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Review

Ionic Doping of Hydroxyapatite for Bone Regeneration: Advances in Structure and Properties over Two Decades—A Narrative Review

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Abstract: Autogenous grafts remain the "gold standard" in bone tissue grafting procedures; however, limitations such as donor site morbidity, invasiveness, and limited availability have spurred research into alternative materials. Hydroxyapatite (HA), a widely used bioceramic, is known for its bioactivity and biocompatibility. Nonetheless, its inherent brittleness and porosity necessitate modifications to enhance its mechanical and functional properties. Ionic doping has emerged as a transformative strategy to improve the properties of HA by integrating ions such as strontium (Sr^{2+}), magnesium (Mg^{2+}), and zinc (Zn^{2+}). These dopants influence HA's crystal structure, morphology, and solubility, resulting in enhanced bioactivity, accelerated bone mineralization, and improved mechanical properties, such as increased fracture resistance and wear durability. Additionally, antimicrobial properties can be achieved through the inclusion of silver ions (Ag^{+}), reducing the risk of peri-implant infections. This review focuses on the effects of ionic doping on the structure and functionality of hydroxyapatite, emphasizing advancements in tailoring its properties to clinical needs. By consolidating two decades of research, this study highlights how ionic doping bridges the gap between synthetic biomaterials and native bone, unlocking new potential in regenerative medicine and orthopedic applications.

Keywords: bone tissue regeneration; hydroxyapatite; ion doping; tissue engineering

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1. Introduction

Significant advancements in bone tissue engineering over the past decades have addressed many challenges associated with hard tissue augmentation procedures, yet notable gaps persist [1]. Bone grafts remain a cornerstone of clinical practice and are classified into biological types (autografts, allografts, xenografts) or synthetic alternatives [2]. Among these, autografts are considered the "gold standard" due to their superior osteogenic properties. Nonetheless, the limited availability of these materials and the associated donor site morbidity underscore the need to explore alternative options that offer comparable efficacy while minimizing risks [3]. Allografts and xenografts have emerged as viable alternatives, offering improved osteoconductive properties and widespread availability.

However, challenges such as immune response and high costs persist [4,5]. Advancements in tissue engineering and material science have also facilitated the development of synthetic materials, particularly hydroxyapatite (HA) which mimics the composition and function of natural bone tissue [6].

Bone tissue regeneration depends on the interplay of osteogenic, osteoinductive, and osteoconductive properties, along with sufficient vascularization—all key elements that are encapsulated in the "diamond concept" of bone healing [7]. Biomaterials for bone repair must meet specific criteria: biocompatibility; adequate mechanical stability; macroporosity to support cell infiltration and vascularization; and controlled degradation rates to integrate seamlessly with native bone [4,8–10]. Hydroxyapatite, a calcium phosphate-based bioceramic, has become a focal point in bone tissue engineering due to its excellent bioactivity and chemical similarity to bone mineral. Its widespread application, however, is limited by inherent brittleness, porosity, and poor mechanical properties [11].

To address these limitations, ionic doping has emerged as a transformative approach to enhancing the structural and functional properties of hydroxyapatite. Doping introduces specific ions into the HA lattice, modifying its crystal structure and influencing key properties such as solubility, mechanical strength, bioactivity, and antimicrobial efficacy [12]. For instance, strontium (Sr^{2+}) enhances bioactivity and promotes bone cell proliferation, while magnesium (Mg^{2+}) improves bone density and mechanical strength. Zinc (Zn^{2+}) and cerium (Ce^{3+}) contribute to osteogenesis and antibacterial properties, while silver (Ag^{+}) provides antimicrobial protection, reducing the risk of peri-implant infections. These modifications bring hydroxyapatite closer to mimicking the hierarchical structure and functionality of native bone, providing customized solutions for clinical applications.

This review focuses on the role of ionic doping in hydroxyapatite, emphasizing its impact on structural, mechanical, and biological properties. By examining the influence of specific ions on hydroxyapatite's characteristics, we aim to highlight advancements in the material's potential for orthopedic and regenerative applications. The integration of ionic doping into HA represents a significant step forward in tailoring biomaterials to meet diverse clinical needs, bridging the gap between synthetic substitutes and the complex requirements of natural bone tissue [12].

The schematic placement of doped hydroxyapatite within the classification of biomaterials is presented in Figure 1.

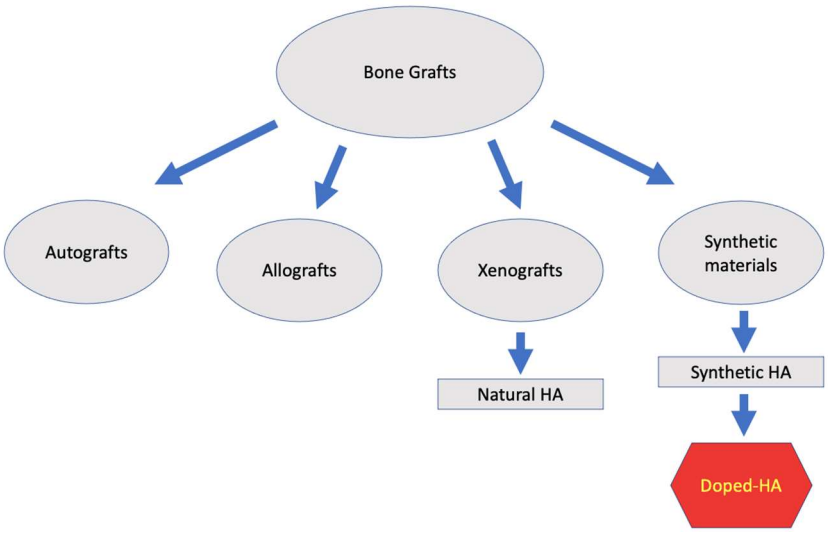


Figure 1. Schematic placement of hydroxyapatite within the classification of biomaterials.

