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Bredigite-containing materials for regenerative medicine applications: A rapid review

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ABSTRACT

Bredigite (BR; $Ca_7MgSi_4O_{16}$) is known as one of the most popular calcium-silicate bioceramics. It has an orthorhombic structure containing calcium silicate magnesium compound, and releases Si ions, thereby inducing precursor cell differentiation and cell growth. This suggests that Br may serve as a promising material for existing orthopedic and dental implants. A new insight into the Br composites structure/activity/application tradeoff is the primary objective of the current review, which helps researchers overcome the existing challenges and recognize the bottlenecks that arose from this intersection. In this rapid review, the state-of-the-art advances in Br-containing composites in terms of preparation techniques and modifying methods for enhancing their functional properties, especially in the field of dental implants are surveyed and discussed.

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1. Introduction

A smile determines whether an individual is happy, pleasant, or laughing [1, 2]. Periodontitis, characterized by inflammation of the periodontium due to microbial colonization and calculus accumulation on oral biofilms, poses significant challenges in clinical management due to the intricate immune-inflammatory response of the host. Current therapeutic modalities often yield unsatisfactory outcomes, necessitating the exploration of novel strategies for the comprehensive repair and regeneration of periodontal tissues, including cementum, periodontal ligament, and alveolar bone. Cementum, an essential component of the periodontium, serves as the mineralized interface between the periodontal ligament and the alveolar bone, synthesized by cementoblasts during tooth root development [3-5].

The periodontal ligament, a fibrous connective tissue anchoring the tooth root to the alveolar bone, holds immense regenerative potential, as evidenced by recent studies highlighting its resemblance to bone marrow mesenchymal stromal cells (BMSCs) [6, 7]. Notably, periodontal ligament cells (PDLCs) exhibit promising characteristics, including the capacity for cementoblastic differentiation both in vitro and in vivo, underscoring their significance in periodontal tissue regeneration [8]. The pivotal role of bioactive materials in facilitating periodontal and bone tissue regeneration is widely acknowledged, with a focus on stimulating cementogenic and osteogenic differentiation of PDLCs to expedite healing processes [5, 9-11].

In the realm of bone tissue engineering (BTE), porous scaffolds offer a promising avenue for the repair and regeneration of damaged bone tissue, obviating the need for permanent implants. The architectural design of porous scaffolds, characterized by interconnected three-dimensional porous structures, facilitates cellular adhesion, proliferation, and differentiation, fostering the ingrowth of new bone tissue. Moreover, the bioactivity of scaffolds plays a crucial role in promoting cell growth and differentiation, particularly beneficial in addressing significant bone defects [12].

The development of biomaterials for bone tissue engineering has garnered significant attention in recent years. Porous β-TCP ceramic, recognized for its bio-resorbable properties and excellent tissue biocompatibility, has emerged as a promising candidate for facilitating bone regeneration and ingrowth [13, 14]. Despite its resorbable characteristics [15, 16], porous β-TCP scaffolds have limitations in stimulating cell growth, particularly in addressing large bone defects [5, 12].

In contrast, Si and Ca-containing bioactive glasses have shown the ability to stimulate cell proliferation and induce bone-like apatite formation in vitro, thereby enhancing bone cell proliferation and differentiation. Recent investigations have extended the scope to include silicate ceramics such as wollastonite and bredigite, which exhibit comparable bioactivity to bioactive glasses [12, 17, 18].

BR bioceramics, characterized by compositions such as $Ca_7MgSi_4O_{16}$, have recently garnered significant attention as promising materials for bone regeneration. Their distinctive combination of superior mineralization, degradation properties, and mechanical strength, coupled with their capacity to facilitate osteoblast attachment and proliferation, positions them at the forefront of biomaterial research [12, 17-19].

The intriguing presence of calcium (Ca), magnesium (Mg), and silicon (Si) within BR renders it a compelling bioactive substance (Fig. 1). Notably, its mechanical robustness surpasses that of traditional hydroxyapatite (HA) [20-24]. Moreover, studies have elucidated that the dissolution of BR, accompanied by the subsequent formation of silicon and calcium-containing ionic byproducts, enhances cell proliferation on its surface [25].

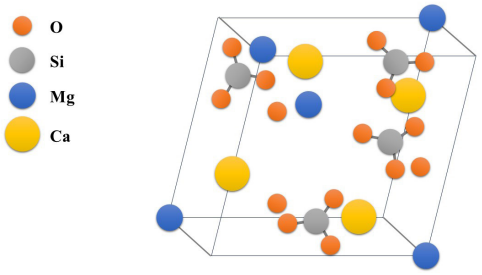

Fig. 1. Ionic arrangement of bredigite.

Consequently, BR powder exhibits promising potential for fostering bonding with living bone tissue and contributing to the repair of bone defects within the human body [25, 26]. This functionality is attributed to its ability to bolster osteoblast cell proliferation, stimulate collagen production, and foster bone growth [25-28].

