THE CURRENT STRATEGIES FOR ENHANCING ANTI-CARIES PROPERTIES OF DENTAL ADHESIVE: A REVIEW

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Abstract

Bacterial microleakage at tooth-restoration interface leading to recurrent infection or secondary caries is the main reason for resin composite restoration failure. The main reason for failure may be the lack of antibacterial and remineralizing properties of dental adhesives. This study reviewed the current strategies used in dental adhesives to enable the anti-caries effects. A total of 65 studies from identified 273 original articles published from May 2015 to May 2020 were included and reviewed. The results revealed that the most common anti-caries strategies were antibacterial strategies (76%) followed by remineralizing strategies (41%), and protein repellent strategies (12%). The most frequently used agents to promote antibacterial, remineralizing, and protein repellent effects were polymerizable quaternary ammonium compounds, nanoparticles of amorphous calcium phosphate, and protein repellent agent (2-methacryloyloxyethyl phosphorylcholine) respectively. The strategies were either single or multi-mode actions. The utilization of the additives at the designated level in the majority of the studies promoted *in vitro* anti-caries actions with no detrimental effect on physical/mechanical properties of the experimental adhesives. This could potentially help prevent secondary caries and increase the longevity of composite restorations when the adhesives are clinically available.

Keywords: Dental adhesives, Remineralization, Antibacterial, Protein repellent, Secondary caries

Introduction

Adhesive restorations such as resin composites with dental adhesives are currently the most commonly used direct dental filling materials to restore the carious cavities. This may be due to its excellent esthetic properties and the materials are suitable for minimally invasive treatments. Additionally, the use of traditional filling such as dental amalgam will be phased down due to Minamata agreement in 2013 to reduce the risk of releasing mercury-containing products to the environment due to the poor management of amalgam waste in dental clinics (Mackey *et al.*, 2014).

Despite the substantial improvement of resin composite and the adhesive systems, the materials

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were susceptible to recurrent caries (secondary caries) which is the most common reason for composite restoration failure (Nedeljkovic *et al.*, 2020). The possible reasons could be the highly sensitive placement techniques or the lack of antibacterial and remineralizing properties of the composites/dental adhesives. This could lead to microleakage at tooth-restoration interfaces resulting in bacterial microleakage (Nedeljkovic *et al.*, 2015), tooth demineralization, and secondary caries. This may ultimately lead to the failure of restoration which requires replacement (Jokstad, 2016).

Antibacterial agents have been incorporated into some commercially available dental adhesives to promote anti-caries properties for the materials. An example product is Clearfil SE Protect (Kuraray, Tokyo, Japan) which contained antibacterial quaternary ammonium methacrylate monomer (12-methacryloxydodecylpyridinium bromide or MDPB) (Cobanoglu *et al.*, 2021). The positively charged ammonium group in MDPB interacted with negatively charged bacterial cell membrane leading to the bacterial cell lysis. The monomers can be polymerized within the polymer network which could reduce the risk of monomer leaching, thereby maintaining physical/mechanical properties of the adhesive layer. The limitation is that the antibacterial action of MDPB required the close contact with bacteria (Mitwalli *et al.*, 2020).

Chlorhexidine (CHX) was also added to a commercial dental adhesive (Peak Universal Bond, ULTRADENT, South Jordan, USA) to inhibit collagenase and promote antibacterial actions. CHX exhibited a wide range of antimicrobial properties and it has been widely used as oral antiseptic. The concern of CHX is the risk of developing the rare but life-threatening hypersensitivity (Pemberton, 2016). Furthermore, the solubility CHX was low, which may limit the release of CHX from the material (Mehdawi *et al.*, 2013). A study demonstrated that the commercial adhesive containing CHX exhibited no superior antibacterial action compared to other conventional adhesives (Boutsiouki *et al.*, 2019).

