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Apatite insights: From synthesis to biomedical applications

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ABSTRACT

Hydroxyapatite (HAp), a calcium phosphate mineral (Ca_{10} $(PO_4)_6$ $(OH)_2$), has established itself as a cornerstone material across diverse fields since its discovery. HAp serves as a crucial component in artificial bone grafts, dental implants, and drug delivery systems. Researchers have diligently explored various synthesis methods, including sol-gel, precipitation, and hydrothermal processes. The advent of nanotechnology has paved the way for the development of nano-sized HAp particles boasting enhanced properties. Its excellent biocompatibility and osteoconductive properties make it invaluable for bone regeneration and repair. HAp's ability to mimic the structure of natural bone minerals has made it essential in tissue engineering, contributing to the development of synthetic bone substitutes. Beyond its role in medical applications, HAp shows promise in water treatment as an effective adsorbent for heavy metal removal. Additionally, it finds use as a filler in polymer composites, enhancing their mechanical and thermal properties. Recent advancements in HAp research encompass the development of HAp-based nanoparticles for targeted drug delivery, bioresorbable implants, and 3D-printed scaffolds personalized for individual needs. The versatility of HAp is further amplified by its combination with other materials like polymers or bioceramics, unlocking its potential in diverse applications. Despite its remarkable properties, challenges remain, including cost considerations, scalability limitations, and potential immunological responses. Future prospects lie in refining HAp synthesis techniques, continued exploration of its biological applications, and venturing into novel uses within emerging fields like regenerative medicine and nanotechnology.

1. Introduction

Hydroxyapatite (HAp) is a bioceramic of significant interest in the biomedical field due to its close chemical resemblance to the mineral component of bone tissue. This has emerged as a biomaterial of significant interest in the field of biomedical engineering due to its unique physicochemical properties [1,2]. These chemical properties include a high calcium content, essential for mimicking the rigidity of natural bones and teeth, as well as key biological attributes such as osteoconductivity, biocompatibility, and bioactivity - fundamental qualities for successful integration with living tissues [3].

The introduction of biomaterials has revolutionized healthcare by providing alternative solutions like tissue-engineered constructs and drug delivery systems. HAp utilization has witnessed a significant rise in recent years due to its non-reactive nature and suitability for bone substitution [4]. Furthermore, HAp-based materials offer a multitude of additional advantages, including processing flexibility, diverse fabrication methods (chemical, microwave, or sol–gel) [5], tunable morphology for specific applications, the ability to control protein adhesion and cell interactions through surface modification, and excellent device stability, strength retention, and interfacial compatibility [6]. However, compared to other load-bearing ceramic composites

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like titanium alloys and synthetic hydrogels, HAp exhibits inferior mechanical performance and susceptibility to degradation, limiting its application in fully functional prostheses or mild disease treatments [7]. Nonetheless, HAp boasts remarkable biomechanical properties, with notable tensile and compressive strengths (around 100 MPa) [8] and exceptional biomimetic fidelity, closely mimicking the matrix architecture of natural tissues [9,10].

The proposed synthesis technique offers the potential to produce HA-pure powders suitable for integration into various biomedical devices. These powders exhibit handling characteristics tailored to specific application scenarios, including intricate geometries and hardware with channels designed for phased controlled release functionalities. Structural modifications, such as protein or hybrid aluminium oxide coatings, may mitigate potential conflicts arising from the inner surface texture of composite substrates, thereby preventing implant dislodgement. Consequently, compatibility issues are anticipated to be negligible [11]. As highlighted by Tazibt et al. [12], to address the global demand for biomedical products, it is crucial to optimize the yield of the HAp component through scaled manufacturing processes.

Pérez-Solis et al. [13] highlighted diverse synthesis techniques for HA, including biomimetic routes, solid-state reactions, and hydrothermal pathways. Cidonio et al. [14] proposed leveraging biomimetic compacted coatings with natural apatite for posterior cranial implants, potentially enabling localized controlled release. Moreover, sophisticated integration methods facilitate the fabrication of micro-, meso-, and nanoscale structures, impacting both physiological efficacy and precision [5,15].

Due to the significant impact of ingestion on pharmacokinetics, using multilayer or spherical particles offers a promising approach for improving drug delivery systems (e.g., a theoretical framework for diffusion–reaction-oriented drug delivery from a…, n.d.). Nanoparticle (NP)-based multi-agent encapsulation techniques facilitate the selective targeting of diseased cells or organisms identified by unique genetic markers, thereby minimizing toxicity towards healthy tissues [16]. This enables targeted cellular-gene editing applications, such as the development of nanoparticles for pulmonary mRNA delivery, as a potential strategy to address acute pathophysiological defects arising from congenital mutations, hybrid infections, and similar factors.