Besides, BR is thought to be a coating material to get around the weak mechanical anchoring and poor osseointegration for hosting bone tissues, as well as to lower the rate of implant loosening [29]. For instance, in terms of Ti-based implants, research studies showed that the bonding strength of the Ti6Al4V implant had been highly improved through the use of a plasma-sprayed BR coating [29]. The use of BR coating led to a significant improvement of apatite mineralization. Furthermore, the proliferation and adherence of BMSCs were notably improved on a BR-coated Ti6Al4V [29]. Prior research has demonstrated that adding BR to pure Mg as a biodegradable orthopedic implant could significantly lower the magnesium's biodegradation rate by up to 24 times [30]. In addition to providing protection against magnesium's rapid corrosion, the BR particles may act as a reinforcing phase within the Mg matrix. It has been noted that the toxicity of pure Mg to BMSCs is reduced upon the integration of BR particles into the Mg matrix [27, 30].

Understanding the properties and potential applications of these materials is vital for advancing the field of bone tissue engineering. In this review, we aim to provide a comprehensive overview of the advancements, challenges, and future prospects associated with the utilization of BR-based bioceramic composites in both dental and bone tissue engineering applications.

2. Applications of BR-based materials

2.1. LED

Driven by numerous advantages, BR mineral has emerged as a promising host material. Its significance transcends the boundaries of crystal chemistry, demonstrating multifaceted applications in cement, clinkers, slags, and even fertilizers [31]. Furthermore, alkaline earth silicates, with BR as a leading representative, have garnered considerable attention for White Light Emitting Diode (WLED) applications. This stems from their exceptional thermal and chemical stability, combined with

Table 1.
First-principles calculations of Bre physicochemical properties [28].

Property	Value
Isothermal bulk modulus	90.6 GPa (with a pressure derivative of 5.7)
Isobaric heat capacity (C_p)	$8.22 \times 10^2 - 3.76 \times 10^3 T^{-0.5} - 1.384 \times 10^7 T^{-2} + 1.61 \times 10^9 T^{-3}$ J mol^{-1} K^{-1} (298–1000 K)
Standard vibrational entropy	$S_{298}^{0} = 534.1$ (22) J mol^{-1} K^{-1}
Stability at ambient *P*	up to ~1372 °C and ~1.2 GPa

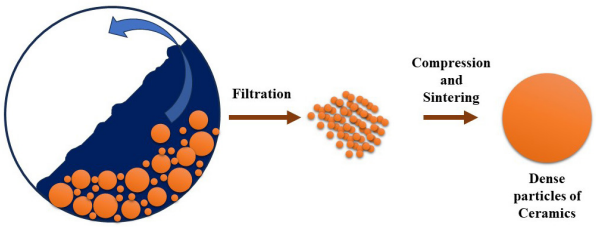

Fig. 2. Schematic illustration of milling methods to fabricate BR composite.

impressive efficiency [32, 33]. As previous studies have meticulously documented, the crystal structure of CMS adopts an orthorhombic system (SG 34) with the space group Pnn2. [34-37]

2.2. Membrane

Guided bone regeneration (GBR) stands as a well-established technique for promoting bone tissue growth in defect sites. Its efficacy relies on creating and maintaining a protected space through a barrier membrane. This membrane shields the osseous defect from the invasion of epithelial and other soft tissues, allowing ample time for bone regeneration. For optimal GBR outcomes, the chosen barrier membrane must fulfill specific criteria, including bioactivity (osteoconductivity), biocompatibility, cell-inclusiveness, mechanical stability, resorbability, and ease of clinical use [38].

Building upon the established effectiveness of GBR, Kouhi et al. [38] introduce a novel approach with their development of poly(hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)/fibrinogen (FG)/BR membranes. These membranes hold significant promise for applications in guided bone tissue engineering.

Key innovations lie in the incorporation of BR and FG into the PHBV matrix. This modification enhances the membrane's hydrophilicity and degradation rate, both crucial factors for optimal cell response. The study demonstrates that these electrospun PHBV/FG/BR nanofibrous membranes promote both cell proliferation and mineralization, essential processes for successful bone regeneration. The experimental data presented by Kouhi et al. strongly suggests that these newly developed membranes possess exceptional potential in advancing guided bone tissue engineering applications [38].

2.3. Drug delivery

Invasive treatments for bone defects raise concerns about osteomyelitis, necessitating antibiotic delivery systems. While antibiotic-loaded poly(methyl methacrylate) cements offered a solution, their non-biodegradability proved problematic [39, 40]. Bioresorbable and bioactive ceramics presented a greener alternative, leading to increased interest in magnesium-calcium biosilicates for their osteoinductivity, osteoconductivity, and bioresorbability [41-43]

Early success was seen with dexamethasone-loaded diopside microspheres promoting bone regeneration [44]. Further studies explored vancomycin release from Mg–Ca silicate microspheres, revealing diffusion and degradation-controlled mechanisms [41, 45]

Zirak et al. (2020) compared drug release kinetics from sol-gel synthesized microspheres loaded with vancomycin, finding diopside exhibited two-step diffusion, while akermanite and BR displayed initial diffusion followed by mixed-mode release dominated by degradation of BR [45, 46].

