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REVIEW

Development and status of resin composite as dental restorative materials

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ABSTRACT: Dental composites are comprised of a polymerizable matrix and reinforcing fillers that can be hardened into a solid restoration in the prepared tooth cavity. Composites are becoming increasingly popular due to their esthetics and improved mechanical and physical properties. However, dental composites still encounter several problems, mainly secondary (recurrent) caries, restoration fracture, excessive wear, marginal degradation, and tooth sensitivity. Therefore, extensive efforts are underway to improve the composite compositions and microstructure, and enhance their clinical performance and longevity. Relying on advances in materials science and technology, dental composites have been continuously improved and their clinical applications have been expanded. In this review article, the development of dental composites was summarized, including compositional changes, performance improvements in key areas, current research hot spots, and outlook for future direction. The intention is to provide a review of the history and development of dental composites with a discussion of strategies on addressing the current challenges facing dental composites. In addition, this review will provide a better understanding of dental composites and their properties for the practicing clinicians, to contribute to improving the quality of composite restorations. The review of literature indicates that while current composites are generally bio-inert and can replace the missing tooth structure, future composites should be bioactive and therapeutic to inhibit caries, modulate biofilms, and protect the surrounding tooth structures, in order to increase the restoration longevity. © 2019 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2019**, *136*, 48180.

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INTRODUCTION

Dental caries is one of the most prevalent human chronic diseases worldwide.[1] Once the tooth tissue defect is formed, restorative treatment is a common approach.[2] Resin composites are increasingly used as the dominant choice of most patients for dental restorations because of their esthetics and direct-filling capability.[3] Composites also overcome some drawbacks of previous materials like amalgam and contribute to preserving natural tooth tissues by a strong chemical bonding to enamel and dentin.[4]

As one of the most common dental filling materials, composites have been widely used in clinical application for nearly 50 years. Their development and evolution are based on acrylate, and their first introduction into dentistry was dated back to the late 1950s and early 1960s. Bowen first reported on a monomer named bisphenol-A diglycidyl methacrylate (bis-GMA;(2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl] propane)) and the successful synthesis of composite by adding inorganic fillers.[5]

Composites have been gradually improved in their formulations, properties, esthetics and become increasingly popular in dentistry.[6] Nearly 200 million dental restorations are placed annually in the United States, and half of all dental restorations failed within 10 years.[7] A lot of factors contribute the composite failure, such as poor oral hygiene, incorrect design of cavity preparation, imperfect manipulation of the composites, composites materials performance, and so forth.[8] There is a need to further improve

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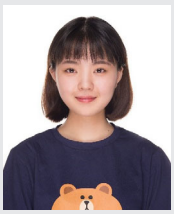

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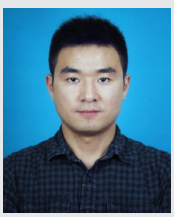

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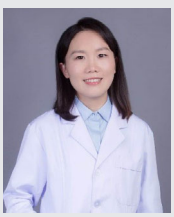

Prof. Xuedong Zhou was the Dean in State Key Laboratory of Oral Diseases, West China School of Stomatology, Sichuan University. She graduated from the Department of Stomatology, Sichuan University, in 1980. After that, she joined the School of Stomatology, Sichuan University, majoring in dental caries and obtained the medical doctor's degree from Sichuan University in 1987. In the same year, she was sent to the Royal College of Dentistry in Aarhus, Denmark, for further study. Now, Prof. Zhou works as a Doctoral Supervisor, and a Director of the State Key Laboratory of Oral Disease.

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the dental composites property to reduce the failure rates and increase the longevity.

Composites have several inherent physical and chemical property drawbacks including polymerization shrinkage, a relatively high coefficient of thermal expansion and a relatively low wear resistance, and so forth.[9,10] The long-term durability in clinical use faces challenges, with potential failures resulting from secondary caries and bulk fractures. Further strategies on developing antibacterial and self-repairing materials, or bioactive materials promoting tissue regeneration, will provide new approaches to enhancing dental composites.

CHEMICAL COMPOSITIONS OF DENTAL COMPOSITES

A composite is defined as a three-dimensional compound which is composed of at least two different chemical components, or can be described as a blend of hard inorganic particles bound together in a resin matrix. A dental composite includes a resin matrix, inorganic fillers after surface treatment, as well as the initiator and catalyst systems (Table I).[8]

The resin-based oligomer matrix is most commonly composed of bis-GMA, a hydroxyethylmethacrylate (HEMA), triethylene glycol dimethacrylate (TEGDMA), and urethane dimethacrylate (UDMA).[2] Inorganic fillers usually include silicon dioxide (silica), quartz, other glass powders, ceramic fillers, and so forth, which can enhance the hardness, wear resistance, and translucency of the composite. The coupling agent system usually consists of organic silane such as 3-methacryloxypropyltrimethoxysilane and 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP), whose chemical functional groups can enhance the bonding strength between the reinforcing filler and the resin matrix.[11] The polymerization of composite is initiated by an initiator system, such as camphorquinone (CQ), phenylpropanedione (PPD), when external energy (light or heat) is applied. Different types of composites require different light energy levels for proper curing, which has been reviewed. Catalyst is added to control the polymerization speed. Other constituents such as dimethylglyoxime can also be used to improve certain physical properties such as flowability.[12,13]

COMPOSITE SYSTEM CLASSIFICATION OF DENTAL COMPOSITES

There are many types of composite products available in clinical use by several different classification systems. Dental composites can be divided into the following categories, according to their different compositions and performance characteristics (Figure 1).

Filler Particle Size

The most common classification system for composites considers the distribution and average filler particle size.[14,15] Based on the classification systems by Lutz and Phillips in 1983, composites can be classified into: macrofilled, microfilled, hybrids, modern hybrids, and nanofilled composites. With filler particle sizes ranging from about 10 to 50 μm, conventional or macrofilled composites were mechanically strong, but difficult to polish and to retain a favorable color match. Later, amorphous spherical silica of approximately 40–50 nm were incorporated to formulate "microfill" composites, which were more esthetic but showed significantly more fractures and a significant loss of anatomical shape due to wear. To address the important issue of long-term esthetics and mechanical properties, the particle size of conventional composites was reduced to produce what was ultimately called the hybrid composites. Hybrid composites can be considered among the best materials for posterior restorations. The new generation of hybrid composites comprises about a couple of micrometers or less filler particles of glass

Table I. Resin Composites Composition

Formulation	Main components and instances	Function
Resin matrix	Methyl acrylate monomers, like bis-GMA, UDMA, HEMA, TEGDMA, and so forth	Many materials have certain strength, plasticity, and curing characteristic
Inorganic filler	Filler particles like colloidal silica, quartz, silica glass containing barium, strontium, and zirconium, ceramic power, and so forth	Improve materials' compressive strength, elastic modulus, hardness and wear resistance, and so forth
Coupling agent	Organic silane like MPTS, and so forth	Chemically link the filler and resin matrix to achieve bonding of these two phases
Initiating systems	Photoinitiator system like CQ, PPD, BPO, and so forth	Polymerization promoting systems, initiate polymerization reaction
Others	Colorant like metallic oxide, stabilizer system, curing-promoting agents like catalyst, and so forth	Auxiliary enhancement effect

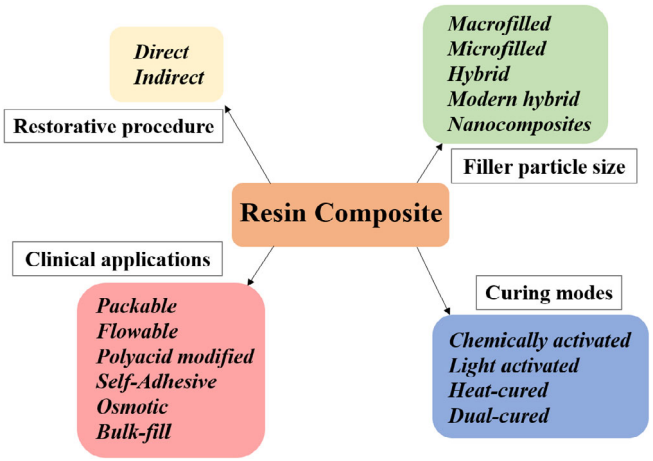

Figure 1. The classification of resin composites. [Color figure can be viewed at wileyonlinelibrary.com]

and small amounts of colloidal silica particles (10–50 μm and 10–50 nm), with lower shrinkage, improved polishing performance, and better esthetics.[4] Compared to the limited range of shades of the early macrofilled and microfilled composites, modern hybrid composites (0.5–1.0 μm and 10–50 nm) are ideal for esthetic restorations of anterior teeth, because of a variety of different shades with tailored opacity and translucency.[16] Furthermore, with the rise of nanotechnology, nanofilled composites came into being with inorganic phases of characteristic dimensions in the range of 10–100 nm.[14] Because of the increased filler loading and reduced amount of resin matrix, nanofilled composites thereby reduced the polymerization shrinkage while providing esthetics and strength.[17]

