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Developments in strontium-doped calcium phosphate composite scaffolds for dental applications and bone tissue engineering

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ABSTRACT

This review shows the potential of strontium-doped calcium phosphate (Sr/CaP) scaffolds in dental and bone tissue engineering. Sr enhances bone regeneration by stimulating osteoblast activity and inhibiting osteoclasts, while also improving the scaffolds' mechanical strength, bioactivity, and corrosion resistance. Despite some changes in crystal structure and setting time, surface modifications optimize scaffold performance. In vitro and in vivo studies confirm that Sr/CaP scaffolds promote cell proliferation, osteogenic differentiation, and new bone formation, making them promising bioactive materials for bone defect repair and implant design.

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1. Introduction

Skeletal dysfunction or loss, a significant socio-economic problem today, can result from trauma, aging, injury, or disease, often leading to serious complications [1]. Tissue engineering combines biomaterials, cellular biology, and biochemical factors to regenerate injured tissues by creating artificial scaffolds [2-4]. Recently, advances in regenerative medicine have focused on effective methods such as stem cell regulation, biological agents, and novel scaffolds like strontium-doped scaffolds for bone repair and strengthening. These scaffolds reduce bone resorption and stimulate bone growth, thereby improving the quality of life for the elderly [5].

In dentistry, tissue engineering has played an important role for decades, moving beyond artificial restorations toward the regeneration of natural tooth structures [6]. Recently, this area has attracted increased attention from researchers focusing on dental applications [7-9]. Notable achievements over the past decade include advances in restoring dental connective tissues [10, 11], enamel [12, 13], and pulp [14]. The clinical repair of entire dental tissues has progressed as well, starting with the use of calcium hydroxide to treat damaged teeth by repairing dentin and pulp [9, 15].

Bone tissue constitutes about 15% of total body weight and is composed of two main parts: highly porous spongy bone (80-90% porosity) in the inner cortex, and mechanically strong compact bone in the outer cortex [16]. Ideal materials for bone defect repair should be biodegradable, biocompatible, angiogenic, osteoconductive, porous, mechanically durable, easy to handle, and cost-effective [17-19]. Although bone transplantation remains a common treatment, it poses challenges such as donor site morbidity and limited tissue supply [20].

To address the challenges of bone defect repair, various bone graft materials have been developed, including xenografts,

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autografts, allografts, and synthetic substitutes. These bone substitutes fall into two main categories: synthetic materials such as biphasic calcium phosphates (b-TCP), hydroxyapatite ceramics (HA) [21], calcium phosphate cements [22], calcium sulfate, bioactive glasses [23], and polymer-based scaffolds [24], and biomaterial-derived substitutes, which include biological agents like insulin-like growth factors, fibroblasts, transforming growth factors, demineralized bone matrix, platelet-rich plasma, and bone morphogenetic proteins [25].

Effective bone regeneration requires a balance between bone resorption and formation. Osteoclasts secrete enzymes that break down bone tissue, while osteoblasts form new bone and build the extracellular matrix, enabling continuous bone remodeling [26]. Šromová et al. [27] showed the importance of this balance for physiological function, noting that an increased bone turnover ratio, favoring resorption over formation, leads to reduced bone mass, mechanical strength, and increased fracture risk. Addressing these challenges demands innovations in bone tissue engineering and repair strategies [28].

Calcium phosphate-based bioceramics, which can absorb strontium ions, closely mimic natural bone tissue. Strontium can be incorporated into calcium phosphate through surface adsorption (a faster process) or by replacing calcium ions within the crystal lattice due to their chemical similarity (a slower process), binding to phosphate groups [29-31]. This phenomenon was first noted in 1870 when strontium was detected in the bones of animals fed strontium salts [32]. Yan et al. [33] demonstrated that Sr-doped calcium phosphate bone substitutes accelerate and enhance bone repair. Likewise, Borciani et al. [34] investigated various biomaterials, including calcium phosphate ceramics, polymers, bioactive glasses, and metals functionalized with strontium, confirming the high potential of Sr to improve bone regeneration in vitro and in vivo.

