Chemically Activated Glass-Ionomer Cements as Bioactive Materials

Subjects: Materials Science, Biomaterials
Contributor: John Makanjuola, Sanjukta Deb

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. Chemically activated GICs, commonly referred to as conventional GICs, typically consist of ion-leachable glasses based on calcium or strontium alumino-fluorosilicate and weak polymeric water-soluble acids of polyacrylic acid (PAA) homopolymer, or acrylic acid, maleic/itaconic acid copolymer. They set by an acid-base reaction, and the setting reaction is initiated by mixing glass powder and polymeric acids.

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

1. 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 [1]. 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 [1].

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 [2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23].

Since its introduction in 1969 by Larry Hench [24], 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 [9]. 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 [6][8][14][15][16][17][18][19][25][26][27][28][29][30][31][32][33]. 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 [6][34][35]. 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 [6][34][35]. 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 [16]. 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 layer formed [6][36]. 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 [16].

β-TCP contains a significant amount of calcium and phosphate, which can promote remineralisation of enamel when incorporated into the glass phase of GIC [37]. 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) [23]. HA nanoparticles are widely used in dentistry because they are biocompatible bio-ceramics that promote enamel remineralisation and have superior osseointegration properties [38][39]. 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 [38][40][41][42]. Forsterite (Mg_2SiO_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 [18][21]. 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 [34][43]. Wollastonite has been reported to promote the formation of an apatite layer on the surface of powder in simulated body fluid [44]. 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 [11]. Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) nanocomplexes have been shown to prevent enamel demineralisation and promote the remineralisation of carious enamel [21][45]. The incorporation of CPP-ACP into the glass phase has been found to enhance the anticariogenic 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 [45][46]. 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 [47]. 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 anticariogenic potential [45][46][47].

2. 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 [48][49][50][51][52][53].

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 [54]. 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 [48][49][50][55][56][57][58][59]. 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 [48][49][50][55][56][57][58][59]. 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 [52][53][60][61].

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 [62][63]. 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 [62][63][64].

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][34][52][54][65][66]. 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][34][52]. 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][34][52]. 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][34][52][54][65][66][67].

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][34][52][54][65][66][67].

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 [62][68][69][70][71]. 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 [34][72]. 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 [68][73][74]. 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 [60][64][73][75][76][77][78][79]. 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 [38][80].

Chitosan is a natural biopolymer that is relevant in the dental (or biomedical) field due to its biocompatibility, natural adhesive properties, and antibacterial properties [7][19]. It acts as a physical or chemical binder between the glass filler and matrix in GIC, thereby improving the mechanical properties [7]. 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 [34][81]. It destroys the cellular structures, inhibits cellular enzymes, and causes intracellular oxidative stress in the bacteria [82][83]. A study has shown that the inclusion of EGCG into GICs at low concentration improved the antibacterial activity and some mechanical properties of GICs [84]. The strength enhancement is attributed to an increase in crosslinking and a high degree of poly-salt bridging [34][85][86]. 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 [87]. The mechanism of its antibacterial property is associated with its activity against cariogenic bacteria and inhibition of glucosyltransferase activity [88]. 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 [89][90]. 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 [91][92]. 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, discolouration, poor marginal adaptation, and decreased interfacial bonding following an increase in concentration [22][38][48][93][94][95][96][97][98]. 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 [66][99][100]. 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 [48]. 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 [48][101][102]. 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 [48][103].

References

1. Sidhu, S.K.; Nicholson, J.W. A Review of Glass-Ionomer Cements for Clinical Dentistry. J. Funct. Biomater. 2016, 7, 16.
2. Kim, H.-J.; Bae, H.E.; Lee, J.-E.; Park, I.-S.; Kim, H.-G.; Kwon, J.; Kim, D.-S. Effects of bioactive glass incorporation int o glass ionomer cement on demineralized dentin. Sci. Rep. 2021, 11, 7016.

