REVIEW ARTICLE

Biomedical applications of ion-doped bioactive glass: a review

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Abstract
Bioactive glasses (BG) have been used in biomedical (dental applications or bone graft replacement for bone healing) and technological applications, and researchers have focused on the use of BGs in wound therapeutic and soft tissue. Researchers are concentrating their efforts on the creation of novel treatments for microbial infections due to the worrisome and rapid rise in drug-resistant microbial-related infections. In this review paper, we will discuss the main representatives of antimicrobial efficiency of metallic ion-doped bioactive glasses and their potential applications in the medical field. We will also go over the most important currently used and newly developed methods for surface and bulk modification of metallic ion-doped BG concerning new surgical therapy, which are used to enhance bio integration, pathogen killing effectiveness, decrease or eliminate cancer cells, mechanistic integration, a reduction in material costs, improved in BG bioactivity, angiogenic potential, biocompatibility, osteoconductive, biodegradability and mechanical integration. The integration and regulated release of antibacterial metallic ions like silver, copper, zinc, manganese, cerium, and gallium cations into the BG are one of the most appealing methods for preventing bacterial growth and reproduction. The porosity of BG matrixes (metallic ion-doped BG with micro-, meso-, and macro-porous porosity types), in combination with their low cytotoxicity, high specific surface area, and tunable pore structure, greatly facilitates the formation of hydroxyapatite or hydroxyl carbonate apatite.

Keywords Antipathogens · Osteogenic · Ion-doping · Bioactive glasses · Infections

Biomaterial materials
Biomaterials are widely used in medical procedures, including osteogenic and angiogenic implants, biosensors, bio-electrodes, skin substitutes, and medication delivery system. Ceramics/bio-glasses, metals, polymers, and composites are the most common classes of biomedical materials, as illustrated in Fig. 1. Most implantation devices available today are made up of these four classes, both individually and in combination (Patel and Gohil 2012; Spałek et al. 2022).

Bioactive glasses (BGs) are a class of synthetic silica-based biomaterials that have been developed. A glass that is compatible with living tissues and capable of forming hydroxyapatite (HA) layers on its surface is referred to as a “bioactive glass” (Kaur et al. 2016a, b). Some necessary conditions for bioactive glasses to be an appropriate biomaterial (Kaur et al. 2014):

1. The ability to be biocompatible is crucial for bioactive glasses. They ought to be non-toxic and encourage both cell adhesion and proliferation.
2. Almost all bioactive glasses need to be thermally heated to be scaffolded, which causes crystalline phases to form and grow inside the glass matrix. These crystalline phases must not harm cells or tissues or obstruct any biological processes.
3. A coating of hydroxyapatite must develop when these glasses come into touch with simulated bodily fluid.
4. There should not be any cytotoxicity, immunogenicity, or inflammatory reactions. Tissue scaffolds must go through neogenesis and serve as a temporary framework for cells to create new tissue; nevertheless, they must eventually break down into harmless substances that the body can readily absorb or eliminate. Additionally, both the surface and the mass of the substance must be sterile.
5. To avoid structural failure during material handling and the patient’s regular daily activities, the bioactive glass
must possess the requisite mechanical qualities to endure any form of pressure or strain. The mechanical characteristics of the bioactive glass scaffolds must be equivalent to those of the tissue being replaced for improved compatibility.

6. To enable vascularization and guide cell growth into the desired physical form, bioactive glass for bone engineering should have adjustable interconnected porosity. For appropriate tissue vascularization, pores must be at least 100 µm in diameter and a typical porosity of 90% is needed.

7. For cell growth, vascularization, and nutrient diffusion, a bioactive glass scaffold’s architecture should have a porous three-dimensional (3D) structure. As a result, a regulated microenvironment is created for the development of new tissues.