This review focuses on the potential of strontium-doped calcium phosphate (Sr/CaP) composite scaffolds in bone tissue engineering, particularly within dental applications. Sr/CaP scaffolds demonstrate promising capabilities to stimulate cell proliferation, enhance osteoblast activity, inhibit osteoclast function, and promote bone regeneration. However, challenges remain in optimizing their biocompatibility and mechanical properties to ensure clinical efficacy. This review critically evaluates the current knowledge on the performance of Sr/CaP composites and discusses various surface modification strategies aimed at improving bone integration and overall scaffold effectiveness.

2. Role of strontium and calcium in bone biology

Strontium significantly affects the process of bone resorption and formation and is usually administered in the form of strontium ranelate (SrRan). This element was first discovered in the 19th century and is located on the periodic table. Strontium occurs in nature as a mixture of four stable isotopes: ^{84}Sr (0.6%), ^{86}Sr (9.9%), ^{87}Sr (7.0%), and ^{88}Sr (with an abundance of 82.6%). The metal usually exists in the form of the mineral compounds strontianite ($SrCO_3$) and celestine ($SrSO_4$), which readily form strontium oxide. However, the exact function of strontium in the human body is not yet fully understood [35]. Strontium, due to its chemical similarity to calcium, has some biological functions such as the secretion of certain hormones, muscle contraction, and blood clotting (although to a lesser extent), and can replace Ca in many animals. Sr can play an important role in bone cells and by increasing bone density, reduce risks such as osteopenia and osteoporosis. However, high doses of intravenous Sr^{2+} contribute to the development of symptoms of hypocalcemia due to increased Ca^{2+} excretion during renal excretion [36]. One of the synthetic bone substitutes is CaP ceramics, which have many applications in alveolar and periodontal bone regeneration [37, 38]. However, due to the limited ability of traditional CaP in bone formation and resorption, researchers have attempted to improve the biological properties of bone substitutes by adding biologically active bio-ions such as Sr to CaP-based materials to enhance their biological performance [39, 40].

Several experiments were conducted to investigate the effect of strontium on the physicochemical properties of CaP bone substitutes [41]. The researchers found that doping CaP with strontium increased its uptake, activated bone precursor molecules, and increased the number of transformed osteoblasts [42-44]. Improved bone growth from in vivo studies demonstrated the properties of the materials enhanced with Sr and CaP [40, 45, 46]. Osteoporosis is a disease characterized by a decrease in bone mass and a disruption in the microscopic structure of bone. Sr ranelate inhibits osteoclasts and stimulates osteoblasts through a multidirectional mechanism. Due to the similarity of calcium to strontium, strontium ions have been used in bone substitute ceramics through calcium-sensitive receptors in bone, which help treat fractures [47].

3. Synthesis and fabrication of Sr-doped CaP scaffolds

The synthesis and fabrication of Sr-doped calcium phosphate scaffolds involve the use of bioactive composite materials together with biodegradable polymers. Various fabrication techniques have been developed, each offering specific properties and applications. Common methods include hydrothermal [48, 49], chemical immersion [50], sol-gel [51], microwave [52], 3D printing [53], and electrospinning [54]. The choice of method largely depends on the type of polymer, desired mechanical strength, and targeted biological function. Among these methods, electrospinning and 3D printing have gained particular attention due to their versatility and effectiveness in scaffold fabrication. For example, electrospinning method combined 10 wt% PCL and 6 wt% CS with TFA solution at a ratio of (7:3) to form an electrospinning suspension. To balance the good biological function with the electrospinning method, about 20 wt% CaP or Sr/CaP was added to the mixture. It was confirmed that Ca and Sr ions on the membrane, acting synergistically, enhanced osteogenic differentiation and angiogenesis. These strategies aim to create Sr-doped CaP scaffolds with suitable biodegradability, porosity, and biocompatibility, thereby improving their effectiveness in tissue engineering applications [54].

Moreover, Oliveira et al. [53] developed a simple method to create Sr-doped 3D-printed calcium phosphate scaffolds by adding strontium carbonate to the printing ink. This induced partial transformation from β-tricalcium phosphate to hydroxyapatite, improving scaffold strength and mineralization. The Sr-doped scaffolds showed high print fidelity and better mechanical properties, while pure β-TCP had higher cell viability. This approach is effective for producing Sr-doped biphasic calcium phosphate scaffolds and could be extended to other therapeutic ions. Fig. 1 shows a schematic of the fabrication of Sr-doped CaP scaffolds.

