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

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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.

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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 [4,5]. 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, MMP 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 where 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:
  - 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                   |

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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 type of MMP inhibitor, type of ageing solution, type of incorporation, included the following elements: Authors’ name, year of publication, investigated findings, 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 heterogeneity: 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 inhibitor 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 (I²) test was performed to indicate the degree of discrepancy between the included data. The I² 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).
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, Proanthocy anidins (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 (I² = 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 (I² = 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 (I² = 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 (I² = 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 (I² = 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 (I² = 0%, P = 0.62) (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 (I² = 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 (I² = 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 (I² = 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 (I² = 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 (I² = 65%, P = 0.006) (Fig. 6A). For 6 m, four data sets from two papers were included. The MD
| Authors/ year | Ageing solution | Adhesive system | MMP inhibitor | 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) |
|  |  |  |  |  |  | 24 h | 48.0 (20.3) |
|  |  |  |  |  |  | 3 m | 34.2 (17.0) |
|  |  |  |  |  |  | 24 h | 34.7 (18.7) |
|  |  |  |  |  |  | 3 m | 36.8 (17.0) |
|  |  |  |  |  |  | 24 h | 41.9 (15.8) |
|  |  |  |  |  |  | 3 m | 31.4 (16.0) |
|  |  |  |  |  |  | 24 h | 43.2 (18.4) |
|  |  |  |  |  |  | 3 m | 46.4 (14.5) |
|  |  |  |  |  |  | 24 h | 48.2 (20.4) |
|  |  |  |  |  |  | 3 m | 42.7 (17.5) |
| Almeida 2017[31] | Distilled water | Adhesive | Experimental (E&R) |  | 2% ZnCl₂ | 24 h | 32.3 (2.1) |
|  |  |  |  |  |  | 12 m | 31.4 (2.1) |
|  |  |  |  |  |  | 24 h | 28.4 (0.6) |
|  |  |  |  |  |  | 12 m | 27.1 (0.7) |
|  |  |  |  |  |  | 24 h | 26.7 (0.8) |
|  |  |  |  |  |  | 12 m | 24.1 (1.1) |
|  |  |  |  |  |  | 24 h | 34.6 (2.5) |
|  |  |  |  |  |  | 12 m | 31.5 (2.4) |
| Barcellos 2016[32] | Distilled and deionised water | Primer | Clearfil SE Bond (SE) |  | 2% ZnCl₂ | 24 h | 22.6 (10.4) |
|  |  |  |  |  |  | 12 m | 19.5 (11.5) |
|  |  |  |  |  |  | 24 h | 24.9 (9.4) |
|  |  |  |  |  |  | 12 m | 28.3 (11.5) |
| Campos 2019[26] | Distilled and deionised water | Primer | Clearfil SE Bond (SE) |  | 2% ZnCl₂ | 24 h | 26.4 (6.1) |
|  |  |  |  |  |  | 6 m | 14.2 (3.6) |
|  |  |  |  |  |  | 12 m | 28.7 (6.1) |
|  |  |  |  |  |  | 6 m | 27.8 (4.0) |
|  |  |  |  |  |  | 24 h | 24.8 (8.0) |
|  |  |  |  |  |  | 6 m | 13.8 (4.3) |
| 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) |
|  |  |  |  |  |  | 24 h | 37.0 (8.9) |
|  |  |  |  |  |  | After 5000 thc | 35.8 (11.4) |
|  |  |  |  |  |  | 24 h | 38.4 (8.1) |
|  |  |  |  |  |  | After 5000 thc | 37.9 (7.1) |
|  |  |  |  |  |  | 24 h | 36.8 (10.2) |
|  |  |  |  |  |  | After 5000 thc | 35.7 (4.6) |
|  |  |  |  |  |  | 24 h | 37.6 (11.3) |
|  |  |  |  |  |  | After 5000 thc | 37.0 (5.3) |
|  |  |  |  |  |  | 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) |
|  |  |  |  |  |  | 24 h | 40.8 (12.4) |
|  |  |  |  |  |  | 12 m | 21.8 (11.6) |
|  |  |  |  |  |  | 24 h | 42.2 (16.8) |
|  |  |  |  |  |  | 12 m | 35.8 (17.5) |
|  |  |  |  |  |  | 24 h | 39.7 (9.4) |
|  |  |  |  |  |  | 12 m | 29.0 (7.8) |
|  |  |  |  |  |  | 24 h | 36.2 (8.7) |
|  |  |  |  |  |  | 12 m | 17.4 (10.5) |
|  |  |  |  |  |  | 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) |
|  |  |  |  |  |  | 24 h | 23.4 (7.7) |
|  |  |  |  |  |  | 6 m | 16.3 (9.6) |
|  |  |  |  |  |  | 12 m | 14.9 (6.9) |

