Antibacterial Dental Resin Composites: A Narrative Review

Ameenah Saad Alansy¹, Thekra Ali Saeed¹, Yuqing Guo¹, Yanwei Yang²*, Bin Liu¹*, Zengjie Fan¹*

¹Key Laboratory of Dental Maxillofacial Reconstruction and Biological Intelligence Manufacturing, Gansu Province School of Stomatology, Lanzhou University, Lanzhou, China
²Department of Stomatology, The 940th Hospital of Joint Logistic Support Force of the Chinese People’s Liberation Army, Lanzhou, China

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, Iionic 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-SiO2 (core-shell structure) | [31] [32] [33]|
|                                        | Titanium dioxide (TiO2)             | Ag decorated TiO2 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 anti-bacterial 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-

DOI: 10.4236/ojst.2022.125015 153 Open Journal of Stomatology
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 (UDM-QAs) 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-(methacryloyloxy) 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.
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](https://example.com)
• 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 TiO₂ 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.

Acknowledgements

The authors deeply appreciate the support from the National Natural Science Foundation of China (81571829), Natural Science Foundation of Gansu Province (20R10RA597), The Fundamental Research Funds for the Central Universities (lzujbky-2020-it29, lzujbky-2019-ct07), The Open Project of State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences (LSL-1907).

Conflicts of Interest

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

References

[1] Heintze, S.D. and Rousson, V. (2012) Clinical Effectiveness of Direct Class II Restorations—A Meta-Analysis. The Journal of Adhesive Dentistry, 14, 407-431.

[2] Nedeljkovic, I., et al. (2015) Is Secondary Caries with Composites a Material-Based Problem? Dental Materials, 31, e247-e277. https://doi.org/10.1016/j.dental.2015.09.001

[3] Moraschini, V., et al. (2015) Amalgam and Resin Composite Longevity of Posterior Restorations: A Systematic Review and Meta-Analysis. Journal of Dentistry, 43, 1043-1050. https://doi.org/10.1016/j.jdent.2015.06.005

[4] Burgess, J. and Cakir, D. (2010) Comparative Properties of Low-Shrinkage Composite Resins. Compendium of Continuing Education in Dentistry (Jamesburg, N.J.: 1995), 31, 10-15.

[5] Ilie, N. and Hickel, R. (2011) Investigations on a Methacrylate-Based Flowable Composite Based on the SDR™ Technology. Dental Materials, 27, 348-355. https://doi.org/10.1016/j.dental.2010.11.014

[6] Shi, X., et al. (2016) Current Status and Further Prospects of Dental Resin-Based Materials with Antibacterial Properties. Chinese Journal of Stomatology, 51, 566-569.

[7] Giachetti, L., Bertini, F. and Bambi, C. (2007) A Rational Use of Dental Materials in Posterior Direct Resin Restorations in Order to Control Polymerization Shrinkage Stress. Minerva Stomatologica, 56, 129-138.

[8] Pereira-Cenci, T., et al. (2013) Antibacterial Agents in Composite Restorations for the Prevention of Dental Caries. John Wiley and Sons Ltd., Hoboken. https://doi.org/10.1002/14651858.CD007819.pub3

[9] Farrugia, C. and Camilleri, J. (2015) Antimicrobial Properties of Conventional Restorative Filling Materials and Advances in Antimicrobial Properties of Composite Resins and Glass Ionomer Cements—A Literature Review. Dental Materials, 31, e89-e99. https://doi.org/10.1016/j.dental.2014.12.005
[10] Imazato, S. (2003) Antibacterial Properties of Resin Composites and Dentin Bonding Systems. *Dental Materials, 19*, 449-457. https://doi.org/10.1016/S0109-5641(02)00102-1

[11] Cunha, D.A., et al. (2018) Materials Physicochemical and Microbiological Assessment of an Experimental Composite Doped with Triclosan-Loaded Halloysite Nanotubes. *Materials, 11*, 1080. https://doi.org/10.3390/ma11071080

[12] Boaro, L.C.C., et al. (2019) Antibacterial Resin-Based Composite Containing Chlorhexidine for Dental Applications. *Dental Materials, 35*, 909-918. https://doi.org/10.1016/j.dental.2019.03.004

