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Unraveling Molecular Mechanisms of Doped Bioglasses -Mediated MicroRNA Modulation in Bone Regeneration: A narrative review

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Abstract

This narrative review elucidates the molecular mechanisms by which doped bioglass scaffolds enhance bone regeneration through microRNA (miRNA) regulation and mesenchymal stem cell (MSC) differentiation. Bioglasses, modified with trace elements like strontium, magnesium, and europium, exhibit superior osteoinductive and angiogenic properties by releasing bioactive ions that modulate miRNAs. For instance, strontium-doped bioglass upregulates miR-26a, targeting GSK3β to activate Wnt/β-catenin signaling, thereby promoting Runx2 expression and osteoblast differentiation. Drawing on literature from 2020 to 2025, we explore how doped bioglasses regulate key pathways (Wnt/β-catenin, BMP/Smad, MAPK) to optimize bone repair. Challenges, such as optimizing miRNA delivery and scaffold biocompatibility, are addressed, alongside strategies like nanoparticle-based systems and 3D-printed mesoporous scaffolds for enhanced therapeutic outcomes. This review highlights the potential of doped bioglass and miRNA-based therapies to revolutionize regenerative medicine, offering insights for researchers and clinicians aiming to address bone defects through innovative biomaterial applications.

Keywords: Doped Bioglass, Stem Cells, MicroRNA Regulation, Bone Regeneration, Wnt/β-catenin Signaling, BMP/Smad Pathway, Tissue Engineering

Introduction

Bone defects affect millions worldwide, necessitating innovative biomaterials for regeneration(1). Bone regeneration is a significant area in regenerative medicine, and novel biomaterials and cell therapies are required. Bioglass, a silicate bioactive glass, has been garnered significant interest due to its bone bonding and osteogenesis-inducing properties. Stem cells, and indeed mesenchymal stem cells (MSCs), are core to bone repair due to their differentiation capability. MicroRNAs (miRNAs), small non-coding RNAs, play significant roles in the regulation of gene expression and are essential to the regulation of stem cell differentiation. The current narrative review aims at clarifying bioglass's influence on stem cell differentiation and the miRNA regulatory functions, with importance placed on literature between 2020 and 2025. The objectives involve summarizing the present advancements, identifying research gaps, and suggesting directions for further studies for bioglass and miRNA therapies in bone regeneration.

Bioglass: Composition and Bioactivity

Bioglass, originally developed by Hench in 1969, Its standard composition, particularly in the 45S5 variant, consists of silicon dioxide (SiO_2), calcium oxide (CaO), sodium oxide (Na_2O), and phosphorus pentoxide (P_2O_5). This formulation enables its bioactivity, which arises from the material's ability to form a hydroxyapatite layer when it interacts with physiological fluids, thereby promoting bone bonding. Its bioactivity stems from the formation of a hydroxyapatite layer upon interaction with

physiological fluids, facilitating bone bonding (2). Bioglass, has garnered significant interest due to its bone-bonding and osteoinductive properties. Mesenchymal stem cells (MSCs) are central to bone repair through their differentiation potential, with microRNAs (miRNAs) serving as key regulators of gene expression. Additionally, combinations like bioglass scaffolds with platelet-rich plasma (PRP) and bone morphogenetic protein 2 (BMP2) have been explored as promising approaches for bone augmentation in craniofacial surgery, though this is not strictly a doping method but a composite strategy (3).

Recent studies have explored modified bioglass compositions, such as those doped with trace elements, to enhance bone regeneration properties. These modifications improve bioactivity, biocompatibility, and specific functionalities like antibacterial or antioxidant effects, making doped bioglasses pivotal in advancing bone tissue engineering. The incorporation of elements such as strontium, magnesium, cobalt, zinc, copper, silver, fluorine, boron, iron, manganese, lithium, cerium, gallium, selenium, and europium into bioglass scaffolds tailors their physicochemical and biological properties to optimize osteogenic differentiation, angiogenesis, and infection resistance. Below is a detailed classification of individual doped bioglasses, outlining their roles, mechanisms, applications, and insights from recent literature (2020–2025) ((table 1).

1. Strontium-Doped Bioglass

Role and Properties: Strontium-doped bioglass plays a key role in enhancing bone regeneration by stimulating osteogenesis and providing an optimal environment for bone formation. It exhibits improved mechanical strength, bioactivity, and antibacterial properties compared to undoped bioglass, with delayed initial degradation and sustained ion release (4,5). The incorporation of strontium ions (Sr^{2+}) into the bioglass lattice modifies its physicochemical characteristics, making it more suitable for tissue engineering applications(6).

Mechanism: The mechanism involves Sr^{2+} ions promoting osteogenic differentiation while inhibiting osteoclast formation, leading to balanced bone remodeling. It enhances cell viability, stimulates angiogenesis, and provides antimicrobial effects through ion release, creating a favorable microenvironment for bone healing(4,7).

Applications: This doped bioglass is applied in scaffolds for bone tissue engineering, coatings for implants, and composites for defect repair, particularly in scenarios requiring enhanced osteogenesis and infection resistance(8,9).

Literature Insights: Studies indicate that strontium doping significantly boosts bone regeneration capacity, with in vitro and in vivo experiments showing superior antibacterial activity and osteointegration. Combined with magnesium, it offers dual benefits in osteogenesis and antimicrobial action. Research highlights its potential in reducing treatment burdens for fractures and improving bone density.

2. Magnesium-Doped Bioglass

Role and Properties: Magnesium-doped bioglass serves a vital role in bone repair by enhancing biocompatibility, mineralization, and vascularization. It improves apatite formation, cell proliferation, and osteointegration, with properties like controlled degradation and bioactivity tailored for tissue engineering(10,11).

Mechanism: The mechanism centers on Mg^{2+} ions promoting osteogenic differentiation, inhibiting certain cellular responses in mesenchymal stem cells (MSCs), and facilitating vascularization through enhanced biocompatibility. It also supports antimicrobial activity when combined with other dopants(12,13).

Applications: It is used in scaffolds, hydrogels, and implants for bone regeneration, particularly in degradable systems for orthopedic repairs and as a dual-function material for anticancer and regenerative therapies(14,15).

Literature Insights: Literature shows magnesium doping regulates degradation and boosts bone repair mechanisms, with studies confirming its role in various tissues like bone and cartilage. Combined with strontium, it enhances antimicrobial and osteogenic effects.

3. Cobalt-Doped Bioglass

Role and Properties: Cobalt-doped bioglass acts as a hypoxia-mimicking agent to promote angiogenesis and osteogenesis in bone regeneration. It features enhanced bioactivity, antibacterial properties, and controlled ion release, making it suitable for multifunctional biomedical products(16–18).

Mechanism: The mechanism involves Co^{2+} ions stimulating angiogenesis, mimicking hypoxic conditions to enhance osteogenic capacity, and providing antibacterial effects. It supports tissue regeneration through ion-mediated cellular responses(19–21).

Applications: Applications include scaffolds,

electrospun composites, and implants for bone tissue engineering, with potential in dental and orthopedic fields for defect repair and infection control(18,19,22).

Literature Insights: Research demonstrates cobalt doping's dual angiogenic and osteogenic benefits, with in vitro/in vivo studies confirming its efficacy in bone defects. However, effects vary by concentration, and co-doping with elements like lithium enhances antibacterial properties.

4. Zinc-Doped Bioglass

Role and Properties: Zinc-doped bioglass contributes to bone mineralization, development, and maintenance, with antibacterial, anti-inflammatory, and osteoconductive properties. It enhances biocompatibility and mechanical stability for long-term bone health(23–25).

Mechanism: Zinc ions (Zn^{2+}) promote DNA synthesis in osteoblasts, reduce osteoclast activity, and support bone metabolism through controlled release, leading to improved regeneration and infection resistance(23,26,27).

Applications: It is utilized in scaffolds, coatings, and biodegradable metals for orthopedic implants, bone repair, and regeneration in defects or diseases(28–30).

Literature Insights: Studies confirm zinc doping's superiority in promoting bone regeneration at optimal concentrations, with nontoxic effects and potential in hybrid materials. It bridges gaps in biological functions for clinical translation.

5. Copper-Doped Bioglass

Role and Properties: Copper-doped bioglass facilitates bone regeneration with antibacterial, angiogenic, and bioactive properties. It exhibits non-toxicity, enhanced bioactivity, and controlled degradation for multifunctional use(31–33).