(continued on next page)
| 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 (2.7) |
| | | | | 6 m | 33.3 (2.7) |
| | | | | 12 m | 25.5 (2.9) |
| Daoood 2020[36] | Artificial saliva | Adhesive | Experimental (SE) | 0.125% RF | 24 h | 30.5 (3.2) |
| | | | | 24 h | 273 (5.1) |
| | | | | 12 m | 29.2 (6.0) |
| | | | Control | 24 h | 21.9 (4.6) |
| | | | | 6 m | 22.3 (4.1) |
| de Macedo 2019[37] | Distilled water | Adhesive | Experimental (SE) | 0.1% EGCG | 24 h | 47.9 (3.4) |
| | | | | 6 m | 38.4 (3.7) |
| | | | | 12 m | 30.7 (2.9) |
| | | | Control | 24 h | 17.6 (3.9) |
| | | | | 6 m | 43.9 (8.7) |
| | | | Experimental (E&R) | 0.1% EGCG | 24 h | 25.5 (6.1) |
| | | | | 6 m | 22.8 (4.4) |
| | | | | Control | 24 h | 44.3 (8.0) |
| 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) |
| | | | | 6 m | 12.4 (3.9) |
| | | | | Control | 24 h | 43.8 (8.0) |
| | | | | | 6 m | 39.1 (8.7) |
| 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) |
| | | | | | | Control | 6 m | 39.1 (8.7) |
| | | | | | | 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) |
| | | | | Etchant | 24 h | 17.1 (8.8) |
| | | | | | | 6 m | 13.9 (8.1) |
| | | | | | | Control | 24 h | 39.5 (10.5) |
| | | | | | | | 6 m | 141.8 (8.7) |
| Fernandes 2020[41] | Artificial saliva | Primer | Clearfil SE Bond (SE) | 0.01% EGCG | 24 h | 36.33 (6.1) |
| | | | | Control | 12 m | 29.2 (7.6) |
| | | | | | 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 h | 24.3 (3.2) |
| | | | | | 0.5% HES | 24 h | 37.5 (3.1) |
| | | | | | | After 10,000 thc | 24 h | 28.7 (2.3) |
| | | | | | | 1% HES | 24 h | 31.4 (2.3) |
| | | | | | | After 10,000 thc | 24 h | 23.1 (4.6) |
| 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) |
| | | | | | 24 h | 41.5 (2.1) |
| | | | | | 6 m | 21.9 (1.0) |