8. The bioactive glass must be affordable while maintaining the desired qualities to be marketed.

9. Therefore, it is desirable to meet all of these requirements to obtain appropriate bioactive glasses for biomedical (dental applications or bone graft replacement for bone healing) and technological applications due to their biocompatibility, osteoconductive, angiogenic potential, and antibacterial properties (Galarraga-Vinueza et al. 2017), and the researcher have focused on the use of BGs in wound therapeutic and soft tissue; including vascularization, heart, nerve, gastrointestinal, lung, and laryngeal tissue repair (Kaur et al. 2014; Miguez-Pacheco et al. 2015). L. Hench created the first bioactive glass (Bioglass 45S5) in 1969 (Baino 2018), and it has been in clinical usage since 1985. 45S5 has a composition of 46.1SiO2–26.9CaO–24.4Na2O–2.6P2O5 (mol%) and many bioactive glasses have the same components in slightly varying proportions (some examples of bioactive glass compositions) (Abbasi et al. 2015; Brauer 2015). After the investigation of the 1st BG; various chemical compositions, such as 28S5, 58S, 63S, 68S, 72S, and 77S (Erol-Taygun et al. 2013) have been produced using various synthesis techniques, including traditional melt quench, flame synthesis, microwave irradiation, sol–gel, spray drying, and spray pyrolysis (Moghanian et al. 2021). The sol–gel technique is the simplest and most successful method for enhancing purity and homogeneity at ambient temperature. Spray drying and spray pyrolysis are two more popular approaches for researchers. Spray pyrolysis is a flexible technique for producing ceramic materials with various compositions, sizes, and nanostructures (Messing et al. 1993). This process includes atomization, evaporation, decomposition and sintering. Initially, the ultrasonic humidifier will atomize the precursor solution into small droplets, which will be conveyed by air through a heated tubular oven divided into three sections: evaporation, calcination, and cooling (Jung et al. 2010; Messing et al. 1993). The particles that resulted were gathered in a cylindrical earthed metal with high voltage applied. It is possible to regulate and repeat the particle size and we used the spray pyrolysis technique to increase workplace safety by lowering the number of dangerous substances to which employees may be exposed (Jamkhande et al. 2019). Bioactive glasses are divided into three types based on pore size: micro-, meso-, and macro-porous. We will examine each one individually depending on their application.

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**Fig. 1** Classification of biomaterials
Micro-porous bioactive glasses

Micro-porous zeolites are one of the most well-known members of a broader category of crystalline porous minerals with pore diameters smaller than 2 nm (Vallet-Regí et al. 2006). Zeolites are unique materials in numerous processes due to their uniform pore diameters with molecular dimensions, selectivity, high stability, and activity due to their crystallinity (Meynen et al. 2009). They have several applications in industrial and residential contexts, including the petrochemical sector as catalysts for petroleum cracking, agriculture as soil treatments, medicine for the manufacture of drug delivery, medical-grade oxygen, water purification, nuclear waste disposal, and detergents have given rise to several national and international research programs (Navrotsky et al. 2009). Despite significant efforts by numerous groups across the world, a thorough understanding of the underlying principles that control the creation of zeolites and mesoporous materials remains elusive.

Mesoporous bioactive glasses

Mesoporous bio-glasses (MBG) were first created in 2004 using a blend of the sol–gel technique and surfactant supramolecular chemistry (Wu and Chang 2012; Zhu et al. 2021). These materials are based on a SiO2–CaO–P2O5 arrangement and have a highly structured mesopore channel with pore diameters ranging from 2 to 50 nm (Nandi et al. 2016). Mesoporous bio-glasses have a stronger cyto-compatibility, enhanced bioactivity (in vitro/in vivo), and virtuous drug delivery potential, which make them an excellent solution to the issue of osteomyelitis (bacterial infection) in bone regeneration. MBG particles have changeable properties (specific surface area, particle size, pore size) (Bari et al. 2018) that can release several therapeutic ions simultaneously and potentially contain and transport medicines and/or biomolecules through the target area. Figure 2 illustrates some properties and applications of mesoporous bioactive glasses.

Macro-porous bioactive glasses

The materials have a highly structured macro-pore channel structure with pore diameters exceeding 50 nm (Baino et al. 2018). The two most essential forms of bones are cortical and cancellous bones, which are macro-pore voids. Cortical bone, also known as compact bone, is a dense structure with excellent mechanical strength. Cancellous or trabecular bone is an interior porous supporting structure found at the extremities of long bones like the femur or inside the limitations of cortical bone in small bones. Trabecular bone is made up of a network of struts (trabeculae) that surround vast holes (macro-pores) (Jones and Hench 2003). According to the earlier research, Miao released the first analysis in the field of macro-porous ceramics. He used a thin coating of “standard” 58S (60SiO2, 36CaO and 4P2O5 (mol%) BG over extremely porous (80%) Al2O3 foams to provide the nearly inert ceramic skeleton the

