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Review Article

The effect of antibacterial agents of composite resin materials in dental caries prevention and reduction of flexural strength of the material: Systematic review and meta-analysis

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Abstract

Background: The present study aimed to evaluate the antibacterial agents of composite resin materials, their efficacy in caries prevention, and their impact on the mechanical properties (flexural strength) of composite resin restorative materials.

Methods: In this systematic review and meta-analysis, all published articles on the effects of antibacterial properties of composite resin materials in the prevention of dental caries (between 2005 to 2020) were evaluated using valid databases, including PubMed, Google Scholar, Web of Science, ISI, Scopus, Cochrane, ProQuest, and Embase, found by searching the keywords "anti-bacterial agents," "composite resins," "dental restoration," and "dental caries" according to the MeSH system. The context of the studies was extracted and subjected to modified CONSORT. The required data were extracted and analyzed with the Comprehensive Meta-Analysis software.

Results: According to the results of the random effect model, the heterogeneity of biofilm colony forming unit (CFU) average was -1.90 (CI: -1.68 to -2.13). The mean value of the control group was higher than the intervention. The heterogeneity of flexural strength (FS) average was -11.92 (CI: -8.30 to -15.55). The mean value of the control group was higher than the intervention group. The heterogeneity of thiazolyl blue tetrazolium bromide (MTT) absorbance average was -0.90 (CI: -0.65 to -1.14). The mean value of the control group was higher than the intervention group.

Conclusion: The results of the present study showed that the antibacterial agents had a significant effect on the caries prevention properties of the composite resin materials; however, due to the bias related to different control groups, laboratory conditions, and mismatch between in vitro and in vivo conditions, more studies are needed in this regard.

Keywords: Anti-bacterial agents, Composite resins, Dental restoration, Dental caries

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Introduction

Dental caries is a multifactorial disease that leads to local loss of minerals from the tooth surface due to the fermentation of food sugars by bacteria active in the biofilm (dental plaque); this process may result in cavity formation.[1,2] Although numerous bacterial species in dental plaque have been discovered to be related to dental caries, there is evidence showing *Streptococcus mutans*, *Streptococcus sobrinus*, and *Lactobacillus* are the major anaerobic pathogens of dental plaque.[3] Composite resin is more frequently used compared to other operative materials in the field of operative and aesthetic dentistry due to its esthetic properties.[4] These composite restorations can be prone to failure due to numerous reasons, including secondary caries and bulk fracture of the material (accounting for more than 90% of failures).[5] Composite resin materials are subject to more bacterial and plaque accumulation on their surface in comparison

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to other materials,[6-10] which can lead to secondary caries[11-13] Micro gaps (microleakage) between the prepared cavity and the filling material can be considered a reason for secondary caries[14] It is reported that replacement of old fillings accounts for about two-thirds of the services offered in operative dentistry; such a high rate of failure suggests that operative approaches are not optimum and there is potential for improvement in this area.[15] Moreover, in the structure-preservation approach, which is regarded as a conservative strategy for caries removal, it is expected that more bacteria remain in the affected dentine.[16,17] The presence of antibacterial agents supplied specifically in the filling materials can affect the initiation and progression of the secondary carious activity close to the filling material. clinical application of these modified materials can benefit the patient directly and the health system indirectly as it can reduce the need for replacement of the material due to secondary caries.[18] However, some drawbacks are reported regarding color change, reduced mechanical properties, and gradual reduction in antibacterial properties,[19] and there is still no composite material available presenting suitable antibacterial characteristics.[15] Since adding antibacterial agents can negatively affect the mechanical properties of the material and increase the costs for the patients, evaluating whether these materials are clinically and economically beneficial to the patients is of great importance.[18] The caries prevention properties of such agents lead to a reduction in the chance of secondary caries and a subsequent need for replacement of the filling and reduce costs for the patients; thus, in the present study we evaluated the relationship between antibacterial features and resulting changes in the mechanical properties (flexural strength) of composite restorations containing antibacterial agents to identify materials with antibacterial properties without loss of mechanical strength.

Methods

In this systematic review and meta-analysis, an electronic search was done on valid databases based on Medical Subject Headings (MeSH) and PICO using "AND" and "OR" operators about the caries prevention effect of composites containing antibacterial agents.

Since the evaluated articles were in vitro, PICO consisted of:

P: In vitro studies that used simulated body fluid (SBF) for calculating bacterial growth inhibition.

I: Application of composite restorative materials with different weight percentages of antibacterial agents

C: Comparison of materials free of antibacterial agents with composite materials with different weight percentages of antibacterial agents

O: Correlation between application of such materials and caries prevention effects and flexural strength of the material (biofilm formation/MTT absorption/biofilm lactic acid production/ flexural strength).

Search strategy

All articles published between 2005 and 2020 on the effect of antibacterial properties of composite resin filling materials on caries prevention were extracted from PubMed, Scopus, ProQuest, Google Scholar, Web of Science, ISI, and Cochrane databases and were evaluated.

The search protocol in PubMed and Embase was as follows:

PubMed:

1. Search "Anti-Bacterial Agents"[MeSH]
2. Search "Anti-Bacterial Compounds"
3. Search "Antibiotics"[MeSH]
4. Search "Dental Caries "[MeSH]
5. Search "Dental Decay"
6. Search "prevention"[MeSH]
7. Search "Composite Resins"[MeSH]
8. Search " Dental Fillings"
9. Search "Dental Restoration"[MeSH]
10. Search (Anti-Bacterial Agents OR Anti-Bacterial Compounds OR Bacteriocides OR Antibiotics) AND (Dental Caries OR Dental Decay OR Dental White Spot) AND (prevention OR control) AND (Composite Resins) AND (Dental Restoration OR Dental Fillings)
11. Search (((((("Anti-Bacterial Agents "[MeSH]) OR " Anti-Bacterial Compounds ") OR " Antibiotics " [Mesh]) OR " Bacteriocides "[MeSH]) " OR"Bacteriocidal Agents"[MeSH]) OR "Antimycobacterial Agents "[MeSH])
12. Search (((((("Anti-Bacterial Agents "[MeSH]) OR " Anti-Bacterial Compounds ") OR" Antibiotics " [MeSH]) OR " Bacteriocides "[MeSH]) " OR "Bacteriocidal Agents"[MeSH]) OR " Anti mycobacterial Agents "[MeSH]) AND (Dental Caries OR Dental Decay OR Dental White Spot) AND (Composite Resins) AND (prevention OR control) AND (Dental Restoration OR Dental Fillings)