3. Nicholson, J.W.; Sidhu, S.K.; Czarnecka, B. Enhancing the Mechanical Properties of Glass-Ionomer Dental Cements: A Review. Materials 2020, 13, 2510.
4. Xie, D.; Zhao, J.; Weng, Y.; Park, J.-G.; Jiang, H.; Platt, J.A. Bioactive glass-ionomer cement with potential therapeutic function to dentin capping mineralization. Eur. J. Oral Sci. 2008, 116, 479–487.
5. Kawashima, N.; Hashimoto, K.; Kuramoto, M.; Bakhit, A.; Wakabayashi, Y.; Okiji, T. A Novel Bioactive Endodontic Sealer Containing Surface-Reaction-Type Prereacted Glass-Ionomer Filler Induces Osteoblast Differentiation. Materials 2020, 13, 4477.
6. de Caluwé, T.; Vercruysse, C.W.J.; Ladik, I.; Convents, R.; Declercq, H.; Martens, L.C.; Verbeeck, R.M.H. Addition of bioactive glass to glass ionomer cements: Effect on the physico-chemical properties and biocompatibility. Dent. Mater. 2017, 33, e186–e203.
7. Kim, D.-A.; Lee, J.-H.; Jun, S.-K.; Kim, H.-W.; Eltohamy, M.; Lee, H.-H. Sol–gel-derived bioactive glass nanoparticle-incorporated glass ionomer cement with or without chitosan for enhanced mechanical and biomineralization properties. Dent. Mater. 2017, 33, 805–817.
8. Makanjuola, J.O.; Essien, E.R.; Bolasodun, B.O.; Umesi, D.C.; Oderinu, O.H.; Adams, L.A.; Adeyemo, W.L. A new hydrolytic route to an experimental glass for use in bioactive glass-ionomer cement. J. Mater. Res. Technol. 2022, 18, 2013–2024.
9. Moraes, J.F.; de Moraes, T.G.; Nunes, F.R.S.; Carvalho, E.M.; Nunes, G.S.; Carvalho, C.N.; Ardenghi, D.M.; Bauer, J. Formation of hydroxyapatite nanoprecursors by the addition of bioactive particles in resin-modified glass ionomer cements. Int. J. Adhes. Adhes. 2021, 110, 102933.
10. Yli-Urpo, H.; Lassila, L.V.; Närhi, T.; Vallittu, P.K. Compressive strength and surface characterization of glass ionomer cements modified by particles of bioactive glass. Dent. Mater. 2005, 21, 201–209.
11. Chen, S.; Cai, Y.; Engqvist, H.; Xia, W. Enhanced bioactivity of glass ionomer cement by incorporating calcium silicates. Biomatter 2016, 6, e1123842.
12. Alaohali, A.; Brauer, D.S.; Gentleman, E.; Sharpe, P.T. A modified glass ionomer cement to mediate dentine repair. Dent. Mater. 2021, 37, 1307–1315.
13. Gomes, F.O.; Pires, R.A.; Reis, R.L. Aluminum-free glass-ionomer bone cements with enhanced bioactivity and biodegradability. Mater. Sci. Eng. C 2013, 33, 1361–1370.
14. Khaghani, M.; Alizadeh, S.; Doostmohammadi, A. Influence of Incorporating Fluoroapatite Nanobioceramic on the Compressive Strength and Bioactivity of Glass Ionomer Cement. J. Dent. Biomater. 2016, 3, 276.
15. Prabhakar, A.R.; Paul, M.J.; Basappa, N. Comparative Evaluation of the Remineralizing Effects and Surface Microhardness of Glass Ionomer Cements Containing Bioactive Glass (S53P4): An in vitro Study. Int. J. Clin. Pediatr. Dent. 2010, 3, 69–77.
16. Valanezhad, A.; Odatsu, T.; Udoh, K.; Shiraishi, T.; Sawase, T.; Watanabe, I. Modification of resin modified glass ionomer cement by addition of bioactive glass nanoparticles. J. Mater. Sci. Mater. Med. 2015, 27, 3.
17. Choi, J.-Y.; Lee, H.-H.; Kim, H.-W. Bioactive sol–gel glass added ionomer cement for the regeneration of tooth structure. J. Mater. Sci. Mater. Med. 2008, 19, 3287–3294.
18. Sayyedan, F.S.; Fathi, M.; Edris, H.; Doostmohammadi, A.; Mortazavi, V.; Shirani, F. Fluoride release and bioactivity evaluation of glass ionomer: Forsterite nanocomposite. Dent. Res. J. 2013, 10, 452–459.
19. Ranjani, M.S.; Kavitha, M.; Venkatesh, S. Comparative evaluation of osteogenic potential of conventional glass-ionomer cement with chitosan-modified glass-ionomer and bioactive glass-modified glass-ionomer cement—An In vitro study. Contemp. Clin. Dent. 2021, 12, 32–36.
20. Zandi Karimi, A.; Rezabeigi, E.; Drew, R.A.L. Aluminum-free glass ionomer cements containing 45S5 Bioglass® and its bioglass-ceramic. J. Mater. Sci. Mater. Med. 2021, 32, 76.
21. Bakar, W.Z.W.; Sajjad, A.; Mohamad, D.; Kannan, T. Various recent reinforcement phase incorporations and modifications in glass ionomer powder compositions: A comprehensive review. J. Int. Oral Health 2018, 10, 161.
22. Alam Moheet, I.; Luddin, N.; Ab Rahman, I.; Kannan, T.P.; Ghani, N.R.N.A.; Masudi, S.M. Modifications of Glass Ionomer Cement Powder by Addition of Recently Fabricated Nano-Fillers and Their Effect on the Properties: A Review. Eur. J. Dent. 2019, 13, 470–477.
23. Sangsuwan, P.; Tannukit, S.; Chotigeat, W.; Kedjarune-Leggat, U. Biological Activities of Glass Ionomer Cement Supplemented with Fortilin on Human Dental Pulp Stem Cells. J. Funct. Biomater. 2022, 13, 132.
24. Hench, L.L. The story of Bioglass®. J. Mater. Sci. Mater. Med. 2006, 17, 967–978.