Shengui et al. [48] were able to fabricate an efficient Sr/CaP coating on porous Ti6Al4V scaffolds with a low elastic modulus (5.19 GPa) using a hydrothermal method. The main material of the coatings was $CaHPO_4$, which easily attached to the substrate. In vivo experiments showed that Ti6Al4V scaffolds with 10% Sr/CaP were biocompatible, promoting the growth of new bone tissue and making them a promising option for bone regeneration.

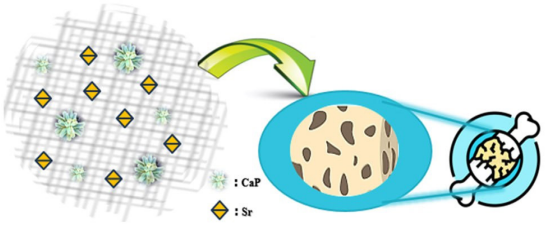

Fig. 1. Fabrication of Sr-Doped CaP Scaffolds.

In other studies, Sr nanoparticles (Sr-BGNPs), which are spherical and bioactive glassy with a diameter of 200 nm, were synthesized by the sol-gel method [55, 56]. Using Sr hardistonite powders i.e., $Sr(NO_3)_2$, $Zn(NO_3)_2.6H_2O$, and $(C_2H_5O)_4Si$ (SZS ceramics) were synthesized by the sol-gel method and investigated for bone repair applications [57].

For cell adhesion and tissue growth enhancement, the surface wettability of polyetheretherketone (PEEK) was significantly enhanced by adding CaP or Sr-doped CaP. On the implant surface, wettability played an important stamp in the integration of the implant and hostess tissue, and increasing surface wettability was essential to enhance the bioactivity of PEEK [58, 59].

In addition, the researchers investigated the cytotoxicity of Sr-doped CaP coatings using an acid etching assay. The ALP level and duplication of bone marrow mesenchymal stem cells (BMSCs) were multiplied by Sulfonated Surface Porous Polyetheretherketone (SP PEEK), Bio-mineralization of Calcium Phosphate on Sulfonated Surface Porous Polyetheretherketone (BSSP PEEK CaP), and BSSP PEEK Sr/CaP, respectively, over a certain period, and the degree of cell adhesion and surface differentiation was improved [60].

Zhang and colleagues [57], reported that SZS ceramics with a relatively low degradation rate are a suitable option for repairing bone defects. The study also showed that SZS ceramics, with their bioactivity, increased the inherence, duplication, and growth of rabbit bone marrow stem cells (rBMSCs). Cells were attached to the PEU-coated BCP-6Sr_2Mg_2Zn scaffold strands and doped with hUC-MSCs, creating a suitable environment for cell growth from the coated scaffolds. These scaffolds improved cell proliferation and distribution, cell-cell contact, cell viability analysis, and spatial arrangement of cells [61].

On a titanium substrate, a coating of CaP doped with Sr and Ag with suitable crystallinity and uniform distribution was synthesized via a single-step hydrothermal deposition method. During this process, $Sr(NO_3)_2$ was used as the source of strontium element [62]. Furthermore, researchers showed that Sr/ Ag coatings have strong antibacterial activity against S. aureus and E. coli bacteria due to their high biocompatibility and antibacterial effects, which have great potential for orthopedic applications [63, 64]. Liu et al. [65] cultured bone marrow stromal cells (MSCs) on SF (silk fibroin)/ $SrCO_3$ composite films with different $SrCO_3$ contents for better cell response. They showed that the lower $SrCO_3$ concentration (0.1%) had better biocompatibility and cell metabolism than higher concentrations and was more suitable for cellular tissue regeneration.

In another study, Cheng and colleagues [66] confirmed the biphasic toxic effect of strontium in a biocompatible assay on MC3T3-E1 cells; Sr promoted bone mineralization and formation and is nontoxic at concentrations of 3–12 mM, but showed toxicity with increasing concentration. This study demonstrated the importance of controlling the concentration of strontium in calcium phosphate scaffolds for bone tissue engineering.

Furthermore, in another study, the Sr-doped CaP solution precursor was prepared by liquid extraction after 10 min of centrifugation. In the Sr/CaP precursor, SSP-PEEK samples were immersed stepwise for 24 h at 4 and 60 °C, forming a coating. Finally, these samples were floated in SBF solution for 7 days for bio-mineralization and formation of the porous BSSP-PEEK-Sr/CaP structure (Fig. 2) [60]. Table 1 summarizes some studies related to calcium phosphate ceramics doped with Sr.

