Adhesive systems modified with antimicrobial agents: a literature review

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ABSTRACT | Secondary caries is the primary cause of restoration failure. Thus, the development of adhesives with antimicrobial action is an advantageous option for their inhibition. However, this effect must be proven, as well as that the additional benefit does not interfere with material mechanical properties or biocompatibility. We analyzed adhesives with antimicrobial action by microbiological tests, bond strength, degree of conversion, and cytotoxicity. We analyzed 32 studies with commercially available antimicrobial adhesives (Clearfil™ SE Protect Bond/ MDPB, Gluma 2Bond/ glutaraldehyde, Peak Universal Bond/chlorhexidine), and experimental materials or commercial adhesives modified with antimicrobial agents, including materials with quaternary ammonium methacrylate (QAM) [dimethylaminododecyl methacrylate (DMADDM) and dimethylaminohexadecyl methacrylate (DMAHDM)], nanoparticles [silver (NAg), titanium dioxide (TiO_2), zinc oxide (ZnO)], silver or zinc doped bioactive active glass (BAG), titanium, copper iodide, and compounds such as triclosan, quercetin, grape seed extract, among others. The use of antimicrobial agents is a favorable perspective for the functionalization of adhesive systems to inhibit secondary caries. However, more clinical studies need to prove the efficacy of these materials.

DESCRIPTORS | Dental Caries; Dentin-Bonding Agents; Anti-Bacterial Agents.

RESUMO | **Sistemas adesivos modificados com agentes antimicrobianos: uma revisão da literatura** • A cárie secundária é a principal causa de falha da restauração. Assim, o desenvolvimento de adesivos com ação antimicrobiana é uma opção vantajosa para sua inibição. No entanto, esse efeito deve ser comprovado, bem como que o benefício adicional não interfere nas propriedades mecânicas do material ou na biocompatibilidade. Analisamos adesivos com ação antimicrobiana por meio de testes microbiológicos, resistência de união, grau de conversão e citotoxicidade. Analisamos 32 estudos com adesivos antimicrobianos disponíveis comercialmente (Clearfil ™ SE Protect Bond / MDPB, Gluma 2Bond / glutaraldeído, Peak Universal Bond / clorexidina) e materiais experimentais ou adesivos comerciais modificados com agentes antimicrobianos, incluindo materiais com metacrilato de amônio quaternário (QAM) [metacrilato de dimetilaminododecil (DMADDM) e metacrilato de dimetilaminohexadecil (DMAHDM)], nanopartículas [prata (NAg), dióxido de titânio (TiO_2), óxido de zinco (ZnO)], vidro bioativo dopado com prata ou zinco (BAG), titânio, iodo de titânio, cobre e compostos como triclosan, quercetina, extrato de semente de uva, entre outros. O uso de agentes antimicrobianos é uma perspectiva favorável para a funcionalização de sistemas adesivos para inibir a cárie secundária. No entanto, mais estudos clínicos precisam provar a eficácia desses materiais.

DESCRITORES | Cáries dentárias; Agentes de ligação à dentina; Agentes Antibacterianos.

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INTRODUCTION

Secondary caries leads to restoration failure.[1-10] In the oral environment, the restorative composite undergoes polymerization shrinkage,[9,11-14] receives masticatory loads,[10,15] and accumulates biofilm;[8,16] being, therefore, susceptible to marginal failure,[10,12,17,18] adhesive interface degradation,[6,8,10,15,17] and micro-infiltration.[1,10,13,15,19] Likewise, residual bacteria may remain after cavity preparation, thus inducing the formation of recurrent caries.[1,19-21] Moreover, some patients are highly prone to develop caries due to low salivary flow, gingival recession, root exposure, hygiene difficulty, and bacterial plaque accumulation.[2,22] Users of orthodontic appliances are also at high risk, especially around the brackets, where white spot lesions occur.[23-30]

Secondary caries seems to be the main factor for restoration replacement;[4-6,9,16,18,31] the use of adhesive systems with bioactivity is of interest for the prevention of secondary caries due to their antibacterial effect, inhibiting residual bacteria that may have remained upon cavity preparation, or those that may invade the tooth restoration interface.

Several studies have suggested the development of new antimicrobial adhesives or the incorporation of antimicrobial agents in materials already available in the market. Therefore, this literature review seeks to explore the main results of these studies, analyzing the advances and perspectives of antibacterial adhesive dentistry.

REVIEW

Firstly, the composition of the substrates that will be attached to these bonding agents must be addressed to understand the characteristics of the adhesive systems. The enamel is a highly mineralized, prismatic structure, consisting of approximately 96%wt of mineral, organic matter, and water.[32] It is a substrate highly favorable to adhesion due to its homogenous composition.[33,34] The dentin, on the other hand, is composed of approximately 50% organic matter, 30% organic matrix, and 20% water, as far as the volume is concerned.[13,35,36] In morphological terms, the dentin may be peritubular or intertubular. The peritubular dentin is mainly composed of apatite crystals and little organic content; so, it is more mineralized than the intertubular dentin, which, in turn, consists of a collagen matrix, mainly type I, with carbonated apatite crystals.[33] The dentinal tubules orientation and density vary according to their location. Near the amelo-cement junction, there are few tubules of smaller diameter, exhibiting less permeability. Near the pulp, these tubules increase in quantity and amplitude; thus, increasing dentin permeability.[33,36] Besides, extensions of the odontoblasts are inside the tubules, establishing a connection with the pulp. This substrate is then a challenge to Adhesive Dentistry due to its complex constitution.[33] The substrate structure and permeability are directly related to resin-based materials adhesion capability.[36] Higher bond strength values are observed in the superficial dentin; on the other hand, lower bond strength values are found in the deep dentin, which is more permeable.[36]

The adhesive systems aim to form a bond between the substrate (enamel and dentin) and the restorative material, either direct or indirect. Thus, the adhesive will establish the desired adhesion to the substrate by either micromechanical retention or chemical bonding, or both. Initially, they were classified according to their generations. Currently, they are divided considering the type of smear layer treatment and their number of steps, etch-and-rinse (2 or 3 steps), and self-etch systems (1 or 2 steps), respectively.[14,33,37] However, a new class emerged, which allows the combination of both strategies, the "universal adhesives".[37,38]

The basic components of the adhesive system are: conditioning agent, primer and adhesive, in addition to photo initiators, polymerization inhibitors, and inorganic fillers.[33] They can also be modified with antimicrobial agents,[1-12,15-20,22,24,26,28-31,39-44] mineralizing

agents,[2,3,16,22,26,30,45] protein repellent,[2] inhibitors of metalloproteinases,[6,46,47] and even inti-inflammatory agents.[5] The understanding of the function of each system component and their careful use, respecting their indications, will be essential for adhesion success.