This review article summarizes recent research on the properties and applications of hydroxyapatite (HAp). We explore strategies for tailoring HAp's physical characteristics to specific structural configurations while adhering to established feasibility constraints. The resulting interactions necessitate rigorous adherence to biomedical regulations to ensure patient safety. Post-interaction mechanisms, such as the production of extracellular signaling molecules or the activation of intercellular signals across matrix components, hold potential for significant advancements. In the field of tissue engineering, optimizing orthopedic functionalities through novel approaches, potentially beyond traditional sutures, emerges as a key area with substantial practical implications. Collaborative networks will be crucial in achieving these goals. Ultimately, the current challenges faced by this industry offer a valuable opportunity to explore future methodologies, prompting scientists to revisit this domain and unlock further breakthroughs in biomedicine..

Table 1
Various methods of HAp synthesis.

SL	Synthesis Method	General Chemical Equation	Benefits	Drawbacks/ Limitations	Uses	Examples	Ref
1	Wet Chemical Synthesis						
1.1	Precipitation Reaction	$Ca(NO_3)_2 + (NH_4)_2HPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2$ + by-products	Simple, cost-effective	Limited control over particle size	Biomedical applications, bone regeneration	Synthetic bone grafts	[17,18]
1.2	Sol-gel Process	$Ca(NO_3)_2$ + TEOS + $(NH_4)_2HPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2$	Better control over particle size/composition	Use of hazardous solvents	Biomedical applications, drug delivery, coatings	HAp-TiO_2 coatings	[19,20]
1.3	Hydrothermal Synthesis	10 $Ca(OH)_2 + 6H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18\ H_2O$	High temperature and pressure conditions promote the formation of highly crystalline well-defined structures; cost-effective	High temperature and pressure requirements can lead to high energy consumption	Targeted drug delivery in bone-related diseases	Encapsulate and deliver drugs or genes directly to target sites	[21,22]
2	Solid state reactions						
2.1	Mechanochemical Synthesis	$CaCO_3 + Ca(H_2PO_4)_2 \rightarrow Ca_{10}(PO_4)_6(OH)_2$ + by-products	Solvent-free, energy-efficient	Longer processing times	Porous materials, metal–organic frameworks	HAp/Chitosan composites	[23,24]
2.2	Sintering						
2.2.1	Solid-state Sintering	$Ca_{10}(PO_4)_6(OH)_2$ (powder) $\rightarrow$ $Ca_{10}(PO_4)_6(OH)_2$ (dense)	Simple, cost-effective	High temperatures, long processing times	Dense, high-strength structures	Dense HAp ceramics	[25,26]
2.2.2	Spark Plasma Sintering	$Ca_{10}(PO_4)_6(OH)_2$ (powder) $\rightarrow$ $Ca_{10}(PO_4)_6(OH)_2$ (dense)	Rapid densification, fine microstructures	Expensive equipment, not suitable for large-scale production	Improved electrical properties	HAp/Al_2O_3 composites	[25,27]
3	Biomimetic Synthesis						
3.1	Biomineralization	Protein-mediated Ca^{2+} and $PO_4^{(3-)} \rightarrow Ca_{10}(PO_4)_6(OH)_2$	Biomimetic, controlled organization	Complex interactions (optimization needed)	Tissue repair, drug delivery systems	HAp-coated implants	[28,29]
3.2	Template-assisted synthesis	Template + Ca^{2+} + $(PO_4)^{3-}$+$OH^- \rightarrow$ Template-HAp + Byproducts	A more uniform distribution of particles, reducing variability in the final HAp product	Efficient removal of the template without altering the HAp structure	Fabrication of biomimetic scaffolds for bone tissue engineering	Nano-hydroxyapatite/ polyamide composite scaffolds	[30,31]

2. Synthesis of hydroxyapatite

The synthesis of HAp is a complex and diverse process, encompassing a wide range of methods from chemical precipitation to biomimetic approaches. Table 1 summarizes the various techniques employed for HAp synthesis.

2.1. Wet precipitation methods

2.1.1. Co-precipitation

The co-precipitation technique remains popular for synthesizing HAp nanoparticles due to its simplicity, cost-effectiveness, and high yield. This method relies on the controlled precipitation of calcium and phosphate ions from the solution, often utilizing calcium chloride and sodium dihydrogen phosphate precursors at moderate pH values (10–11) [32]. For instance, Rusu et al. [32] employed this method to synthesize HAp within a chitosan matrix, paving the way for novel organic–inorganic composites with nanoscale control.

Further research has explored various co-precipitation parameters to tailor HAp properties for specific applications. Khalil et al. [33] synthesized HAp nanorods at 70 °C and varying pH values, while Yin et al. [17] developed silica-modified HAp whiskers for bone repair applications [20,21]. Mortazavi-Derazkola et al. [17] investigated mesoporous HAp for drug delivery, demonstrating its potential through microwave-assisted co-precipitation and characterization. Anwar et al. [18] compared two co-precipitation routes for nanosized HAp synthesis, yielding insights into precursor selection and reaction conditions. Pandele et al. [35] explored the synthesis of cellulose acetate-HAp membranes for water purification and biomedical applications, while Türk et al. [36] investigated the biomimetic synthesis of HAp using microwave irradiation and different calcium sources.