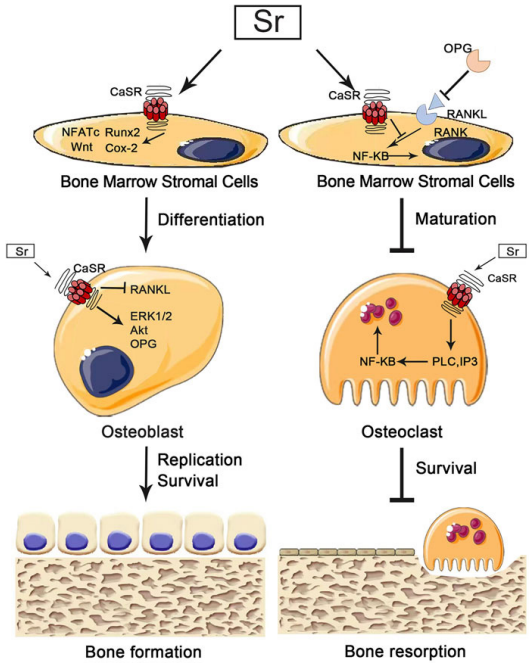

Fig. 2. Implications for the net pharmacological effects of calcium-sensing receptors (CaSr) in osteoblasts and osteoclasts. Sr stimulates osteogenesis by activating CaSr to inform osteoblasts in downstream pathways that develop osteoblast differentiation, proliferation and survival. Sr also inhibits bone resorption by activating CaSR and informing osteoclasts in downstream pathways that inhibit osteoclast maturation and survival [67].

4. Properties strontium-doped calcium phosphate composite scaffolds

4.1. Physicochemical and mechanical

The addition of metals to calcium phosphates, such as strontium, can improve the physical, chemical, and mechanical characteristics of bone implant materials [72]. Mechanically, the scaffold should have the same stiffness and strength as the surrounding bone tissue [73].

Often, biomaterials, especially metal implants, are coated with a layer of CaP such as glass ceramics, HA, or TCP; this bioactive coating improves the bone bond between the implant and the host tissue. The chemical similarity of CaP-based coatings to HA of natural bone has been shown to stimulate a favorable biological response in the tissues [74, 75]. Also, these coatings increase the corrosion resistance of metal implants and reduce the release of harmful metal ions [76].

In biomaterials, especially metal implants and composites, surface modifications are considered ideal for the production of bone implants to improve their biological and mechanical properties [77].

Table 1
Calcium phosphate ceramics doped with Sr.

Materials	Fabrication of Sr-Doped	Synthesis	Amount of used Sr (%W)	Results	Ref.
K/ Sr– Calcium polyphosphate (CaPP) scaffolds	CaPP bioceramic doped with K and Sr	By the doped ceramic synthesis method for improved bone substitute	5%	Better cellular and tissue biocompatibility - increased strength	[68]
Human umbilical vein endothelial cells (HUVEC)	Co-culture model of Sr/CaPP scaffold- synthesis of porous SCPP scaffolds from 8% Sr/CaP monobasic monohydrate powders and 15% phosphoric acid	The optimal ratio of HUVEC and osteoblast co-culture model for angiogenesis was 5:1	3-5%	Stimulates vascularization and bone repair-Tubular structure formation - Expression of platelet endothelial cell adhesion	[69]
Sr-CSM	Mg and Sr-doped wollastonite bioceramic scaffolds (Sr-CSM)	Apatite-forming ability of alkaline phosphatase (ALP)-stimulated rabbit bone marrow stem cells (rBMSCs) with β-TCP and CSM scaffolds	4%	Better apatite formation ability - Better mechanical stability - Higher cell proliferation ability - Osteoblast differentiation - Bone mineralization	[70]
15Sr/CaP nanoparticles	Microwave	Using traditional synthesis, one-step process and continuous flow system	15% w/v	Highly stable nanoparticles - excellent biocompatibility - extremely strong antifungal and antibacterial activity - has bone replacement properties	[52]
Sr/CaP/PCL/CS fibers	TFA solvent-Polycaprolactone (PCL), and Chitosan (CS) solutions with a certain percentage	Mixture of polymers with a weight ratio of 7:3(PCL: CS), forming an electrospinning suspension	About 20% by weight of the PCL/ CS system is CaP or Sr/CaP	Higher Sr density causes more nanoparticle aggregation, and higher roughness of Sr/CaP / PCL / CS fibers improves cell growth, Excellent biocompatibility, increased adhesion and proliferation of BMSCs	[54]
Sr/Cu-DIO	Sr/Cu co-substituted diopside scaffolds	Fabrication of high-strength bone scaffolds by doped ceramic synthesis	Approximately 5%	Increased mechanical and biological resistance	[71]