In the etch-and-rinse systems, the conditioning agent is generally 37% phosphoric acid, which aims to demineralize both enamel and dentin and create microporosities,[14,37] which will favor the micromechanical retention. Moreover, the acid increases the enamel surface energy, favors the wetting of resinous monomers,[33] and exposes the network of dentin collagen.[37]

The primer consists of hydrophilic monomers, mainly 2-hydroxy-ethyl methacrylate (HEMA), associated with a solvent, which may be water, acetone, or ethanol.[14,37] It establishes the bond between the exposed collagen, which is hydrophilic, with the resinous matrix of the adhesive, which is hydrophobic.[33] It should also keep the collagen network expanded and displace the excess water so that the monomers can infiltrate the substrate.[33,37]

Self-etch systems contain the HEMA, solvent, and acidic monomers [10-methacryloyloxydecyl phosphate (10-MDP), 4-methacryloyloxyethyl trimethyl (4-MET), and methacryloyloxy-ethyl (phenyl-P)]. Acidic monomers promote conditioning, infiltrate the substrate and have the ability to bind to the calcium of the hydroxyapatite chemically.[33,35-37]

The adhesives are composed of hydrophobic monomers such as the bisphenol glycidyl methacrylate (Bis-GMA), ethylene glycol dimethacrylate (TEGDMA), urethane dimethacrylate (UDMA), among others that establish a primary bond to HEMA, and on the other side, bind to the resin matrix of the restorative composite.[33] Adhesion requires inorganic tooth material replacement by a polymeric material, incorporating the adhesive resin into the substrate and forming the hybrid layer.[14,33,36,37,48]

Etch-and-rinse adhesives can be divided into three or two-step types. Those of three steps consist of acid conditioning, primer, and bonding application,[14,37,49] which is considered the gold standard adhesion technique.[32] By separating the stages of different components with different mechanisms of action, one step can benefit the most from the others.[14,33] On the other hand, two-step adhesives include the application of acid etching, followed by a single-bottled primer/bonding, which binds hydrophilic, hydrophobic, and solvent components in one step.[14,33,36,37,49]

In etch-and-rinse adhesives, some water remains after acid etching and washing. Regarding the enamel, drying it to obtain an opaque and whitish appearance is an ideal condition for adhesion.[33] However, dentin should remain slightly moist after etch and rinse due to its constitution. This issue is very subjective and makes the technique extremely sensitive, since removing water results in collagen fibers collapse and resinous monomers penetration difficulty.[13,37] On the other hand, excess water in dentin solubilizes the monomers, hindering their penetration in the interfibrillar spaces and impairing their conversion degree.[13,32,34]

The two steps self-etch adhesives, in turn, consist of acidic primer, followed by bond application, whereas in the single-step type, acid, primer, and bonding are applied at once.[14,33,37,49] These systems are further subdivided into categories according to their pH and depth of interaction with dentin. Ultra-soft self-etching (pH > 2.5) presents hybrid layer (HL) depth of 0.2-0.5 μm; the moderate ones (pH~2), approximately 0.5-1 μm HL depth; intermediate (pH 1-2), and HL of 1-2 μm depth; and strong (pH≤1) at a ≥0.5 μm penetration depth.[38,48] According to the "adhesion-decalcification" concept, when a moderate pH system is used, ionic bonds show more stability due to the association of resinous monomers with the calcium salt; therefore, a hydrolytically durable joint is established.[48] However, when using a strong pH-adhesive, the ionic bonds are not stable, leading to ion release,

consequent tooth decalcification and, finally, adhesive interface weakening.[48]

In self-etching adhesives, there is no washing stage, so the subjectivity regarding the amount of moisture left in the dentin is eliminated in these systems. Moreover, the reduction in the steps simplifies the adhesion process and makes these adhesives less sensitive to the technique.[14,48] These systems condition and promote adhesion, so that the smear layer is incorporated into the hybrid layer, reducing the risk of incomplete monomer penetration in the substrate and the presence of voids at the interface, and also reducing the chance of postoperative sensitivity.[14,32,33,48,50] Finally, the functional monomers may chemically interact with the dentin; therefore, in addition to a micromechanical adhesion, a chemical bond is established with the substrate.[33,34,48] However, they do not work very well on the enamel due to their highly mineralized nature. Thus, whenever the enamel is involved, their conditioning with phosphoric acid, followed by washing, is recommended for adhesion improvement.[34]

The last and most recent category of adhesive systems is called "universal". Through a multi-mode proposal to further facilitate clinical routine, the operator can choose to use that material according to the etch-and-rinse technique or self-etch.[34,38,51] But, whenever the preparation involves the enamel, the selective enamel conditioning is still recommended.[34,38,51] Given the versatility of such materials, literature often questions whether old problems of Adhesive Dentistry have been solved, such as problems related to metalloproteinase (MMPs) and cathepsin-mediated degradation of collagen or the presence of nano-infiltration, which promotes the hydrolytic degradation of the hybrid layer.[38,50]

Adhesive Dentistry also expects the new materials to have additional benefits over what they are originally intended, leading to therapeutic action. However, such benefits must be promoted without reducing the material mechanical properties and biocompatibility. Thus, in the last years, several studies have been developed to favor the antimicrobial action of adhesives in order to inhibit secondary caries that could compromise the adhesive interface durability.[1-12,15-20,22,24,26,28-31,39-44]