Fig. 2 General properties and applications of MBG (Kermani et al. 2020; Sharifi et al. 2022; Yan et al. 2006)
Metallic ion-doped BG for anti-pathogens

Pathogens come in a variety of forms, but we will concentrate on the four most common: bacteria, viruses, fungi, and parasites (protozoa and worms) (Khezerlou et al. 2018; Nouri et al. 2022) which viruses and bacteria are the most dangerous human diseases (cause infections). According to the World Health Organization (WHO) reports, antibiotics do not kill viruses and hence are useless as a therapy for viral illnesses. Antiviral drugs may be utilized depending on the virus, whereas antibiotics are used to treat bacterial infections. Antibiotic resistance has emerged in some bacteria strains, making treatment difficult. This can occur spontaneously, but it can also occur because of antibiotic misuse. For example; antimicrobial resistance (AMR) among pathogens has progressively increased over the last decade, with 10 million deaths estimated by 2050, more than cancer (Bhatcharjee et al. 2022; Dadgostar 2019), and a potential cost of USD 100 trillion in the global (Awasthi et al. 2022; Bhat et al. 2021). Hospital-acquired infections (HAIs) are estimated to be 1,00,000 and 37,000 deaths per year in the United States and Europe respectively, according to a 2022 study (Sheridan et al. 2022). Putting a heavy financial burden on the healthcare system and costing the continent of Europe €7 billion. Although the majority of HAIs are caused by bacteria, some fungus and viral strains of Pseudomonas aeruginosa, Candida Auris, and norovirus, respectively, as well as cross-infection, have been shown to contribute to HAIs (Sheridan et al. 2022).

Furthermore, researchers have focused on drug-resistant pathogens (bacterial) by employing noble metallic ion-doped bioactive glasses.

Metallic ion-doped BG for antibacterial activity

Among the most common drug resistance bacteria are Gram-negative (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii) and gram-positive (Staphylococcus aureus, Enterococcus faecalis, Streptococcus pneumoniae, and Enterococcus faecium) (Ismail et al. 2021). World Health Organization (WHO) has issued a red alert for “Highest Priority Critically Important Antimicrobials,” as well as information regarding emerging critical-priority diseases, such as E. coli and Staphylococcus aureus, to address this global public health issue (Al-Ishaq et al. 2020; Organization 2022).

The following issues must be considered in the growing interest in metallic ion BG localization for therapeutic purposes(Mourino et al. 2012): (i) metallic ion interactions with cellular components include (nucleic acids-DNA, RNA–lipids–proteins, carbohydrates, oxidation–reduction substrates, and signaling molecules; (ii) responses in the immediate cellular environment; (iii) integration of metallic ions into cells and distribution to particular organelles and cellular structures; (iv) interactions of metallic ions with enzymes and receptors and their function in metabolic processes and in general, two mechanisms explain metallic ions’ bactericidal effects (Zambanini et al. 2019): in the first case, ROS (reactive oxygen species) are produced; in the second, they interact with cell membranes, biomolecules at the cell membrane, or molecules in the cytoplasm. ROS, such as peroxide, hydroxyl group, superoxide, and singlet oxygen, can damage bacterial membranes and change the functionality of proteins and nucleic acids through chemical interactions. When all of these events occur at the same time, bacteria die. The most well-known antibacterial metallic ion elements are silver, copper, zinc, cerium, manganese, and gallium will be discussed in depth in this review.