[13] Yang, Y., et al. (2021) Novel Core-Shell CHX/ACP Nanoparticles Effectively Improve the Mechanical, Antibacterial and Remineralized Properties of the Dental Resin Composite. *Dental Materials, 37*, 636-647. https://doi.org/10.1016/j.dental.2021.01.007

[14] Wang, J., et al. (2017) Incorporation of Antibacterial Agent Derived Deep Eutectic Solvent into an Active Dental Composite. *Dental Materials, 33*, 1445-1455. https://doi.org/10.1016/j.dental.2017.09.014

[15] Stenhagen, I.S.R., et al. (2019) Effect of Methacrylated Chitosan Incorporated in Experimental Composite and Adhesive on Mechanical Properties and Biofilm Formation. *European Journal of Oral Sciences, 127*, 81-88. https://doi.org/10.1111/eos.12584

[16] Tanaka, C.B., et al. (2020) Development of Novel Dental Restorative Composites with Dibasic Calcium Phosphate Loaded Chitosan Fillers. *Dental Materials, 36*, 551-559. https://doi.org/10.1016/j.dental.2020.02.004

[17] Wu, J., et al. (2015) Effect of Dimethylaminohexadecyl Methacrylate Mass Fraction on Fracture Toughness and Antibacterial Properties of CaP Nanocomposite. *Journal of Dentistry, 43*, 1539-1546. https://doi.org/10.1016/j.jdent.2015.09.004

[18] Al-Dulaijan, Y.A., et al. (2018) Novel Rechargeable Calcium Phosphate Nanocomposite with Antibacterial Activity to Suppress Biofilm Acids and Dental Caries. *Journal of Dentistry, 72*, 44-52. https://doi.org/10.1016/j.jdent.2018.03.003

[19] Zhang, N., et al. (2017) Effects of Long-Term Water-Aging on Novel Anti-Biofilm and Protein-Repellent Dental Composite. *International Journal of Molecular Sciences, 18*, 186. https://doi.org/10.3390/ijms18010186

[20] Xie, X., et al. (2016) Protein-Repellent and Antibacterial Functions of a Calcium Phosphate Rechargeable Nanocomposite. *Journal of Dentistry, 52*, 15-22. https://doi.org/10.1016/j.jdent.2016.06.003

[21] Lee, M.J., et al. (2019) Bioactive Resin-Based Composite with Surface Pre-Reacted Glass-Ionomer Filler and Zwitterionic Material to Prevent the Formation of Multi-Species Biofilm. *Dental Materials, 35*, 1331-1341. https://doi.org/10.1016/j.dental.2019.06.004

[22] Cherchali, F.Z., et al. (2017) Effectiveness of the DHMAI Monomer in the Development of an Antibacterial Dental Composite. *Dental Materials, 33*, 1381-1391. https://doi.org/10.1016/j.dental.2017.09.004

[23] Bienek, D.R., et al. (2018) Ionic Dimethacrylates for Antimicrobial and Remineralizing Dental Composites. *Annals of Dentistry and Oral Disorders, 2*, 108.

[24] Huang, Q., et al. (2018) The Antibacterial, Cytotoxic, and Flexural Properties of a Composite Resin Containing a Quaternary Ammonium Monomer. *Journal of Prosthetic Dentistry, 120*, 609-616. https://doi.org/10.1016/j.prosdent.2017.12.017

[25] Cheng, L., et al. (2016) One-Year Water-Ageing of Calcium Phosphate Composite
Containing Nano-Silver and Quaternary Ammonium to Inhibit Biofilms. *International Journal of Oral Science*, **8**, 172-181. [https://doi.org/10.1038/ijos.2016.13](https://doi.org/10.1038/ijos.2016.13)

[26] Pietrokovski, Y., *et al.* (2016) Antibacterial Effect of Composite Resin Foundation Material Incorporating Quaternary Ammonium Polyethyleneimine Nanoparticles. *Journal of Prosthetic Dentistry*, **116**, 603-609. [https://doi.org/10.1016/j.prosdent.2016.02.022](https://doi.org/10.1016/j.prosdent.2016.02.022)

[27] Ai, M., *et al.* (2017) Composite Resin Reinforced with Silver Nanoparticles-Laden Hydroxyapatite Nanowires for Dental Application. *Dental Materials*, **33**, 12-22. [https://doi.org/10.1016/j.dental.2016.09.038](https://doi.org/10.1016/j.dental.2016.09.038)