Curing Modes

Most dental composites cure via radical chain polymerization in which monomers are converted to polymers. Various types of initiation systems and activation methods can be used to generate a free radical that initiates the polymerization process. They have significant effects on the kinetics of polymerization and the polymer structure, thus affecting various properties of the composites.[18] According to the initiation systems or cure mechanisms, composites can be divided into chemically initiated/self-cured, light-activated, heat-cured, or dual-cured composites.[19]

For self-cured/chemical-cured composites, when the powder-liquid or paste-paste materials are mixed together, polymerization is initiated by and oxidation–reduction initiator system at room temperature. Self-cure composites are composed of a catalyst part containing benzoyl peroxide(BPO) and a base part containing tertiary amine. The tertiary amines, *N*,*N*-dimethyl-*p*-toludine (DMPT) and *N*,*N*-dihydroxyethyl-*p*-toluidine, are also usually used in self-cure composites. When the two parts are mixed, the radicals formed by the reaction of the BPO and amine are able to react with the monomers that would become polymerization later. However, most self-cure composites are now used as resin-based luting cements or core materials, rather than direct restorations.[19] In contrast, the light-cured method uses ultraviolet (UV) or visible light to promote initiation reaction of resin polymerization. Light-activated composites undergo polymerization by irradiation via a blue-light-curing unit in the wavelength range of 410–500 nm.[12] These days, almost all dental restorative composites contain CQ/amine complex initiation, visible light-cured, which is safer compared with UV-curing systems, and one-component systems. The mechanism of the CQ/amine system is different from that of the BPO/amine chemical initiation system. When exposed to visible light, the CQ undergoes excitation first by energy absorption. The CQ molecule in the excited triplet state rapidly interacts via electron transfer with an amine to constitute an excited complex, and then extracts hydrogen from the amine to make up a new compound. The excitation energy is transferred to the amine molecule during the process, the α-amino-alkyl radical is more efficient at initiating polymerization than the relatively inactive CQ-ketyl radical.[20] Heat-cured composites are polymerized by extra-oral cure involving heat that might help reduce the quantity of remaining double bonds resulting in improvements in mechanical properties. In addition, there still exists another kind of dual-cured composites with combination of various curing systems to form polymers.[19,20] They are widely used for cementing endodontic posts and fabricating core buildups (Figure 2).

Components Restorative Procedure

Dental composite restorative materials can be divided into direct and indirect resin composites. Direct composites are widely used by dentists to restore damaged anterior teeth in a clinical setting, which can be challenging and are considered technique sensitive, while indirect composites are cured outside the mouth or involve the laboratory preparation.[21] Since direct composites were introduced initially as dental restorative materials, it has presented excellent optical and mechanical properties along with patients' growing demand for dental composites for nearly 50 years.[22] Indirect composites are introduced by Touati and Mörmann for posterior inlays and onlays in the 1980s, which offer an esthetic alternative for large posterior restorations.[23] The indirect composite is very interesting and pretty advanced. For example, indirect composites dramatically reduce polymerization shrinkage due to better and more complete curing methods, including a variety of combinations of heat, pressure (in a nitrogen atmosphere, water, etc.), light, and vacuum, outside the oral cavity. However, they were also faced with a lot of deficiency such as high incidence of bulk fracture, marginal microleakage, and adhesive failure when first introduced.[24] While many improvements occurred with the development of new second-generation indirect composites, which have been studied and proved that the mechanical properties and wear resistance could be

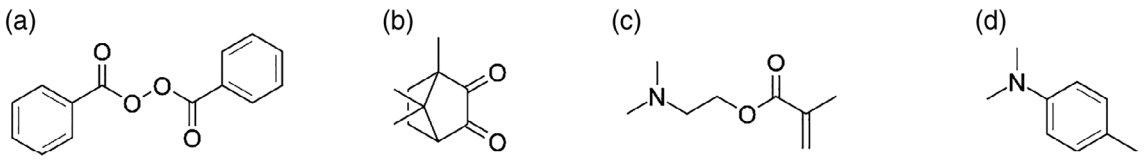

Figure 2. The chemical structures of monomers and initiators (a) BPO; (b) CQ; (c) DMAEMA; and (d) DMPT.

improved by increasing the filler load, and the polymerization shrinkage could be reduced by reducing the organic resin matrix.[25]

Clinical Applications and Functional Requirements

Packable Resin Composites. Packable composites are common dental resin composite that are widely used for posterior restorations as an alternative to amalgam. Introduced in the late 1990s, packable composites are stiffer, less sticky, and easier for clinicians to handle than conventional composites. These materials are characterized by easier shaping ability and better operation performance than that of conventional composites.[26] When packed or forced with an instrument, they can form good proximal contact points. However, some research studies have demonstrated that their mechanical or physical properties are not superior to those of conventional composites.[27] Longer term clinical performance evaluations of packable composites are still needed.

Flowable Composites. Flowable composites have attracted wide attention since their appearance in dentistry for the first time in 1996.[28] They are conventional composites with the decreased filler loading from 50–70% (volume) to 37–53% (volume).[29] Because the viscosity is decreased and the flowability is increased, flowable composites can enter the small cracks or corners of a cavity by an injection syringe, thus simplifying the handling operation and shortened the operating time. However, flowable composites generally showed higher shrinkage than traditional nonflowable composites, as it is one of the key material properties related to clinical applications.

The first-generation flowable composites were used only as cavity lining agent and pit and fissure sealant, due to their lower filler content and lower elastic modulus. Along with improvement in resin matrix and filler systems, newer generation flowable composites have a wider range of applications including preventative resin restorations, minimally invasive Class II restorations, Class V abfraction lesions, and so on.[29] However, because of the decreased filler content and reduced physical properties and wear resistance, the flowable composites are recommended only be used in low-stress bearing areas restorations, not for posterior restorations on occlusal surfaces. The flexural strength, wear, or other mechanical properties have been evaluated in studies, concluding that flowable composites have lower mechanical strength compared to conventional resin composites.[29]

Compomers (Polyacid Modified Resin Composites). Compomers refer to polyacid-modified resin composites, which represent a combination of composites and glass ionomer cements (polyalkenoate acid and glass components). Due to their ease of use and release of fluoride, compomers were rapidly accepted by the dental profession. However, they also face several issues such as brittleness, low strength, long curing time, and water sensitivity, which have limited their applications. The shrinkage of compomers is a little bit less or similar with flowable composite (e.g., total shrinkage strain for compomer systems varies from 2.59 to 3.34%, whereas the flowable composite resin showed a value of 3.50%), so that compomers are usually used as lining or base. Compomers have a dual-setting mechanism, of which the dominant setting reaction is the resinous photopolymerization, but the acid–alkali reaction also plays an important role after the material absorbs water *in vivo*.[4] The clinical performance of compomers has been evaluated.[30] Compomers showed acceptable clinical performance after 24 months clinical evaluation in Class II restorations of primary teeth under evaluation categories like marginal discoloration, anatomic form, secondary caries, and so forth.[31]

Self-Adhesive Composites. Self-adhesive composites combine the benefits of adhesive and composite technology, bringing novel horizons to restorative techniques, as they are claimed to bond to tooth tissue without a separate adhesive.[32] These materials contain self-etching and/ or self-adhesive monomers that are able to etch enamel and dentin surfaces or chemically bond to hydroxyapatite, such as the 4-methacryloxyethyl trimellitic acid, glycerol phosphate dimethacrylate monomers, 10-MDP monomer, and so on.[33] Though several *in vitro* studies on physical properties, bond strength, and marginal sealing potential have been published,[34–36] clinical research studies ongoing on these products are still limited.[33,37] These laboratory studies revealed that there are still many controversies about bonding effectiveness and mechanical properties so far, and some studies reported that self-adhesive composites show limited interaction with dentin or enamel.[33,38] Consequently, critical investigation and clinical assessments are needed for self-adhesive composites.