2. Study Selection

Relevant literature was selected to encompass the most recent advancements in hydroxyapatite research over the past 20 years, focusing on English-language publications. A comprehensive search of five electronic databases (PubMed, Embase, Scopus, Cochrane, Google Scholar) was conducted using relevant keywords. The following keywords were used: bone substitute, natural hydroxyapatite, nanostructured hydroxyapatite, doped hydroxyapatite, magnesium-doped hydroxyapatite, strontium-doped hydroxyapatite, zinc-doped hydroxyapatite, iron-doped hydroxyapatite, and copper-doped hydroxyapatite. Three authors (Z.K.-M., A.P., J.M.) employed the same keywords to conduct independent searches of the databases. Some articles were excluded on the following grounds:

1. They were not in English;
2. They were narrative reviews older than 10 years;
3. The authors were unable to access the full version of the original article;
4. They were not peer-reviewed and therefore belonged to the grey literature.

After completing the search process and identifying potential studies for inclusion in this review, all authors collaboratively assessed them to confirm that they met the inclusion criteria, resulting in the final selection of 97 studies.

3. Results

Hydroxyapatite (HA), with the stoichiometric chemical formula $Ca_{10}(PO_4)_6(OH)_2$, closely resembles the inorganic component of bone, making it a key focus in bone graft research. It is renowned for its high chemical stability and low solubility, being one of the most stable calcium phosphate-based bioceramics, with a Ca/P ratio of 1.67 [13,14]. These characteristics contribute to its superior biocompatibility and osteoconductivity, which are essential for bone regeneration.

Natural hydroxyapatite is characterized by its inherent impurities, which influence its morphology and texture, particularly at the microstructural level. In contrast, synthetic HA offers greater purity and enables precise control over key parameters such as the Ca/P ratio, porosity, and hardness [15]. Synthetic HA is commonly fabricated in particulate, granular, or porous block forms. Its porous nature promotes bioactivity by facilitating osteoblast adhesion and migration, leading to the formation of a strong biological bond with surrounding bone [4,16].

The biodegradation of HA occurs through interactions with biofluids and adsorption of biomolecules. Its resorption is primarily mediated by osteoclasts, although macrophages may occasionally contribute [9,13]. This osteoclastic activity is advantageous, as it recruits osteoblasts and facilitates the replacement of graft material with natural bone tissue [17]. However, HA's slow degradation limits its application in load-bearing bone repairs [9]. Additionally, HA's intrinsic mechanical weaknesses, such as low tensile and compressive strength, hinder its performance in mechanically demanding environments.

To address these limitations, researchers have developed HA composites by incorporating reinforcing agents like collagen, polyacrylamide, and graphene oxide to enhance mechanical properties. However, these modifications often compromise bioactivity compared to pure HA. Hybrid biomimetic composites that integrate biopolymers with HA have shown promise in balancing mechanical performance and bioactivity [18].

Nanostructured HA (nano-HA) has garnered significant attention due to its ability to mimic natural bone more effectively. Its higher surface-to-volume ratio improves biomechanical properties and enhances the adhesion, proliferation, and differentiation of osteogenic progenitor cells [16]. Moreover, the coating of other scaffolding materials with nano-HA expands the range of their potential applications. For instance, the coating of neurotoxic carbon nanotubes with nano-HA enables their use in the regeneration of

damaged nerve fibers by facilitating the directing of axon growth, particularly when the nano-HA is doped with Li^+ and Eu^{3+} ions [19].

3.1. Nanostructured Hydroxyapatite

Nanotechnology has revolutionized bone regeneration by offering innovative approaches to enhance the mechanical, biological, and functional properties of biomaterials. Key applications include the following:

(a) Engineering nanocomposites with improved mechanical strength and biocompatibility;
(b) Modifying material surfaces at the nanoscale to enhance cell adhesion and function;
(c) Developing degradable nanoceramics for better integration with natural tissues;
(d) Employing nanotopography to stimulate osteoblast activity;
(e) Enabling targeted drug delivery systems to facilitate healing and recovery [2].

Nano-hydroxyapatite crystals, due to their excellent biocompatibility and bioactivity, have emerged as a promising material in bone regeneration, offering superior osseointegration and reduced inflammatory responses compared to traditional porous HA [20]. Nano-HA mimics the dimensions of natural calcified tissues such as bone and teeth, with optimal sizes ranging from 10 to 100 nm for biomedical applications [13,20]. These nanostructured materials enhance osteoblast adhesion, proliferation, and differentiation, while promoting calcium deposition, thus supporting effective bone remodeling [13].

The distinctive properties of nanomaterials stem from two primary factors: quantum effects and an enlarged surface-to-volume ratio. Nanomaterials exhibit a 30 to 50% higher surface area compared to their micrometer-scale counterparts, significantly improving protein adsorption and osteoblast attachment [20,21]. The altered surface characteristics of nanostructured materials further facilitate cell interactions, leading to enhanced bioactivity.

Despite its advantages, nano-HA alone often lacks sufficient mechanical properties and resorbability for broader clinical applications. Customized biomaterials that integrate nano-HA with other components are essential for hard tissue replacements. These hybrid materials must be tailored to meet specific requirements, including density, porosity, thermal stability, bioactivity, and mechanical strength [13].

3.2. Methods of Obtaining Nano-Hydroxyapatite

The synthesis of nano-hydroxyapatite (nano-HA) is a key area of focus in biomaterials research, with several techniques developed to optimize its structural, mechanical, and biological properties. Among these, the most commonly employed methods include wet chemical precipitation, hydrothermal synthesis, sol-gel methods, emulsion systems, and microwave-assisted synthesis, each offering unique advantages and limitations [12,13].