Building upon this, Zirak et al. (2022) explored Mg–Ca silicate microspheres encapsulated in biodegradable PLGA for controlled vancomycin release. Diopside, bredigite, and akermanite microspheres were loaded with drugs and coated with PLGA. Their findings suggest diffusion contribution was ranked diopside > akermanite > bredigite, while PLGA dominated diffusion mechanisms. Cytocompatibility assays revealed that PLGA coating improved cell biocompatibility, with akermanite ranking highest due to a balance between ion release and drug release. This study concluded that PLGA-coated Mg–Ca silicate microspheres hold promise for drug-delivery bone tissue engineering [47].

Further work by Jadidi et al. focused on PLGA-coated BR scaffolds loaded with vancomycin. Bare scaffolds exhibited rapid drug release, highlighting the need for PLGA modulation. Coated scaffolds demonstrated controlled release and improved cell viability due to modified drug release and PLGA's buffering effect. They concluded BR scaffolds offer versatility for controlled antibiotic delivery, easily modulated by biopolymer coatings [48, 49].

2.4. Dental and Bone Tissue Engineering

BR has recently garnered attention for its potential applications in dentistry and bone tissue engineering. This bioactive ceramic exhibits favorable properties such as biocompatibility, bioactivity, and osteoinductivity, making it a promising candidate for various dental and orthopedic applications [50-52].

In dentistry, BR holds promise for use in dental materials and implants due to its ability to promote osseointegration, the process by which bone integrates with an implant surface. Studies have shown that BR-based materials can enhance the formation of new bone tissue around dental implants, leading to improved stability and longevity of the implant. Furthermore, the bioactive nature of BR allows for the gradual release of ions that can promote tissue regeneration and combat bacterial colonization, thereby reducing the risk of peri-implant infections [50-52].

In bone tissue engineering, BR scaffolds have emerged as a viable option for repairing and regenerating damaged bone tissue. These scaffolds provide a three-dimensional framework that mimics the structure of natural bone, facilitating cell attachment, proliferation, and differentiation. BR's bioresorbable nature ensures that the scaffold gradually degrades over time, allowing new bone tissue to replace it. Additionally, the release of calcium and magnesium ions from BR scaffolds can stimulate osteogenic activity and enhance the healing process [53].

Recent advancements in fabrication techniques have enabled the production of highly porous BR scaffolds with tailored properties. These scaffolds can be engineered to match the mechanical strength and porosity of native bone, providing an optimal environment for bone regeneration. Furthermore, the incorporation of growth factors, drugs, or stem cells into BR scaffolds can further enhance their regenerative capabilities and promote faster tissue healing. Overall, BR shows great promise in the fields of dentistry and bone tissue engineering, offering innovative solutions for the repair and regeneration of damaged tissues. Continued research and development in this area are expected to lead to the development of advanced biomaterials and treatment modalities that improve patient outcomes and quality of life [50-53].

3. Synthesis methods

3.1. Synthesis of Br-containing bioceramics

Various chemical and mechanical methodologies, such as combustion [54], sol-gel [25, 55], ball milling [56-58], and microwave-assisted, have been previously documented for BR synthesis. However, the mechanical activation process introduces a certain degree of contamination into the resultant product, rendering it unsuitable for medical applications. The wet-chemical synthesis approaches detailed in existing literature necessitate the use of catalysts, expensive precursors, and

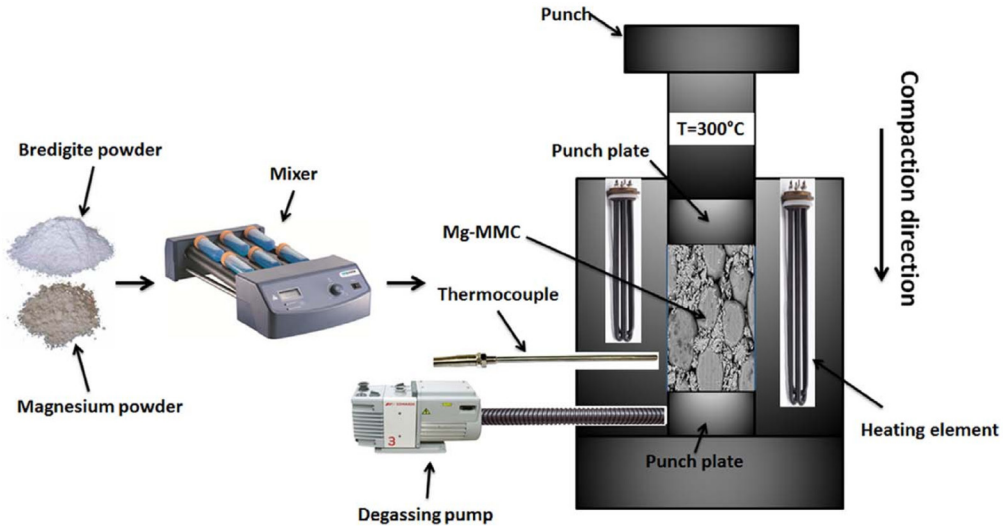

Fig. 3. Schematic illustration of PAS technique [64].