Caries disease remains the main reason for restorations failure, requiring its subsequent replacement.[2,4,9,16,18,19,52,53] One mechanism by which caries can affect the durability of restorations is related to biofilm accumulation on resinous restorative materials.[8,16,52] Therefore, the microbial colonization begins from the acquired film (protein layer from the saliva), forming the oral biofilm.[2,52] The bacteria use dietary carbohydrates for their metabolism and produce acids that lead to pH reduction and teeth demineralization.[5,9,15,16,19,26,52] When this process occurs in a previously restored interface, it receives the denomination of caries adjacent to the restoration or secondary caries.[9,52]

Many researchers develop new antimicrobial adhesives, or modify the materials available in the market with the addition of antimicrobial agents as a resort to secondary caries inhibiting mechanisms.[1-12,15-20,22,24,26,28-31,39-44] Thus, the addition of benefit with potential to increase restoration longevity is desired.[16,52]

In this context, nanotechnology has been used in caries prevention. Nanoparticles (<100 nm) are synthesized to optimize the properties of the materials by increasing the surface area, chemical reactivity, and biological activity.[15,52,54,55] One of the classic examples is the use of silver nanoparticles (NAg)[24,39,45,56] of antibacterial, antifungal, and antiviral action.[40,52]

NAg mechanism of action seems to be based on the action of positively charged ionic silver, which in contact with the negatively charged bacterial cell, promotes an osmotic alteration and causes the bacterial membrane rupture, resulting in cell death.[52,54] Moreover, silver ions are suggested to

inactivate vital bacterial enzymes and inactivate DNA ability to replicate, resulting in bacterial death.[52,54,55]

NAg synthesis techniques include reduction of the silver salt to produce silver nanoparticles (NAg) directly in methacrylate monomers, such as 2-terbutylamino ethyl methacrylate (TBAEMA), which are then mixed with adhesive monomers.[15,52,55] This procedure eliminates the need to incorporate the nanoparticles stabilized with different components in the adhesive, which can form agglomerates and causes the bacterial agent to be trapped in the polymer matrix. Finally, this technique prevents NAg from being released from the material, which would jeopardize its antibacterial effect and the mechanical properties of the material.[52,55]

Furthermore, there is a class of antibacterial monomers, based on ammonium quaternary methacrylates (QAMs), such as 12-methacryloyloxydodecylpyridinium bromide (MDPB),[12,17,20,27,42,44] the first commercially available antibacterial monomer (Clearfil SE Protect, Kuraray),[57,58] methacryloxyethyl cetyl dimethyl ammonium chloride (DMAE-CB) [53], dimethylaminododecyl methacrylate (DMADDM),[1,3,4,7,16,19] dimethylaminohexadecyl methacrylate (DMAHDM),[2,4,15,22] 2-methacryloxy-ethyl dodecyl methyl ammonium bromide (MAE-DB),[10] 2-methacryloxyethyl hexadecyl methyl ammonium (MAE-HB)[29], and poly (dimethylaminoethyl) methacrylate-co-octyldimethyl ammonium ethyl methacrylate bromide-co-methyl methacrylate-co-butyl,[20] among others. These antibacterial monomers copolymerize with the monomers present in the adhesive system; thus, they have a mechanism of action by contact and do not lose their effectiveness, since they are incorporated in the polymeric matrix.[15]

Other antibacterial strategies incorporated into dental biomaterials include titanium dioxide (TiO_2),[24] zinc oxide (ZnO),[24] bio-active glass (BAG) doped with Ag_2O or ZNO,[26] silver methacrylate (Ag),[40] di-n-butildimetacrilatetin (Sn),[40] nanoparticulate with titanate metal complex (nMT),[43] polyacrylic acid copper iodine (PAA-CuI),[17] arginine,[9] nisin peptides,[18] [2 (methacryloyloxy) ethyl] trimethylammonium chloride (METAC or MADQUAT)[28,41], 2- [3-2H-benzotriazol-2yl) -4-hydroxyphenyl] ethyl methacrylate (BTAM),[11] epigallocatechim-3-gallate (EGCG),[8] epigallocatechim-3-O- (3-O-methyl) -galate (EGCG-3Me),[8] 1,3,5-triacryloylhexahydro-1,3,5-triazine (triazine)[30,31], glutaraldehyde,[12,44] chlorhexidine (CHX),[12,44] nanocapsules of triclosan,[5] quercetin, [6] natural essential oils.[59]

The use of antimicrobial agents pre-treating the dentin before adhesive procedures are poly (ε-prolactone) nanocapsules loaded with chlorhexidine (nano PCL/ CHX),[47] nanoparticles of poly (lactic-co-glycolic acid) loaded with chlorhexidine (nano PLGA-CHX),[46] and grape seed extract (e-GSE).[60]

RESULTS

We used the PUBMED database to obtain articles from 2014 to 2019, using the keywords: dental adhesives AND antibacterial and dental adhesives AND antimicrobial. Literature reviews, systematic reviews, case series, editorials, studies without a suitable control group, articles that evaluated the effect of antibacterial agents in dental materials other than adhesives or isolated were excluded. Thirty-four studies of adhesives containing antimicrobial agents were selected. Table 1 shows commercial adhesives and their respective manufacturers and composition. The main results of the studies are described in Table 2.