Furthermore, when strontium is added to hydroxyapatite and calcium phosphate ceramics, their physical, chemical, and mechanical properties can differ. Numerous studies have examined the manner in which the addition of Sr influences the physical and chemical properties of, and in vitro and in vivo behavior of, CaP-based bone substitutes [78]. Tao et al. [41] showed that Sr-doped calcium phosphate had a more rapid absorption in vivo.

Moreover, Guo et al. [79] reported the preparation of calcium phosphate bone cements with Sr^{2+} substituted systems through the substitution of $SrHPO_4$ for $CaHPO_4$ through the tetracalcium phosphate system which displayed an increase in cement strength with the addition Sr^{2+}, but influenced the setting time more slowly. Although It was observed that the crystallite size in the Sr/CaP overlay became smaller than that of the CaP overlay, These changes in the CaP crystal structure probably explain the slight decrease in bond strength [80].

In addition, José S. Rabelo Neto et al. [81] demonstrated that Sr doping has a strong impact on inferred morphological properties of calcium phosphate crystals while inducing highly symmetric structures, some of which take on either pseudo-hexagonal or hexagonal crystal shapes.

Maria Elena Zarif et al. [82] investigated the development of strontium-doped calcium phosphate/chitosan composite layers using radio-frequency magnetron sputtering and matrix-assisted pulsed laser evaporation.

By controlling the substrate temperature during sputtering, Sr-doped tetra calcium phosphate layers were obtained, with the surface morphology evolving from granular to microchannel structures at higher temperatures. FTIR and EDX analyses confirmed the absence of OH groups associated with apatite and revealed a (Ca + Sr)/P atomic ratio of approximately 2, which is consistent with tetra calcium phosphate. The subsequent deposition of chitosan did not alter the structural or compositional characteristics of these films.

4.2. Biological performance

Strontium-doped calcium phosphate biomaterials show promise for bone tissue engineering applications due to their ability to stimulate cell proliferation, adhesion, and osteogenic factor production. This effect has also been observed in vitro with strontium-doped calcium-phosphate biomaterials, as demonstrated by Chung et al. [83] and Capuccini et al. [84], who reported a decrease in osteoclastogenesis.

In vivo studies also help verify the effects of ionic substitution of ceramics on bone formation, with a specific focus on enhancing mechanical strength, the growth of bone-forming cells, and how the material interacts with the body in various animal models and substrates. One in vivo study by Olivier et al. [85], reported that bioceramic materials with strontium significantly enhanced bone-forming cell growth and mineral formation when tested in stem cells. This suggests these materials may have potential for repairing bone where there is sufficient strontium.

Another study showed that the doped calcium phosphate covering had good biocompatibility with mBMSCs. By increasing osteogenic proteins and gene expression, the osteogenic properties of mBMSCs on strontium-doped Ti6Al4V-CaP-10%Sr scaffolds were significantly higher than those on Ti6Al4V and Ti6Al4V-CaP scaffolds. Meanwhile, in vivo experiments showed that Ti6Al4V-CaP-10%Sr scaffolds could ameliorate the formation of new bone tissue within the bioframeworks. Also, the addition of Sr to the coating improved Osteogenic distinction, confirmed by Western blot. According to Western blotting on Ti6Al4V-10% Sr/CaP scaffolds, proteins (RUNX2, COL-1, OPN, OCN, and ALP) in the expanded mBMSCs follow the same pattern in real-time (qRT-PCR) (Fig. 3. a, b) [48].

The mBMSC cells in all scaffolds, whether coated or not, were in a pod-like shape. Therefore, according to Fig. 3, it was concluded that the strontium-doped scaffolds had good cell compatibility for cell migration and adhesion [48].

