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Efficacy of Desensitizing Agents on Bond Strength of Dentin Bonding Agents: A Systematic Review and Meta-Analysis

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ABSTRACT

Aim: To systematically evaluate the effect of dentin desensitizing agents on adhesive–dentin bond strength using evidence from in vitro studies.

Materials and Methods: A comprehensive literature search was conducted across PubMed, Embase, Web of Science, and Cochrane Library without restrictions on publication date or language, in accordance with PRISMA guidelines. In vitro studies assessing the effect of dentin desensitizers on bond strength were included. Two independent reviewers performed study selection, data extraction, and risk of bias assessment. The primary outcome was bond strength, including shear bond strength (SBS), microtensile bond strength (μTBS), and microshear bond strength.

Results: A total of 456 records were identified, of which 9 studies were included in the qualitative synthesis. The findings demonstrated that the effect of desensitizing agents on bond strength is material-dependent. Calcium phosphate-based and chlorhexidine-containing desensitizers generally showed no adverse effect or improved bond strength, whereas oxalate-based agents showed variable outcomes, with some reduction in bond strength. Subgroup analysis revealed high heterogeneity due to differences in desensitizer type, adhesive systems, and testing protocols.

Conclusion: Desensitizing agents exert variable effects on adhesive–dentin bond strength depending on their composition and interaction with adhesive systems. Bioactive desensitizers appear to be more compatible, while oxalate-based agents require cautious use. Because quantitative evidence is limited and methods vary, definitive conclusions cannot be drawn. Further standardised in vitro studies and long-term clinical trials are necessary to validate these findings.

Keywords: bond strengths; in vitro study; sensitivity; systematic review

INTRODUCTION

Dentinal hypersensitivity (DH) is a prevalent clinical condition characterised by short, sharp pain arising from exposed dentin in response to thermal, tactile, osmotic, or chemical stimuli [1]. It affects approximately 10–20% of the adult population and represents a significant challenge in restorative dentistry due to its multifactorial aetiology and impact on patient comfort and quality of life [2]. Exposure of dentin may result from various pathological and physiological processes, including dental caries, attrition, abrasion, erosion, gingival recession, and non-carious cervical lesions [3]. These conditions lead to the loss of enamel or cementum, thereby exposing dentinal tubules to the oral environment [4].

The most widely accepted mechanism underlying dentinal hypersensitivity is the hydrodynamic theory, which proposes that external stimuli induce fluid movement within the dentinal tubules [5]. This fluid shift activates mechanoreceptors located at the pulpal ends of the tubules, resulting in a pain response. In addition, bacterial infiltration into dentinal tubules has been suggested to contribute not only to hypersensitivity but also to pulpal inflammation and disease progression [6]. Consequently, the management of DH primarily focuses on reducing dentinal fluid movement and occluding exposed tubules [7].

Various therapeutic approaches have been proposed for the management of dentinal hypersensitivity, including the use of desensitizing agents that act either by occluding dentinal tubules or by interfering with nerve transmission [8] [9]. Conventional treatment modalities include fluoride compounds, oxalates, calcium hydroxide, varnishes, and adhesive systems. More recently, advancements in biomaterials have led to the development of novel desensitizing agents with enhanced remineralizing and antibacterial properties [10].

Among these, chlorhexidine-based formulations have gained attention due to their dual role as antimicrobial agents and matrix metalloproteinase (MMP) inhibitors, potentially contributing to improved durability of resin–dentin bonds. Similarly, calcium hydroxide has been widely used for its ability to stimulate tertiary dentin formation and provide a protective barrier against bacterial insult [11]. In addition, casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) complexes have emerged as promising remineralizing agents capable of enhancing calcium and phosphate ion bioavailability, thereby promoting dentin remineralization and tubule occlusion [12].

Despite their beneficial effects in reducing hypersensitivity, the interaction between desensitizing agents and dentin bonding systems remains a subject of ongoing debate [12]. Adhesion to dentin is inherently complex due to its heterogeneous composition, intrinsic moisture, and tubular structure [13]. The presence of desensitizing agents on the dentin surface may alter the substrate characteristics, potentially affecting resin infiltration, hybrid layer formation, and ultimately bond strength. While some studies suggest that desensitizers may impair adhesive performance by obstructing dentinal tubules or interfering with resin penetration, others report neutral or even positive effects depending on the type of agent and bonding system employed [14,15].

