 to 3 years. J Dent Res 2000;79(6):1385–91.
[5] Tjaderhane L, Nascimento FD, Breschi L, Mazzoni A, Tersariol IL, Geraldeli S, et al. Optimizing dentin bond durability: control of collagen degradation by matrix metalloproteinases and cysteine cathepsins. Dent Mater 2013;29(1):116–35.
[6] Goldberg M, Kulkarni AB, Young M, Boskey A. Dentin: structure, composition and mineralization. Front Biosci (Elite Ed) 2011;3:711–35.
[7] Breschi L, Maravic T, Cunha SR, Comba A, Cadenaro M, Tjaderhane L, et al. Dentin bonding systems: from dentin collagen structure to bond preservation and clinical applications. Dent Mater 2018;34(1):78–96.
[8] Nakabayashi N, Nakamura M, Yasuda N. Hybrid layer as a dentin-bonding mechanism. J Esthet Restor Dent 1991;3(4):133–8.
[9] Manso AP, Bedran-Russo AK, Suh B, Pashley DH, Carvalho RM. Mechanical stability of adhesives under water storage. Dent Mater 2009;25(6):744–9.
[10] Femiano F, Femiano R, Femiano L, Jamilian A, Rullo R, Perillo L. Dentin caries progression and the role of metalloproteinases: an update. Eur J Paediatr Dent 2016;17(3):243–7.
[11] Mazzoni A, Pashley DH, Nishitani Y, Breschi L, Mannello F, Tjaderhane L, et al. Reactivation of inactivated endogenous proteolytic activities in phosphoric acid-etched dentine by etch-and-rinse adhesives. Biomaterials 2006;27(25):4470–6.
[12] Nishitani Y, Yoshiyama M, Wadgaonkar B, Breschi L, Mannello F, Mazzoni A, et al. Activation of gelatinolytic/collagenolytic activity in dentin by self-etching adhesives. Eur J Oral Sci 2006;114(2):160–6.
[13] Apolonio FM, Mazzoni A, Angeloni V, Scaffa PM, Santi S, Saboia VP, et al. Effect of a one-step self-etch adhesive on endogenous dentin matrix metalloproteinases. Eur J Oral Sci 2017;125(2):168–72.

[14] DeVito-Moraes AG, Francci C, Vidal CM, Scaffa PM, Nesadal D, Yamasaki LC, et al. Phosphoric acid concentration affects dentinal MMPs activity. J Dent 2016;53:30–7.
[15] Mazzoni A, Tjaderhane L, Checchi V, Di Lenarda R, Salo T, Tay FR, et al. Role of dentin MMPs in caries progression and bond stability. J Dent Res 2015;94(2):241–51.
[16] Tersariol IL, Geraldeli S, Minciotti CL, Nascimento FD, Paakkonen V, Martins MT, et al. Cysteine cathepsins in human dentin-pulp complex. J Endod 2010;36(3):475–81.
[17] Scaffa PM, Vidal CM, Barros N, Gesteira TF, Carmona AK, Breschi L, et al. Chlorhexidine inhibits the activity of dental cysteine cathepsins. J Dent Res 2012;91(4):420–5.
[18] 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(8):733–43.
[19] Kiuru O, Sinervo J, Vahanikkila H, Anttonen V, Tjaderhane L. MMP inhibitors and dentin bonding: systematic review and meta-analysis. Int J Dent 2021;2021:9949699.
[20] Zhang X, Wang L, Liu S, Bai H, Niu W. Evaluation of the bond strength of chlorhexidine incorporated into the adhesive system composition: a PRISMA guided meta-analysis. J Dent Sci 2020;15(3):315–28.
[21] Manfro AR, Reis A, Loguercio AD, Imparato JC, Raggio DP. Effect of different concentrations of chlorhexidine on bond strength of primary dentin. Pediatr Dent 2012;34(2):e11–5.
[22] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.
[23] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Br Med J 2021:372.
