Chemically Activated Glass-Ionomer Cements as Bioactive Materials in Dentistry: A Review

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Abstract: The prospect of repair, regeneration, and remineralisation of the tooth tissue is currently transitioning from the exploratory stages to successful clinical applications with materials such as dentine substitutes that offer bioactive stimulation. Glass-ionomer or polyalkenoate cements are widely used in oral healthcare, especially due to their ability to adhere to the tooth structure and fluoride-releasing capacity. Since glass-ionomer cements exhibit an inherent ability to adhere to tooth tissue, they have been the subject of modifications to enhance bioactivity, biomineralisation, and their physical properties. The scope of this review is to assess systematically the modifications of glass-ionomer cements towards bioactive stimulation such as remineralisation, integration with tissues, and enhancement of antibacterial properties.

Keywords: glass-ionomer cements; remineralisation; bioactive glasses; ion

1. Introduction

Glass-ionomer cement (GIC) is a long-established restorative dental material with several clinical applications that have remained relevant because of the chemical adhesive bond it forms at the tooth-restoration interface and its fluoride-releasing and recharging properties. It was invented by Wilson and Kent in 1969 and successfully introduced into clinical practice in 1972 [1–5]. Chemically activated GICs, commonly referred to as conventional GICs, typically consist of ion-leachable glasses based on calcium or strontium aluminofluorosilicate and weak polymeric water-soluble acids of polyacrylic acid (PAA) homopolymer, or acrylic acid, maleic/itaconic acid copolymer [3]. They set by an acid-base reaction, and the setting reaction is initiated by mixing glass powder and polymeric acids. The acid attacks and degrades the glass, which leaches out ions, commonly Ca$^{2+}$ and Al$^{3+}$ ions, into the aqueous medium [1,3]. This results in a self-hardening process, an acid-base neutralisation reaction, which forms ionically cross-linked acidic polymer chains with the multivalent counterions (Ca$^{2+}$ and Al$^{3+}$) [3]. The self-hardening process typically occurs within 2–5 min after mixing the components of the cement mix. During the cement hardening, silica and phosphate ions are also released from the glass condensate to form an inorganic network within the matrix formed [3,6].

GICs at the initial setting stage are susceptible to water exchange across their outer surface either by absorption or via desiccation [1,7,8]. The drying out leads to a chalky appearance due to the formation of a network of micro-cracks on the cement surface [1,7], which compromise the aesthetic appearance. On the other hand, the water absorption of the early-set GIC leads to swelling, which may also cause the development of micro-cracks and a possible loss of network-forming ions [1]. To prevent these water movements, it is recommended that newly set GICs be protected with a layer of either petroleum jelly or varnish after their placement [1,7]. The coating of the GIC surface has been reported to improve flexural strength, which is beneficial in clinical applications [9]. Further reactions occur as the cement continues to mature, which include an increase in ionic cross-linking,
a greater binding of water to co-ordination sites of the ions, and around neutralised polyanion molecules, which leads to an increase in the proportion of bound water within the cement and a change in the co-ordination number of aluminum, from 4- to 6-co-ordination state [1,10,11]. Other additional reactions that occur are the formation of silanol groups on the GIC surface, inorganic network formation from the ion-depleted glass, a reduction in the size of the pores trapped within the cement, and the development of ion exchange bonding to the tooth surface with time [1,10]. All these reactions during GIC maturation enhance both the mechanical and optical properties [1,10,11].

GICs are used clinically in restorative dentistry as long-term temporary restorations, definitive restorations for deciduous and permanent teeth, core build-ups, liners and bases, pulp capping agents, root surface and root end fillings, endodontic sealers, luting agents, fissure sealants, and adhesives in orthodontic brackets [12–18]. In addition, high-viscosity GIC (HVGIC) is the adhesive material of choice for the atraumatic restorative treatment (ART) technique [3,13,19]. The wide array of restorative and preventive applications of GICs in clinical practice is attributed to their biocompatibility, low pulp irritation, similar coefficient of thermal expansion as dentine, adhesion to tooth tissue (by micromechanical interlocking and, more importantly, chemical bonding), bioactivity, low microleakage at the interfaces, long-term fluoride release, and fluoride rechargeability following its depletion [3,8,12,20]. Despite these advantageous properties, GICs have some limitations, such as susceptibility to dehydration and inadequate mechanical properties, which limit their use as a dental restorative [3,8,20].

2. Search Methodology

An electronic search was conducted on the PubMed and Science Direct databases with different combinations of the following search terms: “glass-ionomer cement”, “addition”, “incorporation”, “improvement”, “enhancement”, “modification”, “adhesion”, “bioactivity”, “remineralisation”, “mechanical properties”, “antibiofilm activity”, and “antibacterial activity”. The search was restricted to articles written in English related to the modification of glass-ionomer cements. Only articles published in peer-reviewed journals were included. The search included literature reviews and in vitro and in vivo studies. Articles written in other languages without available abstracts and those related to other fields were excluded.

3. Adhesion

Glass-ionomer cements are water-based cements that facilitate their placement on intrinsically moist hard tissues in the oral environment. Thus, one of the clinical advantages is that elaborate isolation of the affected tooth tissue is not required, especially in the wet oral environment. The acid-base reaction that takes place between the water-soluble acidic polymeric phase and the basic glass causes the cement to form, and they bond particularly well with the mineral phase of the tooth, which has an abundance of calcium ions. There is evidence to support the formation of direct chemical bonds with the polymeric acid [1], which is mainly responsible for the effective adhesion of GICs to the tooth substrates.

The chemical bond GIC forms with tooth tissue, as shown in Figure 1, reduces the incidence of adhesive failures, which in turn increases clinical survival when used in different clinical applications such as tooth repair, preventive, and adhesive measures [1,8].

