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Biodegradation of resin composites and adhesives by oral bacteria and saliva: A rationale for new material designs that consider the clinical environment and treatment challenges

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ABSTRACT

Objective. To survey the recent literature from the late 1980s to recent years in order to assess the relationship between resin degradation, catalyzed by biological factors, and clinical failure outcomes such as marginal breakdown.

Methods. The literature shows that degradation occurs in many manufacturers' products despite varied vinyl acrylate compositions. The authors examine salivary enzyme activity and their ability to degrade the polymeric matrix of resin composites and adhesives, as well as oral microorganisms that can promote demineralization of the tooth surface at the marginal interface. A survey of recent research relating matrix metalloproteinase (MMPs) to the degradation of the exposed collagen at the dentin adhesive interface is also discussed in the context of marginal breakdown.

Results. The literature provides strong support that together, the above factors can breakdown the marginal interface and limit the longevity of resin composite restorations. The authors have found that the field's current understanding of resin biodegradation in the oral cavity is just beginning to grasp the role of bacteria and enzymes in the failure of resin-based restorations.

Significance. Knowledge of these biodegradation processes is pertinent to areas where innovative strategies in the chemistry of restorative materials are anticipated to enhance the longevity of resin composites.

1. Introduction

Resin composite is the most widely used dental restorative material in practice today due to its superior esthetics and ease of handling [1]. Despite the extensive use of polymeric composites that contain vinyl resins, the resultant restorations lack the durability of amalgam fillings in terms of both inherent mechanical properties and inherent chemical stability, thereby limiting their lifetime *in vivo* [2–4]. The shorter

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longevity has been attributed in-part to material degradation, compromised adhesion by clinical factors, fracture, polymerization shrinkage, and secondary caries [1,2]. Secondary caries is the recurrence of caries at the tooth–restoration interface [5]. Secondary caries is often cited as the most frequent reason for restoration replacement, accounting for approximately 50% of the reported replacements regardless of the restorative material [6–17]. The latter studies reporting on over 18,229 restorations worldwide and spanning 20 years, provide data explaining the reasons for their replacement, ranking secondary caries as the predominant cause [18]. Upon the degradation of margin interfaces, acid-producing bacteria such as *Streptococcus mutans* can infiltrate the margins and contribute to the progression of recurrent caries [5]. It is believed that the accumulation of such microorganisms in the marginal gap can promote the demineralization of the tooth interface, thereby contributing to the progression of caries [5,18].

Over the years, many groups have studied the degradation of resin composites in the oral cavity. In the earlier years of this research most of the work focused on material loss as a result of wear and mechanical function [19–21]. However, beginning in the early 1990s, the focus of the studies shifted toward the chemical breakdown of these restorative materials because it was suggested that enzymes in the oral cavity may contribute to the degradation of resin composites [22,23]. Since then, a number of studies have investigated the degradation of resin composites in the presence of salivary-like enzymes [24–27], and the subsequent biological effects of the by-products on the surrounding bacteria and mammalian cells [1,28–33]. These biological processes that render commercial resins and adhesives vulnerable to premature failure are currently beyond the control of the clinicians.

The article will first report on the inherent vulnerability of modern day restorative resin chemistry with respect to degradation and then survey the literature of the biological factors present in the oral cavity, which challenge this chemistry. Lastly, strategies that are being pursued to address these processes will be reported on.

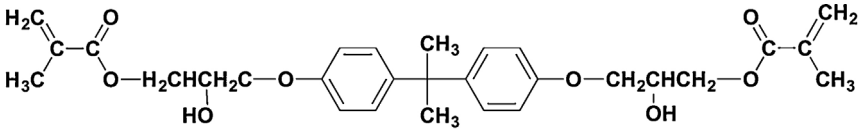
2. Dominant factors influencing bio-degradation

2.1. *Chemistry of resin composites*

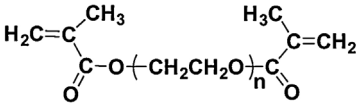
A composite by definition is formulated from two or more components with inter-atomic interactions, producing a product that has superior properties to those of the individual components alone [34]. Dental resin composites are composed of four major components: a polymeric matrix that is usually methacrylate based (several examples of commonly used monomers are illustrated in Fig. 1), filler particles (commonly glass, quartz, or ceramic oxides), coupling agents between the filler and the matrix such as silanes, and an initiator/inhibitor polymerization system. The major constituent by weight and volume are the filler particles, usually inorganic, which provide the composite with improved mechanical properties such as compressive strength and modulus of elasticity, and reduced polymerization shrinkage, water absorption, and thermal expansion coefficient [2].

A very commonly used monomer for the polymeric matrix is 2,2-bis [4(2-hydroxy-3-methacryloxypropoxy)-phenyl]propane, also known as bisphenol A glycidyl methacrylate (BisGMA), which was first introduced in late 50's by Bowen [36]. This hybrid molecule was initially synthesized by the reaction of glycidyl methacrylate and bisphenol A [36]; however, it was later produced by the coupling of methacrylic acid and diglycidyl ether of bisphenol A *via* an ester linkage [37]. In comparison to methyl methacrylate that was originally used in the early 1930s, BisGMA has superior mechanical properties, undergoes less polymerization shrinkage, and hardens more rapidly under oral conditions [36]. BisGMA contains hydrophobic aromatic rings in the backbone that provide the resin with low chain mobility and less deformation upon mechanical loading relative to linear non-aromatic monomers. The pendent hydroxyl groups in the alkyl chain further enhance the mechanical properties by participating in hydrogen bonding with the carbonyl groups on the methacrylate moiety. As a result of the aforementioned hydrogen bonding and the pi–pi interactions between aromatic rings of BisGMA molecules, this high molecular weight monomer has a viscosity that is 10^5–10^6 orders of magnitude greater than water at room temperature [38,39]. The high viscosity prevents the addition of high amounts of filler and reduces the degree of conversion (polymerization) when this monomer is used on its own. Therefore, diluent monomers are used in conjunction with BisGMA to enhance resin mobility for ease of handling and operation [40]. Among diluent monomers, triethylene glycol dimethacryate (TEGDMA) is the most extensively used in current resin restorations. TEGDMA is a low molecular weight di-vinyl monomer that enhances the efficiency of polymerization by reducing the overall viscosity. This allows for better mixing and blending of the different constituents within resin composites. However, there is a limit to the amount of diluent that can be added to resin composites, as it greatly increases water sorption due to the triethylene oxide spacers in TEGDMA [41]. Furthermore, with increasing TEGDMA content, the overall resin composite experiences a greater volumetric shrinkage upon polymerization [41], which results in the potential for a greater marginal gap upon curing.