Mechanism: The mechanism includes Cu^{2+} ions promoting mitophagy, biomineralization, and matrix vesicle-mediated mineralization, while enhancing angiogenesis and collagen development for bone protection and repair(34–36).

Applications: Applications encompass scaffolds, coatings, and powders for bone tissue engineering, implant surfaces, and therapies targeting defects with infection risks(32,33).

Literature Insights: In vitro/in vivo research validates copper's role in augmenting regeneration through antibacterial mechanisms and bioactivity, with co-doping (e.g., with magnesium) optimizing concentrations for cell proliferation and clinical potential.

6. Silver-Doped Bioglass

Role and Properties: Silver-doped bioglass plays a crucial role in bone regeneration by combining bioactivity with strong antibacterial properties, preventing infections while promoting tissue healing. It exhibits enhanced long-term antimicrobial efficacy, bioactivity, and controlled ion release, making it suitable for multifunctional biomaterials in regenerative applications(37–39).

Mechanism:The mechanism involves silver ions (Ag^{+}) providing sustained antibacterial action against pathogens, while maintaining the bioactive glass's ability to form hydroxyapatite layers for bone bonding. It inhibits bacterial growth through ion-mediated disruption and supports tissue regeneration via bioactivity without compromising cytocompatibility(37,40).

Applications: It is applied in scaffolds, coatings for implants, and particles for in vivo bone defect repair, particularly in scenarios prone to infection, such as orthopedic and dental reconstructions(41–43).

Literature Insights: Studies highlight silver doping's superiority in enhancing antimicrobial properties and bioactivity, with in vitro and in vivo evidence showing reduced infection risks and improved bone integration. Optimal silver concentrations are key to balancing efficacy and biocompatibility, with potential in hybrid materials for advanced therapies.

7. Fluorine-Doped Bioglass

Role and Properties: Fluorine-doped bioglass (often as fluoride-releasing) contributes to bone regeneration by improving osteogenic and anti-inflammatory properties, acting as a novel bone substitute. It features enhanced bioactivity, ion release control, and biocompatibility, suitable for hard tissue engineering(44,45).

Mechanism: The mechanism relies on fluoride ions promoting bone mineralization and osteogenesis, while reducing inflammation through controlled release, facilitating faster bone healing and integration with host tissues(46).

Applications: Applications include scaffolds for bone tissue engineering, dental implants, and hybrid composites for defect repair, especially in areas requiring anti-inflammatory effects and bone substitution(44,47).

Literature Insights: Research indicates fluorine doping enhances bioactivity and osteogenic potential, with studies showing improved performance in combination with zinc or other ions. Challenges include optimizing degradation rates, but it shows promise for clinical translation in

regenerative medicine.

8. Boron-Doped Bioglass
Role and Properties: Boron-doped bioglass (often as borate or borosilicate bioactive glasses) excels in bone regeneration due to its superior bioactivity, adjustable degradation, and enhanced mechanical properties compared to silicate glasses(48–50).
Mechanism: The mechanism involves boron ions accelerating apatite formation, promoting angiogenesis and osteogenesis, with tunable degradation rates aligning to tissue healing timelines for optimal regeneration(50,51).
Applications: It is used in scaffolds, wound healing dressings, and clinical bone repair, particularly for defects requiring rapid healing and vascularization support(52).
Literature Insights: Insights reveal boron's role in superior bone healing, with in vitro/in vivo studies confirming enhanced osteogenic commitment and angiogenic properties when co-doped with Mg/Sr. Concentration adjustments are vital for matching tissue needs.
9. Iron-Doped Bioglass
Role and Properties: Iron-doped bioglass supports bone regeneration with multifunctional properties, including bioactivity, magnetic potential, and shielding capabilities, enhancing porosity and biocompatibility for tissue engineering(53–55).
Mechanism: Iron ions (Fe^{3+}) facilitate osteogenic differentiation and bone mineralization, potentially through magnetic stimulation and ion release, promoting tissue integration and regeneration (56,57).
Applications: Applications encompass porous scaffolds, implant coatings, and nanoparticles for bone defect repair and multifunctional biomedical uses, including radiation shielding (55,58).
Literature Insights: Research emphasizes iron's versatility in enhancing regeneration, with studies on nanoparticles showing improved bioactivity. It bridges gaps in mechanical and biological functions, though more in vivo validation is needed.
10. Manganese-Doped Bioglass
Role and Properties: Manganese-doped bioglass aids bone regeneration by influencing mineralization and skeletal strength, with properties like enhanced bioactivity, cytocompatibility, and controlled reactivity(59–61).
Mechanism: Manganese ions (Mn^{2+}) synergize with calcium to promote bone bonding and tissue stimulation, slightly modulating reactivity in simulated body fluid for sustained regenera-(59,61,62).
Applications: It is utilized in coatings for alloys like Ti6Al4V, scaffolds with gelatin, and orthopedic implants for bone repair and antibacterial enhancements(63–65).
Literature Insights: In vitro studies show manganese's role in bone health, with synergetic effects improving bioactivity. Co-doping with zinc enhances antibacterial properties, indicating potential for advanced composites.
11. Lithium-Doped Bioglass
Role and Properties:Lithium-doped bioglass serves as a promising biomaterial for bone regeneration, with immunomodulatory, osteogenic, and antibacterial properties, enhancing biocompatibility and ion release(66–68).
Mechanism: Lithium ions (Li^{+}) stimulate osteogenic differentiation, sustain antibacterial action via dual mechanisms, and modulate immune responses through miRNA regulation for enhanced bone formation(69,70).
Applications: Applications include scaffolds, surface modifications for polyetheretherketone implants, and mesoporous glasses for bone defect repair and tissue engineering(68,70,71).
Literature Insights: Studies confirm lithium's efficacy in promoting regeneration, with evidence of enhanced osteogenesis and immunomodulation. Co-doping with cobalt boosts antibacterial effects, highlighting its broad potential in clinical settings.
12. Cerium-Doped Bioglass
Role and Properties: Cerium-doped bioglass enhances bone regeneration by providing antioxidant, osteogenic and antibacterial properties. It improves bioactivity and cytocompatibility, with controlled ion release for tissue engineering.
Mechanism: Cerium ions (Ce^{3+}/Ce^{4+}) exhibit antioxidant effects by scavenging reactive oxygen species (ROS), reducing oxidative stress in bone healing environments. They promote osteogenic differentiation and provide antibacterial action through ion-mediated disruption of bacterial membranes.
Applications: Used in scaffolds, coatings, and nanoparticles for bone defect repair, particularly in environments requiring antioxidant and infection-resistant properties .
Literature Insights: Studies demonstrate cerium’s dual role in osteogenesis and antibacterial activity, with in vitro evidence showing enhanced cell proliferation and bone mineralization. Optimal cerium concentrations are critical to avoid cytotoxicity, and co-doping with other elements like zinc enhances efficacy(72,73).

13. Gallium-Doped Bioglass
Role and Properties: Gallium-doped bioglass supports bone regeneration with potent antibacterial and osteogenic properties. It enhances bioactivity and mechanical stability, making it suitable for orthopedic applications.
Mechanism: Gallium ions (Ga^{3+}) disrupt bacterial iron metabolism, providing strong antibacterial

effects, particularly against resistant strains. They also promote osteoblast activity and bone mineralization through controlled ion release.
Applications: Applied in scaffolds, implant coatings, and composites for bone repair, especially in infection-prone defects or osteoporotic conditions.
Literature Insights: Research highlights gallium's ability to combat multidrug-resistant bacteria while supporting bone regeneration. In vivo studies show improved bone formation, with potential in combination with other dopants like strontium for enhanced effects(74,75).
14. Selenium-Doped Bioglass
Role and Properties: Selenium-doped bioglass contributes to bone regeneration by offering antioxidant, anti-inflammatory, and osteogenic properties. It enhances bioactivity and biocompatibility for tissue engineering.
Mechanism: Selenium ions (Se^{4+}/Se^{6+}) reduce oxidative stress, promote osteoblast proliferation, and inhibit inflammatory responses. They also exhibit mild antibacterial effects, supporting bone healing in compromised environments.
Applications: Utilized in scaffolds, hydrogels, and bioactive coatings for bone defect repair and regeneration, particularly in cases requiring anti-inflammatory support.
Literature Insights: Literature indicates selenium's role in enhancing bone regeneration through antioxidant mechanisms. Studies suggest it improves osteogenic differentiation, with co-doping strategies (e.g., with zinc) optimizing regenerative outcomes(76–78).
15. Europium-Doped Bioglass
Role and Properties: Europium-doped bioglass enhances bone regeneration with luminescent, osteogenic, and antibacterial properties. Its fluorescence aids in imaging, while bioactivity supports tissue repair.
Mechanism: Europium ions (Eu^{3+}) promote osteogenic differentiation and angiogenesis through ion release, with luminescent properties enabling tracking of material degradation. They also provide mild antibacterial effects.
Applications: Used in scaffolds, imaging-guided implants, and composites for bone regeneration, particularly in applications requiring diagnostic and therapeutic functions.
Literature Insights: Research shows europium's potential in theranostic applications, with in vitro studies confirming enhanced osteogenesis and ERK pathway, enhancing RUNX2 and OCN expression in MSCs. Studies from 2020–2025 indicate that bioglass scaffolds with optimized stiffness and topography further stimulate MAPK signaling, promoting osteogenesis by modulating cellular mechanotransduction (85). The synergistic effect of ion release and scaffold architecture creates a microenvironment conducive to MSC differentiation.