Furthermore, contemporary adhesive systems, particularly self-etch adhesives, rely on both micromechanical interlocking and chemical interactions with residual hydroxyapatite [10]. The compatibility of these systems with various desensitizing agents is therefore critical for achieving optimal bonding performance and long-term clinical success [10]. Although several in vitro studies have evaluated the effect of desensitizing agents on dentin bond strength, the evidence remains heterogeneous and inconclusive, particularly with respect to newer bioactive and nanostructured materials [11]. Additionally, variations in study design, testing methodologies, and types of adhesives used further complicate the interpretation of results [12].

Therefore, there is a need for a comprehensive synthesis of available evidence to better understand the influence of different desensitizing agents on adhesive–dentin bond strength. The present systematic review and meta-analysis aims to evaluate the effect of dentin pretreatment with commonly used desensitizing agents—including CPP–ACP-based, chlorhexidine-based, and calcium hydroxide-based formulations—on the bond strength of various dentin bonding systems. The null hypothesis tested was that the application of desensitizing agents does not significantly affect the bond strength of adhesive systems to dentin.

METHODOLOGY

Protocol And Registration:
The research protocol is designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines 2020.[16] The protocol of this systematic review was registered with the International Prospective Register of Systematic Review **(PROSPERO CRD420251116629).**

Study Design
The focused research question was formulated depending on population, intervention, comparator and outcome (PICO) format:
Population (P) - extracted teeth.
Intervention (I) - application of dentin desensitizing agents
Comparison (C) - without application of a desensitizing agent (studies with control)
Outcome (O) - increases or decreases in bond strength
Study design (S) - In-vitro study

Eligibility Criteria:
Inclusion Criteria: studies were considered eligible for inclusion if they fulfilled the following criteria:

1. **I**n vitro experimental studies evaluating dentin bonding.
2. Extracted human teeth (permanent teeth), including molars or premolars.
3. Application of dentin desensitizing agents prior to or during the bonding procedure.
    a. Desensitizers including, but not limited to:
        i. Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP)
        ii. Chlorhexidine-based agents
        iii. Calcium hydroxide-based agents
        iv. Oxalates, arginine-based, calcium phosphate-based or similar formulations
4. Control group without application of any desensitizing agent.

5. Quantitative assessment of dentin bond strength, including: shear bond strength (SBS), microtensile bond strength (μTBS) and microshear bond strength
6. Studies assessing any adhesive system, including: etch-and-rinse systems, self-etch systems and universal/multimode adhesives
7. **Timing of Outcome Assessment**: immediate and/or aged bond strength (e.g., thermocycling, storage conditions).
8. **Language and Publication Status**: no restrictions on language or year of publication and full-text articles available.

Exclusion Criteria: studies were excluded if they met any of the following criteria:

1. **Study Design Limitations**
    a. Clinical studies, case reports, case series, reviews, systematic reviews, meta-analyses, editorials, or letters.
    b. Animal studies not involving extracted human teeth.
2. **Irrelevant Intervention**
    a. Studies not involving dentin desensitizing agents.
    b. Studies evaluating only enamel bonding.
3. **Lack of Appropriate Comparator**
    a. Studies without a control group (no desensitizer).
4. **Outcome Not Relevant**
    a. Studies not reporting bond strength outcomes.
    b. Studies focusing only on microleakage, hardness, or morphology without bond strength evaluation.
5. **Insufficient Data**
    a. Studies with incomplete or non-extractable data for analysis.
    b. Conference abstracts without full-text availability.
6. **Duplications**
    a. Duplicate publications or overlapping datasets (most complete dataset included).

Search Strategy

Database search was performed till December 2025 for studies published: PubMed, google scholar and EBSCOhost. Key words and Medical Subject Heading (MeSH) terms were selected and combined with Boolean operators like AND/OR as shown below

Search Strategy according to PICO Format:
"desensitizer OR desensitizers OR dentin desensitizer OR dentin desensitizers OR desensitizing product OR desensitizing products OR desensitizing agent OR desensitizing agents OR desensitizing paste OR desensitizing pastes AND dentin bond OR dentin bond strength OR bond strength"

In addition to the electronic search, a hand search was also made, and reference lists of the selected articles were screened. The reference lists of identified studies and relevant reviews on the subject were also scanned for possible additional studies.