3.2.1. Wet Chemical Precipitation

This method remains the most widely used due to its simplicity and cost-effectiveness. The process involves the precipitation of HA by reacting with aqueous solutions containing calcium ions (Ca^{2+}) and phosphate ions (PO_4^{3-}) [15,22]. Parameters such as temperature, reaction time, surfactants, and sintering conditions significantly influence the morphology and crystallinity of the final product. For instance, sintering temperatures can lead to phase transitions, such as the formation of α- and β-tricalcium phosphate [15,23]. Studies have shown a direct relationship between synthesis temperature and nano-HA particle size, with lower temperatures yielding smaller, thinner particles and higher temperatures resulting in larger, denser structures [24]. At pH 9, spherical particles of 30–50 nm were produced, while higher pH values yielded more complex morphologies like rods and flakes [25]. The primary advantage of this method is that water is the only byproduct, making it environmentally friendly [26].

3.2.2. Hydrothermal Synthesis

This method is highly effective for producing well-crystallized HA powders with a homogeneous composition. Operating at relatively low temperatures, the hydrothermal process allows for precise control of pH and ion concentrations, resulting in varied morphologies, including nanowires, nanorods, and microspheres [15,27]. It avoids the need for surfactants and complex process controls, yielding materials with superior crystallinity and structural integrity [28]. The hydrothermal approach is particularly suited for creating doped apatite materials with enhanced properties for clinical applications.

3.2.3. Emulsion and Microemulsion Processes

These techniques utilize immiscible liquids (typically oil and water) to form a dispersed phase in which HA particles are synthesized. The process relies on the collision of water droplets to complete the reaction, producing uniform particle sizes and large surface areas [29]. The microemulsion method offers advantages such as thermodynamic stability, shape control, and prevention of particle aggregation, resulting in spherical nanoparticles ideal for biomedical applications [30,31].

3.2.4. Sol-Gel Method

The sol-gel technique is valued for its ability to produce high-purity ceramic powders at relatively low temperatures. This method enables strict control over process parameters, allowing for the synthesis of nano-HA with fine-grained microstructures and submicron-sized particles [32]. Sol-gel synthesis is also used to create thin film coatings for biomedical implants, providing an alternative to thermal spraying [33]. Its primary advantages include room-temperature reactions, high reactivity, and the elimination of grinding steps, making it a versatile method for fabricating nano-HA [34–37].

3.2.5. Microwave-Assisted Synthesis

Microwave irradiation has emerged as a rapid and energy-efficient method for producing nano-HA. This technique reduces the kinetic barriers of ionic reactions, facilitating the synthesis of highly crystalline materials in significantly shorter times compared to conventional methods [27,38]. Studies demonstrate that parameters such as aging time, microwave power, and exposure duration influence the thermal stability and crystallinity of the final product [39–41]. The internal and volumetric heating provided by microwave processing ensures homogeneous nanostructures, making it an ideal choice for scalable production [12].

The summary of differences between methods of nano-HA obtaining has been presented in Table 1.

Table 1. Synthesis methods of nano-HA.

Method	Process Complexity	Cost	Size (nm)	Purity	Doping Possibilities	References
Wet chemical precipitation	Low	Low	30–50	Medium	High	Loo et al. (2010) [24], Rodríguez-Lugo et al. (2018) [25]
Hydrothermal	Medium	Medium	20–40	High	Very high	Hassan et al. (2016) [27], Feng et al. (2022) [28]

Table 1. *Cont.*

Method	Process Complexity	Cost	Size (nm)	Purity	Doping Possibilities	References
Microemulsion processing	Medium	Medium	24–70	High	High	Collins et al. [30] Sun et al. (2011) [31]
Sol-Gel	Low	Low	28–60	High	High	Kaygili (2014) [35] Ziani (2013) [36] Prodan (2019) [37]
Microwave-Assisted synthesis	Low	Low	11–32	High	High	Shkir (2017) [40] Mishra (2014) [41]

3.3. Doping of HA Nanoparticles

Doping of hydroxyapatite (HA) nanoparticles is a critical strategy to overcome its inherent limitations, enhance its properties, and improve its integration with polymer matrices and other biomaterials. This approach increases dispersion stability in various media and optimizes the interface between nanoparticles and surrounding materials, particularly in composite systems [42]. Recent advancements in HA composite research have focused on surface modification with polymers to leverage HA's bioactivity while addressing its mechanical and functional shortcomings [42–75].

Various organic molecules and polymers have been grafted onto HA nanoparticles to enhance their performance. Examples include silane coupling agents, stearic acid, titanate coupling agents, chitosan, RGD-containing peptides, poly(N-isopropylacrylamide), and poly(γ-benzyl-l-glutamic acid) [43]. These surface modifications not only improve the chemical compatibility of HA in composite systems but also enhance its biological stimulation properties. Furthermore, the incorporation of trace amounts of ions, typically found in natural bone minerals, into HA has gained considerable attention as an effective strategy to address its limitations and improve its biofunctionality [44].

Metal ion doping, in particular, has emerged as a transformative approach to enhance HA's properties. Ions such as silver (Ag^+), zinc (Zn^{2+}), magnesium (Mg^{2+}), and strontium (Sr^{2+}) significantly influence bone regeneration by supporting bone formation and contributing to metabolic processes during healing. Additionally, anions like chloride (Cl^-), fluoride (F^-), and carbonate ($CO_3{}^{2-}$) play essential roles in the physiological function of hard tissues, affecting HA's crystallinity, mechanical strength, degradation, and bioactivity [45]. For example, Sr^{2+} enhances osteoblast differentiation and bone mineralization, while Ag^+ offers antimicrobial properties to reduce the risk of infection around implants. These modifications allow HA to mimic natural bone more closely, improving its integration and functionality within the physiological environment [11].

Notable effects of doping of the chosen metals and non-metals on hydroxyapatite are shown in Table 2.

Table 2. Effect of doping hydroxyapatite with chosen ions.

