BJOS
Brazilian Journal of Oral Sciences

Original Research

Volume 24
2025
e255144

Properties of bioceramic materials for endodontic use: a narrative review

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Editor: Dr. Altair A. Del Bel Cury

Received: December 4, 2023
Accepted: February 17, 2024

Aim: Review the characteristics of endodontic bioceramics in comparison with other endodontic materials using the currently available literature. **Methods:** A bibliographical research was carried out using the electronic databases Public Medline (PubMed), Scopus, Embase, Scielo and Web of Science, using the search terms "Bioceramics", "Endodontic cements", "BIO-C TEMP", "Antimicrobial activity", "Biocompatibility' and "Osteclastogenic potential". Inclusion criteria were original research articles published in English within the last 10 years, with exceptions for classic articles on Mineral Trioxide Aggregate (MTA) published before 2013. **Results:** 464 articles were found on the topic and 223 were selected for this Review, including a search of the physical-chemical and biological properties of endodontic bioceramic sealer, bioceramic repair, and bioceramic intracanal medication over a period of 10 years. The main characteristics found in the studies were antimicrobial activity, biocompatibility, cytotoxicity, and osteoclastogenic potential. A total of 30 studies were included. **Conclusion:** The physicochemical and biological properties were favorable to the success of endodontic treatment. However, the bioactivity of BIO-C TEMP medication needs to be better studied.

Keywords: Ceramics. Anti-bacterial agents. Root canal filling materials. Dental cavity preparation. Dental materials.

Introduction

Bioceramic materials, based on calcium silicate and calcium phosphate, were launched on the market more than 10 years ago. They have attracted attention due to their excellent physicochemical and biological properties[1]. The physicochemical properties of endodontic bioceramics are carefully selected to meet specific requirements within the root canal environment. First, biocompatibility is a crucial feature, ensuring that these materials do not elicit adverse reactions in surrounding tissues[2]. Next, radiopacity is essential for enabling precise radiographic visualization during procedures and post-treatment monitoring[3]. In addition, high solubility is a distinctive feature of many endodontic bioceramics, but this solubility is controlled for specific purposes[4]. Controlled solubility can trigger the gradual release of beneficial ions, such as calcium and silicate, which possess antimicrobial properties and can promote the formation of mineralized tissue[5]. However, excessive solubility may pose long-term challenges[4].

Long-term solubility can be compromised due to premature material degradation, leading to the loss of the structural integrity of the seal within the root canal[4]. This concern is especially relevant when the solubility rate is too rapid. The durability of endodontic bioceramics can be negatively affected if not properly controlled, influencing the effectiveness of the treatment. To mitigate potential long-term issues, strategies for optimizing the composition of bioceramics were implemented. The development of bioceramic cements with controlled solubility that also facilitate the beneficial release of ions without compromising the structural stability of the material has provided increasingly high-quality products[6]. Even so, long-term studies are crucial for assessing the performance of these materials over time, and identifying and addressing any challenges that may arise.

In addition to possessing the above characteristics, bioceramic materials are ideal materials for different uses in the endodontic environment (Figure 1). They are inorganic materials capable of an active response when in direct contact with different tissues. They have excellent biocompatibility and bioactivity properties, a fact which results in the stimulation of hydroxyapatite formation and thus makes it possible to achieve tooth repair with a very similar physical structure[7]. Notable among these materials are Mineral Trioxide Aggregate (MTA) and bioceramic cements, which have unique properties and specific applications that make them important in dental practice. MTA, composed mainly of mineral trioxide, calcium sulfate and other oxides, emerged in the 1990s, initially intended for sealing perforations and retro-filling, evolving to use in pulp capping and apexification[8]. Its physicochemical and biological properties, combined with the ability to stimulate the formation of hydroxyapatite, contribute to effective tooth repair[8]. MTA is finely ground, with an average particle size in the micrometer range[9]. The presence of these fine particles contributes to the ability of MTA to adapt to the details of the root canal anatomy.

