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Organic antibacterial modifications of high-viscosity glass ionomer cement for atraumatic restorative treatment: A review

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ABSTRACT

High viscosity glass ionomer cement (HVGIC) has been employed as a restorative material for Atraumatic Restorative Treatment (ART). As residual caries persist after caries removal in ART, the antibacterial activity of HVGIC gains importance. Organic and inorganic substances with antibacterial properties have been incorporated into HVGIC over the years, and their effects on the antibacterial and physical properties have been studied. The objective of this paper is to review the various alterations made to HVGIC using organic compounds, their effect on the antibacterial activity, and the physical properties of the cement. Various in vitro investigations have been conducted by adding antiseptics, antibiotics, and naturally occurring antibacterial substances. Most of these compounds render superior antibacterial properties to HVGIC, but higher concentrations affect physical properties in a dose-dependent manner. However, some naturally occurring antibacterial substances, such as chitosan, improve the physical properties of HVGIC, as they enhance cross-linking and polysalt bridging. There is potential for clinical benefits to be gained from the addition of organic antibacterial compounds to HVGIC. In-depth research is required to determine the optimum concentration at which the antibacterial effect is maximum without affecting the physical properties of the cement.

1. Introduction

High viscosity glass ionomer cement (HVGIC) has been employed as a restorative material for Atraumatic Restorative Treatment (ART), a minimally invasive technique that employs hand instruments for dental caries excavation [1]. HVGIC is preferred over conventional glass ionomer cement (GIC) due to its better mechanical properties, marginal seal, and longer clinical durability [2,3].

As residual caries persist following manual excavation, the antibacterial activity of GIC employed with the ART approach gains importance [4]. In addition, the material's antimicrobial surface characteristics are essential for preventing biofilm formation and hence marginal caries [4,5]. Evidence from in vitro investigations shows that fluoride release and low pH during setting account for the antibacterial activity of GIC [6–8]. The release of metallic ions such as strontium, aluminum, zinc, and calcium also contributes to its antimicrobial properties [8–10]. The initial 'burst effect' of fluoride release during setting affects bacterial enzymes responsible for bacterial cell metabolism, decreases intracellular pH and has a bacteriostatic effect, particularly for *Streptococcus mutans* and *Lactobacillus acidophilus* [10–12].

During the initial months, the innate fluoride content experiences fast depletion [7]. The cement can absorb additional fluoride when exposed to fluoride in solution, based on the concentration gradient, and is anticipated to persist throughout the time frame of the restoration [7,11]. Thus, GIC restoration becomes a repository of fluoride, which is gradually discharged into the biofilm, saliva, and dental tissues [11]. It impacts the tooth tissue in proximity by promoting remineralization. The ability to release fluoride is dependent on the porosity and solubility of the cement [10].

Although the fluoride released from GIC has an inhibitory effect on bacteria in vitro, the clinical effect of low-level fluoride release on dental plaque remains unclear [11]. Although some laboratory and anecdotal evidence supports the cariostatic properties of GIC, clinical investigations into the occurrence of secondary caries often do not substantiate this claim [11,13–15]. The occurrence of internal fissures and air pockets within GIC can give rise to microleakage and biofilm formation along the restoration margins, leading to secondary caries [16]. Therefore, it is necessary to improve the antibacterial properties of

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HVGIC to decrease biofilm formation on the surface and inhibit bacterial growth along the restoration margins [16]. Incorporating antimicrobial compounds that prevent the growth of caries-causing bacteria such as *S. mutans* increases the antibacterial capabilities of GIC and hence can improve the clinical results of ART.

Organic and inorganic substances with antibacterial properties have been incorporated into HVGIC over the years, and the effect on the antibacterial and physical properties has been studied. The purpose of this paper is to review the various alterations made to HVGIC using organic materials, their effect on the antibacterial activity, and the material's physical properties.

2. Methodology

A literature search using different combinations of keywords, "antibacterial action," "surface antibacterial property," "physical properties," "high viscosity glass ionomer," "chlorhexidine," "chitosan," "miswak," "cetylpyridinium chloride," "benzalkonium chloride," "propolis," "turmeric," "sage," and "epigallocatechin-3-gallate", was undertaken through the electronic databases PubMed and Google Scholar to identify literature limited to the English language. The types of articles included were in vitro and in vivo studies and narrative, critical and systematic reviews. Published articles were included if the antibacterial action, surface antibacterial properties, or physical properties of HVGIC were studied after the incorporation of antibacterial substances. Articles were excluded if other GICs or other dental materials were studied after the addition of antibacterial substances. The screening process involved a comprehensive review of published literature up to February 2023 without any restrictions on publication year. The initial screening was based on the title, abstract, and keywords, followed by a more focused evaluation of the full text by two authors (DMH and BSS). Finally, 68 articles that met our criteria were selected for this review.

3. Antibacterial modifications of HVGIC

Based on the articles finalized after the literature search, three major categories of modifications are described: 1. Synthetic antimicrobial agents 2. Antibiotics 3. Natural antimicrobial agents.