Table 1 | Commercial dental adhesives addressed in the study, with their respective manufacturers, composition, classification, and antimicrobial agent

Commercial adhesive	Manufacturer	Composition	Classification	Antimicrobial agent
Adper Single Bond 2	3M	Bis-GMA, HEMA, polyalkanoic acid copolymer, photo initiators, ethanol, water.[8]	Two-step etch-and-rinse	–
All-Bond 2™	Bisco	Primer A: 50-75% acetone, 10-30% ethanol, 1-5% NTG-GMA sodium. Primer B: Ethanol, acetone, 2-hydroxyethyl methacrylate, 3,4,3 ‘, 4-biphenyltetracarboxylic anhydride (Source: Bisco Data Sheet).[61]	Three-step etch-and-rinse	–
Clearfil™ SE Bond	Kuraray	Primer: 2-hydroxyethyl methacrylate, dihydrogen 10-methacryloyloxydecyl phosphate, hydrophilic aliphatic dimethacrylate, di-camphorquinone, water, accelerators, dyes, others. Bond: Bisphenol A diglycidyl methacrylate, 2-hydroxyethyl methacrylate, dihydrogen 10-methacryloyloxylate, hydrophobic aliphatic methacrylate, colloidal silica, di-camphorquinone, initiators, accelerators, others.[44]	Two-step self-etch	–
Clearfil™ SE Protect Bond	Kuraray	Primer: 2-hydroxyethyl methacrylate, dihydrogen 10-methacryloyloxydecyl phosphate, 12-methacryloyloxydodecylpyridinium bromide (MDPB), hydrophilic aliphatic dimethacrylate, water, initiators, accelerators, colorants, others. Bond: Bisphenol A diglycidyl methacrylate, 2-hydroxyethyl methacrylate, sodium fluoride, dihydrogen 10-methacryloyloxylate, hydrophobic aliphatic methacrylate, colloidal silica, di-camphorquinone, initiators, accelerators, others.[44]	Two-step self-etch	MDPB
Gluma 2Bond	Heraeus Kulzer	Ethanol, 2-hydroxy-methyl methacrylate, poly (acrylic acid oligo-methacrylic acid), 4-methacryloxyethyltrimellitic acid anhydrate, glutaradeide, amorphous silica.[44]	Two-step etch-and-rinse	Glutaraldehyde
Gluma Comfort Bond	Heraeus Kulzer	Ethanol, 2-hydroxyethyl methacrylate, poly (acrylic acid oligo-methacrylic acid), 4-methacryloxyethyl trimeric acid anhydrate.[44]	Two-step etch-and-rinse	–
Optibond Solo Plus	Kerr	Bis-GMA, HEMA, GPDM, ethanol, barium aluminum borosilicate glass, silicon dioxide, sodium hexafluorum silicate, camphorquinone.[17]	Two-step etch-and-rinse	–
Optibond XTR	Kerr	Primer: 30-50% HEMA, 25-35% acetone, 4-15% ethyl alcohol. Bond: 20-30% ethyl alcohol, 47-68% resin alkyl dimethacrylate, 5-15% barium aluminoborosilicate glass, 3-10% silicon dioxide, 0.5-3% sodium hexafluorosilicate.[17]	Two-step self-etch	–
Peak LC Bond	Ultradent	2-hydroxyethyl methacrylate, methacrylic acid, ethyl-4-dimethylamino benzoate, ethyl alcohol.[44]	Two-step etch-and-rinse	–
Peak Universal Bond	Ultradent	Ethyl alcohol, 2-hydroxyethyl methacrylate, methacrylic acid, 0.2% chlorhexidine diacetate.[44]	Universal	Chlorhexidine
Prime & Bond NT	Dentsply	30% methacrylates, 10% methyl methacrylate, 60% acetone.[22]	Two-step etch-and-rinse	–
Scotchbond™ Multi-Purpose (SBMP)	3M	Primer: 35-45% HEMA, 10-20% of an acrylic and itacomic acid copolymer, 40-50% water. Bond: 60-70% BisGMA, 30-40% HEMA, tertiary amine and photo initiator.[62]	Three-step etch-and-rinse	–
Transbond™ XT	3M	Primer: 40-55% Bisphenol A diglycidyl ether dimethacrylate (BISGMA), 45-55% triethylene glycol dimethacrylate, triphenylantimoni, 4- (dimethylamine) benzene ethanol, dl-camphorquinone, hydroquinone. Adhesive: 70-80% silane treated quartz, 10-20% bisphenol A diglycidyl ether dimethacrylate (BISGMA), 5-10% bisphenol A bis (2-hydroxyethyl ether) dimethacrylate, silane-treated silica, diphenyl iodonium hexafluorophosphate (Source: 3M Data Sheet).[63]	Three-step etch-and-rinse	–
XP Bond	Dentsply	TCB resin, PENTA, UDMA, TEGDMA, HEMA, butylated benzenediol, ethyl-4-dimethylaminobenzoate, camphorquinone, amorphous silica, t-butanol.[17]	Two-step etch-and-rinse	–

Table 2 | Characteristics of the studies

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
Chen et al., 2014[16]	DMADDM	Scotchbond™ Multi-Purpose with 5% DMADDM in the primer and 5% DMADDM in the adhesive, and NACP at concentrations of 0%, 10%, 20%, 30% or 40%.	microcosm biofilm model	The addition of antibacterial and remineralizing agents provided bond strength values similar to control, but decreased metabolic activity, lactic acid production and colony-forming units (CFU) of the biofilm.
	–	Scotchbond™ Multi-Purpose (negative control)		
Li et al., 2014[3]	DMADDM	Scotchbond™ Multi-Purpose with 5% DMADDM in the primer and 5% DMADDM in the adhesive, associated with 5% DMADDM in the composite.	Did not evaluate antibacterial activity	The incorporation of antimicrobial and remineralizing agents into adhesive and composite resulted in mild inflammatory pulp response, and formation of tertiary dentin in rat teeth.
	–	Scotchbond™ Multi-Purpose with 30% NACP in the adhesive and 30% NACP in the composite.		
	–	Scotchbond™ Multi-Purpose (Negative Control)		
Pupo et al., 2014[20]	QAMP	Clearfil™ SE Bond containing 5% QAMP	*Streptococcus mutans*	Adhesives with antimicrobials inhibited the growth of microorganisms, did not affect bond strength and did not interfere with the adhesive conversion degree.
	MDPB	Clearfil™ SE Protect (positive control)	*Lactobacillus casei*	
	–	Clearfil™ SE Bond (Negative Control)	*Actinomyces naeslundii*	
Wang et al., 2014[19]	DMADDM	Clearfil™ SE Bond containing 5% DMADDM	*Streptococcus mutans*	Adhesives with DMADDM reduced the metabolic activity of the biofilm, the production of lactic acid and decreased the bacterial population and exopolysaccharides (EPS) of the biofilm.
		Clearfil™ SE Bond containing 2.5% DMADDM		
	–	Clearfil™ SE Bond (Negative Control)		
André et al., 2015[44]	Glutaraldehyde	Gluma 2Bond	*Stafilococcus aureus*	The incorporation of antimicrobials did not affect bond strength. The bactericidal activity was dependent on the time and type of adhesive.
	–	Gluma Comfort Bond	*Enterococcus faecalis*	
	MDPB	Clearfil SE Protect	*Lactobacillus casei*	
	–	Clearfil SE Bond	*Streptococcus mutans*	
	Chlorhexidine	Peak Universal Bond	*Porfiromonas gingivalis*	
	–	Peak LC Bond	*Prevotella intermedia*	
			Prevotella nigrescens	
			Fusobacterium nucleatum	
Centenaro et al., 2015[11]	BTAM	Experimental adhesive system + 1% of BTAM	*Streptococcus mutans*	The materials functionalized with BTAM had antimicrobial action similar to the control adhesive, in addition to reducing their degree of conversion.
	-	Experimental adhesive system + 2.5% of BTAM		
		Experimental adhesive system + 5% of BTAM		
		Experimental adhesive system with 50% Bis-GMA, 25% TEGDMA, 25% HEMA; camphorquinone, DMAEMA and diphenyl iodine salt.		