Silver-doped BG for antibacterial activity

Bacterial infections have been severe problems in clinical practice for effective tissue repair/implant/regeneration (Zheng et al. 2019), mostly due to multi-resistant bacteria that are resistant to a wide variety of medications. Antimicrobial resistance is currently posing a danger to world health. E. coli and S. aureus are the most harmful bacteria linked to a variety of illnesses ranging from mild to severe (Akhtach et al. 2021). Silver (Ag), particularly free ions, is widely recognized to have powerful inhibitory and antibacterial effects on a variety of bacteria. Furthermore, the Ag⁺ ion is superior to organic antibacterial agents in terms of heat resistance, antimicrobial persistence, and safety (Matsumoto et al. 2009; Palza et al. 2013). Adding silver to bioactive glasses would benefit from the possible bacteriostatic and bactericidal action of the leaching Ag⁺ ions in reducing the danger of microbial contamination while keeping bioactivity without causing harm to human cells (El-Rashidy et al. 2018). Bacteriostatic and bactericidal effects of leached Ag⁺ ions on Gram-negative (E. coli) and Gram-positive (S.
Concentrations of 1–3 μg mL⁻¹ (Peetsch et al. 2013) and nanoparticles on human and prokaryotic cells at lethal silver. For example, the effect of silver-doped calcium phosphate bulk structure and main properties of BG (Kaya et al. 2018). The ability to surface functionalize glasses while preserving the cytotoxicity, decreased material costs, and increased the BG’s bioactivity, biocompatibility, and biodegradability.

Silver may be harmful if released in excessive quantities, hence the amount of Ag injected must be carefully controlled. Ion-exchange treatments are well known for their advantages: increased bacterial killing efficiency decreased cytotoxicity, decreased material costs, and increased the BG’s bioactivity, biocompatibility, and biodegradability.

Copper-doped BG for antibacterial activity

Copper is one of the most plentiful elements in the earth’s crust, following zinc and iron as the most abundant necessity for the human body (Chitra et al. 2020). Copper ions deserve special attention among metal ions due to their low cost and high stability. Both Gram-positive and Gram-negative bacteria are susceptible to the antibacterial effects of copper ions (Baino 2020; Li et al. 2019; Paterson et al. 2020). Copper ions have been shown in several studies to have a remarkable antibacterial effect. *Escherichia coli*, *S. aureus*, and *S. epidermidis* were three separate bacterial strains that the Cu-MBG nanoparticles and their ionic dissolution extracts were found to be antibacterial against (Bari et al. 2017). Kim et al. prepared copper-doped BG incorporating hydroxyapatite (HA), and they found that it was extremely effective against *S. aureus* and *E. coli* bacterium (Wang et al. 2021). Increased copper ion concentrations on the surface of HA nanoparticles made it possible for poisonous Cu ions to penetrate the medium more quickly, killing bacteria by penetrating and killing them. Additionally, Rau et al. discovered that mixing 45S5 bioactive glass with 5% CuO was efficient against Gram-negative bacteria (Wang et al. 2021). Copper protects against a drug-resistant bacteria infection, therefore if an infection develops in the updated implantations/surgeries, these percentages can dual or triple. The majority of infections are caused by a class of pathogenic biofilm-producing multidrug-resistant (MDR) strains that are resistant to standard antibiotic therapy. Copper is an intriguing tool among the many potential antibacterial chemicals because of its capacity to destroy germs via the “contact killing” method (Jacobs et al. 2020). According to Sampath et al., the release of ions from copper-doped bioactive glass networks raises the pH in the physiological environment, which discourages bacteria development by inactivating enzymes and proteins, and so copper exerts its antibacterial efficiency (Chitra et al. 2020). An increase in the intrinsic quantity of Cu causes significant oxidative stress, which leads to redox cycling among the different forms of copper: Cu, Cu (I), and Cu (II) (Jacobs et al. 2020). Cu²⁺, CuO, and Cu each have a distinct toxicity mechanism and biological target. For example, Cu nanoparticles are more hazardous to bacteria than CuO nanoparticles and cause membrane damage through local H₂O₂ production (Fan et al. 2021), whereas CuO nanoparticles do not, which results in bacterial death (YF Goh et al. 2014a, b; Miola et al. 2018). The advantages of Cu²⁺ ions; the preparation of Cu-containing BG may be a promising strategy for expediting wound healing (Li et al. 2016). However, one disadvantage of BG particles employed as wound therapeutic materials is that they lack mechanical support and are difficult to treat. Furthermore, because BG particles have sharp shapes, they may cause an inflammatory reaction when directly in contact with tissue cells (Li et al. 2016).
| Composition/group type | Method          | Morphology/shape | Bacteria          | Ag/other concentration | Properties                                                                                   | References                  |
|-----------------------|-----------------|------------------|-------------------|------------------------|---------------------------------------------------------------------------------------------|-----------------------------|
| 60SiO₂–31CaO–4P₂O₅–5Li₂O (%) | Sol–gel         | Spherical        | *E. coli*         | Ag = 0, 1, 5, and 10 mol% | Antibacterial effectiveness was achieved by adding 1 mol% of Ag                               | Rahmani et al. (2021a)      |
| 76SiO₂–19CaO–5P₂O₅–3Ag₂O (wt%) | Sol–gel         | –                | *E. coli, S. epidermidisa* and *S. aureus* | Ag = 3 wt% | 99.9% of *S. aureus, E. coli,* and *P. aeruginosa* were killed at mixture specimen to bacterium ratios of 0.5, 1, and 0.5 mg/mL, respectively | Bellantone et al. (2002)     |
| 64SiO₂–26CaO–5P₂O₅–5Ag₂O | Sol–gel         | Cylindrical      | *E. coli*         | Ag = 5 mol% | > 99% killing efficiency toward *E. coli* after 72 h                                        | Balamurugan et al. (2008)   |
| 70SiO₂–20CaO–10P₂O₅ | Sol–gel         | Spherical        | *E. coli* and *S. aureus* | Ag = 0.5, 1 and 1.5 mol% | All concentrations of Ag; 100% killing efficiency toward *E. coli* and 1.5 mol% Ag 100% killing *S. aureus* after 24 h | Akhtach et al. (2021)       |
| βTCP                  | Spray pyrolysis | Smooth spherical | *E. coli*         | Ag = or Zn = 0, 2.87, 5.75 and 2.87Ag/2.87Zn (mol%) | Antibacterial activity is 99.9 and 98.9% at 5.75 mol% Ag and 2.87Ag/2.87Zn co-doped respectively | Chou et al. (2020)          |
| 80.00–16.0Ti–1.1Ce–2.9Ag, AgCe–TNT@AnNP | Hydrothermal     | Tubular          | *E. coli* and *S. aureus* strains | Ag/Ce = 2.9/1.1 at.% | 98 and 84% killing efficiency toward *E. coli* and *S. aureus* respectively after 24 h | Sales et al. (2020)         |
Zinc-doped BG for antibacterial activity