The adhesion process begins with the wetting of the hydrophilic tooth surface following the placement of freshly mixed cement paste. The cement forms an intimate contact with the tooth, and this leads to adhesion through hydrogen bond formation between the free carboxyl groups of GIC and the bound water on the tooth surface [1,8]. These bonds are gradually replaced by true ionic bonds formed between calcium ions in the tooth and the anionic carboxylate functional groups of the polyacid molecules of the cement. This results in the slow formation of an interfacial zone of ion exchange, which leads to the formation of a strong adhesion of the cement with the tooth tissue, and the strength continues to increase over several days [1,8,10,18,21]. Adhesion of GIC to the tooth can be further improved by using conditioners, commonly 10–20% polyacrylic acid, on the tooth
surface prior to the cement placement [1,8,22]. This surface treatment leads to self-etching that helps remove the smear layer, opening the dentinal tubules and partially demineralizing the tooth surface, which results in a thin hybrid layer between hydroxyapatite-coated collagen fibrils at the tooth and the cement surface [1,8]. This self-etching process increases the adhesion through micromechanical interlocking by the formation of short cement tags within the dentine surface, thereby increasing the surface area for retention [1,8]. The increased clinical survival of GIC is attributed to the adhesion process as discussed, which contributes to its retention to the tooth and reduces the marginal leakage, which in turn lowers the incidence of secondary caries since micro-organisms are unable to enter the space under restorations [1,8,21].

![Conventional glass-ionomer cement setting reaction and chemical adhesion to tooth tissue](image)

**Figure 1.** Chemical adhesion of glass-ionomer cement to tooth tissue.
4. Bioactivity

Bioactive materials are those that possess the ability to leach specific ions at the bonding interface, which usually results in a therapeutic effect and possible biominalisation [8,23]. In relation to this, GICs are considered ‘bioactive’ or ‘smart’ materials because they release biologically active ions such as fluoride, calcium, strontium, sodium, phosphate, and silicate into the surrounding environment at therapeutic levels under acidic conditions that result in adhesive bonding [8,23]. Although fluoride ions do not participate in cement formation or adhesion, their release is generally considered to have clinical benefits, even though the reports supporting this are not fully convincing and are debatable [8]. Fluoride ions are reported to inhibit the formation of secondary caries, encourage the remineralisation process via the formation of fluoroapatites, which resist demineralisation due to their low solubility, disrupt ionic bonding to the tooth surface during pellicle and plaque formation, reduce the acidogenicity of bacteria, and slow down bacterial metabolic activities [24–29]. However, other studies suggest that the antibacterial activity of GICs is most likely due to the low pH of the GIC setting reaction and that the fluoride ions have minimal antibacterial effects [30]. This is plausible since the effect may be mainly due to the reduction in acidogenicity of the bacteria and disruption of plaque and pellicle formation. Since fluoride ions are not a part of the setting reaction but essentially remain present in the cement matrix, it is possible to recharge them, enabling both release and recharge at high concentrations of fluoride. In the long term, the fluoride re-released after recharging may be much more important than the initial ‘burst’, which is short-lasting [31]. In addition to the leaching of fluoride, other caries inhibitory species such as strontium, zinc, calcium, and aluminium have been suggested to play a role in the antibacterial activity of GICs [24,25,32]. Calcium and phosphate are the main component ions of hydroxyapatite (HA), and they encourage tooth remineralisation when present in a mildly acidic medium [8]. GICs also take up calcium and phosphate ions present in saliva, and this leads to a harder surface [8,33]. Silicate can be incorporated into the hydroxyapatite of the tooth without having a negative impact on the crystal geometry, although it remains unclear whether this occurs under clinical conditions [8,34]. In essence, the ability of GICs to exchange ions with their surroundings leads to the formation of an ion-rich layer over time that is resistant to acid attack. This in turn results in a low incidence of secondary caries at the tooth-restoration interface when GIC is used as a restorative material [8].

The focus of recent glass-ionomer research has been on bioactivation, with the aim of improving the mechanical properties [35–38]. The term ‘bioactivity’ has several meanings depending on context, but recent research has referenced the following definitions when investigating the bioactivity of GICs: Firstly, bioactivity can be defined, based on adhesion, as the ability of a material to be biologically active and form a bond with living tissue without the formation of a fibrous layer in vivo [35,39]. With reference to this definition, GIC is regarded as bioactive since its polyalkenoic acid component forms a chemical bond with the apatite component of enamel, dentine, and bone [35].

On the other hand, GIC is not yet typically regarded as bioactive based on other definitions focused on the biominalisation induction capacity of materials. Such definitions describe a material as bioactive when it can form a layer of material, such as apatite, that is inherent to and integrates with the body [23,35,40,41]. In this context, materials are commonly referred to as bioactive if they can interact with living tissues and prompt a cellular response to stimulate HA formation [42]. A material’s bioactivity is therefore commonly defined as the ability of a material to induce apatite formation on its surface in vitro after immersion in a simulated body fluid (SBF) solution [23,39,43,44] and in vivo likewise [23,39,44]. Therefore, the bioactivity of dental materials commonly relates to their potential to induce specific and intentionally desired mineral attachment to the dentine substrate at the material-tooth tissue interface. It is important that these bioactive materials convert to HA in a controlled manner and time [39]. The bioactivity of glass-ionomers, as conducted in several in vitro studies, is predicated on its HA formation ability on the material surface upon immersion in a physiological fluid, commonly SBF [35,36,42,45–47].
This method has the drawback of reporting false positive and false negative results; therefore, it is recommended that, in addition to in vitro cell tests, in vivo studies be performed to validate the bioactivity results that are obtained when tested in simulated body fluid (SBF) [35,48].