[28] Barot, T., Rawtani, D. and Kulkarni, P. (2020) Physicochemical and Biological Assessment of Silver Nanoparticles Immobilized Halloysite Nanotubes-Based Resin Composite for Dental Applications. *Heliyon*, **6**, e03601. [https://doi.org/10.1016/j.heliyon.2020.e03601](https://doi.org/10.1016/j.heliyon.2020.e03601)

[29] Srivastava, R. and Sun, Y. (2017) Silver Sulfadiazine Immobilized Glass as Antimicrobial Fillers for Dental Restorative Materials. *Materials Science and Engineering C*, **75**, 524-534. [https://doi.org/10.1016/j.msec.2017.02.069](https://doi.org/10.1016/j.msec.2017.02.069)

[30] Dias, H.B., *et al.* (2019) Synthesis, Characterization and Application of Ag Doped ZnO Nanoparticles in a Composite Resin. *Materials Science and Engineering C*, **96**, 391-401. [https://doi.org/10.1016/j.msec.2018.10.063](https://doi.org/10.1016/j.msec.2018.10.063)

[31] Wang, Y., *et al.* (2019) Strong Antibacterial Dental Resin Composites Containing Cellulose Nanocrystal/Zinc Oxide Nanohybrids. *Journal of Dentistry*, **80**, 23-29. [https://doi.org/10.1016/j.jdent.2018.11.002](https://doi.org/10.1016/j.jdent.2018.11.002)

[32] Chen, H., *et al.* (2018) Synthesis of Core-Shell Structured ZnO@m-SiO₂ with Excellent Reinforcing Effect and Antimicrobial Activity for Dental Resin Composites. *Dental Materials*, **34**, 1846-1855. [https://doi.org/10.1016/j.dental.2018.10.002](https://doi.org/10.1016/j.dental.2018.10.002)

[33] Korkut, E., Torlak, E. and Altunsoy, M. (2016) Antimicrobial and Mechanical Properties of Dental Resin Composite Containing Bioactive Glass. *Journal of Applied Biomaterials and Functional Materials*, **14**, e296-e301. [https://doi.org/10.5301/jabfm.5000271](https://doi.org/10.5301/jabfm.5000271)

[34] Chatzistavrou, X. *et al.* (2018) Bactericidal and Bioactive Dental Composites. *Frontiers in Physiology*, **9**, 103. [https://doi.org/10.3389/fphys.2018.00103](https://doi.org/10.3389/fphys.2018.00103)

[35] Miki, S., *et al.* (2016) Antibacterial Activity of Resin Composites Containing Surface Pre-Reacted Glass-Ionomer (S-PRG) Filler. *Dental Materials*, **32**, 1095-1102. [https://doi.org/10.1016/j.dental.2016.06.018](https://doi.org/10.1016/j.dental.2016.06.018)

[36] Kaffashi, B., Davoodi, S. and Oliaei, E. (2016) Poly(ε-caprolactone)/Triclosan Loaded Polyactic Acid Nanoparticles Composite: A Long-Term Antibacterial Bionano-composite with Sustained Release. *International Journal of Pharmaceutics*, **508**, 10-21. [https://doi.org/10.1016/j.ijpharm.2016.05.009](https://doi.org/10.1016/j.ijpharm.2016.05.009)

[37] Rathke, A., *et al.* (2010) Antibacterial Activity of a Triclosan-Containing Resin Composite Matrix against Three Common Oral Bacteria. *Journal of Materials Science. Materials in Medicine*, **21**, 2971-2977. [https://doi.org/10.1007/s10856-010-4126-1](https://doi.org/10.1007/s10856-010-4126-1)

[38] Degrazia, F.W., *et al.* (2018) Polymerisation, Antibacterial and Bioactivity Proper-
ties of Experimental Orthodontic Adhesives Containing Triclosan-Loaded Halloysite Nanotubes. Journal of Dentistry, 69, 77-82. https://doi.org/10.1016/j.jdent.2017.11.002

[41] Du, M., Guo, B. and Jia, D. (2010) Newly Emerging Applications of Halloysite Nanotubes: A Review. John Wiley & Sons, Ltd., Hoboken, 574-582. https://doi.org/10.1002/pi.2754