Environmental cues, such as scaffold topography and stiffness, significantly influence MSC fate. Bioglass scaffolds with tailored porosity and mechanical properties provide biomechanical signals that enhance osteogenic differentiation. For example, 3D-printed bioglass scaffolds with microscale topography have been shown to upregulate integrin-mediated signaling, which intersects with Wnt and MAPK pathways to promote osteoblast formation (3). Recent advances (2020–2025) highlight how bioglass scaffolds, particularly those incorporating magnesium or cobalt, modulate these pathways through ion release and surface characteristics, optimizing MSC differentiation for bone regeneration (83–85).

MicroRNAs Role in Osteogenic Differentiation

Role of MicroRNAs in Osteogenic Differentiation MicroRNAs (miRNAs) are small non-coding RNAs, typically 18–25 nucleotides in length, that post-transcriptionally regulate gene expression by binding to the 3' untranslated regions (3' UTRs) of target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression. Discovered in the early 1990s, miRNAs play crucial roles in diverse biological processes, including development, cell proliferation, apoptosis, and differentiation. In the context of regenerative medicine, miRNAs are pivotal in modulating cellular responses to environmental cues, making them essential regulators in tissue engineering applications. miRNAs significantly influence stem cell differentiation, particularly in directing mesenchymal stem cells (MSCs) toward osteogenic lineages. For instance, miR-21 promotes osteogenic differentiation by targeting PTEN, activating the PI3K/Akt pathway, and enhancing Runx2 expression, a key transcription factor for osteoblast formation (84). Similarly, miR-26a enhances osteogenesis by inhibiting GSK3β and CTGF, promoting Wnt/β-catenin signaling and reducing osteoclast activity (86). Other miRNAs, such as miR-148b, target noggin to amplify BMP signaling, while miR-140 protects against cartilage degradation but can inhibit osteogenesis in certain contexts (87). Mechanosensitive miRNAs, like miR-365, respond to mechanical stimuli to regulate HDAC4 and SOX9, facilitating chondrogenesis and osteogenesis in MSCs under tensile strain (88). These mechanisms highlight miRNAs' role in fine-tuning stem cell fate through signaling

imaging capabilities. Its antibacterial effects are less pronounced

Table 1: Summarized Roles, Mechanisms, Applications, and References of Doped Bioglasses (2020–2025)

Dopant	Role and Properties	Mechanism	Applications	References
Strontium	Enhances osteogenesis, mechanical strength, antibacterial properties.	Sr^{2+} promotes osteogenesis, inhibits osteoclasts, supports angiogenesis.	Scaffolds, implant coatings, defect repair composites.	[3,4,5,6,7,8]
Magnesium	Improves biocompatibility, mineralization, vascularization.	Mg^{2+} promotes osteogenesis, vascularization, and antimicrobial effects.	Scaffolds, hydrogels, orthopedic implants.	[9,10,11,12,13,14]
Cobalt	Hypoxia-mimicking for angiogenesis, osteogenesis; antibacterial.	Co^{2+} stimulates angiogenesis, osteogenesis via hypoxic conditions.	Scaffolds, electrospun composites, dental/orthopedic implants.	[15,16,17,18,19,20,21]
Zinc	Supports bone mineralization, antibacterial, anti-inflammatory.	Zn^{2+} enhances osteoblast DNA synthesis, reduces osteoclast activity.	Scaffolds, coatings, biodegradable metals for implants.	[22,23,24,25,26,27,28,29]
Copper	Antibacterial, angiogenic, bioactive; nontoxic.	Cu^{2+} promotes mitophagy, biomineralization, angiogenesis.	Scaffolds, coatings, powders for defect repair.	[30,31,32,33,34,35]
Silver	Strong antibacterial, bioactive; promotes tissue healing.	Ag^{+} provides antibacterial action, supports hydroxyapatite formation.	Scaffolds, implant coatings, particles for defect repair.	[36,37,38,39,40,41,42]
Fluorine	Osteogenic, anti-inflammatory; enhanced bioactivity.	F^{-} promotes bone mineralization, reduces inflammation.	Scaffolds, dental implants, hybrid composites.	[43,44,45,46]
Boron	Superior bioactivity, adjustable degradation, mechanical strength.	B^{3+} accelerates apatite formation, promotes angiogenesis, osteogenesis.	Scaffolds, wound dressings, bone repair.	[47,48,49,50,51]
Iron	Bioactive, magnetic, shielding; enhances porosity.	Fe^{3+} facilitates osteogenesis, bone mineralization via ion release.	Porous scaffolds, coatings, nanoparticles for defect repair.	[52,53,54,55,56,57]
Manganese	Enhances mineralization, skeletal strength; cytocompatible.	Mn^{2+} synergizes with calcium for bone bonding, tissue stimulation.	Coatings, scaffolds, orthopedic implants.	[58,59,60,61,62,63,64]
Lithium	Immunomodulatory, osteogenic, antibacterial; biocompatible.	Li^{+} stimulates osteogenesis, antibacterial action, immune modulation.	Scaffolds, polyetheretherketone implants, mesoporous glasses.	[65,66,67,68,69,70]
Cerium	Antioxidant, osteogenic, antibacterial; cytocompatible.	Ce^{3+}/Ce^{4+} scavenges ROS, promotes osteogenesis, antibacterial action.	Scaffolds, coatings, nanoparticles for defect repair.	[71,72]
Gallium	Antibacterial, osteogenic; enhances mechanical stability.	Ga^{3+} disrupts bacterial iron metabolism, promotes osteoblast activity.	Scaffolds, coatings, composites for infection-prone defects.	[73,74]
Selenium	Antioxidant, anti-inflammatory, osteogenic; biocompatible.	Se^{4+}/Se^{6+} reduces oxidative stress, promotes osteoblast proliferation.	Scaffolds, hydrogels, coatings for bone repair.	[75,76,77]
Europium	Luminescent, osteogenic, antibacterial; aids imaging.	Eu^{3+} promotes osteogenesis, angiogenesis, enables material tracking.	Scaffolds, imaging-guided implants, composites.	[78,79,80]

pathways like BMP/Smad, Wnt/β-catenin, and MAPK, ensuring balanced proliferation and differentiation for bone regeneration.