Embase:

#1. "Anti-Bacterial "
#2. "Agents "
#3. "Anti-Bacterial Agents OR Anti-Bacterial Compounds OR Antibiotics OR Bacteriocides"
#4. "Dental Caries OR Dental Decay OR Dental White Spot"
#5. "Prevention OR control"
#6. "Composite Resins"
#7. "Dental Restoration OR Dental Fillings"
#8. #1 OR #2
#9. #1 OR #2 OR #3
#10 #1 OR #2 OR #3 AND #4 AND #5 AND #6 AND #7

A simple search in references of the published articles and available dissertations was also done.

Study selection and data extraction

Two authors independently searched the above-mentioned keywords in titles and abstracts of articles from the databases; in case of any disagreement, the third author was consulted to arrive at a consensus. The PRISMA guideline was considered as the reference for inclusion criteria of the study in the present systematic review and meta-analysis, including a combination of different aspects of a research question and also characteristics of different types of studies that evaluated this question. Population, intervention, and comparisons that were considered in the research question were applied directly to the inclusion criteria. Moreover, specific aspects of the study design and study behavior in the extracted articles were also considered. In the first step of the study selection, the titles of the articles were evaluated. After applying inclusion and exclusion criteria and evaluation based on the related checklist, 21 articles were considered citable.

Inclusion criteria

In vitro articles evaluating the effect of antibacterial properties of different dental composite materials in tooth caries prevention were included in the present study.

Exclusion criteria

1. Studies related to our systematic review were evaluated regarding their quality, and if they did not meet the minimum score of 10 in the Modified CONSORT checklist, they were excluded from this study.[20]
2. Articles reporting our intended indices (observation and area by area evaluation of slides using a microscope) as qualitative data, which makes meta-analysis impossible, were excluded from this study.
3. Studies lacking a proper control group for evaluating the effect of the combination of nanoparticles on the antibacterial capacity of the composite resin were also excluded from our study.

Also, in the case of similar articles, more recent articles with a more comprehensive method, a higher number of samples, and longer follow-up periods were included in this systematic review.

Quality assessment of included studies

The extracted articles were first selected based on the title and abstract; then, full texts were carefully evaluated by the three principal researchers individually using the modified CONSORT checklists of items for reporting in vitro studies of dental material. Characteristics and results of the articles included in the present study are summarized and presented in Figure 1.

It is worth noting that the above-mentioned checklist consists of 14 items for evaluating different parts of the articles and assessing the overall quality with yes/no questions; the Quality assessment was reported as good/poor, and poor studies were excluded from the study. Each item of the checklist is a predetermined question. The question “Is the case correctly reported?” is answered based on the contents of the article being evaluated. The answer can be “Yes, it is reported correctly” and “No, it is not reported correctly.” All included studies (based on the consultation and overall consensus between the three principal researchers) whose data was used for the analysis, were evaluated based on the checklist and the outcome is available for review.

Statistical analysis

Comprehensive Meta-Analysis software was used for statistical analysis of extracted data. As the outcome of different studies is not equal in value, binominal distribution was used for the calculation of the variance of each article, and it was then statistically weighted proportionately to its inverse variance. Evaluation of the heterogeneity was done using the Q test and I-squared index, and since the I-squared index was statistically significant, studies were not homogenous, and the random effect model was used for meta-analysis.

Publication bias was assessed using conical diagrams and Egger’s and Begg’s tests. In conical diagrams, the proportionate risk is presented as doubled inversed squared standard deviation. In case of publication bias, a conical diagram will present asymmetry in the wider part. Finally, the mean difference was calculated and is presented in the forest plot.

Results and Discussion

The aim of the present study was to evaluate the efficacy of antibacterial agents in composite resin filling materials in caries prevention. For this purpose, the colony forming units (CFUs) of the dental plaque accumulated on composite resins with various concentrations of antibacterial agents (case groups) were calculated and compared with composite resins without antibacterial agents (control groups). For evaluating the efficacy of the antibacterial agents on biofilm bacteria, determining the number of living bacteria in the biofilm or the relative reduction of living bacteria is necessary. Different methods are available for quantification of the number of surviving bacteria. However, these indices are generally suitable for the evaluation of planktonic samples. The classic method of determining the number of surviving bacteria is CFU. Another index for the evaluation of bacteria on the restored surfaces is measuring their activity and biofilm lactic acid production. This factor can be used for studying both the quantity of the bacteria and quantitative changes of bacteria on the composite surface containing antibacterial agents. MTT is another method that is widely used for the evaluation of cell survival. This method is a colorimetric technique that