All biological tissues contain zinc, an essential microelement, in levels ranging from 1.5 to 2.5 g, with 85% of it concentrated in bones and muscle, 11% in the skin and liver, and 4% in other tissues (Cacciotti 2017). The addition of zinc to a BG matrix can result in increased chemical stability and densification (Zhao et al. 2020). Zinc is a cofactor for several enzymes that promote protein synthesis, which is necessary for DNA replication as well as bone cell proliferation, development, and differentiation. Although the antibacterial properties of Zn-doped BGs have not been completely studied, they may have an impact on these processes (Rivadeneira and Gorustovich 2017). Inappropriate concentrations can inhibit bacteria adhesion and reproduction (both E. coli and S. aureus are inhibited in their growth at the same time) but not induce cytotoxicity (Zhang et al. 2018). The researcher obtained the following results for the glass composition of (80 – x)SiO2, 5CaO, 5P2O5, and (x)ZnO (x = 4 and 7 mol%): in 4Zn and 7Zn (mol%) MBG scaffolds, the percentage of viable S. aureus was decreased from 75 to 30% and 10% (Sánchez-Salcedo et al. 2014), respectively using sol–gel preparation method, and MBGs composition of 70SiO2, 4P2O5, (26 – x) CaO and (x)ZnO (x = 0, 3 and 5 mol %) prepared using a combination of polymer templating and sol–gel methods. They were evaluated for the antibacterial property against B. subtilis and P. aeruginosa, and the results showed that at a concentration of 5 mol% ZnO-doped MBGs; 89.4% for P. aeruginosa and 91.3% for B. subtilis (Atkinson et al. 2016; Punj et al. 2021).

