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Antibacterial Dental Resin Composites: A Narrative Review

Ameenah Saad Alansy[1], Thekra Ali Saeed[1], Yuqing Guo[1], Yanwei Yang[2*], Bin Liu[1*], Zengjie Fan[1*]

[1]Key Laboratory of Dental Maxillofacial Reconstruction and Biological Intelligence Manufacturing, Gansu Province School of Stomatology, Lanzhou University, Lanzhou, China
[2]Department of Stomatology, The 940th Hospital of Joint Logistic Support Force of the Chinese People's Liberation Army, Lanzhou, China
Email: *yangyanwei85@163.com, *liubkq@lzu.edu.cn, *zjfan@lzu.edu.cn

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Abstract

Lack of antibacterial properties in resin-based composites (RBCs) is one of the flaws that cause the failure of filling clinically. Several agents have been incorporated to endow RBCs with antibacterial properties. In this review, we summarize the recent antibacterial agents between 2015 and 2020 using keywords of antibacterial or antimicrobial dental resin composites by PubMed databases. The most effective strategies are concerned with polymerizable monomers (50%), followed by filler particles (39%) and leachable agents (11%). A recent modification of the antibacterial agent is either by combining two agents from the same category or mixing agents from different categories in one. More than two methods were used in one study to assess antibacterial efficacy. The most common method was biofilm colony-forming units (CFUs) counting method (40%), followed by live/dead bacteria staining assay of biofilms (25%), metabolic activity assay of biofilms using MTT assay (16%), lactic acid production assay of biofilms (8%), agar diffusion test (8%), and other methods (3%) such as minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC).

Keywords

Dental Resin Composite, Antibacterial Agents, Antibacterial Strategies, Antibacterial Property, Antibacterial Assessment

1. Introduction

The progressive developments in RBCs over 50 years endow composites with adequate mechanical and high aesthetic properties, making them the preferred

restoration materials used clinically for anterior or posterior teeth [1]. However, clinical trials have shown that the risk of failure of RBCs is twice as high as that of silver amalgam, mainly due to the marginal microleakage caused by polymerization shrinkage during the curing process, which makes it easier for bacteria to invade and lead to secondary caries [2] [3]. In addition, the cured composites have higher biofilm and plaque aggregation rates than silver amalgam and glass ionomer [4] [5] [6].

In recent years, massive modifications have been done to composite monomer systems to reduce polymerization shrinkage stress by over 70% [4] [5] [7]. On the other hand, numerous studies have tended to endow RBCs with antibacterial properties by incorporating antibacterial additives to reduce biofilm formation and prevent caries. Several studies have reported that various antibacterial additives were added into resin-based material [6], resin composite [8], glass ionomer cement [9], and dentine bonding system [10], and their antibacterial activities were subsequently evaluated. These antibacterial additives were mainly classified into releasing and non-releasing additives, incorporated into either resin matrix or filler particles.

This review summarizes the recent antibacterial agents added to RBCs, which included articles from January 2015 to May 2020, using antibacterial or antimicrobial dental resin composites as keywords by PubMed databases. The dental resin composites used for restoration purposes were included, whereas those used for orthodontic, endodontic, or sealing purposes were excluded. Adhesives and resin-modified glass ionomer cement were also excluded.

2. Material and Methods

2.1. Inclusion Criteria

1) All studies which added new antibacterial additives to restorative resin composites;

2) Scientific papers were published in English from January 2015 to May 2020, where full text was available.

2.2. Exclusion Criteria

1) Studies about the antibacterial resin composite used for orthodontic, intracanal post cementation, core build-up restoration, and sealer;

2) Studies that did not include *Streptococcus mutans* (*S. mutans*, which are the primary bacteria responsible for dental caries formation) in the antibacterial test;

3) Studies whose antibacterial analysis was not clear;

4) Studies not in the range from January 2015 to May 2020.

3. Results

3.1. Search Strategy

A search using keywords of antibacterial or antimicrobial dental resin compo-

sites by PubMed databases was conducted, which identified 369 studies from January 2015 to May 2020. 102 studies were initially selected through screening title/abstract and removing the duplicates. According to the inclusion and exclusion criteria, 32 full-text literature were eventually included in this review. Figure 1 illustrates a flow chart of the literature search method.