time-consuming procedures to achieve a singular-phase BR structure [25, 54]. Conversely, BR exhibits a higher degradation rate in physiological environments due to its low silicon concentration and consequent scarcity of bridging oxygens, unlike other Mg–Ca silicates such as diopside and akermanite. This accelerated degradation leads to a marked increase in pH within the surrounding media, which, despite imparting beneficial antibacterial properties [59-61], exerts an inhibitory effect on cell proliferation and metabolism [18, 62].

3.1.1. Sol-gel

Bredigite powders can be fabricated via the sol-gel method using TEOS, magnesium nitrate hexahydrate, and calcium nitrate tetrahydrate in a specific ratio. The process involves hydrolysis, reaction, drying, and calcination steps. The resulting powders should be dispersed in a PVA solution to create a slurry. This slurry is then used to coat a polyurethane foam template, which is subsequently dried and sintered to obtain the final bredigite product [12]. Table 2 summarizes the performed studies about sol-gel derived BR.

Wu et al. [26] prepared BR by sintering powder compacts of sol–gel-derived BR at 1350 °C for 8 hours. They found that the fracture toughness, bending strength, and Young's modulus of BR were about 1.57 MPa $m^{1/2}$, 156 MPa, and 43 GPa, respectively. Also, it was found that BR ceramics could induce the formation of HA in SBF. Within a given concentration range, the compounds resulting from the dissolution of BR substantially boosted cell growth. Furthermore, osteoblasts adhered and spread effectively on BR ceramics.

Kouhi et al. [63] synthesized HA/BR nanoparticles containing 25% and 50% BR using the sol–gel method. They produced HA/BR nanoparticles with a homogenous distribution of bredigite and an average particle size of less than 50 nm. After 72 hours, mesenchymal stem cells in the HA/BR extract proliferated far more than those in the extract of the original HA and the control group. Given that the HA/BR nanoparticles' characteristics were significantly better than those of pure HA, it is possible that these composite nanoparticles will work well as bioactive materials in applications involving bone regeneration.

3.1.2. Microwave-assisted method

During the microwave-assisted method, calcium nitrate tetrahydrate and magnesium nitrate hexahydrate are dissolved in ethanol, with tetraethyl orthosilicate (TEOS) added to the solution. The pH is adjusted to 9 using an ammonium hydroxide solution. After stirring, the solution is irradiated in a microwave oven and then dried at 100 °C for 12 hours. The dried powder is subsequently heat-treated at various temperatures to obtain the final product [27].

The literature leads to the conclusion that extended processing durations and high temperatures are necessary for the initial stage of conventional procedures used to synthesize pure BR nanoparticles. As a result, the method for creating bredigite nanoparticles that has been created is unique, facile, quick, low energy consuming, and provides high-purity nanoscale products [27].

3.1.3. Mechanical Milling Route and subsequent sintering process

This method is used to fabricate the composite powder of BR with other materials such as Fe_3O_4. The nanocomposite containing bredigite is synthesized using a planetary ball mill. An alcohol medium is employed to achieve a uniform mixture, with milling conducted for 30 to 60 minutes [56].

Khandan and Ozada synthesized nanostructured BR/Fe_3O_4 powders with different percentages (0, 10, 20, and 30 wt. %). They realized that the sample with the highest amount of magnetite leads to a higher hyperthermia effect. Their results confirmed that BR/30 wt.% Fe_3O_4 nanocomposite had enough released heat under alternating magnetic fields during the hyperthermia process [56].

3.1.4. Pressure-Assisted Sintering (PAS)

Bredigite synthesis via Pressure pressure-assisted sintering (PAS) involves heating powder mixtures containing Mg and BR particles in a cylindrical die. The process begins with heating under a pre-pressure of 100 MPa followed by uniaxial compaction at 500 MPa. Sintering is then conducted at special temperatures (between 150-350 °C) for different durations (1-4 h) under the compaction pressure of 500 MPa to achieve high densification. Finally, specimens are air-cooled to 25 °C after sintering. The schematic of the PAS technique is illustrated in Fig. 3 [64].

3.1.5. Co-precipitation

In order to synthesize the BR via a coprecipitation method, calcium chloride, and magnesium chloride are dissolved in ethanol, with magnesium fluoride substituted for a portion of the magnesium chloride for

Table 2.
Sol-gel derived Bredigite.