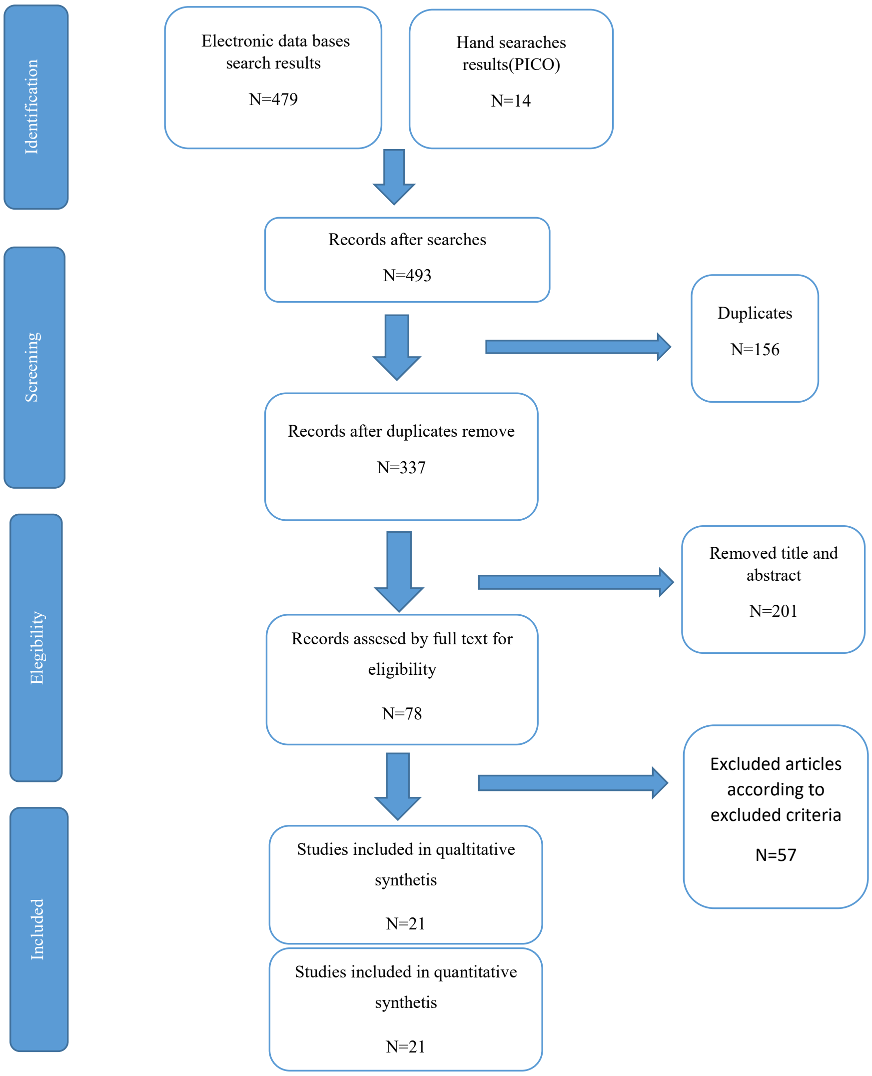

Figure 1. PRISMA diagram of included studies

is based on mitochondrial respiration and, therefore, is used for indirect evaluation of cellular energy capacity. Thus, this index also helps calculation, assessment, and observation of bacterial quantitative changes on the surface of antibacterial composite resin restorations.

Adding antibacterial agents to the composite resin filling materials can affect their mechanical properties; therefore, the flexural strength (FS) of antibacterial composite resins compared to materials without antibacterial agents is another factor that was studied in this systematic review. FS is defined as the ability of the material to resist bending deflection when energy is applied to the structure. To sum up, the indices that were evaluated in the present study were biofilm formation, lactic acid production, MTT absorption, flexural strength.

Lactic acid production

Based on the results of the homogeneity test for the LACTIC variable, Cochran's Q was 11773/19 with the degree of freedom (df) of 36 which was considered significant (P value = 0.0001). On the other hand, I-squared index results were reported as 99.7%. Overall, the results of these two indices showed that the difference of the mean amounts of LACTIC among 37 dental composite samples in the 21 studies was not homogenous; in other words, the outcomes of different studies varied significantly. Thus, the random effect model was used for evaluating the difference of the mean amounts of LACTIC.

Figure 2 shows the forest-plot of the accumulation of the difference of the mean amounts of LACTIC. Based on the random effect model, this variable was reported as -9.78; also, the confidence interval (CI) was calculated as -11.90 and -7.67. As difference of the mean amounts of LACTIC was calculated by subtracting the case group results from the control group results, it can be inferred lactic acid production in dental plaque on antibacterial composite resins and the tooth surface decreased, and bacterial count and dental biofilm also decreased in comparison with composite resins without antibacterial agents.