Three main antibacterial strategies depend upon the antibacterial mechanisms of the antibacterial constituents incorporated into the RBCs. Leachable agents can be released into the local environment around restorations under oral conditions. In contrast, non-leachable agents or polymerizable monomers can be immobilized in the dental resin matrix, while bacterial filler particles added to fillers or resin matrix can release small ions to create antibacterial effects (Table 1). The summery of antibacterial modifications of RBCs is shown in Figure 2.

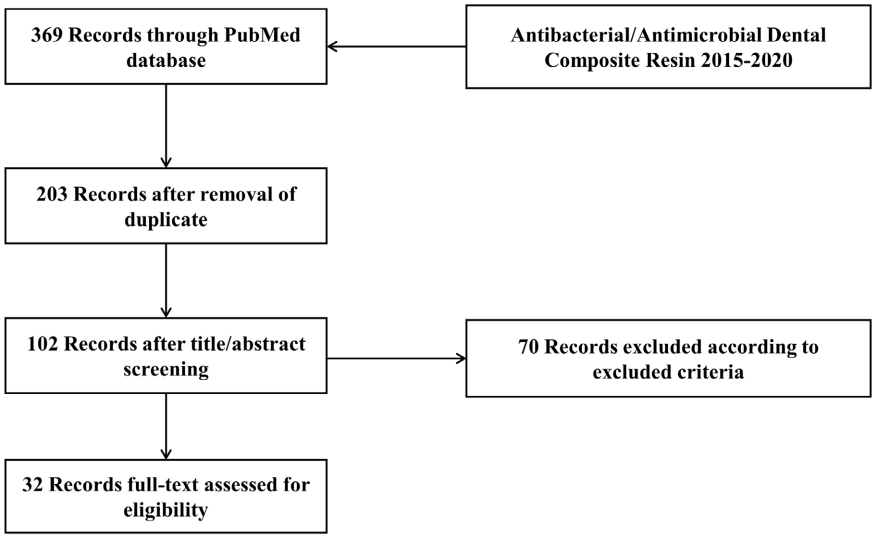

Figure 1. Flow chart of literature search.

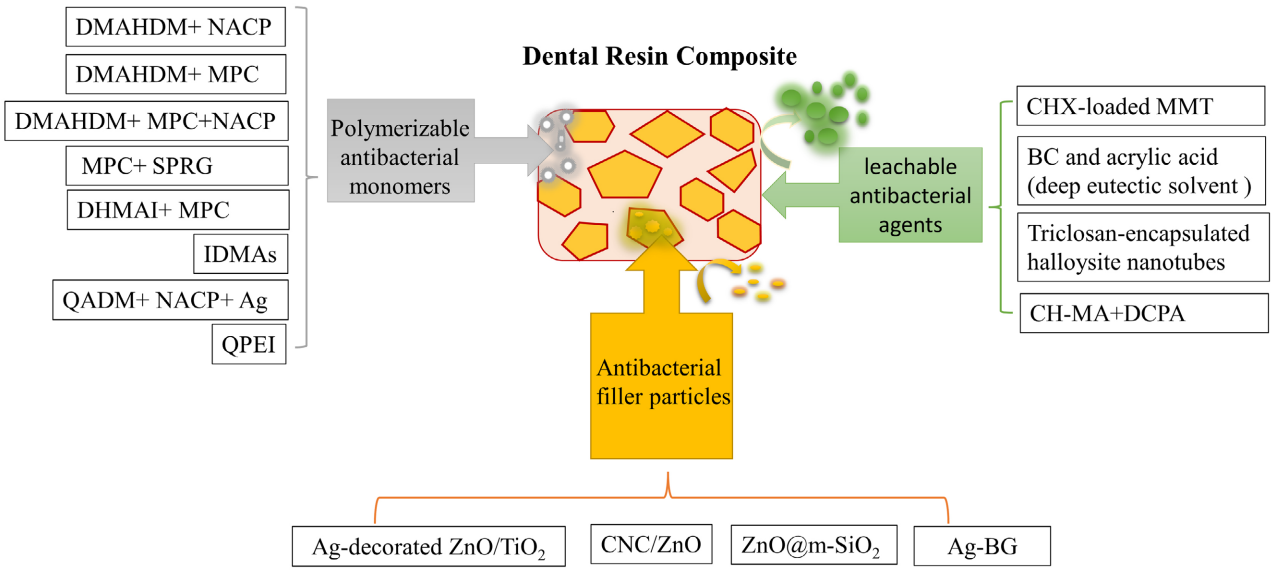

Figure 2. Summary of antibacterial agents added to dental resin composite and their categories.