While offering control over HAp morphology, size, and crystallinity, the co-precipitation method can also lead to agglomeration and size distribution issues, potentially hindering its application in specific biomedical fields. Therefore, optimizing synthesis parameters, such as pH, temperature, and precursor concentration, remains crucial for achieving desired HAp properties [37].

2.1.2. Sol-gel

Sol-gel synthesis stands as a well-established method for HAp production, leveraging hydrolysis and polycondensation reactions of metal alkoxides or other precursors to form a gel-like network [38]. This technique offers distinct advantages, including precise control over the material's chemical composition, homogeneity, and the ability to fabricate intricate shapes [39].

Extensive research has explored the versatility of sol–gel synthesis for HAp production. Indrani et al. [40] investigated the impact of calcination temperatures on HAp prepared via wet precipitation methods, while Ramesh et al. [39] compared the characteristics and properties of sol–gel and wet chemical precipitation methods, highlighting significant differences in HAp morphology [39,40]. Ben-Arfa et al. (2018) employed the Taguchi method to optimize sol–gel synthesized HAp, analyzing five key parameters like pH and precursor concentration with only 16 experiments, demonstrating the efficiency of this approach [41].

Further research has explored alternative routes within the sol–gel framework. Lunz et al. [42] investigated two wet chemical methods utilizing mechanical stirring, providing additional options for HAp production while maintaining nanoscale properties. George et al. [38] reviewed diverse techniques for synthesizing biogenic, synthetic, composite, and modified forms of HAp, including sol–gel, for water defluoridation applications. Cahyaningrum et al. [43] successfully synthesized HAp from eggshells via wet precipitation, showcasing the potential of utilizing natural sources as precursors [43]. Additionally, Wahyudi et al. [44] studied the phase transformation of wet-precipitated HAp derived from Indonesian natural sources at varying calcination temperatures, highlighting the possibility of tailoring properties through alternative resources.

These studies collectively demonstrate the versatility of sol–gel synthesis in producing HAp with controlled properties and compositions. By combining this method with other approaches like mechanical stirring and wet precipitation, researchers can further optimize and tailor HAp for diverse applications in fields ranging from biomedicine to water treatment.

2.1.3. Hydrothermal synthesis

Hydrothermal synthesis stands out as an attractive method for producing high-quality and uniform HAp nanoparticles due to its ability to achieve this under relatively mild conditions [21,45]. This versatility has led to the development of diverse techniques capable of controlling the size, shape, and properties of HAp nanoparticles, including microwave-assisted hydrothermal synthesis [46] and ultrasonic atomization precipitation [22].

Cao et al. [46] demonstrated a groundbreaking approach by synthesizing HAp nanorods at room temperature using microwave-assisted solid-state methods. This innovation offers the advantages of rapid nanostructure synthesis and eliminates the need for high-temperature solid-state methods, which have dominated HAp synthesis for decades [22]. Additionally, microwave-assisted hydrothermal synthesis boasts benefits like reduced reaction times, enhanced reaction rates, and improved product quality [46]. Expanding on wet precipitation methods, Pham et al. [47] reported the successful production of HAp microspheres with diverse shapes and drug loading capabilities. This method's scalability for commercial applications further underlines the vast potential of hydrothermal synthesis for HAp production.

Beyond conventional precursors, the eco-friendly and cost-effective use of biosources like eggshells, fish scales, and bovine bones is being explored for HAp synthesis [48]. Bardhan et al. [49] successfully produced HAp powder from eggshell waste through a wet precipitation process at moderate temperatures (50–55 °C). Likewise, Mondal et al. [48] demonstrated the synthesis of HAp from various bio sources for tissue engineering applications.

For optimizing hydrothermal synthesis parameters, the Taguchi method has proven valuable. Ben-Arfa et al. [41] utilized this method to evaluate the effects of four variations in each of five parameters with only 16 experiments, effectively assessing their impact on crystallite size, surface area, Ca/P atomic ratio, and mol% of HAp. This strategy provided valuable insights into the influence of synthesis parameters on HAp properties. Further research delving into this area, as illustrated by Kuśnieruk et al. [21], who investigated the influence of parameters on nanoparticle properties using Scherrer's equation and web-based tools, continues to advance our understanding. Additionally, Cai et al. [22] developed a combined microwave-hydrothermal and ultrasonic atomization precipitation method for efficient large-scale synthesis of nano-Hap powder.

In conclusion, hydrothermal synthesis offers numerous advantages for HAp production, including unparalleled control over nanostructure properties, scalability, and compatibility with various sources. Continued research exploring and optimizing these versatile techniques holds immense potential for advancing HAp synthesis and expanding its applications across diverse fields.