3.1. Synthetic antimicrobial agents

3.1.1. Chlorhexidine-modified HVGIC

Adding chlorhexidine (CHX) in its diacetate, gluconate, or hydrochloride forms to GIC positively affects the antibacterial properties against bacteria responsible for dental caries [16–18]. The efficacy of this bisbiguanide against cariogenic microorganisms has been demonstrated [19,20]. The metabolic activity of *S. mutans* is disrupted by eliminating phosphonylpyruvate activity [21].

The concentration of CHX influences the fluoride-releasing ability of GIC [16]. An increase in CHX concentration increases fluoride release only at concentrations exceeding 11.5 wt% [16,22]. At lower CHX concentrations, the interaction between fluoride ions and cationic CHX results in the precipitation of salts with lower solubility, reducing fluoride release [20,22–24]. The addition of chlorhexidine hexametaphosphate to GIC results in a CHX release period of up to 14 months. This sustained release is longer than that for digluconate or diacetate, and the amount released is dose-dependent [15].

The incorporation of CHX into GIC often leads to differences in the physical and mechanical properties of the material [17,25]. The addition of high quantities of CHX to GIC results in decreased bond strength and longer setting time [16,17]. At higher concentrations of CHX, the diametrical tensile strength, compressive strength, and surface hardness of GICs are also affected [15,25]. The reduction in mechanical properties may be ascribed to CHX salts that can impede the reaction of polyacrylic acid. The cationic characteristics exhibited by CHX may impede the setting mechanisms, including proton attack and ion leaching of GIC [17]. The effect of adding CHX to HVGIC on its antibacterial and mechanical properties is summarized in Table 1.

In vivo studies, although scarce, have shown comparable survival rates for both CHX-modified HVGIC and conventional HVGIC (in both primary and permanent teeth) over 24 months, with CHX-modified HVGIC edging past conventional in deeper cavities **(**Table 2**)**. Better antibacterial effects for CHX-modified GIC without affecting the restoration longevity have been observed when added in low concentrations. Most clinical studies have found chlorhexidine concentrations of less than 1.25% (w/w) and in its diacetate form to be the most effective in enhancing the antibacterial properties, with no effect on survival rates of HVGIC restoration **(**Table 2**)**. A recent systematic review on the effect of the addition of CHX on the antibacterial activity and survival of restorations concluded that the addition of CHX in the range of 0.5–2% to GIC decreases *S. mutans and L. acidophilus* load in the saliva without affecting the survival of the restoration. [26].

3.1.2. HVGIC modified with other organic antimicrobials

In addition to chlorhexidine, organic antimicrobials such as benzalkonium chloride, cetylpyridinium chloride, cetrimide, triclosan, chloroxylenol, and thymol have been employed to improve the antibacterial properties of HVGIC **(**Table 3**)**. The antibacterial action of various organic antimicrobials is as follows:

Cetylpyridinium chloride (CPC) has potent bactericidal action on gram-positive pathogens and a fungicidal effect. It can absorb negatively charged phosphates from bacterial cell membranes since it is a cationic surface-active agent, which could damage the cell wall and increase permeability. Compared to CHX, CPC has fewer lingering side effects, such as discoloration, but has a weaker antibacterial impact [27,28]. Some studies have shown a better bactericidal effect of CPC than CHX, particularly against bacteria such as *Staphylococcus aureus, Escherichia coli,* and *S. mutans* [29,30], while the antibacterial effect of CPC against other bacteria is equivalent to CHX [29]. The better antibacterial impact, particularly in the dentinal tubules, is attributed to the greater permeability of the CPC in the form of 12-methacryloyloxydodecylpyridinum bromide [30]. The antibacterial effect of CPC is enhanced when used with chlorhexidine and zinc lactate [27,28]. The minimum inhibitory concentration (MIC) of CPC decreases when combined with CHX [29].

Benzalkonium chloride (BAC) is a potent biological agent that inhibits the proliferation of bacteria, specific viruses, fungi, and protozoa; it possesses a cationic action similar to CPC. It can be either bacteriostatic or bactericidal, depending on the concentration. Gram-positive bacteria are more sensitive to BAC than gram-negative bacteria [28]. Cetrimide is a quaternary ammonium salt containing cetrimonium bromide. It is a cationic surfactant known to prevent bacterial colonization in biofilms [31]. Cetrimide GIC combinations have been shown to have higher antibacterial action against *lactobacilli* than *S. mutans* [32].

Widely used in mouthwashes and dentifrices, triclosan is a broad-spectrum antibacterial agent that is effective against both gram-positive and gram-negative microorganisms [33]. Triclosan's main antibacterial effect targets the production of RNA and protein in bacteria [34]. Chloroxylenol (4-chloro-3,5-dimethylphenol; p-chloro-m-xylenol) is bactericidal due to its phenolic composition [35]. Thymol, a phenolic monoterpene, is an essential oil derived from *Thymus vulgaris* or common thyme and is effective against both positive and harmful bacteria. It can cross bacterial cell membranes and coagulate the cytoplasm [35,36].

All these agents are nontoxic at antimicrobial concentrations [36,37]. HVGIC modified with the above-described organic antimicrobial substances has shown enhanced antimicrobial action. BAC outperformed CPC and CT in both antimicrobial action and microhardness of the modified cement [23,28]. However, studies have shown that when added in higher concentrations, all these agents have altered the physical properties of the cement in some way or another. Evidence based on in vivo studies regarding the addition of these antiseptic agents to HVGIC is not available in the literature.