Table 1. Antibacterial agents incorporated into the resin composites.

Antibacterial strategy	Basic agent	Modification	Reference
Leachable antibacterial agents	- Triclosan	- Triclosan-encapsulated halloysite nanotubes (HNT/TCN)	[11]
	- Chlorhexidine (CHX)	- CHX loaded Montmorillonite (MMT), amorphous calcium phosphate (ACP) + CHX	[12] [13]
	- Benzalkonium chloride (BC)	- BC and acrylic acid (deep eutectic solvent)	[14]
	- Chitosan	- Methacrylate chitosan (CH-MA), chitosan microspheres with dibasic calcium phosphate anhydrous (DCPA)	[15] [16]
Polymerizable antibacterial monomers	Dimethylaminohexadecyl methacrylate (DMAHDM)	- DMAHDM + nanoparticles of amorphous calcium phosphate (NACP)/rechargeable NACP	[17] [18]
	- 2-methacryloyloxyethyl phosphorylcholine (MPC)	- DMAHDM + MPC, DMAHDM + MPC + rechargeable NACP, MPC + SPRG	[19] [20] [21]
	- Quaternary ammonium dimethacrylate (QADM)	- Dimethyl Hexadecyl Methacryloxyethyl Ammonium Iodide (DHMAI) + MPC, Ionic dimethacrylates (IDMA1, IDMA2), Urethane dimethacrylate quaternary ammonium monomers (-UDMQA-12), QADM + NACP + silver nanoparticles (AgNPs)	[22] [23] [24] [25]
	- Quaternary ammonium polyethyleneimine (QPEI)	- QPEI	[26]
Antibacterial filler particles	- Silver Nanoparticles (AgNPs)	Hydroxyapatite (HA) + Polydopamine (PDA) + AgNPs, Halloysite nanotubes (HNT) + Ag (HNT/Ag), Silver sulfadiazine, Ag decorated ZnO NPs	[27] [28] [29] [30]
	- Zinc Oxide (ZnO)	- ZnO 3D microstructures, cellulose nanocrystal/zinc oxide (CNC/ZnO) nanohybrids, ZnO@m-SiO_2 (core-shell structure)	[31] [32] [33]
	- Titanium dioxide (TiO_2)	- Ag decorated TiO_2 NPs	[34]
	- Bioactive glass (BG)	- Ag doped BG	[35] [36]
	- Surface pre-reacted glass-ionomer (S-PRG)	- SPRG	[37]

Each study involved in this review included at least one of the above three strategies: leachable agents, polymerizable monomers, and filler particles. When the antibacterial additives used in a study were in the same category, the count for that category increased by one. When a study included antibacterial additives referring to various categories, the counts for different categories increased by one. Therefore, the total number of different additives from these three strategies found among the 32 studies was counted as 100%, as seen in **Figure 3**.

3.2. Classification of Antibacterial Strategies

Leachable agents

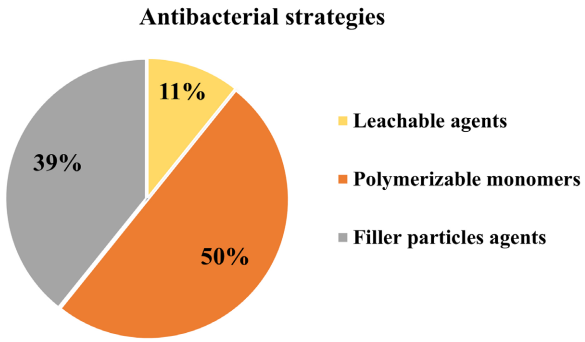

Figure 3. Categorization statistical graph of the antibacterial strategies of dental resin composites.