2.2. Solid-state reactions

2.2.1. Mechanochemical synthesis

Mechanochemical synthesis has emerged as a powerful alternative to traditional wet-chemical methods for preparing hydroxyapatite and other materials. This approach utilizes mechanical energy to drive solid-state reactions between precursor powders. A key example is the work of Romeo et al. [50], who demonstrated the synthesis of tetracalcium phosphate (TTCP) through the mechanochemical activation of $CaCO_3$ and $(NH_4)_2HPO_4$ mixtures. This method offers advantages such as

reduced reaction times, energy efficiency, and environmentally friendly processes.

Emerging mechanochemical methods, such as liquid-assisted grinding (LAG) or ion- and liquid-assisted grinding (ILAG) further enhance reaction efficiency by incorporating small amounts of liquids and exploiting catalytic or templating effects [23]. Friščić [23] highlighted the exciting areas of application for these mild mechanochemical methods, such as the one-pot assembly of "soft" metal–organic and organic materials, and the rapid room-temperature synthesis of porous metal–organic frameworks directly from a metal oxide.

Belenguer et al. [24] demonstrated the reversibility and thermodynamic control in covalent mechanosynthesis by using the base-catalyzed metathesis of aromatic disulfides as a model reaction. This approach enables a solvent-free synthesis, thereby directly leading to adduct-free alane, as reported by Hlova et al. [51]. Mechanochemical and vapour-mediated reactions have been monitored by powder X-ray diffraction and IR-ATR methods, respectively [52]. Pisk et al. [52] studied effective methods for the synthesis of hydrazones, quinazolines, and Schiff bases using a chemometric approach. The chemometric analysis of these data using principal component analysis provided insight into the reaction profiles and reaction times.

Other influential work in this area includes Balema et al. [53], Gajović et al. [54], Pommerin et al. [55], Ahmad et al. [56], and Noh et al. [57]. In conclusion, mechanochemical synthesis presents a versatile and advantageous alternative for preparing hydroxyapatite and diverse materials. This approach offers reduced reaction times, energy efficiency, environmental benefits, and unique reaction control, opening doors for applications in biomedicine, energy storage, catalysis, and beyond.

2.2.2. Sintering

Sintering is a crucial step in the fabrication of various biomaterials, as it allows the consolidation of powders into dense, high-strength structures with tailored properties [26]. Several sintering methods have been developed to optimize the characteristics of biomaterials, including solid-state sintering, spark plasma sintering, and sol–gel synthesis.

Solid-state sintering is a traditional technique that offers versatility for synthesizing diverse biomaterials like Ni/YSZ cermets [25], magnesium silicide [27], and HAp [26]. It leverages heat to promote atomic diffusion between particles, ultimately leading to densification and grain growth [54]. In a study by Pramanik et al. [26], high-strength HAp was successfully synthesized using a solid-state sintering process. The HAp was mixed with β-tricalcium phosphate (β-TCP) and sintered to form a suite of biphasic calcium phosphate (BCP) materials with varying HAp/β-TCP ratios [58]. While relatively simple and cost-effective, solid-state sintering often requires high temperatures and extended processing times, potentially inducing undesirable grain growth and compromising mechanical properties [26].

Spark plasma sintering (SPS) is a more advanced sintering method that employs pulsed electrical currents for rapid heating and consolidation of powders. It has been successfully applied to fabricate magnesium silicide [27] and Ni/YSZ cermets [25], resulting in significantly improved electrical properties compared to conventional methods. Compared to solid-state sintering, SPS achieves densification at lower temperatures and shorter durations, leading to finer microstructures and enhanced mechanical properties [27]. However, the relatively high cost and limitations for large-scale production pose challenges for its wider applicability.

Sol-gel synthesis is a versatile, low-temperature method for the preparation of various biomaterials, including zinc aluminate [19] and calcium hydroxyapatite (CHAp) [20]. The process involves precursor mixing in a solvent, followed by gel network formation and subsequent heat treatment to remove the solvent and induce densification. Grigoraviciute-Puroniene et al. reported an environmentally friendly approach using food products as calcium and phosphorus sources for CHAp synthesis [19]. While offering superior control over particle size and composition [19], sol–gel synthesis may involve multiple processing steps and potentially utilize hazardous solvents.

The selection of an optimal sintering technique hinges on the specific application requirements, carefully considering factors like cost, processing time, and desired material properties. Solid-state sintering offers cost-effectiveness but demands high temperatures and long processing times [26]. Spark plasma sintering delivers rapid densification and fine microstructures but may not be suitable for large-scale production [27]. Sol-gel synthesis provides superior control over composition and particle size but involves multiple steps and potentially hazardous solvents [19]. By understanding the distinct advantages and limitations of each technique, researchers can make informed decisions to produce biomaterials with tailored properties for diverse biomedical applications.

2.3. Biomimetic synthesis

2.3.1. Biomineralization

Living organisms possess the remarkable ability to create intricate mineral structures through biomineralization, sparking inspiration for the development of innovative materials in biomedicine and engineering. A central focus within this field is the synthesis of HAp, a key component of bone and tooth enamel, holding promise for tissue repair applications [59]. Recent advancements have enabled the fabrication of diverse biominerals, including HAp, calcium silicate, and various carbonates [60], offering a wider palette of functionalities.