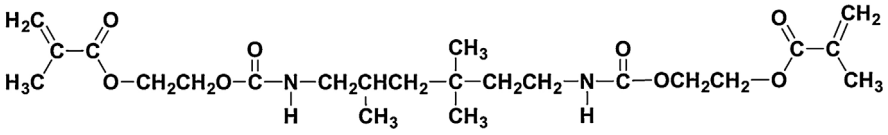
The majority of dental composites undergo solidification *via* free radical chain polymerization of di-vinyl oligomers, which enables the formation of a cross-linked network. The reaction is commonly initiated by predominantly photochemical means, but also by chemical means [42]. As monomers polymerize, chain motion becomes increasingly restricted, and ultimately the free volume occupied by the molecules decreases. The increase in cross-linking density increases the hardness and stiffness of the composite, therefore enhancing the overall modulus and strength. However, with further cross-linking and the additive effect of van der Waals interactions, the resin material experiences a volumetric contraction upon polymerization [2]. It is believed that the internal stresses generated by this process can ultimately lead to adhesive or cohesive failure at the tooth/resin interface [43]. Volumetric contraction can further result in tooth distortion and/or gap formation between the restoration and tooth structure, which allows for microleakage of salivary fluids,



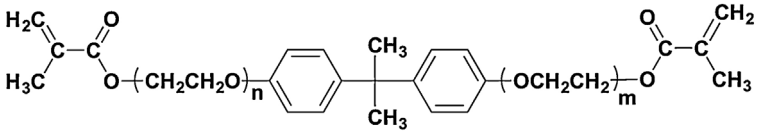
2,2-bis [4(2-hydroxy-3-methacryloxypropoxy)-phenyl] propane (BisGMA)



n=1: Ethylene glycol dimethacrylate (EGDMA), n=2: Diethylene glycol dimethacrylate (DEGDMA), n=3: Triethylene glycol dimethacrylate (TEGDMA)



Urethane dimethacrylate (UDMA)



Ethoxylated bisphenol A based dimethacrylates (Bis-EMAs)

Fig. 1 – Common methacrylate based di-vinyl monomers used in dental resin materials [35].

enzymes, and microorganisms into the margins of restoration and teeth [44,45].

Resin composites and adhesives are also subject to a significant amount of biological breakdown in the oral cavity due to the presence of condensation type bonds within the resin [2]. These bonds, which include esters, urethanes, and amides, are predominantly found in the di-vinyl monomers, and they are all prone to chemical hydrolysis, catalyzed by acids, bases, or enzymes [46]. The rate of hydrolysis for these bonds depends on several structural factors. For instance, steric crowding around the hydrolytically sensitive chemical bonds may reduce hydrolysis by reducing the ability of water to come into close proximity. This phenomenon is seen in BisGMA where hydrophobic aromatic rings in the backbone partially shield the polar groups that are susceptible to hydrolysis from water molecules. Furthermore, the interaction of water with electron-withdrawing or donating substituents in the vicinity of the susceptible bonds may also affect the rate of hydrolysis [47]. For instance, ethylene oxide groups such as those that are present in TEGDMA have a high affinity for water molecules; therefore their presence increases water uptake and the likelihood of hydrolysis. Other monomers such as urethane dimethacryate (UDMA), and BisGMA contain functional groups such as urethanes and hydroxyls respectively, that attract water molecules. Among the three monomers, the hydrophilic ether linkage attracts the greatest amount of water [48–50], and therefore leads to monomers that are more susceptible to enzymatic hydrolysis [23,26]. Lastly, the rate of hydrolysis also depends on the type of condensation bond; for instance, esters are more susceptible to nucleophilic attack by water, and are thus more readily hydrolyzed at physiological pH when compared to carbonates, carbamates, urethanes, and amides.

Structural factors of many polymers containing heterogeneous atomic make-ups can also affect the rate of degradation by the ease at which enzymes bind to the polymeric substrate [50]. For instance, poly-ether-urea-urethanes that are extensively used in biomedical applications have hard segments (region containing a high density of hydrogen-bonding groups) that affect the manner in which cholesterol esterase adsorbs, binds, and catalyzes the hydrolysis of susceptible bonds [51]. Similarly, structural differences among commercial composites and adhesives result in differing rates of degradation. For instance, the commercial composite TPH (L.D. Caulk) has been found to be more resistant to enzymatic hydrolysis in laboratory controlled studies relative to Z100 (3M) [52] and Z250 (3M) [53], which are two other commercial resin composites (refer to Table 1 for composition). It is speculated that the greater resistance of TPH to degradation occurs because of the presence of urethane modified BisGMA (uBisGMA), which participates in extensive hydrogen bonding. However, the three composites have substantially different fillers and relative resin composition, and therefore other confounding factors may also influence biodegradation.

Table 1 – Composition of commercial resins specified by the manufacturer.

Material	Filler type	Filler (wt%)	Monomer components
Z100 (3M)[a]	Silanized zirconia/silica	77–87	BisGMA (5–9%) TEGDMA (5–9%)
Z250 (3M)[b]	Silane treated ceramic	75–85	BisGMA (5–10%) UDMA (5–10%) BisEMA (5–10%) TEGDMA (1–5%)
TPH (L.D. Caulk)[c]	Barium glass/Silica	77.5	uBisGMA, BisGMA, TEGDMA, modified TEGDMA

[a] MSDS manufacturer number: 05-4615-0.
[b] MSDS manufacturer number: 08-2286-6.
[c] MSDS manufacturer number: 542699.

To better understand the increased stability of TPH, Finer and Santerre conducted a study where they recreated a modified version of TPH and compared it to non-urethane traditional BisGMA/TEGDMA-based materials [27]. These modified composites all consisted of the same initiator systems, filler type and weight fraction of the filler. The composites were incubated with cholesterol esterases for 16 and 32 days, and the degradation by-products were quantified using high performance liquid chromatography. The composite containing uBisGMA released lower quantities of residual monomer and degradation by-products. The difference in degradation can be attributed to several factors. Firstly, uBisGMA was more hydrophobic and more stable against hydrolysis in comparison to BisGMA [54]. Composites containing higher quantities of BisGMA attracted a greater amount of water, and would therefore be more prone to degradation [55,56]. In addition, the traditional BisGMA composite may have also experienced greater amount of water uptake due to the larger quantity of TEGDMA in its formulation, 45% weight fraction of TEGDMA in comparison to 10–20% weight fraction in the uBisGMA composites. The remaining constituent of the uBisGMA composite was substituted with ethoxylated bisphenol-A dimethacrylate (bisEMA), a less water-soluble monomer. With greater water uptake, the polymeric matrix undergoes more swelling, which allows for unreacted monomers and degradation by-products to more easily diffuse out of the composite. Since all other parameters were kept constant, such as the degree of vinyl group conversion and filler percentage, it was concluded that the urethane groups associated with the uBisGMA were likely responsible for the difference in stability [27]. Urethane groups are capable of extensive hydrogen bonding, which allow for greater stability and resistance to hydrolysis. Therefore, bio-chemical stability of resin composites can be greatly influenced by their inherent chemistry.