25. Qiu, Z.-Y.; Noh, I.-S.; Zhang, S.-M. Silicate-doped hydroxyapatite and its promotive effect on bone mineralization. Fron t. Mater. Sci. 2013, 7, 40–50.

26. Proença, M.A.M.; Carvalho, E.M.; e Silva, A.S.; Ribeiro, G.A.C.; Ferreira, P.V.C.; Carvalho, C.N.; Bauer, J. Orthodontic resin containing bioactive glass: Preparation, physicochemical characterization, antimicrobial activity, bioactivity and bo nding to enamel. Int. J. Adhes. Adhes. 2020, 99, 102575.

27. Liou, S.C.; Chen, S.Y.; Liu, D.M. Synthesis and characterization of needlelike apatitic nanocomposite with controlled as pect ratios. Biomaterials 2003, 24, 3981–3988.

28. Wang, Q.; Wang, X.M.; Tian, L.L.; Cheng, Z.J.; Cui, F.Z. In situ remineralizaiton of partially demineralized human dentin e mediated by a biomimetic non-collagen peptide. Soft Matter 2011, 7, 9673–9680.

29. Mousavinasab, S.M.; Khoroushi, M.; Keshani, F.; Hashemi, S. Flexural strength and morphological characteristics of re sin-modified glass-ionomer containing bioactive glass. J. Contemp. Dent. Pract. 2011, 12, 41–46.

30. Huang, X.; Yang, T.; Zhao, S.; Huang, C.; Du, X. Anti-biofilm effect of glass ionomer cements incorporated with chlorhe xidine and bioactive glass. J. Wuhan Univ. Technol.-Mater. Sci. Ed. 2012, 27, 270–275.

31. Sasaki, J.-I.; Kiba, W.; Abe, G.L.; Katata, C.; Hashimoto, M.; Kitagawa, H.; Imazato, S. Fabrication of strontium-releasa ble inorganic cement by incorporation of bioactive glass. Dent. Mater. 2019, 35, 780–788.