- Leachable agents are soluble antibacterial agents incorporated into the resin matrix and released under the oral environment. The foremost commonly utilized leachable antibacterial agents are benzalkonium chloride (BAC) and chlorhexidine [10]. The main disadvantage of these materials is a short-lasting effect (burst effect), resulting in large amounts of leachate in the surrounding environment and showing an antibacterial effect within a few days, followed by a dramatic decrease in the drug concentration.
- Triclosan (TCN) is a common leachable antibacterial agent used as a component of dental toothpaste, mouthwashes, and RBCs [38] [39]. Likewise, due to the short-term burst effect, TCN is usually incorporated in particular "vehicles" known as nanotubes [40]. A recent study accomplished by Cunha *et al.* [11] used biocompatible nanomaterial halloysite nanotubes (HNT), which were previously used as a reinforcing nanofiller and reservoir for controlled discharge of an assortment of therapeutic drugs [41] [42]. TCN was successfully encapsulated into halloysite nanotubes (HNT/TCN) which were incorporated at 8% w/w to prepare the micro-hybrid dental resin composite, showing enhancements of the mechanical properties and no significant difference in antibacterial properties over 5 days.
- Chlorhexidine (CHX) is another common leachable antibacterial agent used in limited concentrations due to cytotoxicity toward human fibroblasts [43]. Therefore, it is incorporated into mouthwashes as well as glass ionomer cement (GICs), resin composite, and resin-modified glass ionomer cement (RMGICs) materials in low concentration, exhibiting antibacterial activity with short-term CHX release [44] [45] [46]. Montmorillonite (MMT) is a common ingredient in pharmaceutical products, which is used as an excipient and active substance due to its good adsorptive ability, drug-loading, and cationic interchange capacities [47] [48]. Previous studies have prepared CHX-copper (II)/MMT nanocomposites and chitosan/MMT composite films containing CHX to get long and effective antibacterial properties with low cytotoxicity [49]. In the same way, a recent study was done by Boaro *et al.* [12] developed a composite modified by CHX-loaded MMT. The composite showed inhibition of bacterial adhesion and constant CHX release without a

change in the mechanical properties or cytotoxic effect. To improve the antibacterial and remineralization properties, our group has recently synthesized CHX with amorphous calcium phosphate in core-shell structure (CHX/ACP), and then we merged CHX/ACP nanoparticles into the experimental composite resin [13]. The modified composite could continuously release CHX with calcium and phosphate (Ca and P) ions and improve antibacterial and remineralization properties.

- Benzalkonium chloride (BC) is a common leachable antibacterial agent incorporated into dental materials [50]. Wang J *et al.* [14] converted BC to deep eutectic solvent (DES) by blending BC with acrylic acid (AA) to serve as the donor of hydrogen bond, which is essential in DES formulation. Then this DES was merged into the resin composite to produce antibacterial activity. The results from the DES-modified composite resin showed better mechanical properties and antibacterial inhibition compared with the BC-modified composite.
- Chitosan is a natural polysaccharide polymer with a wide spectrum of antimicrobial activity [51]. Chitosan has been added to adhesives, glass-ionomer cement, and sealants to enhance its mechanical and antimicrobial properties [52] [53] [54]. Methacrylate chitosan (CH-MA) was prepared and incorporated into the adhesive that showed comparable bond strengths to the control system [55]. Stenhagen *et al.* [15] prepared dental composite and adhesive containing CH-MA and confirmed that the antibacterial effect was correlated with CH-MA amounts. Different synthesis methods are applied to chitosan powder to modify its properties, creating nanofiber and microspheres of chitosan [54] [56] [57]. Chitosan microspheres could encapsulate other bioactive compounds. For example, Tanaka *et al.* [16] synthesized novel chitosan microspheres encapsulate dibasic calcium phosphate anhydrous (DCPA) using the electrospray technique, which was incorporated into an experimental composite. The composites containing 0.5 wt% chitosan/DCPA showed an effective antimicrobial property compared to the control group.

Polymerizable monomers

Polymerizable antibacterial monomers are immobilized into a resin matrix based on copolymerization among the resin monomers to overcome the short-lasting release of the antibacterial agents. Their antibacterial effects occur through the contact of bacteria with the composite surface. Cationic groups like quaternary ammonium, pyridinium, and phosphonium are commonly found in the functional groups of polymerizable antibacterial monomers.

Polymerizable monomers used alone

• A series of quaternary ammonium compounds (QACs) monomers with one or multiple methacrylate groups was considered the most effective immobilized antimicrobial monomer [58] [59]. Zhang *et al.* [60] synthesized quaternary ammonium methacrylates (QAMs) with different chain lengths (CL) varying from 3 to 18 and merged them into the amorphous calcium phosphate (NACP) composite. This study demonstrated that as the CL increased, the antibacterial effects

increased, with the strongest result achieved with a CL of 16. In contrast, the antibacterial property was reduced as the CL was increased to 18.