Material	Particle size	Formation of apatite	Ref.
BR powder	1–10 μm	10 days	[25]
BR nanopowder	38-48 nm	3 days	[55]
BR powder	234-463 nm	4 days	[54]
HA/X5 BR (25 and 50%)	50 nm	-	[63]

fluoride doping (if applicable). Silicon tetrachloride is added to the solution at 0 °C, followed by the dropwise addition of ammonia solution to raise the pH to 10. The resulting precipitates are washed, dried, and then subjected to calcination at various temperatures to obtain the BR powder. [62]

3.2. Synthesis of BR-containing scaffolds

3.2.1. Space holder Method

The space holder technique in which a volatile or solute material such as carbamide, starch, ammonium bicarbonate, or sodium chloride is used as a space holder has been reported extensively [65]. The technique consists of mixing particles of the space holder (with different sizes and shapes) with ceramic or metal powders, compacting the powder mixture, and leaching or evaporating space holder materials to leave a high-volume fraction of porosity before, during, or after sintering. Sintering the samples reduces secondary porosity and supplies good mechanical properties [65-67].

Generally, there are two types of spacers: volatile pore-creating particles such as ammonium bicarbonate, which are burnt out during sintering or removed by increasing the temperature before sintering, and soluble pore-forming particles such as sodium chloride, which are dissolved and removed by a solvent. Among various space holder materials mentioned, sodium chloride is preferred because it is rigid, inexpensive, extensively available, and easily leachable by water [66].

With this approach, the spacer has a direct impact on the majority of the final scaffolds' characteristics, including the porosity, size, and shape of the pores. Thus, the most crucial factors are the choice of the right spacer, the quantity of spacer, and the even mixing of powder and spacer. Generally speaking, spacers come in two varieties: soluble pore-forming particles like sodium chloride, which dissolve and are removed by a solvent, and volatile pore-forming particles like ammonium bicarbonate, which are burned out during sintering or eliminated by raising the temperature prior to sintering. Sodium chloride is the material of choice for space holders among the others stated because it is readily available, inexpensive, stiff, and easily soluble in water [60].

In order to synthesize BR scaffolds using the Space Holder Method, BR powders and NaCl are mixed in a polyethylene container using an amalgamator. The volume percentage of NaCl is adjusted to achieve a final porosity of 80-90%. The weight percentage of BR powder to space former is determined based on the density of each component. To ensure proper adhesion and prevent agglomeration, 2 wt.% vegetable oil is added to the mixture. The resulting powders are then uniaxially pressed into cylindrical samples under 50 MPa for a couple of minutes. These green samples are sintered. Subsequently, the sintered samples are immersed in double deionized water to eliminate the NaCl space holder, with water changes every 6 hours. [66]

3.2.2. Electrospinning technique

The most popular method for producing nanoparticles incorporated in nanofibrous scaffolds is electrospinning because of its inexpensive setup costs and ease of use. Kouhi et al. developed PHBV nanofibrous scaffolds containing treated BR nanoparticles using an electrospinning technique. In their study, BR nanoparticles were modified with GPTMS and incorporated into PHBV nanofibers. When compared to PHBV and PHBV/BR, they discovered that the PHBV/G-BR scaffold indicated superior mechanical properties, particularly at greater nanoparticle concentrations [68, 69].

3.2.3. 3D-printing

Bioceramic implants should have specialized forms and offer structural support to fill the deficiency area in order to promote effective bone ingrowth and bone support. With its recent emergence as a breakthrough manufacturing method, 3D-printing holds enormous promise in several sectors, including dentistry and bone tissue engineering [70, 71]. Using 3D printing techniques, a variety of tailored porous ceramic scaffolds have been devised and manufactured for bone regeneration and dental applications [72, 73]. Recent research has demonstrated that 3D porous bioceramic scaffolds can support the growth of cells and tissues and have the mechanical strength appropriate for use as dental and bone implant materials [17, 74-77].

3.3. Synthesis of BR-containing biocomposite coatings

3.3.1. Laser additive manufacturing

This technology utilized a laser beam to selectively melt thin powder layers, allowing for the rapid layer-by-layer construction of complex-shaped parts [78-80]. Additionally, it alludes to a quick solidification process that promotes microstructure homogenization and refinement, resulting in composites with improved performance [81-84].

3.3.2. Electrophoretic deposition (EPD) technique:

As a coating technique, EPD has numerous benefits, such as ease of use, environmentally friendly processing, and affordability [85, 86]. Additionally, EPD has previously been used to coat the bioceramics on the biometal surface of orthopedic implants [87-89].

Razavi et al [89]. used the nanostructured BR coating created by micro-arc oxidation and electrophoretic deposition techniques to increase the bioactivity and corrosion resistance of the Mg-alloy AZ91. According to their findings, the AZ91 substrate's corrosion resistance and bioactivity were both improved by this surface treatment, qualifying it for use in dental applications.

3.3.3. Spin Coating Technique

Dip- and spin-coating techniques are among the simplest for producing thin layers on a variety of substrates [51, 90, 91].