Ion	Effects of Doping Hydroxyapatite	References
Strontium	Reduced cytotoxicity, enhanced bio-protein absorption, increased osteoconductive capabilities	Wang et al. (2023) [45], Zhang et al. (2023) [47], Song et al. (2021) [48]
Zinc	Enhanced bioactivity, stimulation of osteogenic activity, antibacterial properties, promotion of fibroblast proliferation	Kurzyk et al. (2023) [44], Cuypers et al. (2024) [49]
Magnesium	Increased mineralization, enhanced osseointegration capability, osteogenesis and bone regeneration promotion	Kurzyk et al. (2023) [44] Sartori et al. (2014) [51]
Silver	Antibacterial properties	Méndez-Lozano et al. (2023) [53]
Selenium	Enhanced osteoinductive properties, oncolytic activity	Gao et al. (2021) [56]
Boron	Stimulation of osteoblasts, improved osteogenic differentiation of mesenchymal stem cells	Arslan et al. (2018) [57], Gizer et al. (2020) [58], Çiftci Dede et al. (2022) [59]
Cobalt	Oxidative stress reduction, angiogenesis promotion, antibacterial effect	Kumar et al. (2024) [60], Kulanthaivel (2016) [61], Radulescu et al. (2023) [62]
Copper	Bacterial biofilm inhibitor, angiogenesis promotion, increased biocompatibility	Radulescu et al. (2023) [62], Noori et al. (2024) [65], Unabia et al. (2019) [67]
Iron	Acceleration of mature bone formation, enhanced bioactivity and solubility	Predoi (2021) [69], Ereiba et al. (2013) [70]
Cerium	Antibacterial properties, promotion of osteoblast proliferation and differentiation	Liu et al. (2023) [71], Vieira et al. (2011) [72]
Fluorine	Antibacterial properties, stimulation of bone formation, tooth decay prophylaxis	Hidalgo-Robatto et al. (2018) [74], Herman et al. (2021) [75]

3.3.1. Strontium-Doped Nano-Hydroxyapatite (Sr-Nano-HA)

Strontium (Sr), a trace element with chemical properties similar to calcium (Ca), constitutes approximately 98% of its presence in osseous tissue [12]. Sr follows physiological pathways akin to calcium, with a pronounced tendency to accumulate in bones and teeth, where it supports mineral metabolism and structural integrity [11]. At low concentrations, Sr promotes bone formation by enhancing osteoblast activity, reducing bone resorption, and inhibiting osteoblast apoptosis. However, excessive Sr concentrations can disrupt bone remodeling by interfering with metabolic processes and inhibiting osteoclast apoptosis, which may adversely affect bone health [44].

The incorporation of Sr^{2+} ions into nano-hydroxyapatite (nano-HA) has been shown to significantly improve its biological properties. Sr^{2+} doping enhances bioactivity, osteoinductivity, and protein adsorption, while also reducing cytotoxicity and increasing drug-loading potential [45]. Zhao et al. demonstrate that Sr-doped HA coatings on titanium substrates significantly improve cell adherence [46]. This improved cell attachment is crucial for applications in orthopedic and dental implants.

Angiogenesis, a critical process linked to osteogenesis, is positively influenced by Sr^{2+} doping, making Sr-nano-HA a promising material for hard tissue regeneration [44]. Sr-doped nano-HA has also been shown to enhance the regenerative capacity of biomaterials, resulting in the formation of abundant and mature bone tissue at defect

sites [47,48]. These findings highlight its potential in addressing bone defects and improving implant integration.

3.3.2. Zinc-Doped Nano-Hydroxyapatite (Zn-Nano-HA)

Zinc (Zn) is an essential trace element and cofactor for numerous enzymes involved in the synthesis of DNA, RNA, and proteins, playing a pivotal role in cellular repair and the regeneration of musculoskeletal tissues [44]. In bone metabolism, zinc is critical for enhancing bone formation and mineralization by stimulating collagen production and increasing alkaline phosphatase (ALP) activity, a marker of osteoblast differentiation [12]. Additionally, zinc inhibits osteoclast activity, thereby preventing bone resorption, which is vital for maintaining bone homeostasis and supporting regeneration [38].

When combined with hydroxyapatite (HA), zinc enhances bioactivity by improving osteoblast viability, promoting osteogenic activity, and accelerating bone healing. Zinc-doped HA (Zn-HA) has demonstrated antibacterial properties, making it a dual-function material for bone tissue engineering applications [49]. However, zinc's effects are dose-dependent: concentrations in the range of 1–50 μM optimally stimulate osteoblast activity, while higher concentrations may inhibit osteogenesis [44].

The mechanisms underlying zinc's bioactivity include its role as a catalytic cofactor in protein synthesis and as a secondary messenger in signaling pathways that regulate cell division and proliferation. Zinc ions (Zn^{2+}) released from Zn-HA surfaces increase intracellular zinc levels, which protect cells from oxidative stress and apoptosis. Furthermore, zinc ions stimulate fibroblast proliferation in the oral system, contributing to enhanced tissue regeneration [45].

Zn-HA scaffolds containing less than 1% zinc ions have been shown to exhibit significant antibacterial properties, reducing the risk of infection while supporting bone regeneration. Additionally, zinc ions can modulate immune cell responses, further enhancing the biological performance of Zn-HA scaffolds [11]. These properties make Zn-HA an invaluable material in bone tissue engineering, combining osteogenic potential, antibacterial efficacy, and immune modulation to create advanced scaffolds for clinical applications.

3.3.3. Magnesium-Doped Nano-Hydroxyapatite (Mg-Nano-HA)

Magnesium (Mg) is a vital element in the human body, with 60–65% stored in bones and teeth and the remaining distributed across other tissues [46]. Magnesium ions (Mg^{2+}) are critical for early cartilage and bone development, though their concentration decreases as bones mature [12]. Mg plays a central role in bone regeneration by promoting the proliferation of osteoblasts and fibroblasts, which support osteogenesis. Magnesium deficiency can significantly impact bone health, leading to reduced stiffness, lower osteoblast activity, and increased oxidative stress, ultimately resulting in bone fragility and loss.