Screening Process

The search and screening, according to previously established protocol were conducted by two authors. A two-phase selection of articles was conducted. In phase one, two reviewers reviewed titles and abstracts of all articles. Articles that did meet inclusion criteria were excluded. In phase-two, selected full articles were independently reviewed and screened by same reviewers. Any disagreement was resolved by discussion. When mutual agreement between two reviewers was not reached, a third reviewer was involved to make final decision. The final selection was based on consensus among all three authors. The corresponding authors of study were contacted via email where further information was required.

Quality Assessment Of Studies

The methodological quality among included studies was executed by using Cochrane collaboration risk of bias (ROB) - 2 tool [17]. The tool has various domains like random sequence generation (selection bias), allocation concealment (selection bias), blinding of personnel and equipments (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases through their signalling questions in Review Manager (RevMan) 5.3 software. The overall risk for individual studies was assessed as low, moderate or high risk based on domains and criteria. The study was assessed to have a low overall risk only if all domains were found to have low risk. High overall risk was assessed if one or more of the six domains were found to be at high risk. A moderate risk assessment was provided to studies when one or more domains were found to be uncertain, with none at high risk.

Statistical Analysis

Statistical analysis was performed with standardized mean difference (SMD) and risk ratio (RR) serving as summary measure. Significance was determined at the threshold of $p<0.05$ [18].

Assessment Of Heterogeneity

The Cochranes test for heterogeneity was employed to assess the significance of any differences in treatment effect estimations among trials. Heterogeneity was deemed statistically significant if the P-value was <0.01 [19].

Investigation Of Publication Bias

The study assessed publication bias using Begg's funnel plot, which plots the effect size against standard error. Asymmetry in the funnel plot may indicate potential publication bias [20].