[42] Zhu, H., et al. (2012) Green Synthesis of Au Nanoparticles Immobilized on Halloysite Nanotubes for Surface-Enhanced Raman Scattering Substrates. Dalton Transactions, 41, 10465-10471. https://doi.org/10.1039/c2dt30998j

[43] Liu, J.X., et al. (2018) Cytotoxicity Evaluation of Chlorhexidine Gluconate on Human Fibroblasts, Myoblasts, and Osteoblasts. Journal of Bone and Joint Infection, 3, 165-172. https://doi.org/10.7150/jbji.26355

[44] Takahashi, Y., et al. (2006) Antibacterial Effects and Physical Properties of Glass-Ionomer Cements Containing Chlorhexidine for the ART Approach. Dental Materials, 22, 647-652. https://doi.org/10.1016/j.dental.2005.08.003

[45] Sanders, B.J., et al. (2002) Antibacterial and Physical Properties of Resin Modified Glass-Ionomers Combined with Chlorhexidine. Journal of Oral Rehabilitation, 29, 553-558. https://doi.org/10.1046/j.1365-2842.2002.00876.x

[46] Leung, D., et al. (2005) Chlorhexidine-Releasing Methacrylate Dental Composite Materials. Biomaterials, 26, 7145-7153. https://doi.org/10.1016/j.biomaterials.2005.05.014

[47] Wu, Y., et al. (2013) Long-Term and Controlled Release of Chlorhexidine-Copper(II) from Organically Modified Montmorillonite (OMMT) Nanocomposites. Materials Science and Engineering C, 33, 752-757. https://doi.org/10.1016/j.msec.2012.10.028

[48] He, H., et al. (2006) A Novel Organoclay with Antibacterial Activity Prepared from Montmorillonite and Chlorhexidine Acetas. Journal of Colloid and Interface Science, 297, 235-243. https://doi.org/10.1016/j.jcis.2005.10.031

[49] Ambrogi, V., et al. (2017) Montmorillonite-Chitosan-Chlorhexidine Composite Films with Antibiofilm Activity and Improved Cytotoxicity for Wound Dressing. Journal of Colloid and Interface Science, 491, 265-272. https://doi.org/10.1016/j.jcis.2016.12.058

[50] Pashley, D.H., et al. (2011) State of the Art Etch-and-Rinse Adhesives. Dental Materials, 27, 1-16. https://doi.org/10.1016/j.dental.2010.10.016

[51] Kumar, M.N.V.R., et al. (2004) Chitosan Chemistry and Pharmaceutical Perspectives. Chemical Reviews, 104, 6017-6084. https://doi.org/10.1021/cr030441b

[52] Petri, D.F.S., et al. (2007) Preliminary Study on Chitosan Modified Glass Ionomer Restoratives. Dental Materials, 23, 1004-1010. https://doi.org/10.1016/j.dental.2006.06.038

[53] Ibrahim, M.A., et al. (2015) Characterization of Antibacterial and Adhesion Properties of Chitosan-Modified Glass Ionomer Cement. Journal of Biomaterials Applications, 30, 409-419. https://doi.org/10.1177/0885328215589672

[54] Hamilton, M.F., et al. (2015) Physicomechanical and Antibacterial Properties of Experimental Resin-Based Dental Sealants Modified with Nylon-6 and Chitosan Nanofibers. Journal of Biomedical Materials Research—Part B Applied Biomaterials, 103, 1560-1568. https://doi.org/10.1002/jbmb.33342

[55] Diolosà, M., et al. (2014) Use of Methacrylate-Modified Chitosan to Increase the Durability of Dentine Bonding Systems. Biomacromolecules, 15, 4606-4613. https://doi.org/10.1021/bm5014124
[56] Qasim, S.B., et al. (2017) Potential of Electrospun Chitosan Fibers as a Surface Layer in Functionally Graded GTR Membrane for Periodontal Regeneration. *Dental Materials, 33*, 71-83. https://doi.org/10.1016/j.dental.2016.10.003

[57] Chen, Y., Mu, X. and Wang, F. (2018) Preparation and Drug Release of PVA Composite Nanofibers Loaded Chitosan Microsphere. *Polymer Science Series A, 60*, 311-321. https://doi.org/10.1134/S0965545X18030112