- Quaternary ammonium polyethyleneimine (QPEI) nanoparticles are a potential antimicrobial polymer incorporated into RBCs, exhibiting a powerful antibacterial capability [61]. Pietrokovski *et al.* [26] proved that the RBC containing QPEI nanoparticles had considerable antibacterial effects against Streptococcus mutans and Actinomyces viscosus.
- A composite with antibacterial and remineralization capabilities was synthesized by integrating a strong antibacterial compound dimethyl amino hexadecyl methacrylate (DMAHDM, a kind of QACs) with NACP [17]. The best result was achieved when a 3% mass fraction of DMAHDM was integrated into the NACP resin composite without adversely affecting the mechanical properties. Similarly, adding DMAHDM into the rechargeable NACP composite has been reported by Al-Dulaijan *et al.* [18], the rechargeable NACP-DMAHDM composite showed Ca and P ions release with persisting remineralization and a potent antibacterial effect.
- Zhang *et al.* [19] have integrated 2-methacryloyloxyethyl phosphorylcholine (MPC, a kind of QACs) with DMAHDM in an attempt to synthesize an anti-biofilm and protein-repellent dental composite. After water aging for six months, resin composite modified by 3% MPC combined with 1.5% DMAHDM exhibited higher resistance to bacterial adhesion than the control group. The protein-repellent and antibacterial effects were durable and showed no loss in water aging from 1 to 180 days, with mechanical properties matching a commercial composite. Similarly, antibacterial DMAHDM monomer and MPC were incorporated into the rechargeable NACP composite [20]. Compared to a commercial control group, the composite with 3% MPC and 3% DMAHDM impaired bacterial growth and decreased the CFU count of biofilm by three orders of magnitude.
- A recent study reported by Lee *et al.* [21] added MPC to S-PRG filler to modify a resin-based composite to get the benefits of both materials (antibacterial ability, anti-biofouling function, acid resistance, and prevention of demineralization). The authors reported that as the percentage of MPC increased, the number of ions released from the S-PRG filler increased. So, the RBC containing S-PRG filler and 5% MPC had a significant anti-biofilm formation effect and improved release of ions and acid neutralization properties.
- To overcome the drawback of mono-methacrylate QAMs monomers, QAMs monomers with dimethacrylate were prepared and synthesized, such as dimethyl hexadecyl methacryloxyethyl ammonium iodide (DHMAI) and ionic dimethacrylates (IDMAs) [62]. Cherchali *et al.* [22] have assessed the antibacterial activity of an experimental dental composite, including DHMAI. DHMAI was added to MPC to test both the new composite's antibacterial activity and mechanical properties. The above study showed that the composite incorporated with 7.5% DHMAI had a strong antibacterial effect with a reduction in CFU (by 98%), metabolic activity (by 50%), and acceptable me-

chanical properties. However, the joint addition of both DHMAI and MPC monomers to composite didn't significantly improve antibacterial activity, but resulted in worse mechanical properties.

- IDMAs have been applied in dentistry, with an antibacterial effect equivalent to methacryloyloxydodecyl pyrimidinium bromide (MDPB) [58]. Bienek *et al.* [23] synthesized purity-enhanced IDMA1 and IDMA2, and then assessed the biological, physicochemical, mechanical, and antibacterial properties of the IDMAs-modified resin composites. The authors concluded that IDMAs showed minimal or no cellular toxicity, and incorporation of IDMAs improved the degree of vinyl conversion (DVC) of the resins without affecting their wettability.
- A series of urethane dimethacrylate quaternary ammonium monomers (UDMQAs) have been synthesized, such as UDMQA-12, used at 30% to 40% in BisGMA/TEGDMA resin systems with significant antibacterial activity [63] [64]. A recent study reported by Huang et al. [24] prepared a photo-polymerized resin matrix with 30% UDMQA-12, mixed with silanated glass fillers at a mass ratio of 30:70. The new composite showed a significant antibacterial effect against *S. mutans*, better than commercial composite but still worse than glass ionomer cement (GIC). Moreover, its mechanical properties were similar to commercially available resin composites.
- A new dental resin system without Bis-GMA used Tricyclodecane dimethanol diacrylate (SR833s) and diurethane dimethacrylate (UDMA) monomers as a base resin, then N, N-bis [2-(3-(methacryl oyloxy) propanamide)-ethyl]-N-methylhexadecyl ammonium bromide (IMQ-16) was incorporated to obtain an antibacterial dental resin [65]. UDMA/SR833s/IMQ-16 resin system showed higher physicochemical properties compared to Bis-GMA/TEGDMA formulation. Incorporating IMQ-16 into this system at 17% or 20% produced a considerable antibacterial resin system.