Several factors, such as the concentration of calcium and phosphate ions, pH, the presence or addition of bioactive particles, and the GIC composition (the ions present in the glass phase, PAA, monomers, primers, and the size and volume of particles) have been suggested to account for HA nucleation and growth [46,49,50]. It has been reported that PAA inhibits HA formation because of the intermediate compound formed by the reaction of anions from the PAA with calcium cations, and this compound delays the interaction of the calcium and phosphate ions to form HA precursors [43,46,51,52]. However, it has also been reported that this intermediate compound serves either as nucleators or inhibitors of HA to regulate the deposition of minerals [46,53].

Incorporation of bioactive particles into GIC has been of concern due to reports on the detrimental effects it has on the mechanical properties despite its promotion of bioactivity [54,55]. However, more recent literature suggests that attempts to promote bioactivity while optimising or even enhancing the mechanical properties are viable [35,36,46,56]. The promotion of remineralisation potential of GICs would broaden its clinical applications, particularly when used in long-term ART restorations, since apatite integration within the tooth structures would lead to proliferation of dental cells and further enhance adhesion, which in turn would improve the physical properties and retention within demineralised dentine tissue [35].

5. Remineralisation Properties of GIC

Calcium and phosphate ions play an important role in the balance of the HA mineral phase of dental hard tissues, and under mildly acidic conditions, they can promote tooth remineralisation [8]. Due to the ability of GIC to exchange ions with the surroundings, which is also applicable to tooth tissue, an ion-rich layer is formed over time at the GIC-tooth interface, which is resistant to acid attack, therefore reducing the incidence of secondary caries [8].

The mineralisation potential of GIC is a desirable property, which has prompted researchers to explore different ways to enhance the bioactivity of GIC by exploring the chemistry and developing new routes to glass synthesis and, more commonly, modification of the GIC-matrix by incorporating bioactive glasses (BAG), hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), casein phosphopeptide–amorphous calcium phosphate, and other bioactive materials into the glass-ionomer powder and/or the liquid phases [5,12,14,15,35,36,45,46,55–68].

Since its introduction in 1969 by Larry Hench [69], BAG has widely been used in dental materials such as gutta percha, dental adhesives, GIC and composite resins, pulp protective dressings, endodontic sealants, and orthodontic cements [46]. The combination of BAG and GIC has benefits, with a significant increase in remineralisation capacity; however, the effect of BAG on the mechanical properties and setting kinetics of GIC are often contradictory [34,35,45,49,52,53,59–64,70–74]. This is in agreement with other studies reporting that higher amounts of BAG additives in GIC cements compromise the mechanical properties, which are attributed to the partial replacement of the fluoro-alumino silicate glass powder phase. This results in a decrease in the amount of Al\(^{3+}\) in the glass, resulting from its replacement of Na\(^+\) in BAG, and a reduction in the bond strength between PAA and the ions released [3,35,54]. The addition of Al\(^{3+}\) to the BAG composition has been reported to be beneficial in improving the strength of BAG-GIC composites, but this decreases bioactivity [3,35,54]. The inclusion of nano-sized particles of BAG into glass-ionomers is also believed to at least reduce the likelihood of the extent of compromise in mechanical properties. The BAG nanoparticles may occupy the voids between the larger glass-ionomer particles and act as additional PAA bonding sites, thereby improving the mechanical properties [61]. The reactivity of the BAG nanoparticles with the GI matrix is higher, and the pH rapidly increases, which could further develop the silica gel and apatite
The incorporation of BAG nanoparticles into GICs can enhance their odontogenic and osteogenic properties for clinical applications such as root surface fillings and bone regeneration [61].

β-TCP contains a significant amount of calcium and phosphate, which can promote remineralisation of enamel when incorporated into the glass phase of GIC [76]. A recent report has shown that the addition of fortilin (which is also referred to as ‘translationally controlled tumour protein’) to β-TCP as a GIC additive further promotes odontogenic differentiation and mineral deposition in human dental pulp stem cells (hDPSCs) [68]. HA nanoparticles are widely used in dentistry because they are biocompatible bio-ceramics that promote enamel remineralisation and have superior osseointegration properties [77,78]. Numerous studies have revealed that the incorporation of hydroxyapatite nanoparticles into GIC can significantly improve the interfacial bond strength, improve marginal adaptation to tooth tissue, enhance the mechanical properties, reduce cytotoxicity, and leave the sustained release of fluoride unaffected [77,79–81].

Forsterite (Mg\(_2\)SiO\(_4\)) has been reported to be more effective as nanoparticles in promoting bioactivity and enhancing the mechanical properties of GIC. This is attributed to the higher surface energy and increased reactivity [63,66]. Wollastonite (also known as calcium silicate) is another material known to promote bioactivity. It is available in nature or can be synthesised from mine-silica and limestone. Its inclusion into the powder phase of GIC reinforces the mechanical properties, reduces cracks, and decreases shrinkage, due to its acicular nature [3,82]. Wollastonite has been reported to promote the formation of an apatite layer on the surface of powder in simulated body fluid [83]. Published data related to the combination of wollastonite with GICs are limited, but it has been reported that the incorporation of wollastonite into GIC promotes the bioactivity without compromising compressive strength [56]. Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) nanocomplexes have been shown to prevent enamel demineralisation and promote the remineralisation of carious enamel [66,84]. The incorporation of CPP-ACP into the glass phase has been found to enhance the anti-cariogenic properties of GIC. This is because of the localisation of casein phosphopeptide to amorphous calcium phosphate at the tooth surface, which results in a prolonged state of supersaturation of the tooth mineral [38,84]. CPP-ACP as GIC additives has shown to increase the release of calcium, phosphate, and fluoride ions from the cement, and this leads to increased protection of the adjacent dentine from acid demineralisation [85]. In addition, CPP-ACP interacts with fluoride ions released from GIC to form a stabilised amorphous calcium fluoride phosphate complex, and this further augments its anti-cariogenic potential [38,84,85]. The various strategies that have been used so far in promoting the remineralisation of GICs are summarised in Table 1 [5,15,16,35–38,55–59,62–65,68,76,86].