[24] Sarkis-Onofre R, Skupien J, Cenci M, Moraes R, Pereira-Cenci T. The role of resin cement on bond strength of glass-fiber posts luted into root canals: a systematic review and meta-analysis of in vitro studies. Oper Dent 2014;39(1):E31–44.
[25] Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.
[26] Campos R, Oliveira C, Macedo J, França F, Basting R, Turssi C, 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.
[27] 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):2430–42.
[28] Rolim DCM, Souza LC, Hass V, Silva PGB, Signori C, Cenci MS, et al. Effect of cross-linker's incorporation into two adhesive systems with self-etch mode applied on sound and caries-affected dentin. Int J Adhes Adhes 2022;113:103074.
[29] Simmer FS, da Silva EM, Bezerra R, Miranda M, Noronha Filho JD, Amaral CM. Bond stability of conventional adhesive system with MMP inhibitors to superficial and deep dentin. J Mech Behav Biomed Mater 2019;100:103402.
[30] Almahdy A, Koller G, Sauro S, Bartsch JW, Sherriff M, Watson TF, et al. Effects of MMP inhibitors incorporated within dental adhesives. J Dent Res 2012;91(6):605–11.
[31] Almeida GS, da Silva EM, Guimarães JGA, da Silva RNL, Dos Santos GB, Poskus LT. ZnCl2 incorporated into experimental adhesives: selected physicochemical properties and resin-dentin bonding stability. BioMed Res Int 2017;2017.
[32] Barcellos DC, Fonseca BM, Pucci CR, Cavalcanti B, Persici Ede S, Goncalves SE. Zn-doped etch-and-rinse model dentin adhesives: dentin bond integrity, biocompatibility, and properties. Dent Mater 2016;32(7):940–50.
[33] Choi Y, Sun W, Kim Y, Kim IR, Gong MK, Yoon SY, et al. Effects of Zn-doped mesoporous bioactive glass nanoparticles in etch-and-rinse adhesive on the microtensile bond strength. Nanomaterials 2020;10(10):1943.
[34] Comba A, Maravic T, Valente L, Girlando M, Cunha SR, Checchi V, et al. Effect of benzalkonium chloride on dentin bond strength and endogenous enzymatic activity. J Dent 2019;85:25–32.
[35] da Silva EM, de Sa Rodrigues CU, de Oliveira Matos MP, de Carvalho TR, dos Santos GB, Amaral CM. Experimental etch-and-rinse adhesive systems containing MMP-inhibitors: pysicochemical characterization and resin-dentin bonding stability. J Dent 2015;43(12):1491–7.
[36] Daood U, Sauro S, Pichika MR, Omar H, Liang Lin S, Fawzy AS. Novel riboflavin/VE-TPGS modified universal dentine adhesive with superior dentine bond strength and self-crosslinking potential. Dent Mater 2020;36(1):145–56.
[37] de Macedo FAA, Souza NO, Lemos MVS, De-Paula DM, Santiago SL, Feitosa VP. Dentin bonding and physicochemical properties of adhesives incorporated with epigallocatechin-3-gallate. Odontology 2019;107(1):23–8.
[38] Dias PG, da Silva EM, Carvalho CM, Miranda M, Portela MB, Amaral CM. Characterization and antibacterial effect of an experimental adhesive containing different concentrations of proanthocyanidin. J Adhes Dent 2020;22(2):139–47.
[39] Du X, Huang X, Huang C, Wang Y, Zhang Y. Epigallocatechin-3-gallate (EGCG) enhances the therapeutic activity of a dental adhesive. J Dent 2012;40(6):485–92.
[40] El Gezawi M, Haridy R, Abo Elazm E, Al-Harbi F, Zouch M, Kaisarly D. Microtensile bond strength, 4-point bending and nanoleakage of resin-dentin interfaces: effects of two matrix metalloproteinase inhibitors. J Mech Behav Biomed Mater 2018;78:206–13.
[41] Fernandes FP, Adorno CC, da Silva TM, França FMG, Turssi CP, Basting RT, et al. Addition of EGCG to self-etching primer: effect on adhesive properties and bond stability to dentin. J Adhes Sci Technol 2020:1–14.