Gallium-doped BG for antibacterial activity

Gallium (Ga3+) is an important ion in modulating immunosuppressive and antibacterial activities. Gallium ions (Ga3+) in the structure of enzymes are replaced by iron (Fe3+) during the bacterial growth and multiplication process, suppressing bacterial growth (Shokri et al. 2022). Iron-containing enzymes are required for bacterial purposes like respiration, DNA replication and repair, energy metabolism, and oxidative stress responses (Mehrabi et al. 2020). As a result, substituting gallium for iron in these enzymes may disrupt bacterial function. Gallium nitrate, it was discovered, can speed up the formation of blood clots inside wounds, which can help with hemostasis or the initial phase of wound healing (Mehrabi et al. 2020).
Numerous microbial strains have been evaluated, primarily those implicated in bioactive glass material-associated infections like *S. aureus*, *S. epidermidis*, *P. aeruginosa*, and *E. coli*, as well as human oral pathogens linked to some oral infections like *Streptococcus gordonii*, *Porphyromonas gingivalis* and *S. mutants* (Rawlings, 1993). Glasses made of gallium-substituted phosphate were found to have bactericidal properties against *E. coli*, methicillin-resistant *S. aureus*, *P. aeruginosa*, *S. aureus* and *Clostridium difficile* (1–5 mol% Ga$_2$O$_3$) (Stan et al. 2020). Ga$^{3+}$ ions’ bactericidal activity was discovered to be effective at concentrations as low as 1 mol% Ga$_2$O$_3$ (Stan et al. 2020). Ga-substituted silica-based bioactive glass has demonstrated the potential antibacterial action of gallium against *E. coli*, *P. aeruginosa*, and *S. aureus* (Stan et al. 2020).

**Metallic ion-doped BG for osteogenic**

In the realm of orthopedics, bioactive glasses have received extensive research (Workie and Sefene 2022). Dental fields are subject to a well-known process that results in the formation of physiologically active hydroxyapatite (HAp) on their surface. This process includes rapid ion exchange between the glass and encompassing physiological fluids, the formation of a layer rich in silica, the combination of phosphates and calcium, and the crystallization of Hap (Miola et al. 2021). So, dental fields can chemically connect to the living bone as a result (Dai et al. 2020; Miola and Verné 2016; Wang et al. 2016).

Hydroxyapatite (HA), a popular orthopedic material, has numerous benefits including biocompatibility, osteo-conductivity and osteo-inductivity (Zhong et al. 2022). Many factors, such as particle size, morphology, and crystallinity, must still be considered when designing a hydroxyapatite-based biomaterial to achieve enhanced bone regeneration (Zhong et al. 2022). Since several authors emphasized the multi-step process for forming the HAp layer, which was believed to be the crucial step for bone regeneration. The formation of hydroxyapatite can be divided into four stages, according to the Hench formalism (Mariappan and Ranga 2017; Rahmani et al. 2021b):

1. In blood plasma solution, H$^+$ is used to replace Ca$^{2+}$ cations from BG.
2. The Si–O–Si bonds are broken, the BG lattice is disturbed, and silanol groups are produced, releasing silica as Si(OH)$_4$ into an SBF solution.
3. The process of polymerizing a layer rich in silica to produce hydrated silica gel.
4. Moving phosphate groups and calcium ions to the surface, creating a (P$_2$O$_5$)-(CaO)-rich film on a silica-rich layer and allowing that film to continue to expand.

**Table 2** Cerium-doped BG with different concentrations and killing efficiency of bacteria

| Composition/group type | Method       | Morphology/shape | Bacteria         | Ce-concentration (mol%) | Properties                                                                 | References                        |
|-----------------------|--------------|------------------|------------------|--------------------------|---------------------------------------------------------------------------|-----------------------------------|
| 50SiO$_2$–(45 – x) CaO–5P$_2$O$_5$–xCeO$_2$ | Sol–gel      | Spherical        | *E. coli*         | Ce = x = 0, 1, 5, 10      | At 5Ce and 10Ce, antibacterial activity is around 90% after 24 h           | Goh et al. (2014a, b)              |
| 60SiO$_2$–(40 – x) CaO–xCe$_2$O$_3$ | Sol–gel      | Spheroidal and pineal | *E. coli* and *S. aureus* | Ce = x = 0, 1, 3, 5      | 100% and around 90% killing efficiency toward *E. coli* and *S. aureus* respectively above 3 mol% Ce after 24 h | Kurtuldu et al. (2021a, b) |
| (80 – x)SiO$_2$–15CaO–5P$_2$O$_5$–xCeO$_2$ | Freeze-drying | Spherical        | *E. coli* and *S. aureus* | Ce = x = 2, 4 and 6      | At the concentration of 4 mol% Ce: 93.36% killing efficiency toward *S. aureus* and 2 mol% Ce 83% killing *E. coli* after 12 h | Liu et al. (2022) |
5. Calcium phosphate crystallization of the amorphous layer by adding $\text{OH}^-$ and $\text{CO}_3^{2-}$ anions to the solution to produce hydroxyl and carbonyl groups. It demonstrates how the bioactive glass may adhere to human living hard tissue without sacrificing its antibacterial properties.