2.2. *Biological factors*

The long-term clinical success of resin composite restorations strongly depends on the physical and chemical integrity of the tooth and restoration interface [57]. In the oral cavity, chemical changes at the marginal interface are evident with material discoloration that occurs over time [58]. While this change may be related to many events including the collection of salivary contaminants and debris at the margins, it may also be caused by microleakage and degradation of the interface [2]. Since the 1990s, many studies have confirmed that saliva contains enzymes that are capable of degrading resin composites *via* cleavage of the susceptible condensation linkages. Several of these studies are summarized in Table 2 [5,23–26,52,53,59–78], and highlight that almost all vinyl resin composites, independent of their manufacturer and composition, are susceptible to some degree of degradation.

Enzymes in the oral cavity have been classified into five major groups: carbohydrates, esterases, transferring enzymes such as catalases and oxidases, proteolytic enzymes such as proteinase, and others such as carbonic anhydrase [79]. Esterases are the most extensively studied class of enzymes against resin composites. This class of enzymes is derived from many different biological sources including salivary glands, inflammatory responses, microorganisms, and mononuclear phagocytic cells such as macrophages and monocytes that are commonly found in both normal and inflamed gingival tissues [79]. Since the 1990s, many model esterases have been used to assess the degradation of resin composites. Several of these esterase models are now used to investigate the stability of new resin technologies.

Hydrolytic degradation and water uptake render the material more prone to mechanical wear during mastication, as a result of the surface undergoing softening [61,80]. As the surface layer is removed by wear, the underlying material becomes exposed to chemical degradation; creating an ongoing cycle of surface change and material loss by wear. Furthermore, hydrolytic degradation exposes susceptible bonds, located deeper within the matrix, to water molecules. This is particularly evident at the marginal interface. With the infiltration of salivary enzymes into the marginal gap, ongoing destruction of the interface can be promoted [5,76].

In addition to salivary enzyme infiltration, a compromised interface allows for the microleakage of bacteria into the margins between tooth and restoration [5]. *In vitro* studies have shown that exposure to salivary-like enzymes accelerates bacterial microleakage, which ultimately increases the marginal gap over time [5]. The presence of bacteria between the tooth and restoration is a major challenge and a potential cause of postoperative sensitivity, secondary caries, pulp inflammation, and necrosis [60,64,78]. *S. mutans*, a major etiological agent responsible for dental caries, is one of

Table 2 – Relevant studies assessing the impact of biological agents on resin composites.

Reference	Biological source	Main conclusions drawn from the study
Weitmann RT, 1975 [59]	Oral plaque	Regardless of finishing techniques, a higher accumulation of plaque is observed on resin composites than adjacent control teeth
Svanberg M, 1990 [60]	*Streptococcus mutans*	A greater accumulation of *Streptococcus mutans*, etiological agent responsible for dental caries, is observed on composite resin than amalgam restorations and the enamel
Munksgaard EC, 1990 [23]	Pork liver esterase	Degradation was evident with a greater mean material loss of BisGMA/TEGDMA specimens incubated with esterases than samples incubated with no enzyme
Larsen IB, 1991 [61]	Human whole saliva, Porcine liver esterases	Human whole saliva was found to have esterase activity capable of degrading TEGDMA. Furthermore, exposure of unfilled BisGMA/TEGDMA polymers to porcine liver esterases resulted in a decreased surface micro-hardness and increase wear
Van Dijken J, 1991 [62]	*Streptococcus mutans* and *Lactobacilli*	Plaque accumulation in the cervical margins was compared intra-individually. Isolated amounts *Streptococcus mutans* and *lactobacilli* from glass ionomer cements (GICs), resin composites, and enamel were not significantly different. Hence, the amount of released fluoride from GICs is not sufficient to inhibit plaque buildup
Larsen IB, 1992 [24]	Porcine liver esterases	Porcine liver esterase, a carboxylate hydrolase, reduced the surface mean micro-hardness of composite resins by approximately 15% after 60 days. The observed decrease in hardness can be attributed to surface degradation
Bean TA, 1994 [63]	Porcine liver esterases and pancreases, lipases, rat and mouse liver enzyme extracts	Enzymatic hydrolysis of both mono- and di-methacrylate monomers such as HEMA, TEGDMA, BisGMA was observed. TEGDMA underwent greater degradation in comparison to BisGMA (degradation products were isolated but structures were not confirmed). Highlighting the importance of enzymatic specificity for particular chemical structures
De Gee AJ, 1996 [64]	Porcine liver esterases	Surface wear was studied in the presence of esterases. Silux showed no significant wear while Z100 showed a significant increase in material loss in the presence of esterases
Hansel C, 1998 [65]	*Streptococcus sobrinus*, *Lactobacillus acidophilus*	TEGDMA was found to stimulate growth of *Streptococcus sobrinus* while monomers of BisGMA and UDMA inhibited the growth of *Lactobacillus acidophilus*. Although the underlying mechanism was not determined, the possible contribution of resin monomers to plaque formation at the marginal interface was highlighted
Santerre JP, 1999 [52]	Cholesterol esterases	Cholesterol esterase was capable of degrading the resin composites Silux Plus XL and Z100 A2 (3M), and TPH XL (L.D. Caulk). The latter, TPH XL, was found to have the highest stability (ten fold fewer degradation by-products were produced)
Willershausen B, 1999 [66]	*Streptococcus mutans*	With colonization of bacteria on the surface of resin composites, an increase in surface roughness is observed. Suggesting that bacteria may cause surface degradation
Yap AU, 2000 [67]	Artificial saliva	Degradation of four commercially available resin composites in the presence of artificial saliva was studied by monitoring the release of methacrylic acid over 7 days. Ariston pHc (Vivadent) released the highest amount followed by, Surefil (Dentsply), Silux Plus (3M), and lastly Z100 (3M), respectively
Yourtee DM, 2001 [68]	Acetylcholinesterase, cholesterol esterase, porcine liver esterase, pancreatic lipase	Aromatic derivatives and those with branching in methacrylate linkages were more resistant to degradation in comparison to TEGDMA
Jaffer F, 2002 [53]	Human saliva	Human saliva completely degraded BisGMA and TEGDMA within 24 h and was able to degrade the surface of Z250 (3M) and Spectrum TPH (L.D. Caulk) composites
Steinberg D, 2002 [69]	*Streptococcus sobrinus*	*Streptococcus sobrinus* was able to accumulate and form biofilms on all tested specimens. Acrylic and Durafil materials had the highest affinity for proteins (albumin and amylase) and Fuji LC and Fuji GC had the highest accumulation of bacteria with the highest viability
Finer Y, 2003 [26]	Cholesterol esterases, pseudocholinesterase	Both enzymes are capable of hydrolyzing esters. Cholesterol esterases preferentially degraded BisGMA and PCE showed higher specificity toward TEGDMA. Rate of degradation was also found to depend on concentration of enzymes
Finer Y, 2004 [70]	Human saliva, Cholesterol esterases Pseudocholinesterase	Human saliva, Cholesterol esterase (CE) and pseudocholinesterases (PCE)-like activities at levels capable of degrading ester-containing composites. Therefore, CE and PCE can be used as model enzymes

– Table 2 (*Continued*)