Table 1
Summary of in vitro studies on CHX-modified HVGIC.

Author and Year	HVGIC Modification	Antibacterial Action	Effect on Mechanical Properties	Optimal Concentration of CHX (w/w)
Takahashi et al. [17]	• Fuji IX • CHX diacetate and hydrochloride (1/0,2/0,3/0,1/1,2/2 w/w) mixed with GIC powder.	• Agar disc diffusion test (ADD) against *S mutans, L acidophilus, A naeslundi* showed concentration-independent inhibition in all groups	• Compressive strength, and bond strength to dentin adversely affected by the addition of CHX diacetate at 2%. • Setting time slightly prolonged (15–30 s) in all groups.	• 1% CHX Diacetate
Türkün et al. [25]	• ChemFil Superior • CHX diacetate and digluconate (0.5%,1.25%, 2% w/w) mixed with GIC powder.	• ADD against *S mutans, L acidophilus, and C albicans* showed concentration-dependent inhibition with diacetate > digluconate. • 2.5% diacetate showed highest and longest inhibition (90 days *S mutans*, 60 days *L acidophilus*)	• 1.25% and 2.5% groups of CHX diacetate had significantly lower compressive strengths. • Lower hardness values in 0.5% and 2.5% chlorhexidine digluconate groups. • Setting time, working time, acid erosion, diametral tensile strength, and biaxial flexural strength showed no significant difference.	• 1.25% CHX Diacetate
Tüzüner et al. [23]	• Fuji IX and Ketac Molar • CHX diacetate and cetrimide (both 2.5% w/w) mixed with GIC powder.	• ADD against *S mutans, L casei* showed significant inhibition in both experimental groups.	• Microhardness significantly lower in the experimental groups. • Cumulative fluoride release was lower than the control with no significant difference.	• 2.5% CHX diacetate
Huang et al. [58]	• Fuji IX • CHX diacetate and bioactive glass (1% and 10% w/w, respectively) mixed with powder.	• Optical density values for *S mutans* after 24 h showed a significant reduction in CHX groups. • No significant difference in the bioactive glass group.	• No change in microhardness of the CHX group. • Reduction in compressive strength in bioactive glass group.	• 1% CHX diacetate
Matthew et al. [59]	• Fuji IX • CHX diacetate (1% w/w) mixed with powder.	————	• Dye penetration microleakage test with basic fuschin showed no significant difference with 1% CHX	• 1% CHX diacetate
Marti et al. [60]	• Ketac Molar EasyMix • CHX digluconate (0.5%,1%,2% w/w) mixed with powder.	• ADD against *S mutans, L acidophilus* showed dose-independent inhibition zones (*L acidophilus*>*S mutans*)	• Setting time, surface hardness, compressive strength, and tensile bond strength adversely affected at 1% and 2% CHX concentrations.	• 0.5% CHX digluconate
Becci et al. [61]	• Ketac Molar EasyMix • CHX diacetate (0.5%,1%,2% w/w) mixed with GIC powder.	————	• Micro shear bond strength to caries and noncaries affected dentin were comparable with the control.	• 0.5% and 1% CHX diacetate
Bellis et al. [15]	• Diamond Carve • CHX hexamonophosphate (HMP) (0.17, 0.34, 0.85,1.70% w/w) paste mixed with GIC powder	• ADD against *S mutans* showed zones of inhibition at 0.34% CHX-HMP concentration.	• Release of soluble CHX for over 14 months in a dose-dependent manner. • 0.17% and 0.34% CHX–HMP did not adversely affect compressive strength and diametrical tensile strength at baseline. • 0.17% CHX–HMP did not affect strength after aging.	• 0.17% CHX-HMP
Jaidka et al. [62]	• Fuji IX • CHX (0.5,1.25,2.5% w/w) added to GIC powder. • Triclosan (0.5,1.25,2.5% w/w) added to GIC powder.	————	• Compressive strength, diametral tensile strength, and shear bond strength of 0.5% groups for both CHX and triclosan showed no significant difference when compared to the conventional control group.	• 0.5% CHX
Duque et al. [20]	• Ketac Molar EasyMix • CHX digluconate (1.25,2.5% w/w) added to GIC powder.	• ADD against *S mutans, L acidophilus, C albicans,* biofilm assays, and cytotoxicity assays conducted. • 1.25% and 2.5% both improved antibacterial activity invitro • In vivo study revealed a significant reduction of *S mutans* in saliva seven days after treatment in both groups. • 2.5% CHX was cytotoxic	• Compressive strength, tensile strength, microhardness, and fluoride release assessed. • RCT involving 36 children who received ART restorations with and without CHX. • Survival rates estimated at seven days, three months, and one year. • No significant difference in mechanical properties and survival rates between the control and 1.25% CHX group.	• 1.25% CHX digluconate
Neelima et al. [63]	• Fuji IX • CHX diacetate 1%, Propolis 25%, Chitosan 10% v/v added to GIC powder	• In ADD against *S mutans, L acidophilus,* CHX performed better than chitosan and propolis, both were better than the control	————	• 1% CHX diacetate

3.2. *Antibiotic-modified HVGIC*

Antibiotics are added to HVGIC to reduce viable bacteria beneath the restorations [38]. It was demonstrated that combining ciprofloxacin, metronidazole, and minocycline antibiotics effectively reduces the bacterial count in carious lesion samples. Dentin staining was frequently reported when minocycline was included in the antibiotic mixture. Numerous variations in the original triple antibiotic mixture have been proposed, including the omission of minocycline [39]. Certain studies have replaced minocycline with cephalosporins such as cefaclor [40].