A polymeric binder that has excellent film-forming capacity can be utilized to improve the wetting and adherence of the ceramic phase to the substrate and to facilitate an efficient coating process [92, 93]. For example, polyvinyl alcohol (PVA) is a gel-forming, biocompatible, nontoxic substance that encourages the ceramic phase to crystallize and co-depose while retaining high bioactivity [92]. Additional potential crosslinking between the hydroxyl groups of PVA molecules and calcium phosphate particles could result in an enhancement in the biomaterial's mechanical capabilities [94]. With the potential to be employed as a binder for calcium silicate coating on Ti alloy, it has been demonstrated that adding 0.05% of PVA to calcium silicate did not alter the phase composition of the silicate structure [51].

4. BR-containing biocomposites

Using selective laser melting, new Fe-palladium (Pd)-BR biocomposites were synthesized in the Gao et al. [95] work with the goal of enhancing Fe's bioactivity and degrading behavior. Their findings demonstrated that whilst the BR phase was dispersed at the grain boundaries, the majority of Pd formed Pd-rich intermetallic phases (IMPs) with a practically continuous network. Furthermore, a significant number of far nobler IMPs bonded with the Fe matrix to create micro-galvanic pairs, which greatly increased micro-galvanic corrosion. The high concentration of Pd^{2+} and strong reduction potential found in the IMPs increased the effectiveness of micro-galvanic corrosion. Furthermore, the corrosion medium's penetration was made easier by the quick deterioration of BR. The Fe-4Pd-5BR biocomposite consequently demonstrated a homogeneous disintegration at a rate six times faster than that of Fe.

Table 3.
BR-containing materials for dental and bone tissue engineering applications.

No.	Composition	Fabrication method	Biological Behavior	Other Results	Ref.
1	PHBV nanofibers containing different amounts (0, 5, 10, and 15 wt. %) of HA, BR, or HABR	Electrospinning	10% HABR incorporated PHBV nanofibers show a high ability for apatite formation	10% HABR-incorporated PHBV nanofibers show optimized mechanical properties	[100]
2	PHBV nanofibers containing different amounts (0, 5, 10, and 15 wt. %) of BR	Electrospinning	PHBV-BR nanofibers demonstrated excellent bioactivity, and hFOB cells grown on nanofibrous scaffolds showed higher cell proliferation and osteogenic differentiation than pure PHBV scaffolds	-	[101]
3	GPTMS-modified BR	Electrospinning	the synergetic effect of BR and GPTMS provided an enhanced hFob cell attachment and proliferation	PHBV/G-BR scaffold indicated improved mechanical properties compared to PHBV and PHBV/BR, especially at the higher concentration of nanoparticles	[102]
4	Mg-matrix composites containing 20–40% uniformly dispersed BR particles	Ball-mill sintering	The degradation rate of magnesium was decreased by up to 24 times. The viability and proliferation of rat bone marrow stromal cells were Improved	The mechanical functionality of Mg might be increased from 3 days to more than 12 days. After 12 days of soaking, the strengths of the composites could be maintained at a strength level of cortical bone.	[30]
5	Mg-matrix composites containing BR particles	PAS method	The Mg-20% BR composite degraded 24 times slower in an in vitro setting in a cell culture medium, in comparison to monolithic magnesium	Low-porosity Mg-BR composites with robust interfaces between uniformly distributed BR particles and the Mg matrix could be produced by optimizing the PAS process parameters. The final compressive strength and ductility of magnesium rose by 67% and 111%, respectively, upon reinforcing with 20 vol% BR particles. These increases are similar to those observed in cortical bone.	[64]
6	BR-coated AZ91	ASD and EPD	Improvement was made to BR-coated AZ91's mechanical integrity, bioactivity, degradation resistance, and cytocompatibility.	BR coating can be used to fabricate biodegradable metallic orthopedic implants	[103]
7	BR/ASD coated AZ91	ASD and EPD	Using BR/ASD-coated implants resulted in decreased bone inflammation and better bone regeneration in the greater trochanter of rabbits, according to the findings of the in-vivo animal tests.	-	[104]
8	B-doped BR-coated Ti6Al4V	PVA-assisted sol-gel spin-coating technique	High osteoblast cell growth was seen in all coatings during the in-vitro contact cytotoxicity tests, suggesting potential uses of the coatings in orthopedics and dentistry.	The mechanical properties decreased by the boron addition	[51]
9	PCL and PLA containing Sr-doped BR nanoparticles	3D-printing technique	The scaffolds supported the viability and proliferation of human osteoblasts. Gene expression and calcium deposition in the scaffolds were highly significant. The nanocomposite scaffolds exhibited a high potential to regenerate bone tissue, by implanting into the calvarial defects in rats for 3 months.	The PLA/PCL/BR-5%Sr nanocomposite scaffolds showed an improvement in mechanical strength and a faster degradation rate.	[105]
10	HA/BR scaffolds (0, 5, 10, and 15 wt.%)	Space holder technique	As the BR concentration increased, the composite scaffolds demonstrated improved bioactivity and biodegradability. The HA-15 wt.% BR scaffold considerably increased cell proliferation in comparison to the HA scaffold, as demonstrated by the MTT assay.	The addition of BR content from 0 to 15 wt.% greatly increased the scaffolds' Young modulus and compression strength.	[106]
11	Porous BR scaffolds coated with PLGA	Sol-gel, sacrificial sponge replica, and sintering processes	The incorporation of PLGA coatings up to 10% did not suppress the porosity characteristics of the scaffolds suitable for tissue engineering. the viability of stem cells on the BR scaffolds is improved by using the PLGA coatings, with the optimal concentration of 10% PLGA.	Polymeric coatings considerably increase the ceramic scaffolds' compressive strength.	[107]
12	B-incorporated biphasic larnite/BR calcium magnesium silicate cement	Low-temperature sol-gel route	The cement suspensions showed excellent antibacterial activity against all tested bacteria, including Enterococcus faecalis, Escherichia coli, and Staphylococcus aureus.	The CaMgSi/0.5B cement's final setting time dropped from 30 minutes (for undoped cement) to 19 minutes, while the DTS and CTS nearly doubled to reach their maximum values of 8.8 MPa and 85 MPa, respectively.	[50]