Infiltration Resins. Recently, a caries infiltration technique was introduced along with low-viscosity light-curing resins called infiltration resins, which can infiltrate the subsurface caries lesions by capillary action.[39] Infiltration resins have been claimed as a promising approach for the treatment of uncavitated caries lesions such as "caries-like lesion," "white spot lesion," or "enamel demineralization."[40] The resin infiltration is based on the hydrochloric acid erosion of the lesion surface and posterior infiltration of a low-viscosity resin into the intercrystalline spaces of hypocalcified or demineralized enamel, and this alters the refractive index of the porous enamel, so this kind of resin contains less filler, which lead to a lower wear resisitance.[41] Studies have shown that the infiltration of caries lesions with infiltration resins could inhibit further demineralization *in vitro* and prevent caries lesion progression *in situ*.[42] The application of infiltration resins on interproximal caries lesions was also shown to be a novel treatment option for interproximal caries.[43] However, the evidence for clinical recommendation of this technique is not strong, and further randomized controlled trial studies should be conducted.[41]

Bulk-Fill Resin Composites. Classically, dental resin composite should be cured separately, and every layer should less than 4 mm.[44] Bulk-fill composites were developed to improve the time-consuming incremental cavity-filling technique.[45] The newly bulk-fill composites, allowing incremental filling of up to 4 mm in thickness, have been shown to guarantee sufficient polymerization at this depth due to high color translucency of these materials increasing the depth of cure and more innovative initiator system shortening the light-curing time.[46,47] The composition of bulk-fill resin composites depend on their strategies, a lower filler content makes the resin more flowable.[44] Apart from facilitating the placement of deep composite restorations, bulk-fill composites also were found to provide better cervical interfacial quality and similar marginal performance during bulk-fill versus

incremental-fill Class II composite restorations.[48,49] As more attention were applied to the bulk-fill composites, exploring the clinical benefits of bulk-fill composites seems to be significant.[44]

MATERIAL PROPERTIES

Polymerization Shrinkage

Polymerization shrinkage, the dimensional changes that develop during curing, is one of the major deficiencies of composites. During polymerization, the monomer molecules of the matrix are converted into a three-dimensional crosslinked network structure, accompanied by a closer packing of the molecules, leading to volumetric contraction. This shrinkage is typically on the order of 1.5–5% for dental composites, along with shrinkage stresses in the composite and at the tooth-composite bonded interface.[25] Previous studies proved that most of the shrinkage occurs in early hours, and the reported volumetric shrinkage of composites ranged from 2 to 6% at 30 min.[50] The polymerization shrinkage can weaken the bond between the tooth structure and the restoration, which can sometimes lead to gaps at the restoration margins, discoloration, postoperative sensitivity, recurrent caries, fracture of the restorations, and restoration failure.[51,52]

To eliminate or minimize the polymerization shrinkage of composites, many efforts evolving associated with low-shrink monomers, light curing code, fillers, filling techniques in the manipulation of restorative procedures, have been put into developing nonshrinking or ideally improved composite materials.[53] The introduction of various newer monomer systems (such as siloranes) may help overcome the problem of shrinkage stress through a photocationic ring-opening reaction.[54] The reported silorane-based composites exhibited lower polymerization shrinkage than the methacrylate-based ones, due to the ring-opening oxirane moieties which are responsible for the physical properties and low shrinkage.[55] Though fillers are widely utilized to enhance the mechanical properties of composites, polymerization stress is likely to increase due to the higher elastic modulus achieved by the addition of fillers. Composites containing lower levels of inorganic filler particles have been evaluated that produced high levels of polymerization stress during restorations. Apart from many efforts on modification of the composite, clinical methods are developed such as the control of curing light irradiance, flowable resin liner application, and incremental layering techniques; however, no method has been shown to be totally effective. By choosing proper composite materials and irradiation conditions (light type, light spectrum, irradiance, time, etc.), combined with good clinical manipulation technique, clinicians try to minimize the shrinkage and associated stresses.[13] Incremental filling techniques were proved to be able to reduce cuspal deflection and C-factor of cavity in direct composite restorations than bulk filling group, result in reducing polymerization shrinkage.[56] While recent studies also showed that the new category of flowable composites allowing the clinician to bulk fill (up to 4.0 mm) a restoration decreased shrinkage stresses generated during polymerization.[44,57]

Wear Resistance

Wear can be defined as a consequence of mechanical interaction between two contacting surfaces, resulting in the progressive loss of materials. The usual underlying processes of wear include abrasion, adhesive effects, fatigue, and corrosive effects due to various chemical reactions, which contribute to wear. Abrasion refers to the physiological movement of hard protrusions on the surface of relative moving objects to achieve occlusal equilibrium through non-masticatory motion when deglutition, occlusion, and chewing. Adhesive effects refer to the material adhesion on the contact surface will be sheared and fractured when stressed, and the dropped fillers will migrate from one surface to another, reducing the friction coefficient. Fatigue wear is caused by cyclic contact stress, which forms cracks on the surface of the material.[58] Corrosive effects are when acidity weakens the forces between surface molecules. It can enhance the process of other wear behaviors.[59] The source of the acid may come from food and oral microorganism[60](Figure 3). Wear resistance of dental composites was one of the major clinical concerns for posterior restorations about a decade ago, while the current composites are fine.[61,62]

The wear resistance of composites is mainly determined by the resin formulation and filler particle distribution.[61] Different shapes and combinations of size of filler particles are associated with the wear performance of composites. Studies have mentioned that increased loading of filler content may also help enhance the wear resistance of composites. Smaller spherical fillers result in better mechanical strength and higher wear resistance. However, due to the agglomeration of nanometer, it is difficult to add enough fillers, so the researchers found hybrid resin composites. Ayatollahi *et al.*[59] found the mechanical properties and abrasion resistance of the nanofiller resin composites were improved compared with traditional filler resin composites. Lawson and Burgess[61] suggested that the content of the nanofiller should be controlled between 25 and 50% to achieve better mechanical properties of the material, while higher than 50% of the filler will coagulate and lead to fracture defects. The degree of cure of the polymer matrix also has been shown to have significant effect on intraoral wear resistance of composites. Thus, adequate and sufficient light should be

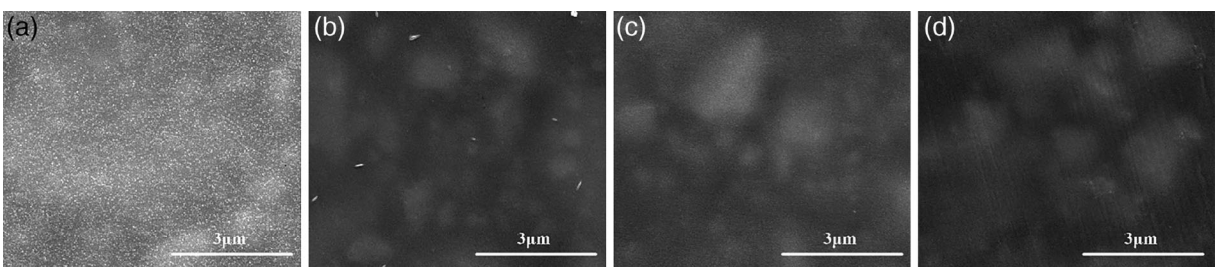

Figure 3. Representative scanning electron microscopy images of dental resin composites surfaces before and after aging treatments. (a) without any aging treatments; (b) resin composites were immersed in water; (c) resin composites were immersed in salivary; and (d) *S. mutans* suspensions.

provided by the clinicians to reduce the wear of composites. Jing *et al.*[63] initiated the polymerization reaction of a new type of resin composite with bisphenol-S-bis(3-methacrylato-2-hydroxypropyl) ether (bis-SGMA) as the matrix monomer through the photosensitive initiator system of CQ, DMAEMA, and $C_{12}H_{10}F_6IP$. The results showed that the polymerization conversion rate, polymerization degree, and mechanical properties of the resin composite were improved.

Some researchers also found that porous and fibrous nanofillers can better increase the combination between the fillers and the matrix, enhance the wear resistance, hydrolysis resistance of the resin, and improve the polishing performance.[64] Wang *et al.*[65] found that the application of nanometer and silanization technology can reduce the size of the filler, improve the resin conversion, and enhance the binding force between the filler and the matrix.