32. Martins, R.A.; Marti, L.M.; Mendes, A.C.B.; Fragelli, C.; Cilense, M.; Zuanon, A.C.C. Brushing Effect on the Properties o f Glass Ionomer Cement Modified by Hydroxyapatite Nanoparticles or by Bioactive Glasses. Int. J. Dent. 2022, 2022, 1 641041.

33. Osorio, E.; Fagundes, T.; Navarro, M.F.; Zanotto, E.D.; Peitl, O.; Osorio, R.; Toledano-Osorio, M.; Toledano, M. A novel bioactive agent improves adhesion of resin-modified glass-ionomer to dentin. J. Adhes. Sci. Technol. 2015, 29, 1543–1 552.

34. Ching, H.S.; Luddin, N.; Kannan, T.P.; Ab Rahman, I.; Ghani, N.R.N.A. Modification of glass ionomer cements on their p hysical-mechanical and antimicrobial properties. J. Esthet. Restor. Dent. 2018, 30, 557–571.

35. Ana, I.D.; Matsuya, S.; Ohta, M.; Ishikawa, K. Effects of added bioactive glass on the setting and mechanical properties of resin-modified glass ionomer cement. Biomaterials 2003, 24, 3061–3067.

36. Lusvardi, G.; Malavasi, G.; Menabue, L.; Aina, V.; Morterra, C. Fluoride-containing bioactive glasses: Surface reactivity in simulated body fluids solutions. Acta Biomater. 2009, 5, 3548–3562.

37. Hong, Y.; Kim, J.; Lee, B.; Lee, Y.K.; Choi, B.; Lee, J.H.; Choi, H. The Effect of Nano-Sized β-Tricalcium Phosphate on Remineralization in Glass Ionomer Dental Luting Cement. Key Eng. Mater. 2007, 361, 861–864.

38. Zhu, K.; Zheng, L.; Xing, J.; Chen, S.; Chen, R.; Ren, L. Mechanical, antibacterial, biocompatible and microleakage eva luation of glass ionomer cement modified by nanohydroxyapatite/polyhexamethylene biguanide. Dent. Mater. J. 2022, 4 1, 197–208.

39. Farooq, I.; Alam Moheet, I.; AlShwaimi, E. In vitro dentin tubule occlusion and remineralization competence of various t oothpastes. Arch. Oral Biol. 2015, 60, 1246–1253.

40. Luddin, N.; Hii, S.; Kannan, T.; Ab Rahman, I.; Ghani, N.R.N.A. The biological evaluation of conventional and nano-hydr oxyapatite-silica glass ionomer cement on dental pulp stem cells: A comparative study. Contemp. Clin. Dent. 2019, 10, 324–332.

41. Kheur, M.; Kantharia, N.; Iakha, T.; Kheur, S.; Husain, N.A.-H.; Özcan, M. Evaluation of mechanical and adhesion prop erties of glass ionomer cement incorporating nano-sized hydroxyapatite particles. Odontology 2019, 108, 66–73.

42. Sharafeddin, F.; Feizi, N. Evaluation of the effect of adding micro-hydroxyapatite and nano-hydroxyapatite on the microl eakage of conventional and resin-modified Glass-ionomer Cl V restorations. J. Clin. Exp. Dent. 2017, 9, e242–e248.

43. Greish, Y.E.; Brown, P.W. Characterization of wollastonite-reinforced HAp-Ca polycarboxylate composites. J. Biomed. Mater. Res. 2001, 55, 618–628.

44. Wan, X.; Chang, C.; Mao, D.; Jiang, L.; Li, M. Preparation and in vitro bioactivities of calcium silicate nanophase materi als. Mater. Sci. Eng. C 2005, 25, 455–461.

45. Mazzaoui, S.A.; Burrow, M.F.; Tyas, M.; Dashper, S.; Eakins, D.; Reynolds, E. Incorporation of Casein Phosphopeptide-Amorphous Calcium Phosphate into a Glass-ionomer Cement. J. Dent. Res. 2003, 82, 914–918.