It can be seen that the clinical effectiveness of the available commercial adhesives containing antibacterial agents are yet to be concluded. Several studies therefore introduced various strategies to enhance anticaries properties for the materials such as the incorporation of alternative antibacterial and remineralizing agents or the use of biomimetic analogue to promote mineral precipitation. Hence, the aim of this literature review was to summarize the current novel strategies used in the dental adhesive to promote anti-caries actions.

Materials and Methods

The search of peer review literature was performed using keywords (" dental adhesive" and "antibacterial") and ("dental adhesive" and "remineralizing"). The search was performed in Medline (PubMed) and Ovid databases to retrieve articles published from May 2015 to May 2020. The duplicated publications were removed by Madeley reference management software. Titles and abstract were read and analyzed to identify the potentially eligible studies. Studies were selected following inclusion and exclusion criteria as follows:

- Dental adhesive with added reactive components to promote antibacterial or remineralizing actions;
- Original experimental based studies (*in vitro* or *in situ*, *in vivo*, or clinical trial).

The exclusion criteria for the review were:

- Literature published in non-English format;
- Literature which involves the development of materials in other purposes apart from dental adhesive such as resin composite, resin cement, glass ionomer cement, orthodontic cement;
- Systematic review or review articles.

The searching and data selection were performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.*, 2009). The data extracted were summarized based on the author, year of publication, strategies used to promote anti-caries effects, reactive agents, and main outcomes. The data were organized using Microsoft Excel version 2019. The study relied on secondary data analysis; hence, ethical approval was not required.

Results and Discussion

The initial search found 273 potentially eligible articles. Then, 32 duplicates articles were removed. The remaining articles were manually screened based on title, abstract, and keywords. After screening, 151 articles were removed and the full text of eligible 90 articles was retrieved for assessment. Then, 13 review articles, 3 non-English articles, and 9 irrelevant articles were excluded. The total of 65 articles were included for the review (Table1).

The common strategies used in the experimental dental adhesives in the included studies were antibacterial strategies (76%) followed by remineralizing strategies (41%), and protein repellent strategies (12%) (Figure 1). These strategies can be used as either single, dual, or multimode of actions. From, the most frequently

used anti-caries actions was single antibacterial action (33 articles), followed by single remineralizing action (15 articles), dual antibacterial/remineralizing actions (8 articles), dual antibacterial/protein repellent actions (3 articles), triple antibacterial/remineralizing/protein repellent actions (3 articles), and dual remineralization/protein repellent actions (1 article).

Table 1. Summary of studies based on the development of dental that can promote antibacterial actions.