continues...

Table 2 | Continuation

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
Zhang et al., 2015[1]	DMADDM	Clearfil™ SE Bond with 5% of DMADDM	*Streptococcus mutans*	DMADDM promoted antibacterial action and reduced the synthesis of exopolysaccharides – EPS.
		Clearfil™ SE Bond with 2.5% of DMADDM	*Streptococcus gordonii*	
	–	Clearfil™ SE Bond (negative control)	*Streptococcus sanguinis*	
Zhang et al., 2015[2]	DMAHDM	Scotchbond™ Multi Uso with 7.5% MPC and 5% DMAHDM in adhesive, and 0%, 20%, 30% or 40% NACP.	microcosm biofilm model	The addition of protein-repellent, antibacterial and remineralizing agents provided resistance values similar to control, but decreased metabolic activity, lactic acid production and CFU count of the biofilm.
	–	Scotchbond™ Multi Uso (negative control)		
Degrazia et al., 2016[39]	NAg	Transbond XT with 0.11% NAg	*Streptococcus mutans*	The addition of NAg decreased the bacterial count. However, bond strength and degree of conversion of the adhesive increased.
		Transbond XT with 0.18% NAg		
		Transbond XT with 0.33% NAg		
	–	Transbond XT (negative control)		
Deng et al., 2016[43]	nMT	All-Bond 2TM + 10% nMT in primer	Did not evaluate antibacterial activity	The addition of nMT in both the primer and the adhesive did not affect the bond strength or micro-infiltration.
	nMT	All-BondTM + 10% nMT in adhesive		
	-	All-Bond 2TM (negative control)		
Melo et al., 2016[15]	DMAHDM and NAg	Scotchbond™ Multi-Purpose with 5% of DMAHDM and 0.1% NAg + Composite with 5% of DMAHDM, 0.1% NAg and 30% NACP.	microcosm biofilm model	By associating the antimicrobial adhesive and composite, interface had more bacteria with the compromised membrane. There were more viable bacteria compared to the adhesive and composite control.
	–	Scotchbond™ Multi-Purpose + Composite (negative control)		
Reddy et al., 2016[24]	NAg	Transbond XT with 1% NAg	Did not evaluate antibacterial action	There was a decline in bond strength values in groups with addition of antimicrobial agents.
	TiO2	Transbond XT with 1% TiO2		
	ZnO	Transbond XT with 1% ZNO		
	–	Transbond XT (negative control)		
Villat et al., 2016[42]	MDBP	Clearfil™ SE Protect	Did not evaluate antibacterial activity	The clinical study aimed to: 1) compare the effectiveness of complete or partial removal of carious dentin in deep cavities; 2) Compare the use of an antibacterial adhesive system with a conventional one. For both objectives, 1-year clinical success was achieved in the restorations.
	–	Clearfil™ SE Bond (negative control)		

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Table 2 | Continuation

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
Wang et al., 2016[22]	–	Experimental primer with: PMGDM and HEMA (mass ratio of 10:3) and 50% of acetone. Experimental adhesive with: PMGDM, EBPADMA, HEMA and BisGMA (ratio 45/40/10/5) and 30% NACP and 1% of photo-initiator.	*Porphyromonas gingivalis*	Adhesives with antimicrobial addition were effective in combating periodontal and endodontic pathogens.
			Prevotella intermedia	
			Prevotella nigrescens	
	–	Experimental primer + adhesive with 30% NACP	*Aggregatibacter actinomycetemcomitans*	
	DMAHDM	Experimental primer with 5% DMAHDM + adhesive with 5% DMAHDM and 30% NACP	*Fusobacterium nucleatum*	
			Parvimonas micra	
	–	Prime & Bond NT (negative control)	*Enterococcus faecalis*	
			Enterococcus faecium	
Zhou et al., 2016[10]	MAE-DB	Single Bond 2 + 10% MAE-DB	*Streptococcus mutans*	According to the study, increasing the pressure applied to the adhesive dispersion associated with the use of antimicrobial adhesive reduces the progression of secondary caries.
	–	Single Bond 2 (negative control)		
ALGhanem et al., 2017[17]	PAA–CuI	Optibond XTR + 0.1 or 0.5 mg/ml of PAA-CuI	Did not evaluate antibacterial activity	Addition of antimicrobial agents did not affect the tensile strength. For the groups Optibond Solo Plus and XP Bond, cell viability decreased for the two concentrations studied. Resistance decreased after 6 months and 1 year for all groups evaluated.
		Optibond Solo Plus + 0.1 or 0.5 mg/ml of PAA-CuI		
		XP Bond + 0.1 or 0.5 mg/ml of PAA-CuI		
	–	Optibond XTR (negative control)		
		Optibond Solo Plus (negative control)		
		XP Bond (negative control)		
	MDPB	Clearfil™ SE Protect (positive control)		
Altmann et al., 2017[30]	Triazine	Experimental adhesive system + 20%-Triazine + 10 mol% niobium pentoxides	*Streptococcus mutans*	The triazine patch exhibited higher antibacterial activity. In addition, experimental and antimicrobial control adhesives showed a higher degree of conversion than commercial control, however, they reduced immediate bond strength and after aging.
	–	Transbond XT (commercial negative control)		
	–	Experimental adhesive system with 75% Bis-GMA 25% TEGDMA; 1mol% camphorquinone, EDAB and DPIHFP; 5% silica (experimental negative control)		

continues...