HA: hydroxyapatite, BR: bredigite, HABR: hydroxyapatite/bredigite (50:50), PHBV: Poly(3-hydroxybutyrate-co-3-hydroxyvalerate), GPTMS: 3-glycidoxypropyltrimethoxysilane, PAS: Pressure Assisted Sintering, PCL: polycaprolactone, PLA: poly lactic acid, PLGA: poly(lactic-co-glycolic acid), PVA: polyvinyl alcohol, CTS: compressive tensile strengths, DTS: diametral tensile strengths, ASD: anodic spark deposition, ASD: anodic spark deposition, EPD: electrophoretic deposition.

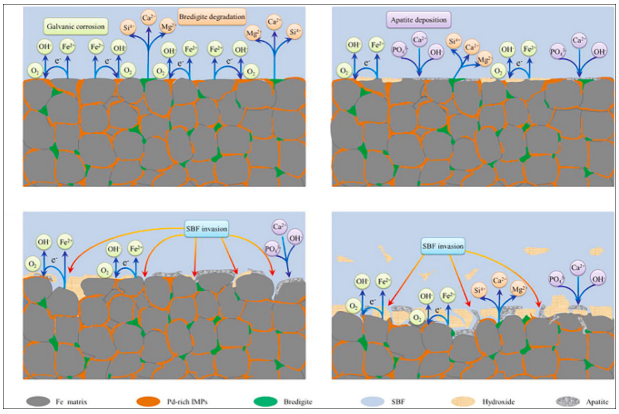

Fig. 4. The process of fast degradation and apatite deposition for Fe-Pd-BR bioceramic [95].

The produced Fe-Pd-BR biocomposites (Fig. 4) also had good mechanical properties, cytocompatibility, and bioactivity, as evidenced by the quick apatite deposition, regular growth of human osteoblast-like cells (MG-63), and similar strength and microhardness to natural bone. All things considered, this work provides a fresh approach to enhancing the bioactivity and degradation of Fe-based composites, which could lead to further opportunities for using them as biodegradable implants for tissue/organ restoration [95].

In another work, Razavi et al. [96] synthesized a bioceramic composite coating composed of diopside, BR, and fluoridated hydroxyapatite on the AZ91 alloy. The degradation data of samples imply that the composite coating enhances the bioactivity of the AZ91 Mg alloy substrate while reducing the rate of degradation. After four weeks of immersion, there was no discernible decline in the coated samples' compression strength as compared to the sample without coating. According to cytotoxicity tests, the coatings increase the AZ91 alloy's cell compatibility with L-929 cells.

Deng et al. [97] harnessed the controlled surface micro/nanometer structure of bioactive scaffolds in conjunction with biomaterial chemistry to address osteochondral defects. By merging 3D printing with a hydrothermal process, model bioactive biomaterials, BR scaffolds, with regulated surface micro/nanostructure are successfully created. The in-vivo investigation demonstrates that the 3D printed scaffolds' micro/nanostructured surface clearly encourages the regeneration of subchondral bone tissues as well as cartilage. This study reveals that a clever way to promote bilineage bioactivities for osteochondral regeneration is to build tailored micro/nanostructured surfaces in porous 3D scaffolds.

Khandan et al. [98] investigated the biological and mechanical characteristics of the BR-magnetite nanocomposite with varying concentrations of magnetite (0, 10, 20, and 30 wt%). The obtained results showed that the Fe_3O_4 concentration had a notable impact on the characteristics of the developed scaffolds. The best sample in this study, which was BR-30 wt.% magnetite, had a Young's modulus of 29 GPa and a fracture toughness of 2.69 MPa m1/2. The SBF solution's pH values increased as the amount of BR increased. The Ca^{2+} ion exchange and interaction on the scaffold surface was the source of this. The sample with 10% magnetite showed a rough, rocky surface, but the sample with 30% magnetite indicated a smooth, flat outer layer with sharp projections. The findings verified that the pure BR's biodegradation rate surpasses that of the 20 wt. % sample.