Studies, such as by Palmer et al. [59], have successfully replicated bone and enamel mineralization processes in synthetic environments, leading to the formation of 3D HAp crystals, paving the way for potential therapies for tissue regeneration [30]. Tailoring properties for specific applications necessitates precise control over size, morphology, and ultrastructure of the biominerals. Ren et al. [61] demonstrated a systematic approach to hydrothermally grow carbonated apatite nanoparticles with tunable size and morphology, contributing to our understanding of biomineralization mechanisms. Lin et al. [62] reviewed the state-of-the-art synthesis of CaP crystals, including diverse shapes and sizes, from nano- to macroscale, and three-dimensional structures mimicking biological bone and tooth. Biomimetic nanoparticle templates have also been explored to influence mineralization rates and particle size/morphology. Vasconcellos et al. [63] studied templates with mixed monolayers of uncharged polyethylene glycol (PEG) molecules and highly charged polynucleotide and amino acid molecules. Their work provided insights into enhancing calcium phosphate mineralization using biomimetic systems.

Beyond biomedical applications, biomineralization principles are being translated to other fields. The integration of computational simulation and experimental fabrication has led to the development of novel biomaterial-based nanoporous membranes for water purification [64], showcasing the potential of this approach for addressing environmental challenges.

In conclusion, biomineralization research has yielded significant progress in both the synthesis and understanding of biominerals, unlocking their potential for applications ranging from tissue repair to water purification. By harnessing nature's blueprints, researchers are able to design materials with unique properties and structures, propelling advancements in various fields of science and engineering.

2.3.2. Template-assisted synthesis

Template-assisted synthesis represents a powerful tool for crafting biomimetic materials. By leveraging templates to direct the organization and deposition of desired materials, researchers achieve controlled growth of intricate nanostructures. This section delves into notable works within this field, exploring their methodologies, achievements, and limitations.

Spoerke et al. [30] pioneered an in vitro biomineralization process to cultivate 3D HAp structures within biomimetic systems [28]. This holds

significant promise for therapeutic applications in tissue repair, particularly concerning bone and enamel mineralization. Sundrarajan et al. [29] championed a green approach to synthesize HA nanoplates, utilizing *Moringa oleifera* flower extract and an ionic liquid [30]. This biomimetic strategy not only yielded desirable nanostructures but also adhered to green chemistry principles. Aiming to replicate the natural intrafibrillar mineralization process, Ping et al. [31] designed a multifunctional protein, (MBP)-BSP-HAP [31]. This protein, inspired by bone sialoprotein (BSP) and hydroxyapatite binding protein (HAP), guided the organization of intrafibrillar mineralization, showcasing the potential of protein-based templates in biomimetic synthesis.

Wu et al. [65] developed a two-step method for the in situ synthesis of carbonated HAp layers on enamel slices using acidic amino acids [65]. The resulting rod-like carbonated HAp crystals exhibited a morphology similar to the prisms found in human enamel. Miculescu et al. [66] optimized Rathje synthesis to fabricate biogenic calcium phosphates by adjusting the chemical composition of the reagents used [66]. This work demonstrated the importance of controlling the synthesis parameters in producing biomimetic materials. Fang et al. [67] synthesized biomimetic hydroxyapatite microspheres (GHM-S) from nanocrystalline hydroxyapatites to investigate their therapeutic potential and effects on bone regeneration [67]. This template-assisted synthesis contributed to the development of novel biomaterials for bone tissue engineering applications.

Naudot et al. [68] evaluated the bone regeneration properties of a composite 3D honeycomb structure created via electrostatic template-assisted deposition [68]. The process involved the alternate deposition of electrospun polycaprolactone (PCL) nanofibers and electrosprayed HAp nanoparticles on a honeycomb micropatterned substrate. The resulting composite showed promising results for bone regeneration applications.

Template-assisted synthesis has emerged as a valuable tool for developing biomimetic materials, facilitating controlled growth and organization of nanostructures. However, optimizing synthesis parameters and understanding the intricate interactions between templates and materials remain ongoing challenges. Further research is necessary to fully unlock the potential of this approach in advancing novel biomaterials and their applications.

2.4. Comparison of synthesis methods and their impact on HAp properties

HAp and its composites exhibit diverse properties dependent on the chosen synthesis method. This text explores various approaches and their distinct outcomes.

One study incorporated ultra-fine glass fibers (UFGF) and nano-hydroxyapatite (nano-HAp) synthesized hydrothermally into polymethylmethacrylate (PMMA) bone cement (BC) [69]. This resulted in antibacterial and antifungal activities, assessed using the microplate Alamar Blue assay (MABA) method [70]. In contrast, Sporysh et al. [71] adopted a simpler room-temperature mixing approach. Infrared spectra analysis revealed interactions between components, indicated by significant distortions and shifts in characteristic absorption bands. Another study utilized aqueous solutions of $CaCl_2{\cdot}2H_2O$ and $Na_2HPO_4{\cdot}12H_2O$ to prepare HAp nanorods and amorphous calcium phosphate (ACP) nanoparticles for zinc delivery [72].