Table 2 | Continuation

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
André et al., 2017[12]	Glutaraldehyde	Gluma 2Bond	*Staphylococcus aureus*	The antibacterial action was dependent on the type of adhesive and microorganism tested. There was no difference regarding the resin-dentin interface related to the adhesives with antimicrobials and their correspondents without these agents.
	–	Gluma Comfort Bond	*Enterococcus faecalis*	
	MDPB	Clearfil SE Protect	*Lactobacillus casei*	
	–	Clearfil SE Bond	*Streptococcus mutans*	
	Chlorhexidine	Peak Universal Bond	*Porfiromonas gingivalis*	
	–	Peak LC Bond	*Prevotella intermedia*	
			Prevotella nigrescens	
			Fusobacterium nucleatum	
Collares et al., 2017[41]	METAC	Experimental adhesive system + 1% of METAC	*Streptococcus mutans*	The METAC monomer promoted an anti-microbial action onto the adhesive, apart from increasing its conversion rate.
		Experimental adhesive system + 2.5% of METAC		
		Experimental adhesive system + 5% of METAC		
	–	Experimental adhesive system with 50% BisGMA, 25% TEGDMA, 25% HEMA, camphorquinone, DMAEMA, and diphenyl iodonium salt (negative control)		
Genari et al., 2017[5]	Triclosan	Scotchbond™ Multi-Purpose primer with 2% nanocapsules of indomethacin and triclosan. Adhesive experimental (66/33% BisGMA/Hema, 1mol% photo-initiator) associated with indomethacin and triclosan nanocapsules at 0, 1, 2, 5 or 10%.	*Streptococcus mutans*	The nanocapsule-modified adhesives were biocompatible, showed anti-microbial effect, and did not affect the degree of conversion of the adhesive.
Geraldeli et al., 2017[9]	Arginine	Experimental adhesive system + 5% L-arginine	*Streptococcus mutans*	The addition of 7% of arginine maintained the mechanical properties of the adhesive and inhibited the plaktonic growth of the bacterial strains tested.
		Experimental adhesive system + 7% L-arginine	*Streptococcus gordonii*	
		Experimental adhesive system + 10% L-arginine		
	–	Experimental adhesive system with primer: 15% Bis-EMA, 10% HEMA, 10% UDMA, 10% TEGDMA, 15% water, 40% ethanol; Adhesive: 40% UDMA, 30% TEGDMA, 17% BisEMA, 10% BisGMA, 1.5% DPIHP and 0.5% camphorquinone, 1% amine (negative control).		

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Table 2 | Continuation

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
Han et al., 2017[4]	DMAPM	Clearfil™ SE Bond with 5% DMAPM (CL=3)	*Streptococcus mutans*	The incorporation of different chain lengths (CL) did not change the bond strength of the adhesive. However, from CL = 6 there was a decrease in the metabolic activity and lactic acid production of the biofilm.
	DMAHM	Clearfil™ SE Bond with 5% DMAHM (CL=6)	*Streptococcus gordonii*	
	DMANM	Clearfil™ SE Bond with 5% DMANM (CL=9)	*Streptococcus sanguinis*	
	DMADDM	Clearfil™ SE Bond with 5% DMADDM (CL=12)		
	DMAHDM	Clearfil™ SE Bond with 5% DMAHDM (CL=16)		
	–	Clearfil™ SE Bond (negative control)		
Lee et al., 2017[26]	BAG	Transbond XT + 0.2% or 1% bio-active glass (BAG)	*Streptococcus mutans*	The groups with bioactive glass elevated the resistance values, even in the presence of antimicrobials Ag and Zn. Cell viability, in general, remained close to control. There was a significant increase in antibacterial properties for all test groups.
	BAG and Ag	Transbond XT + 0.2% or 1% bio-active glass (BAG) + 1% Ag2O		
	BAG and Zn	Transbond XT + 0.2% or 1% bio-active glass (BAG) + 5% ZnO		
	–	Transbond XT (negative control)		
Nascimento et al., 2017[28]	MADQUAT	Experimental adhesive system + 5% of MADQUAT	Microcosm biofilm model	Addition of 5% MADQUAT did not affect the bond strength. However, incorporation of the antimicrobial monomer, in the two concentrations evaluated, increased the degree of conversion of the adhesive.
		Experimental adhesive system + 10% of MADQUAT		
	–	Experimental adhesive system with 2-hydroxyethyl methacrylate, Bis-phenol A diglycidyl dimethacrylate, 0.4% dl-camphorquinone, 0.8% tertiary amine, 0.01% inhibitor 2,6-di-tert-butyl-4-methylphenol and 1% diphenyl iodonium hexafluorphate, 30% ethanol (negative control)		
Oz et al., 2017[27]	MDPB	Clearfil™ SE Protect	Did not evaluate antibacterial activity	The *in vivo* study showed that no patch tested reduced the volume and depth of white spot lesions after 8 weeks of evaluation.
	–	Transbond XT (negative control)		
Schinoky et al., 2017[31]	Triazine	Experimental adhesive system + 1% triazine	*Streptococcus mutans*	Triazine exhibited antimicrobial activity, without compromising the degree of conversion of the adhesive.
		Experimental adhesive system + 2.5% triazine		
		Experimental adhesive system + 5% triazine		
	–	Experimental adhesive system with 50% BisGMA, 25% TEGDMA, 25% HEMA, camphorquinone and ethyl 4-dimethylaminobenzoate (negative control)		
Yang et al., 2017[6]	Quercetin	Adper™ Single Bond + 100 µg/ml quercetin	*Streptococcus mutans*	The addition of quercetin decreased the viability of S. mutans at all tested concentrations. Immediate binding strength and conversion degree declined only for the 1000 µg/ml quercetin group.
		Adper™ Single Bond + 500 µg/ml quercetin		
		Adper™ Single Bond + 1000 µg/ml quercetin		
	–	Adper™ Single Bond (negative control)		