46. Kirthika, N.; Vidhya, S.; Sujatha, V.; Mahalaxmi, S.; Kumar, R.S. Comparative evaluation of compressive and flexural st rength, fluoride release and bacterial adhesion of GIC modified with CPP-ACP, bioactive glass, chitosan and MDPB. J. Dent. Res. Dent. Clin. Dent. Prospect. 2021, 15, 16–21.

47. Moshaverinia, A.; Roohpour, N.; Chee, W.W.L.; Schricker, S.R. A review of powder modifications in conventional glass-i onomer dental cements. J. Mater. Chem. 2011, 21, 1319–1328.

48. Sun, L.; Yan, Z.; Duan, Y.; Zhang, J.; Liu, B. Improvement of the mechanical, tribological and antibacterial properties of glass ionomer cements by fluorinated graphene. Dent. Mater. 2018, 34, e115–e127.

49. Sidhu, S.K. Glass-ionomer cement restorative materials: A sticky subject? Aust. Dent. J. 2011, 56, 23–30.

50. Sobh, E.; Hamama, H.; Palamara, J.; Mahmoud, S.; Burrow, M. Effect of CPP-ACP modified-GIC on prevention of demi neralization in comparison to other fluoride-containing restorative materials. Aust. Dent. J. 2022, 67, 220–229.

51. Guida, A.; Towler, M.R.; Wall, J.G.; Hill, R.; Eramo, S. Preliminary work on the antibacterial effect of strontium in glass i onomer cements. J. Mater. Sci. Lett. 2003, 22, 1401–1403.

52. Ibrahim, M.A.; Neo, J.; Esguerra, R.J.; Fawzy, A.S. Characterization of antibacterial and adhesion properties of chitosa n-modified glass ionomer cement. J. Biomater. Appl. 2015, 30, 409–419.

53. Vermeersch, G.; Leloup, G.; Delmee, M.; Vreven, J. Antibacterial activity of glass-ionomer cements, compomers and re sin composites: Relationship between acidity and material setting phase. J. Oral Rehabil. 2005, 32, 368–374.

54. Tüzüner, T.; Dimkov, A.; Nicholson, J.W. The effect of antimicrobial additives on the properties of dental glass-ionomer cements: A review. Acta Biomater. Odontol. Scand. 2019, 5, 9–21.

55. de Caluwé, T.; Vercruysse, C.W.J.; Fraeyman, S.; Verbeeck, R.M.H. The influence of particle size and fluorine content of aluminosilicate glass on the glass ionomer cement properties. Dent. Mater. 2014, 30, 1029–1038.

56. Simmons, J.O.; Meyers, E.J.; Lien, W.; Banfield, R.L.; Roberts, H.W.; Vandewalle, K.S. Effect of surface treatments on t he mechanical properties and antimicrobial activity of desiccated glass ionomers. Dent. Mater. 2016, 32, 1343–1351.

57. Farrugia, C.; Camilleri, J. Antimicrobial properties of conventional restorative filling materials and advances in antimicro bial properties of composite resins and glass ionomer cements—A literature review. Dent. Mater. 2015, 31, e89–e99.

58. Hafshejani, T.M.; Zamanian, A.; Venugopal, J.R.; Rezvani, Z.; Sefat, F.; Saeb, M.R.; Vahabi, H.; Zarrintaj, P.; Mozafari, M. Antibacterial glass-ionomer cement restorative materials: A critical review on the current status of extended release f ormulations. J. Control. Release 2017, 262, 317–328.

59. Al-Taee, L.; Banerjee, A.; Deb, S. In-vitro adhesive and interfacial analysis of a phosphorylated resin polyalkenoate ce ment bonded to dental hard tissues. J. Dent. 2022, 118, 104050.

60. Yesilyurt, C.; Er, K.; Tasdemir, T.; Buruk, K.; Celik, D. Antibacterial Activity and Physical Properties of Glass-ionomer Ce ments Containing Antibiotics. Oper. Dent. 2009, 34, 18–23.