Conventional synthesis methods, such as physical blending, have also been compared with in situ copolymerization methods for the production of organic–inorganic nanocomposite materials [73]. Goto et al. synthesized TiO_2-modified HAp with various morphologies through hydrothermal treatment using urea decomposition at 160 °C for 6 h [74]. Nano-bioceramic powders have been produced from organ pipe red coral (*Tubipora musica*) using two different chemical conversion methods, offering alternative synthesis routes to the common hydrothermal method [75]. Yu et al. [76] aimed to compare the characteristics of alginate (Alg)/hyaluronic acid (HA) hydrogels, which mimic cartilage, with alginate (Alg)/hydroxyapatite (HAp) hydrogels, which mimic subchondral bone.

In conclusion, HAp and its composites offer a wide range of potential applications, each requiring careful selection of a suitable synthesis method based on desired properties. Each approach presents unique advantages and limitations, underscoring the critical role of method choice in optimizing material performance.

3. Properties of hydroxyapatite

3.1. Structural and compositional properties

HAp holds immense potential as a biomaterial due to its biocompatibility, osteoconductivity, and resemblance to the inorganic component of bone and teeth. However, its structural and compositional properties significantly impact its performance in various biomedical applications. Researchers like Ansorge et al. [77] are developing models to quantitatively predict how these parameters influence HAp's mechanical properties, offering valuable insights for optimization. Additionally, combining HAp with other materials offers a promising avenue for performance enhancement. For example, Unosson et al. [78] utilized a combinatorial approach to manufacture and test a single sample containing a binary Ag-Ti oxide gradient, aiming to design a structure with adequate Ag(+) release while maintaining biocompatibility.

Beyond pure HAp, understanding the intricate hierarchical structure and functionalities of natural bone is crucial for biomimetic material development. Machado et al. [79] highlight this by designing biocompatible and fluorescent HAp nanoparticles for cell imaging, meticulously investigating their structural, compositional, and morphological properties to ensure biocompatibility. Similarly, Bødker et al. [80] employ statistical mechanics and topological constraint theory to predict the dependence of glass transition temperature and superstructural units on composition in various materials, including HAp. Further pushing the boundaries, Luo et al. [81] present a biomimetic scaffold for bone tissue engineering by co-electrospinning a structural/compositional gradient nano-microfibrous mesh using silk fibroin-poly(ε-caprolactone) and PCL fibers.

In conclusion, HAp's performance in biomedical applications hinges on its structural and compositional features. Understanding and manipulating these properties, as exemplified by the presented research, paves the way for advanced materials with improved mechanical strength, antibacterial activity, and biocompatibility, ultimately leading to better medical solutions.

3.1.1. Crystal structure

The crystal structure of HAp is an intricate dance of atoms, dictating its physicochemical and mechanical properties. The hydroxyapatite potential model derived in the work of de Leeuw [82] accurately reproduces experimental properties and relative enthalpies of formation and is further validated by Density Functional Theory (DFT) calculations of fluoride defects in bulk hydroxyapatite.

Beyond the pure mineral, organic modulators like collagen and DMP1 exert their influence on crystal formation [83]. Here, computational tools come to the rescue, offering atomistic insights into complex structures and processes that evade traditional techniques. De Leeuw [84] combined complementary computational techniques to investigate several topical issues relevant to hydroxyapatite in biomaterial applications, including the bulk and surface structures of the pure material, the structure and location of carbonate impurities in the lattice, the uptake of fluoride and its effect on hydroxyapatite dissolution, and crystal growth inhibition by citric acid.

Ag-doped nanocrystalline hydroxyapatite has been synthesized using a method proposed by Ciobanu et al. [85]. In contrast, iron-doped HA was synthesized via a simple ion-exchange procedure and characterized thoroughly for crystal structure and phase purity using X-ray diffraction, energy-dispersive X-ray spectroscopy, inductively coupled plasma atomic emission spectroscopy. Fourier transform infrared spectroscopy

[86]. Lin et al. [87] provided a comprehensive discussion of the key properties of HAp, including chemical composition, crystal structure and ion substitution, crystal growth kinetics and preferred orientation, charge distribution of the crystal faces, general aggregates of the crystals in the synthesis process, and the relationship between the structures and properties.

Beyond these highlighted works, further research has shed light on crucial aspects of HAp's crystal structure. Zahn et al. [88] explored the HAp-water interface computationally, while Qin et al. [89] focused on tailoring the collagen-HAp interface for improved mechanical properties. Xu et al. [90] investigated the correlation between carbonate distribution and mechanical properties in enamel, and Hunter [91] delved into the role of osteopontin in HAp formation modulation. These collective efforts have illuminated the intricate relationship between HAp's crystal structure and its diverse applications in the realm of biomaterials. By unlocking the secrets of its structure, researchers pave the way for designing advanced materials with tailored properties, ultimately leading to breakthrough advancements in biomedicine and beyond.