Antibiotic modification could benefit ART restorations, as studies have shown that antibiotics containing GIC reduced the bacterial load in the infected dentin compared to unmodified GIC (**Table 4**). GIC-containing antibiotics, however, must carefully be considered for their safety due to the risk of side effects or the development of resistance [39]. No long-term in vivo studies are available assessing the success rates and the potential of developing resistance.

3.2.1. *Sodium fusidate modified HVGIC*

Fusidic acid obtained from the fungus *Fusidium coccineum* is effective against gram-positive bacteria, particularly staphylococci [37]. It acts by inhibiting bacterial protein synthesis. The sodium salt of fusidic acid is used to treat various infections in the body [41].

Research has been done on the controlled release of sodium fusidate from HVGIC. Reverse-phase high-performance liquid chromatography was used to track the release of sodium fusidate at predetermined time intervals after sodium fusidate powder was mixed into the cement at 1% and 5% w/w. After two weeks, 20.4% and 22.8% sodium fusidate was

Table 2
Summary of in vivo studies on CHX-modified HVGIC.

Author and Year	HVGIC modification	Objective	Methodology	Results
Frencken et al. [18]	• Fuji IX • CHX diacetate 1% (w/w)	• To test in vivo the antibacterial effect of this CHX-containing GIC compared to a non-CHX-containing GIC.	• 6- to 11-year-old children with one occlusal lesion on the molar included (n = 50) • Randomized into CHX GIC and GIC groups. • Restorations removed after seven days. • The baseline and seven days affected and infected dentin samples cultivated to obtain *S mutans, Lactobacillus*, and total viable bacterial count (TVC).	• Lower *lactobacilli* count, TVC, but not *S mutans*, in the test group infected dentin compared to the control group after seven days. • *S. mutans, lactobacilli* count, and TVC were significantly lower in the test group affected dentin seven days after treatment.
Du et al. [22]	• Fuji IX • CHX diacetate 2% (w/w)	• Antibacterial activities of GICs and RMGICs incorporated with CHX diacetate on the early established biofilm.	• 32 permanent molars in 8 volunteers bonded with the control and test specimens on the buccal surface of permanent molars. • Split Mouth Study • After 24 h, bacterial vitality of plaque analyzed by confocal laser scanning microscopy (CLSM). • The bacterial morphology and biofilm accumulation determined by scanning electron microscopy (SEM). • pH value of biofilm assessed by plaque indicator kits.	• CLSM analysis revealed that the bacterial vitality of the biofilm on CHXGIC and CHXRMGIC was significantly lower than on GIC and RMGIC. • SEM analysis indicated that the bacteria morphology on CHXGIC and CHXRMGIC was irregular. • The pH value of the biofilm on the experimental materials presented no statistically significant difference.
Mobarak et al. [64]	• Fuji IX • 1% CHX (w/w)	• To assess if the use of high-viscosity glass-ionomer with chlorhexidine (HVGIC/CHX) for the restoration of ART-prepared cavities could achieve a higher restoration survival percentage and be more effective for preventing dentine carious lesions adjacent to the restoration than the use of HVGIC without CHX.	• 100 Patients with at least two small to medium-sized occlusal cavities included. • Replica of all restorations and digital photographs at baseline and after 0.5, 1, 1.5, and 2 years evaluated by two examiners using the ART and Federation Dentaire International (FDI) restoration assessment criteria.	• No significant difference in the survival rates according to both criteria after two years • The development of carious dentine lesions adjacent to the restorations not observed in both groups.
Mohamed et al. [65]	• Fuji IX • 1% CHX diacetate (w/w)	• To assess the influence of cavity size on the survival of conventional and CHX-modified GIC in single-surface primary molars receiving ART.	• Ninety children with symmetrical bilateral single-surface carious lesions on primary molars. (Randomized split-mouth design, n = 90 molars in each group) • Survival of ART restorations measured at 6, 12, 18, and 24 months	• Survival of conventional GIC at 24 months was 83.9%, and CHX-modified GIC was 82.7%
Ratnayake et al. [66]	• ChemFil Superior • 5% CHX digluconate (v/v)	• To assess the clinical effectiveness and patient acceptability of CHX modified GIC in the ART technique to treat root caries and to conduct microbiological analysis of the restored sites.	• Two teeth in 26 patients received ART restorations with either modified GIC or the control. • Patient acceptability and survival of restoration assessed at baseline and after six months. • Plaque and saliva samples collected and assessed for *S mutans, Lactobacillus spp*, and *Candida spp* at 1, 3, and 6 months.	• 48% of the GIC-CHX restorations with continuous anatomic form as opposed to 24% for the GIC restorations, which was statistically significant. • No statistically significant reduction in the mean count of the tested microorganisms in the plaque samples for either type of restorations. • Participants were satisfied with the restorations (96%) and did not feel anxious (92%).

released by GIC modified with 1% and 5% concentrations of sodium fusidate, respectively, with no significant difference between the two concentrations. [41].