### Table 1. Modification of GIC using various additives for the promotion of bioactivity [5,15,16,35–38,55–59,62–65,68,76,86].

<table>
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<tr>
<th>Bioactive Additives</th>
<th>Effect on Remineralising and Mechanical Properties</th>
<th>GIC Modification Studies</th>
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<tr>
<td><strong>1 (Bioactive Glass)</strong></td>
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<td>10% and 30% commercially available S53P4 bioactive glass (BAG) having a composition SiO(_2) 53%, Na(_2)O 23%, CaO 20% and P(_2)O(_5) 4%, with average particle size of 20 µm</td>
<td>The incorporation of BAG particles into conventional GIC powders compromised the CS, VHN and YM. The higher the BAG concentration, the further the reduction in mechanical properties but BAG inclusion improved bioactivity by surface deposition of calcium-rich precipitates.</td>
<td>Yli-Urpo et al. (2005)</td>
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<td>10 and 30% sol–gel-derived glass with an average size of 2.45µm and a composition, 70SiO(_2)-25CaO-5P(_2)O(_5)</td>
<td>The inclusion of sol–gel derived BAG (10–30%) additives to glass-ionomer promoted the induction of apatite mineral deposits on the surface and produced higher cell viability, without compromising the DTS.</td>
<td>Choi et al. (2008)</td>
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<td>5% of sol-gel-derived bioactive glass nanoparticles (nBAG)~42 nm with or without 0.5% (low molecular weight) chitosan was added into the GI liquid</td>
<td>5% nBAG and 0.5% chitosan or 5% nBAG nanoparticles only, significantly increased CS, FS, DTS. The incorporation of nBAG into GIC led to increased biomineralisation with human dental pulp cells without cytotoxicity.</td>
<td>Kim et al. (2017)</td>
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<td>Two types of (modified) BAGs were synthesised by the melt method and added to LG26 at 10, 20 and 30% concentrations (45S5 bioglass with composition SiO₂, 48%; P₂O₅, 26%; CaO, 14%; Na₂O, 25.45%; CaF₂, 10%; and BAG)</td>
<td>The inclusion of BAG &gt; 10% into GIC increased bioactivity but compromised the CS. However, the CS increased but at the expense of its bioactivity following the addition of Al³⁺ into the BAG (particularly the CF9 BAG combinations containing maximum 10 mol% Al³⁺), before incorporating the 20% of the modified BAG into the GI powder.</td>
<td>De Caluwe et al. (2017)</td>
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<td>2, 5, 10, 15 and 20 wt% of 45S5 bioglass-ceramic particles containing a mechanically strong combeite phase (mean particle size = 4.6 µm)</td>
<td>5 wt% bioglass-ceramic incorporation into GIC significantly increased CS and DTS and enhanced remineralizing properties. However, there was a reduction in HN.</td>
<td>Zandi Karimi et al. (2019)</td>
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<td>10% conventional 45S5 bioactive glass or 10–40% Lithium-containing bioactive glass (prepared by substitution of Li₂O for Na₂O in 45S5 bioglass) (&lt;38 µm in diameter)</td>
<td>Lithium-containing bioactive glass-GIC (LithGlassGIC) released lithium early at a safe dose and stimulated Wnt/β-catenin activity. Increasing the lithium concentration in LithGlassGIC-treated teeth had significantly more mineralised tissue and higher tertiary dentine thickness compared to conventional GIC radiopaque and 10% 45S5-GIC.</td>
<td>Alaohali et al. (2021)</td>
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<td>2 additives were used: 10% and 50% chitosan 10% and 30% BAG</td>
<td>BAG or chitosan addition to GIC (as a bone cement and root end filling material) significantly increased proliferative and alkaline phosphatase activity.</td>
<td>Ranjani et al. (2021)</td>
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<td>5%, 10% and 20% sol–gel-derived, sodium-free BAG, 35% SiO₂, 31% CaO, 6% P₂O₅ (&gt;99% of BAG were &lt;20 µm sized particles)</td>
<td>The incorporation of sodium-free BAG into GIC resulted in fluorapatite precipitates on their surface and on the GIC-approximated demineralised dentine surface which covered the dentinal tubules. As BAG increased to 20%, the bioactivity was enhanced without compromising the shear bond strength.</td>
<td>Kim et al. (2021)</td>
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<td>Glass component prepared by mixing of 45S5 Bioglass⁶ and 45S5 bioglass-ceramics (74% crystallinity, size ranged from 0.3 to 100 µm; mean size = 6.3 µm)</td>
<td>The aluminium-free GIC with the solid component containing 50 wt% Bioglass⁶ and 50 wt% bioglass-ceramic improved the CS and HN. It was suggested that bimodal particle size distribution of the solid component in these GICs may have contributed to their high packing density and structural integrity after setting where smaller particles mostly take part in the setting reaction while larger particles participate in strengthening mechanisms such as crack deflection.</td>
<td>Zandi Karimi et al. (2021)</td>
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<td>(2) Surface-reaction-type prereacted glass-ionomer (S-PRG) fillers</td>
<td>S-PRG induced the differentiation and mineralisation of osteoblastic cells when used as fillers in endodontic sealers.</td>
<td>Kawashima et al. (2020)</td>
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<td>(3) nano-β-tricalcium phosphate (nano-β-TCP)</td>
<td>S-PRG (average particle size 3 µm) glass-ionomer endodontic root canal sealer was shown to have significantly more antibacterial and anti-inflammatory effects compared to sealers containing conventional silica fillers.</td>
<td>Miyaji et al. (2020)</td>
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<td>(4) Al-free glass of composition 0.3SiO₂·0.333ZrO₂·0.25(α- b)CaO·2SrO·0.015Na₂O·0.06P₂O₅ (where a,b = 0.000 or 0.125, respectively)</td>
<td>The combination of SrO and CaO in an aluminium-free GIC (Zn-containing) produced a glass composition that generated cements with enhanced mechanical performance and bioactivity, although the strength was not suitable for use in load-bearing areas.</td>
<td>Gomes et al. (2013)</td>
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<td>(5) Forsterite (Mg₃SiO₄) nanoparticles</td>
<td>The addition of 3% forsterite to glass-ionomer powder promoted bioactivity by formation of apatite deposits on the surface whilst improving the CS, FS, and DTS significantly up to 75%, 78%, and 30%, respectively. However, there was a reduction in F⁻ release.</td>
<td>Sayyedan et al. (2013)</td>
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<td>(6) Fluorapatite</td>
<td>The incorporation of 3 wt% fluorapatite nanoparticles into GI powder resulted in a significantly higher CS and promoted the nucleation of apatite layer on the surface of GIC specimen.</td>
<td>Khaghani et al. (2016)</td>
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<td>1, 3 and 5 wt% of sol-gel fluorapatite nanoceramic particles (~70 nm)</td>
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<td>(7) Wollasonite and Mineral Trioxide Aggregate (MTA)</td>
<td>The inclusion of either wollasonite or MTA (20% or below) into glass-ionomer powders resulted in a mineralised surface layer following storage of specimen in SBF without compromising CS or setting properties. The MTA additives increased the CS as the modified GIC matured compared to the control.</td>
<td>Chen et al. (2016)</td>
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<td>10, 20 and 30% wollasonite (β-CaSiO₃) or MTA (200 µm)</td>
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<td>(8) Casein phosphopeptide amorphous calcium phosphate (CPP-ACP)</td>
<td>The incorporation of 3% CPP-ACP into GIC promoted remineralisation and did not adversely affect the adhesion to artificial caries-affected dentine.</td>
<td>Zhao et al. (2017)</td>
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<td>3% CPP-ACP</td>
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<td>(9) Beta-tricalcium phosphate</td>
<td>GIC incorporated with fortilin and TCP induces odontogenic differentiation and mineral deposition in human dental pulp stem cells.</td>
<td>Sangsuwan et al. (2022)</td>
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<td>0.05% tricalcium phosphate and 1 µg fortilin (a translationally controlled tumour protein)</td>
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Abbreviations: CS Compressive strength, VHN Vickers Microhardness, YM Young’s Modulus, DTS Diametral tensile strength, HN Microhardness, SBF Simulated body fluid, FS Flexural strength.