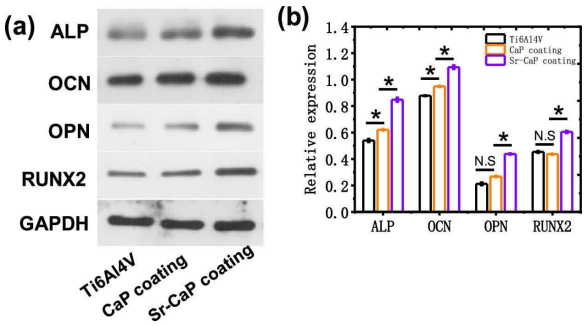

Fig. 3. (a) Western blot investigation (b) After 14 days (n = 3), N.S (means P ≥0.05. *P < 0.05.) were examined on mBMSCs cultured on different engineered Ti6Al4V structure [48].

5. Effects of strontium in clinical dental applications

Strontium has emerged as a potent bioactive element in the field of dental tissue engineering and regenerative dentistry due to its beneficial effects on bone metabolism and tissue repair [86]. Sr ions are known to promote osteoblast activity and inhibit osteoclast-mediated bone resorption, contributing to enhanced bone formation and improved implant osseointegration. This dual effect makes strontium-based materials highly valuable for applications in dental regeneration and repair [28].

Additionally, strontium's low toxicity and chemical similarity to calcium allow it to replace Ca in dental materials, enhancing radiopacity without compromising their properties. Since the 1980s, Sr has been incorporated into glass fillers, glass ionomer cements, mineral trioxide aggregate (MTA), Biodentine, adhesives, and calcium phosphate cements, improving radiographic visibility and, in some cases, mechanical strength [8].

Recent research shows the potential of strontium-doped biomaterials for improving dental treatment outcomes. In the study, strontium folate (SrFO) was incorporated into β-tricalcium phosphate (β-TCP) and chitosan-polyethylene glycol dimethacrylate (CS-PEGDMA) hybrid scaffolds, which were then cultured with human dental pulp stem cells (hDPSCs). This biohybrid system accelerated bone regeneration and enhanced cellular compliance in animal models, showing promise for effective repair of damaged bone tissue in dental applications [86].

Moreover, Qin et al. [87] showed that 1% strontium-doped calcium polyphosphate (Sr/CaPP) promotes angiogenesis by increasing VEGF and bFGF in human dental pulp cells (hDPCs). SEM, CLSM, and MTT indicated superior hDPC growth and proliferation on 1%Sr/CaPP versus CaPP and HA. ELISA confirmed higher VEGF and bFGF levels on 1%Sr/CaPP. Fig. 4 shows that fluorescence microscopy on day 20 revealed dense, continuous, fiber-like hDPC layers encasing the Sr/CaPP pores, with greater cell viability compared with CaPP or HA.

Strontium's role extends beyond scaffolds as it can enhance the biological properties of dental implants. Surface modifications with Sr-containing compounds have been shown to improve the adhesion and function of osteoblasts, as well as increase the rate of bone fusion around implants, thereby improving initial stability and long-term success rates [8, 88, 89].

While strontium is the focus in this paper, it is worth noting that successful dental tissue engineering also relies on the integration of stem cells, growth factors, and biocompatible scaffolds. For instance, DPSCs, with their multidirectional differentiation capabilities, combined with Sr-enriched scaffolds, represent a promising strategy for regenerating complex dental tissues, including dentin and bone [90, 91].

Overall, the incorporation of strontium into various biomaterials markedly enhances their bioactivity, osteogenic potential, and clinical utility in dental tissue engineering [92]. Continued research and development of Sr-based scaffolds and composites are likely to pave the way for improved clinical therapies targeting tooth loss, bone defects, and implant integration [93, 94].