No.	Author	Antibacterial strategies	Remineralizing strategies	Protein repellent strategies
1	Andre *et al.* (2015)	Glutaraldehyde, MDPB, CHX	-	-
2	Zhang *et al.* (2015c)	DMAHDM	NACP	MPC
3	Zhang *et al.* (2015d)	DMAHDM	-	MPC
4	Pinto *et al.* (2015)	MDPB	Fluoroaluminosilicate glass	-
5	Zhang *et al.* (2015a)	DMADDM	-	-
6	Sabatini *et al.* (2015)	Polyacrylic acid (PAA) coated with Copper Iodide (CuI)	-	-
7	Centenaro *et al.* (2015)	BTAM	-	-
8	Zhang *et al.* (2015b)	-	NACP	-
9	Toledano *et al.* (2015)	-	ZnO nanoparticles + $ZnCl_2$	-
10	Toledano *et al.* (2016)	-	ZnO nanoparticles + $ZnCl_2$	-
11	Abuna *et al.* (2016)	-	NACP, polyacrylic acid, TMP	-
12	Melo *et al.* (2016)	AgNPs, DMAHDM	NACP	-
13	Deng *et al.* (2016)	Nanoparticulate gold-loaded titanate complexes (nMT)	-	-
14	Zhou *et al.* (2016b)	MAE-DB	-	-
15	Zhou *et al.* (2016a)	DMAHDM	-	-
16	Geraldeli *et al.* (2017)	Arginine (Ar)	-	-
17	Sun *et al.* (2017)	TiO_2 nanoparticle	-	-
18	Degrazia *et al.* (2017)	-	BNNT	-
19	Yu *et al.* (2017)	EGCE and EGCG-3Me	-	-
20	Yang *et al.* (2017)	Quercetin	-	-
21	Collares *et al.* (2017)	METAC	-	-
22	Garcia *et al.* (2017)	-	α-tricalcium phosphate (α-TCP)	-
23	Ge *et al.* (2017)	DMADDM	PAMAM	-
24	Xie *et al.* (2017)	DMAHDM	NACP	MPC
25	Wang *et al.* (2017)	DMADHM	NACP	MPC
26	Priyadarshini *et al.* (2017)	CHX-loaded PLGA-nanoparticles	-	-
27	Schiroky *et al.* (2017)	Triazine compound	-	-
28	Wang *et al.* (2018)	-	PAA-ACP	-
29	Esteban Florez *et al.* (2018)	N_TiO2	-	-
30	Su *et al.* (2018)	Nisin	-	-
31	Krishnamurthy *et al.* (2018)	MDPB	-	-
32	Dutra-Correa *et al.* (2018)	AgNPs	-	-
33	Yan *et al.* (2018)	CHX-encapsulated mesoporous silica	-	-
34	Genari *et al.* (2018)	Indomethacin and triclosan loaded nanoparticles (NC)	-	-
35	Zhang *et al.* (2018)	DMAHDM	-	MPC
36	Wu *et al.* (2018)	DMADDM	-	-
37	Garcia *et al.* (2018)	-	Tantalum oxide (T_2O_5)	-
38	Dos Santos *et al.* (2018)	Glucose- Methacrylate (MA), Sucrose-MA, Chitosan-MA	-	-
39	Jun *et al.* (2018)	-	Cu-doped nanoscale mesoporous bioactive glass (CuBGn)	-
40	Yue *et al.* (2018)	DMAHDM	NACP	-
41	Li *et al.* (2018)	DMAHDM	NACP	-
42	Gou *et al.* (2018)	Quaternary ammonium chloride	-	-
43	Liang *et al.* (2018)	-	NACP, PAMAM	-
44	Al-Qarni *et al.* (2018)	-	NACP	MPC
45	Stewart *et al.* (2018)	OCT-DMSNs	-	-
46	Rezaeian *et al.* (2019)	Thymol	-	-
47	Kuper *et al.* (2019)	MDPB	-	-
48	Eskandarizadeh *et al.* (2019)	Zinc dimethacrylate ionomer (ZDMA)	-	-
49	Li *et al.* (2019)	DMAHDM	NACP	-
50	Tao *et al.* (2019)	NACP	-	-
51	Stenhagen *et al.* (2019)	Methacrylate-chitosan	-	-
52	Ochiai *et al.* (2019)	MDPB	$CaCl_2$	-
53	Demirel *et al.* (2019)	MDPB and S-PRG	-	-
54	Boutsiouki *et al.* (2019)	CHX	-	-
55	Garcia *et al.* (2019)	Tiatania	-	-
56	Delaviz *et al.* (2019)	Ciprofloxacin, Metronidazole	-	-
57	Liang *et al.* (2019)	-	NACP and PAMAM	-
58	Matsuo *et al.* (2019)	Cetylpyridinium chloride (CPC)	-	-
59	Wu *et al.* (2019)	DMAHDM	NACP	-
60	Machado *et al.* (2019)	Pure chitosan, Triclosan-loaded chitosan	-	-
61	Balbinot *et al.* (2020)	-	Sol-gel Niobium (BAGNb)	-
62	Carvalho *et al.* (2020)	-	SrHAp	-
63	Garcia *et al.* (2020)	Quantum dots of tantalum oxide with imidazolium ionic liquid (Ta_2O_5QDs)	-	-
64	Dias *et al.* (2020)	Proanthocyanidin (PA)	-	-
65	Gao *et al.* (2020)	-	NACP, PAMAM	-