(continued on next page)
| Authors year | Year | Ageing solution | Adhesive system (mode of application) | MMP inhibitor | MMP inhibitor/ control groups | Ageing period | Bond strength means (MPa) (SD) |
|--------------|------|-----------------|--------------------------------------|--------------|-------------------------------|---------------|-------------------------------|
| Kalagi 2020[44] | 2020 | Water Primer | Adper Scotchbond Multipurpose (E&R) | 10% CHX | 57.4 (11.2) | 24 h | 67.0 (10.6) |
| | | | | 20% CHX | 62.9 (15.7) | 6 m | 52.4 (11.2) |
| | | | | Adhesive | | | |
| | | | | 10% CHX | 56.4 (10.9) | 24 h | 6 m | 52.7 (13.1) |
| | | | | 20% CHX | 60.6 (6.4) | 24 h | 6 m | 52.1 (8.0) |
| | | | | Control | | 24 h | 6 m | 60.8 (12.7) |
| Khamverdi 2015[45] | 2015 | Distilled water Adhesive | Clearfil SE Bond (SE) | 25 µM EGC | 24 h | 60.8 (12.7) | 24 h | 28.1 (5.3) |
| | | | | 50 µM EGC | 29.5 (3.3) | After 2500 thc and 6 m | 28.2 (6.7) |
| | | | | 100 µM EGC | 30.3 (3.9) | After 2500 thc and 6 m | 25.9 (2.8) |
| | | | | Control | 24 h | 60.8 (12.7) | 24 h | 28.1 (5.3) |
| Loguercio 2016[46] | 2016 | Distilled water Etchant | Adper Single Bond 2 (E&R) | 2% CHX | 39.5 (4.1) | 24 h | 26.9 (2.3) |
| | | | | 1% BAC | 40.2 (3.3) | 24 h | 5 y | 16.3 (2.1) |
| | | | | 2% PAC | 36.2 (3.9) | 24 h | 5 y | 21.3 (2.9) |
| | | | | Control | 35.1 (3.1) | 24 h | 5 y | 11.2 (2.7) |
| Loguercio 2017[47] | 2017 | Distilled water Etchant | Adper Single Bond 2 (E&R) | 2% CHX | 42.1 (3.8) | 24 h | 37.1 (3.9) |
| | | | | 1% BAC | 38.1 (5.1) | 24 h | 12 m | 39.4 (4.6) |
| | | | | 2% PAC | 43.2 (3.2) | 24 h | 12 m | 38.8 (4.7) |
| | | | | Control | 38.4 (5.4) | 24 h | 12 m | 30.1 (4.3) |
| Malaquias 2018[48] | 2018 | Distilled water Adhesive | Ambar (E&R) | 0.01% CHX | 53.8 (4.0) | 24 h | 44.8 (2.3) |
| | | | | 0.05% CHX | 50.0 (4.7) | 24 h | 2 y | 41.5 (4.0) |
| | | | | 0.1% CHX | 52.7 (3.5) | 24 h | 2 y | 47.4 (3.4) |
| | | | | 0.2% CHX | 55.6 (3.3) | 24 h | 2 y | 40.8 (3.1) |
| | | | | Control | 50.3 (4.1) | 24 h | 2 y | 30.1 (4.3) |
| | | | | XP Bond (E&R) | 63.3 (4.7) | 24 h | 2 y | 41.9 (3.9) |
| | | | | 0.01% CHX | 59.4 (4.0) | 24 h | 2 y | 40.3 (3.9) |
| | | | | 0.05% CHX | 41.9 (3.9) | 24 h | 2 y | 64.1 (4.0) |
| | | | | 0.1% CHX | 45.5 (3.9) | 24 h | 2 y | 63.2 (3.1) |
| | | | | 0.2% CHX | 44.7 (3.9) | 24 h | 2 y | 60.2 (3.1) |
| | | | | Control | 28.1 (3.9) | 24 h | 2 y | 28.1 (3.9) |
| Authors year | Year | Ageing solution | MMP inhibitor | Adhesive system (mode of application) | MMP inhibitor/ control groups | Ageing period | Bond strength means (MPa) (SD) |
|-------------|------|----------------|---------------|---------------------------------------|-------------------------------|--------------|--------------------------------|
| Maravic 2019[49] | 2019 | Artificial saliva | Adhesive | Peak Universal Bond (E&R) 0.2% CHX | 24 h | 50.1 (11) | |
| | | | | | 12 m | 40.7 (8.6) | |
| | | | | | | 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] | 2020 | Distilled water | Adhesive | Experimental (E&R) 1 µM GM1489 | 24 h | 21.4 (4.2) | |
| | | | | | | 12 m | 22.2 (2.6) | |
| | | | | | | | 6 m | 31.0 (7.2) | |
| | | | | | | | 12 m | 29.4 (8.2) | |
| | | | | | | Adper Single Bond 2 (E&R) 1 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) | |
| | | | | | | 5 µM GM1489 | 24 h | 20.9 (4.9) | |
| | | | | | | | 12 m | 20.9 (4.9) | |
| | | | | | | Control | 24 h | 15.6 (10.7) | |
| | | | | | | | 12 m | 23.6 (10.7) | |
| | | | | | | | 6 m | 15.6 (10.7) | |
| Nakajima 2003[51] | 2003 | 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] | 2022 | Distilled water | Adhesive | Ambar Universal (SE) 1% PAC | 24 h | 22.1 (5.8) | |
| | | | | | | | 12 m | 23.9 (7.5) | |
| | | | | | | | Control | 24 h | 28.5 (8.8) | |
| | | | | | | | | 12 m | 21.9 (10.0) | |
| | | | | | | | 1% EGCG | 24 h | 29.0 (13.4) | |
| | | | | | | | | 12 m | 21.6 (7.7) | |
| | | | | | | | Control | 24 h | 40.1 (9.3) | |
| | | | | | | | | 12 m | 40.1 (9.3) | |
| | | | | | | | 1% EGCG | 12 m | 23.1 (4.1) | |
| | | | | | | | 1% EGCG | 24 h | 21.2 (4.9) | |
| | | | | | | | | 12 m | 23.9 (6.1) | |
| | | | | | | | Clearfil SE Bond (SE) 1% PAC | 24 h | 27.4 (4.2) | |
| | | | | | | | | 12 m | 27.4 (4.2) | |
| | | | | | | | Clearfil SE Bond (SE) 1% PAC | 24 h | 35.3 (11.2) | |
| | | | | | | | | 12 m | 27.1 (5.1) | |
| | | | | | | | 1% EGCG | 24 h | 31.6 (13.3) | |
| | | | | | | | | 12 m | 32.8 (10.1) | |
| | | | | | | | Control | 24 h | 39.7 (14.2) | |
| | | | | | | | | 12 m | 39.7 (14.2) | |
| | | | | | | | 1% EGCG | 24 h | 23.4 (4.2) | |
| | | | | | | | | 12 m | 23.4 (4.2) | |
| Sabatini 2014[52] | 2014 | 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) | |