3.3. Natural antimicrobial agents

3.3.1. Chitosan-modified HVGIC

Chitosan (CH) is a natural linear biopolyaminosaccharide generated by the alkaline deacetylation of chitin and is found in crab and shrimp shells. Due to its antibacterial and antibiofilm properties, it has been incorporated into HVGIC to enhance its antibacterial and physical properties [42].

A preliminary study conducted to assess the effect of chitosan on the flexural strength and fluoride release of GIC concluded that the addition of 0.0044 wt% CH significantly increased the flexural resistance. CH concentrations exceeding 0.022 wt% were detrimental. The fluoride ions released by CH-modified GIC were significantly greater than those released by commercial GIC [42].

Following this study, CH was added to HVGIC, and its antibacterial effect and physical properties were studied. Most studies recommend adding 10% v/v chitosan to HVGIC (**Table 5**). However, one study reported that the microhardness of GIC is adversely affected after one year even at this concentration [43]. Chitosan variants with quaternary ammonium groups are known to have better antibacterial activity. Mesoporous silica nanoparticles (MSNs) can be used as effective carriers for quaternized chitosan because they are porous and biocompatible [44]. Comparable survival rates at six-month follow-up for CH-modified GIC in primary molar ART were observed in a clinical study [45]. More long-term clinical studies are needed for CH-modified GIC to be the material of choice for ART.

3.3.2. Epigallocatechin-3-gallate (EGCG)-modified HVGIC

Epigallocatechin-3-gallate (EGCG), the polyphenol in green tea (*Camellia sinensis*), has long been recognized to possess benefits such as antioxidant, anti-inflammatory, antidiabetic, and cancer-preventive capabilities [46]. Due to its antimicrobial activity against oral streptococci, particularly *S. mutans*, and suppression of the specific virulence factors linked to its carcinogenicity, EGCG is a natural anti-cariogenic agent [47]. The main component of EGCG's antibacterial action is its ability to prevent bacteria's initial surface adherence. Inflicting permanent damage to the cytoplasmic membrane of microorganisms also decreases the synthesis of acidic compounds [46,47].

Hu et al. conducted an in vitro investigation to determine the impact of adding epigallocatechin-3-gallate (EGCG) on the antibacterial and physical characteristics of HVGIC. HVGIC with 0.1% w/w EGCG was the experimental group, and 1% (w/w) CHX was added to HVGIC as the

Table 3
Summary of studies on HVGIC modified with Organic Antimicrobials: Cetylpyridinium Chloride, Benzalkonium Chloride, Triclosan, Cetrimide, Thymol, Chloroxylenol and Boric Acid.

Author and Year	HVGIC Modification and Study Design	Antibacterial Action	Effect on Mechanical Properties	Optimal concentration of antibacterial agent
Botelho [32]	• Fuji IX • CHX hydrochloride • Cetylpyridinium chloride • Cetrimide (w/w) (1,2,4%) was added to the GIC powder, • Benzalkonium Chloride (1,2,4% w/w) was added to the GIC liquid. • Invitro study	• ADD against S mutans, S salivarius, L casei, L acidophilus, An odontolyticus, A naeslundi showed dose-dependent inhibition in test groups. • Cetrimide group showed the highest inhibition against the four microorganisms	————	• 4% cetrimide
Sainulabdeen et al. [33]	• Fuji IX • Control- CHX Diacetate GIC 2.5% • Triclosan GIC (0.5,1.25,2.5% w/w) • Invitro study	• ADD against L. acidophilus and S mutans at 1,7 and 30 days showed triclosan-incorporated GIC was more effective against L. acidophilus and S. mutans than CHX-incorporated GIC showed triclosan at 2.5% more effective at all time points.	————	• 2.5% triclosan
Tüzüner et al. [37]	• Fuji IX • Cetrimide (CT) • Cetylpyridinium chloride (CPC) • CHX added to the powder. • Benzalkonium chloride (BAC) added to the liquid at concentrations 1% and 2% w/w. • In vitro study	————	• Vickers Hardness measurements (VHN) recorded at 1, 7, 15, 30, 60, and 90 days after storage in 37 °C distilled water. • After seven days, VHNs decreased in all experimental groups, increased in the control group. • BAC and CHX groups demonstrated the least difference in VHN. • CT and CPC groups exhibited the most adverse effect on the hardness.	• 1% BAC and 1% CHX
Dimkov et al. [67]	• Fuji IX • ChemFlex • Cetylpyridinium Chloride (CPC) • Benzalkonium Chloride (BAC) • 1,2,3% w/w • In vitro study	————	• No significant difference in setting time. • Compressive strength decreases with increase in the concentration of the antimicrobial compounds, except ChemFlex + BAC; BAC>CPC	• 1.2% BAC and CPC
Prasad et al. [35]	• Fuji IX • Thymol • Chloroxylenol • Boric Acid • 2,5% w/w mixed in the GIC powder. • In vitro study	• ADD against *S mutans* showed the antibacterial effect of Thymol>Chloroxylenol> Boric Acid	————	• 5% Thymol and Chloroxylenol • 2% Boric Acid
Dimkov et al. [28]	• ChemFlex GIC • Cetylpyridinium Chloride (CPC) • Benzalkonium Chloride (BAC) • 1,2,3% w/w • In vitro study	• ADD against *S mutans, L casei, A viscosus* showed dose-dependent inhibition • BAC > CPC	————	• 3% BAC
Mishra et al. [31]	• Ketac Molar • CHX-Cetrimide combination (2.5%w/w) • Chitosan (10% v/v) • In vivo study	• Fifty children with split-mouth design. • Slabs cemented on the buccal surface of molars. • ADD against *S mutans* and *L acidophilus* after 48 h showed chitosan> CHX-CT	• Chitosan>Control> CHX-CT for compressive strength. • Control>CHX-CT>Chitosan for flexural strength.	• 10% Chitosan
Kurt et al. [68]	• Ketac Molar EasyMix • CHX • Cetrimide (CT) • Cetylpyridinium Chloride (CPC) • Benzalkonium Chloride (BAC) (1% w/w) • In vitro study	• ADD against *S mutans, L casei* showed the antibacterial effect of experimental groups> Control Group • No significant difference was seen between the experimental groups.	• Control>experimental groups for VHN • No significant difference in between groups for fluoride release.	• 1% BAC, CHX, CT, CPC
Nunes et al. [36]	• GIC Maxxion • Thymol 2,4% w/w • In vitro study	• ADD against *S mutans* showed 2% thymol modified GIC most effective against *S mutans* biofilm. • Toxicity tests suggested no pertinent toxicity to human cells.	————	• 2% thymol