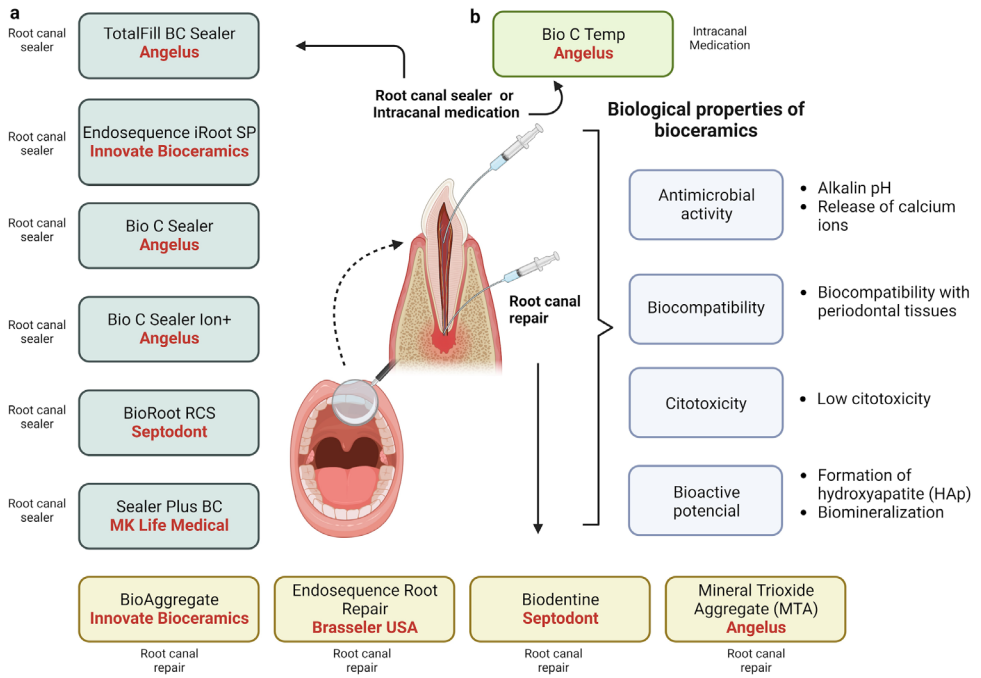

Figure 1. Schematic figure simplifying the main characteristics of endodontic bioceramic products. A: Root canal sealer, used for root canal sealing of permanent teeth and internal resorptive treatment; and root canal repair, used for root perforation repair, direct pulp protection, apexification, root apical plug, pulp capping, furcal perforation, internal resorption, cervical root lesions and apexigenesis; B: Intracanal medication, used for retreatment of necrotic root canal and for sealing root perforation. Created by Biorender.com

In contrast, bioceramic cements, composed of ceramics such as tricalcium phosphate and calcium silicate, have a wider range of applications, including canal filling, perforation repair and pulp capping, in addition to a variety of products available on the market[1]. Particles in bioceramic cements are often nanoparticles, meaning they have sizes in the nanometer scale[10]. The presence of nanoparticles contributes to the flowability and adaptation of bioceramic cements in complex root canals. Nanoparticles can enhance the material's penetration into microfissures and anatomical details, thus improving sealing effectiveness[10]. In summary, the particles present in these materials are responsible for providing mechanical properties, radiopacity, bioactivity, and biocompatibility. The specific size and composition of the particles directly influence the clinical performance of materials in endodontic procedures, such as root canal filling and perforation repair[9,10].

Based on continuous advances in scientific research and technological innovations in the field of endodontics, bioceramic materials are emerging as fundamental elements for the success of endodontic treatments, assuming the role of a crucial tool at the forefront of these practices. The constant evolution of these materials, exemplified by MTA and bioceramic cements, reflects not only a search for improvements in properties regarding their shape, antimicrobial activity, biocompatibility,

and osteogenic potential, but also a response to the varied and complex needs of dental procedures. MTA, with its history since the 1990s, stands out as a pioneer with specific properties for dental repair, while bioceramic cements, with their compositional diversity, offer exceptional versatility, as they are applied in various clinical situations, from root canal filling to pulp capping[8].

MTA and endodontic bioceramic cements are materials with distinct physicochemical characteristics, yet both play crucial roles in dental procedures. MTA is primarily composed of tricalcium silicate, dicalcium silicate, bismuth oxide, and calcium trioxide[11]. This composition impacts the radiopacity, sealing effectiveness, and biocompatible properties of MTA. Due to its finely ground particles in the micrometer range, MTA allows for precise adaptation to the details of the root canal. In contrast, bioceramic cements have varied compositions, typically including calcium oxides, silica, alumina, and zirconia, often with nanoparticles. Both materials exhibit sealing, bioactive, and biocompatible properties, playing crucial roles in endodontic procedures, though their distinct formulations influence specific physicochemical characteristics[12]. In this context, this article thoroughly revisits the distinctive features of these materials, analyzing their characteristics in comparison to other endodontic materials. Furthermore, it reinforces the pressing need for additional research to deepen the understanding of clinical expectations, providing a solid foundation for the continued evolution of these materials and further improving the effectiveness of endodontic treatments.

Materials and Methods

To carry out this Narrative Review, using the keywords “Bioceramics”, “Endodontic cements”, “BIO-C TEMP”, “Antimicrobial activity”, “Biocompatibility” and “Osteoclastogenic potential”, a bibliographic search was carried out via Public Medline (PubMed), Scopus, Embase, Scielo and Web of Science. The inclusion criteria were original research articles published in English in the last 10 years (January 2013 to December 2023) that contained information on the physicochemical and/or biological properties of these cements (Figure 2). The most recent research in this study was carried out in 2022 by Badawy and Mohamed[7]. This study evaluated the chemical composition and elemental distribution and elemental mapping after root canal filling, both coronal and apical. Articles that did not contain information about the physicochemical or biological properties of bioceramic cements and those that were not written in English were excluded.