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Table 2 | Continuation

Study	Antimicrobial agent	Adhesives	Microorganisms tested	Main results
Yu et al., 2017[8]	EGCG	Adper Single Bond 2 + 200, 400 or 600 µg EGCG	*Streptococcus mutans*	Functionalized adhesives reduced the number of microorganisms did not interfere with the immediate bond strength and promoted adhesion stability after thermocycling.
	EGCG-3Me	Adper Single Bond 2 + 200, 400 or 600 µg EGCG-3Me		
	–	Adper Single Bond 2 (negative control)		
Yu et al., 2017[29]	MAE-HB	Transbond XT + 1% MAE-HB	*Streptococcus mutans*	The monomer incorporated in the commercial adhesive promoted antimicrobial action, without compromising adhesion.
		Transbond XT + 3% MAE-HB		
		Transbond XT + 5% MAE-HB		
	–	Transbond XT (negative control)		
Rubin Cocco et al., 2018[40]	Ag	Experimental adhesive system + 0.5%, 1% or 2% of silver methacrylate (Ag)	Microcosm biofilm model	In general, addition of the antimicrobial agents did not affect the tensile strength and the degree of conversion of the adhesive. However, the groups showed no difference regarding the count of total microorganisms with the addition of antimicrobial agents when compared with the control group.
	Zn	Experimental adhesive system + 0.5%, 1% or 2% of di-n-butildimetacrilatetin (Zn)		
	–	Experimental adhesive system with primer: 30% HEMA, 30% GDMA-P, 20% distilled water and 20% ethanol; Adhesive: 25% HEMA, 50% Bis-GMA, 25% TEGDMA, 0.4 mol% camphorquinone, 1 mol% EDAB and 1 mol% DPI (negative control).		
Su et al., 2018[18]	Nisin	Single Bond 2 + 1% nisin	*Streptococcus mutans*	The addition of nisin in the adhesive system reduced the bacterial count and the metabolic activity of the biofilm. However, it maintained the conversion degree of the patch with antimicrobials, and reduction in bond strength values for the highest nisin concentrations.
		Single Bond 2 + 3% nisin		
		Single Bond 2 + 5% nisin		
	–	Single Bond 2 (negative control)		
Wu et al., 2018[7]	DMADDM	Clearfil™ SE Bond + 5% of DMADDM	*Streptococcus mutans*	After treatment with experimental and experimental adhesive and induction of secondary caries in rats, it was observed that the DMADDM addition group reduced the depth of the lesion and mineral loss in relation to the control.
		Clearfil™ SE Bond (negative control)		
Delaviz et al. 2019[64]	oligomers synthesized from ciprofloxacin (CF) and metronidazole (MN)	Experimental formulation: BisGMA + HEMA + antimicrobial oligomers	*Streptococcus mutans*	Incorporating antibiotics into dental adhesive systems using hydrolysable linkages provides a means to delivery antibiotics at the margins of the tooth and filling material to control bacteria accumulation.

DISCUSSION

We analyzed studies showing that the adhesives presented antibacterial activity without affecting the mechanical properties or compromising their biocompatibility, being promising to inhibit secondary caries. Thirty-two studies with antimicrobial agents in adhesives from 2014 to 2018 were analyzed: 28 studies *in vitro*; 2 studies used animal models, one of which did not evaluate antimicrobial effects, but the pulp inflammatory response,[3] and the other performed restorations on rats with antimicrobial adhesives (DMADDM), and after inducing secondary caries, measured mineral loss and depth of injury;[7] and 2 *in vivo*, one of which was aimed at evaluating the success of restorations after complete or partial removal of carious dentin with the subsequent use of antimicrobial (MDPB) or conventional adhesive,[42] and the other evaluated the demineralization of the enamel after 8 weeks of the brackets cementation with antibacterial and fluoride adhesive (Clearfil Protect Bond).[27] Moreover, some of these studies used experimental adhesives;[9,11,22,28,30,31,40,41] others used commercially available antimicrobial adhesives, such as Clearfil Protect Bond (MDPB),[12,17,20,27,42,44] Gluma 2 Bond (glutaraldehyde),[12,44] and Peak universal bond (chlorhexidine);[12,44] or conventional commercial adhesives combined with antimicrobial agents.[1-8,10,15-20,24,26,29,39,42,43] Therefore, given the diversity of new agents of union with antimicrobial activity, the analysis of the results of these studies requires caution. Hence, well-conducted clinical studies and long-term analysis may validate their use as secondary caries inhibitors.

Different methods to evaluate antibacterial activity are available, such as the diffusion test on agar,[12,18,23,29,39,40,44] biofilm activity measured by (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) (MTT),[4,16,19,22] production of lactic acid,[1,4,16,19] counting of colony forming units (UFC),[1,5,11,16,22,31,40,41] analysis of biofilm exopolysaccharides (EPS) by confocal laser scanning microscopy (MVLC)[1,19] or using a spectrophotometer,[22] minimum inhibitory concentration (ICM),[20] minimum bactericidal concentration (MCB),[20] epifluorescence live/dead test,[2,22] or MVLC,[1,4,6,8,9,16,18,19,29] scanning electron microscopy (SEM),[2,4,8,12,17,19,29] and molecular techniques such as real-time polymerase chain reaction (q-PCR).[1] Many studies have used only *S. mutans* to estimate bacterial activity,[5-8,10,11,18,19,26,29-31,39,41] which is the main etiological agent of dental caries. However, the use of a microcosm biofilm model[2,15,16,28,40] is closer to clinical reality, considering the diversity and complexity of microorganisms present in the oral cavity.[28]