positive control. The optical density (OD) values obtained using a spectrophotometer to test the antibacterial activity in the HVGIC-EGCG group were significantly lower at 4 h compared to the control group, with no significant difference seen at 24 h. The agar diffusion test showed no inhibition zones in the control group during the study period, but substantial differences in the inhibition zones were seen across the groups. When compared to the control group, the HVGIC-EGCG group exhibited a significantly higher level of surface microhardness and flexural strength because the polyphenols allow cross-linkage and a high degree of polysalt bridging during the setting of GIC due to chelation

Table 4
Summary of studies with antibiotic-modified HVGIC.

Author and Year	HVGIC Modification and Study design	Antibacterial Action	Effect on Mechanical Properties	Optimal concentration of the antibiotic mixture
Yesilyurt et al. [38]	• Fuji IX • Ciprofloxacin, Metronidazole and Minocycline mixture at 1.5, 3, 4.5% w/w were added to the powder (triple antibiotic mixture). • Invitro study	• ADD against *S mutans, L case* showed dose-dependent inhibition, experimental groups had higher inhibition compared to the control. • Antibiotic release analyzed by liquid chromatography showed higher release at seven days than at 24 h.	• At 3% and 4.5% concentrations of antibiotics, the compressive and shear bond strength was significantly decreased.	• 1.5% triple antibiotic mixture
Prabhakar et al. [39]	• Fuji IX Gold Label • Ciprofloxacin and Metronidazole mixture at 1% and 2% w/w added to the GIC powder. • Invitro study	• ADD against *S mutans, L casei* showed dose-dependent inhibition.	• Fluoride release enhanced at both concentrations of the antibiotics. • Compressive strength, shear bond strength, setting time, microleakage significantly affected at 2% antibiotic concentration.	• 1% double antibiotic mixture
Mittal et al. [69]	• Fuji IX • Ciprofloxacin, Metronidazole and Minocycline mixture at 1.5, 3% w/w were added to the powder • Invitro study	• ADD against *S mutans* showed dose-dependent inhibition.	• Compressive strength significantly reduced in 3% group.	• 1.5% triple antibiotic mixture

reaction with the carboxyl group. The release of fluoride ions was unaffected significantly by EGCG addition. It was concluded that GIC with 0.1% (w/w) EGCG is a potential restorative material with superior mechanical and antibacterial properties [47].

3.3.3. *Propolis-modified HVGIC*

Propolis is a resin collected by the *Apis mellifera* honeybee, which is used to protect the hive from microorganisms. It has been extensively used in medicine for centuries due to its antibacterial, antifungal, and anti-inflammatory properties. Propolis has been demonstrated to be antibacterial against various oral microorganisms [48]. Commercially available propolis is a lyophilized and ethanolic extract of propolis (EEP). EEP has been utilized as an antibacterial ingredient in mouth rinses, toothpaste, and lozenges. EEP has an antibacterial effect on *S mutans* due to the inhibition of glucosyltransferase [49]. Most of the studies demonstrated antibacterial activity with 50% EEP-incorporated HVGIC, but evidence regarding the effect on the mechanical properties of EEP-modified HVGIC is lacking **(**Table 6**)**.