6. Antibacterial Properties

With an increasing clinical demand for tooth-coloured materials with superior mechanical properties, wear resistance, remineralisation, and antibacterial effects, improvements to these properties in GIC have gained the interest of researchers. The low pH during the initial setting of GIC, the fluoride-releasing properties of GIC, as well as its ability to leach other therapeutic ions such as strontium and zinc, have all been suggested to play a role in the antibacterial property of GIC; however, these effects are minimal [2,24,25,32,87,88].

The slight antimicrobial properties displayed by unmodified GIC are attributed to the fluoride ions that are released, which have therapeutic benefits against bacteria remnants at the restoration-dentine interface following excavation of infected dentine [89]. The fluoride release has been shown to encourage the remineralisation process in addition to the formation of low-soluble fluorapatite (FAP), which is more resistant to demineralisation [2,24–29,90]. FAP formation disrupts ionic bonding to the tooth surface during pellicle and plaque formation, reduces the bacteria’s acidogenicity, and slows down bacterial metabolic activities [2,24–29,90]. However, it has been reported that fluoride release most likely has minimal antibacterial effects and that this antibacterial property ceases after the GIC hardens since it is attributed to the low pH of the GIC setting reaction [30,87,88,91].

In addition to its mechanical, remineralising, and adhesive properties, improvements in GIC’s antibacterial properties would be highly beneficial in treating residual cariogenic bacteria and preventing the recurrence of caries. This ultimately is expected to increase the clinical survival rates when used as restorative dental material and improve its efficacy as a lining material by serving as an antibacterial seal under restorations and as a fissure sealant over the occlusal surfaces of teeth highly susceptible to caries [92,93]. Enhancing antibacterial activity would be particularly useful in ART, which involves the removal of carious lesions and placement of HVGIC with the use of manual instruments only. ART
is usually performed in constrained environments where functional dental equipment is lacking or in cases of uncooperative patients, such as special needs patients, where it is difficult to manage the patient and when it is unlikely to completely remove infected caries [92–94].

The limited antibacterial activity of GICs has led to studies to augment this property by the addition of a range of antimicrobial agents to the powder or liquid phase of GIC that can interfere with metabolic activity and inhibit biofilm formation and the adherence of cariogenic bacteria [3,12,87,89,95,96]. Enhancement of the antibacterial activity of GIC is largely dependent on the concentration and type of antimicrobial agent used as an additive and its release rate from the cement surface layer [3,12,87]. However, it is of utmost importance that if the inclusion of these antimicrobial additives into glass-ionomer fillers or liquids does not improve the physical properties, fluoride release, and adhesive properties of the cement, it should at least not compromise these properties for it to remain clinically relevant [3,12,87]. So far, the incorporation of these antibacterial modifiers into conventional GICs has led to promising results, with the potential for these modified GICs to be more clinically beneficial [3,12,87,95–97].