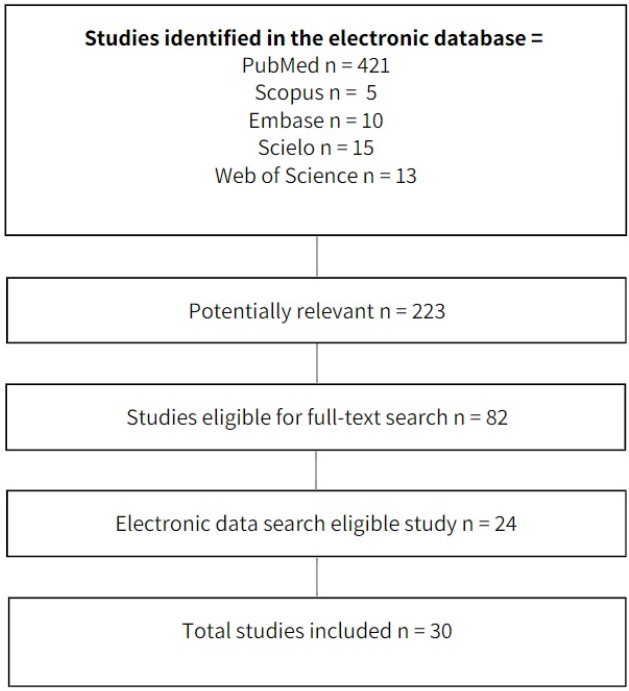

Figure 2. Flowchart for reviewing articles.

Results

A survey of the physicochemical and biological properties of bioceramic endodontic cement, bioceramic repair and bioceramic intracanal medication was carried out over a period of 10 years (2013 – 2023) (Figure 2). The main characteristics explored in the studies were antimicrobial activity, biocompatibility and osteoclastogenic potential (Figure 3). Most studies demonstrated greater efficiency in biocompatibility and bioactivity of bioceramics compared to other materials (Table 1). Although BIO-C TEMP cement is new on the market, there are some studies reporting good results regarding its biocompatibility and osteogenic activity.

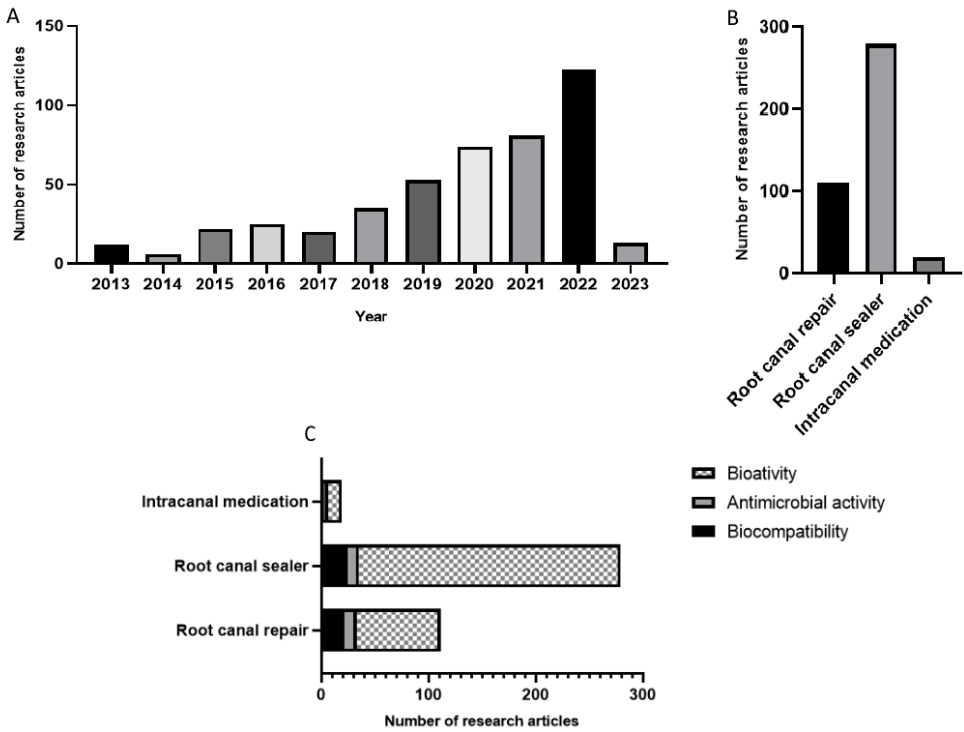

Figure 3. Overview of bioceramic products for endodontic use. A: Number of published research articles related to bioceramics and endodontics per year; B: Number of research articles published for each bioceramic product for endodontic use; C: Number of research articles published for each bioceramic product for endodontic use, separated by each analyzed topic. PubMed search (https://www.ncbi.nlm.nih.gov/pubmed?keywords) including the keywords: bioceramic root canal repair and sealer and medication.

Table 1. Search for data on biocompatibility and bioactivity

Article title Authors	Materials	Study type	Main result
Elemental Analysis of Crystal Precipitate from Gray and White MTA. Journal of Endodontics. Bozeman et al.[13], 2006	Mineral Trioxide Aggregate, white MTA and Dentalcrete	*In vitro*	Both MTA materials released more Ca initially, followed by a decline and then rise in elution. GMTA produced the most surface crystal, which may be clinically significant. The crystals on GMTA and WMTA were chemically and structurally similar to hydroxyapatite.
Cytotoxicity Comparison of Mineral Trioxide Aggregates and EndoSequence Bioceramic Root Repair Materials. Journal of Endodontics. Damas et al.[14], 2011	ProRoot MTA, MTA-Angelus, Brasseler EndoSequence Root Repair Material and Brasseler EndoSequence Root Repair Putty	*In vitro*	Brasseler EndoSequence Root Repair Materials were shown to have similar cytotoxicity levels to those of ProRoot MTA and MTA-Angelus.
Setting Properties and Cytotoxicity Evaluation of a Premixed Bioceramic Root Canal Sealer. Journal of Endodontics. Loushine et al.[15], 2011	EndoSequence BC Sealer and AH Plus	*In vitro*	All hardened cements exhibited severe cytotoxicity within 24 hours. The cytotoxicity of AH Plus gradually decreased and became non-cytotoxic, while BC Sealer remained moderately cytotoxic over the 6-week period.