STRATEGIES TO ADDRESS CHALLENGES FACING DENTAL COMPOSITES

Restoration Fractures

Many studies indicate that bulk fracture is one of the main reasons for composite restoration failure, and researchers have implemented various techniques to increase the flexure strength and fracture toughness.[66] Filler size and composition in composites have been related to fracture toughness.[67] One study showed that hybrid and nanofilled composites have significantly higher fracture toughness (KIC) than microfilled composites.[68] In general, KIC values were higher in the more heavily filled resins. *In vitro* studies have shown that higher filler levels enhance the fracture toughness of restoratives.[69] Reinforcement of composites with ceramic whiskers fused with silica particles improved the mechanical properties. Recently, self-healing composites were developed with capability of regaining the load-bearing capability after fracture, indicating the promise for tooth cavity restorations to combat bulk fracture.[70–73]

Secondary Caries

Secondary/recurrent caries refers to dental decay/lesion occurring at the margin between the existing restoration and tooth tissues, which is one of the primary reasons for clinical failure and restoration replacement.[74]

Several studies have focused on the factors affecting secondary caries, from microleakage, filling materials types, to biofilms.[75] Large numbers of experimental and clinical research studies have focused on various improvement methods. For example, anticaries composite filling materials have been an active research area, and antibacterial and remineralizing dental composites have been developed to inhibit oral biofilms and combat secondary caries.[76–80]

Antibacterial Dental Composites. ***Releasing type antibacterial composites.*** Composites containing releasing antibacterial ingredients can exert a strong antibacterial effect. Research studies on releasing antibacterial ingredients in recent years mainly include fluoride, chlorhexidine, nanosilver, and so forth[3,81] However, with the release of antimicrobial agents, the antibacterial effect will reduce gradually, and voids/porosity will appear in the composite which will negatively influence the mechanical properties of the composite.

Calcium fluoride (CaF_2) nanoparticles have been incorporated into composite as inorganic fillers. Nano-CaF_2 composites can exert long-term releasing of fluoride and calcium ions, which are advantageous to inhibit tooth demineralization, promote mineralization. The fluoride ions not only adjust the balance of mineralization of tooth hard tissues, but also possess bacteriostasis to combat secondary caries.[82] Kulshrestha *et al.*[83] studied the effect of CaF_2 nanoparticles on bacteria *in vitro* and *in vivo*. The results showed that CaF_2 nanoparticles had strong antibacterial activity against *Streptococcus mutans*: biofilm formation was reduced by nearly 90%, bacterial acid was reduced, and extracellular polysaccharide production was reduced. At low pH, fluorine ions combine with hydrogen ions to form hydrofluoric acid that penetrates the bacterial membrane. Hydrofluoric acid dissociation in bacteria inhibits enolase and ATPase.[84] In addition, fluorine also has adverse effects on the metabolism and adhesion of bacterial cells.[85] In the presence of CaF_2, the microbial adhesion to biofilm decreased and the sensitivity to acidic environment increased. In addition, CaF_2 nanoparticles inhibit the formation of biofilms due to the large release of fluoride ions and their effects on bacteria, thereby reducing the development of dental caries. Another study demonstrated the application of chlorhexidine in dental composite to inhibit both planktonic bacterial growth and biofilm formation.[86] The cell membrane of bacteria is mainly composed of phospholipid bilayer and protein. Since the phospholipid functional groups in the outer layer of the cell membrane are negatively charged, chlorhexidine as a cationic molecule is prone to interact with the phospholipid molecules on the cell membrane, thus will destroy the cell membrane of bacteria. McLellan *et al.*[87] showed that the bactericidal effect of chlorhexidine was not affected even in the presence of human organic substances. In addition, composites containing silver nanoparticles, which was considered to be a broad-spectrum antibacterial agent, exhibited a potent antibacterial activity.[88,89] Silver nanoparticles will contact with the cell membrane of bacteria and form obvious irregular perforation on the cell membrane, resulting in changes and degradation of the membrane system structure, leading to bacteria death.[90] And other researchers found the antibacterial mechanism of silver nanoparticles might be related to its ability to induce excessive reactive oxygen species (ROS) in cells.[91] Lansdown[92] found silver nanoparticles inhibited the bacteria by blocking DNA replication. The cellulose nanocrystal/zinc oxide (ZnO) nanohybrids on dental resin composites have a positive influence on the mechanical and antibacterial properties of dental resin composites.[93] The antibacterial mechanism of ZnO nanoparticles has been proposed, including nanoparticle internalization leads to cell death,[94] induced oxidative stress, and DNA damage.[95] The most plausible cause is induced oxidative stress. Xu *et al.*[96] have proved the cause of bacterial cell death caused by ROS generated by nano-ZnO interaction.

Nonreleasing antibacterial composites. Quaternary ammonium compounds have broad-spectrum antimicrobial properties against bacteria, fungi, and viruses. Novel polymerizable quaternary ammonium monomers (QAMs) were synthesized and copolymerized in dental resins to offer nonreleasing and long-lasting antibacterial activity. These QAMs include

12-methacryloyloxydodecylpyridinium bromide (MDPB), methacryloxylethyl cetyl ammonium chloride (DMAE-CB), quaternary ammonium polyethylenimine, quaternary ammonium dimethacrylate, QAMs with different alkyl chain lengths including dimethylaminododecyl methacrylate (DMADDM), dimethylaminohexadecyl methacrylate (DMAHDM), and so forth.[97,98]

The general chemical formula of quaternary ammonium salt is ending with a positively charged antibacterial group at one side, and double bond on the other side. After being added into a resin, its double bond can be aggregated with the resin matrix to form a crosslinking structure, therefore it is immobilized in the resin. Its antibacterial mechanism is described as "contact inhibition." Once the positive quaternary amine charge (N^+) contacts the bacterial cell walls, its positive charge can disrupt the negatively charged bacterial cell membranes, leading to bacterium exploding under its osmotic pressure (Figure 4).[99,100]

MDPB was incorporated into composite to effectively inhibit the adhesion and growth of *S. mutans* even after 90 days of water aging.[101] The antibacterial effect of resin-based adhesive containing DMAE-CB against *S. mutans* has been evaluated and it exhibited an inhibitory effect on *S. mutans* growth obviously.[102] Another 3-month-aged study proved that restorative composites containing 1% w/w of octyl-alkylated QA-PEI could totally inhibited *S. mutans* growth, with the alkyl chain lengths playing the significant role on antibacterial activity.[103] Recently, a protein-repellent composite incorporating 2-methacryloyloxyethyl phosphorylcholine (MPC) was developed. The incorporation of MPC into composite at 3% greatly reduced protein adsorption, bacteria attachment, and biofilm CFU, without compromising mechanical properties, which may contribute to reducing secondary caries.[104] Another study used a rat tooth cavity model to evaluate the effects of nanoparticles of amorphous calcium phosphate (NACP) and antibacterial DMADDM on dental pulp, showing that the composite and adhesive containing NACP and DMADDM caused milder pulpal inflammation and

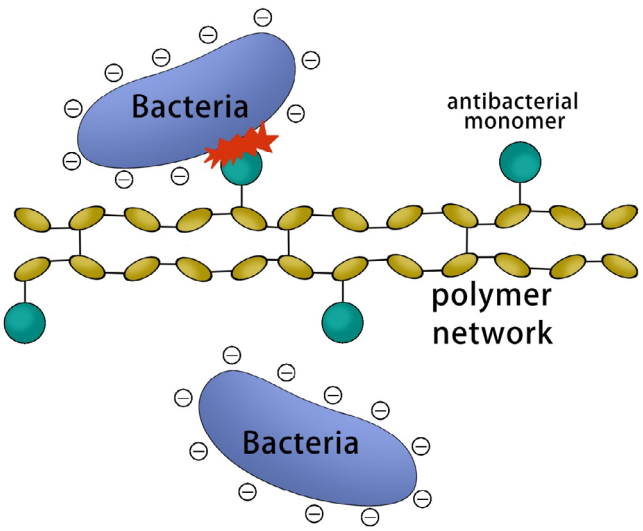

Figure 4. The antibacterial mechanism of QAMs. [Color figure can be viewed at wileyonlinelibrary.com]

generated more tertiary dentin than control.[76] What is more, the new antibacterial monomer DMAHDM showed anti-biofilm properties and modulated the biofilm species composition toward a noncariogenic tendency.[105] Most studies on the assessment of antibacterial restoratives were *in vitro*. Human models *in vivo* and clinical studies are needed to confirm the success of antibacterial restorative application in the future dental clinic.