Reference	Biological source	Main conclusions drawn from the study
Finer Y, 2004 [25]	Combination of cholesterol esterases and pseudocholinesterases	Two enzymes had a synergetic effect on the degradation of restorative resins (i.e. enhanced stability, activity, and degradation abilities) when combined. The effect was greater than the sum of the individual enzyme alone. Highlighting the importance of the dynamic and multi-component environment in the oral cavity
Montanaro L, 2004 [71]	*Streptococcus mutans*	Assessed the bacterial adhesion on several commercially available materials: microhybrid composites (Z250, Clearfil APX, Solitaire 2), Flowable composites (Tetric Flow, Arabesk Flow, Filtek Flow), Ormocer (Admira), Compomer (F2000), Resin-modified glass ionomer cements (Fuji IX, Fuji IX fast). None of the aforementioned material exhibited less bacterial adhesion in comparison to a polystyrene surface. Specimens that released fluoride (Fuji IX, F2000, etc.) were not able to reduce early bacterial adhesion
Lin BA, 2005 [72]	Human saliva	Cholesterol esterase-like and pseudocholinesterase-like activity were collected from human saliva. Solutions with higher CE-like activity were found to degrade aromatic monomers more than fractions with elevated PCE-like activity. Thus, salivary enzymes have preferences for distinct components of the resin composite
Hagio M, 2006 [73]	Human Saliva	Alternative methacrylate monomers were synthesized and stability was studied in the presence of human saliva. Urethane modified BisGMA molecules were found to have the greatest stability and resistance to salivary hydrolysis
Beyth N, 2008 [74]	*Streptococcus mutans*	*Streptococcus mutans* experiences accelerated growth on polymerized resin composites *in vitro*
	Streptococcus mutans and *Lactobacillus*	Bacteria identified in plaque formed at the marginal gap between restoration and tooth
Kostoryz EL, 2008 [75]	Porcine liver esterases	A significantly higher amount of MAA was released when adhesive systems (HEMA/BisGMA) were incubated enzymes
Kermanshahi S, 2010 [5]	Cholesterol esterases, pseudocholinesterases, *Streptococcus mutans*	Degradation of the resin composite and adhesive by esterase activity accelerates marginal micro-leakage
Shokati B, 2010 [76]	Salivary derived esterases	Degradation and fracture toughness after exposure to salivary esterases was measured in composite resin (Z250) specimens bound to dentin with a Scotchbond Multi Purpose adhesive. This study suggested that degradation is an on-going challenge that will gradually compromise the integrity of the resin–dentin interface
Park J, 2012 [77]	*Streptococcus mutans*	Surface topography (size and depth of depression) can affect biofilm formation on resin composites
Bourbia M, 2013 [78]	*Streptococcus mutans*	*Streptococcus mutans* (UA159) has esterase activities at levels that can degrade cured commercial Z250 resin composites, total etch (Scotchbond), and self-etch (Easybond) adhesives. Among the three, Easybond, the self etch system, released the greatest amount of BisHPPP

the primary inhabitants present at the marginal interface [81]. These microorganisms have a higher affinity for resin composites in comparison to the enamel and other restorative material such as ceramics and metals [60,82]. This is possibly due to the higher affinity of salivary proteins for polymeric materials [69,83]. *S. mutans* also have an accelerated growth on resin composites *in vitro* [74]. It is unclear if this is due to unreacted monomers leaching out and promoting the growth of such cariogenic bacteria, or surface roughness features that allow for better bacterial adhesion [74,84]. It may nevertheless be that both factors play a role in the accumulation of bacteria on resin composites. Studies have shown that exposure to *S. mutans* increases surface roughness by degrading the resin material [74]. Furthermore, recent studies are suggesting that the etiological agent responsible for dental caries, *S. mutans*, also has esterase activities at levels capable of degrading dental resin composites and adhesive system [78]. Consequently, the formation of bacteria-dense-biofilm can result in the ongoing destruction of the resin composite.

With respect to inhibiting bacterial growth, resin composites pose an inherent drawback in comparison to amalgam and glass ionomer cements (GICs), two other commonly used restoration materials. Amalgam restorations release ions capable of killing adhered bacteria [85] and GICs release fluoride to reduce the acidogenicity (acid production) of bacteria [86]. In contrast, unreacted monomers used in resin composites and a number of its degradation by-products can alter virulence factors and promote the growth of several bacterial strains in the immediate vicinity of the restoration, as summarized in Table 3 [28,30,65,84,87–96]. A number of resin-associated products have been shown to enhance the growth of several microorganisms involved in caries lesion such as *S. mutans* and *Streptococcus sobrinus* [65,84,91]. To increase the longevity of current resin composites, a means for effectively reducing and controlling the growth of cariogenic bacteria

Table 3 – Biological effects of unreacted monomers and degradation by-products of conventional resin composites.

Reference	Compounds	Biological effect
Oliva A, 1996 [87]	HEMA	Unreacted monomer cultures on osteoblasts was found to be toxic at concentrations of 1–2 mM
Hansel C, 1998 [65]	TEGDMA	Promotes the growth of cariogenic bacteria such as *Lactobacillus acidophilus* and *Streptococcus sobrinus*
	EGDMA	Promotes the growth of cariogenic bacteria such as *Lactobacillus acidophilus* and *Streptococcus sobrinus*
	BisGMA, UDMA	Both monomers inhibited the growth of *Lactotobacillus acidophilus* during the log phase
Schweiki H, 1998 [88]	TEGDMA	Exhibits mutagenic behavior as it induced a dose-dependent rise in V79 cell cultures by deletions in the *hprt* gene
Kawai K, 2000 [84]	TEGDMA	Enhances activity of glucosyltransferase in *Streptococcus sobrinus* and further promotes plaque formation
	EGDMA	Enhances activity of glucosyltransferase in *Streptococcus sobrinus*
Theilig C, 2000 [89]	TEGDMA	At concentrations greater than 0.25 mM it inhibited proliferation of human gingival fibroblasts and human keratinocytes
	BisGMA	At concentrations greater than 0.01 mM it inhibited proliferation of human gingival fibroblasts and human keratinocytes
Schweikl H, 2001 [90]	BisGMA, UDMA, TEGDMA, HEMA, MAA	TEGDMA induces gene mutation and DNA sequence deletion in hprt gene of V79 cells The cytotoxicity ranking was as follows: BisGMA > UDMA > TEGDMA > HEMA > MAA
Khalichi P, 2004 [91]	TEG	Enhance the growth of *Streptococcus mutans* NG8 in acidic environments (pH 5.5)
	MAA	Inhibit bacterial growth of strains *Streptococcus mutans* (NG8), *Streptococcus mutans* (JH1005), and *streptococcus salivarius* (AT2) at pH 5.5
Lefeuvre M, 2005 [92]	TEGDMA	Induced mitochondrial damage in human gingival fibroblasts
Reichl FX, 2006 [28]	HEMA, TEGDMA, BisGMA, UDMA	The cytotoxicity of the monomers against human gingival fibroblasts (HGFs) increased as follows: BisGMA > UDMA > TEGDMA > HEMA. TEGDMA mainly caused apoptosis while the remaining three mainly caused necrotic cell death
Lee DH, 2006 [93]	HEMA, TEGDMA	Both monomers exhibited dose dependent cytotoxic and genotoxic effects with greater toxicity observed from TEGDMA
Emmler J, 2008 [94]	TEG	TEG showed no signs of cytotoxic effect up to a concentration of 10 mM
Khalichi P, 2009 [1]	TEG	Modulate the expression levels of gtfB and yfiV as a putative transcription regulator gene in *Streptococcus mutans*.
Singh J, 2009 [95]	TEG	Affects *gtfB* and *yfiV* expression in a concentration dependent manner
	BisHPPP	At pH 5.5 inhibition of *Streptococcus mutans* (NG8) growth was observed at concentrations 1–2.5 ($\times 10^2$) μM.
Imazato S, 2009 [96]	HEMA	Unreacted monomer inhibited proliferation, alkaline phosphatase activities, the expression of osteocalcin, and mineralized tissue formation at concentrations of 200 μg/mL (~1.54 mM)
Cheng MC, 2009 [30]	BisGMA	BisGMA was cytotoxic to human pulp fibroblasts at concentrates greater than 0.075 mM