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Continuation

Mineral Trioxide Aggregate–based Endodontic Sealer Stimulates Hydroxyapatite Nucleation in Human Osteoblast-like Cell Culture. Journal of Endodontics. Salles et al.[11], 2012	Mineral Trioxide Aggregate (MTA) and MTA Fillapex	*In vitro*	After setting, the cytotoxicity of MTA-F decreased, and the cement presented adequate bioactivity to stimulate the nucleation of the hydroxyapatite crystal.
The setting characteristics of MTA Plus in different environmental conditions. International Endodontic Journal. Camilleri et al.[16], 2013	MTA Plus and ProRoot MTA	*In vitro*	New MTA Plus was thinner than the ProRoot MTA but had a similar chemical composition. MTA Plus in direct contact with fluids showed partial decalcification of the hydrated calcium silicate in contact with the solution, microcracking and leaching of calcium hydroxide. Interaction with a physiological solution resulted in inhibition of hydration.
Cytotoxicity, genotoxicity and antibacterial effectiveness of a bioceramic endodontic sealer. International Endodontic Journal. Candeiro et al.[17], 2015	Endosequence BC and AH Plus	*In vitro*	Cultures subjected to Endosequence BC cement showed a significantly higher number of viable cells and less formation of micronuclei than AH Plus cement. Endosequence BC cement exhibited significantly smaller zones of inhibition than AH Plus cement. Bioceramic-based cement showed lower cytotoxicity compared to AH Plus cement.
Chemistry and Bioactivity of NeoMTA Plus™ versus MTA Angelus® Root Repair Materials. Journal of Spectroscopy. Zeid et al.[18], 2017	MTA Angelus and NeoMTA Plus	*In vitro*	NeoMTA Plus showed better apatite formation, greater crystallinity, and calcium/phosphate, but a lower carbonate/phosphate ratio than MTA Angelus. Scanning electron microscope with energy dispersive X-ray showed globular structure with small particle size in NeoMTA Plus, while spherical structure with large particle size was seen in MTA Angelus. Due to the fast setting, higher crystallinity, and better bioactivity of NeoMTA Plus, it can be used as a pulp and root repair material.
A New Calcium Silicate-Based Root Canal Dressing: Physical and Chemical Properties, Cytotoxicity and Dentinal Tubule Penetration. Brazilian Dental Journal Villa et al.[19], 2020	Bio-C Temp and Ultracal XS	*In vitro*	Both materials presented alkaline pH at all experimental times. The pH values of the calcium hydroxide paste were higher than those of the bioceramic paste. The release of calcium ions from bioceramics was lower than that from calcium hydroxide paste only at 24 h. The bioceramic was more radiopaque than the calcium hydroxide paste. The bioceramic paste showed a dose-dependent cytotoxic effect after MTT testing. Bio C Temp showed dose- and time-dependent cytotoxicity and lack of penetration into dentinal tubules.

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Antibacterial activity, cytocompatibility and effect of Bio-C Temp bioceramic intracanal medicament on osteoblast biology. International Endodontic Journal Guerreiro et al.[20], 2021	Bio-C Temp, Calen and UltraCal XS	*In vitro*	Bio-C Temp showed similar cytocompatibility at higher dilutions and greater or similar induction of ALP activity and deposition of mineralized nodules compared to Calen and UltraCal XS. However, it had significantly less antibacterial and antibiofilm activity than Calen and UltraCal XS.
Evaluation of new bioceramic endodontic sealers: An *in vitro* study. Dental and Medical Problems. Badawy and Mohamed[7], 2022	AH Plus, TotalFill, BC, BioRoot and EndoSeal	*In vitro*	All cements tested, except AH Plus, revealed high peaks in calcium/phosphorus ratio, suggesting *in vitro* regenerative potential, with acceptable purity and surface texture, and supporting their biocompatibility, with chemical bonding to root dentin.
Cytotoxicity and biocompatibility of a new bioceramic endodontic sealer containing calcium hydroxide. Brazilian Oral Research. Benetti et al.[21], 2019	Sealer Plus BC MTA Fillapex and AH Plus	*In vivo*	Sealer Plus BC is less cytotoxic to L929 fibroblast cells when a less diluted extract is used. Furthermore, it is more biocompatible than MTA Fillapex and AH Plus.
A laboratory evaluation of cell viability, radiopacity and tooth discoloration induced by regenerative endodontic materials. International Endodontic Journal, Oliveira et al.[3], 2020	MTA Flow, UltraCal XS and Bio-C Temp	*In vivo*	New bioceramic material showed acceptable cell viability, similar to that of MTA and UltraCal XS at the highest dilutions, and Bio-C Temp resulted in less change in tooth color than MTA and UltraCal XS. Despite the lower radiopacity, Bio-C Temp was identified radiographically.
Biocompatibility of a High-Plasticity, Calcium Silicate- Based, Ready-to-Use Material. Materials. Okamura et al.[22], 2020	Bio-C Sealer and Calcipex II	*In vivo*	Bio-C Sealer presented weaker cytotoxicity than Calcipex II sealer containing $Ca(OH)_2$ in an *in vivo* system. In addition, Bio-C sealer is biocompatible and safe to use in close contact with the periapical tissue. Although the induction of periradicular inflammation was not reported, Bio-C sealer was shown to favor tissue repair. Furthermore, sealer may contribute to the mineralization process of the periapical tissue, which demonstrates its bioactive potential.