Integrating Bioglass, Stem Cells, and miRNAs

Bioglass plays a multifaceted role in osteoinduction through miRNA modulation, primarily by releasing bioactive ions (e.g., silicon, calcium) that alter miRNA expression profiles in MSCs, thereby enhancing osteogenic differentiation. The mechanism begins with bioglass dissolution in physiological fluids, forming a hydroxyapatite layer that facilitates ion exchange and creates a microenvironment conducive to cellular signaling. Silicon ions from bioglass upregulate miRNAs such as miR-23a-3p, which is delivered via small extracellular vesicles (sEVs) to promote vascularized bone regeneration by targeting inhibitors of osteoblast differentiation and enhancing calcium accumulation and angiogenesis (89). Similarly, strontium-doped bioglass scaffolds stimulate miR-26a expression, which targets GSK3β to activate Wnt/β-catenin signaling, leading to increased Runx2 and Osterix (Osx) expression, thereby accelerating MSC osteogenesis (82,86). Recent studies (2020–2025) demonstrate that bioglass-integrated delivery systems, such as 3D nanofiber aerogels combining bioglass with PLGA-collagen-gelatin, provide sustained miRNA release (e.g., miR-26a), protecting miRNAs from degradation while leveraging bioglass's osteoinductive properties to enhance scaffold biocompatibility and bone repair (86). Additionally, bioglass's porous structure enables efficient miRNA loading, as seen in mesoporous bioactive glass nanoparticles that facilitate targeted delivery, modulating pathways like PTEN/PI3K/Akt and BMP/Smad to inhibit osteoclastogenesis and promote osteoblast proliferation (90). This ion-mediated miRNA upregulation not only amplifies osteogenic gene expression but also integrates with mechanosensitive cues, where bioglass scaffold topography influences miRNA-responsive pathways like MAPK, fostering a synergistic effect for effective osteoinduction in bone tissue engineering (Fig1).

5. Copper-Doped Bioglass

Copper-doped bioglass enhances osteogenesis by releasing Cu^{2+} ions, which upregulate miR-21 to activate PI3K/Akt, promoting Runx2 and collagen development (34,91). Cu^{2+} ions stimulate BMP/Smad signaling by increasing BMP-2 expression, driving Smad1/5/8 phosphorylation and matrix mineralization (35,91). Additionally, copper activates MAPK pathways (ERK/p38), enhancing Runx2/OCN expression, and supports angiogenesis via VEGF upregulation, creating an osteogenic microenvironment (36,89).

6. Silver-Doped Bioglass

Silver-doped bioglass promotes bone regeneration through Ag^{+} ion release, which indirectly influences miR-26a to enhance Wnt/β-catenin signaling by targeting GSK3β, upregulating Runx2 (37,86). Ag^{+} ions support hydroxyapatite formation, activating BMP/Smad pathways via Smad1/5/8 phosphorylation(83). Their antibacterial action disrupts bacterial membranes, reducing infection risks, while biomechanical cues from scaffolds amplify MAPK signaling, promoting MSC osteoblast differentiation (40,41).

7. Fluorine-Doped Bioglass

Fluorine-doped bioglass enhances osteogenesis via fluoride ion release, which upregulates miR-148b to inhibit Noggin, amplifying BMP/Smad signaling and Runx2/ALP expression (46,87). Fluoride ions also modulate Wnt/β-catenin signaling by stabilizing β-catenin, promoting Osterix expression(82). Additionally, biomechanical cues from fluorine-doped scaffolds activate MAPK (ERK) pathways, enhancing osteogenic gene expression and reducing inflammation for faster MSC differentiation and bone healing (44,46).

8. Boron-Doped Bioglass

Boron-doped bioglass accelerates osteogenesis through boron ion release, which upregulates miR-23a-3p to promote angiogenesis and calcium accumulation via VEGF and Runx2(51,89). Boron enhances BMP/Smad signaling by increasing BMP-2 expression, driving Smad1/5/8 phosphorylation(83). It also activates MAPK pathways (p38/ERK), upregulating Runx2/OCN, while scaffold topography amplifies integrin-mediated signaling, fostering MSC differentiation and rapid bone regeneration (50,52).

9. Iron-Doped Bioglass

Iron-doped bioglass supports osteogenesis through Fe^{3+} ion release, which indirectly upregulates miR-21 to activate PI3K/Akt, enhancing Runx2 expression(56,84). Fe^{3+} ions stimulate BMP/Smad signaling by promoting BMP-2 expression, driving Smad1/5/8 phosphorylation(83). Magnetic properties of iron-doped scaffolds activate MAPK (ERK) pathways, upregulating OCN, while biomechanical cues enhance integrin signaling, promoting MSC differentiation and bone mineralization(57,58).

10. Manganese-Doped Bioglass

Manganese-doped bioglass enhances bone regeneration by releasing Mn^{2+} ions, which synergize with calcium to upregulate miR-26a, targeting GSK3β to

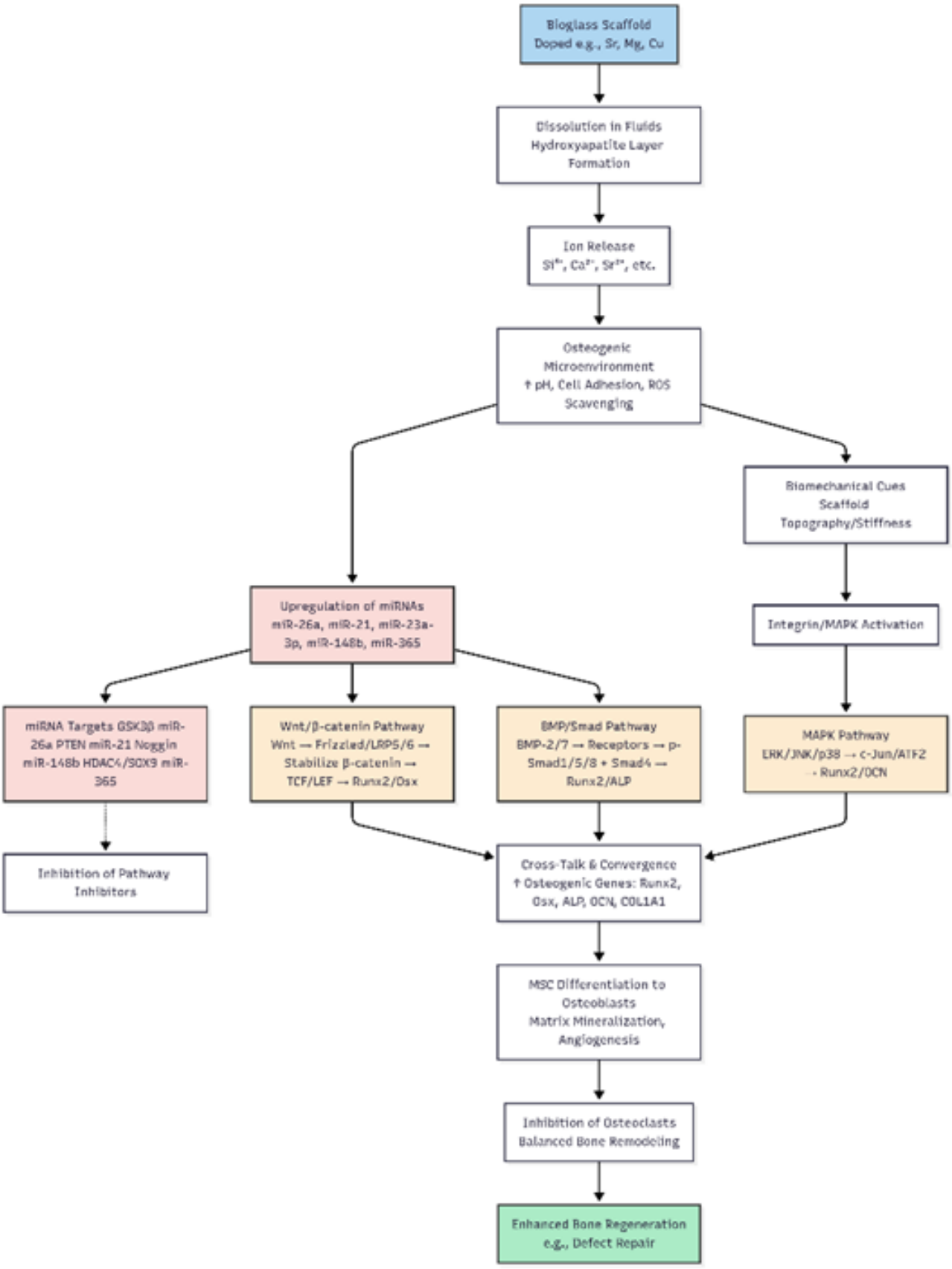

Figure 1: this is a graphical representation of the molecular pathway for bioglass-mediated bone regeneration, integrating ion release, miRNA modulation, and key signaling pathways (Wnt/β-catenin, BMP/Smad, MAPK) leading to MSC differentiation. I've used Mermaid syntax for a flowchart, which can be pasted into tools like Mermaid.live or GitHub for rendering as an interactive diagram. This is based on the provided text and literature sources