Abbreviations: TEGMA, triethylene glycol dimethacrylate; EGDMA, ethylene glycol dimethacrylate; TEG, triethylene glycol; MAA, methacrylic acid; UDMA, urethane dimethacrylate; BisHPPP, bis-hydroxy-propoxyphenyl propane; HEMA, 2-hydroxyethyl methacrylate; BisGMA, 2,2-bis [4(2-hydroxy-3-methacryloxypropoxy)-phenyl]propane.

may be required to overcome the adverse effect of such degradation by-products.

Resin adhesive systems are designed to bond resin composites to tooth structure and help to retain composite restorations while also sealing the interface with the tooth. Traditionally, adhesives contain similar components as resin composite: acrylic resin monomers such as 2-hydroxyethyl methacrylate (HEMA), BisGMA and TEGDMA, organic solvents, initiators, inhibitors and at times reduced amounts of fillers. The bonding capacity of dental adhesives is based on twofold adhesion: they mechanically interlock with dentin/enamel from one side and become integrated into the polymerizing composite from the other. The latter mechanism of adhesion has been shown to be a process involving the co-polymerization of acrylic monomers in composite and adhesives. Currently, two types of adhesive systems are used: the etch and rinse technique that is reported to remove the smear layer (a thin layer of microcrystalline and organic particle debris left on the dentin surface by dental instrumentation procedures), and the self-etch technique that the literature describes as being able to modify the smear layer such as to create a substrate for bonding [97]. In the etch and rinse technique, a gel of phosphoric acid is first applied as an etching step to demineralize and remove the superficial tooth layer, and is later rinsed away [98]. This process allows for the primer (which contains hydrophilic acrylic monomers that can re-wet dentin to prevent collagen collapse) to be initially applied and then followed by the application of the adhesive resin. This allows the more hydrophobic adhesive to infiltrate into the created micro-pores, producing a matrix that

mechanically interlocks the resin to the dentin or enamel, and produces what has become known as the hybrid layer [99]. In the etch and rinse technique, the primer and adhesive can be combined into a single bottle. Therefore, this adhesive can be applied in either a two or a three-step technique. Conversely, the self-etch technique eliminates the rinsing step by combining either etching and priming or etching, priming, and bonding agent together, which results in the etchant and priming agent remaining within the smear layer [100]. The self-etch adhesives can be comprised of a one or a two-step technique depending on whether the etching/primer agent is combined with the bonding agent into a single application [100]. Several studies are suggesting that the hydrophilic nature of self-etch adhesives, due to the presence of acidic monomers, renders them more vulnerable to water sorption, which may result in greater susceptibility to degradation in comparison to conventional total-etch techniques [101]. Furthermore, water sorption can enhance leaching of hydrophilic monomers to further permit movement of water molecules across the bonding resin, even after curing [102,103].

The hybrid layer is susceptible to degradation by a family of calcium-dependent zinc-containing proteolytic enzymes known as matrix metalloproteinases (MMPs) [104]. MMPs are present in human saliva, and are secreted by a variety of connective tissues and pro-inflammatory cells including fibroblasts, endothelial cells, macrophages, neutrophils, lymphocytes, and odontoblasts [104,105]. To date many MMPs have been isolated and identified in dentin including stromelysin-1 (MMP-3) [106], neutrophil collagenase (MMP-8) [107] and gelatinases A and B (MMP-2 and MMP-9, respectively) [108]. MMPs are involved in many physiological processes including dentinogenesis [109]. However, these endopeptidases are also capable of degrading components of the extracellular matrix (ECM) including fibrillar and non-fibrillar collagens, fibronectin, laminin, and basement membrane glycoproteins [109]. Several MMPs including MMP-2, MMP-8, MMP-9, and MMP-20 participate in caries lesions by hydrolyzing collagen fibrils at specific amino acid sites [110,111]. Consequently, the dentin–resin interface becomes compromised [105]. However, for this process to occur, these MMP enzymes must be activated.

MMPs require metal ions such as calcium or zinc to bind to the active site for their catalytic activation through a so-called cysteine switch [109]. However, recent studies are suggesting that MMPs from saliva and those that are normally bound to mineralized collagen fibrils may become catalytically activated under acidic conditions [105,109,111]. A low pH alters the conformation of the protein, and induces the cysteine switch that activates the catalytic activity [112–114]. Therefore, MMPs may become activated during acid etching, or upon bacterial acid production at the tooth and restoration interface [105,112]. With large quantities of water present in the dentin and saliva, activated MMPs are able to hydrolyze the collagen, and compromise the stability of the resin–dentin interface [111]. Most of current literature is focused more specifically on the relevance of MMPs bound to dentin.

More recently, the presence of other collagen-degrading enzymes such as cysteine cathepsins, has been identified in dentin [115]. Similar to MMPs, a variety of cysteine cathepsins are expressed in the dentin–pulp complex cells, including human pulp tissue and odontoblasts [116]. These enzymes can degrade the extracellular matrix proteins such as type I collagen [117], laminin, fibronectin [118], and proteoglycans [119]. It is hypothesized that along with MMPs, cysteine cathepsins have an active role in collagen degradation in dentin, with stronger expressed activity observed with increasing depth of the carious lesion [116]. The majority of cysteine cathepsins are unstable in neutral pH and become activated and functional under slightly acidic environments [116] Hence, similar to MMPs, these cysteine proteases may become activated during acid etching or upon acid production by oral microorganisms. It is further hypothesized that MMPs and cysteine cathepsins may act in a synergistic manner and adjunctively on caries pathogenesis and hybrid layer degradation.