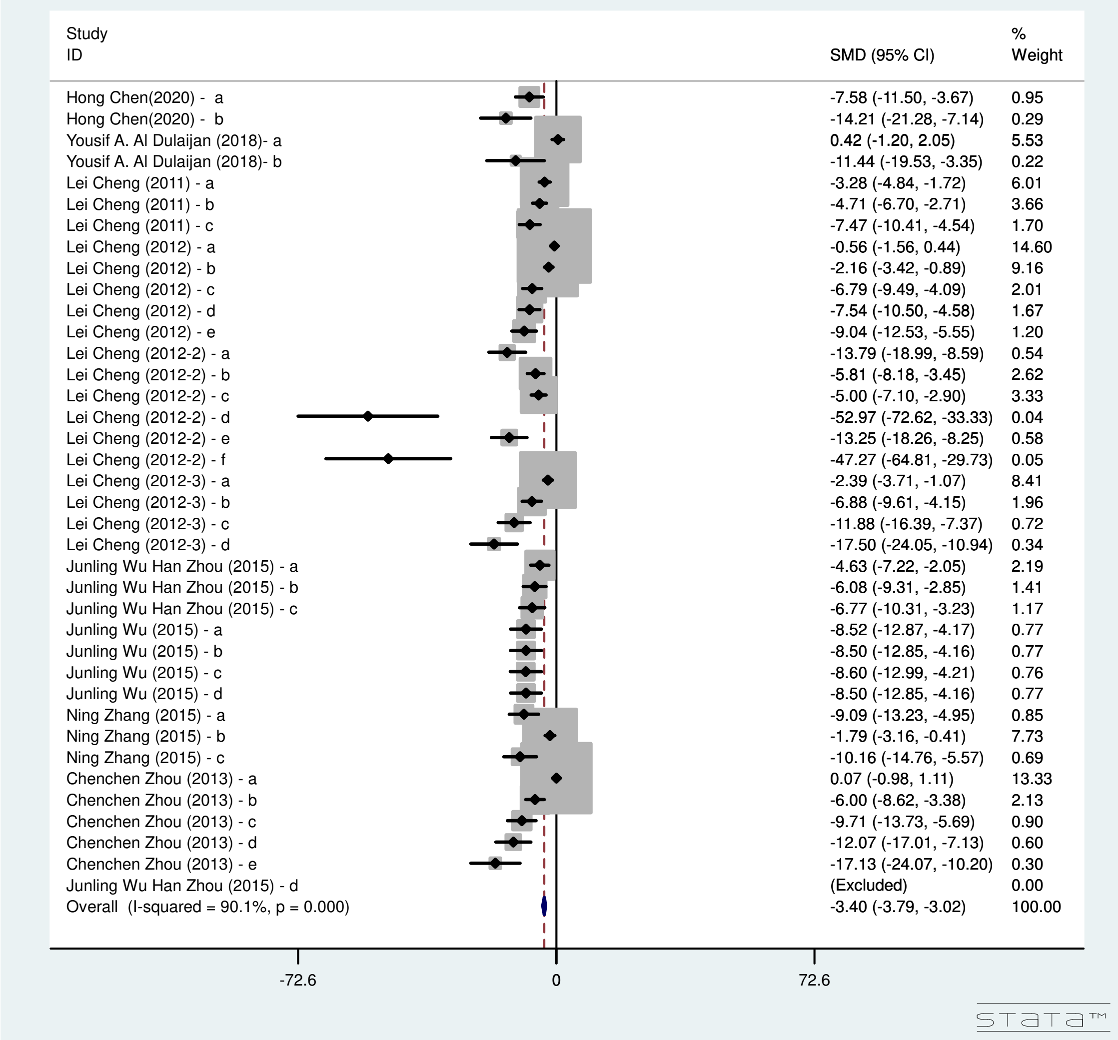

Figure 2. The forest plot of the accumulation of the difference of the mean amounts of LACTIC

Based on the Egger's test of the publication bias results of the LACTIC variable (P value = 0.734), it can be concluded that there was no publication bias.

Based on the outcomes of the homogeneity test for the biofilm variable, Cochran's Q test was 480.12 with a *df* of 59, which is considered significant (P value = 0.0001). On the other hand, I-squared index results were 99.7%. Overall, the results of these two indices showed that the difference of the mean amounts of biofilm among 59 dental composite samples in the 21 studies was not homogenous; in other words, it can be concluded that the outcomes of different studies varied significantly. Thus, the random effect model was applicable for evaluation of difference of the mean amounts of the biofilm variable.

Figure 3 shows the forest plot of the accumulation of the difference of the mean amounts of biofilm. Based on the random effect model, this variable was reported as -1.90; also, the CI was calculated as -2.13 and -1.68. As difference of the mean amounts of biofilm was calculated by subtracting the case group results from the control group results, it can be inferred that CFU in dental plaque on antibacterial composite resins and the tooth surface decreased in comparison with composite resins without antibacterial agents.

Based on the Egger's test of the results of the biofilm variable publication bias test (P value = 0.0001), it can be concluded that there was publication bias.

Based on the results of the homogeneity test for the FS variable, Cochran's Q test was 551.68 with a df of 57, which is considered significant (P value = 0.0001). On the other hand, I-squared index results were reported as 89.8%. Overall, the results of these two indices showed that the difference of the mean amounts of FS among 57 dental composite samples in 21 studies was not homogenous; in other words, it can be concluded that the outcomes of different studies varied significantly. Thus, the random effect model was applicable for evaluation of the difference of the mean amounts of the FS variable.

Figure 4 shows the accumulation of the difference of the mean amounts of FS. Based on the random effect model, this variable was reported as -11.92; also, the CI was calculated as -15.55 and -8.30. As the difference of the mean amounts of FS was calculated by subtracting the case group results from the control group results, it