Polymerizable monomers in combination with leachable agents

- To overcome the drawback of short-term release of antibacterial agents, they were immobilized with cationic polymers to create dental resins with a dual antibacterial mode that possesses both contacts and release antibacterial capabilities. The first study in this field was reported by Cao *et al.* [66] has developed photocurable core-shell silver bromide (AgBr)/cationic quaternary ammonium methacrylates (BHPVP) nanocomposites, releasing the active Ag^+ ions for a long term and possess the high antibacterial potency due to cationic polymers and Ag^+ ions.
- Another study was reported by Cheng L *et al.* [25], modified resin composite using NACP, quaternary ammonium dimethacrylate (QADM), and silver nanoparticles (AgNPs). This study lasted for one year and demonstrated that a NACP composite containing QADM and AgNPs showed high antibacterial effects and comparable mechanical properties matching a commercial composite.

- De Paula *et al.* [67] have synthesized and incorporated Triclosan methacrylate monomer (TM) into RBCs. The modified composite showed low biofilm accumulation and comparable mechanical properties without a significant difference from the control group.

Antibacterial filler particles

Antibacterial filler particles are usually incorporated into the RBCs, mainly metal, metal oxide, and bioactive glass filler. They are water-insoluble, but a small number of ions can be released into the surrounding environment. Silver is the most common antibacterial filler particle used for dental material [68].

Metal filler

- Silver nanoparticles (AgNPs), a kind of metal, are a broad-spectrum antibacterial agent incorporated into the RBCs to produce a high antibacterial activity by releasing Ag^{+} ions [69] [70]. The problem faced by adding nanoparticles is the aggregation and incomplete dispersion in the polymeric matrix, which affects various properties of the composites [71]. Some studies have overcome this drawback [72] [73]. Surface modification on nano-scale fillers with mussel-inspired dopamine (DA) has recently been highlighted in the preparation of organic-inorganic composites. The catechol group in DA can reduce silver ions to AgNPs and firmly bond the nanoparticles [74] [75] [76]. Ai *et al.* [27] synthesized hydroxyapatite (HA) nanowires using the hydrothermal technique, followed by surface modification via mussel-inspired dopamine (DA) to prepare polydopamine (PDA)-coated HA (HA-PDA) nanowires. The HA-PDA nanowires were further loaded with AgNPs to prepare the target product HA-PDA-Ag nanowires, which were finally incorporated into the resin composite. The authors reported that the composite reinforced by HA-PDA-Ag nanowires showed long-lasting antibacterial efficacy and no cytotoxicity.
- Barot *et al.* [28] used halloysite nanotubes (HNT) to load AgNPs. The HNT/Ag nanotubes were incorporated into BisGMA/TEGDMA-based dental resin composite, showing a high antibacterial activity on S. mutans and improved mechanical properties when 1 - 5 wt% of HNT/Ag nanotubes were added. Another study [29] mixed silver sulfadiazine, a kind of metal salt, with commercial barium borosilicate glass powders to obtain antibacterial glass powders, which were added to BisGMA-based dental resins. The target composite showed a potent antimicrobial effect persisting for more than eight weeks and no changes in mechanical properties.

Metal oxide filler

- Another way to achieve antibacterial activity is by adding metal oxides [77]. One metal oxide is zinc oxide (ZnO) nanoparticles added to resin-based restorative materials, resulting in high anti-biofilm effects [78] [79]. The smaller ZnO particles in size have higher antibacterial capacity than the larger ones. The rod-shaped or wire-shaped ZnO particles have better antibacterial results than spherical ones [80] [81]. Many other shapes of ZnO have been tested, and it is concluded that the antibacterial effect of ZnO is shape-dependent

[82] [83]. According to this conclusion, Dias *et al.* [31] synthesized ZnO particles with 3D microstructures and incorporated them as antimicrobial fillers in resin composites. The resin composite modified by 0.5 wt% of ZnO microrods exhibited a significant decrease in the bacterial accumulation on the composite surface without compromising its mechanical properties. Recently, Wang *et al.* [32] prepared cellulose nanocrystal/zinc oxide (CNC/ZnO) nanohybrids and incorporated them into dental resin composites. When 2% CNC/ZnO nanohybrids were added, the modified composite showed significant antibacterial properties without statistically different mechanical properties compared to the control composite.