Table 2: Summary of Doped Bioglasses: Key Ions, miRNAs, Pathways, and References

Dopant	Key Ions	miRNAs	Pathways	References
Strontium	Sr^{2+}	miR-26a	Wnt/β-catenin, BMP/Smad	[2,6,81,86]
Magnesium	Mg^{2+}	miR-21	PI3K/Akt, BMP/Smad, MAPK	[9,11,82,83,84]
Cobalt	Co^{2+}	miR-23a-3p	Wnt/β-catenin, MAPK, BMP/Smad	[15,18,20,82,89]
Zinc	Zn^{2+}	miR-148b, miR-21	BMP/Smad, PI3K/Akt, MAPK	[22,25,26,86,90]
Copper	Cu^{2+}	miR-21	PI3K/Akt, BMP/Smad, MAPK	[33,34,35,88,90]
Silver	Ag^{+}	miR-26a	Wnt/β-catenin, BMP/Smad, MAPK	[36,39,40,83,85]
Fluorine	F^{-}	miR-148b	BMP/Smad, Wnt/β-catenin, MAPK	[43,45,81,86]
Boron	B^{3+}	miR-23a-3p	BMP/Smad, MAPK	[49,50,51,82,88]
Iron	Fe^{3+}	miR-21	PI3K/Akt, BMP/Smad, MAPK	[55,56,57,82,83]
Manganese	Mn^{2+}	miR-26a	Wnt/β-catenin, BMP/Smad, MAPK	[58,60,82,85,91]
Lithium	Li^{+}	miR-26a, miR-21	Wnt/β-catenin, PI3K/Akt, BMP/Smad, MAPK	[66,69,70,83,85,90]
Cerium	Ce^{3+}/Ce^{4+}	miR-23a-3p	BMP/Smad, MAPK	[82,88,92,93]
Gallium	Ga^{3+}	miR-148b	BMP/Smad, MAPK	[86,94,95]
Selenium	Se^{4+}/Se^{6+}	miR-23a-3p	BMP/Smad, MAPK	[88,96,97,98]
Europium	Eu^{3+}	miR-26a	Wnt/β-catenin, BMP/Smad, MAPK	[80,100,N7,N8]

activate Wnt/β-catenin signaling and Runx2 expression(61,86). Mn^{2+} ions also promote BMP/Smad signaling via BMP-2, enhancing Smad1/5/8 phosphorylation(83). MAPK (ERK) activation by scaffold topography further upregulates OCN, supporting MSC osteoblast differentiation and bone bonding(59,92).

11. Lithium-Doped Bioglass

Lithium-doped bioglass drives osteogenesis through Li^{+} ion release, which upregulates miR-26a and miR-21, targeting GSK3β and PTEN to activate Wnt/β-catenin and PI3K/Akt pathways, respectively, boosting Runx2(67,86,91). Li^{+} ions enhance BMP/Smad signaling by increasing BMP-2 expression, promoting Smad1/5/8 phosphorylation(83). Immunomodulatory effects via miRNA regulation and MAPK activation further support MSC differentiation and bone formation (70,71).

12. Cerium-Doped Bioglass

Cerium-doped bioglass promotes osteogenesis by releasing Ce^{3+}/Ce^{4+} ions, which upregulate miR-23a -3p to enhance angiogenesis and Runx2 expression via VEGF(89,93). These ions scavenge ROS, reducing oxidative stress, and activate BMP/Smad signaling through BMP-2, driving Smad1/5/8 phosphorylation (83,93). MAPK (ERK) activation by cerium-doped scaffolds further upregulates OCN, fostering MSC differentiation and bone regeneration(94).

13. Gallium-Doped Bioglass

Gallium-doped bioglass enhances osteogenesis through Ga^{3+} ion release, which upregulates miR-148b to inhibit Noggin, amplifying BMP/Smad signaling and Runx2/ALP expression(87,95). Ga^{3+} ions disrupt bacterial iron metabolism, supporting an osteogenic microenvironment, and activate MAPK (ERK) pathways, enhancing OCN expression. Biomechanical cues from scaffolds further promote integrin-mediated MSC differentiation(95,96).

14. Selenium-Doped Bioglass

Selenium-doped bioglass drives osteogenesis by releasing Se^{4+}/Se^{6+} ions, which upregulate miR-23a-3p to promote angiogenesis and calcium accumulation via VEGF and Runx2(89,97). Se ions reduce oxidative stress, enhancing BMP/Smad signaling through BMP-2 and Smad1/5/8 phosphorylation (98). MAPK (p38) activation by scaffold topography upregulates osteogenic genes, supporting MSC differentiation and anti-inflammatory bone repair (99).

15. Europium-Doped Bioglass

(100)-doped bioglass enhances osteogenesis through Eu^{3+} ion release, which upregulates miR-26a to target GSK3β, activating Wnt/β-catenin signaling and Runx2 expression . Eu^{3+} ions promote BMP/Smad signaling via BMP-2, driving

Smad1/5/8 phosphorylation. Luminescent properties aid scaffold tracking, while MAPK (ERK) activation and biomechanical cues enhance OCN expression, fostering MSC differentiation(81,101).

The synergy between bioglass, stem cells, and miRNAs offers a promising approach to bone regeneration. This section integrates findings from previous sections, discussing how bioglass scaffolds enhance stem cell differentiation through miRNA regulation. Recent studies (2020–2025) show that bioglass upregulates specific miRNAs, which modulate osteogenic pathways (90).

Challenges, such as optimizing miRNA delivery and ensuring scaffold biocompatibility, are addressed, along with strategies like nanoparticle-based miRNA delivery systems.

Despite significant advances, gaps remain in understanding the long-term effects of bioglass on miRNA expression and stem cell behavior. This section proposes future research directions, including the development of personalized miRNA therapies, advanced bioglass composites, and in vivo studies to validate preclinical findings. The integration of bioinformatics and machine learning to predict miRNA-target interactions is also highlighted as a promising avenue for optimizing therapeutic outcomes.

Conclusion

This narrative review highlights the critical roles of bioglass, stem cell differentiation, and miRNAs in advancing bone regeneration. By synthesizing recent literature (2020–2025), we underscore the potential of bioglass-based scaffolds and miRNA-based therapies to revolutionize regenerative medicine. Continued research is needed to translate these findings into clinical applications, paving the way for innovative treatments for bone defects.

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References:

1.De Pace R, Molinari S, Mazzoni E, Perale G. Bone Regeneration: A Review of Current Treatment Strategies. J Clin Med. 2025 Mar 8;14(6):1838.

2.Hosseini Aghozbeni EA, Imani Fooladi AA, Mohammad reza Nourani. Evaluation of biocompatible bioglass/gelatin scaffold enhanced by mesenchymal stem cell for bone tissue regeneration. J Appl Tissue Eng. 2014;1(1):8–14.

3.Taha Chartab Mohammadi, Mostafa Eslami. Calvarial bone augmentation using Bioglas Scaffold enhanced by Platelet-Rich Plasma and BMP2. Life Sciences Student Journal. 2023 May 11;1(1):56–62.

4.Silva AV, Gomes DDS, Victor R de S, Santana LN de L, Neves GA, Menezes RR. Influence of Strontium on the Biological Behavior of Bioactive Glasses for Bone Regeneration. Materials (Basel). 2023 Dec 15;16(24).

5.Sheng X, Li C, Wang Z, Xu Y, Sun Y, Zhang W, et al. Advanced applications of strontium-containing biomaterials in bone tissue engineering. Mater Today Bio. 2023 Jun;20:100636.

6.Baheiraei N, Eyni H, Bakhshi B, Najafloo R, Rabiee N. Effects of strontium ions with potential antibacterial activity on in vivo bone regeneration. Sci Rep. 2021 Apr 22;11(1):8745.

7.Xu Z, Miao L, Meng X, Sui J, Chen M, Zheng Z, et al. Strontium-doped bioactive glass-functionalized polyetheretherketone enhances osseointegration by facilitating cell adhesion. Colloids Surf B Biointerfaces. 2024 Sep;241:114042.

8.Manoochehri H, Ghorbani M, Moosazadeh Moghaddam M, Nourani MR, Makvandi P, Sharifi E. Retraction Note: Strontium doped bioglass incorporated hydrogel-based scaffold for amplified bone tissue regeneration. Sci Rep. 2024 Oct 22;14(1):24874.