Moreover, using microorganisms in biofilms seems more appropriate than in planktonic form, since planktonic microorganisms are a thousand times more susceptible to antimicrobial action than when they form biofilm.[52] The study that incorporated 7% of arginine into adhesive [9] inhibited the planktonic growth of the strains tested; however, the use of biofilm is the ideal to evaluate the real antimicrobial potential. Among the antimicrobial substances, some are metals such as Ag,[15,24,26,39,40] TiO_2,[24] Zn,[24,26,40] nMT,[43] PAA-CUI;[17] others are part of the quaternary ammonium methacrylate group (QAM) as MDPB,[12,17,20,27,42,44] which was the first antibacterial monomer incorporated into a commercial adhesive, in addition to DMADDM,[1,3,4,7,16,19] DMAHDM,[2,4,15,22] QAMP;[20] and other agents such as glutaraldehyde,[12,44] chlorhexidine,[12,44] triazine,[30,31] triclosan,[5] arginine,[9] quercetin,[6] EGCG,[8] EGCG-3Me,[8] nisin,[18] among others.

Antibacterial action mechanism occurs through the ionic release in some materials, especially in metal compounds, so the positive charge of the antibacterial agent in contact with the negative charge of the bacterial membrane increases the membrane bacterial permeability, rupture and cell death.[52] For agents such as QAM, the mechanism of inhibition is by contact, since the antibacterial monomer copolymerizes with the monomers of the adhesive system and is attached to the polymer matrix.[3,7,15,19] Most of the studies reported immediate

antibacterial action, or analysis for up to one year of aging.[1,6,8,16-18,20,28-30,39,40,43,44]

Antimicrobial potential is also influenced by the adhesive pH.[21] Adhesives with low pH exhibit antimicrobial action, whether or not associated with antimicrobial agents.[21] Modified binding agents also have the purpose of being used in orthodontic adhesives. Users of orthodontic devices are more likely to have white spot lesions, since orthodontic devices accumulate more biofilm.[23,24,26,27,39]

To potentiate the antimicrobial action, several studies associate more than one antimicrobial agent within adhesives, such as NAg and DMAHDM,[15] or added an antimicrobial to a remineralizing agent such as amorphous calcium phosphate,[2,3,16] in addition to integrating protein-repellent agents like the MPC.[2] QAMs with different alkyl chain lengths were also tested, which showed that the increase in the chain increases the hydrophobicity, thus facilitating the penetration into the bacterial cell membrane.[4]

In addition to decreasing the viability of microorganisms, the modified adhesives do not negatively affect mechanical properties such as the bond strength[4,8,9,16,17,20,26,29,40] and the degree of conversion (GC) of the material.[5,9,18,20,28,30,31,40,41] We showed that adhesives with 5%-QMAP and MDPB[20] and chlorhexidine binding agents did not interfere with bond strength, not even after 1 year of storage compared to their counterparts with no antimicrobial substances.[44] Moreover, the incorporation of DMADDM,[16] DMAHDM,[2] nMT,[43] EGCG,[8] EGCG-3Me,[8] MAE-HB,[29] silver methacrylate, Zn,[40] and different QAM chain lengths[4] did not interfere with material strength. However, shear strength decreased due to the inclusion of NAg in the Transbond XT, in concentrations between 0.11% to 0.33%, as well as with GC.[39] Regarding this same adhesive, the addition of 1%-NAg, TiO2, or ZnO promoted bond strength decrease.[24] Furthermore, the addition of 3 to 5%-nisin in Single Bond 2 reduced its micro tensile strength.[18] On the other hand, triazine-modified adhesives,[30] METAC,[41] triclosan[5] and MADQUAT[28] increased the degree of conversion of the adhesive. And the experimental adhesive with BTAM showed similar antibacterial activity to the ones shown within control and reduced the conversion of monomers to polymer.[11]

Another relevant aspect is the adhesive biocompatibility after the incorporation of antimicrobial agents. Monomers present in the adhesives and photo initiators, such as the camphorquinone, are potentially cytotoxic;[56] nevertheless, the addition of antimicrobial agents must not increase material cytotoxicity. Thus, the DMADDM associated with the NACP[3] showed a mild inflammatory response in rat teeth; however, the addition of 0.5 mg/ml PAI-CuI in Optibond Solo Plus and 0.1 or 0.5 mg/ml PAACuI reduced cell viability.[17] Cell viability also reduced with the combination of Transbond XT with bioactive glass + 1% Ag.[26] Likewise, when the bio-glass was bound to 0.2% or 1% Zn, similar viability was observed within control.[26] Few studies have addressed this issue; cytotoxicity should, therefore, be further studied to ensure the safety of modified adhesives.

However, antimicrobial agents are not directly added in other studies; only after acid conditioning the dentin is treated to receive the adhesive. In addition to potent antimicrobial activity,[46] nanoparticles loaded with chlorhexidine present low cytotoxicity in dental pulp stem cells,[46] with gradual release of the drug into the dentinal tubules.[46,47] The chlorhexidine is a positively charged molecule that binds to the negatively charged dentin matrix[13] and is an inhibitor of metalloproteinases, which protects the collagen network and consequently increases adhesion durability.[44,46,47] Another agent previously used for the application of the adhesive was the grape seed extract, which inhibited secondary caries in the adhesive interface.[60] On the other hand, it increases the number of operative steps, possibly overlapping the benefits with the increasing clinical time.

Several antimicrobials are incorporated into adhesive systems; however, most of these studies

are *in vitro* – they use a single microorganism to test the antimicrobial effect – and are conducted for a short time. Finally, more long-term clinical studies using the microcosm biofilm model are needed, so these functionalized adhesives prove their potential to inhibit secondary caries.

CONCLUSION

New adhesive and restorative biomaterials should add antibacterial properties. Thus, antibacterial adhesives have been proposed; however, most studies are *in vitro* and conducted in a short time. Therefore, more long-term clinical studies are needed to evaluate the real effect of these new materials.

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