[58] Antonucci, J.M., et al. (2012) Synthesis and Characterization of Dimethacrylates Containing Quaternary Ammonium Functionalities for Dental Applications. *Dental Materials, 28*, 219-228. https://doi.org/10.1016/j.dental.2011.10.004

[59] Xu, X., et al. (2012) Synthesis and Characterization of Antibacterial Dental Monomers and Composites. *Journal of Biomedical Materials Research Part B Applied Biomaterials, 100B*, 1151-1162. https://doi.org/10.1002/jbm.b.32683

[60] Zhang, K., et al. (2016) Effects of Quaternary Ammonium Chain Length on the Antibacterial and Remineralizing Effects of a Calcium Phosphate Nanocomposite. *International Journal of Oral Science, 8*, 45-53. https://doi.org/10.1038/ijos.2015.33

[61] Beyth, N., et al. (2006) Antibacterial Activity of Dental Composites Containing Quaternary Ammonium Polyethylenimine Nanoparticles against *Streptococcus mutans*. *Biomaterials, 27*, 3995-4002. https://doi.org/10.1016/j.biomaterials.2006.03.003

[62] He, J., et al. (2011) Synthesis of Methacrylate Monomers with Antibacterial Effects against *S. mutans*. *Molecules, 16*, 9755-9763. https://doi.org/10.3390/molecules16119755

[63] Liang, X., et al. (2013) Synthesis of Novel Antibacterial Monomers (UDMQA) and Their Potential Application in Dental Resin. *Journal of Applied Polymer Science, 129*, 3373-3381. https://doi.org/10.1002/app.39113

[64] Huang, Q., et al. (2014) Preparation and Characterization of Antibacterial Dental Resin with UDMQA-12. *Advances in Polymer Technology, 33*, 1-6. https://doi.org/10.1002/adv.21395

[65] Huang, Q.T., et al. (2016) Physical and Chemical Properties of an Antimicrobial Bis-GMA Free Dental Resin with Quaternary Ammonium Dimethacrylate Monomer. *Journal of the Mechanical Behavior of Biomedical Materials, 56*, 68-76. https://doi.org/10.1016/j.jmbbm.2015.10.028

[66] Cao, W., et al. (2017) Development of a Novel Resin-Based Dental Material with Dual Biocidal Modes and Sustained Release of Ag’ Ions Based on Photocurable Core-Shell AgBr/Cationic Polymer Nanocomposites. *Journal of Materials Science: Materials in Medicine, 28*, 103. https://doi.org/10.1007/s10856-017-5918-3

[67] de Paula, A.B., et al. (2019) Synthesis and Application of Triclosan Methacrylate Monomer in Resin Composites. *Clinical Oral Investigations, 23*, 965-974. https://doi.org/10.1007/s00784-018-2521-z

[68] Rai, M., Yadav, A. and Gade, A. (2009) Silver Nanoparticles as a New Generation of Antimicrobials. *Biotechnology Advances, 27*, 76-83. https://doi.org/10.1016/j.biotechnadv.2008.09.002

[69] Nath, S., Kalmodia, S. and Basu, B. (2010) Densification, Phase Stability and in Vitro Biocompatibility Property of Hydroxyapatite-10 wt% Silver Composites. *Journal of Materials Science: Materials in Medicine, 21*, 1273-1287. https://doi.org/10.1007/s10856-009-3939-2

[70] Mocanu, A., et al. (2014) Synthesis; Characterization and Antimicrobial Effects of Composites Based on Multi-Substituted Hydroxyapatite and Silver Nanoparticles. *Applied Surface Science, 298*, 225-235. https://doi.org/10.1016/j.apsusc.2014.01.166

[71] Viswanathan, V., et al. (2006) Challenges and Advances in Nanocomposite Processing
Techniques. Elsevier, Amsterdam, 121-285.  
https://doi.org/10.1016/j.mser.2006.11.002

[72] Cheng, Y.J., et al. (2011) In Situ Formation of Silver Nanoparticles in Photocross-linking Polymers. Journal of Biomedical Materials Research—Part B Applied Biomaterials, 97, 124-131.  
https://doi.org/10.1002/jbm.b.31793