- Some efforts have been focused on filler components, morphology, drug-loading, and size to get dental composites with perfect physical-mechanical properties. Porous mesoporous filler has been introduced into the dental composites to increase the resin-filler interfacial bonding, aiming to improve the mechanical performance of the composites [84] [85]. For example, mesoporous SiO_2 has been introduced to enhance the micromechanical properties of resin matrix via the formation of interlocking structures in dental composites [86] [87]. Chen *et al.* [33] inserted an antibacterial agent into mesoporous filler to form a mesoporous core-shell structure filler (ZnO@m-SiO_2) and used it as a functional filler in the dental composite. The composite modified by 70 wt% of ZnO@m-SiO_2 filler demonstrated the best mechanical properties compared to the control composite and a superior antimicrobial activity (Antibacterial ratio > 99.9%.)
- Titanium dioxide nanoparticles (TiO_2 NPs), another kind of metal oxide, are often used as an antibacterial agent to modify resin composite. A recent study was done by Dias *et al.* [34] added pure TiO_2 NPs and Ag-decorated TiO_2 NPs into the resin composite, and then the antibacterial activities of the synthesized resin composites were evaluated. The two modified composites significantly reduced biofilm formation without differences between them.
- Many other strategies also demonstrated a high and long-lasting antibacterial efficiency. Like silver-decorated TiO_2 NPs, the synergetic antibacterial effect of other nanohybrid materials was also highlighted, such as ZnO-Ag and ZnO-Au NPs. For example, a study done by Dias *et al.* [30] modified commercial resin composite with Ag-decorated ZnO nanoparticles. The modified resin composite showed biofilm inhibition on the surface without compromising its compressive strength.

Bioactive filler

- Bioactive glass (BG) is a biocompatible filler that can release Ca and P ions and possess a remineralizing effect. In addition to the cytocompatibility of BG resin composites, their mechanical properties are similar to commercial composites [88] [89]. Korkut *et al.* [35] reported that the antibacterial activity of resin composite modified by BG lasted for about 90 minutes. Its compressive and flexural strengths presented a decreased trend and a concentration-dependent effect on BG contents. In addition, several studies have been

done to develop antibacterial and bioactive restorative materials [90]. However, these materials showed retrograded mechanical properties or color changes, limiting their clinical use [91]. Chatzistavrou *et al.* [36] synthesized a silver-doped bioactive glass modified resin composite (Ag-BG), which showed a homogeneous dispersion of Ag-BG particles within the resin composite. The enhanced remineralizing properties and the long-lasting biofilm inhibition were correlated to the amount of Ag-BG. There were no significant differences in mechanical properties compared to the control samples.

- A surface pre-reacted glass-ionomer (S-PRG) filler has been incorporated into dental materials, making them have the capacity to release multiple ions, such as fluoride, aluminum (Al^{3+}), sodium (Na^{+}), and strontium (Sr^{2-}) ions [92] [93] [94]. Therefore, the modified composites effectively prevented the demineralization of dentin, imparted acid resistance to enamel, and promoted mineralization [95] [96] [97]. Resin composite modified by S-PRG filler also showed less bacterial attachment and plaque accumulation [98] [99]. In 2016, Miki *et al.* [37] evaluated and demonstrated the ability of resin composites modified by S-PRG filler to impede the growth of *S. mutans* on the surface.

3.3. The Measuring Methods of Antibacterial Efficacy

- The measuring methods for antibacterial efficacy are collected and categorized. Generally, more than one method is used in one study to confirm the results and support the conclusion. The most commonly used test method in this review was the biofilm colony-forming units (CFUs) counting method (40%), followed by live/dead bacteria staining assay of biofilms (25%), metabolic activity assay of biofilms using MTT assay (16%), lactic acid production assay of biofilms (8%), agar diffusion test (8%), and other methods (3%) such as minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) (**Figure 4**).