3.1.2. Chemical composition

The chemical heart of a biomaterial, like hydroxyapatite, holds the key to its physical and mechanical properties. Researchers have employed diverse methodologies to unlock this information and tailor biomaterials for specific uses.

Weltje [92] demonstrated the consistency of conceptual models of sediment provenance with numerical-statistical models such as linear mixing models and compositional linear models. Hall et al. [93] directly imaged nanomechanical and chemical gradients across cross-sections of an organosilicon coating fabricated via microwave plasma-enhanced chemical vapor deposition (PECVD). These studies contribute to understanding the relationship between compositional and mechanical properties in biomaterials. Karacan et al. [94] mapped the ultimate analyses parts of the Springfield coal from an Indiana section of the Illinois basin, USA, using sequential Gaussian simulation of isometric log-ratio transformed compositions. This approach can potentially be applied to study compositional variations in biomaterials, providing valuable information for material optimization. Machado et al. [95] designed biocompatible and multicolour fluorescent hydroxyapatite nanoparticles for cell-imaging applications and provided a detailed description of structural, compositional, and morphological analysis, as well as cytotoxicity assays. This study highlights the importance of understanding the chemical composition of biomaterials for their safe and efficient use in biomedical applications.

Luo et al. [81] fabricated a structural/compositional gradient nano-/microfibrous mesh by co-electrospinning using silk fibroin-poly(ε-caprolactone) (SF-PCL) nanofibers and PCL microfibers. This research showcases the potential of gradient compositional structures for the development of advanced biomaterials with tailored properties. Großwendt et al. [96] investigated the impact of the allowed chemical composition range of AISI 316L stainless steel on its processability in additive manufacturing and the resulting part properties. This work underscores the significance of understanding and controlling the chemical composition of materials in additive manufacturing processes.

Beyond biomaterials, the influence of composition extends to broader fields. Matsubara et al. [97] demonstrated the inheritance of compositional information in a general class of autocatalytic chemical systems subject to serial dilution, highlighting the importance of understanding compositional heredity in the context of prebiotic compartments. Other influential studies in understanding the relationship between compositional properties and material behavior include Blaszczyk-Lezak et al. [98] on the dependencies of silicon carbonitride film properties, Billingsley et al. [99] on hydrocarbon fuel compositional variability for aerospace propulsion systems, and McKee et al. [100] on the characterization of toxicological hazards of hydrocarbon solvents.

These collective efforts illuminate the fundamental principle that a material's chemical fingerprint dictates its behavior. By deciphering this code, researchers are unlocking the potential to design biomaterials and other materials with precisely tailored properties, paving the way for advancements in diverse fields.

3.2. Mechanical properties

3.2.1. Elastic modulus and hardness

Determining the suitability of biomaterials for diverse applications hinges critically on their mechanical properties, such as elastic modulus and hardness. Nanoindentation emerges as a potent tool for evaluating these properties across a spectrum of materials, encompassing bioceramic powders and functionally graded coatings [101]. Notably, Kumar et al. [101] employed nanoindentation with a Berkovich indenter to measure hardness and elastic modulus in sintered bioceramics, refining the analysis of load–displacement data [32].

Nath et al. [102] demonstrated that the incorporation of both bioinert and bioactive ceramic fillers considerably enhances the stiffness and hardness of high-density polyethylene (HDPE), thereby improving its mechanical properties and biocompatibility. Furthermore, Saber-Samandari et al. [103] explored the utility of nanoindentation in analyzing coating thickness variations, offering deeper insights into their mechanical behavior. The thermal stability of HDPE is effectively augmented by nano-hydroxyapatite (nHA) fillers, as evidenced by thermogravimetric analysis and heat deflection temperature measurements [104]. Abere et al. [105] investigated the impact of reinforcing HAp with alumina (Al) and chitosan nanofiber (CH) to enhance its load-bearing capacity. Sun et al. [106] delved into the mechanical properties of deproteinized bone and cortical bone with varying water content using nanoindentation experiments, yielding valuable knowledge about their behavior.

From a practical standpoint, Pandey et al. [107] exemplified the role of carbon nanotube (CNT) reinforcement with ceria (CeO_2) and silver (Ag) in HAp on titanium alloy (TiAl6V4) substrate, achieved through plasma-spraying. This study underscores the potential for improved mechanical properties in HAp-based materials through the inclusion of diverse reinforcements. Additional noteworthy works include Gross et al. [108], Wu et al. [109], and Majdi et al. [110].

In conclusion, assessing the elastic modulus and hardness of biomaterials is of paramount importance in determining their suitability for various applications. Nanoindentation techniques offer invaluable insights into these mechanical properties, while the incorporation of specific reinforcements can enhance their performance for targeted uses.