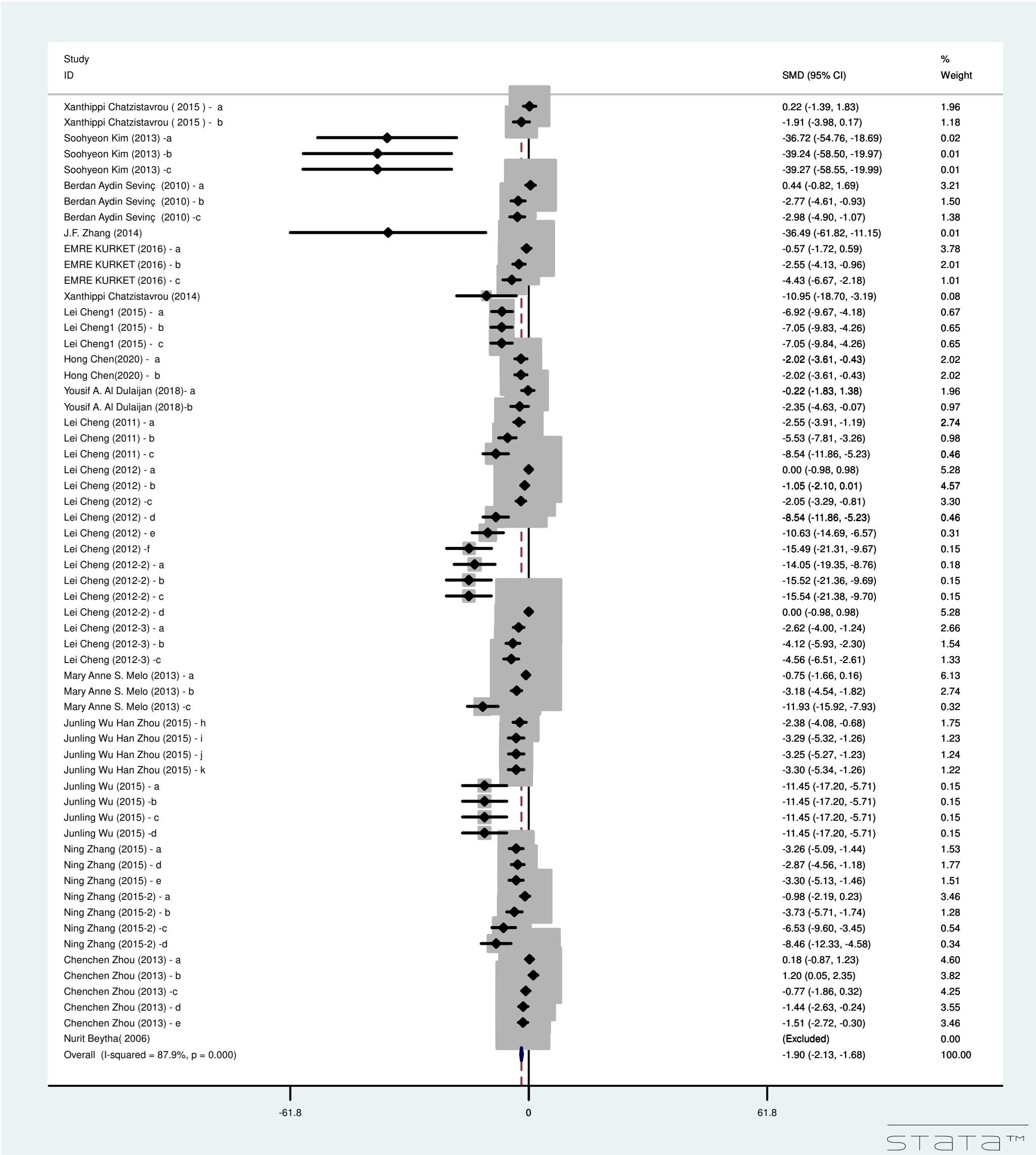

Figure 3. The forest plot of the accumulation of the difference of the mean amounts of biofilm

can be inferred that the FS (MPa) of restorative materials decreased in comparison with composite resins without antibacterial agents.

Based on the Egger's test of the results of the publication bias test of the FS variable, it can be concluded that there was no publication bias.

MTT absorbance

Based on the outcomes of the homogeneity test for the MTT variable, Cochran's Q test was 27 228 with a *df* of 38, which is considered significant (*P* value = 0.0001). On the other hand, I-squared index results were reported as 99.9%. Overall, the results of these two indices showed that difference of the mean amounts of MTT among 39 dental composite samples in the 21 studies was not homogenous; in other words, it can be concluded that the outcomes of different studies varied significantly. Thus, the random effect model was applicable for evaluation of the difference of the mean amounts of the MTT variable.

Figure 5 shows the accumulation of the difference of the mean amounts of MTT. Based on the random effect model, the MTT difference of the mean amounts of MTT was calculated by subtracting the case group results from the control group results, it can be inferred that bacterial count on the surface of the tooth and antibacterial composite resins decreased in comparison with composite resins without antibacterial agents.

Based on the *P* value = 0.017 of the Egger's test of the results of the publication bias test for the MTT variable, it can be concluded that there was publication bias.

Adding antibacterial agents to restorative materials to improve their durability and efficacy is a new field

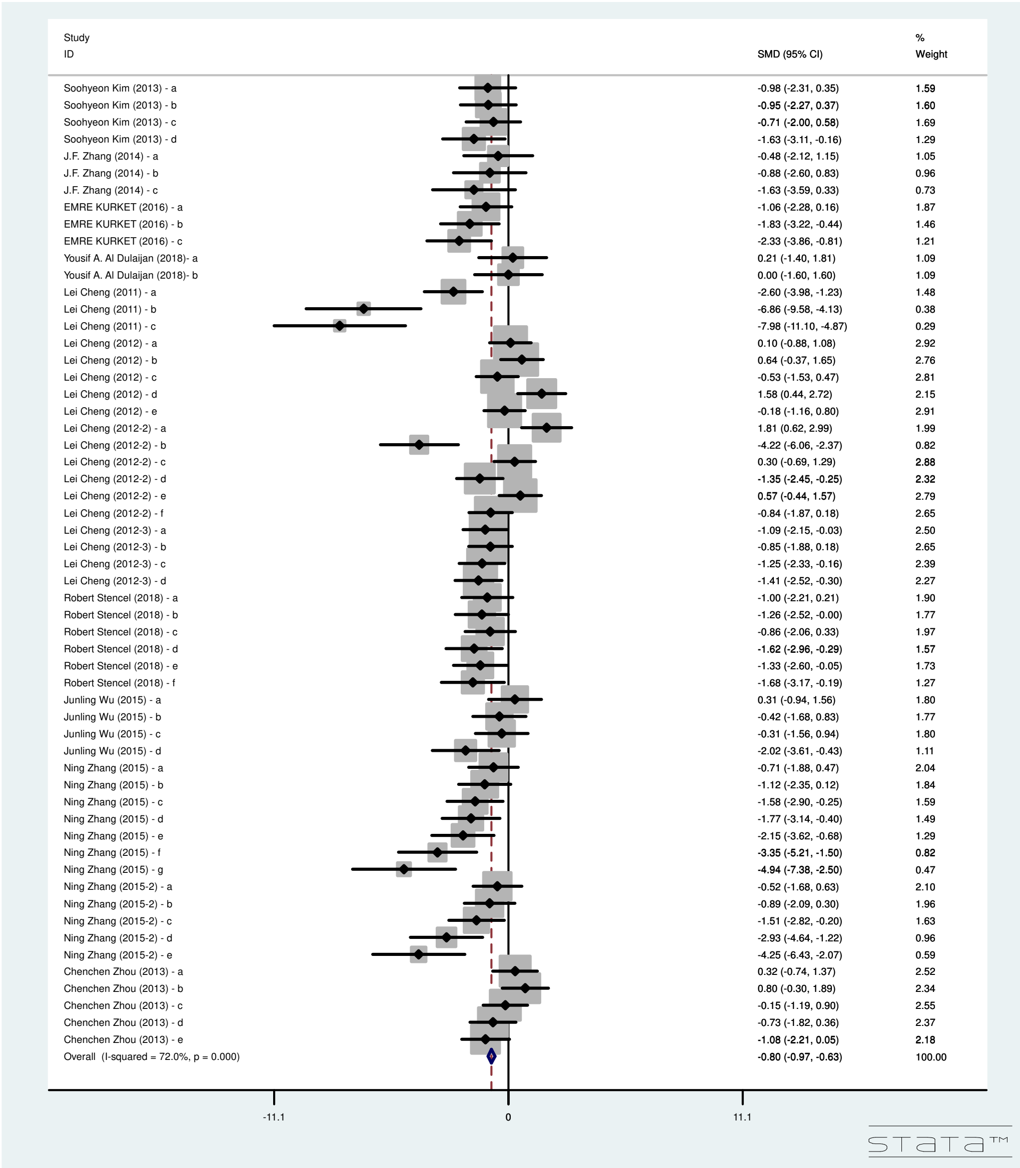

Figure 4. The forest plot of the accumulation of the difference of the mean amounts of FS

that has gained attention in recent years. There is a wide range of in vitro studies evaluating various antibacterial agents with different concentrations (weight percentage), optimum amount, and their combination with a restorative material to achieve a composite resin material that can resist bacterial-induced caries.[21] In the present systematic review, 21 articles were included and evaluated, all of which were in vitro studies (Table 1).