In summary, based on recent evidence, the degradation of resin and the breakdown of margins involve the activity of several factors. More specifically, salivary enzymes degrade the resin, while oral microorganisms promote demineralization of the tooth surface. Additionally, the process may be enhanced by MMPs and cysteine proteases, which have the potential to degrade exposed collagen at the dentin and adhesive interface.

3. Dominant strategies for enhancing bio-stability

With respect to clinical practice, it is important to understand that the marginal interface and resin composites are vulnerable to breaking down in the oral cavity. In this review, the avenues by which the bio-stability and longevity of resin composites could be enhanced are highlighted. Some of the technologies discussed also have the potential to minimize the variability related to clinical decision-making which attempt to circumvent the above limitations of the different materials, and that may exist from one clinician to another [11]. Examples of several different monomers proposed throughout the section are illustrated in Table 4 [120–130].

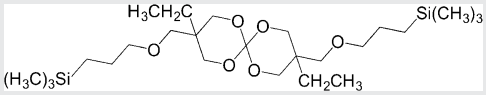
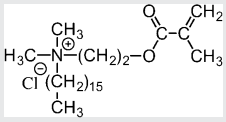
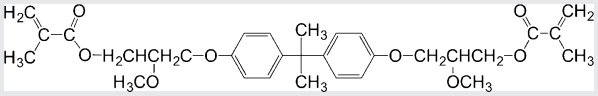
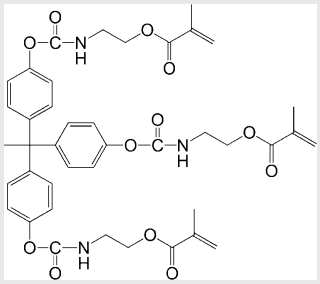
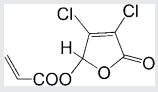
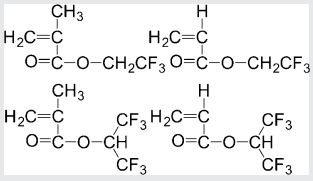
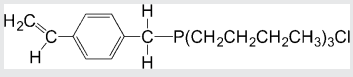
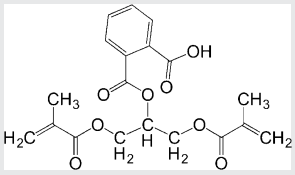
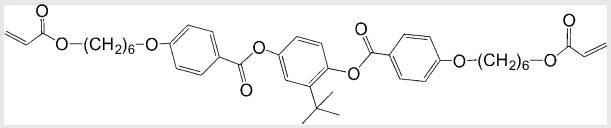
3.1. *Enhancing bio-stability by reducing volumetric shrinkage*

One approach to improving the longevity of restoration materials is to improve the initial seal of the resin–tooth interfacial margins that will reduce the amount of salivary enzymes and bacteria that penetrate into the marginal interface. One way to achieve this is by reducing polymerization shrinkage upon curing. Different approaches have been investigated, such as, the use of bulkier monomers, hyperbranched structures, and alternative polymerization methods such as ring-opening polymerization.

3.1.1. *Altering the chemical structure*

The development of new monomers has long been a challenge. An ideal monomer is one that has an acceptable viscosity, and undergoes little volumetric shrinkage upon curing without compromising the degree of conversion or mechanical

Table 4 – The latest proposed monomers for dental restorations and adhesive materials.

Monomer	Reference	Comment
Hyperbranched monomers	Tomasik AK, 2010 [120]	Less volumetric shrinkage and lower viscosity in comparison to BisGMA
	Eick JD, 2007 [121]	Used in conjunction with conventional monomers. Less volumetric shrinkage relative to pure methacrylate-based resins
	Xiao Y, 2008 [122]; Li F, 2009 [123]	*In vitro* inhibits accumulation of *Streptococcus mutans* and prevents biofilm formation by down-regulation of the *gtf* gene expression
	Kim JW, 2006 [124]	Substituted the hydroxyl groups in BisGMA with methoxy groups. The resulting monomer is less viscous requiring less TEGDMA. Less shrinkage and less water uptake was observed
	Park JG, 2009 [125]	Tri-methacrylate monomer with urethane-linked groups achieved a higher degree of vinyl group conversion with greater stability against porcine liver esterases
	Weng Y, 2012 [126]	With 5–30% addition of this molecule, a 16–68% reduction in *Streptococcus mutans* viability was observed with no significant change in the overall compressive strength of the composite
	Kadoma Y, 2010 [127]	Fluorine compounds can provide water repellent properties, chemical stability, stain and discoloration resistance. However, some of the investigated monomers had longer curing times at room temperature
	Kurata S, 2011 [128]	The associated polymer had antibacterial activity against *Streptococcus mutans*. However, the mechanical properties decreased with an increase in monomer content
	Park J, 2011 [129]	Proposed as a co-monomer for dentin adhesives. Lower viscosity relative to BisGMA and achieves a higher degree of conversion under wet conditions
	Satsangi N, 2005 [130]	A liquid crystal monomer. These monomers polymerize at a faster rate and result in less volumetric shrinkage relative to BisGMA

properties. The viscosity is particularly relevant in order to allow for maximal filler loading, ease of manufacturing, and use by the clinician. One approach undertaken to reducing volumetric shrinkage has been the synthesis of dimethacrylate monomers that are bulkier and of higher molecular weight.

Larger molecules generally have a smaller range of movement and fewer functional groups per volume in comparison to their equivalent lower molecular weight structure, and thus upon polymerization experience less volumetric shrinkage. In the current resin composite systems, BisGMA alone experiences a volumetric shrinkage of approximately 5.2%, while TEGDMA undergoes shrinkage of about 12.5%; however, the resulting composite (that includes filler) undergoes a shrinkage of about 2–3% depending on the ratios of each monomer used [131]. As it could be anticipated, bulkier and higher molecular weight molecules generally have higher viscosities that reduce the mobility of radicals and lead to premature termination and incomplete polymerization. For such monomers, often a higher volume of diluent (i.e. TEGDMA) will be required to enhance the efficiency of polymerization. For this reason, hyperbranched monomers have been of significant interest because they can be used to reduce the experienced volumetric shrinkage without significantly increasing the viscosity. It has been previously reported that these hyperbranched molecules increase their viscosity with molecular weight. However, relative to the equivalent linear counterparts the increase in viscosity is significantly less [132]. Therefore, several studies have looked at incorporating hyperbranched monomers in dimethacrylate based dental resins to reduce the incidence of marginal gap formation [133–136]. Other potential monomers studied with the aforementioned properties include dendritic monomers [137] and liquid crystalline methacrylate [130,138].

Liquid crystal methacrylates are designed to transform from a highly pre-ordered closed packed liquid crystal in the monomer state to a completely loose-packed amorphous polymer during polymerization. The loss of structural order in the monomer compensates for the change in volume upon vinyl group conversion. An example of a liquid crystal monomer is illustrated in Table 4. These monomers have been reported to have fast polymerization rates at room temperature and significantly lower shrinkage values in comparison to conventional monomers [130]. Furthermore, these monomers have relatively low viscosities that enable the addition of filler particles. They have also been reported to have less cytotoxicity relative to BisGMA, and are therefore proposed as alternative dental restoration materials [139]. The clinical application of these liquid crystal monomers however, is limited by their high manufacturing costs [140].