Discussion

Antimicrobial activity

Endodontic infections are polymicrobial, including a predominance of strictly anaerobic bacteria, especially in primary infections. According to the literature, the main antimicrobial properties of an endodontic sealer are its alkalinity and release of calcium ions that stimulate repair through the deposition of mineralized tissue[23]. Several types of sealers with different compositions are currently available, including those based on zinc oxide and eugenol, epoxy resin, methacrylate resin cements and

calcium-silicate based materials[23]. However, studies on the antimicrobial activity of ready-to-use bioceramic sealers are still scarce.

The most common method to validate the antimicrobial activity of endodontic sealers is through the agar diffusion test. Another very common test includes the counting of microbial colony forming units after direct contact with the tested sealer[23]. In addition to the agar diffusion and direct contact method to evaluate the antibacterial activity of an endodontic sealer, Farrugia et al.[24] (2017) performed a study using a different method, the intratubular infection method[25]. The question was whether the presence of blood could alter the antimicrobial activity of MTA Fillapex® (Angelus) and AH Plus® (Dentsply). In the agar diffusion method, there was no bacterial inhibition in contact with blood, and the direct contact method and the intratubular infection method resulted in a decrease in the antimicrobial activity[19].

Using the same gold standard, AH Plus sealer (Dentsply), Candeiro et al.[17] (2016) compared the antimicrobial activity of Endosequence BC® (Brasseler USA) by agar diffusion method and a direct contact method, both using the bacterium *E. faecalis*[23]. Endosequence BC (Brasseler USA) demonstrated superior antimicrobial activity to AH Plus (Dentsply) after 24 hours using the direct patch test method, due to the high pH and active diffusion of calcium hydroxide, which provides a technological advance in relation to antimicrobial activity, as it belongs to the third generation. In another study, Simundic et al.[26] (2020) compared TotalFill BC® sealant (FKG Dentaire), considered a third-generation cement, and MTA sealant Fillapex ® (Angelus), and concluded that bioceramic TotalFill BC® (FKG Dentaire) presented greater antimicrobial efficacy because its formulation has high alkalinity[27].

Antimicrobial analysis was also performed in the presence of Bio-C Sealer® (Angelus). Using the agar diffusion test, it was demonstrated that Bio-C sealant (Angelus), due to its evolutionary characteristics, such as pH ~12, inhibited the growth of *E. faecalis, E. coli, P. aeruginosa* and *S. aureus*. Furthermore, when it was in contact with mature biofilm for 48 hours, there was a slight antimicrobial effect[18]. In addition to the studies carried out with filling sealers, another analysis was carried out using repair sealers against *E. faecalis*, *E. coli*, *P. aeruginosa* and *S. aureus* by agar diffusion test. MTA ProRoot (Dentsply/De Trey GmbH, Konstanz, Germany), classified as a first-generation cement, was not effective against *E. faecalis*, *S. aureus* and *E. coli*[28]. Estrela et al.[29] (2000) also found similar results and mention only diffusion zones against *E. faecalis* and *S. aureus* in the presence of MTA ProRoot (Dentsply) and Portland cement. In another study, Ribeiro et al.[27] (2006) concluded that MTA Angelus (Angelus), MTA ProRoot (Dentsply) and Portland only inhibited the growth of the bacterium *P. aeruginosa*, but were ineffective against other microorganisms.

Bioceramic-based products have also been developed for intracanal medication purposes. BIO-C TEMP (Angelus) contains calcium silicate in its composition and was the first bioceramic product launched as an intracanal medication. Regarding this product, Guerreiro et al.[20] (2021) compared its antimicrobial effects with Calen (S.S White, Rio de Janeiro, RJ, Brazil) and UltraCal®XS (Ultradent, São Paulo, SP, Brazil). All the tested drugs reduced the planktonic form and biofilm biomass of *E. faecalis*, but Calen (S.S White) showed the greatest reduction, followed by UltraCal®XS (Ultradent) and BIO-C TEMP (Angelus). Therefore, Guerreiro et al.[20] (2021)

concluded that the antimicrobial activity of BIO-C TEMP (Angelus) was less effective compared to calcium hydroxide-based drugs[30].