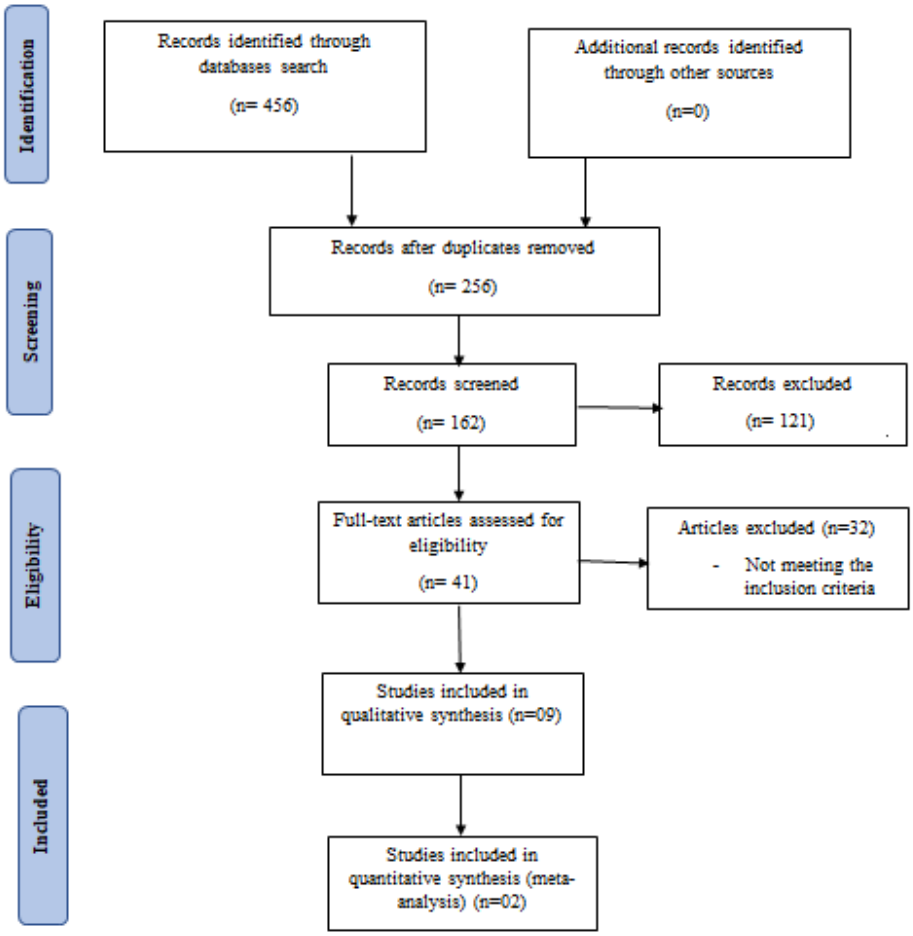


Figure 1. PRISMA Flow Diagram Assessment

Quality Assessment:

The high risk of bias (ROB) was seen for random sequence generation followed by incomplete outcome data. All of the included studies reported moderate to lowest ROB. Domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting and other bias were given the lowest ROB as depicted in **Figure 2 and 3.**

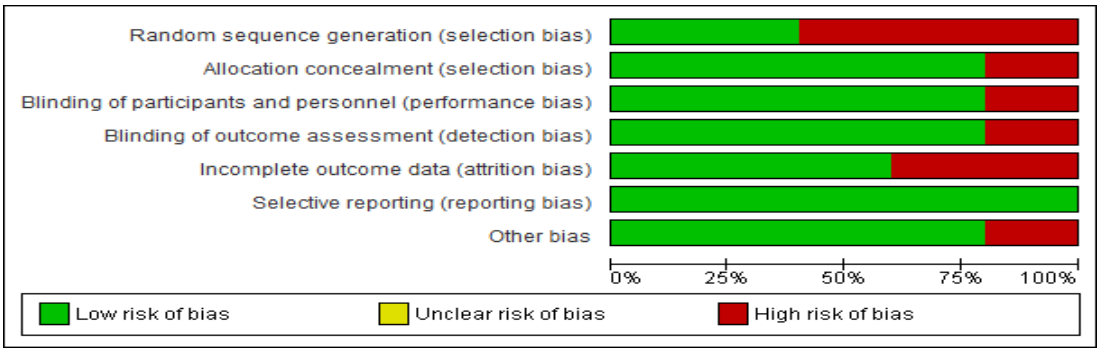


Figure 2: ROB: shown as percentages across all included studies.