Abbreviations: DMAHDM; dimethylaminohexadecyl methacrylate, BTAM; 2-(3-(2H-Benzitriazol-2-YL)-4-Hydroxyphenyl)Ethyl Methacrylate, MAE-DB; methyl ammonium bromide, METAC; 2-(methacryloyloxy)ethyl]trimethylammonium chloride, CHX; chlorhexidine, PLGA; poly-(lactic-co-glycolic acid), N_TiO_2; nitrogen-doped titanium dioxide nanoparticles, MDPB; methacryloy-loxydodecylpyridinium bromide, AgNPs; silver nanoparticles, CPC; Cetylpyridinium chloride, EGCE; epigallocatechin-3-gallate, EGCG-3Me; epigallocatechin-3-O-(3-O-methyl)-gallate, DMADDM; dimethylaminododecyl methacrylate, NACP; nanoparticles of amorphous calcium phosphate, OCT-DMSNs; octenidine dihydrochloride- drug-eluting mesoporous silica nanoparticle, BNNT; boron nitride nanotubes, PAA-ACP; polyacrylic acid stabilized amorphous calcium phosphate, CuBGn; copper-doped bioactive glass nanoparticles, PAMAM; poly (amidoamine) dendrimer, SrHAp; strontium hydroxyapatite nanofiller, MPC; 2-methacryloyloxyethyl phosphorylcholine.

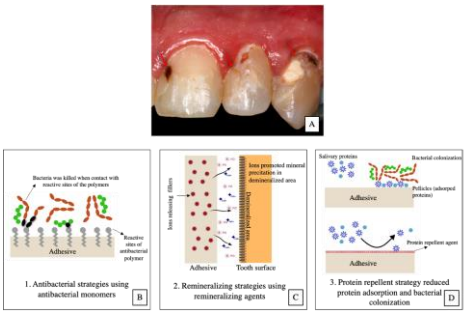

Figure 1. (A) The failure of resin composite restoration due to bacterial microleakage at tooth-restoration interface (credited to Mitwalli *et al*., 2020). The most common strategies to enhance anti-caries properties of dental adhesive at the interface were antibacterial (B), remineralizing (C), and protein repellent strategies (D).

Antibacterial Strategies

Antibacterial monomers

The most commonly used antibacterial agent in the included studies was antibacterial monomers such as dimethacrylate quaternary ammonium monomers (QAMs). The monomer contained the polymerizable methacrylate group so it can be polymerized in the resin matrix. The antibacterial mechanism of QAMs was contact killing via the direct interaction between the negatively charged bacterial cell membrane and the positively charged sites in QAMs resulting in membrane disruption and cytoplasmic leakage of bacteria (Cocco *et al*., 2015; Melo *et al*., 2016) (Figure 1(B)). It was demonstrated that rising the amine charge density increased the antibacterial potency of QAMs (Zhang *et al*., 2015a). Additionally, the increase of alkyl chain length from 5 to 16 units also enhanced the antibacterial action of the monomers (Zhang *et al*., 2015c). Several types of QAMs were available such as quaternary ammonium dimethylaminohexadecyl methacrylate (DMAHDM), dimethylaminododecyl methacrylate (DMADDM), 2-methacryloxylethyl dodecyl methyl ammonium bromide (MAE-DB), Cetylpyridinium chloride (CPC) and (2-(methacryloyloxy) ethyl) trimethylammonium chloride (METAC) (Zhou *et al*., 2016b; Collares *et al*., 2017; Ge *et al*., 2017; Wu *et al*., 2018; Matsuo *et al*., 2019).