Biocompatibility and Cytotoxicity

The efficacy of endodontic sealers depends on their biocompatibility, due to the risk of periradicular extrusion and direct contact with periodontal tissues[7]. The biocompatibility of endodontic products, as sealers or intracanal medication, is crucial, as they will remain in contact with periapical and periodontal tissues. Bioceramic endodontic materials have demonstrated promising biocompatibility and bioactivity, favoring their increased clinical use. Among these products, Mineral Trioxide Aggregate (MTA) was the first bioceramic material introduced in endodontics; it stood out for its high biocompatibility and bioactivity[21]. Then, different bioceramic sealers were developed, presenting excellent biocompatibility because they encouraged the formation of hydroxyapatite in a manner that is very similar to the physical structure[7].

Bioceramics are bioactive endodontic sealers, as they promote tissue response, leading to tissue regeneration[1]. According to Vidovic Zdrilic et al.[31] (2017), MTA induces the regeneration of injured periodontal ligament and alveolar bone. Those authors observed the differentiation of murine mesenchymal progenitor cells (SMA9+ cells) into osteoblasts (Col2.3GFP+ cells), in the presence of two dilutions of MTA-conditioned media. Transgenic mice, in which αSMA serves as a progenitor cell marker in PDL, were used in this study. The effects of MTA were examined in vivo during repair of the periodontium and surrounding alveolar bone, using cell lineage tracing experiments following an experimental furcal lesion in mouse molars. The healing of the periodontal ligament and alveolar bone was detected at days 17-30 after MTA use[32].

In another in vitro study using fibroblasts, Damas et al.[14] (2011) compared the cytotoxic effect of ProRoot MTA (Dentsply) and third-generation MTA cements, EndoSequence Root Repair Material (Brasseler USA, Savannah, GA) and EndoSequence Root Repair Putty (Brasseler USA) also by MTT assay. EndoSequence Root Repair Materials (Brasseler USA) demonstrated levels of cytotoxicity similar to ProRoot MTA (Dentsply) and MTA-Angelus (Angelus)[26].

According to Pereira et al.[33] (2016) MTA interacts with fats from fluids, leading to apatite precipitation, which not only explains its biocompatibility and bioactivity but may also contribute to its sealing ability. The basic pH also favors hemostasis and causes superficial pulp cell necrosis. All these processes stimulate odontoblast differentiation by undifferentiated mesenchymal cells, leading to dentin repair by dentin bridge formation[34]. Okiji and Yoshiba[32] (2009) demonstrated that MTA has satisfactory physical properties, including good sealing ability, a lower degree of immunity and structural stability[35].

MTA can also interact with phosphate-respecting fluids to spontaneously form apatite precipitates, which not only explains its biocompatibility and bioactivity, but may also contribute to its sealing ability. MTA biocompatibility was evaluated by a meta-analysis study[36]. The authors observed that MTA is more biocompatible than Super EBA and IRM. In another study, ERRM Putty sealer (Brasseler USA) and ERRM Paste sealer

(Brasseler USA), based on calcium silicate, showed *in vitro* biocompatibility similar to MTA[8]. Like ERRM sealer (Brasseler USA), the use of Biodentine (Septodont) and iRoot BP (Innovative Bioceramix) were also the focus of a systematic review, demonstrating promising *in vitro* dental pulp cell viability[37].

In another study related to sealer toxicity, Bin et al.[38] (2012) observed that the cytotoxicity of Sealer Plus BC (MK Life, Porto Alegre, RS, Brazil) depends on the dilution of sealer extract, demonstrating dose-dependent toxicity[18]. The cytotoxicity of some endodontic sealers, such as MTA Fillapex (Angelus) and AH Plus (Dentsply), was already reduced with less diluted extracts. Sealer Plus BC (MK Life) was less cytotoxic to L929 fibroblast cells when a less-diluted extract was used. Additionally, it was more biocompatible than MTA Fillapex (Angelus) and AH Plus (Dentsply)[21].

In another *in vitro* study with fibroblasts, BC Sealer (Angelus, Londrina, PR, Brazil), which is a bioactive and biocompatible product, achieved better tissue healing when compared to MTA Fillapex (Angelus, Londrina, PR, Brazil) and AH Plus (Dentsply/De Trey GmbH, Konstanz, Brazil). These findings were part of a cell viability study using fibroblast cells, analyzed by colorimetric assay based on the 3-(4,5-dimethylthiazol-2-yl)bromide -2 assay, 5-diphenyltetrazolium (MTT). MTA Fillapex (Angelus) was shown to be more cytotoxic than BC cement (Angelus)[39].

A recent study revealed that bioceramics have an excellent biocompatibility characteristic because they closely resemble the biogeochemical formation of hydroxyapatite, which is essential for bonding dentin to filling material[7]. When these bioactive materials come into contact with tissue fluids, they release calcium hydroxide ($Ca[OH]_2$), which can interact with and induce surrounding tissues to promote their protection[40].

Another bioactive material based on bioceramics is BIO-C TEMP (Angelus, Londrina, PR, Brazil), which serves as an intracanal medication and presents a constant release of Ca^{2+}. It is biocompatible, not producing symptoms or painful symptomatology. In an *in vitro* study, BIO-C TEMP (Angelus) was shown not to be cytotoxic, and it led to osteogenic activity in human osteoblastic lineage cells (SaOs-2)[3]. Other studies also demonstrated a non-cytotoxic effect of diluted extracts of BIO-C TEMP (Angelus) on fibroblasts and human dental pulp cells[41].