In vitro studies are subject to bias due to the necessity for standardization, and in vivo studies lead to more valid outcomes[39]; however, in most cases, ethical considerations may be a limiting factor for the latter kind. In vitro studies cannot completely simulate the oral and dental environment, which results in systematic errors; thus, the outcome cannot be generalized to the clinical application.[21] Another source of bias in in vitro studies is various control groups in different studies which leads to reduced precision in comparing studies with each other. Nevertheless, such bias can be controlled to a point as each case group (antibacterial composites) is compared to its specific control group (composites without antibacterial agents).

Adding antibacterial agents to dental composites follows the purpose of forming a reinforced material to better resist bacterial invasion and subsequent secondary caries.[21] Among the detected bacterial species in dental plaque, *Streptococcus mutans* and *Lactobacillus acidophilus* play a major role in tooth decay; therefore, these two species are used for antibacterial tests[40]; however, other species, including *Staphylococcus aureus*,[41,42,25] *Pseudomonas aeruginosa*,[25] *Porphyromonas gingivalis*,[43-46] and *Actinomyces viscosus*,[26] have also been evaluated in studies.

Many of the included studies in the present systematic

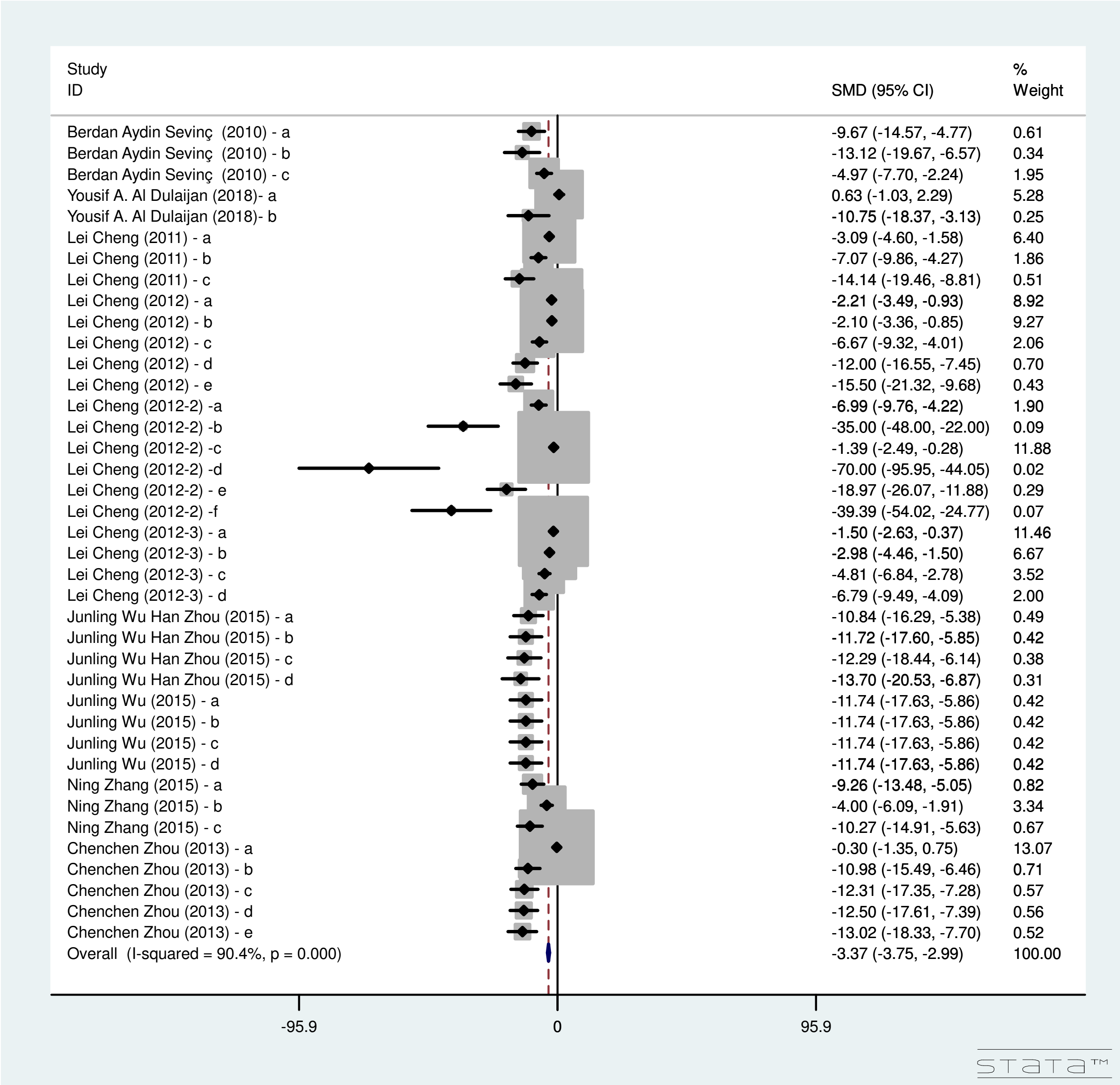

Figure 5. The forest plot of the accumulation of the difference of the mean amounts of MTT

review concluded that comparing modified composite resins with antibacterial agents with nonmodified composite resins (control group) in laboratory conditions showed antibacterial properties, which implies that such agents improve antibacterial properties of restorative material.[27]

In the reviewed studies, CFU was the most commonly used index for bacterial count. In the present study, this index was used for 59 samples in the 21 articles. The most common method was the quantitative evaluation of the bacterial count after restoring a tooth with antibacterial composite resins.