DMAHDM is the most frequently used QAMs in the included studies. It was demonstrated that the experimental adhesives containing DMAHDM reduced viability and the growth of bacterial biofilm by almost four order of magnitude compared with the controls (Zhang *et al*., 2015d; Zhou *et al*., 2016a; Ge *et al*., 2017; Xie *et al*., 2017; Li *et al*., 2018). The studies also showed that the experimental adhesive maintained their antibacterial actions even after aging in water for 6-12 months (Wu *et al*., 2018; Zhang *et al*., 2018; Li *et al*., 2019). The possible explanation could be due to the fact that DMAHDM monomers can be polymerized in the resin matrix, thus limiting the loss of antibacterial sites from the materials. Several studies demonstrated that the addition of DMAHDM to the experimental adhesive showed no detrimental effect on monomer conversion (Zhang *et al*., 2015d) and dentin bond strength (Ge *et al*., 2017; Xie *et al*., 2017; Yue *et al*., 2018; Zhang *et al*., 2018). The incorporation of DMAHDM with silver nanoparticles and remineralizing agent (nanoparticle of amorphous calcium phosphate) into dental adhesive enhanced the fatigue resistance of resin-dentin interface upon the acid attack (Melo *et al*., 2016).

Another frequently used QAMs in the adhesives was 12-methacryloxydodecylpyridinium bromide (MDPB). This monomer has been incorporated into the commercial adhesive (Clearfil SE Protect, Kuraray, Tokyo, Japan). The *in vitro* study showed that Clearfil SE Protect exhibited greater antibacterial action compared with convetional adhesives even when it was diluted by 40 times (Krishnamurthy *et al*., 2018).

Antibacterial metallic fillers

Several metallic-based fillers were added to dental adhesives to promote antibacterial actions. The example of fillers included silver nanoparticles (Melo *et al*., 2016; Dutra-Correa *et al*., 2018), titanium dioxide (Sun *et al*., 2017), tantalum oxide particles (Garcia *et al*., 2020), zinc ionomer particles (Eskandarizadeh *et al*., 2019), gold-loaded titanate complexes (Deng *et al*., 2016), and polyacrylic acid-coated with copper iodide (Sabatini *et al*., 2015). The most commonly used metallic filler is silver nanoparticles (AgNPs) which exhibited the wide antimicrobial spectrum through various mechanisms including cell membrane rupture, the formation of reactive oxygen species, and the inhibition DNA replication process (Melo *et al*., 2016; Dutra-Correa *et al*., 2018). The high surface area of AgNPs also facilitate interaction and increasing contact area for killing bacteria. The functionalization of AgNPs also promoted the diffusion and stabilized the dispersion of AgNPs within dental adhesives. The concern of AgNPs is the metallic color which may compromise esthetic outcomes of tooth-colored resin composite restorations.

Antiseptics and Antibiotics

Another example of antibacterial fillers is an antiseptic such as chlorhexidine (CHX) (Andre *et al*., 2015; Boutsiouki *et al*., 2019). CHX is

a cationic biguanide that is widely used in oral antiseptic products. The limitation of CHX is its low solubility in water (0.8 mg/mL at 20°C) which may lead to phase separation or low level of CHX release. Studies demonstrated that the experimental adhesive containing 0.1% CHX or the commercial adhesive containing 0.2% chlorhexidine (Peak Universal Bond, ULTRADENT, Cologne, Germany) provided no significant effect against secondary caries in dentin (Andre *et al*., 2015; Boutsiouki *et al*., 2019).

It was demonstrated that the use of hydrophilic poly-(lactic-co-glycolic acid) or PLGA loaded with CHX enhanced CHX release from the adhesive (Priyadarshini *et al*., 2017). The CHX-loaded PLGA particles exhibited high antibacterial effects for up to 28 days. The increase in hydrophilicity of the particles also promoted the infiltration of the particles into dentinal tubules. Antibiotics such as ciprofloxacin and metronidazole were incorporated into dental adhesives. The adhesive containing oligomer of ciprofloxacin/metronidazole showed comparable fracture toughness to a commercial adhesive (Delaviz *et al*., 2019).