Bioactive potential

The interaction of bioceramic materials with surrounding tissues can lead to the formation of mineralized tissue. This formation is triggered by the release of calcium hydroxide, leading to the induction of a mineralized barrier[1]. The formation of hydrated calcium silicate and the release of calcium ions interact with carbon dioxide in tissue to form calcite crystals, leading to mineralized tissue formation and fibronectin deposition. All this process results in cell differentiation into fibroblasts, odontoblasts and cementoblasts, conferring bioactivity on the material[13]. In addition, the alkaline pH of bioceramic leads to an environment that is inhospitable to pathogenic microorganisms and positively induces tissue repair and bone neoformation[23].

The bioactivity of bioceramic sealers enables the rehabilitation of dental regions that have suffered root perforation[21]. On the other hand, when used as a retrograde filling

material, these bioactive materials have the ability to perform a stable connection. This connection takes place with living tissues through the deposition of calcium silicate and hydroxyapatite (HAp), in an interfacial layer formed between the biomaterial and the dentin tubules[15]. This interfacial layer also induces the remineralization of cementum and periodontal ligament, since this direct contact with the applied material stimulates the precipitation of apatite crystals in these other regions[8] (Figure 4).

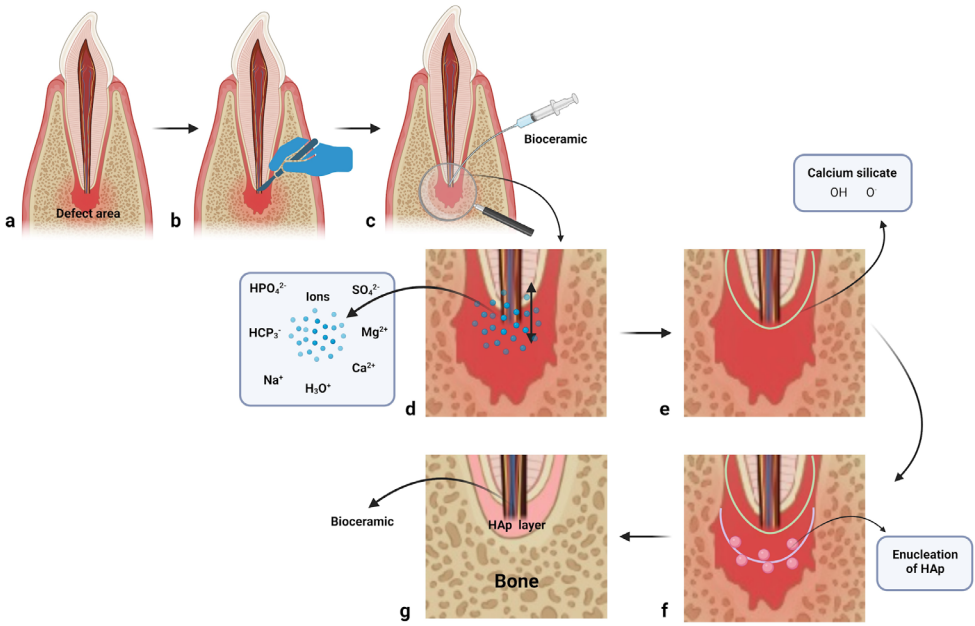

Figure 4. Repair bioceramic used as root end filling material. A: Area of periapical lesion; B: Surgical access and removal of periapical lesion; C: Application of bioceramic as root end filling material; D: Contact of the material with tissue fluids and release of ions; E: Formation of calcium silicate; F: Beginning of enucleation of the hydroxyapatite layer; G: Deposition of the interfacial hydroxyapatite layer. Created by BioRender.com.

The ability to induce the formation of hydroxyapatite and allow the material to bond with both dentin and cellular neoformation is one of the main properties of bioceramic materials such as MTA[22]. Following studies with MTA-based materials performed by direct contact between material and cell culture, Camilleri et al.[16] (2013) observed similar osteogenic potential in both MTA Plus (Avalon Biomed Inc. Bradenton, FL, USA) and ProRoot MTA (Dentsply). Those authors also detected calcium ions released when MTA was in contact with a wet environment or Hank's saline solution (HBSS)[30].

Other studies were carried out with MTA Plus (Avalon Biomed) and biodentine™ (Septodont, Saint Maurdes-Fosses, France), which are cements classified as second generation, where these sealers were evaluated in extract form. Gomes-Cornélio et al.[42] (2016) observed greater SaOs-2 cell viability in cultures exposed to the most diluted extracts, i.e. in a dilution of 1:8, in comparison to 1:1, 1:2 and 1:4 bioceramic dilutions, after 24 hours. The authors also demonstrated a greater osteoclastogenic potential in the presence of the most diluted bioceramic extracts[43].