3.1.2. *Method of polymerization*

Prior to the use of methacrylate monomers, epoxy resins were studied for dental restoration materials [36]. These resins had satisfactory initial performance but were later dismissed due to the longer curing time required for adequate polymerization [141,142]. With the current challenges of volumetric shrinkage associated with methacrylate-based resins and the degradation of the marginal interfaces that result from the generated gap, there has been a renewed interest in epoxy resins and cyclic monomers.

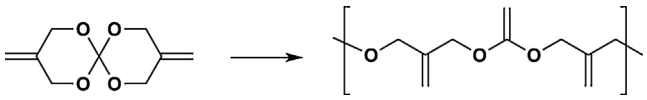


Fig. 2 – Ring-opening polymerization of a spiro-orthocarbonate monomer [140].

Ring-opening monomers first introduced by Bailey in 1972 have been extensively studied to reduce the initial volumetric shrinkage upon polymerization [143]. These monomers solidify by means of ring-opening polymerization *via* a cationic double ring opening reaction that results in less volumetric shrinkage upon curing [144]. In comparison to the conventional 1,2-addition polymerization of acrylic monomers, ring-opening polymerization can achieve higher degree of conversions [145]. Fig. 2 illustrates the ring-opening polymerization for a spiro-orthocarbonate monomer. Other examples of cyclic monomers with reduced polymerization shrinkage include spiro-carbonates, cyclic ethers and cyclic acrylates [146].

Methacrylate monomers undergo shrinkage as monomers originally separated by van der Waals interactions come into closer proximity with the formation of single covalent carbon–carbon bonds. In contrast, cyclic monomers overcome the decrease in spacing by compensating with the increase in length between broken bonds. Furthermore, many cyclic monomers have higher dipole moments that diminish upon polymerization, leading to a further increase in volume. Several cyclic monomers were reported to undergo volume expansion upon curing [147–149]. Therefore, cyclic monomers are generally used with conventional dimethacrylate monomers to reduce the initial gap formation upon polymerization [149]. Combinations with methacrylate-based monomers can result in negligible non-shrinking effects [141,150]. However, several of the cyclic monomers such as spiro-orthocarbonates, vinylcyclopropanes, and cyclic allyl sulfides were less reactive in comparison to methacrylates at room temperature resulting in an increased curing time, which makes them relatively less favorable for clinical applications. Furthermore, for several monomers, incomplete polymerization was observed at room temperature [140]. Given that both free monomer and resin composites are susceptible to enzymatic-catalyzed degradation at different rates [2,26], the generation and profile of degradation by-products will therefore vary between these different products. In addition, the limitation of volumetric shrinkage still exists with the combined use of conventional monomers with ring-opening monomers.

An important question to consider is whether the introduction of these new monomers into resin composites will enhance the long-term stability of resin composites and overcome the current problem of marginal breakdown and secondary caries. In a randomized one-year clinical trial, 100 restorations were placed into patients: 50 containing silorane-based Filtek P90 Low Shrink Posterior Restorative (3M/ESPE) and the remaining with Filtek P60 Posterior Restorative (3M/ESPE) with only conventional monomers. The silorane-based resin consists of siloxane and oxirane functional moieties, with siloxane providing hydrophobicity and oxirane, defined by its cyclic ethers, providing the system

with the low shrinkage characteristics. It was found that the reduced initial volumetric shrinkage associated with the silorane-based resins did not show any significant difference in clinical performance after one year [151]. Based on this short-term study, it could be assumed that a reduced initial volumetric shrinkage may not alone overcome the problem of marginal breakdown and that the recurrence of caries at the tooth–restoration interface, depends on other factors among which is biochemical degradation at the marginal interface. Consequently, a probiotic approach may be necessary to overcome the initial marginal gap that forms between the restoration and tooth upon polymerization.

Cyclic monomers are now commercially available, such as silorane containing resins being developed by 3M-ESPE. These hybrid resins contains both siloxane and oxirane structure moieties that are photo-initiated and cured by means of cationic ring-opening polymerization [152]. These monomers have been reported to have superior shelf stability to ambient light that makes handling the resin easier [152] and decreased polymerization shrinkage and stress [153]. Polymerization shrinkage was reported to be less than 1% and was a significant improvement in comparison to traditional methacrylate based resins. However, these resins were shown to have a lower initial reactivity at room temperature in comparison to methacrylates, that require lengthening the curing time [152] and potentially leading to more exchange of molecules with aqueous saliva (i.e. saliva and its constituents penetrate in and labile monomers leach out).

3.2. *Enhancing bio-stability by shielding susceptible bonds*

Alternatively, fluorinated monomers were investigated as such compounds can provide water repellent properties, chemical stability and stain and discoloration resistance [127]. However, many of the investigated monomers required a longer curing time at room temperature including 1,1,1,3,3,3-hexafluoroisopropyl methacrylate (HFIPMA), as shown in Table 4, which was not cured even after 2 h at room temperature [127]. Fluorinated derivatives of BisGMA have also been investigated. These monomers have been shown to have greater hydrophobicity and reduced water sorption, with no significant effect on mechanical properties [154,155]. Alternatively, fluorinated diluent monomers have been investigated such as fluorinated triethyleneglycol dimethacrylate (F-TEGDMA). In comparison to traditional TEGDMA, this monomer resulted in a lower water uptake and less volumetric shrinkage upon polymerization [156].

3.3. *Enhancing bio-stability by reducing adherence of bacteria*

Another approach to improving the longevity of restorative materials is to control bacterial accumulation and growth at the marginal interface. This can be done by two means; an active approach or a passive approach. The passive approach prevents the adhesion of bacteria and the active approach kills bacteria by releasing antimicrobial agents such as silver ions, fluoride ions, or chlorohexidine (CHX) from resin composite [157–159].

Polymerizable cationic monomers can provide a means of antibacterial activity by contact, as bacterial adherence and biofilm formation on such restorative material becomes inhibited [160]. These monomers can be copolymerized with other monomers and covalently coupled to the polymeric matrix. Several studies have described the incorporation of quaternary ammonium (QAC) monomers such as methacryloyloxydodecyl pyrimidinium bromide (MDPB) with long-term bactericidal activity against *S. mutans* [160–163]. However, none of these materials appear to have generated practical commercial products, possibly due to the elevated water uptake that such monomers could introduce into the composite.

Recent studies have found that the presence of saliva reduced the activity of the above compounds, potentially due to electrostatic interaction between proteins from saliva and the cationic compounds [126,164]. Furthermore, it has been found that incorporation of QAC into the resin composite significantly affects the mechanical properties by increasing water absorption which acts as plasticizers and significantly alters the mechanical properties [165,166]. The hydrophilic nature of these compounds bearing permanent ionic charges is responsible for the increase in water uptake, which can further increase the rate of degradation of such composites [165]. With water uptake the resin is subjected to swelling and peeling stresses [2].