Naturally Derived Compounds

The naturally derived compounds with antibacterial properties were added to an experimental dental adhesive to reduce bacterial colonization. Examples of the compounds are proanthocyanidin (Dias *et al*., 2020), quercetin (Yang *et al*., 2017), arginine (Geraldeli *et al*., 2017), thymols, and chitosan (Machado *et al*., 2019; Stenhagen *et al*., 2019). The addition of the natural-derived agents enhanced antibacterial properties for the adhesives. For example, the adhesive containing 7 wt% arginine inhibited the formation of dental biofilm with no detrimental effect on the dentin bond strength of the adhesive (Geraldeli *et al*., 2017).

Another example is chitosan, which is a cationic molecule synthesized from chitin. The compound can be found in exoskeletal of arthropods. The experimental adhesive containing 5wt% triclosan-loaded chitosan inhibited the formation of biofilm immediately and after aging for 6 months without significantly affect dentin/adhesive interfacial stability (Machado *et al*., 2019).

Remineralizing Strategies

Calcium Phosphate Fillers

The majority of remineralizing agents incorporated in dental adhesive was primarily based on ion-releasing fillers. The most frequently used remineralizing fillers in the included studies is nano amorphous calcium phosphate (NACP). The average diameter of NAPC was 116 nm (Al-Qarni *et al*., 2018; Liang *et al*., 2018; Liang *et al*., 2019; Tao *et al*., 2019; Gao *et al*., 2020) which was much smaller than that of conventional ACP (10-50 μm). The diameter in the nano-scale increased surface area of reactive fillers promoting calcium and phosphate ions release. The released ions are expected to neutralize acids produced by cariogenic bacteria and encourage mineral precipitation in demineralized enamel/dentin (Figure 1(C)).

It was reported that the acidic environment enhanced the release of calcium and phosphate ions from NACP in experimental dental adhesive (Gao *et al*., 2020). The adhesive containing NACP promoted the rapid increase of pH from 4 to greater than 5.5 (Zhang *et al*., 2015c). The released ions encouraged the supersaturated condition for mineral precipitation in dentinal tubules (Liang *et al*., 2019).

Studies showed that the addition of NACP for up to 30 wt% exhibited no detrimental effect on the bond strength of adhesive to enamel (Gao *et al*., 2020) and dentin (Wang *et al*., 2017; Xie *et al*., 2017; Al-Qarni *et al*., 2018). The addition of NACP increased dentin hardness due probably to the increase in mineral precipitation (Tao *et al*., 2019; Gao *et al*., 2020). The release of calcium and phosphate ions was decreased with time. The addition of pyromellitic glycerol dimethacrylate enabled ions re- charge and re-release for the adhesive (Al-Qarni *et al*., 2018). The pyromellitic glycerol dimethacrylate contains carboxylic groups which could chelate and bond with calcium ions from the solution thus encouraging the uptake of calcium ion for the adhesive.

Mineralization Templates

The template for nucleation of mineral apatite is essential to promote remineralizing actions of ions releasing adhesives. An example of the nucleation template is dendrimer which is the highly branched and star-shaped macromolecules. The monomer contained various terminated groups such as carboxylic, hydroxyl, or amine groups that could enhance the absorption of calcium and phosphate ions (Liang *et al*., 2019). An example of dendrimers used in the experimental adhesive was poly amidoamine dendrimer (PAMAM). It was demonstrated that PAMAM (Gao *et al*., 2020) increased the degree of mineralization in demineralized dentin (Liang *et al*., 2019).

Other mineralization templates used in dental adhesives were phosphoprotein biomimetic analogs such as polyacrylic acid (PAA) or sodium trimetaphosphate (TMP). It was expected that anionic groups in PAA could help to recruit the pre-nucleation cluster of minerals for apatite formation. Additionally, TMP served as biomimetic analog of matrix phosphoproteins that bind to collagen fibrils,

thus increasing the precipitation in the collagen network (Abuna *et al*., 2016). The study also demonstrated that the adhesive containing PAA-TMP and NACP promoted mineral deposit in both extra-fibrillar and intra-fibrillar collagen network of demineralized dentin (Abuna *et al*., 2016).