In synthetic hydroxyapatite, magnesium influences crystal size, strength, and structural integrity [11]. Incorporating magnesium into hydroxyapatite (Mg-HA) combines the beneficial properties of both materials, making Mg-based composites highly relevant in orthopedic applications due to their biocompatibility and biodegradability [47]. When applied as a coating on titanium implants, Mg-HA demonstrates superior mineralization and greater osseointegration compared to pure or natural HA [12]. These properties enhance the performance of implants, facilitating stronger integration with surrounding bone tissue.

Magnesium doping also modifies the surface characteristics of HA, increasing surface roughness, which contributes to antibacterial properties. Porous Mg-containing implants create an environment where new bone can grow within the pores, forming a stable bond between the implant and adjacent tissue [50]. However, the relationship between porosity and mechanical strength must be carefully managed. Excessive porosity can weaken the

scaffold's structure, but controlled doping of Mg^{2+} ions ensures an optimal balance between structural integrity and biological performance [45].

These multifunctional benefits of Mg-nano-HA, including enhanced osteogenesis, improved antibacterial activity, and superior implant integration, underscore its potential for advanced applications in bone tissue engineering and orthopedic implants [50].

3.3.4. Silver-Doped Nano-Hydroxyapatite (Ag-Nano-HA)

Silver (Ag) is a highly effective antibacterial agent widely recognized for its ability to prevent microbial colonization while maintaining biocompatibility and low toxicity at controlled concentrations [51]. Its antibacterial efficacy is attributed to its interaction with bacterial cellular components, particularly the plasma membrane. Silver disrupts electron transfer processes, inhibits ATP synthesis, and stimulates the production of reactive oxygen species (ROS), which collectively lead to bacterial cell damage and death [43,52].

Silver-doped hydroxyapatite (Ag-HA) nanoparticles, synthesized through methods such as precipitation at 100 °C, have shown potent antibacterial effects against both Gram-positive and Gram-negative bacteria [46]. The antibacterial properties of Ag-HA are primarily driven by the release of Ag^{+} ions, which interact with bacterial membranes to inhibit growth and promote lysis. Despite the cytotoxic potential of Ag^{+} ions, studies indicate that their concentrations in most Ag-nano-HA samples remain below the toxic threshold for human blood, minimizing cytotoxic effects on human cells across a wide range of applications [45].

The safety and efficacy of Ag-nano-HA can be optimized by precisely regulating the amount of silver ions during synthesis. This careful control ensures that Ag^{+} ion release provides sufficient antibacterial activity without compromising biocompatibility. These properties make Ag-nano-HA an attractive material for use in bone tissue engineering, particularly in preventing infections around implants and scaffolds.

3.3.5. Selenium-Doped Nano-Hydroxyapatite (Se-Nano-HA)

Selenium (Se) is an essential microelement known for its antioxidant properties, which play a critical role in protecting the body against free radicals and carcinogens [48]. Selenium ions are integral to selenoproteins, which contribute to immune function, catalyze the production of active thyroid hormone, and promote cellular proliferation. Selenium deficiency has been linked to increased risks of various cancers, including those affecting the prostate, colon, lungs, liver, and thyroid. Insufficient selenium intake can elevate reactive oxygen species (ROS) levels, leading to reduced type-I collagen synthesis, suppressed alkaline phosphatase expression, and impaired osteoblast differentiation—all of which are closely tied to selenoprotein expression.

In the context of biomaterials, selenium has been explored extensively for orthopedic implants due to its antimicrobial, anticancer, and osteoinductive properties. Selenium-doped hydroxyapatite nanoparticles (Se-nano-HA) are typically synthesized through co-precipitation or hydrothermal methods, with the latter involving temperatures up to 160 °C [55]. These doping processes enable the incorporation of selenium into the hydroxyapatite matrix, imparting unique biological activities.

Se-nano-HA has shown significant potential in combating osteosarcoma. For example, studies by Wang et al. demonstrated that selenium-doped HA induces apoptosis in MG-63 osteosarcoma cells by activating the intrinsic mitochondrial apoptotic pathway [56]. This mechanism involves oxidative damage to DNA and mitochondria, leading to mitochondrial dysfunction and cell death. These findings suggest selenium's potential as an anti-osteosarcoma agent, offering dual benefits of anticancer and osteoinductive activity.

By integrating selenium into hydroxyapatite, Se-nano-HA provides a multifunctional scaffold for bone regeneration that combines antioxidant, antimicrobial, and anticancer properties, making it a promising material for advanced orthopedic applications.

3.3.6. Boron-Doped Nano-Hydroxyapatite (B-Nano-HA)

Recent advancements in enhancing the osteoinductive properties of hydroxyapatite (HA) involve the incorporation of boron (B), a trace element crucial for human health and bone metabolism [57]. Boron-doped nano-hydroxyapatite (B-nano-HA) has shown promising potential in promoting bone formation and regeneration. Studies reveal that boron enhances mesenchymal stem cell proliferation and osteogenic differentiation, as evidenced by increased alkaline phosphatase activity—a marker of osteoblast differentiation—compared to standard nano-HA or boric acid alone [58].

Gizer et al. demonstrated that boron-infused nano-HA improved mesenchymal stem cell activity, with higher doses promoting cell proliferation, although effects on osteoblasts varied. Similarly, research by Gümüşderelioğlu et al. showed that encapsulated B-nano-HA stimulated the proliferation and differentiation of MC3T3-E1 pre-osteoblastic cells in vitro. In their study, boron-doped HA was synthesized using microwave-assisted biomimetic precipitation and encapsulated within poly(butylene adipate-co-terephthalate) fibers at a 5% (w/w) ratio, significantly improving scaffold osteogenic activity [57].