Remineralizing Dental Composites. To overcome demineralization leading to secondary caries, NACP and nanoparticles of dicalcium phosphate anhydrous (DCPA) have been added into composites. The addition and release of calcium phosphate ions may help remineralize the surrounding dentin to help inhibit secondary caries.[106,107] These therapeutic composites with calcium and phosphate ions have been shown to effectively remineralize enamel and dentin lesions *in vitro*. However, most calcium phosphate composites had relatively lower flexural strength.[77] Hence, the nano-DCPA–whisker composites, with a combination with high strength and Ca and P ion release, may have promise for dental restorations to inhibit caries.[108]

Postoperative Sensitivity

Postoperative hypersensitivity can be defined as pain in a tooth or sensitivity to hot, cold, and sweet stimuli that occurs either transitorily or lasting a relatively long time after restoration.[109] A large number of clinical studies show that postoperative hypersensitivity still remains a concern for resin-based restorations. The main reason related to hypersensitivity lies in polymerization shrinkage, monomer dissolution, and acidic fluid accumulation between the restoration and dentin.[110] Clinical studies on postoperative hypersensitivity focused on the use of cavity lining, material formulations, and bonding systems, but lack a standardized measurement and consistent reporting system for postoperative hypersensitivity.[111]

A previous systematic review and meta-analysis concluded that whether using the self-etch or the etch-and-rinse adhesive strategy for posterior composite restorations had no influence on the risk and intensity of pain or hypersensitivity.[112] Recent studies found that the use of chlorhexidine could significantly decrease immediate postoperative sensitivity and reduce the extent of pain associated with posterior composites restorations.[113]

Biocompatibility

Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific situation or without producing an adverse effect. Good biocompatibility is an important prerequisite for biological materials to be used in living organisms. Current research on the compatibility of dental composites is focused on cytotoxicity, genotoxicity, carcinogenicity, hypersensitivity, and antibacterial effects of components.[114]

Cytotoxicity and genotoxicity of methacrylates have been confirmed in the past several decades.[115] Monomers released from components in the composites, including bis-GMA, HEMA, and TEGDMA, were found to have significant toxic effects on human pulp fibroblasts, human gingival fibroblasts, or immortalized human keratinocytes and could cause gene mutations *in vitro*. Bis-GMA-induced cytotoxicity to dental pulp cells at a concentration higher than 0.075 mM. Bis-GMA (0.1 mM) also stimulated Cyclooxygenase-2 mRNA, protein expression, extracellular regulated

protein kinases phosphorylation, and ROS production as well as PGE2 production in dental pulp cells to affect the vitality of dental pulp.[116] These side effects may potentially contribute to tumorigenesis. [117] Research studies showed that several chemical components like ethylene glycol dimethacrylate and TEGDMA from composites showed growth-stimulating effects on the caries-associated bacteria *Streptococcus sobrinus* and *Lactobacillus acidophilus*. Even some resin biodegradation products can stimulate the growth of *S. mutans* and *Streptococcus salivarius* in a pH-dependent manner.[118]

Therefore, manufacturers have tried to introduce improved and biocompatible materials, and dentists have made effort to employ sufficient light curing intensity, reduce the curing tip distance, and increase the curing time, in order to increase the degree of conversion and minimize the release of uncured monomers.[119–121] Further studies are needed to develop dental resin composites with less leachable components and to synthesize more biocompatible monomers and resin matrices.[122,123]

Longevity

With composites gaining a dominant role in restorative dentistry, their longevity has been evaluated by systematic reviews.[124,125] The major causes of restoration failure are secondary caries and restoration fracture.[126,127] However, beyond that, the long-term durability of composite restorations depends on a number of factors such as mechanical, physical, adhesive, and handling properties of the various composites and adhesive systems.[124,126] The patients' socio-economic factors, individual caries risk and habits such as bruxism, and the oral environment including tooth type and location, also influence the longevity.[128,129] Therefore, to enhance longevity of composite restorations, it is recommended that researchers and clinicians take into consideration the material-, operator-, patient-, and tooth-related factors in future investigations and clinical operations.[130] While current composites are bio-inert and can replace the missing tooth structure, future composites should be bioactive and therapeutic to inhibit caries, modulate biofilms, and protect the surrounding tooth structures, in order to increase the composite restoration longevity.

CONCLUSIONS

This article reviews the historical evolution, current problems, feasible approaches, research hot spots, and advanced technologies on the development of dental composites. With an understanding of the achievements and challenges in the evolution of composites, clinicians can better appreciate both the connections with and the gaps between laboratory research and clinical applications. There is much potential for further improvement by developing enhanced composites with long-term durability. With the development of material science and biomaterials, dental composites with antimicrobial and self-repairing properties, as well as composites for dental hard tissue regeneration will become a reality in clinical applications. Such new composites will contribute to reducing the caries risk, increasing the restoration longevity, providing better dental caries prevention, and improving the oral health and quality of life for mankind.

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AUTHOR CONTRIBUTIONS

M.L., X.P., S.W., X.Z., and L.C. edited and added valuable insights into the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Ferracane, J. L. *Dent. Mater.* **2011**, *27*, 29. https://doi.org/10.1016/j.dental.2010.10.020.
2. Ferracane, J. L. *Dent. Mater.* **2013**, *29*, 51. https://doi.org/10.1016/j.dental.2012.06.013.
3. Cheng, L.; Weir, M. D.; Xu, H. H.; Kraigsley, A. M.; Lin, N. J.; Lin-Gibson, S.; Zhou, X. *Dent. Mater.* **2012**, *28*, 573. https://doi.org/10.1016/j.dental.2012.01.006.
4. Ilie, N.; Hickel, R. *Aust. Dent. J.* **2011**, *56*(Suppl. 1), 59. https://doi.org/10.1111/j.1834-7819.2010.01296.x.
5. Stein, P. S.; Sullivan, J.; Haubenreich, J. E.; Osborne, P. B. *J. Long Term Eff. Med. Implants.* **2005**, *15*, 641.
6. Samuel, S. P.; Li, S.; Mukherjee, I.; Guo, Y.; Patel, A. C.; Baran, G.; Wei, Y. *Dent. Mater.* **2009**, *25*, 296. https://doi.org/10.1016/j.dental.2008.07.012.
7. Drummond, J. L. *J. Dent. Res.* **2008**, *87*, 710.
8. Makvandi, P.; Jamaledin, R.; Jabbari, M.; Nikfarjam, N.; Borzacchiello, A. *Dent. Mater.* **2018**, *34*, 851. https://doi.org/10.1016/j.dental.2018.03.014.
9. Sevkusic, M.; Schuster, L.; Rothmund, L.; Dettinger, K.; Maier, M.; Hickel, R.; Van Landhuyt, K. L.; Durner, J.; Hogg, C.; Reichl, F. X. *Dent. Mater.* **2014**, *30*, 619. https://doi.org/10.1016/j.dental.2014.02.022.
10. Randolph, L. D.; Palin, W. M.; Bebelman, S.; Devaux, J.; Gallez, B.; Leloup, G.; Leprince, J. G. *Dent. Mater.* **2014**, *30*, 594. https://doi.org/10.1016/j.dental.2014.02.023.
11. Rebholz-Zaribaf, N.; Özcan, M. *J. Adhes. Sci. Technol.* **2016**, *31*, 1408. https://doi.org/10.1080/01694243.2016.1259727.
12. Santini, A.; Gallegos, I. T.; Felix, C. M. *Prim. Dent. J.* **2013**, *2*, 30.
13. Leprince, J. G.; Palin, W. M.; Hadis, M. A.; Devaux, J.; Leloup, G. *Dent. Mater.* **2013**, *29*, 139. https://doi.org/10.1016/j.dental.2012.11.005.
14. Randolph, L. D.; Palin, W. M.; Leloup, G.; Leprince, J. G. *Dent. Mater.* **2016**, *32*, 1586. https://doi.org/10.1016/j.dental.2016.09.034.