In another study, Zeid et al.[18] (2017) demonstrated that although NeoMTA Plus bioceramics (Avalon Biomed Inc. Bradenton, FL, USA) and White MTA (Angelus, Londrina, PR, Brazil) showed bioactivity, NeoMTA Plus bioceramics (Avalon Biomed Inc. Bradenton) demonstrated better bioactivity than White MTA. The authors' explanation of these results includes the fact that NeoMTA (Avalon Biomed) presented a shorter setting time and thus obtained better bioactivity and consequently better osteogenic potential[16].

Bioceramic materials were also formulated to be used as endodontic sealers. It was demonstrated that MTA Fillapex sealer (Angelus) increased the activity of ALP enzyme and the formation of mineralized nodules when used for long periods, enhancing its bioactivity after setting[11]. ALP is one of the enzymes present in the plasmatic membrane that is allied to the mineralization process and is also one of the main indications of osteoblast activity[44].

Studies carried out with Bio C Sealer (Angelus) in dogs' endodontically treated teeth demonstrated that a high amount of calcium silicate was released, emphasizing its osteogenic potential[45]. In another study, Alves Silva et al.[46] (2020) analyzed the osteogenic potential of Bio C Sealer (Angelus) by implanting polyethylene tubes filled with this sealer in rat subcutaneous tissue. Researchers found positive marking for osteocalcin[47]. In another study, Lopez-Garcia et al.[48] (2020) detected calcium accumulations, suggesting the formation of a mineralizing matrix, also confirming the osteogenic potential of Bio C Sealer (Angelus)[1]. Seo et al.[49] (2019) demonstrated that sealers with a pH above 7 can prevent the dissolution of mineralized dentin components and neutralize the lactic acid produced by osteoclasts. In this way, these sealers can help in the formation of hard tissues through an alkaline phosphatase activation mechanism[50]. This response can be recognized by the increase in the expression of DMP-1, where there is a high regulation of the expression of the osteogenic marker gene and by the greater accumulation of the mineral[44].

AL-Haddad et al.[51] (2016) concluded that the bioceramics EndoSequence BC Sealer (Brasseler USA) and iRoot SP (Innovative Bioceramix) have high osteogenic activity, given that their study showed a pH above 11 and a strong propensity to release calcium ions[17]. It was certified that bioceramics have a pH of 12.7 during the setting time, similar to calcium hydroxide, resulting in osteogenic activity[52]. On the other hand, Giacomino et al.[53] (2019) analyzed the osteogenic potential of both EndoSequence BC (Brasseler USA) and ProRoot MTA (Dentsply), and both promoted osteoblastic differentiation, while the bioceramic EndoSequence BC (Brasseler USA) obtained greater responses in differentiation[53].

In addition to these studies with bioceramic sealers, a study with the new bioceramic intracanal medication carried out by Guerreiro et al.[20] (2021) pointed out that BIO-C TEMP (Angelus) induced osteogenic activity in an *in vitro* assay including SaOs-2 lineage cells. A similar deposition of mineralized nodules and ALP activity was demonstrated with the use of BIO-C TEMP (Angelus) and calcium hydroxide-based medications, namely UltraCal®XS (Ultradent) and Calen (S.S White)[3].

Results from most studies suggest the effectiveness of the osteogenic potential of bioceramic materials compared to other endodontic sealers and medications.

However, there is a need for further studies with high-quality *in vitro* and *in vivo* research evidence. New studies must be well controlled and should include long-term analysis, so that bioceramics have greater credibility in relation to their bioactive potential in endodontic clinical practice. Most of the comparative studies that were analyzed in this review on the bioactivity of bioceramics were carried out with commercial materials. A laboratory analysis with the active compounds of the products may suggest more consistent results and thus promote a better quality of response to the bioactive potential of bioceramics. Therefore, further research and evaluation of the properties of this product are suggested.

In conclusion, this review presented a summary of the antimicrobial activity, biocompatibility, cytotoxicity, and osteoclastogenic potential of bioceramic-based materials for endodontic use. Most studies reported that bioceramics demonstrated greater efficiency in biocompatibility and bioactivity compared to other materials. However, with regard to intracanal bioceramic medication cements, studies reported lesser results than recorded with other medications. As the bioceramic intracanal drug is new, the published studies on the physicochemical properties of BIO-C TEMP are limited. Thus, further research into and evaluation of the physicochemical properties of this medication are suggested. An ongoing evaluation of the long-term performance of products on the market should be performed to correctly assess their favorable use in endodontic therapy.

Acknowledgments

This study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (305242/2022), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (200085891), and Fundação de Apoio à Pesquisa do Distrito Federal (FAPDF) (00193 – 00000782/2021-63 and 00193- 00001118/2021-31).

Data Availability

Datasets related to this article will be available upon request to the corresponding author.

Conflict of Interest Statement

None.

Author Contribution

Raquel Figuerêdo Ramos: Conceptualization, Investigation, Methodology, Resources, Software, Validation, Writing-original draft. **Larissa Barbosa de Sousa:** Conceptualization, Investigation, Methodology, Resources, Software, Validation, Writing-original draft. **Paula Ribeiro Garcia:** Conceptualization, Data curation, Formal analysis, Resources, Validation, Writing-original draft. **Taia Maria Berto Rezende:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing-review & Editing. All authors revised and approved the final version of the manuscript.

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