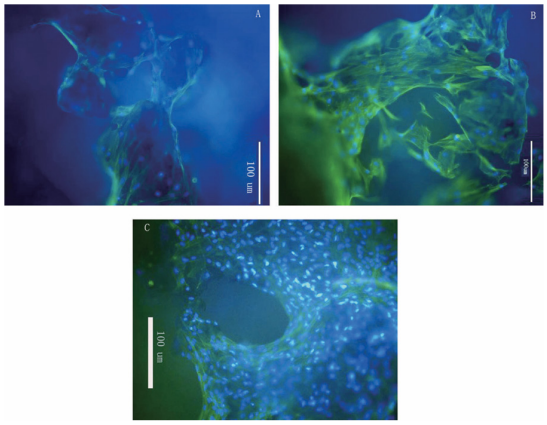

Fig. 4. Fluorescent images of hDPCs grown on porous HA, CaPP, and 1% Sr/CaPP scaffolds after 20 days. Green indicates F-actin, and blue indicates nuclei. Panels: HA (A), CaPP (B), Sr/CaPP (C) [87].

6. Clinical relevance and challenges

Bone integrity, which is a highly vascular tissue, depends on the strong linkage of bone cells in time, angiogenesis, and case. For this reason, angiogenesis plays an important impress in bone growth and reparation [95]. Also, in the primary stages after transplantation, local angiogenesis will provide nutrients necessary for osteogenic activity and will establish strong connections between abutting tissues, bone, and organs [96]. Osteogenesis refers to the mechanism of stem cell disjunction into osteoblasts under the influence of the microenvironment and plays a key role in the success of bone regeneration [97, 98]. Angiogenesis is essential in dental tissue engineering. Therefore, dental tissue engineering would greatly benefit from developing a new scaffold with bioactivity to induce angiogenesis [87]. CaP has gained popularity due to its excellent biocompatibility, controllable degradation, having good mechanical properties, and its chemical composition being similar to that of natural bone. Many in vivo studies have also shown that CPP scaffolds have excellent osteoconductivity and might provide a suitable alterative to bone [99]. Using strontium nanoparticles (SrNPs) for treatment of osteoporosis and bone infections is an important step forward in the field of medicine [100]. Osteoporosis is a condition characterized by low bone mass and damage, resulting in fractures and disabilities. Bone infections such as osteomyelitis are difficult to treat. SrNPs are beneficial because they promote bone regeneration, and they have high antimicrobial properties, making them interesting materials for orthopedic and dental applications where infections can inhibit healing [101].

Advances in Sr-doped HA nanoparticle-based scaffolds highlight the material's potential to balance biocompatibility with mechanical performance. By combining the osteogenic and anti-resorptive properties of Sr with HA's structural benefits, these scaffolds mark a major breakthrough in creating bioactive, mechanically resilient materials for clinical use. Ongoing research to optimize these systems is expanding the field of bone tissue engineering, offering better patient outcomes in treating bone defects and fractures [100, 102] In addition, Strontium-doped calcium phosphate scaffolds show promise for dental and bone tissue engineering applications. These scaffolds demonstrate

excellent cytocompatibility, promoting human dental pulp cell growth and proliferation [87]. The incorporation of strontium in the scaffolds increase osteogenesis by activating osteoblasts as well as inhibiting osteoclasts while facilitating angiogenesis and enhancing bone regeneration. Strontium ions can also stimulate calcium sensitive receptor pathways when included in Sr-doped CaP or SrCSH/Sr-TCP type osteoconductive composite scaffolds and even enhance biocompatibility, thus promoting fracture healing. However, the greatest challenge related to scaffolds is to maintain control over the strontium release rate and the scaffold degradation profile since slow and/or unequally balanced degradation can limit the extent of new bone growth and the long-term performance of the implant [103, 104].

7. Conclusion

Strontium-doped calcium phosphate composite scaffolds can enhance cell growth and biosynthesis. Sr chondral inhibits osteoclasts and stimulates osteoblasts through a multidirectional mechanism. Due to the similarity of calcium to strontium, strontium ions have been used in bone substitute ceramics through calcium-sensitive receptors in bone, which help in fracture healing. Mechanically, the scaffold should have a stiffness and strength similar to the surrounding bone tissue. The advancement of bone scaffolds with both increased biocompatibility and good mechanical properties is considered a major concern for biomaterials. Therefore, surface modification of biomaterials with good mechanical properties to improve their biocompatibility could be a promising approach to achieve an ideal bone implant. Overall, Sr/CaP composites could be the next generation of materials that can be used in applications for both bone regeneration, regenerative medicine, and dental tissue engineering applications.

Author contributions

Faezeh Khan Ahmadi: Investigation**,** Writing – original draft, Writing – review & editing; **Ketevan Mikeladze:** Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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