3.3.4. *Miswak modified HVGIC*

Miswak is derived from *Salvadora persica,* a tree commonly found worldwide. The extract from the twigs or root of the tree has been used in dentifrices and mouth rinses [50]. *Salvadora* persica extract (SPE) has been shown to have a significant antibacterial effect on oral pathogens [51]. Studies conducted with the addition of miswak extract have shown mixed results regarding antibacterial and mechanical properties. An in vitro study with the addition of 1%, 2% and 4% w/w SPE to HVGIC (Fuji IX) and the addition of 5% CHX as the positive control demonstrated effectiveness against various microorganisms, such as *C albicans, S. mutans, S. sanguis, S. mitis, S. salivarius, and A. naeslundii,* but the effects were inferior to those of the control group. Compressive strength and diametrical tensile strength were significantly weaker [51]. A clinical study with a 9-month follow-up, where 100% aqueous extract of SPE added HVGIC was used to restore deep caries lesions in young permanent molars of 6- to 9-year-old children, demonstrated fewer marginal defects and better clinical success at the nine-month follow-up than the control (CHX-modified HVGIC) group. Antimicrobial action was demonstrated against *S. mutans* in the same study for the SPE-modified HVGIC but was less than that of the control group [52].

3.3.5. *Turmeric-modified HVGIC*

Turmeric (*Curcuma longa*) obtained from a perennial tuberous plant has an active ingredient called "curcumin." The Ayurvedic, Siddha, and Unani systems have used turmeric for its anti-inflammatory, antioxidant, antimicrobial, and antiallergic characteristics [53]. The addition of turmeric at 0.5% and 1% w/w showed significant inhibition of *S. mutans* by the agar disc diffusion test. Significantly higher fluoride release with no significant differences in the setting time, shear bond strength, fluoride release, and microleakage were observed compared to the conventional HVGIC control [54]. They also showed a reduction in *S mutans* counts beneath the ART restorations [55].

3.3.6. *Sage-modified HVGIC*

Salvia officinalis, popularly known as Sage, is a Mediterranean perennial evergreen plant that is supported by a lengthy history of pharmacological applications. Antimicrobial, analgesic, anti-inflammatory, and antioxidant properties are present in *S. officinalis* extract. *S. officinalis* was found in an in vitro study to reduce the number of *S mutans* and *L casei* colonies in bacterial plaques [56].

With the rise in the use of natural remedies for dental problems through phytotherapeutics, an avenue for modification of the HVGIC with traditionally proven antibacterial materials has unfolded. However, further research with standardization of the extracts is needed.

4. Discussion

The literature review revealed various organic substances added to HVGIC, including antiseptics, antibiotics, and naturally occurring antibacterial substances. Various in vitro investigations have shown that most of these compounds render antibacterial properties to HVGIC. Higher concentrations affect physical properties in a dose-dependent manner. However, some naturally occurring antibacterial substances, such as chitosan and EGCG, have been shown to improve the physical properties, as they enhance cross-linking and polysalt bridging. The sustained release of the antibacterial substances over time, the quantum of release, and their effect on fluoride release of the HVGIC need to be studied further to establish the enhancement in the antibacterial properties of the cement. There is a concern that the sustained release of these antibacterial additions can lead to the deterioration of the mechanical qualities of the cement over time and the development of microbial resistance, particularly with antimicrobials [16,37]. Hence, non-releasing bactericides such as triclosan may be considered for further research. Although many antibacterial additives have been added to HVGIC, our literature review reveals that the research on the mechanical and surface properties of a given antibacterial additive is limited to only a few properties, and there is a lack of data on long-term effects.

A variety of methods, such as agar disc diffusion tests, direct contact

Table 5
Summary of studies with chitosan-modified HVGIC.

Author and Year	HVGIC Modification and Study design	Antibacterial Action	Effect on Mechanical properties	Optimal concentration of chitosan
Abraham et al. [70]	• Fuji IX • Chitosan 10% v/v • Invitro study	————	• No significant difference in microleakage between the groups.	• 10% Chitosan
Ibrahim et al. [71]	• GC Gold Label • Chitosan 5,10,25,50% v/v • Invitro study	• SEM, CLSM, colony forming units count, and cell viability assay of *S mutans* biofilm showed dose-dependent antibacterial action.	• At 25% and 50% concentrations, microtensile bond strength was adversely affected.	• 5–10% Chitosan
Debnath et al. [72]	• Fuji IX • Chitosan 10% v/v • Invitro study	• SEM characterization of *S mutans* biofilm showed antibacterial property better in the chitosan group, with sparse biofilm formation.	• Significant improvement in microshear bond strength of chitosan group.	• 10% Chitosan
Jose et al. [43]	• Fuji IX • Chitosan 10% v/v • CHX 1% w/w • Invitro study	————	• Control group significantly outperformed the test groups: Control>CHX-GIC>Chitosan GIC in microhardness assessed over a year.	• 10% chitosan adversely affected the microhardness of the HVGIC
Soygun et al. [73]	• Fuji IX GP Extra • Chitosan 5,10% v/v • Invitro study	————	• Positive effect on microhardness of test groups. • Low effect of gastric acid erosive cycle in the test group. • Surface roughness not significantly affected in test groups.	• 5–10% Chitosan
Hodhod et al. [45]	• Fuji IX • Chitosan 10% v/v • In vivo study	————	• 26 primary molars of 4–8 years (13 per group) • Six months recall • Success of restorations measured using USPHS criteria.	• No significant difference in success rates of both groups
Nishanthine et al. [74]	• Type II light cure universal restorative, Type II universal restorative, GC Fuji VII [pink], and GC HS posterior • Chitosan 10% v/v	————	• Fluoride release assessed at 1,7,14 and 21 days. • At all-time points, chitosan modified GICs released more fluoride than conventional GICs with fluoride release increasing from the first day to the 28th day.	• 10% chitosan
Labib et al. [75]	• GC Gold Posterior • 10% Chitosan v/v nanoparticles to the powder	• Nanochitosan modified GIC exhibited greater antibacterial activity in direct contact test against *S mutans.*	• Nanochitosan did not interfere with the setting reaction when assessed with Fourier Transform Infrared spectroscopy (FTIR). • Nanochitosan modified GIC had significantly higher mean fluoride ion release values.	• 10% Chitosan
Elshenawy et al. [44]	• Fuji IX GP • 1,3, 5% w/w quaternized chitosan-coated mesoporous silica nanoparticles (HTCC@MSNs) to the powder	• ADD against *S mutans* showed concentration-dependent increase in the antibacterial activity among modified groups.	• Flexural strength, elastic modulus, VHN, and wear resistance of the GICs improved significantly by adding 1–3% HTCC@MSNs, while 5% HTCC@MSNs group showed no significant difference compared to the control group. • Concentration-dependent increase in fluoride release • The effect of 1- and 3-month water aging on the properties also studied. All properties improved with aging	• 1–3% HTCC@MSNs