[73] Melo, M.A.S., et al. (2013) Novel Dental Adhesives Containing Nanoparticles of Silver and Amorphous Calcium Phosphate. Dental Materials, 29, 199-210.  
https://doi.org/10.1016/j.dental.2012.10.005

[74] Wang, W., et al. (2012) Preparation of PET/Ag Hybrid Fibers via a Biomimetic Surface Functionalization Method. Electrochimica Acta, 79, 37-45.  
https://doi.org/10.1016/j.electacta.2012.06.063

[75] Wang, W., et al. (2011) Fabrication of Silver-Coated Silica Microspheres through Mussel-Inspired Surface Functionalization. Journal of Colloid and Interface Science, 358, 567-574.  
https://doi.org/10.1016/j.jcis.2011.03.023

[76] Yang, L., et al. (2011) A Biomimetic Approach to Enhancing Interfacial Interactions: Polydopamine-Coated Clay as Reinforcement for Epoxy Resin. ACS Applied Materials and Interfaces, 3, 3026-3032.  
https://doi.org/10.1021/am200532j

[77] Wang, Z., Shen, Y. and Haapasalo, M. (2014) Dental Materials with Antibiofilm Properties. Dental Materials, 30, e1-16.  
https://doi.org/10.1016/j.dental.2013.12.001

[78] Tavassoli Hojati, S., et al. (2013) Antibacterial, Physical and Mechanical Properties of Flowable Resin Composites Containing Zinc Oxide Nanoparticles. Dental Materials, 29, 495-505.  
https://doi.org/10.1016/j.dental.2013.03.011

[79] Kasraei, S., et al. (2014) Antibacterial Properties of Composite Resins Incorporating Silver and Zinc Oxide Nanoparticles on Streptococcus mutans and Lactobacillus. Restorative Dentistry & Endodontics, 39, 109-109.  
https://doi.org/10.5395/rde.2014.39.2.109

[80] Sirelkhatim, A., et al. (2015) Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism. Nano-Micro Letters, 7, 219-242.  
https://doi.org/10.1007/s40820-015-0040-x

[81] Yang, H., et al. (2009) Comparative Study of Cytotoxicity, Oxidative Stress and Genotoxicity Induced by Four Typical Nanomaterials: The Role of Particle Size, Shape and Composition. Journal of Applied Toxicology, 29, 69-78.  
https://doi.org/10.1002/jat.1385

[82] Wahab, R., et al. (2010) Formation of ZnO Micro-Flowers Prepared via Solution Process and Their Antibacterial Activity. Nanoscale Research Letters, 5, 1675-1681.  
https://doi.org/10.1007/s11671-010-9694-y

[83] Wahab, R., et al. (2012) Fabrication, Growth Mechanism and Antibacterial Activity of ZnO Micro-Spheres Prepared via Solution Process. Biomass and Bioenergy, 39, 227-236.  
https://doi.org/10.1016/j.biombioe.2012.01.005

[84] Samuel, S.P., et al. (2009) Mechanical Properties of Experimental Dental Composites Containing a Combination of Mesoporous and Nonporous Spherical Silica as Fillers. Dental Materials, 25, 296-301.  
https://doi.org/10.1016/j.dental.2008.07.012

[85] Curtis, A.R., et al. (2009) The Mechanical Properties of Nanofilled Resin-Based Composites: Characterizing Discrete Filler Particles and Agglomerates Using a Micromanipulation Technique. Dental Materials, 25, 180-187.  
https://doi.org/10.1016/j.dental.2008.05.013

[86] Praveen, S., et al. (2006) Compression and Aging Properties of Experimental Dental Composites Containing Mesoporous Silica as Fillers. Molecular Crystals and Liquid
[87] Wang, R., Habib, E. and Zhu, X.X. (2017) Synthesis of Wrinkled Mesoporous Silica and Its Reinforcing Effect for Dental Resin Composites. *Dental Materials*, **33**, 1139-1148. [https://doi.org/10.1016/j.dental.2017.07.012](https://doi.org/10.1016/j.dental.2017.07.012)

[88] Salehi, S., *et al.* (2015) Cytotoxicity of Resin Composites Containing Bioactive Glass Fillers. *Dental Materials*, **31**, 195-203. [https://doi.org/10.1016/j.dental.2014.12.004](https://doi.org/10.1016/j.dental.2014.12.004)

[89] Khvostenko, D., *et al.* (2013) Mechanical Performance of Novel Bioactive Glass Containing Dental Restorative Composites. *Dental Materials*, **29**, 1139-1148. [https://doi.org/10.1016/j.dental.2013.08.207](https://doi.org/10.1016/j.dental.2013.08.207)

[90] Chen, L., Shen, H. and Suh, B.I.N. (2012) Antibacterial Dental Restorative Materials: A State-of-the-Art Review. *American Journal of Dentistry*, **25**, 337-346.