Laboratory conditions were different in different studies. For instance, in the 21 studies, sterilization of the composite samples before application of the materials was considered, but in other studies it was not.[19,47,48] The method of sterilization was different among the studies. In most of the cases, sterilization was done using ethylene oxide.[19,22,28-31,36,38,49-52] Other sterilization methods were autoclave,[32] gamma radiation,[33,34] light and ultraviolet radiation,[35,37] and incubation in 70% ethanol.[53]

Polishing the prepared composite restorations with antibacterial agents before exposing them to the bacterial environment was only done in 4 studies out of 21; two of them used silicon carbide paper for polishing purposes.[27,35] The other two studies used other polishing methods; in Aydin Sevinç and Hanley's and Das Neves and colleagues' studies, polishing was done using Soft-Lex disks.[7,23] It is worth noting that polishing the samples before analysis could result in difference between the studies.

Also, the incubation time of the samples after culturing was different, and the outcomes of the biofilm evaluation

Table 1. Included articles in meta-analysis according to modified CONSORT checklist

Author (Ref.)	Study design	Type of composite	Type of NP	Type of microorganism	No. of samples	Type of polishing system	Type of test	Conclusion
Skjorland et al [6]	Original research report	Bonding agent	Nag QADM NACP	*S. mutans*	- Seven composite groups - Six disks in each group	-	CFU count	Novel dental bonding agents containing Nag, QADM, and NACP were developed with the potential to kill residual bacteria in the tooth cavity and inhibit the invading bacteria along tooth-restoration margins, with NACP to remineralize tooth lesions
Aydin Sevinç and Hanley [7]	Original research report	Composite	ZnO-NPs	*Streptococcus sobrinus* ATCC 27352	Ten groups that each group included two samples	Polished using a commercial system (superfine-grit discs, Sof-Lex disc system, 3M ESPE)	DCT, disc diffusion test	ZnO-NP-containing composites (10%) qualitatively showed less biofilm after 1-day-anaerobic growth of a three-species initial colonizer biofilm after being compared with unmodified composites, but did not significantly reduce growth after 3 days
Chatzistavrou et al [15]	Original article	Flowable dental composite	Ag-doped bioactive glass (Ag-BG)	*E. coli, S. mutans*	3 Composite groups	-	CFU count	Reducing bacteria invasion and enhancing remineralization of the surrounding tooth lesion
Kasraei et al [19]	Research article	Composite resins	AgNPs ZnONPs	*S. mutans, Lactobacillus*	90 Discoid tablets	Both surface-600, 800, and 1200 grit SiC papers (Matador 991A, Soflex, Starcke's Co., Melle, Germany)	DCT	Composite resins containing Ag or ZnO NPs exhibited antibacterial activity against *S. mutans*
Li et al [22]	Original article	Bonding agent	QADM NAg	*S. mutans*	- Eight human - third molar - three groups	The dentin surface was polished 600-grit sic paper, etch with 37% phosphoric acid gel for 15 s, and rinsed	Long distance inhibition	QADM-containing adhesive had contact-inhibition and inhibited bacteria on its surface, but not away from its surface. NAg-containing adhesive had long-distance killing capability and inhibited bacteria on its surface and away from its surface. The novel antibacterial adhesives are promising for caries-inhibition restorations, and QADM and Nag could be complimentary agents in inhibiting bacteria on resin surface as well as away from resin surface.
das Neves et al [23]	Original article	Light-activated composite	NAg	*S. mutans, Lactobacillus acidophilus*	171 resin discs in total groups.	Enhance silicone tips (Dentsply, Adlestone, Surrey, UK)	Counting CFU	No significant differences for roughness among the three groups. The MR03 was stronger to compression than CG, and MR06 was statistically lower than CG and MR03 were less conducive to biofilm growth, without compromising the strength in compression and surface roughness.
Al-Dulaijan et al (2018) [24]	Original article	Rechargeable CaP composite	DMAHDM	*S. mutans*	Two composites - Six disks in each group	-	CFU count	Adding DMAHDM into the rechargeable NACP composite did not adversely affect the Ca and P ion release and recharge, and the composite had much less biofilm growth and lactic acid production
Argueta-Figueroa et al [25]	Original article	Orthodontic adhesive	CN	*S. aureus, E. coli, S. mutans*	Sixty extracted bicuspids	-	Disk diffusion test	Orthodontic adhesive, which included CN, significantly increased material SBS without adverse side effects on colour and appearance. The adhesive interface was strengthened by homogeneously dispersed CN added as a nanofiller.
Pietrokovski et al [26]	Original article	Composite resin foundation material	QA-PEI	*S. mutans, A. viscosus*	8 disk for each test	Polishing diamond rotary instruments (E5 shaped fine [50 μm] and E5 shaped extra fine [30 μm] [Strauss Co])	DCT ADT	Antibacterial properties can be achieved in a commercially available foundation material by incorporating polycationic antibacterial nanoparticles. This antibacterial effect did not diminish after surface polishing
Gutiérrez et al [27]	Original article	Etch and rinse (2-ER) adhesive system ambar	CN	*S. mutans*	Seven adhesives/ Five extracted third molar of human for each group.	600 grit Sic paper	ADT	The addition of CN provided AMA to the adhesives at all concentrations. Hiigher CR was observed in adhesives with higher concentration of CN. UTS, DC, WS and SO were not influenced.