Biologically generated HA contains naturally doped ions, such as $\text{Sr}^{2+}$, $\text{Si}^{4+}$, $\text{Na}^+$, $\text{Mn}^{2+}$, $\text{Mg}^{2+}$, $\text{Zn}^{2+}$, $\text{K}^+$, $\text{CO}_3^{2-}$, $\text{Cl}^-$, and $\text{F}^-$ (Guan et al. 2022b; Kulanthaivel et al. 2015), also synthetically co-doped into the HA structure. This family has recently included certain rare-earth elements (Yilmaz et al. 2019) and Table 3 demonstrates that various studies investigated the use of the BG, metallic-doped BG, and co-doped BG in tissue engineering applications.

As previously shown, strontium is an element that induces osteogenesis and could easily replace calcium in the BG network (Kermani et al. 2020). Strontium ion ($\text{Sr}^{2+}$) has a +2 charge and may improve bone density; it can be incorporated into the HA structure by replacing the $\text{Ca}^{2+}$ ion (Pourreza et al. 2017). Sr is a bone-substituting trace element (Guo et al. 2022), accounting for 98% of the total Sr in the body. It is a medication used to increase bone density in osteoporotic (bone loss) patients. Sr stimulates bone formation through a dual mode of action: it stimulates bone-forming osteoblast cells while inhibiting bone-resorbing osteoblast cells (Mouriño et al. 2019). As a result, depending on the dose, it can be both beneficial and detrimental to bone. Low Sr doses can improve bone formation, whereas high doses cause abnormal bone mineralization.

Huang et al. (Bari et al. 2018) and Shih et al. (Peter Richardo et al. 2022) developed Sr–Cu and Sr–Ag co-substituted hydroxyapatite coatings, respectively, and demonstrated the ability to combine antimicrobial and osteogenic differentiation stimuli in a single formulation.

Bone and teeth make up about 65% of the body’s total magnesium, which is the tenth most plentiful element in the human body (Bose et al. 2013a, b). High magnesium dosages were found to have reactions in vitro, demonstrating that magnesium is directly and crucially involved in sustaining vascular function (Bose et al. 2013a). Researchers found that adding magnesium to calcium phosphate (CaP) materials enhances alkaline phosphatase (ALP) synthesis, osteoblastic cellular adhesion, proliferation, and densification. A femoral bone defect treated with hydroxyapatite (HA), a particular composition and phase of calcium phosphate, doped with magnesium phosphate showed higher osteogenic characteristics than a pure control, according to in vivo investigations. Magnesium has been employed in some different bioactive glass compositions and magnesium phosphate bone cement in clinical situations (Bose et al. 2013b). Using a variety of various trace metal ion BG additions, the researchers modified the kinetics of degradation, the inhibitory influence on osteoclast generation and the stimulatory
effect on osteogenesis in CaPs. An effective strength degradation rate over time in a simulated bodily fluid (SBF) was shown using magnesium and strontium-containing system. This property is necessary for bone tissue engineering. Additionally, the outcomes demonstrated quicker defect healing in comparison to undoped-BG, as demonstrated by enhanced bone remodeling and higher early bone formation (Bose et al. 2013b).

Fluoride (F\(^-\)) also stimulates the proliferation and differentiation of bone-forming cells, so it is used to increase bone volume in osteoporosis patients. When used systemically or topically, it can also help to prevent dental caries.