Some of the additives that have been explored are natural products such as graphene, chitosan, propolis, turmeric, and epigallocatechin-3-gallate; antibiotics such as metronidazole, ciprofloxacin, and minocycline; antiseptics such as chlorhexidine (CHX) [CHX diacetate and CHX digluconate], triclosan, quaternary ammonium salts such as cetrimide, benzalkonium chloride, and cetyl pyridinium chloride; and metallic dopants such as silver, zinc, magnesium, and titanium [3,12,87,89,95–97]. Chlorhexidine (CHX) has a wide spectrum of activity against Gram-positive bacteria, especially mutans streptococci, Gram-negative, aerobic and facultative anaerobic bacteria, and fungi. Whilst some studies have reported that the incorporation of CHX salts into GIC increases their antimicrobial activity without compromising their physical properties, other studies have reported that CHX additives negatively impart mechanical properties, fluoride release, and biocompatibility at high doses. Following extensive research, it has been suggested that an addition of not more than 1% of CHX into GIC provides optimal antibacterial activity without compromising the physical properties [92,98–101]. A higher concentration of CHX is not contributory to the formation of the glass-ionomer network and would weaken the scaffold, thereby affecting the physical properties of GICs [5,102]. CHX has also been reported to have long-term antibacterial properties because of its substantivity effect by binding to hydroxyapatite. This leads to a gradual release of CHX over an extended period [98,103,104]. The addition of quaternary ammonium salts as well as antibiotics have also been reported to be dose-dependent in order to be effective without compromising physical properties [30,94,103,105–109]. Polyhexamethylene biguanide (PHMB) is another broad-spectrum bactericidal agent that has recently been explored as a glass-ionomer additive. It has been widely used in trauma treatment, ophthalmic disinfection, and many other biomedical fields. PHMB eliminates bacteria by binding protonated groups to the anionic membrane of bacteria, which results in a leak in the cytoplasm. Unlike chlorhexidine and quaternary ammonium compounds, PHMB not only has superior antibacterial activity but has also been reported to be biocompatible at high concentrations [77,110].

Chitosan is a natural biopolymer that is relevant in the dental (or biomedical) field due to its biocompatibility, natural adhesive properties, and antibacterial properties [36,64]. It acts as a physical or chemical binder between the glass filler and matrix in GIC, thereby improving the mechanical properties [36]. Epigallocatechin-3-gallate (EGCG) is another antibacterial agent that is worth exploring as an additive. It is a major polyphenol present in green tea, and it has been reported to be effective against both Gram-positive and Gram-negative bacteria [3,111]. It destroys the cellular structures, inhibits cellular enzymes, and causes intracellular oxidative stress in the bacteria [112,113]. A study has shown that the inclusion of EGCG into GICs at low concentration improved the antibacterial activity and some mechanical properties of GICs [114]. The strength enhancement is attributed to
an increase in crosslinking and a high degree of poly-salt bridging [3,115,116]. Another natural product that can serve as an antibacterial additive is propolis. It is a natural resin sourced from honeybees. Ethanolic extracts of propolis (EEP) are the most used form for antibacterial activity [117]. The mechanism of its antibacterial property is associated with its activity against cariogenic bacteria and inhibition of glucosyltransferase activity [118]. Despite its well-known antimicrobial activity against oral microorganisms, only a few studies have investigated the effect on the physical properties of GIC when EEP is used as an additive [119,120]. The paucity of data investigating the effect of EGCG and EEP on GIC properties shows that more in vitro studies still need to be carried out before it can be used for clinical applications.

Ionic dopants such as magnesium, zinc, silver, copper, and titanium are of interest for use in biomaterials due to their antimicrobial properties against bacteria, spores, and viruses [121,122]. Most nano-metallic dopants such as these have been reported to be cytotoxic as the concentration increases. Despite the mechanical reinforcement observed when nano-metallic dopants such as zinc, silver, copper, and titanium oxides are incorporated into GIC, there have been reports of cytotoxicity, discoloration, poor marginal adaptation, and decreased interfacial bonding following an increase in concentration [2,67,77,123–128]. On the other hand, magnesium nanoparticles have been reported to be biocompatible and thermally stable; however, they compromise the physical properties of GIC when added in high concentrations [96,129,130]. Little research has been performed on investigating the effects of fluorinated graphene (FG) (a derivative of graphene). FG can serve as an antibacterial material since graphene has been reported to be effective against bacteria [2]. FG has been reported to be a biocompatible material because it enhances the proliferation and polarisation of mesenchymal stem cells and the neuro-induction of stem cells [2,131,132]. The inclusion of FG in GIC has been reported to be highly beneficial for the property enhancement of GIC. Studies have shown that it significantly improves the mechanical and antibacterial properties of GIC without interfering with fluoride release [2,133].

A summary of attempts made by various researchers to improve the antibacterial activity alongside other properties is shown in Table 2 below [2,4,30,77,87,91–94,96–99,101,103,105–109,114,119,120,123,127,129,133–146].