[91] Fan, C., *et al.* (2011) Development of an Antimicrobial Resin—A Pilot Study. *Dental Materials*, **27**, 322-328. [https://doi.org/10.1016/j.dental.2010.11.008](https://doi.org/10.1016/j.dental.2010.11.008)

[92] Itota, T., *et al.* (2004) Fluoride Release and Recharge in Giomer, Compomer and Resin Composite. *Dental Materials*, **20**, 789-795. [https://doi.org/10.1016/j.dental.2003.11.009](https://doi.org/10.1016/j.dental.2003.11.009)

[93] Ito, S., *et al.* (2011) Effects of Surface Pre-Reacted Glass-Ionomer Fillers on Mineral Induction by Phosphoprotein. *Journal of Dentistry*, **39**, 72-79. [https://doi.org/10.1016/j.jdent.2010.10.011](https://doi.org/10.1016/j.jdent.2010.10.011)

[94] Fujimoto, Y., *et al.* (2010) Detection of Ions Released from S-PRG Fillers and Their Modulation Effect. *Dental Materials Journal*, **29**, 392-397. [https://doi.org/10.4012/dmj.2010-015](https://doi.org/10.4012/dmj.2010-015)

[95] Ma, S., *et al.* (2012) Effects of a Coating Resin Containing S-PRG Filler to Prevent Demineralization of Root Surfaces. *Dental Materials Journal*, **31**, 909-915. [https://doi.org/10.4012/dmj.2012-061](https://doi.org/10.4012/dmj.2012-061)

[96] Kawasaki, K. and Kambara, M. (2014) Effects of Ion-Releasing Tooth-Coating Material on Demineralization of Bovine Tooth Enamel. *International Journal of Dentistry*, **2014**, Article ID: 463149. [https://doi.org/10.1155/2014/463149](https://doi.org/10.1155/2014/463149)

[97] Kaga, M., *et al.* (2014) Inhibition of Enamel Demineralization by Buffering Effect of S-PRG Filler-Containing Dental Sealant. *European Journal of Oral Sciences*, **122**, 78-83. [https://doi.org/10.1111/eos.12107](https://doi.org/10.1111/eos.12107)

[98] Saku, S., *et al.* (2010) Antibacterial Activity of Composite Resin with Glass-Ionomer Filler Particles. *Dental Materials Journal*, **29**, 193-198. [https://doi.org/10.4012/dmj.2009-050](https://doi.org/10.4012/dmj.2009-050)

[99] Hahnel, S., *et al.* (2014) *Streptococcus mutans* Biofilm Formation and Release of Fluoride from Experimental Resin-Based Composites Depending on Surface Treatment and S-PRG Filler Particle Fraction. *The Journal of Adhesive Dentistry (JAD)*, **16**, 313-321.

[100] Lin, N.J. (2017) Biofilm over Teeth and Restorations: What Do We Need to Know? *Dental Materials*, **33**, 667-680. [https://doi.org/10.1016/j.dental.2017.03.003](https://doi.org/10.1016/j.dental.2017.03.003)

[101] Ibrahim, M.S., *et al.* (2020) How We Are Assessing the Developing Antibacterial Resin-Based Dental Materials? A Scoping Review. *Journal of Dentistry*, **99**, Article ID: 103369. [https://doi.org/10.1016/j.jdent.2020.103369](https://doi.org/10.1016/j.jdent.2020.103369)

[102] Ferreira, C., *et al.* (2011) Physiological Changes Induced by the Quaternary Ammonium Compound Benzyltrimethyldecylammonium Chloride on *Pseudomonas fluorescens*. *Journal of Antimicrobial Chemotherapy*, **66**, 1036-1043. [https://doi.org/10.1093/jac/dkr028](https://doi.org/10.1093/jac/dkr028)