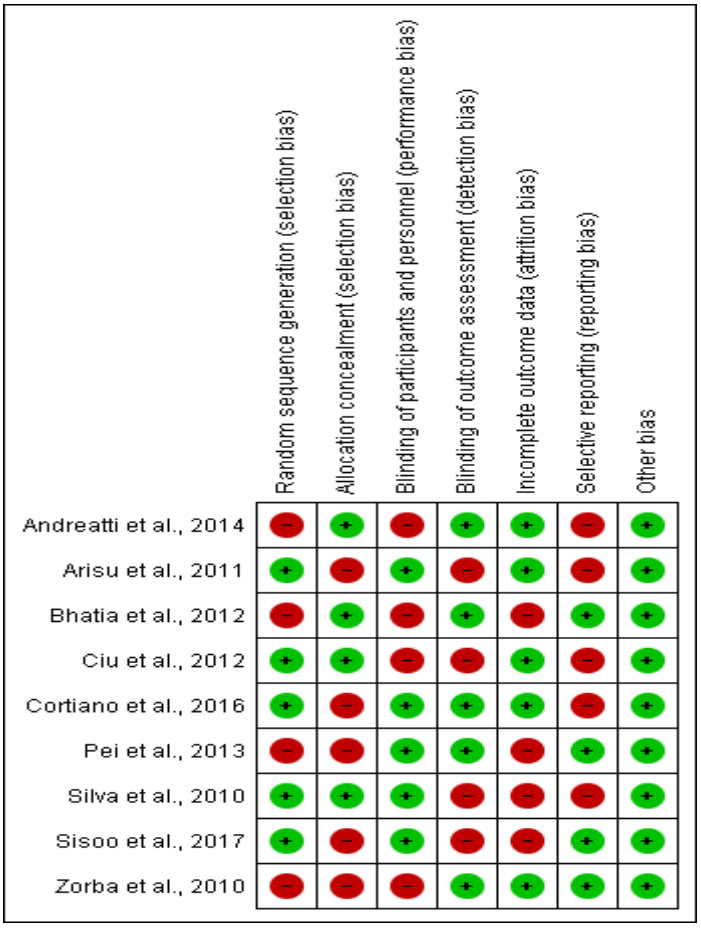


Figure 3: ROB summary: for each study

Synthesis of results/Meta-analysis

Effectiveness was assessed for mean overall shear bond strength **as shown in figures below.** Two studies[23,26] with data on 1154 samples, which were evaluated for mean increase in shear bond strength. As shown in **the figure.** the SMD is 1.84 (0.79 – 4.29) signifying that shear bond strength on an average was 1.84 times more in control group (***p>0.05***).