In vivo studies also highlight the potential of boron-infused nano-HA in bone tissue engineering. Çiftci Dede et al. evaluated the impact of injectable boron-containing nano-HA composites combined with hyaluronan in osteoporotic rabbit femurs. Although the increase in bone mineralization and new bone formation was not statistically significant compared to the nano-HA group, the findings suggest that boron composites may aid in preventing fractures in osteoporotic femurs by enhancing bone mineral density over time [59].

B-nano-HA offers a versatile material for scaffolds and injectable systems in orthopedic applications, combining osteogenic stimulation with tissue engineering advancements. While further research is required to optimize its efficacy, boron-doped composites show considerable potential for preventing fractures and supporting bone regeneration in patients with osteoporosis.

3.3.7. Cobalt-Doped Nano-Hydroxyapatite (Co-Nano-HA)

Cobalt (Co), a transition metal known for its redox-active properties, has garnered attention in the field of bone tissue engineering due to its ability to enhance both osteogenesis and angiogenesis. When cobalt ions (Co^{2+}) are incorporated into hydroxyapatite (HA), the resulting Co-doped HA (Co-HA) exhibits unique properties, including the ability to scavenge reactive oxygen species (ROS), which mitigates oxidative stress and inflammation during implantation [60]. Cobalt's redox activity plays a pivotal role in creating a microenvironment conducive to bone regeneration by reducing oxidative damage.

Cobalt ions are also known to stabilize hypoxia-inducible factor-1 alpha (HIF-1α), a critical regulator of angiogenesis. By simulating hypoxic conditions, HIF-1α promotes the secretion of vascular endothelial growth factor (VEGF), facilitating the link between angiogenesis and osteogenesis, processes essential for effective bone formation [61]. Studies confirm that Co doping enhances the angiogenic potential of HA without impairing its osteogenic properties, making Co-HA a promising biomaterial for bone regeneration [62].

Research by Kulanthaivel et al. demonstrated that Co^{2+}-doped HA promotes osteoblast differentiation, enhances osteoconductivity, and increases VEGF secretion, highlighting its potential as a scaffold material for bone tissue engineering [61]. Additionally, Co-HA has been shown to reduce bacterial infections, providing an added antimicrobial

benefit [63]. The magnetic properties of Co-HA nanoparticles have also enabled their use as magnetic resonance imaging (MRI) contrast agents, expanding their applications beyond bone repair [61].

Despite its advantages, the release of cobalt ions raises concerns about potential toxicity, as excessive cobalt exposure can lead to adverse effects such as nausea, hypothyroidism, and goiter [61]. Variations in osteogenic, angiogenic, and inflammatory responses observed with cobalt-based biomaterials may be attributed to differences in the release rates of Co^{2+} ions [64]. Limiting cobalt ion release through controlled doping strategies ensures the material's safety and efficacy in clinical applications.

Co-nano-HA presents a multifunctional platform for bone tissue engineering, combining osteogenic, angiogenic, and antimicrobial properties while supporting advanced diagnostic imaging. Careful regulation of cobalt content is essential to maximize its therapeutic benefits and minimize potential risks.

3.3.8. Copper-Doped Nano-Hydroxyapatite (Cu-Nano-HA)

Copper (Cu), an essential trace element in the human body, plays a critical role in various biological processes, including hematopoiesis, neurological function, and skeletal development. Its role in the skeletal system is particularly significant, as copper acts as a cofactor for lysyl oxidase, an enzyme crucial for the cross-linking of collagen fibers to form stable bone matrices [59]. Copper deficiency can result in severe conditions such as anemia, pancytopenia, neurodegeneration, and impaired bone formation, highlighting its importance for overall health and bone regeneration.

The incorporation of copper ions (Cu^{2+}) into hydroxyapatite (HA) creates a multifunctional material with enhanced biological and antibacterial properties [66]. Cu-HA has been shown to promote mesenchymal stem cell differentiation into osteoblasts, stimulate endothelial cell proliferation during wound healing, and enhance the delivery of vascular endothelial growth factor (VEGF), which supports angiogenesis [62,67]. These pro-angiogenic effects improve the viability of bone-forming cells within implants, further aiding in bone regeneration.

In addition to its osteogenic benefits, Cu-HA exhibits strong antibacterial properties, effectively reducing the risk of implant-related infections. Studies by Hidalgo-Robatto et al. demonstrated that Cu-HA not only promotes osseointegration between bone and implant surfaces but also inhibits bacterial biofilm formation, addressing two critical challenges in orthopedic and dental implantology [62]. However, the release of excessive copper ions poses a risk of cytotoxicity, emphasizing the need for controlled doping to balance biological efficacy and safety.

Copper doping in HA also influences the material's physicochemical properties, making it suitable for metallic implants designed for repairing severely damaged or fractured bone tissue. The effectiveness of Cu-HA in bone healing can be monitored using imaging techniques, such as digital panoramic radiography, by calculating parameters like fractal dimension (FD), lacunarity, and Feret diameter (FeD), which assess changes in bone density and structure over time [68].

By combining osteogenic, angiogenic, and antibacterial properties, Cu-nano-HA offers a versatile and effective solution for bone tissue engineering. Its potential to enhance both biological functionality and implant integration underscores its value in advanced regenerative medicine applications.

3.3.9. Hydroxyapatite Doped with Other Metals

Doping hydroxyapatite (HA) with metals introduces enhanced biological, mechanical, and antimicrobial properties, making it highly relevant for biomedical applications. Sev-

eral metal-doped variants of HA have shown potential in promoting bone regeneration, improving material bioactivity, and preventing microbial infections [76–85].