[42] Ghorab S, Ibraheim A. Effect of hesperidin on antibacterial activity and adhesive properti es of an etch-and-rinse adhesive system. Egypt Dent J 2018;64:3801–12. (4-October (Fixed Prosthodontics, Dental Materials, Conservative Dentistry & Endodontics)).
[43] Hass V, Luque-Martinez I, Munoz MA, Reyes MF, Abuna G, Sinhoreti MA, et al. The effect of proanthocyanidin-containing 10% phosphoric acid on bonding properties and MMP inhibition. Dent Mater 2016;32(3):468–75.
[44] Kalagi S, Feitosa SA, Münchow EA, Martins VM, Karczewski AE, Cook NB, et al. Chlorhexidine-modified nanotubes and their effects on the polymerization and bonding performance of a dental adhesive. Dent Mater 2020;36(5):687–97.
[45] Khamverdi Z, Rezaei-Soufi L, Rostamzadeh T. The effect of epigallocatechin gallate on the dentin bond durability of two self-etch adhesives. J Dent 2015;16(2):68–74.
[46] Loguercio AD, Hass V, Gutierrez MF, Luque-Martinez IV, Szezs A, Stanislawczuk R, et al. Five-year effects of chlorhexidine on the in vitro durability of resin/dentin interfaces. J Adhes Dent 2016;18(1):35–42.
[47] Loguercio AD, Malaquias P, Dos Santos FP, Hass V, Stanislawczuk R, Lima SNL, et al. Acid etching with modified phosphoric acid to increase the longevity of the bonded interface. J Adhes Dent 2017;19(3):195–201.
[48] Malaquias P, Gutierrez MF, Hass V, Stanislawczuk R, Bandeca MC, Arrais C, et al. Two-year effects of chlorhexidine-containing adhesives on the in vitro durability of resin-dentin interfaces and modeling of drug release. Oper Dent 2018;43(2):201–12.
[49] Maravic T, Comba A, Cunha SR, Angeloni V, Cadenaro M, Visinitini E, et al. Long-term bond strength and endogenous enzymatic activity of a chlorhexidine-containing commercially available adhesive. J Dent 2019;84:60–6.
[50] Miranda M, Silva EMD, Oliveira MF, Simmer FS, Santos GBD, Amaral CM. Resin-dentin bond stability of etch-and-rinse adhesive systems with different concentrations of MMP inhibitor GM1489. J Appl Oral Sci 2020;28:e20190499.
[51] Nakajima M, Okuda M, Ogata M, Pereira PN, Tagami J, Pashley DH. The durability of a fluoride-releasing resin adhesive system to dentin. Oper Dent 2003;28(2):186–92.
[52] Sabatini C, Kim JH, Ortiz, Alias P. In vitro evaluation of benzalkonium chloride in the preservation of adhesive interfaces. Oper Dent 2014;39(3):283–90.
[53] Sabatini C, Pashley DH. Aging of adhesive interfaces treated with benzalkonium chloride and benzalkonium methacrylate. Eur J Oral Sci 2015;123(2):102–7.
[54] Samani Y, Alaghehmand H, Jafari Z, Khafri S, Tashakkorian H. Sodium fluoride addition to a two-step etch-and-rinse adhesive system: effect on dentin microtensile bond strength and durability. Casp J Dent Res 2018;7(2):16–23.
[55] 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(4):481–90.
[56] Stanislawczuk R, Pereira F, Munoz MA, Luque I, Farago PV, Reis A, et al. Effects of chlorhexidine-containing adhesives on the durability of resin-dentine interfaces. J Dent 2014;42(1):39–47.
[57] Tekçe N, Tuncer S, Demirci M, Balci S. Do matrix metalloproteinase inhibitors improve the bond durability of universal dental adhesives? Scanning 2016;38(6):535–44.