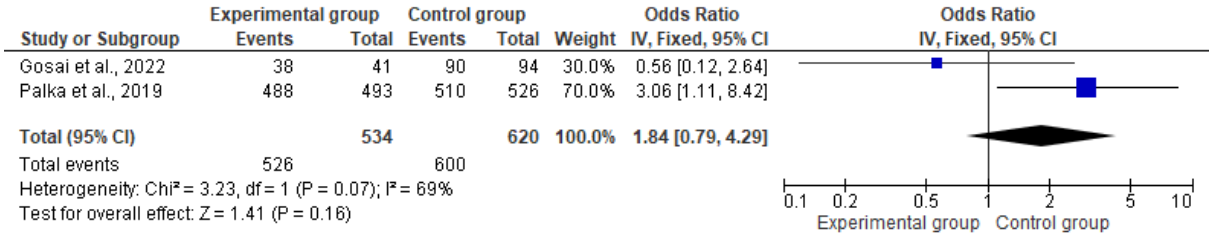


Fig. 4: shear bond strength

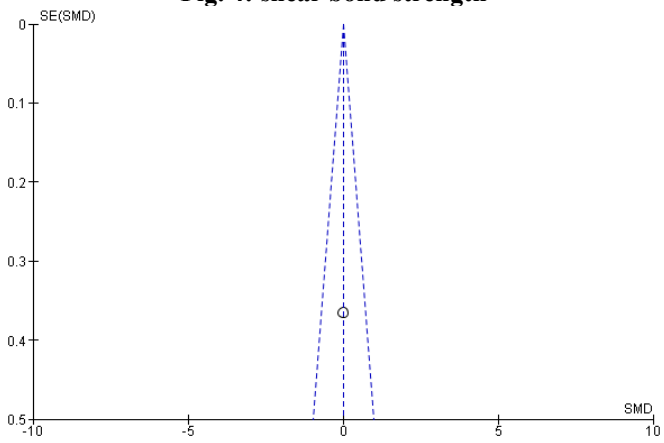


Fig. 5: mean shear bond strength

RESULTS

Study characteristics

Study	Aim	Sample Size & Grouping	Desensitizing Agents	Adhesive Systems	Bond Strength Test	conclusion
Zorba et al., 2010[21]	Evaluate effect of 3 desensitizing agents on shear bond strength (SBS) of 4 bonding agents	160 molars → 4 groups (n=40); subdivided into 4 subgroups (n=10)	Tooth Mousse, Ultra-EZ, Cervitec Plus	XP Bond, AdheSE, Adper Prompt L-pop, G-Bond	Shear Bond Strength (Universal Testing Machine)	No significant SBS difference except Control/AdheSE & Ultra-EZ/XP Bond. Desensitizers had no adverse effect.
Arisu et al., 2011[22]	Evaluate effect of desensitizing treatments (laser/conventional) on microtensile bond strength (μTBS)	42 molars → 6 groups	Vivasens, BisBlock, Fluoride gel, Nd:YAG laser	Clearfil SE (except group 5: Clearfil SE + laser)	Microtensile Bond Strength	Control group had significantly higher μTBS than most groups. Only Clearfil SE + Nd:YAG preserved bond strength.
Bhatia et al., 2012[23]	Compare effect of 2 desensitizers on SBS of 2 fifth-gen adhesives	60 premolars → 6 groups (n=10)	Denshield™, SensodentK™	Single Bond, Prime & Bond NT	Shear Bond Strength	Prime & Bond NT > Single Bond in control. SensodentK™ improved SBS with Prime & Bond NT. No significant difference with Denshield™.
Pei et al., 2013[24]	Evaluate bonding performance of 2 self-etch adhesives with 3 calcium-containing desensitizers	n = 20 beams per group	Arginine–$CaCO_3$, CPP-ACP, Hydroxyapatite paste	G-Bond, Clearfil S3 Bond	Microtensile Bond Strength	CPP-ACP reduced μTBS with G-Bond. G-Bond + hydroxyapatite and arginine showed similar μTBS to control. Failure: mostly adhesive.
Andreatti et al., 2014[25]	Evaluate influence of bioglass and arginine desensitizers on microshear bond strength	48 molars → 6 groups	Biosilicate® (bioglass), Sensitive Pro-Relief™ (arginine)	Scotchbond Multipurpose, Clearfil SE Bond	Microshear Bond Strength	Biosilicate® increased SBS for both adhesives. Arginine had no significant effect.
Cortiano et al., 2016[26]	Evaluate effect of desensitizers on SBS of etch-and-rinse adhesives	42 molars → 3 groups (n=14)	BisBlock (oxalic acid), Desensibilize Nano-P (calcium phosphate)	Adper Single Bond Plus, One-Step Plus	Microtensile Bond Strength	Oxalic acid reduced bond strength. Calcium phosphate had no negative effect. Mixed failures were common.
Siso et	Investigate effect	12 molars	Teethmate	Clearfil	Microtensile	TMD reduced

al., 2016[27]	of TMD (calcium phosphate) on MTBS & microleakage with multimode adhesive	(MTBS), 20 premolars (microleakage)	Desensitizer (TMD)	Universal Bond + Clearfil APX	Bond Strength & Microleakag e	MTBS but also reduced microleakage. SEM showed morphological compatibility.

Table 2: samples used and ethical consideration

Author, years of study	Sample size	Teeth used	Ethical consideration
Zorba et al., 2010[21]	44	Permanent molars4	All experimental protocols were reviewed and approved by the Local Ethics Committee of Pomeranian Medical University, Szczecin, Poland (approval number KB 0012/39/11).
Arisu et al., 2011[22]	28	Maxillary and mandibular molars	All experimental procedures were reviewed and approved by the Local Ethical Committee, Pomeranian Medical University, Szczecin, Poland (approval number KB–0012/39/11).
Bhatia et al., 2012[23]	24	Permanent molars	Not mentioned
Pei et al., 2013[24]		Not mentioned	Ethical approval for this study was obtained from the Institutional Review Board (no.154/13).
Andreatti et al., 2014[25]	59	Permanent teeth	This study was approved by the Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand and registered in the Thai Clinical Trials Registry
Cortiano et al., 2016[26]	525	Permanent molars	The study was conducted at the Department of Restorative Dentistry, Faculty of Dentistry, Ege University, Turkey. The study protocol was approved by the Ethical Committee of Ege University (ref no:2013018/09).
Siso et al., 2016[27]	45	Permanent molars	The proto col was approved by the Institutional Ethical Committee, Faculty of Dentistry, Alexandria University (IRB NO 00010556-IORG 0008839)