Alternatively, the release of antimicrobial agents such as fluoride ions from restorative material has been extensively studied. Fluoride has been introduced into resin composites by a variety of compounds including with the use of inorganic salts (NaF or SnF_2), leachable glasses or organic fluoride [167]. The benefits of reducing caries prevalence *versus* concerns such as dental fluorosis, for the release of fluoride from dental restorative materials such as glass ionomer cements, resin-modified glass ionomers cements and compomers have been an on-going debate for many years [168,169]. Fluoride release from restorations can provide bactericidal activity and further increase remineralization by the formation of fluoroapatite [170]. Fluoroapatite is more stable than hydroxyapatite as it is more resistant to acid attacks [170]. Furthermore, *in vitro* fluoride ions in high concentrations also inhibits metabolism of the two prominent microorganisms involved in the initiation of dental caries, *S. mutans* and *S. sobrinus* [171–174].

With conventional and resin modified glass ionomer cements (GICs), the amount of fluoride released is highest within the first 24 h after setting of the material but declines rapidly over the course of several weeks until it stabilizes at a lower level [175]. In acidic environments a greater amount of fluoride is released from restorations [176]. The rate at which fluoride is released may increase with acid production by cariogenic bacteria. Similarly, polyacid-modified resin composites (compomers) are restorative materials that release fluoride ions, although at much slower rates since the movement aqueous solutions with their dissolved salts is compromised by the presence of the hydrophobic resins. Compomers have combined polyacids used in glass ionomer cements (GICs) with methacrylate moieties linked *via* ester groups to the central monomer block [167]. These restorative materials are initially polymerized by light-activation

followed by acid–base reaction that arises from the absorption of water. Compomers benefit from the quick hardening and the initial mechanical strength of composites and the release of antimicrobial fluoride ions from GICs. However, the rationale of incorporating an acid catalyst that can hydrolyze ester groups, into a composite material must be questioned by the dental community. In both conventional GICs and compomers, the burst of fluoride from the restoration during the first several days limits the long-term antibacterial activity [78].

A more recent approach that is currently under investigation is related to the incorporation of antimicrobial agents covalently bound into the backbone of the polymeric matrix. This may provide a means for long-term antibacterial activity. A dimethacrylate monomer has been synthesized using the antibiotic ciprofloxacin [177]. The antimicrobial agent is incorporated into the monomer *via* hydrolyzable condensation type bonds. These antimicrobial agents are inactive while bound to a polymer [178]. Furthermore, with the hydrolysis of inherent ester groups within such resin composites, ciprofloxacin could be released as one of the degradation by-products. However, the mechanical and clinical performance, and their degradation profiles and long-term function have not yet been fully elucidated. Nevertheless, such monomers highlight a stragegy for controlling biofilm formation at the marginal interface in order to improve longevity of restoration materials.

3.4. *Enhancing bio-stability by reducing the rate of collagen degradation by MMPs and cysteine cathepsins*

To reduce the rate of collagen degradation by MMPs and cysteine cathepsins, superior monomer infiltration is required to seal the dentin matrix and protect collagen against degradation [179]. Alternatively, to overcome over-activation of MMPs during acid etching, MMP inhibitors such as CHX and green tea polyphenol epigallocatechin-3-gallate (EGCG) can be added as adhesive additives in dental restorations [180,181]. CHX inhibits the proteolytic activity of dentin-extracted cysteine cathepsins [182]. CHX also has a broad spectrum of antimicrobial activity and is used to treat various oral diseases. Studies have reported that 0.2–2% application of CHX as a preconditioner applied prior to the placement of dental adhesive may improve the marginal durability by altering the initial bond strength and sealing ability, thus inhibiting MMP activities [183]. EGCG has been shown to degrade the MMP molecule and inhibit the activation of proMMP-2, MMP-2, and MMP-9 [110]. Furthermore, EGCG is a natural anti-cariogenic agent that could provide antibacterial activity against *S. mutans* by suppressing specific virulence factors associated with *S. mutans*, such as acid production and acid tolerance. It is further suspected to being able to inhibit glucosyltranferases activity and suppress the growth of *S. mutans* [184]. Galardin, a potent and broad-spectrum hydroxamate-type synthetic MMP inhibitor, has also been investigated as a potential additive to dental adhesive systems. This compound is reported to inhibit MMP activity by entering the active site and binding to critical zinc atoms [185]. Galardin has been proposed to inhibit both MMP-2 and MMP-9 without compromising bond strength [186]. Further research is still required to confirm the success of these strategies *in vivo*.

4. Conclusion

Since the early reported mechanistic studies of biodegradation in the early 1990s, a vast majority of published literature has now validated that the degradation of resin composites in the oral cavity by salivary enzymes is an unavoidable outcome of conventional and many recent commercial formulations of composites and adhesives, regardless of the clinician's skills or techniques. An important challenge is that the resin is prone to hydrolysis. However, other limitations within the system include the volumetric shrinkage upon curing that generates a marginal gap at the adhesive interface between the restoration and tooth structure. This weak link allows for the microleakage of bacteria and salivary enzyme into the marginal gap, and this ultimately reduces the longevity of these restorative materials *via* biochemical destruction of both the resin and protein structures within the interface.

To reduce volumetric shrinkage, two main strategies have been considered: increasing the filler content, and secondly, modifying the organic monomer component. The current challenge of resins that undergo volumetric shrinkage upon curing is achieving volume stability while simultaneously achieving a high degree of polymerization without affecting clinical handling. Strategies such as ring-opening polymerization have been developed, however these materials require longer curing times at room temperature. Hence, it requires the use of dimethacryalte-based monomers in conjunction with them in order to achieve a faster setting time and higher bond conversion. With the inclusion of conventional monomers, the current weak link still exists with these technologies. Clinical studies demonstrate that the small reduction in volumetric shrinkage does not result in significant improvement in the longevity of these restoration materials [146]. The key to ultimately impacting secondary caries and marginal breakdown may be to effectively control and reduce the growth of cariogenic bacteria at the marginal interface. To date, fluoride-releasing composites have become the prominent antimicrobial treatment used in the oral cavity. However, most of these systems release fluoride by diffusion, which implies the exchange of water with the resin material in order to move the fluoride ions out and therefore raises concerns of resin plasticization. As a result, the antibacterial properties become depleted early on, resulting in a decrease in fluoride diffusion from the composite as fluoride concentrations decreases, limiting their long-term performance and the ultimate loss of mechanical integrity. Furthermore, with present day diets that contain high amounts of fermentable carbohydrates and frequent food intake, these composites have been incapable of fully preventing caries from occurring [187]. An alternative probiotic approach that could provide long-term antibacterial activity may be necessary to overcome the challenges associated with volumetric shrinkage and marginal breakdown. Such approaches, while non-conventional, may give clinicians on upper hand on a challenge that has eluded their ability to resolve with techniques alone.

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