15. Wang, R.; Habib, E.; Zhu, X. X. *Dent. Mater.* **2018**, *34*, 1014. https://doi.org/10.1016/j.dental.2018.03.022.
16. Heintze, S. D.; Rousson, V.; Hickel, R. *Dent. Mater.* **2015**, *31*, 481. https://doi.org/10.1016/j.dental.2015.01.015.
17. Chen, M. H. *J. Dent. Res.* **2010**, *89*, 549. https://doi.org/10.1177/0022034510363765.
18. Feng, L.; Suh, B. I. *J. Biomed. Mater. Res. B Appl. Biomater.* **2006**, *76*, 196. https://doi.org/10.1002/jbm.b.30355.
19. Kwon, T. Y.; Bagheri, R.; Kim, Y. K.; Kim, K. H.; Burrow, M. F. *J. Investig. Clin. Dent.* **2012**, *3*, 3. https://doi.org/10.1111/j.2041-1626.2012.00114.x.
20. Ilie, N.; Simon, A. *Clin. Oral Investig.* **2012**, *16*, 505. https://doi.org/10.1007/s00784-011-0527-x.
21. Lee, Y. K.; Yu, B.; Lim, H. N.; Lim, J. I. *J. Appl. Oral Sci.* **2011**, *19*, 154.
22. Mackenzie, L.; Parmar, D.; Shortall, A. C.; Burke, F. J. *Dent Update*. **2013**, *40*, 297 301–292, 305–298 passim.
23. Leinfelder, K. F. *Compend. Contin. Educ. Dent.* **2005**, *26*, 495 quiz 504, 527.
24. Nandini, S. *J. Conserv. Dent.* **2010**, *13*, 184. https://doi.org/10.4103/0972-0707.73377.
25. Ilie, N.; Hilton, T. J.; Heintze, S. D.; Hickel, R.; Watts, D. C.; Silikas, N.; Stansbury, J. W.; Cadenaro, M.; Ferracane, J. L. *Dent. Mater.* **2017**, *33*, 880. https://doi.org/10.1016/j.dental.2017.04.013.
26. Cobb, D. S.; MacGregor, K. M.; Vargas, M. A.; Denehy, G. E. *J. Am. Dent. Assoc.* **2000**, *131*, 1610.
27. Kiremitci, A.; Alpaslan, T.; Gurgan, S. *Oper. Dent.* **2009**, *34*, 11. https://doi.org/10.2341/08-48.
28. Hervas-Garcia, A.; Martinez-Lozano, M. A.; Cabanes-Vila, J.; Barjau-Escribano, A.; Fos-Galve, P. *Med. Oral Patol. Oral Cir. Bucal.* **2006**, *11*, E215.
29. Baroudi, K.; Rodrigues, J. C. *J. Clin. Diagn. Res.* **2015**, *9*, ZE18. https://doi.org/10.7860/JCDR/2015/12294.6129.
30. Kramer, N.; Garcia-Godoy, F.; Reinelt, C.; Frankenberger, R. *Am. J. Dent.* **2006**, *19*, 61.
31. Ermis, R. B. *Quintessence Int.* **2002**, *33*, 542.
32. Naga, A. A. E.; Yousef, M.; Ramadan, R.; Fayez Bahgat, S.; Alshawwa, L. *Clin. Cosm. Investig. Dent.* **2015**, *7*, 55. https://doi.org/10.2147/CCIDE.S80462.
33. Peterson, J.; Rizk, M.; Hoch, M.; Wiegand, A. *Odontology*. **2018**, *106*, 171. https://doi.org/10.1007/s10266-017-0324-3.
34. Poitevin, A.; De Munck, J.; Van Ende, A.; Suyama, Y.; Mine, A.; Peumans, M.; Van Meerbeek, B. *Dent. Mater.* **2013**, *29*, 221. https://doi.org/10.1016/j.dental.2012.10.001.
35. Bektas, O. O.; Eren, D.; Akin, E. G.; Akin, H. *Acta Odontol. Scand.* **2013**, *71*, 541. https://doi.org/10.3109/00016357.2012.696697.
36. Sadeghi, M. *Dent. Res. J.* **2012**, *9*, 460.
37. Pinna, R.; Bortone, A.; Sotgiu, G.; Dore, S.; Usai, P.; Milia, E. *Clin. Oral Investig.* **2015**, *19*, 1663. https://doi.org/10.1007/s00784-014-1390-3.
38. Mine, A.; De Munck, J.; Van Ende, A.; Poitevin, A.; Matsumoto, M.; Yoshida, Y.; Kuboki, T.; Van Landuyt, K. L.; Yatani, H.; Van Meerbeek, B. *Dent. Mater.* **2017**, *33*, 209. https://doi.org/10.1016/j.dental.2016.11.010.
39. Kugel, G.; Arsenault, P.; Papas, A. *Compend. Contin. Educ. Dent.* **2009**, 30 Spec No 3, 1 quiz 11-12.
40. Kantovitz, K. R.; Pascon, F. M.; Nobre-dos-Santos, M.; Puppin-Rontani, R. M. *Oral Health Prev. Dent.* **2010**, *8*, 295.
41. Borges, A. B.; Caneppele, T. M.; Masterson, D.; Maia, L. C. *J. Dent.* **2017**, *56*, 11. https://doi.org/10.1016/j.jdent.2016.10.010.
42. Paris, S.; Meyer-Lueckel, H. *Caries Res.* **2010**, *44*, 47. https://doi.org/10.1159/000275917.
43. Phark, J. H.; Duarte, S., Jr.; Meyer-Lueckel, H.; Paris, S. *Compend. Contin. Educ. Dent.* **2009**, 30 Spec No 3, 13.
44. Van Ende, A.; De Munck, J.; Lise, D. P.; Van Meerbeek, B. *J. Adhes. Dent.* **2017**, *19*, 95. https://doi.org/10.3290/j.jad.a38141.
45. Kim, R. J.; Kim, Y. J.; Choi, N. S.; Lee, I. B. *J. Dent.* **2015**, *43*, 430. https://doi.org/10.1016/j.jdent.2015.02.002.
46. Zorzin, J.; Maier, E.; Harre, S.; Fey, T.; Belli, R.; Lohbauer, U.; Petschelt, A.; Taschner, M. *Dent. Mater.* **2015**, *31*, 293. https://doi.org/10.1016/j.dental.2014.12.010.
47. Orłowski, M.; Tarczydło, B.; Chałas, R. *Sci. World J.* **2015**, *2015*, 701262. https://doi.org/10.1155/2015/701262.
48. Al-Harbi, F.; Kaisarly, D.; Michna, A.; ArRejaie, A.; Bader, D.; El Gezawi, M. *Oper. Dent.* **2015**, *40*, 622. https://doi.org/10.2341/14-152-l.
49. Al-Harbi, F.; Kaisarly, D.; Bader, D.; El Gezawi, M. *Oper. Dent.* **2015**, *41*, 146. https://doi.org/10.2341/14-306-l.
50. Kleverlaan, C. J.; Feilzer, A. J. *Dent. Mater.* **2005**, *21*, 1150. https://doi.org/10.1016/j.dental.2005.02.004.
51. Ferracane, J. L.; Hilton, T. J. *Dent. Mater.* **2015**, *32*(1), 1. https://doi.org/10.1016/j.dental.2015.06.020.
52. Soares, C. J.; Faria, E. S. A. L.; Rodrigues, M. P.; Vilela, A. B. F.; Pfeifer, C. S.; Tantbirojn, D.; Versluis, A. *Braz. Oral Res.* **2017**, *31*, e62. https://doi.org/10.1590/1807-3107BOR-2017.vol31.0062.
53. Fu, J.; Liu, W.; Hao, Z.; Wu, X.; Yin, J.; Panjiyar, A.; Liu, X.; Shen, J.; Wang, H. *Int. J. Mol. Sci.* **2014**, *15*, 2400. https://doi.org/10.3390/ijms15022400.
54. Porto, I. C. C. D. M.; de Aguiar, F. H. B.; Brandt, W. C.; Liporoni, P. C. S. *J. Dent.* **2013**, *41*, 732. https://doi.org/10.1016/j.jdent.2013.05.012.
55. Son, S. A.; Roh, H. M.; Hur, B.; Kwon, Y. H.; Park, J. K. *Restor. Dent. Endod.* **2014**, *39*, 310. https://doi.org/10.5395/rde.2014.39.4.310.
56. Park, J.; Chang, J.; Ferracane, J.; Lee, I. B. *Dent. Mater.* **2008**, *24*, 1501. https://doi.org/10.1016/j.dental.2008.03.013.
57. Conte, N. R., Jr.; Goodchild, J. H. *Compend. Contin. Educ. Dent.* **2013**, 34 Spec No 4, 1 quiz 7.
58. Garcia-Godoy, F.; Frankenberger, R.; Lohbauer, U.; Feilzer, A. J.; Kramer, N. *J. Biomed. Mater. Res. B Appl. Biomater.* **2012**, *100*, 903. https://doi.org/10.1002/jbm.b.32651.