61. Elsaka, S.E.; Hamouda, I.M.; Swain, M.V. Titanium dioxide nanoparticles addition to a conventional glass-ionomer rest orative: Influence on physical and antibacterial properties. J. Dent. 2011, 39, 589–598.

62. Takahashi, Y.; Imazato, S.; Kaneshiro, A.V.; Ebisu, S.; Frencken, J.E.; Tay, F.R. Antibacterial effects and physical proper ties of glass-ionomer cements containing chlorhexidine for the ART approach. Dent. Mater. 2006, 22, 647–652.

63. Hook, E.R.; Owen, O.J.; Bellis, C.A.; Holder, J.A.; O'Sullivan, D.J.; Barbour, M.E. Development of a novel antimicrobial-releasing glass ionomer cement functionalized with chlorhexidine hexametaphosphate nanoparticles. J. Nanobiotechno l. 2014, 12, 3.

64. Tüzüner, T.; Kuşgöz, A.; Er, K.; Taşdemir, T.; Buruk, K.; Kemer, B. Antibacterial Activity and Physical Properties of Conv entional Glass-ionomer Cements Containing Chlorhexidine Diacetate/Cetrimide Mixtures. J. Esthet. Restor. Dent. 2011, 23, 46–55.

65. Xie, D.; Weng, Y.; Guo, X.; Zhao, J.; Gregory, R.L.; Zheng, C. Preparation and evaluation of a novel glass-ionomer cem ent with antibacterial functions. Dent. Mater. 2011, 27, 487–496.

66. Noori, A.J.; Kareem, F.A. The effect of magnesium oxide nanoparticles on the antibacterial and antibiofilm properties of glass-ionomer cement. Heliyon 2019, 5, e02568.

67. Ibrahim, M.A.; Priyadarshini, B.M.; Neo, J.; Fawzy, A.S. Characterization of Chitosan/TiO2 Nano-Powder Modified Glas s-Ionomer Cement for Restorative Dental Applications. J. Esthet. Restor. Dent. 2017, 29, 146–156.

68. Duque, C.; Aida, K.L.; Pereira, J.A.; Teixeira, G.S.; Caldo-Teixeira, A.S.; Perrone, L.R.; Caiaffa, K.S.; Negrini, T.D.C.; C astilho, A.; Costa, C.A.D.S. In vitro and in vivo evaluations of glass-ionomer cement containing chlorhexidine for Atraum atic Restorative Treatment. J. Appl. Oral Sci. 2017, 25, 541–550.

69. Marti, L.M.; Da Mata, M.; Ferraz-Santos, B.; Azevedo, E.R.; Giro, E.M.A.; Zuanon, A.C.C. Addition of Chlorhexidine Glu conate to a Glass Ionomer Cement: A Study on Mechanical, Physical and Antibacterial Properties. Braz. Dent. J. 2014, 25, 33–37.

70. Hoszek, A.; Ericson, D. In Vitro Fluoride Release and the Antibacterial Effect of Glass Ionomers Containing Chlorhexidi ne Gluconate. Oper. Dent. 2008, 33, 696–701.

71. Türkün, L.S.; Türkün, M.; Ertuğrul, F.; Ates¸, M.; Brugger, S. Long-Term Antibacterial Effects and Physical Properties of a Chlorhexidine-Containing Glass Ionomer Cement. J. Esthet. Restor. Dent. 2008, 20, 29–44.

72. Sanders, B.J.; Gregory, R.L.; Moore, K.; Avery, D.R. Antibacterial and physical properties of resin modified glass-ionomers combined with chlorhexidine. J. Oral Rehabil. 2002, 29, 553–558.

73. Deepalakshmi, M.; Poorni, S.; Miglani, R.; Rajamani, I.; Ramachandran, S. Evaluation of the antibacterial and physical properties of glass ionomer cements containing chlorhexidine and cetrimide: An in-vitro study. Indian J. Dent. Res. 2010, 21, 552–556.

74. Duque, C.; Negrini, T.D.C.; Hebling, J.; Spolidorio, D.M.P. Inhibitory activity of glass-ionomer cements on cariogenic bacteria. Oper. Dent. 2005, 30, 636–640.