Table 1. Continued

Author (Ref.)	Study design	Type of composite	Type of NP	Type of microorganism	No. of samples	Type of polishing system	Type of test	Conclusion
Degrazia et al [28]	Original article	Orthodontic adhesive	AgNP solutions	*S. mutans*	48 bovine incisors for assessment of SBS - 12 disks prepared for evaluation of growth of *S. mutans*	- The labial surface - #600 and #1200 grid silicon carbide papers for 30 s	- CFU count - inhibition halo	The addition of AgNP solutions to Transbond™ XT adhesive primer inhibited *S. mutans* growth. SBS, DC, and SFE values decreased after incorporation up to 0.33% AgNP solution without compromising the chemical and physical properties of the adhesive
Cheng et al [29]	Original article	Nano composites	QADM NAg NACP	*S. mutans*	Four composite groups	-	CFU count	These nanocomposites are promising to have the double benefits of remineralization and antibacterial capabilities to inhibit dental caries
Cheng et al [30]	Original article	NACP nanocomposite	NAg	*S. mutans, S. sobrinus*	Five NACP nanocomposites	-	CFU counts	Novel NACP–NAg nanocomposites were developed which possessed good mechanical properties and potent antibacterial properties, with substantially reduced biofilm viability and lactic acid production. Hence, the NACP–NAg nanocomposites are promising for dental restorations with remineralizing and antibacterial capability
Cheng et al [31]	Original article	Composite	NAg QADM NACP	*Streptococcus*	Four composites	-	CFU count	The NACP-QADM-NAg composite decreased biofilm viability and lactic acid production, while matching the loadbearing capability of a commercial composite. There was no decrease in its antibacterial properties after 1 year of water-ageing. The durable antibacterial and mechanical properties indicate that NACP-QADM-NAg composites may be useful in dental restorations to combat caries
Azarsina et al[32]	Original research	Composite resin	NAg	*S. mutans, Lactobacillus*	Three composite groups – Each group included 12 samples	600, 800, 1200 grit SiC papers (991A softlex, Germany	DCT	Addition of Nag to Z250 composite could significantly inhibit the growth of *S. mutans* and *Lactobacillus* on the surface of this composite
Sodagar et al [33]	Original article	Orthodontics composite	TiO2 NPs 0%, 1%, 5% and 10%	*S. mutans* *S. sanguinis*	180 Orthodontics composite	-	ADT, biofilm inhibition test	Incorporating TiO2 NPs into composite resins confer antibacterial properties to adhesives, while the mean shear bond of composite containing 1% and 5% NPs still in an acceptable range.
Sodagar et al [34]	Original article	Orthodontic composite	curcNPs	*S. mutans,* *S. sanguinis* *Lactobacillus acidophilus*	180 discs were fabricated of the four composites	-	Component test, disc diffusion test, biofilm test	At 1% concentration, curcNPs have significant antimicrobial activity against cariogenic bacteria with no adverse effect on SBS. However, insolubility of curcNPs remains a major drawback
Gutiérrez et al [35]	Original article	Etch and rinse adhesive (ER)	CN	*S. mutans*	Seven experimental ER adhesives	600-grit SiC paper	ADT	CN addition up to 0.5 wt.% may provide antimicrobial properties to ER adhesives and prevent the degradation of the adhesive interface, without reducing the mechanical properties of the formulations.
Kim et al [36]	Research article	Composite	UA	*S. mutans*	6 Resin disks	Polishing the margin-sterilized by EO gas	Growth inhibition test	UA included in the composite showed inhibitory effect on *S. mutans* biofilm formation and growth
Tavassoli Hojati et al (2013) [37]	Original article	Flowable resine composite	ZnO-NPs	*S. mutans*	six experimental groups - five resin composites	- Both surfaces - 600 grit silicon carbide paper - moist environment	- ADT - DCT - Aging test	Agar diffusion test reveals no significant difference between the groups, the direct contact test demonstrates that by increasing the nanoparticle content, the bacterial growth is significantly. In the aging test, however, the antibacterial properties reduce significantly
junling et al (2015) [38]	Original article	Nanocomposite	DMAHDM NACP	*S. mutans*	Five groups of composites each group had six disks.	-	CFU count	DMAHDM-NACP nanocomposite had good fracture resistance, strong antibacterial potency and NACP for remineraliozation.

SBS, shear bond strength; EO, ethylene oxide; SFE, surface free energy; CFU: colony forming unit; DCT, direct contact test; ADT, agar diffusion test; AMA, adhesive on antimicrobial activity; CR, copper release; UTS, ultimate tensile strength; DC, degree of conversion; WS, water sorption; SO, solubility; CG, control group; DMAHDM, dimethylaminohexadecyl methacrylate; CN, Copper nanoparticled; QA-PEI, quaternary ammonium polyethylenimine; AgNP, silver nanoparticle; NACP, Nanoparticles of Amorphous calcium phosphate; QADM, Quaternary Ammonium Dimethacrylate; NAg, Nanoparticles of silver; curcNPs, curcumin nanoparticles; UA, ursolic acid.

tests were related to this parameter. Incubation time varied between 1 minute[54] and 30 days[55] in different studies.

Due to the different control groups and antibacterial agents, homogeneity test results were reported as heterogeneous; in other words, it can be said that the difference among outcomes of different studies was highly significant which is mostly related to the various antibacterial agents, control groups, and laboratory conditions.

Publication bias test results for biofilm formation and MTT absorbance were positive, which can be related to different control groups and laboratory conditions; however, these outcomes showed no publication bias for FS and MTT absorbance. One probable reason may be the smaller numerical value of these two parameters, which offsets the effect of various control groups.

Since the outcomes of the present review are based on in vitro studies, it is worth noting that these antibacterial agents added to the composite resins may not play a major role in caries prevention in clinical settings. Other protective factors including mechanical plaque control, diet, or pH of the oral environment affect caries progression.[56] Moreover, as acid production is considered the major factor for dental caries and is affected by phenotypic and genotypic factors in the oral environment, microflora of the oral cavity are of significant importance in this regard.[57]

The technique of dental composite reinforcement with antibacterial agents is one of the recent advances in dentistry. Although first reports were published between 2006 and 2008,[58] the majority of the studies have been conducted in the last 6 years and most of them confirm the caries prevention properties of such materials, reporting improvement in antibacterial characteristics of composite resins using these added compounds. While the outcomes of these studies have been promising, heterogeneity and publication bias from the four models of meta-analysis in the present systematic review as well as the high risk of bias in most of the analyzed studies suggests the need for more studies to make more precise and valid conclusions.

Conclusion

Qualitative analysis of the included studies shows that although numerous studies are evaluating the caries prevention properties of antibacterial composite resins, the concentration of the applied antibacterial agents, the laboratory conditions, incubation time, and the preservation and manipulation of the samples are different among various studies. Despite the heterogeneity and biases of the results in the present meta-analysis, it can still be inferred that adding antibacterial agents to the dental composite resin filling materials leads to improvement in antibacterial properties, and regarding the insignificant effects on their mechanical properties, a brighter future can be expected for the use of these new materials in restoration. Still, more studies are needed in this regard.

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Competing Interest

None.

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