9.Kargozar S, Montazerian M, Fiume E, Baino F. Multiple and Promising Applications of Strontium (Sr)-Containing Bioactive Glasses in Bone Tissue Engineering. Front Bioeng Biotechnol. 2019 Jul 5;7.

10. Awoke AT, Zhu L, Ding X. Characterization and Performance of Magnesium Doped Bioactive Glass Nanoparticles. Open Journal of Polymer Chemistry. 2024;14(02):95–111.

11. Chen Z, Yang D, Wang S, Hao C. The role of magnesium hydrogels in bone regeneration: a systematic review and meta-analysis. J Mater Sci Mater Med. 2025 Aug 18;36(1):66.

12.Li Z, Li Z, Wang J, Liao L, Li X, Zhang Z, et al. Binary Doping of Strontium–Magnesium to Bioactive Glasses to Enhance Antibacterial and Osteogenic Effects. ACS Omega. 2025 Jan 14;10(1):215–29.

13. Hohenbild F, Arango Ospina M, Schmitz SI, Moghaddam A, Boccaccini AR, Westhauser F. An In Vitro Evaluation of the Biological and Osteogenic Properties of Magnesium-Doped Bioactive Glasses for Application in Bone Tissue Engineering. Int J Mol Sci. 2021 Nov 24;22(23):12703.

14. Tao M, Cui Y, Sun S, Zhang Y, Ge J, Yin W, et al. Versatile application of magnesium-related bone implants in the treatment of bone defects. Mater Today Bio. 2025 Apr;31:101635.

15. Shoaib M, Bahadur A, Iqbal S, AL-Anazy MM, Laref A, Tahir MA, et al. Magnesium doped mesoporous bioactive glass nanoparticles: A promising material for apatite formation and mitomycin c delivery to the MG-63 cancer cells. J Alloys Compd. 2021 Jun;866:159013.

16. Ahad Saeidi, Sara Banijamali, Mojgan Heydari. Cobalt Doped Bioactive Glasses: Sinterability, Crystallization Trend, and Biodegradation Assessment of Relevant Glass -Ceramic Scaffolds. Iranian Journal of Materials Science and Engineering. 2024 Jun;21(2).

17.Solanki AK, Lali F V., Autefage H, Agarwal S, Nommeots-Nomm A, Metcalfe AD, et al. Bioactive glasses and electrospun composites that release cobalt to stimulate the HIF pathway for wound healing applications. Biomater Res. 2021 Feb 12;25(1).

18. Baino F, Montazerian M, Verné E. Cobalt-Doped Bioactive Glasses for Biomedical Applications: A Review. Materials. 2023 Jul 14;16(14):4994.

19.Deng Z, Lin B, Jiang Z, Huang W, Li J, Zeng X, et al. Hypoxia-Mimicking Cobalt-Doped Borosilicate Bioactive Glass Scaffolds with Enhanced Angiogenic and Osteogenic Capacity for Bone Regeneration. Int J Biol Sci. 2019;15(6):1113–24.

20.Alasvand N, Simorgh S, Malekzadeh Kebria M, Bozorgi A, Moradi S, Hosseinpour Sarmadi V, et al. Copper / cobalt doped strontium-bioactive glasses for bone tissue engineering applications. Open Ceramics. 2023 Jun;14:100358.

21.de Souza JR, Anselmi C, Cardoso LM, Kito LT, dos Reis-Prado AH, de Oliveira PHC, et al. Electrospun SilkMA/silicate-chlorinated cobalt-doped bioactive glass composite for bone regeneration. J Mech Behav Biomed Mater. 2025 Apr;164:106929.

22.Zhang X, Nan K, Zhang Y, Song K, Geng Z, Shang D, et al. Lithium and cobalt co-doped mesoporous bioactive glass nanoparticles promote osteogenesis and angiogenesis in bone regeneration. Front Bioeng Biotechnol. 2023;11:1288393.

23.Ahmed MM, Omar AE, Zayed HS, Moaness M. Bioactive glass doped with zinc-based metal–organic frameworks (Zn/MOF) nanoparticles for antibiotic delivery applications. Applied Physics A. 2024 Mar 2;130(3):209.

24.Chen L, Zhou C, Xie Q, Xia L, Liu L, Bao W, et al. Zinc Doped Synthetic Polymer Composites for Bone Regeneration: A Promising Strategy to Repair Bone Defects. Int J Nanomedicine. 2025 Jul;Volume 20:8567–86.

25.Sharifianjazi F, Sharifianjazi M, Irandoost M, Tavamaishvili K, Mohabatkhah M, Montazerian M. Advances in Zinc-Containing Bioactive Glasses: A Comprehensive Review. J Funct Biomater. 2024 Sep 8;15(9):258.

26.Balasubramanian P, Strobel LA, Kneser U, Boccaccini AR. Zinc-containing bioactive glasses for bone regeneration, dental and orthopedic applications. Biomedical glasses. 2015 Jan 29;1(1).

27.Wang S, Li R, Xia D, Zhao X, Zhu Y, Gu R, et al. The impact of Zn-doped synthetic polymer materials on bone regeneration: a systematic review. Stem Cell Res Ther. 2021 Dec 12;12(1):123.

28.Elahpour N, Niesner I, Bossard C, Abdellaoui N, Montouillout V, Fayon F, et al. Zinc-Doped Bioactive Glass/Polycaprolactone Hybrid Scaffolds Manufactured by Direct and Indirect 3D Printing Methods for Bone Regeneration. Cells. 2023 Jun 30;12(13):1759.

29.Li P, Dai J, Li Y, Alexander D, Čapek J, Geis-Gerstorfer J, et al. Zinc based biodegradable metals for bone repair and regeneration: Bioactivity and molecular mechanisms. Mater Today Bio. 2024 Apr;25:100932.

30.Liu X, Xia Z, Wang Y, Luo D, Li Z, Meng Z, et al. Zinc-doped inorganic bioactive materials: a comprehensive review of properties and their applications in osteogenesis, antibacterial, and hemostasis. Appl Mater Today. 2024 Oct;40:102393.

31.Brogini S, Tschon M, Vivarelli L, Gambardella A, De Bonis A, Giavaresi G, et al. Enhanced Bioactivity of Cu-Doped Bioactive Glass Coatings on Human Freeze-Dried Cortical Bone: An In Vitro Study. Bioengineering. 2025 Mar 29;12(4):354.

32. Baino F. Copper-doped Ordered Mesoporous Bioactive Glass: A Promising Multifunctional Platform for Bone Tissue Engineering †. Bioengineering (Basel). 2020 May 21;7(2).

33. Shendage SS, Gaikwad K, Kachare K, Kashte S, Ghule AV. In vitro and in vivo study of copper-doped bioactive glass for bone regeneration application. Mater Chem Phys. 2024 Feb;313:128789.

34.Anand A, Kaňková H, Hájovská Z, Galusek D, Boccaccini AR, Galusková D. Bio-response of copper–magnesium co-substituted mesoporous bioactive glass for bone tissue regeneration. J Mater Chem B. 2024;12(7):1875–91.

35. Li K, Cao H, Huang H, Tang S, Wang H, Yang Q, et al. Advances in copper-containing biomaterials for managing bone-related diseases. Regen Biomater. 2025 Jan 6;12.

36. Ling Z, Ge X, Jin C, Song Z, Zhang H, Fu Y, et al. Copper doped bioactive glass promotes matrix vesicles-mediated biomineralization via osteoblast mitophagy and mitochondrial dynamics during bone regeneration. Bioact Mater. 2025 Apr;46:195–212.

37. Pajares-Chamorro N, Wagley Y, Maduka C V., Youngstrom DW, Yeger A, Badylak SF, et al. Silver-doped bioactive glass particles for in vivo bone tissue regeneration and enhanced methicillin-resistant Staphylococcus aureus (MRSA) inhibition. Materials Science and Engineering: C. 2021 Jan;120:111693.

38. Abodunrin OD, Semlali A, EL Mabrouk K, Bricha M. Biocompatibility and antimicrobial efficacy of silver-doped borosilicate bioactive glass for tissue engineering application. Ceram Int. 2024 Dec;50 (23):50535–47.

39. Qian G, Zhang L, Liu X, Wu S, Peng S, Shuai C. Silver-doped bioglass modified scaffolds: A sustained antibacterial efficacy. Materials Science and Engineering: C. 2021 Oct;129:112425.