75. Korkmaz, F.M.; Tüzüner, T.; Baygin, O.; Buruk, C.K.; Durkan, R.; Bagis, B. Antibacterial activity, surface roughness, flexural strength, and solubility of conventional luting cements containing chlorhexidine diacetate/cetrimide mixtures. J. Prosthet. Dent. 2013, 110, 107–115.

76. Botelho, M.G. Inhibitory Effects on Selected Oral Bacteria of Antibacterial Agents Incorporated in a Glass Ionomer Cement. Caries Res. 2003, 37, 108–114.

77. Botelho, M.G. Compressive strength of glass ionomer cements with dental antibacterial agents. S. Afr. Dent. J. 2004, 59, 51–53.

78. Dimkov, A.G.; Nicholson, J.W.; Gjorgievska, E.S. Physical and mechanical properties of conventional glass ionomer cement incorporated with cationic substances. Acta Stomatol. Naissi 2021, 37, 2125–2135.

79. Mittal, S.; Soni, H.; Sharma, D.K.; Mittal, K.; Pathania, V.; Sharma, S. Comparative evaluation of the antibacterial and physical properties of conventional glass ionomer cement containing chlorhexidine and antibiotics. J. Int. Soc. Prev. Community Dent. 2015, 5, 268–275.

80. Celik, E.U.; Tunac, A.T.; Ates, M.; Sen, B.H. Antimicrobial activity of different disinfectants against cariogenic microorganisms. Braz. Oral Res. 2016, 30, e125.

81. Ferrazzano, G.F.; Amato, I.; Ingenito, A.; Zarrelli, A.; Pinto, G.; Pollio, A. Plant Polyphenols and Their Anti-Cariogenic Properties: A Review. Molecules 2011, 16, 1486–1507.

82. Steinmann, J.; Buer, J.; Pietschmann, T.; Steinmann, E. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. Br. J. Pharmacol. 2013, 168, 1059–1073.

83. Reygaert, W.C. The antimicrobial possibilities of green tea. Front. Microbiol. 2014, 5, 434.

84. Hu, J.; Du, X.; Huang, C.; Fu, D.; Ouyang, X.; Wang, Y. Antibacterial and physical properties of EGCG-containing glass ionomer cements. J. Dent. 2013, 41, 927–934.

85. Prentice, L.; Tyas, M.; Burrow, M. The effect of particle size distribution on an experimental glass-ionomer cement. Dent. Mater. 2005, 21, 505–510.

86. Lucas, M.E.; Arita, K.; Nishino, M. Toughness, bonding and fluoride-release properties of hydroxyapatite-added glass ionomer cement. Biomaterials 2003, 24, 3787–3794.

87. Oliveira, M.A.; Costa, L.R. Clinical performance of CTZ pulpotomies in deciduous molars: A retrospective study. Rev. Odontol. Bras. Cent. 2006, 15, 37–45.

88. Hayacibara, M.F.; Koo, H.; Rosalen, P.L.; Duarte, S.; Franco, E.M.; Bowen, W.H.; Ikegaki, M.; Cury, J.A. In vitro and in vivo effects of isolated fractions of Brazilian propolis on caries development. J. Ethnopharmacol. 2005, 101, 110–115.

89. Topcuoglu, N.; Ozan, F.; Ozyurt, M.; Kulekci, G. In vitro antibacterial effects of glassionomer cement containing ethanolic extract of propolis on Streptococcus mutans. Eur. J. Dent. 2012, 6, 428–433.

90. Altunsoy, M.; Tanrıver, M.; Türkan, U.; Uslu, M.E.; Silici, S. In Vitro Evaluation of Microleakage and Microhardness of Ethanolic Extracts of Propolis in Different Proportions Added to Glass Ionomer Cement. J. Clin. Pediatr. Dent. 2016, 40, 136–140.

91. Stanić, V.; Tanasković, S.B. Antibacterial activity of metal oxide nanoparticles. In Nanotoxicity; Elsevier: Amsterdam, The Netherlands, 2020; pp. 241–274.