59. Ayatollahi, M. R.; Yahya, M. Y.; Karimzadeh, A.; Nikkhooyifar, M.; Ayob, A. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2015**, *54*, 69. https://doi.org/10.1016/j.msec.2015.05.004.
60. Zhou, X.; Wang, S.; Peng, X.; Hu, Y.; Ren, B.; Li, M.; Hao, L.; Feng, M.; Cheng, L.; Zhou, X. *J. Mech. Behav. Biomed. Mater.* **2018**, *80*, 42. https://doi.org/10.1016/j.jmbbm.2018.01.023.
61. Lawson, N. C.; Burgess, J. O. *J. Biomed. Mater. Res. B Appl. Biomater.* **2015**, *103*, 424. https://doi.org/10.1002/jbm.b.33212.
62. Lazaridou, D.; Belli, R.; Petschelt, A.; Lohbauer, U. *Clin. Oral Investig.* **2015**, *19*, 1485. https://doi.org/10.1007/s00784-014-1373-4.
63. Jing, F.; Fang, J.; Xu, H.; Ji, B.; Liu, X. *J. Wuhan Univ. Technol.* **2011**, *26*, 236.
64. Passos, S. P.; Torrealba, Y.; Major, P.; Linke, B.; Flores-Mir, C.; Nychka, J. A. *J. Prosthodont.* **2014**, *23*, 593. https://doi.org/10.1111/jopr.12167.
65. Wang, R.; Bao, S.; Liu, F.; Jiang, X.; Zhang, Q.; Sun, B.; Zhu, M. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2013**, *33*, 4759. https://doi.org/10.1016/j.msec.2013.07.039.
66. Ilie, N.; Hickel, R.; Valceanu, A. S.; Huth, K. C. *Clin. Oral Investig.* **2012**, *16*, 489. https://doi.org/10.1007/s00784-011-0525-z.
67. Elbishari, H.; Silikas, N.; Satterthwaite, J. *Dent. Mater. J.* **2012**, *31*, 523.
68. Watanabe, H.; Khera, S. C.; Vargas, M. A.; Qian, F. *Dent. Mater.* **2008**, *24*, 418. https://doi.org/10.1016/j.dental.2007.06.018.
69. Lohbauer, U.; Belli, R.; Ferracane, J. L. *J. Dent. Res.* **2013**, *92*, 584. https://doi.org/10.1177/0022034513490734.
70. Wu, J.; Weir, M. D.; Melo, M. A.; Xu, H. H. *J. Dent.* **2015**, *43*, 317. https://doi.org/10.1016/j.jdent.2015.01.009.
71. Li, Q.; Siddaramaiah; Kim, N. H.; Hui, D.; Lee, J. H. *Compos. Part B: Eng.* **2013**, *55*, 79. https://doi.org/10.1016/j.compositesb.2013.06.006.
72. Yuan, L.; Huang, S.; Gu, A.; Liang, G.; Chen, F.; Hu, Y.; Nutt, S. *Compos. Sci. Technol.* **2013**, *87*, 111. https://doi.org/10.1016/j.compscitech.2013.08.005.
73. Huyang, G.; Debertin, A. E.; Sun, J. *Mater. Des.* **2016**, *94*, 295. https://doi.org/10.1016/j.matdes.2016.01.046.
74. Pereira-Cenci, T.; Cenci, M. S.; Fedorowicz, Z.; Azevedo, M. *Cochrane Database Syst. Rev.* **2013**, *12*, CD007819. https://doi.org/10.1002/14651858.CD007819.pub3.
75. Jokstad, A. *Dent. Mater.* **2016**, *32*, 11. https://doi.org/10.1016/j.dental.2015.09.006.
76. Li, F.; Wang, P.; Weir, M. D.; Fouad, A. F.; Xu, H. H. *Acta Biomater.* **2014**, *10*, 2804. https://doi.org/10.1016/j.actbio.2014.02.033.
77. Mehdawi, I. M.; Pratten, J.; Spratt, D. A.; Knowles, J. C.; Young, A. M. *Dent. Mater.* **2013**, *29*, 473. https://doi.org/10.1016/j.dental.2013.01.010.
78. Farrugia, C.; Camilleri, J. *Dent. Mater.* **2015**, *31*, e89. https://doi.org/10.1016/j.dental.2014.12.005.
79. Cheng, L.; Weir, M. D.; Zhang, K.; Wu, E. J.; Xu, S. M.; Zhou, X.; Xu, H. H. *Dent. Mater.* **2012**, *28*, 853. https://doi.org/10.1016/j.dental.2012.04.024.
80. Brouwer, F.; Askar, H.; Paris, S.; Schwendicke, F. *J. Dent. Res.* **2016**, *95*, 143. https://doi.org/10.1177/0022034515611041.
81. Ten Cate, J. M. *J. Dent. Res.* **2012**, *91*, 813. https://doi.org/10.1177/0022034512455032.
82. Xu, H. H.; Weir, M. D.; Sun, L.; Moreau, J. L.; Takagi, S.; Chow, L. C.; Antonucci, J. M. *J. Dent. Res.* **2010**, *89*, 19. https://doi.org/10.1177/0022034509351969.
83. Kulshrestha, S.; Khan, S.; Hasan, S.; Khan, M. E.; Misba, L.; Khan, A. U. *Appl. Microbiol. Biotechnol.* **2016**, *100*, 1901. https://doi.org/10.1007/s00253-015-7154-4.
84. Wiegand, A.; Buchalla, W.; Attin, T. *Dent. Mater.* **2007**, *23*, 343. https://doi.org/10.1016/j.dental.2006.01.022.
85. Naorungroj, S.; Wei, H. H.; Arnold, R. R.; Swift, E. J., Jr.; Walter, R. *J. Dent.* **2010**, *38*, 387. https://doi.org/10.1016/j.jdent.2010.01.005.
86. Zhang, J. F.; Wu, R.; Fan, Y.; Liao, S.; Wang, Y.; Wen, Z. T.; Xu, X. *J. Dent. Res.* **2014**, *93*, 1283. https://doi.org/10.1177/0022034514555143.
87. McLellan, E.; Townsend, R.; Parsons, H. K. *J. Infect.* **2008**, *57*, 459. https://doi.org/10.1016/j.jinf.2008.08.012.
88. Kasraei, S.; Sami, L.; Hendi, S.; Alikhani, M. Y.; Rezaei-Soufi, L.; Khamverdi, Z. *Restor. Dent. Endod.* **2014**, *39*, 109. https://doi.org/10.5395/rde.2014.39.2.109.
89. Stencel, R.; Kasperski, J.; Pakiela, W.; Mertas, A.; Bobela, E.; Barszczewska-Rybarek, I.; Chladek, G. *Materials*. **2018**, *11*(11), 2173. https://doi.org/10.3390/ma11112173 Materials 2018, 11, 1031, 11.
90. Sondi, I.; Salopek-Sondi, B. *J. Colloid Interface Sci.* **2004**, *275*, 177. https://doi.org/10.1016/j.jcis.2004.02.012.
91. Kim, S.; Ryu, D. Y. *J. Appl. Toxicol.* **2013**, *33*, 78. https://doi.org/10.1002/jat.2792.
92. Lansdown, A. B. *Br. J. Nurs.* **2004**, *13*, S6. https://doi.org/10.12968/bjon.2004.13.Sup1.12535.
93. Wang, Y.; Hua, H.; Li, W.; Wang, R.; Jiang, X.; Zhu, M. *J. Dent.* **2018**, *80*, 23. https://doi.org/10.1016/j.jdent.2018.11.002.
94. Padmavathy, N.; Vijayaraghavan, R. *Sci. Technol. Adv. Mater.* **2008**, *9*, 035004. https://doi.org/10.1088/1468-6996/9/3/035004.
95. Lakshmi Prasanna, V.; Vijayaraghavan, R. *Langmuir*. **2015**, *31*, 9155. https://doi.org/10.1021/acs.langmuir.5b02266.
96. Xu, X.; Chen, D.; Yi, Z.; Jiang, M.; Wang, L.; Zhou, Z.; Fan, X.; Wang, Y.; Hui, D. *Langmuir*. **2013**, *29*, 5573. https://doi.org/10.1021/la400378t.
97. Cheng, L.; Weir, M. D.; Zhang, K.; Xu, S. M.; Chen, Q.; Zhou, X.; Xu, H. H. *J. Dent. Res.* **2012**, *91*, 460. https://doi.org/10.1177/0022034512440579.
98. Li, F.; Weir, M. D.; Chen, J.; Xu, H. H. *Dent. Mater.* **2014**, *30*, 433. https://doi.org/10.1016/j.dental.2014.01.002.