tests, spectrophotometry, methyl thiazolyl tetrazolium (MTT) assays, scanning electron microscopy (SEM), broth culture tests, and MBC (minimum bactericidal concentration) and MIC (minimum inhibitory concentration) determination, were used to determine the antibacterial effects [57]. This makes the comparison of the results across studies difficult. The agar disc diffusion test was the most common method, but the diffusibility of the antibacterial additive limits the test results [37]. The use of varied strains of bacteria further complicates the comparisons, although *S. mutans* has been frequently used. The effect on multispecies biofilms, as seen in the oral cavity, is not yet known. In addition, the effect of antibacterial additives on the setting reaction of cement and their reaction with various cement components are not known. Research on the interaction between protein macromolecules in saliva and antibacterial additives is desirable to study the effect of saliva on the antibacterial effectiveness of the modified HVGIC [16].

While the effect of CHX addition appears to be extensively studied, the literature on other organic antibacterial additives to HVGIC is limited. Further comparative studies with CHX as a positive control can be conducted. Finally, the clinical evidence regarding the antibacterial modifications of HVGIC is limited. Clinical studies on the organic antibacterial modifications of HVGIC showing effects on secondary caries and longevity of the restorations can pave a path for clinical acceptance of the antibacterial modifications.

5. Conclusion

There is potential for clinical benefits to be gained from the addition of organic antibacterial compounds to HVGIC. The available literature shows that the effect on antibacterial and physical properties is concentration dependent. In-depth research is required to determine the optimum concentration at which the antibacterial effect is maximum without affecting the physical properties of the cement. Additional in vitro research and long-term clinical studies can confirm the effectiveness of HVGIC modified with organic antibacterial compounds.

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Table 6
Summary of studies using HVGIC modified with propolis.

Author and Year	HVGIC Modified	Antibacterial Action	Effect on Mechanical Properties	Optimal concentration of the agent
Topcuoglu et al. [76]	• Kavitan Pro • 25, 50% Ethanolic extract of propolis (EPP)	• Minimum inhibitory concentration (MIC) against *S mutans* was 25 µg/ml. • ADD to assess antibacterial property showed dose-dependent bacterial reduction with maximum reduction at 50%.	————	• 50% EEP modified HVGIC
Prabhakar et al. [48]	• Fuji IX Gold Label • 1% EPP v/v to GIC liquid	————	• No statistically significant difference in shear bond strength between the groups. • Statistically significant difference in fluoride release among the groups after the first and seventh day. The release was lower in both groups after the first day.	• 1% EEP modified HVGIC
Altunsoy et al. [49]	• Imicryl SC GIC • 10,25,50% v/v EEP	————	• No statistically significant differences in microleakage between the groups. • Statistically significant differences between the VHN values of the groups.	• 50% EEP modified HVGIC
Paulraj et al. [77]	• Fuji IX • 10% triphala extract, 50% EEP	• ADD against *S mutans* and *Lactobacillus spp.* showed statistically significant reduction in the test groups with no significant differences between the groups.	————	• 10% triphala modified HVGIC. • 50% EEP modified HVGIC.
Biria et al. [78]	• Fuji II and IX • 25,50% EEP	• ADD against *S mutans* demonstrated no antibacterial activity in any groups.	• No significant differences in flexural strength between EEP-modified and conventional groups.	————

CRediT authorship contribution statement

Conception and design of the study, or acquisition of data, or analysis and interpretation of data: Hegde D, Suprabha BS. Drafting the article or revising it critically for important intellectual content: Hegde D, Suprabha BS, Rao A. Final approval of the version to be submitted: Suprabha BS.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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