(continued on next page)
| Authors year | Ageing solution | MMP inhibitor | 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) |
| | | | | 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 | Solobond M (E&R) | 5 µM BAT | 24 h | 33.3 (4.9)* |
| | | | | 12 m | 29.5 (1.8)** |
| | | | | 5 µM GM1489 | 24 h | 34.1 (6.0)* |
| | | | | 12 m | 28.8 (1.8)** |
| | | | | 2% CHX | 24 h | 24.9 (5.2)* |
| | | | | 12 m | 19.7 (4.7)** |
| | | | | Control | 24 h | 32.2 (4.2)* |
| | | | | 12 m | 22.5 (5.2)** |
| 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) |
| | | | | 5% CHX | 24 h | 28.4 (4.4) |
| | | | | 6 m | 27.1 (3.1) |
| | | | | 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) |

(continued on next page)
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 pre-treatment 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
| 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           | N                | 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           | N                | N                         | N                    | Medium      |
| da Silva 2015 [35]              | N             | Y                   | Y                                 | N                        | Y              | Y           | N                | N                         | N                    | High        |
| Daood 2020 [36]                 | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | High        |
| de Macedo 2019 [37]             | Y             | Y                   | Y                                 | N                        | Y              | Y           | N                | N                         | N                    | Medium      |
| 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 Gazawi 2018 [40]             | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Fernandes 2020 [41]             | Y             | Y                   | Y                                 | N                        | Y              | Y           | N                | Y                         | N                    | Medium      |
| Ghorab and Ibrahim 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      |
| Kalaci 2020 [44]                | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Khanverdi 2015 [45]             | Y             | Y                   | Y                                 | N                        | Y              | Y           | N                | N                         | N                    | High        |
| Loguercio 2016 [46]             | Y             | Y                   | Y                                 | N                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Loguercio 2017 [47]             | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Malquist 2018 [48]              | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Marozic 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                                 | Y                        | Y              | Y           | N                | N                         | N                    | High        |
| Rohim 2022 [28]                 | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Sabatini 2014 [52]              | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Sabatini and Pasheley 2018 [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      |
| Stanisławczuk 2009 [55]         | Y             | Y                   | Y                                 | N                        | Y              | Y           | N                | N                         | N                    | Medium      |
| Stanisławczuk 2014 [56]         | Y             | Y                   | Y                                 | Y                        | Y              | Y           | N                | 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
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.
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 the 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. 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.
The only effect that appears is delaying but not preventing the potential of the agent will not be reflected in the bond strength and out of the inhibitor from the hybrid layer; hence, the MMP inhibition inhibitor agent that can be covalently bonded in the adhesive strength only in 6 m ageing. Possibly, the low binding ability of BAC adhesives has similar results to incorporation of 2% CHX into the adhesives has significant positive effect on bond strength by intermolecular interactions of 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 etchant 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 tests, 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 binding of the operator and sample size calculation, whereas among all included studies, none of them reported the binding 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/re-storation interface. Importantly, gaps between laboratory and clinical studies should be taken seriously in interpreting 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.

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Data are contained within the manuscript.

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