92. Khezerlou, A.; Alizadeh-Sani, M.; Azizi-Lalabadi, M.; Ehsani, A. Nanoparticles and their antimicrobial properties against pathogens including bacteria, fungi, parasites and viruses. Microb. Pathog. 2018, 123, 505–526.

93. Paiva, L.; Fidalgo, T.K.S.; da Costa, L.P.; Maia, L.C.; Balan, L.; Anselme, K.; Ploux, L.; Thiré, R.M.S.M. Antibacterial properties and compressive strength of new one-step preparation silver nanoparticles in glass ionomer cements (NanoAg-GIC). J. Dent. 2018, 69, 102–109.

94. Kantovitz, K.R.; Fernandes, F.P.; Feitosa, I.V.; Lazzarini, M.O.; Denucci, G.C.; Gomes, O.P.; Giovani, P.A.; Moreira, K. M.S.; Pecorari, V.G.A.; Borges, A.F.S.; et al. TiO2 nanotubes improve physico-mechanical properties of glass ionomer c ement. Dent. Mater. 2020, 36, e85–e92.
95. Aguilar-Perez, D.; Vargas-Coronado, R.; Cervantes-Uc, J.M.; Rodriguez-Fuentes, N.; Aparicio, C.; Covarrubias, C.; Alv arez-Perez, M.; Garcia-Perez, V.; Martinez-Hernandez, M.; Cauich-Rodriguez, J.V. Antibacterial activity of a glass iono mer cement doped with copper nanoparticles. Dent. Mater. J. 2020, 39, 389–396.
96. Malekhoseini, Z.; Rezvani, M.B.; Niakan, M.; Atai, M.; Mohammadi Bassir, M.; Alizade, H.S.; Siabani, S. Effect of zinc o xide nanoparticles on physical and antimicrobial properties of resin-modified glass ionomer cement. Dent. Res. J. 2021, 18, 73.
97. Garcia, P.P.N.S.; Cardia, M.F.B.; Francisconi, R.S.; Dovigo, L.N.; Spolidório, D.M.P.; Rastelli, A.N.D.S.; Botta, A.C. Antib acterial activity of glass ionomer cement modified by zinc oxide nanoparticles. Microsc. Res. Tech. 2016, 80, 456–461.
98. Jowkar, Z.; Fattah, Z.; Ghanbarian, S.; Shafiei, F. The Effects of Silver, Zinc Oxide, and Titanium Dioxide Nanoparticles Used as Dentin Pretreatments on the Microshear Bond Strength of a Conventional Glass Ionomer Cement to Dentin. In t. J. Nanomed. 2020, 15, 4755–4762.
99. Noori, A.J.; Kareem, F.A. Setting time, mechanical and adhesive properties of magnesium oxide nanoparticles modified glass-ionomer cement. J. Mater. Res. Technol. 2019, 9, 1809–1818.
100. Dizaj, S.M.; Lotfipour, F.; Barzegar-Jalali, M.; Zarrintan, M.H.; Adibkia, K. Antimicrobial activity of the metals and metal o xide nanoparticles. Mater. Sci. Eng. C 2014, 44, 278–284.
101. Ji, H.; Sun, H.; Qu, X. Antibacterial applications of graphene-based nanomaterials: Recent achievements and challeng es. Adv. Drug Deliv. Rev. 2016, 105, 176–189.
102. Wang, Y.; Lee, W.C.; Manga, K.K.; Ang, P.K.; Lu, J.; Liu, Y.P.; Lim, C.T.; Loh, K.P. Fluorinated graphene for promoting n euro-induction of stem cells. Adv. Mater. 2012, 24, 4285–4290.
103. Liu, R.; Wang, E.; Guo, Y.; Zhou, Q.; Zheng, Y.; Zhai, J.; Zhang, K.; Zhang, B. Enhanced antibacterial properties and pr omoted cell proliferation in glass ionomer cement by modified with fluorinated graphene-doped. J. Appl. Biomater. Func t. Mater. 2021, 19.