Table 3: conclusion/findings by authors of included studies

Author, years of study	Conclusion
Zorba et al., 2010[21]	- With the exception of the Control/AdheSE and Ultra-EZ/XP Bond groups, no statistically significant differences were found in the shear bond strength values of the groups tested. - These findings suggest that the use of different desensitizing agents does not affect the shear bond strength of various adhesive systems used to bond resin composite to dentin.
Arisu et al., 2011[22]	- The microtensile bond strengths of the control group were significantly higher than those found for group 1, group 2, group 3, and group 4(p,0.05). - No significant difference was found between group5andthecontrolgroup.Mostof the premature failures were seen in group 2 (80%), and the fewest premature failures were seen in group 5 (13.3%). - The SEM findings verified the microtensile test findings. In con clusion, desensitizing treatment procedures (with the exception of Clearfil SE + Nd:YAG laser) reduced the microtensile bond strength of a two-step self-etch adhesive to dentin.
Bhatia et al., 2012[23]	- Statistically significant difference existed between the two bonding agents in the control groups (group 1 and 2), with Prime and Bond NT showing higher bond strength than Single Bond. No statistically significant difference existed between either control or pretreated with any desensitizer when either of the adhesive systems was used. - Prime and Bond NT showed statistically higher bond strength value when teeth were pretreated with Sensodent-K™ (groups 5 and 6). No statistically significant difference in bond strength values were observed between the bonding agents when pretreated with Denshield™ desensitizer.
Pei et al., 2013[24]	- The mean (SD) TBS values, expressed in MPa, of groups 1, 2, and 3 and the control group were, respectively, 30.81 (7.79), 44.41 (8.02), 31.49 (6.13), and 41.40 (8.67) for G-Bond and 39.63 (9.59), 32.55 (7.86), 37.50 (8.60), 27.90 (6.52) for S3 Bond.

	- Most failures were recorded as adhesive failure (69.375%), instead of cohesive failure or mixed failure. The dentinal tubules were seldom plugged in group 2, but were mostly occluded in groups 1 and 3. Two-way ANOVA indicated that desensitizer application in association with a compatible adhesive system should be used when endeavouring to control hypersensitivity without adverse interference in bonding
Andreatti et al., 2014[25]	- The bond strength (MPa) was 17.03 for SBCV; 21.19 for SBAR; 26.24 for SBBG; 21.37 for CFCV; 27.09 for CFAR and 29.51 for CFBG group. A significant increase in bond strength was observed when Biosilicate® was used prior to the conventional and self-etching adhesive systems. - Fracture pattern analysis by means of optical microscopy showed a predominance of mixed type fractures, with the exception of the CFCV group, where adhesive fractures predominated. - It is concluded that arginine did not interfere with the bond strength with dentin, while the use of Biosilicate® tended to strengthen the bond between dentin and the adhesive systems used.
Cortiano et al., 2016[26]	- The CT-SB group exhibited the highest bond strength, differing significantly from BB SB and BB-OSP groups. Mixed failures were prevalent for all groups. Scanning electron microscopy revealed a continuous hybrid layer and resin tags in all groups. - Dentin bond strength of etch-and-rinse adhesive systems was reduced by an oxalic acid desensitizer but was not affected by a calcium phosphate-containing desensitizer.
Siso et al., 2016[27]	- Control groups exhibited a higher mean MTBS value than TMD groups, and there were statistical differences between the groups. TMD groups also demonstrated significantly less microleakage than control groups ($P < 0.05$). - This study proves that the application of TMD with a multimode adhesive bonding system produced significantly lower MTBS and microleakage.

Certainty Of Evidence

All the included studies were largely comparable in methodological quality. For the domains present, all the included studies answered a low risk of bias with overall risk of bias being not serious. Assessment of methodological quality through GRADE assessment reveals that all the included studies had moderate level of certainty indicating presence of low to moderate level of bias with good level of evidence present.

DISCUSSION

The present systematic review and meta-analysis evaluated the influence of dentin desensitizing agents on adhesive–dentin bond strength. The findings demonstrate that the effect of desensitizers is **material-dependent and influenced by the type of adhesive system**, with overall heterogeneous outcomes across the included studies. The meta-analysis, although limited to two studies, indicated variability in bond strength outcomes, reflecting the diversity in desensitizer composition and bonding protocols.

The qualitative synthesis revealed that **calcium phosphate-based and bioactive desensitizers** generally exhibited either neutral or beneficial effects on bond strength. These findings may be attributed to their **remineralization potential and chemical interaction with dentin**, which can enhance substrate stability without significantly interfering with adhesive infiltration. Similarly, **chlorhexidine-based desensitizers** were found to preserve bond strength, likely due to their inhibitory action on matrix metalloproteinases (MMPs), thereby reducing collagen degradation within the hybrid layer.

In contrast, **oxalate-based desensitizers** demonstrated inconsistent outcomes, with several studies reporting a reduction in bond strength. This effect can be explained by the **precipitation of calcium oxalate crystals**, which may occlude dentinal tubules and hinder resin monomer penetration, particularly in self-etch adhesive systems. However, when used in conjunction with etch-and-rinse systems, prior phosphoric acid etching may partially mitigate this effect by redistributing or dissolving surface precipitates.