<table>
<thead>
<tr>
<th>Antimicrobial Additives</th>
<th>Effect on Antibacterial Activity and Mechanical Properties</th>
<th>GIC Modification Studies</th>
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<tr>
<td>(1) Chlorhexidine (CHX)</td>
<td>Incorporation of 1% CHX diacetate was found to improve AA against S. mutans, L. casei and A. naeslundii without compromising CS, bond strength to dentine and without interfering with the setting characteristics. Concentrations of 2% or higher extended ST and reduced CS.</td>
<td>Takahashi et al. (2006)</td>
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<td>The addition of 0.5% CHX diacetate or 1.25% CHX digluconate added to GIC can exhibit long-term antibacterial effects against S. mutans and L. acidophilus without compromising the CS, DTS, VHN, BFS, working or setting times.</td>
<td>Turkun et al. (2008)</td>
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<td>In a clinical study, the bacterial vitality was significantly lower when 2% CHX additives were used cGIC and RMGIC compared to unmodified GICs.</td>
<td>Du et al. (2012)</td>
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<td>The AA against S. mutans and L. acidophilus increased following the addition of 0.5% CHX without affecting the TBS, VHN, and ST.</td>
<td>Marti et al. (2014)</td>
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<td>The antibacterial effect of a novel GIC incorporated with CHX-HMP nanoparticles was shown to be dose-dependent. The release of CHX without affecting DTS and fluoride ion release when the CHX-HMP concentration was below 10%.</td>
<td>Hook et al. (2014)</td>
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<td>CHX digluconate at 1.25% improved the AA against S. mutans and did not affect the CS, KHN, FR or cell viability. The CHX-GIC used at this concentration in the in vivo section of this study showed a significant reduction in S. mutans level in saliva and biofilm of study participants without affecting the 1-year clinical survival when used for ART restorations.</td>
<td>Duque et al. (2017)</td>
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<td>Antimicrobial Additives</td>
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<td>(2) Quaternary ammonium salts</td>
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<td>(a) Cetrimide (CT) and/or chlorhexidine (CHX)</td>
<td>1% CHX-GIC and 1% CT-GIC groups did not affect the CS or ST whilst improving the AA against <em>L. casei</em>.</td>
<td>Deepalakshmi et al. (2010)</td>
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<td>The inclusion of 2.5% CHX/2.5% CT mixture into the powder phase of GIC resulted in AA against <em>S. mutans</em> and <em>L. casei</em>, over an extended period but a decrease in VHN and cumulative FR.</td>
<td>Tüzüner et al. (2011)</td>
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<td>The addition of 2.5% CHX diacetate/2.5% CT mixture into the powder phase of luting GIC resulted in AA against <em>S. mutans</em> and <em>L. casei</em>, over a 180-day period but compromised SR, FS and increased SL.</td>
<td>Korkmaz et al. (2013)</td>
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<td>(b) Benzalkonium chloride (BC), cetylpyridinium chloride (CPC), CHX and CT</td>
<td>The addition to CHX hydrochloride, CPC and CT into the powder and benzalkonium chloride into the liquid component of GIC at a concentration greater than 1% compromised CS.</td>
<td>Botehlo (2003) Botehlo (2004)</td>
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<td>(c) Benzalkonium chloride and cetylpyridinium chloride</td>
<td>The release of BC and CPC when used as additives (1–3%) to modify GIC occurred at early hours (2–3 h) following setting. However, these additives had an effect on CS and slightly altered ST.</td>
<td>Dimkov et al. (2021)</td>
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<td>(3) Polyhexamethylene biguanide (PHMB)</td>
<td>The addition of 0.2 or 0.4% PHMB to 6% nano-HA for use as a GI additive significantly increased the AA of the cement against <em>S. mutans</em> without having any cytotoxic effect. This was an added property enhancement of GIC in addition to improvement of CS, VHN and decrease in microleakage.</td>
<td>Zhu et al. (2022)</td>
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<td>(4) Triclosan</td>
<td>Triclosan (2.5%) incorporated GIC was more effective against <em>L. acidophilus</em> and <em>S. mutans</em> than CHX incorporated GIC. Its effect on the physical properties were not investigated in this study.</td>
<td>Sainulabdeen et al. (2010)</td>
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<td>There was no difference in the microleakage of 2.5% triclosan incorporated GIC and that of the cGIC. SBS was found to be higher than SBS of the cGIC. The extent of its AA was not investigated.</td>
<td>Somani et al. (2014) Somani et al. (2015)</td>
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<td>(5) Antibiotics</td>
<td>The addition of 1.5% concentration ratios of antibiotics (ciprofloxacin, metronidazole, and minocycline) into the glass phase of GIC were effective against <em>S. mutans</em> and <em>L. casei</em> with satisfactory CS and bond strength to dentine. Greater concentration of 3% and 4.5% led to a significant decrease in these physical properties.</td>
<td>Yesilyurt et al. (2009)</td>
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<td>The addition of 1% ciprofloxacin and metronidazole into GIC was effective against <em>S. mutans</em> and <em>L. casei</em> and enhanced its fluoride-releasing ability without interfering with ST or compromising the CS, SBS and microleakage.</td>
<td>Prabhakar et al. (2013)</td>
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<td>The incorporation of CHX diacetate and antibiotics (ciprofloxacin, metronidazole, and minocycline) at 1.5% into GIC was reported to be the optimal concentration for effective inhibition of <em>S. mutans</em> without compromising the CS.</td>
<td>Mittal et al. (2015)</td>
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<td>(6) Natural products</td>
<td>Incorporation of acidic solutions of CH into the PAA liquid of GIC at 5–10% vol. ratio improved the antibacterial properties against <em>S. mutans</em> without affecting the bond strength to dentine.</td>
<td>Ibrahim et al. (2015)</td>
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<td>(a) Chitosan (CH)</td>
<td>Dual modification of GIC using 10% CH in the liquid phase and 3% TiO$_2$ nanoparticles in the powder phase led to significant improvement in the AA. These additives led to the enhancement of FS and CS, without adversely affecting surface hardness.</td>
<td>Ibrahim et al. (2017)</td>
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<td>The addition of 10% CH solution into the liquid phase of GIC resulted in an improved AA against <em>S. mutans</em> and significant increase in SBS.</td>
<td>Debnath et al. (2017)</td>
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<td>CH-modified GIC (10% w/w) and CHX-CT modified GIC (2.5/2.5% w/w) were used in an in vivo study. Results revealed that CH modified GIC was more superior in AA against <em>S. mutans</em> &amp; Lactobacillus and CS compared to CHX-CT modified and cGIC.</td>
<td>Mishra et al. (2017)</td>
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<tr>
<td>(6) Natural products</td>
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<tr>
<td>(b)  Ethanol Extract of Propolis (EEP)</td>
<td>An effective AA and antibiofilm activity against <em>S. mutans</em> were observed following addition of 25% and 50% EEP to GIC liquid phase. However, its effect on physical properties was not reported.</td>
<td>Topcuoglu et al. (2012)</td>
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<td>GIC modification with an increasing concentration of EEP up to 50% in the liquid phase increased the VHN without affecting microleakage.</td>
<td>Altunsoy et al. (2016)</td>
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<td>(c)  Epigallocatechin-3-gallate (EGCG)</td>
<td>EGCG incorporated into GIC at the concentration of 0.1% (wt/wt) improved antibacterial properties against <em>S. mutans</em> and significantly enhanced the FS and VHN with no influence on FR.</td>
<td>Hu et al. (2013)</td>
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<td>(7) Inorganic dopants</td>
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<td>(a)  Graphene</td>
<td>The addition of 2% fluorinated graphene (FG) of whitish colour into the glass phase of GIC improved AA effectively against <em>S. mutans</em> and <em>S. aureus</em>. Incorporation of 2% FG did not alter the colour of the GIC and led to a significant increase in the VHN and CS. The WR, FR and the dissolving-resistance ability were also improved.</td>
<td>Sun et al. (2018)</td>
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<td>(b)  Silver nanoparticles (nano-Ag)</td>
<td>The inclusion of nano-Ag into the glass phase of orthodontic GIC showed to be effective against <em>S. mutans</em> but decreased the bond strength with increasing concentration. However, all specimens still met the bond strength specification.</td>
<td>Li et al. (2013)</td>
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<td>(c)  Reduced graphene-silver nanoparticles composite (R-GNs/Ag)</td>
<td>The incorporation of up to 0.5% nano-Ag to the liquid phase of GIC led to a significant improvement of AA against <em>S. mutans</em> and <em>E. coli</em> and a marked increase in CS whilst maintaining the ST within the ISO limits.</td>
<td>Paiva et al. (2018)</td>
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<td>(d)  Titanium oxide nanoparticles (nano-TiO₂)</td>
<td>The incorporation of 3% nano-TiO₂ into GI powder increased the AA against <em>S. mutans</em> and resulted in significant improvement in CS, FS, FT and a slight increase in VHN and TBS.</td>
<td>Elsaka et al. (2011)</td>
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<td>Unlike modification of GIC used as a liner and core build up, the addition of 3% or 5% nano-TiO₂ to restorative GIC significantly enhanced AA against <em>S. mutans</em> and caused a marked increase in CS, FS, VHN, without interfering with bond strength to enamel and dentine.</td>
<td>Garcia Contreras et al. (2015)</td>
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<td>(e)  TiO₂ nanoparticles and cellulose nanocrystals (CNCs) co-dopants</td>
<td>Co-doping of GI powder with 2% nano-TiO₂ and 1% CNC significantly improved the CS, SBS, and AA against <em>C. albicans</em>, and reduced the WR and dissolution of the cement. However, it had a slightly negative effect on the viability of L-929 cells.</td>
<td>Sun et al. (2019)</td>
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<td>(f)  Magnesium nanoparticles (nano-MgO)</td>
<td>Addition of nano-MgO into GIC showed a marked increase in AA and antibiofilm activity (against <em>S. mutans</em> and <em>S. sobrinus</em>) from 2.5% to 1% concentration, respectively.</td>
<td>Noori &amp; Kareem (2019)</td>
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<td>Incorporation of 1% nano-MgO into GIC did not interfere with the setting time and did affect CS, DTS and SBS of enamel and dentine. Higher concentrations compromised the setting characteristics and physical properties.</td>
<td>Noori &amp; Kareem (2020)</td>
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<td>(g)  Zinc nanoparticles (nano-ZnO)</td>
<td>A concentration of 3% nano-ZnO into GI powder led to significant increase in AA against <em>S. mutans</em> without compromising CS and SBS.</td>
<td>Vanajassun et al. (2014)</td>
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<td>The inclusion of 1% and 2% nano-ZnO into the cGIC and RMGIC did not promote AA against <em>S. mutans</em>. This study did not investigate the effects of nano-ZnO on setting, physical or adhesive properties.</td>
<td>Garcia et al. (2017)</td>
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Table 2. Cont.