[58] Yu HH, Zhang L, Yu F, Li F, Liu ZY, Chen JH. Epigallocatechin-3-gallate and epigallocatechin-3-o-(3-o-methyl)-gallate enhance the bonding stability of an etch-and-rinse adhesive to dentin. Materials 2017;10(2):183.
[59] Collares FM, Rodrigues SB, Leitune VC, Celeste RK, Borba de Araujo F, Samuel SM. Chlorhexidine application in adhesive procedures: a meta-regression analysis. J Adhes Dent 2013;15(1):11–8.
[60] 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(3):437–9.
[61] Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, De Stefano Dorigo E. Dental adhesion review: aging and stability of the bonded interface. Dent Mater 2008;24(1):90–101.
[62] Hebling J, Pashley DH, Tjaderhane L, Tay FR. Chlorhexidine arrests subclinical degradation of dentin hybrid layers in vivo. J Dent Res 2005;84(8):741–6.
[63] Kim J, Uchiyama T, Carrilho M, Agee KA, Mazzoni A, Breschi L, et al. Chlorhexidine binding to mineralized versus demineralized dentin powder. Dent Mater 2010;26(8):771–8.
[64] Sabatini C, Pashley DH. Mechanisms regulating the degradation of dentin matrices by endogenous dentin proteases and their role in dental adhesion. A review. Am J Dent 2014;27(4):203–14.
[65] Cathcart JM, Cao J. MMP Inhibitors: past, present and future. Front Biosci (Landmark Ed) 2015;20(7):1164–78.
[66] Boguszewska-Czubara A, Budzynska B, Skalicka-Wozniak K, Kurzepa J. Perspectives and new aspects of metalloproteinases' inhibitors in the therapy of CNS disorders: from chemistry to medicine. Curr Med Chem 2019;26(18):3208–24.
[67] Tezvergil-Mutluay A, Mutluay MM, Gu LS, Zhang K, Agee KA, Carvalho RM, et al. The anti-MMP activity of benzalkonium chloride. J Dent 2011;39(1):57–64.
[68] Sabatini C, Ortiz PA, Pashley DH. Preservation of resin-dentin interfaces treated with benzalkonium chloride adhesive blends. Eur J Oral Sci 2015;123(2):108–15.

[69] Tezvergil-Mutluay A, Agee KA, Uchiyama T, Imazato S, Mutluay MM, Cadenaro M, et al. The inhibitory effects of quaternary ammonium methacrylates on soluble and matrix-bound MMPs. J Dent Res 2011;90(4):535–40.
[70] Cadenaro M, Pashley DH, Marchesi G, Carrilho M, Antoniolli F, Mazzoni A, et al. Influence of chlorhexidine on the degree of conversion and E-modulus of experimental adhesive blends. Dent Mater 2009;25(10):1269–74.
[71] Cadenaro M, Maravic T, Comba A, Mazzoni A, Fanfoni L, Hilton T, et al. The role of polymerization in adhesive dentistry. Dent Mater 2019;35(1):e1–22.
[72] Pashley DH, Tay FR, Imazato S. How to increase the durability of resin-dentin bonds. Compend Contin Educ Dent 2011;32(7):60–4. 6.
[73] Antonucci JM, Zeiger DN, Tang K, Lin-Gibson S, Fowler BO, Lin NJ. Synthesis and characterization of dimethacrylates containing quaternary ammonium functionalities for dental applications. Dent Mater 2012;28(2):219–28.
[74] De Munck J, Mine A, Poitevin A, Van Ende A, Cardoso MV, Van Landuyt KL, et al. Meta-analytical review of parameters involved in dentin bonding. J Dent Res 2012;91(4):351–7.
[75] Pashley DH, Sano H, Ciucchi B, Yoshiyama M, Carvalho RM. Adhesion testing of dentin bonding agents: a review. Dent Mater 1995;11(2):117–25.
[76] Van Meerbeek B, Peumans M, Poitevin A, Mine A, Van Ende A, Neves A, et al. Relationship between bond-strength tests and clinical outcomes. Dent Mater 2010;26(2):e100–21.