40. Pajares-Chamorro N, Lensmire JM, Hammer ND, Hardy JW, Chatzistavrou X. Unraveling the mechanisms of inhibition of silver-doped bioactive <scp>glass–ceramic</scp> particles. J Biomed Mater Res A. 2023 Jul 30;111(7):975–94.

41. Korukonda HV, Suresh N, K S. Fabrication and Characterization of an Innovative Silver- and Gadolinium-Doped Bioglass for Bone Regeneration. Cureus. 2023 Dec 25;

42. Abodunrin OD, Semlali A, EL Mabrouk K, Bricha M. Biocompatibility and antimicrobial efficacy of silver-doped borosilicate bioactive glass for tissue engineering application. Ceram Int. 2024 Dec;50 (23):50535–47.

43. Qian G, Zhang L, Liu X, Wu S, Peng S, Shuai C. Silver-doped bioglass modified scaffolds: A sustained antibacterial efficacy. Materials Science and Engineering: C. 2021 Oct;129:112425.

44. T. Kondo, K. Otake, H. Egusa. Zinc- and Fluoride-Releasing Bioactive Glass as a Novel Bone Substitute. J Dent Res. 2024;103(5).

45. Abdul Jalil R, Amin Matori K, Mohd Zaid MH, Zainuddin N, Ahmad Khiri MZ, Abdul Rahman NA, et al. A Study of Fluoride-Containing Bioglass System for Dental Materials Derived from Clam Shell and Soda Lime Silica Glass. Journal of Spectroscopy. 2020 Apr 21;2020:1–9.

46. Nawaz Q, Blaeß C, Müller R, Boccaccini AR. Processing and cytocompatibility of Cu-doped and undoped fluoride-containing bioactive glasses. Open Ceramics. 2024 Jun;18:100586.

47. Al-Harbi N, Mohammed H, Al-Hadeethi Y, Bakry AS, Umar A, Hussein MA, et al. Silica-Based Bioactive Glasses and Their Applications in Hard Tissue Regeneration: A Review. Pharmaceuticals. 2021 Jan 20;14(2):75.

48. Fakher S, Westenberg D. Borate-based bioactive glasses properties: Clinical and biomedical applications. Ceram Int. 2024 Dec;50 (24):52190–204.

49. Li X, Su K, Zhao L, Zhang H, Yang Q, Du P, et al. Unraveling osteogenesis mechanisms of the empowered VitaFlux adaptive regeneration biomaterials for bone tissue engineering: Insights into the role of BBGs/BSBGs. Bioact Mater. 2025 Jul;49:271–90.

50. Ege D, Zheng K, Boccaccini AR. Borate Bioactive Glasses (BBG): Bone Regeneration, Wound Healing Applications, and Future Directions. ACS Appl Bio Mater. 2022 Aug 15;5(8):3608–22.

51. Tainio JM, Vanhatupa S, Miettinen S, Massera J. Borosilicate bioactive glasses with added Mg/Sr enhances human adipose-derived stem cells osteogenic commitment and angiogenic properties. J Mater Sci Mater Med. 2024 Nov 30;35(1):71.

52. Aslam AA, Akram J, Mehmood RA, Mubarak A, Khatoon A, Akbar U, et al. Boron-based bioactive glasses: Properties, processing, characterization and applications. Ceram Int. 2023 Jun;49(12):19595–605.

53. Chiu KY, Chen KK, Wang YH, Lin FH, Huang JY. Formability of Fe-doped bioglass scaffold via selective laser sintering. Ceram Int. 2020 Jul;46(10):16510–7.

54. Wang N, Xie Y, Xi Z, Mi Z, Deng R, Liu X, et al. Hope for bone regeneration: The versatility of iron oxide nanoparticles. Front Bioeng Biotechnol. 2022 Aug 25;10.

55. Zakaly HMH, Alotaibi BM, Issa SAM, Ali AS, Hassan AM. Porous iron-doped bioactive glass nanoparticles: synthesis, detailed structural and optical analysis for advanced application in radiation shielding. Journal of the Korean Ceramic Society. 2025 Sep 11;

56. Nandi SK, Mahato A, Kundu B, Mukherjee P. Doped Bioactive Glass Materials in Bone Regeneration. In: Advanced Techniques in Bone Regeneration. InTech; 2016.

57. Kaou MH, Furkó M, Balázsi K, Balázsi C. Advanced Bioactive Glasses: The Newest Achievements and Breakthroughs in the Area. Nanomaterials. 2023 Aug 9;13(16):2287.

Zhu Y, Zhang X, Chang G, Deng S, Chan HF. Bioactive Glass in Tissue Regeneration: Unveiling Recent Advances in Regenerative Strategies and Applications. Advanced Materials. 2025 Jan 16;37(2).

59. Queiroz PM, Barrioni BR, Valverde TM, de Goes AM, Gomes DA, Pereira M de M. Study of the manganese and calcium synergetic influence on mesoporous bioactive glass characteristic. J Non Cryst Solids. 2023 Dec;622:122656.

60. Abbasi F, Ahmadian M, Eslami A. Fabrication and characterization of Mn-doped 45S5 bioglass coatings for Ti6Al4V implants. Journal of Science: Advanced Materials and Devices. 2025 Jun;10 (2):100894.

61. Taskozhina G, Batyrova G, Umarova G, Issanguzhina Z, Kereyeva N. The Manganese–Bone Connection: Investigating the Role of Manganese in Bone Health. J Clin Med. 2024 Aug 9;13(16):4679.

62. Miola M, Brovarone CV, Maina G, Rossi F, Bergandi L, Ghigo D, et al. In vitro study of manganese-doped bioactive glasses for bone regeneration. Materials Science and Engineering: C. 2014 May;38:107 –18.

63. Batool SA, Ahmad K, Irfan M, Ur Rehman MA. Zn–Mn-Doped Mesoporous Bioactive Glass Nanoparticle-Loaded Zein Coatings for Bioactive and Antibacterial Orthopedic Implants. J Funct Biomater. 2022 Jul 16;13(3):97.

64. Abbasi F, Ahmadian M, Eslami A. Fabrication and characterization of Mn-doped 45S5 bioglass coatings for Ti6Al4V implants. Journal of Science: Advanced Materials and Devices. 2025 Jun;10 (2):100894.

65. Nawaz Q, Ur Rehman MA, Roether JA, Yufei L, Grünewald A, Detsch R, et al. Bioactive glass based scaffolds incorporating gelatin/manganese doped mesoporous bioactive glass nanoparticle coating. Ceram Int. 2019 Aug;45(12):14608–13.

66. Farmani AR, Salmeh MA, Golkar Z, Moeinzadeh A, Ghiasi FF, Amirabad SZ, et al. Li-Doped Bioactive Ceramics: Promising Biomaterials for Tissue Engineering and Regenerative Medicine. J Funct Biomater. 2022 Sep 24;13(4):162.

67.Liu S, Tang Y, Zhang X, Zhang Y. Lithium-Doped Mesoporous Bioactive Glass with Dual Antibacterial Mechanisms: Sustained Ion Release and Osteogenic Activity for Bone Regeneration. Colloids Surf A Physicochem Eng Asp. 2025 Sep;138356.

68.Su XJ, Liu S, Huo SC, Wang F, Song QX, Shen HX, et al. Polyetheretherketone surface modification by lithium-doped bioglass nanospheres to regulate bone immunity and promote osseointegration. Mater Des. 2024 Feb;238:112646.

69.Liu S, Tang Y, Zhang X, Zhang Y. Lithium-Doped Mesoporous Bioactive Glass with Dual Antibacterial Mechanisms: Sustained Ion Release and Osteogenic Activity for Bone Regeneration. Colloids Surf A Physicochem Eng Asp. 2025 Sep;138356.

70. Kuo TY, Lin TL, Lin YH, Chen CY, Cho DY, Chen YW, et al. Lithium-doped calcium silicate scaffolds-activated M2-polarized macrophage-derived miR-145-5p-riched extracellular vesicles to enhance osteoimmunomodulation for accelerating bone regeneration. J Nanobiotechnology. 2025 Aug 25;23 (1):586.

71. Zhang X, Nan K, Zhang Y, Song K, Geng Z, Shang D, et al. Lithium and cobalt co-doped mesoporous bioactive glass nanoparticles promote osteogenesis and angiogenesis in bone regeneration. Front Bioeng Biotechnol. 2023;11:1288393.