99. Cheng, L.; Zhang, K.; Weir, M. D.; Liu, H.; Zhou, X.; Xu, H. H. *Dent. Mater.* **2013**, *29*, 462. https://doi.org/10.1016/j.dental.2013.01.011.
100. Cheng, L.; Weir, M. D.; Zhang, K.; Arola, D. D.; Zhou, X.; Xu, H. H. *J. Dent.* **2013**, *41*, 345. https://doi.org/10.1016/j.jdent.2013.01.004.
101. Imazato, S.; Tarumi, H.; Kato, S.; Ebisu, S. *J. Dent.* **1999**, *27*, 279.
102. Xiao, Y.-H.; Ma, S.; Chen, J.-H.; Chai, Z.-G.; Li, F.; Wang, Y.-J. *J. Biomed. Mater. Res. B Appl. Biomater.* **2009**, *90B*, 813. https://doi.org/10.1002/jbm.b.31350.
103. Yudovin-Farber, I.; Beyth, N.; Weiss, E.; Domb, A. *J. Nanopart. Res.* **2010**, *12*, 591. https://doi.org/10.1007/s11051-009-9628-8.
104. Zhang, N.; Chen, C.; Melo, M. A.; Bai, Y. X.; Cheng, L.; Xu, H. H. *Int. J. Oral Sci.* **2015**, *7*, 103. https://doi.org/10.1038/ijos.2014.77.
105. Wang, H.; Wang, S.; Cheng, L.; Jiang, Y.; Melo, M. A. S.; Weir, M. D.; Oates, T. W.; Zhou, X.; Xu, H. H. K. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *94*, 587. https://doi.org/10.1016/j.msec.2018.10.004.
106. Vanichvatana, S.; Auychai, P. *Int. J. Oral Sci.* **2013**, *5*, 224. https://doi.org/10.1038/ijos.2013.67.
107. Zhang, K.; Zhang, N.; Weir, M. D.; Reynolds, M. A.; Bai, Y.; Xu, H. H. K. *Dent. Clin. N. Am.* **2017**, *61*, 669. https://doi.org/10.1016/j.cden.2017.05.002.
108. Xu, H. H.; Weir, M. D.; Sun, L. *Dent. Mater.* **2007**, *23*, 1482. https://doi.org/10.1016/j.dental.2007.01.002.
109. Berkowitz, G.; Spielman, H.; Matthews, A.; Vena, D.; Craig, R.; Curro, F.; Thompson, V. *Compend. Contin. Educ. Dent.* **2013**, *34*, e44.
110. Auschill, T. M.; Koch, C. A.; Wolkewitz, M.; Hellwig, E.; Arweiler, N. B. *Oper. Dent.* **2009**, *34*, 3. https://doi.org/10.2341/08-7.
111. Strober, B.; Veitz-Keenan, A.; Barna, J. A.; Matthews, A. G.; Vena, D.; Craig, R. G.; Curro, F. A.; Thompson, V. P. *J. Am. Dent. Assoc.* **2013**, *144*, 886.
112. Reis, A.; Dourado Loguercio, A.; Schroeder, M.; Luque-Martinez, I.; Masterson, D.; Cople Maia, L. *Dent. Mater.* **2015**, *31*, 1052. https://doi.org/10.1016/j.dental.2015.06.001.
113. Hajizadeh, H.; Ghavamnasiri, M.; Majidinia, S. *Quintessence Int.* **2013**, *44*, 793. https://doi.org/10.3290/j.qi.a30176.
114. Mallineni, S. K.; Nuvvula, S.; Matinlinna, J. P.; Yiu, C. K.; King, N. M. *J. Investig. Clin. Dent.* **2013**, *4*, 9. https://doi.org/10.1111/j.2041-1626.2012.00140.x.
115. Schweikl, H.; Spagnuolo, G.; Schmalz, G. *J. Dent. Res.* **2006**, *85*, 870.
116. Chang, M. C.; Lin, L. D.; Chan, C. P.; Chang, H. H.; Chen, L. I.; Lin, H. J.; Yeh, H. W.; Tseng, W. Y.; Lin, P. S.; Lin, C. C.; Jeng, J. H. *Biomaterials*. **2009**, *30*, 4070. https://doi.org/10.1016/j.biomaterials.2009.04.034.
117. Kleinsasser, N. H.; Schmid, K.; Sassen, A. W.; Harreus, U. A.; Staudenmaier, R.; Folwaczny, M.; Glas, J.; Reichl, F. X. *Biomaterials*. **2006**, *27*, 1762. https://doi.org/10.1016/j.biomaterials.2005.09.023.
118. Khalichi, P.; Cvitkovitch, D. G.; Santerre, J. P. *Biomaterials*. **2004**, *25*, 5467. https://doi.org/10.1016/j.biomaterials.2003.12.056.
119. Ergun, G.; Egilmez, F.; Cekic-Nagas, I. *Med. Oral Patol. Oral Cir. Bucal*. **2011**, *16*, e252.
120. Sigusch, B. W.; Pflaum, T.; Volpel, A.; Gretsch, K.; Hoy, S.; Watts, D. C.; Jandt, K. D. *Dent. Mater.* **2012**, *28*, 312. https://doi.org/10.1016/j.dental.2011.12.007.
121. Castaneda, E. R.; Silva, L. A.; Gaton-Hernandez, P.; Consolaro, A.; Rodriguez, E. G.; Silva, R. A.; Queiroz, A. M.; Nelson-Filho, P. *Braz. Dent. J.* **2011**, *22*, 105.
122. Lederman, M.; Sharon, E.; Lipovezky-Adler, M.; Smidt, A. *Refuat Hapeh Vehashinayim*. **2015**, *32*, 21 60.
123. Schweikl, H.; Buchalla, W.; Krifka, S. *Dent. Mater.* **2017**, *33*, 514. https://doi.org/10.1016/j.dental.2017.02.006.
124. Kubo, S.; Kawasaki, A.; Hayashi, Y. *Dent. Mater. J.* **2011**, *30*, 374.
125. Ástvaldsdóttir, Á.; Dagerhamn, J.; van Dijken, J. W. V.; Naimi-Akbar, A.; Sandborgh-Englund, G.; Tranæus, S.; Nilsson, M. *J. Dent.* **2015**, *43*, 934. https://doi.org/10.1016/j.jdent.2015.05.001.
126. Moraschini, V.; Fai, C. K.; Alto, R. M.; dos Santos, G. O. *J. Dent.* **2015**, *43*, 1043. https://doi.org/10.1016/j.jdent.2015.06.005.
127. da Veiga, A. M.; Cunha, A. C.; Ferreira, D. M.; da Silva Fidalgo, T. K.; Chianca, T. K.; Reis, K. R.; Maia, L. C. *J. Dent.* **2016**, *54*, 1. https://doi.org/10.1016/j.jdent.2016.08.003.
128. Demarco, F. F.; Correa, M. B.; Cenci, M. S.; Moraes, R. R.; Opdam, N. J. *Dent. Mater.* **2012**, *28*, 87. https://doi.org/10.1016/j.dental.2011.09.003.
129. Opdam, N. J.; van de Sande, F. H.; Bronkhorst, E.; Cenci, M. S.; Bottenberg, P.; Pallesen, U.; Gaengler, P.; Lindberg, A.; Huysmans, M. C.; van Dijken, J. W. *J. Dent. Res.* **2014**, *93*, 943. https://doi.org/10.1177/0022034514544217.
130. Fernandez, E.; Martin, J.; Vildosola, P.; Oliveira Junior, O. B.; Gordan, V.; Mjor, I.; Bersezio, C.; Estay, J.; de Andrade, M. F.; Moncada, G. *J. Dent.* **2015**, *43*, 279. https://doi.org/10.1016/j.jdent.2014.05.015.