Iron-Doped Hydroxyapatite (Fe-HA)

Iron (Fe^{3+})-doped HA has been extensively studied for its unique properties, particularly its application in magnetic scaffolds for bone regeneration. Iron imparts redox-active and magnetic properties, transitioning HA from diamagnetic to superparamagnetic as Fe^{3+} concentration increases. This also affects the material's crystallinity, morphology, and solubility, with higher iron content leading to reduced crystallite size, rod-like particle morphology, and increased bioactivity and dissolution rates [69]. In vitro studies by Ereiba et al. demonstrated that Fe-HA generates an electric field that enhances HA nucleation and crystallization, further increasing apatite layer thickness on surfaces. These findings underscore the potential of Fe-HA in supporting accelerated bone formation [70].

Cerium-Doped Hydroxyapatite (Ce-HA)

Cerium (Ce), known for mimicking calcium ions, plays a role in stimulating metabolic activity and promoting bone regeneration. Ce-doped HA combines biocompatibility, osteoconductivity, and antibacterial properties, making it a promising material for biomedical applications [71]. Ce-HA coatings effectively inhibited hospital-associated pathogens such as *Escherichia coli* and *Staphylococcus aureus*, while in vitro studies confirmed its hemocompatibility and its ability to promote osteoblast proliferation and mineralization [72]. Ce-HA's neuroprotective effects and ability to inhibit oxidative stress add further value to its use in regenerative medicine.

Fluoride-Doped Hydroxyapatite (F-HA)

Fluoride (F), essential for bone and dental health, enhances mineralization by stimulating osteoprogenitor cell proliferation and differentiation. Fluoride-doped hydroxyapatite (F-HA) exhibits greater density and mechanical strength compared to pure HA, primarily due to the incorporation of fluoride ions into its structure. This improves ion adsorption, bioactivity, and cytocompatibility under controlled sintering conditions [73]. F-HA delivers therapeutic fluoride ions, making it particularly effective in treating osteoporosis and supporting bone mass growth. Its antibacterial properties against oral bacteria reduce the risk of cariogenic species development, offering additional benefits in dental applications [74]. The unique ability of F-HA to slowly release fluoride ions in the oral environment is also utilized in tooth decay prophylaxis [75].

3.4. Hydroxyapatite Enriched with Curcumin

Curcumin (Cur), the active polyphenolic compound derived from *Curcuma longa*, has garnered attention for its wide-ranging pharmacological effects. These include anti-inflammatory, antioxidant, hypolipidemic, anticoagulant, anti-angiogenic, and anticancer properties [86,87]. By regulating key biological processes such as cytokine production, redox balance, and transcription factor activity, curcumin offers therapeutic potential in managing chronic conditions, including metabolic, autoimmune, and neoplastic disorders [87]. Moreover, its anti-cancer activity, particularly in inhibiting tumor cell proliferation, underscores its potential in oncology [88]. However, its clinical application is hindered by poor bioavailability, rapid metabolism, and fast systemic clearance. To address these challenges, nanoparticle-based delivery systems, such as nanogels, micelles, and lipid nanoparticles, have been developed to enhance curcumin's therapeutic potential [89].

In bone metabolism, curcumin's effects remain controversial. While its anti-osteoclastogenic properties suggest a role in regulating bone resorption, high concentrations have been shown to inhibit osteoblast proliferation and even induce osteoblast death under

certain conditions [87]. Despite these limitations, combining curcumin with hydroxyapatite (HA) offers significant promise in treating bone-related disorders, particularly when engineered into nanostructured platforms.

The combination of curcumin with HA has been achieved using various methods. Sharifi et al. [89] synthesized hydroxyapatite-curcumin fibers via electrospinning, while Xidaki et al. [87] utilized wet precipitation, followed by curcumin incubation in ethanol to enhance HA surface functionalization. The high porosity of HA surfaces is critical for effective curcumin attachment, making nanostructured HA ideal for targeted drug delivery platforms. These platforms have demonstrated potential for delivering curcumin to fight cancers like osteosarcoma, suppressing tumor growth while simultaneously promoting bone repair [88].

Additionally, curcumin-loaded HA scaffolds have shown promise in addressing oxidative stress-related complications in bone regeneration. In type 2 diabetes mellitus, elevated reactive oxygen species (ROS) impair mesenchymal stem cell (MSC) differentiation and delay osteogenesis. A study by Yu Li and Zhan-Zhao Zhang demonstrated that curcumin-loaded microspheres incorporated into fish collagen-HA scaffolds reduced ROS production, enhancing bone regeneration and vascularization in diabetic conditions [90]. This dual role of curcumin in suppressing oxidative stress and promoting bone repair highlights its therapeutic value.

The challenges associated with doping HA have been presented in Table 3.

Table 3. Challenges and possibilities for doping HA.

Challenge	Suggested Solution	Potential Use	References
Low strength	Mg^{2+} or Sr^{2+} doping	Orthopedic implants	Wang et al. (2023) [45], Zhang et al. (2023) [47], Song et al. (2021) [48], Sartori et al. (2014) [51],
No antibacterial activity	Ag^{+} or Zn^{2+} doping	Preventing infection around implants	Cuypers et al. (2024) [49], Méndez-Lozano et al. (2023) [53]
Only osteoconductive activity	Zn^{2+}, Se, B^{3+} doping	Promoting bone regeneration	Cuypers et al. (2024) [49], Gao et al. (2021) [56], Arslan et al. (2018) [57], Gizer et al. (2020) [58], Çiftci Dede et al. (2022) [59]
Lack of angiogenetic activity	Co^{2+}, Cu^{2+} doping	Increasing vascularisation of implanted area	Kumar et al. (2024) [60], Kulanthaivel (2016) [61], Radulescu et al. (2023) [62], Noori et al. (2024) [65], Unabia et al. (2019) [66]

The impact of different ions on the HA properties and structure have been presented in Table 4.