CPP–ACP-based desensitizers showed variable performance across studies. While their remineralizing properties promote tubule occlusion and mineral deposition, excessive surface precipitation may interfere with micromechanical interlocking, especially when mild self-etch adhesives are used. This highlights the importance of **substrate condition and adhesive strategy compatibility**.

The findings of this review are consistent with previous systematic reviews, such as those by Li et al. [27] and Anithakumari et al., [28] which also reported **inconclusive and material-specific effects** of desensitizers on dentin bond strength. Similar to the present review, these studies emphasized that **bioactive desensitizers tend to be more compatible with adhesive systems**, whereas oxalate-based agents may compromise bonding under certain conditions.

Furthermore, earlier in vitro investigations have demonstrated that **functional monomers such as 10-MDP** in modern adhesive systems can chemically interact with residual hydroxyapatite, potentially counteracting the negative effects of some desensitizing agents. This may explain why certain studies included in the present review reported **no significant reduction in bond strength despite prior desensitizer application**.

However, discrepancies among studies remain evident. These differences may be attributed to **variations in experimental design**, including differences in dentin surface preparation, desensitizer application protocols, storage conditions, aging methods (e.g., thermocycling), and bond strength testing techniques. Such methodological diversity complicates direct comparison and contributes to the observed heterogeneity.

From a clinical perspective, the findings suggest that the **use of desensitizing agents prior to adhesive procedures should be carefully selected based on their compatibility with the chosen bonding system**. Bioactive and calcium phosphate-based desensitizers appear to be safer options, whereas oxalate-based agents should be used with caution, particularly with self-etch adhesives. Additionally, chlorhexidine may offer the added benefit of improving bond durability without compromising immediate bond strength.

Limitations: several limitations of this systematic review must be acknowledged

1. **Limited number of studies in meta-analysis**, restricting statistical robustness.
2. Inclusion of **only in vitro studies**, which may not fully replicate intraoral conditions such as saliva, occlusal forces, and long-term aging.
3. **High heterogeneity** in study protocols, including differences in desensitizer formulations, adhesive systems, and testing methods.
4. Inconsistent reporting of **randomization, blinding, and sample size calculation**, contributing to potential risk of bias.
5. Lack of standardized aging protocols, making it difficult to assess the **long-term durability of bonding**.

Future Recommendations: future research should aim to address these limitations through

1. **Standardization of in vitro methodologies**, including uniform protocols for dentin preparation, desensitizer application, and bond strength testing.
2. Conduct of **well-designed randomized controlled clinical trials** to validate in vitro findings under clinical conditions.
3. Evaluation of **long-term bond durability**, incorporating artificial aging methods such as thermocycling and mechanical loading.
4. Investigation of **interactions between newer universal adhesives and emerging bioactive desensitizers**.
5. Use of **advanced analytical techniques** (e.g., SEM, TEM, nanoleakage analysis) to better understand the adhesive interface.
6. Inclusion of **larger sample sizes and proper statistical power calculations** to improve reliability.

CONCLUSION

Within the limitations of this systematic review and meta-analysis, dentin desensitizing agents exhibit variable, material-dependent effects on adhesive–dentin bond strength. Bioactive agents, particularly calcium phosphate-based and chlorhexidine-containing formulations, generally showed no adverse impact and may enhance bond stability, whereas oxalate-based desensitizers demonstrated inconsistent outcomes, with potential reduction in bond strength under certain conditions. The limited number of studies included in the meta-analysis and the high heterogeneity among methodologies restrict the strength of the evidence.

Clinically, the selection of desensitizing agents should be carefully aligned with the adhesive system to ensure optimal bonding performance. Further standardized in vitro investigations and long-term clinical studies are essential to establish definitive conclusions regarding their compatibility and durability.

Declarations:
Funding: The authors received no financial support for the research.
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.

Ethical statement: As this study is a systematic review and meta-analysis of previously published studies, ethical approval was not required.
The study protocol was registered in PROSPERO 2025 (Registration number – CRD420251116629)

Data availability: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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