In terms of dental applications, if left untreated, periodontitis can cause the host's damaging inflammatory response in response to a bacterial biofilm that has adhered to the tooth surface. This can end in the loss of the teeth as well as the surrounding tissues, including the alveolar bone. An integral component of the periodontium, cementum is a specialized calcified tissue that covers the tooth root and facilitates the attachment of the periodontal ligament to both the root and the surrounding alveolar bone. A potential cell source for periodontal tissue engineering is periodontal ligament cells (PDLCs) [5].

Since cementogenesis is a crucial step in the regeneration of periodontal tissues, Zhou et al. studied the possibility of stimulating PDLC proliferation and cementogenic differentiation with inorganic stimuli derived from bioactive BR bioceramics. Additionally, by analyzing the gene/protein expression of PDLCs that interacted with BR extracts, the involvement of the Wnt/b-catenin signaling pathway during this process was further investigated [5].

Their findings demonstrated that, in a concentration-dependent manner, the ionic products derived from BR powder extracts resulted in notably enhanced cementogenic differentiation and proliferation, including mineralization–nodule formation, ALP activity, and a number of gene/proteins related to bone/cementum (OPN, ALP, OCN, CAP, BSP, and CEMP1) [5].

Additionally, the pro-cementogenesis effect of the BR extracts was diminished by the addition of cardamonin, an inhibitor of Wnt/b-catenin signaling, suggesting that the Wnt/b-catenin signaling pathway is involved in the cementogenesis of PDLCs produced by BR extracts. According to their investigations, PDLCs can be induced to differentiate into a cementogenic lineage by means of a completely inorganic stimulus that has a certain composition of BR bioceramics. This can result in the activation of the Wnt/b-catenin signaling pathway. The outcomes show that BR ceramics have therapeutic promise when used in periodontal tissue engineering applications [5].

In a study, Askari et al. [99] added bovine serum albumin-reduced graphene oxide (BSA-rGO) to the BR bioceramic to enhance its mechanical properties. It was shown that the BSA could efficiently shrink the GO nanosheets and offer the right kind of contact for the BR particles and the rGO nanosheets. It was discovered that the porosity was reduced by the BSA-rGO nanosheets' homogeneous dispersion throughout the BR matrix. The MTT test was used to assess the nanocomposite's biocompatibility, and the results showed that the inclusion of graphene had no unfavorable effects. The incorporation of BSA-rGO nanosheets into the matrix resulted in an increase in G-292 cell adhesion. Additionally, the nanocomposite's ALP activity showed a considerable increase when compared to the BR tablet, indicating its high osteogenic bioactivity.

Chen and colleagues [52] examined the impact of bioceramics extracts on the pluripotency and multilineage differentiation capacity of human dental pulp cells (hDPCs), encompassing silicate BR and standard β-tricalcium phosphate (β-TCP study).

BR extracts kept hDPCs in a presenescent state and markedly increased cell growth, proliferation, and TERT expression. BR extracts stimulated multilineage differentiation of hDPCs following odontogenic/adipogenic induction and markedly up-regulated the expression of pluripotency-related genes such as Oct4, Sox2, and Stro1. Their findings opened the door for further uses in regenerative medicine by indicating that BR extracts can increase the pluripotency of stem cells produced from teeth for the first time [52].

5. Conclusions and future insights

In conclusion, this rapid review has shed light on the potential of bredigite (Br) as a key player in the realm of regenerative medicine, particularly in the context of orthopedic and dental implants. Through its orthorhombic structure and the release of essential ions, Br holds promise in facilitating cell differentiation and growth, making it a valuable candidate for enhancing implant integration and tissue regeneration.

The synthesis methods discussed, ranging from powder preparation to scaffold fabrication and composite coatings, illustrate the versatility and adaptability of BR-based materials in various biomedical applications. Researchers have made significant strides in understanding the

structure-activity application tradeoff of BR composites, paving the way for innovative approaches to address existing challenges and bottlenecks.

Looking ahead, several ways for future research emerge. Firstly, further exploration into novel synthesis techniques and modifying methods can optimize the functional properties of BR-containing materials, thereby enhancing their biocompatibility, mechanical strength, and osteoconductivity. Additionally, comprehensive in-vitro and in-vivo studies are warranted to evaluate the long-term performance, biodegradability, and host tissue response of BR-based implants.

Moreover, the integration of advanced technologies such as additive manufacturing and biofunctionalization strategies holds great potential for tailoring BR composites to meet specific clinical needs, including patient-specific implant designs and targeted drug delivery systems. Collaborative efforts between material scientists, bioengineers, and clinicians will be essential to translate these advancements from the laboratory to clinical practice.

In summary, the ongoing exploration of BR-containing materials in regenerative medicine underscores their significance in revolutionizing the landscape of implantology and tissue engineering. By addressing current limitations and embracing future opportunities, researchers can unlock the full potential of bredigite for improving patient outcomes and advancing the field of biomedical engineering.

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Conflict of interest

The authors declare that there is no conflict of interest.

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