Metallic Remineralizing Fillers

Metallic based fillers such as ZnO nanoparticles and $ZnCl_2$ were incorporated to the dental adhesive to promote mineralization. It was demonstrated that the Zn-containing adhesive affected signaling pathways and stimulated the metabolic effects for enhancing mineralization (Toledano *et al*., 2015). Additionally, Zn-incorporated adhesives encouraged the crystal precipitation in demineralized collagen which could enhance functional recovery of the carious dentin (Toledano *et al*., 2015). Furthermore, Zn^{2+} inhibited collagenase such as matrix metallopeptidase (MMPs), which may help reduce the collagen degradation in the adhesive layer at tooth-resin interface (Toledano *et al*., 2012). However, the study showed that the addition of ZnO or $ZnCl_2$ into dental adhesive reduced dentin bond strength (Toledano *et al*., 2015). It was hypothesized that Zn might interfere with the interaction between adhesive monomer (10-methacryloyloxi-decyl-dihydrogen-phosphate or MDP-10) and calcium ions in tooth minerals (Carrilho *et al*., 2019).

Protein Repellent Strategies

The acquired pellicle on the tooth or restoration surfaces formed by the selective adsorption of proteins in saliva. The adsorbed proteins may promote bacterial attachment and subsequently dental biofilm formation (Fischer and Aparicio, 2021) (Figure 1(D)). Therefore, it is expected that the prevention of protein adsorption on the surfaces may reduce bacterial colonization and bacterial microleakage at tooth-restoration interfaces. The commonly used chemical to enhance protein repellent properties on the surface of dental adhesive was 2-methacryloyloxyethyl phosphorylcholine (MPC), which is the methacrylate monomer containing phospholipid polar group. The addition of MPC promoted hydrophilic properties on the surface of adhesive, thus reducing the adhering of salivary proteins and bacteria (Zhang *et al*., 2015d; Wang *et al*., 2017; Xie *et al*., 2017; Al-Qarni *et al*., 2018; Zhang *et al*., 2018).

The adhesive containing MPC reduced protein adsorbed on the surface by 20 folds compared with the commercial materials (Zhang *et al*., 2015d). The combination of antibacterial monomer (DMAHDM) and MPC also enabled synergistic effects of antibacterial actions for the adhesive (Zhang *et al*., 2015d; Wang *et al*., 2017; Xie *et al*., 2017). It was demonstrated that the protein repellent action of the experimental adhesive was maintained even after aging in water for 6 months (Zhang *et al*., 2018). The addition of MPC alone for up to 7.5 wt% showed minimal effect on dentin shear bond strength after immersion in water for 24 h (Zhang *et al*., 2015d). The combination of 7.5 wt% MCP and 5 wt% DMAHDM however significantly reduced the bond strength of the material (Wang *et al*., 2017).

Conclusions

The current review summarized the current and most common anti-caries strategies used in dental adhesives which were antibacterial, followed by remineralizing, and protein repellent strategies. The main antibacterial agent added in the adhesives was polymerizable quaternary ammonium monomers. For remineralizing action, the nano-amorphous calcium phosphate was commonly used to enhance ion release and promote mineral precipitation in demineralized dentin. Furthermore, protein repellent agent, such as 2-methacryloyloxyethyl phosphorylcholine, was used to promote hydrophilic surface which could decrease protein adsorption on the surface, thus reducing bacterial attachment.

The majority of studies showed that the addition of additives at the designated level exhibited no detrimentally effect on mechanical/ physical properties of the materials. The use of novel adhesives with anti-caries effects could potentially reduce the failure of composite restorations due to secondary caries and increase the longevity of the restorations. Most of the adhesives were tested in a laboratory setting. Therefore, further clinical studies are needed to prove the clinical benefits.

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