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<tr>
<td>(h) Hydroxyapatite nanoparticles (nano-HA)</td>
<td>The addition of 8% nano-HA to GI powder improved its FR, CS, AA against S. mutans.</td>
<td>Alatawi et al. (2019)</td>
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<td>(i) Hexametaphosphate microparticles (mHMP) and nanoparticles (nHMP)</td>
<td>nHMP at 9% and 12% concentrations in RMGIC was more effective in FR and AA than mHMP against S. mutans, L. acidophilus, and A. israelii. Inclusion of either mHMP or nHMP at these concentrations decreased enamel demineralization but compromised CS, DTS, KHN.</td>
<td>Hosida et al. (2019)</td>
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Even though GIC modification using these various additives has shown promising findings, more studies are required to elucidate the effect of these additives on the setting characteristics of GIC and its physical properties in conjunction with the efficacy of its antibacterial activity and biocompatibility [3,12,88].

7. Conclusions

The inherent properties of the formation of a chemical bond at the tooth-restoration interface and the fluoride releasing and recharging abilities of GIC have caused this material to remain clinically important in dentistry. The area of bioactivity of GICs remains a topic of interest because of the promising results reported regarding their potential to further enhance the remineralisation and regenerative properties, adhesion by integration with tissues, and antibacterial activity. Improvement of these desirable properties of GICs is expected to be beneficial in preventing secondary caries and failures when used as cements and restorations. The enhancement of these properties will, in turn, improve the clinical survival rate when GIC is used to repair and replace lost and diseased dental tissues.

Several studies have aimed to promote the bioactivity of GICs using innovative strategies of modifying either or both the glass and liquid phases of this biomaterial using various additives. It is important that the incorporation of these modifiers into the GIC matrix does not compromise the physico-chemical properties. According to the literature summarised in this paper, several types of organic and inorganic materials can be added to GICs to enhance these desired properties, but they are dose-dependent. Conflicting reports regarding the use of bioactive glass and antimicrobial additives in promoting bioactivity and its effect on mechanical properties exist. Therefore, greater efforts are still required to optimise this glass modification to ensure bioactivity enhancement does not compromise mechanical properties. Clinical studies are needed following successful in vitro research on GIC modification for this improved material to be considered a clinically acceptable bioactive restorative material.

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