**Metallic ion-doped BG for cancer**

Cancer comes in over a hundred different varieties. A cell’s genetic makeup could be harmed or altered, resulting in mutations that disrupt the process of cell growth and division. Vital organs may be harmed by this procedure, which could even be fatal. The most efficient strategies to lessen the challenges (such as side effects, a low survival rate, etc.) connected with cancer treatment include early identification and carefully focused cancer therapy/therapies (Guan et al. 2022b) and most cancer treatment options are surgery to remove the tumor, radiotherapy to destroy the tumor’s DNA and other vital macromolecules, and chemotherapy to disrupt the cell cycle (Aspasio et al. 2016). Ceramic biomaterials have been the subject of substantial research to enable successful cancer detection and therapy due to their excellent biocompatibility, high bioactivity, acceptable biodegradability, and other distinguishing qualities needed for medical devices in oncology (Guan et al. 2022b). The use of nanotechnology in cancer treatment and diagnosis raises the hopes of millions of patients for better, more effective, safe, and affordable healthcare. Nanobioceramics can be hybridized with other materials and loaded with imaging and therapeutic agents to form multifunctional nano-devices that provide diagnostic and therapeutic functions for cancer patients at the same time (Rosenholm et al. 2012). Many of the present cancer therapy restrictions will likely be overcome with the help of nanotechnology, including more precise therapeutic delivery to molecular targets within tumors and a reduction in hazardous side effects (Rosenholm et al. 2012). The number of innovative applications in cancer nanomedicine has expanded since the food and drug administration of America (FDA) approved the first nanomedical cancer treatment, Doxil (liposomal doxorubicin), in 1995 (Wu et al. 2019). Numerous scientists have investigated the use of multifunctional, dual, or trivalent rare-earth metals doped in nanoscale hydroxyapatite (nHAp) matrix for cancer diagnostics (Veerla et al. 2019). Like Fe\(^{2+}\), Fe\(^{3+}\), Co\(^{2+}\), and Gd\(^{3+}\) are different magnetic ions doped and Sr\(^{2+}/Cu\(^{2+}\), Sr\(^{2+}/Mg\(^{2+}\), Cu\(^{2+}/Zn\(^{2+}\), Co\(^{2+}/Mg\(^{2+}\), and Zn\(^{2+}/F\(^-\)) are co-doped magnetic materials.

Generally, elements (metal, non-metal, and different oxides) are used for antibacterial activity, angiogenesis, and bone cancer (Fig. 3).

**Future challenges**

All implants draw microorganisms and serve as in vivo infection habitats, despite the wide variations in implant forms and applications. This persistent microbial presence impairs implant performance and raises the danger of human usage. Due to their lengthy in vivo use, permanent internal implants in particular confront two difficulties: biomaterial-associated infection (BAI) and a deficiency in native tissue regeneration (Allizond et al. 2022).

Ortho-periodic implants are extremely vulnerable to bacteria when implanted in the host due to the host immune fade zone. On the implant surface, bacterial colonization and bacterial adherence take place within a few hours. Bacteria have developed a variety of strategies for adhering to both natural and synthetic surfaces, resulting in higher survival rates severe post-operative infection at the implant site, along with bone and joint degradation, is one of the main causes of implant failure that is brought on by biofilm formation (Bohara and Suthakorn 2022). As a result, the researcher making noble and efficient bioactive glasses, metallic ions, or co-doped BG with antibacterial properties is an effective way to solve this problem.

**Conclusion**

This review demonstrates that inorganic modification can be used to transform BGs and metallic ions into biomaterials with osteogenic properties, angiogenic potential, antibacterial effects and cancer treatments making it a favorable material for applications in recreating medicine such as wound therapeutic and bone tissue engineering. This strategy provides a modified ion-doped materials’ feature, such as their capacity to inhibit microbial growth, then they may be a
suitable material in this situation. Finding a new class of antibacterial drugs is critical given the problem of a growing number of diseases brought on by pathogen strains that are resistant to antibiotics, due to their broad spectrum of micro-biocidal capabilities and minimal capacity to cause drug resistance. The popular metallic ion-doped BG are silver, copper, zinc, manganese, cerium and gallium as well as co-doped with each other. These therapeutic ions have prevented bacterial and fungal infections in bone and dental implants. To address these issues, the researcher needs to concentrate on the drug-resistant bacteria and look toward noble and effective metallic ion-doped and co-doped BG.

Fig. 3 BGs' biological effects are associated with the release of ions from their structure into the target area (different ions are used for antibacterial activity, osteogenic, angiogenic, and anticancer) (Al-Harbi et al. 2021; Kargozar et al. 2019; Sharifi et al. 2022)
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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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