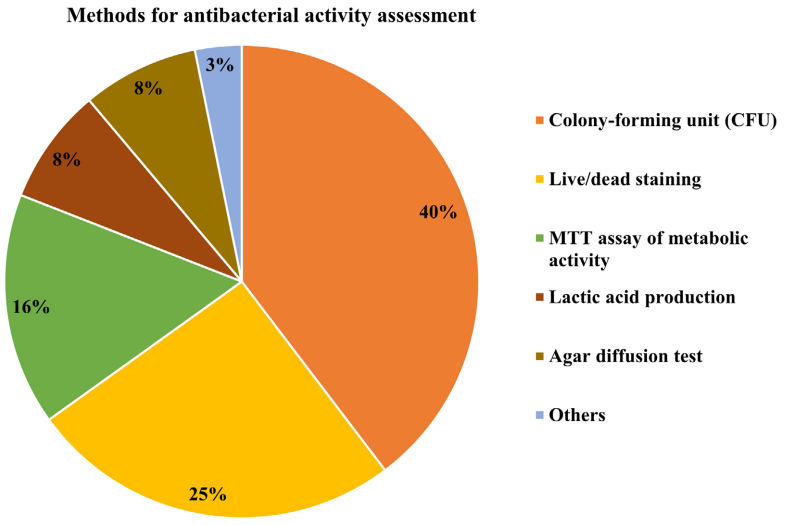

Figure 4. Categorization graph of the methods used for antibacterial activity assessment.

- The CFUs counting method is the most common and direct measuring method based on a viability test reflecting bacteria's fecundity. This method involves several procedures, such as biofilm disruption, multiple dilutions of the dispersed biofilm, inoculation onto broth-containing agar, and colony counting after incubation, which has some advantages and limitations. The perfect result depends on a sufficient dilution of biofilm suspension to reduce the miscalculation of bacterial colonies [100] [101].
- The second most common method is the live/dead bacteria staining assay, which indirectly measures bacteria viability. This method differentiates viable and dead bacteria through cell membrane integrity, using the combination of SYTO 9 and propidium iodide dye. Therefore, it's more suitable for antibacterial agents which act on the cell membranes, such as quaternary ammonium compounds [101].

Metabolic activity assay of biofilms has various indicators to measure, such as a snapshot of the bulk metabolic function at a given time, the evaluation of gene expression, and the measurement of metabolic byproducts. About 16% of the studies used the MTT assay to measure the metabolic activity of biofilms, which depends on the enzymatic reduction of MTT from yellow tetrazole to purple formazan. The metabolic activity is not equal to the biofilm cell viability because some biofilm cells remain viable, but their metabolism is inactive. Therefore, this method has been used as a reinforcing and supplementary assessment to other methods [100] [102]. Because of the advantages and disadvantages of each technique, researchers should completely understand the mechanism, limitations, and operation procedures of each method and then select the appropriate methods to avoid misinterpreting the results. There are no universal protocols for all studies to follow, helping to make comparisons among different studies.

4. Conclusions

This review covered the antibacterial agents incorporated into the resin composite from January 2015 to May 2020, including 32 articles focused on modifying the RBCs using existing antibacterial agents to increase their antibacterial efficacy or prolong their antibacterial period. Generally, most studies were concerned with polymerizable monomers (50%), followed by filler particles (39%) and leachable agents (11%). The problem mostly faced is that the antibacterial effects are in a concentration-dependent manner depending on the contents of antibacterial agents. However, higher contents of antibacterial agents may cause cytotoxicity or interfere with the mechanical properties of the resin composite. Consequently, most antibacterial agents are added in small amounts and modified to have significant antibacterial effects, minimal cytotoxicity, and no effects on mechanical characteristics of the experimental/commercial resin composite.

The recent antibacterial agents focused combination of leachable agents, polymerizable monomers, and metal oxide filler agents. This combination is of two agents from the same category (DMAHDM + MPC, DHMAI + MPC, Ag-decorated

ZnO NPs, and Ag-decorated TiO_2 NPs) or mixing agents from different categories in one (such as QADM + NACP + AgNPs and MPC + SPRG). All these modifications are done to overcome the burst release effect and raise the antibacterial efficacy without compromising the mechanical features of the composite. However, there are no clinical studies for these new modified composites, all of which are still under experimental conditions.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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