72.Kurtuldu F, Mutlu N, Michálek M, Zheng K, Masar M, Liverani L, et al. Cerium and gallium containing mesoporous bioactive glass nanoparticles for bone regeneration: Bioactivity, biocompatibility and antibacterial activity. Materials Science and Engineering: C. 2021 May;124:112050.

73.Jacobsen V, Kunisch E, Merle C, Xue B, Zheng K, Renkawitz T, et al. Cerium-doped mesoporous bioactive glass nanoparticles reduce oxidative stress and adipogenic differentiation in human bone marrow-derived mesenchymal stromal cells. Journal of Trace Elements in Medicine and Biology. 2025 Apr;88:127617.

74.Hanaei SB, Murugesan RC, Souza LP, Cadiz-Miranda JI, Jeys L, Wall IB, et al. Multifunctional gallium doped bioactive glasses: a targeted delivery for antineoplastic agents and tissue repair against osteosarcoma. Biomedical Materials. 2024 Nov 1;19(6):065008.

75. Zeimaran E, Pourshahrestani S, Djordjevic I, Pingguan-Murphy B, Kadri NA, Wren AW, et al. Antibacterial properties of poly (octanediol citrate)/ gallium-containing bioglass composite scaffolds. J Mater Sci Mater Med. 2016 Jan 16;27(1):18.

R S, P T P. The Synthesis and Characterization of Selenium-Doped Bioglass. Cureus. 2024 Jun 5;

77. Hu M, Fang J, Zhang Y, Wang X, Zhong W, Zhou Z. Design and evaluation a kind of functional biomaterial for bone tissue engineering: Selenium/ mesoporous bioactive glass nanospheres. J Colloid Interface Sci. 2020 Nov;579:654–66.

78. Chen D, Liang Z, Su Z, Huang J, Pi Y, Ouyang Y, et al. Selenium-Doped Mesoporous Bioactive Glass Regulates Macrophage Metabolism and Polarization by Scavenging ROS and Promotes Bone Regeneration *In Vivo*. ACS Appl Mater Interfaces. 2023 Jul 26;15(29):34378–96.

79.Wu C, Xia L, Han P, Mao L, Wang J, Zhai D, et al. Europium-Containing Mesoporous Bioactive Glass Scaffolds for Stimulating in Vitro and in Vivo Osteogenesis. ACS Appl Mater Interfaces. 2016 May 11;8(18):11342–54.

80. Wu C, Xia L, Han P, Mao L, Wang J, Zhai D, et al. Europium-Containing Mesoporous Bioactive Glass Scaffolds for Stimulating in Vitro and in Vivo Osteogenesis. ACS Appl Mater Interfaces. 2016 May 11;8(18):11342–54.

81.Li F, Wang M, Pi G, Lei B. Europium Doped Monodispersed Bioactive Glass Nanoparticles Regulate the Osteogenic Differentiation of Human Marrow Mesenchymal Stem Cells. J Biomed Nanotechnol. 2018 Apr 1;14(4):756–64.

82.Zhang X, Cui J, Cheng L, Lin K. Enhancement of osteoporotic bone regeneration by strontium-substituted 45S5 bioglass *via* time-dependent modulation of autophagy and the Akt/mTOR signaling pathway. J Mater Chem B. 2021;9 (16):3489–501.

83.de Carvalho ABG, Cardoso LM, Anselmi C, Dal-Fabbro R, Campos TMB, Borges ALS, et al. Melt electrowriting of bioglass-laden poly(ε-caprolactone) scaffolds for bone regeneration. J Mater Chem B. 2025;13(12):3864–75.

84.Dalle Carbonare L, Cominacini M, Trabetti E, Bombieri C, Pessoa J, Romanelli MG, et al. The bone microenvironment: new insights into the role of stem cells and cell communication in bone regeneration. Stem Cell Res Ther. 2025 Apr 12;16(1):169.

85.Shao M, Rahmdel M, Shayan SK, Hassannia E, khedmatgozar M, Yousefi K, et al. Advancements in Biomaterials for Stem Cell Differentiation. Stem Cell Rev Rep. 2025 Jun 21;21(5):1299–310.

86.Li H, Chu Y, Zhang Z, Zhang G, Jiang L, Wu H, et al. Construction of Bilayered Tissue-Engineered Skin With Human Amniotic Mesenchymal Cells and Human Amniotic Epithelial Cells. Artif Organs. 2012 Oct 20;36(10):911–9.

87.Chaudhry U, Redman S, Mundy S, Barker S, Harvey EJ, Chodavarapu HD, et al. The Role of MicroRNAs in Osteogenesis. Int J Mol Sci. 2022;23 (13):7163.

88. Ehrlich M, Lacey M. DNA Methylation and Differentiation: Silencing, Upregulation and Modulation of Gene Expression. Epigenomics. 2013 Oct 24;5(5):553–68.

89.Hu H, Zhang H, Bu Z, Liu Z, Lv F, Pan M, et al. Small Extracellular Vesicles Released from Bioglass/Hydrogel Scaffold Promote Vascularized Bone Regeneration by Transferring miR-23a-3p. Int J Nanomedicine. 2022 Dec;Volume 17:6201–20.

90.Xue Y, Guo Y, Yu M, Wang M, Ma PX, Lei B. Monodispersed Bioactive Glass Nanoclusters with Ultralarge Pores and Intrinsic Exceptionally High miRNA Loading for Efficiently Enhancing Bone Regeneration. Adv Healthc Mater. 2017 Oct 24;6(20).

91.Dalle Carbonare L, Cominacini M, Trabetti E, Bombieri C, Pessoa J, Romanelli MG, et al. The bone microenvironment: new insights into the role of stem cells and cell communication in bone regeneration. Stem Cell Res Ther. 2025 Apr 12;16(1):169.

92.Miola M, Brovarone CV, Maina G, Rossi F, Bergandi L, Ghigo D, et al. In vitro study of manganese-doped bioactive glasses for bone regeneration. Materials Science and Engineering: C. 2014 May;38:107–18.

93.Salvatori R, Anesi A, Chiarini L, Di Bartolomeo M, Pellacani A, Cavazzoli C, et al. Enhanced bone regeneration with cerium-doped bioactive glasses: In vitro and in vivo study. J Appl Biomater Funct Mater. 2025 Apr 23;23.

94. Shen H, Wang B, Shen Z, Xie Z, Zhang J, Wang C, et al. Cerium-Containing Mesoporous Bioactive Glass Nanoparticles Doped Resin Infiltrants: Synergistic Mechanical Reinforcement and Bioactive Therapy for Early Caries Management. Ceram Int. 2025 Sep;

95.Placek LM, Perry DL, Towler MR, Wren AW. Gallium-Containing Bioactive Glasses: Their Influence on Ion Release and the Bioactivity of Resulting Glass Polyalkenoate Cements. Applied Sciences. 2025 Jul 10;15(14):7756.

96.Hanaei SB, Murugesan RC, Souza LP, Cadiz-Miranda JI, Jeys L, Wall IB, et al. Multifunctional gallium doped bioactive glasses: a targeted delivery for antineoplastic agents and tissue repair against osteosarcoma. Biomedical Materials. 2024 Nov 1;19(6):065008.

97. Chen D, Liang Z, Su Z, Huang J, Ouyang Y, Pi Y, et al. Selenium-Doped Nano-Mesoporous Bioactive Glass Regulates Macrophage Metabolism and Polarization by Scavenging ROS and Promotes Bone Regeneration in Vivo. SSRN Electronic Journal. 2022;

98. Zheng C, Wang J, Liu Y, Yu Q, Liu Y, Deng N, et al. Functional Selenium Nanoparticles Enhanced Stem Cell Osteoblastic Differentiation through BMP Signaling Pathways. Adv Funct Mater. 2014 Nov;24(43):6872–83.

99.Rodríguez-Carballo E, Gámez B, Ventura F. p38 MAPK Signaling in Osteoblast Differentiation. Front Cell Dev Biol. 2016 May 6;4.

100.Fernández-Villa D, Aguilar MR, Rojo L. Europium–tannic acid nanocomplexes devised for bone regeneration under oxidative or inflammatory environments. J Mater Chem B. 2024;12(29):7153–70.

101.Wu L, Yang F, Xue Y, Gu R, Liu H, Xia D, et al. The biological functions of europium-containing biomaterials: A systematic review. Mater Today Bio. 2023 Apr;19:100595.