Table 4. Impact of different ions on the HA properties and structure.

Ion	Impact on the Structure	Bioactivity	Antibacterial Properties	Mechanical Properties	Degradation Pace	References
Sr^{2+}	Higher porosity	High	Low	Higher strength	Moderate	Ran L. et al. (2023) [76] Hiu Zhu (2018) [77]
Zn^{2+}	Smaller grains, Higher porosity	High	High	Improved	Low	Ofudje E. (2019) [78]
Mg^{2+}	Reduced crystallinity	High	Medium to high	Increased flexibility	Facilitated	Predoi (2019) [79]
Se^{4+} Se^{6+}	Reduced crystallinity	Medium	Medium	Increased flexibility	Facilitated	Pajor et al. (2018) [48], Barbanente et al. (2021) [49]

Table 4. *Cont.*

Ion	Impact on the Structure	Bioactivity	Antibacterial Properties	Mechanical Properties	Degradation Pace	References
Ag^{+}	Reduced crystallinity	High	Very high	Strength depends on ion content	Moderate	Yildiz et al. (2023) [46] Mansour et al. (2017) [80]
B^{3+}	Crystallinity decreases or remains unchanged depending on the method; Higher porosity	High	Low	Increased thermal stability; Reduced microhardness	Facilitated	İdil Uysal (2020) [81]
Co^{2+}	Reduced crystallinity	High	Medium	Improved	Facilitated	Kulanthaivel et al. (2016) [55] Safari-Gezaz et al. (2025) [82]
Cu^{2+}	Reduced crystallinity	High	Very high	Improved	Facilitated	Noori (2024) [65]
Fe^{2+} Fe^{3+}	Reduced crystallinity	High	Low	Increased hardness, improved mechanical strength, Magnetization increased	Improved	Balakrishnan et al. (2021) [83]
Ce^{4+} Ce^{3+}	Reduced crystallinity	High	Very high	Improved	Facilitated	Ciobanu et al. (2015) [84]
F^{-}	Higher crystallinity	High	Medium	High mechanical strength	Reduced solubility	Bakhsheshi-Rad et al. (2014) [85]

3.5. Hydroxyapatite Impurities

Fathi et al. emphasized the importance of stringent processing conditions to maintain HA purity, noting that certain manufacturing methods could inadvertently introduce unwanted CaO phases [91]. Maintaining high purity in hydroxyapatite is crucial to optimizing its functionality, mechanical properties, and bioactivity for biomedical applications.

The presence of impurities in hydroxyapatite (HA) can significantly hinder its bioactivity, impairing its ability to facilitate osteoconduction and support new bone formation. Structural anomalies or unwanted phases caused by impurities can weaken the mechanical integrity of HA, making it less durable and more prone to degradation under physiological stress. These impurities often arise from the synthesis process, starting materials, or production environments. For instance, during wet synthesis methods, the use of low preparation temperatures can lead to ionic impurities being incorporated into the crystalline structure from the aqueous solution [92].

Vojevodova et al. identified various impurities in synthetic hydroxyapatite/polyvinyl alcohol (n-HA/PVA) composites, including β-tricalcium phosphate (β-TCP), free CaO, calcium-deficient HA phases, and residual polyvinyl alcohol. These impurities adversely affect the material's osteogenic potential and mechanical properties [93]. Impurities can also originate from natural substrates used for HA synthesis. For example, Hamidi et al. demonstrated that grinding and thermally treating shells can yield smooth, spherical HA particles suitable for bone substitutes, but processing can also introduce impurities such as calcium carbonate [94].

Le et al. reported the presence of calcium sulfate hemihydrate and traces of calcium dihydrate residue in HA materials, while Ismail et al. identified contamination with calcium carbonate and calcium hydroxide phases during production [95,96]. Such contamination can compromise the material's biocompatibility and structural integrity, necessitating precise control during manufacturing.

4. Conclusions and Future Perspectives

Hydroxyapatite (HA) has proven to be an invaluable material for bone synthesis and repair, owing to its osteoinductive, osteoconductive, and biocompatible properties. However, the limited mechanical strength of pure HA has driven researchers to develop various modifications to enhance its performance. Structural and chemical alterations, including ion doping, have enabled HA's properties to be tailored to meet specific clinical needs in orthopaedics, dentistry, and other medical fields. Ion doping modifies the microstructure of HA, reducing its fragility and enhancing its fracture resistance, thus making it more suitable for use in high-stress areas, such as the spine.

Doping with ions such as cerium and carbonate (CO_3^{2-}) can reduce the crystallinity of HA, increasing its solubility in biological environments, which is beneficial for bone regeneration. Additionally, doping with magnesium, strontium, or zinc enhances the biological and mechanical properties of HA, promoting angiogenesis, bone tissue regeneration, and antibacterial activity. For example, the incorporation of silver, zinc, or copper ions imparts antibacterial properties to HA, thereby reducing the risk of infection around implants or during the wound healing process. Moreover, combining HA with natural compounds like curcumin has shown promising results not only in bone cancer treatment but also in enhancing bone regeneration in patients with type II diabetes.

While modified hydroxyapatite demonstrates significant potential in bone healing and regeneration, the synthesis methods and optimal concentrations of ion doping still need further refinement. The future of HA-based materials depends on a deeper understanding of bone regeneration processes and the creation of suitable microenvironments for effective healing. Additionally, impurities in synthetic bone graft materials, including HA, can adversely affect biocompatibility, bioactivity, and mechanical strength, leading to complications such as inflammation or material rejection. Therefore, standardizing production processes and exploring additional doping agents is essential to improve the purity and effectiveness of these biomaterials.

Future research should focus on developing more durable and effective HA-based materials, and long-term clinical trials are necessary to ensure optimal patient outcomes. Enhanced materials and improved understanding of bone regeneration mechanisms will pave the way for more advanced and personalized therapeutic approaches.

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