3.2.2. Fracture toughness

In the realm of load-bearing biomaterials, fracture toughness reigns supreme. It defines a material's ability to resist crack initiation and propagation under stress, directly impacting its suitability for demanding applications. Researchers have undertaken numerous studies to understand and improve this critical property. Kumar et al. [111] examined the microstructure and mechanical properties of spark plasma-sintered zirconia-hydroxyapatite (HAp) nano-composite powders. The study revealed the presence of HA, tricalcium phosphate (TCP), zirconia (t- and c-ZrO_2), and $CaZrO_3$ in the powders and sintered compacts.

Balani et al. [112] investigated the fracture toughness of multi-walled carbon nanotube (CNT) reinforced HAp coatings, produced using plasma spraying. They observed a 56 % improvement in fracture toughness and a 27 % enhancement in crystallinity. Additionally, the biocompatibility of these coatings with human osteoblast hFOB 1.19 cells was established. Thurner et al. [113] suggested that reduced fracture toughness in the osteopontin-deficient bone matrix could contribute to bone fragility, emphasizing the importance of non-collagenous proteins. Bose et al. [114] demonstrated that the mechanical properties of HAp compacts, including compressive strength, hardness, and indentation fracture toughness, increased with a decrease in grain size. Lahiri

et al. [115] proposed boron nitride nanotube (BNNT) reinforced HA as a novel composite material for orthopaedic implant applications, while Zimmermann et al. [116] reported that age-related structural changes significantly degraded the fracture resistance of bone over multiple length scales.

Liu et al. [117] offer a broader perspective, highlighting the importance of mimicking nature's intricate hierarchical structures in bone for achieving superior load-bearing capacity. This biomimetic approach holds immense promise for future advancements in bone tissue engineering.

In conclusion, the quest to unveil and improve fracture toughness in biomaterials remains a key priority for researchers. By deciphering the underlying mechanisms and exploring innovative material combinations, we pave the way for the development of stronger, more reliable biomaterials essential for orthopaedic and other load-bearing applications.

3.3. Biological properties

3.3.1. Biocompatibility

The successful implementation of any biomaterial hinges on its biocompatibility, which requires the material to foster cell adhesion, proliferation, and seamless integration with the host tissue, all while evading adverse effects and immune responses [118]. This section delves into the findings of multiple studies that have assessed the biocompatibility of diverse HAp-based materials and composites.

Huang et al. [118] investigated the influence of $CaO\text{-}SiO_2\text{-}P_2O_5$-based bioglass on zirconia-toughened hydroxyapatite (ZTA) materials. They found that the binary materials exhibited good biocompatibility, demonstrating the potential of ZTA for bone replacement applications. Evis et al. [119] provided a comprehensive review of nanosize hydroxyapatite doping with various ions, focusing on their synthesis methods, biocompatibility, and physical, microstructural, and nanostructural properties. Shahoon et al. [120] compared the biocompatibility of nano-silver and hydroxyapatite nanoparticles on L929 fibroblast cells, demonstrating that both materials exhibit acceptable biocompatibility levels for their potential use in biomedical applications. In a study by Kumar et al. [121], HAp-Ti-based bulk composites were processed to improve fracture toughness and strength without compromising biocompatibility, demonstrating the potential of these composites for bone tissue engineering applications.

Turlybekuly et al. [122] examined the biocompatibility and antibacterial properties of multiphase nanocomposite materials based on HAp-Alg-ZnO (hydroxyapatite-sodium alginate-biphasic zinc oxide) and HAp-ZnO (hydroxyapatite-zinc oxide). The synthesized materials showed promising biocompatibility and antibacterial properties, indicating their potential use in orthopaedic and dental applications. Ying et al. [123] prepared a homogenously dispersed nano-hydroxyapatite (nHAp) colloidal solution using a co-precipitation method to reinforce chitosan. The resulting composite exhibited excellent biocompatibility, opening up possibilities for bone repair and regenerative medicine applications. Nica et al. [124] developed novel antibacterial coatings containing hydroxyapatite nanoparticles doped with two different concentrations of samarium (5SmHAp and 10SmHAp) using the dip coating method. These coatings demonstrated promising biocompatibility and anti-biofilm properties. Malysheva et al. [125] demonstrated the potential of fluorapatite and hydroxyapatite-containing composite scaffolds to stimulate the early stages of mesenchymal stem cells' osteoblast differentiation. These findings highlight the importance of biocompatibility in the development of novel biomaterials for bone tissue engineering and regeneration applications.

In conclusion, biocompatibility is a critical aspect of the successful integration of biomaterials into host tissue. Various hydroxyapatite-based materials and composites have shown promising biocompatibility, making them suitable candidates for bone tissue engineering and regeneration applications.

3.3.2. Bioactivity and osteoconductivity

Bioactivity and osteoconductivity are two cornerstones for successful bone tissue engineering biomaterials, as they directly influence bone formation and integration with host tissue. Researchers have employed innovative materials and fabrication techniques to further enhance these critical properties.

Shinzato et al. [126] compared the mechanical properties and osteoconductivity of a newly designed bioactive bone cement (GBC) containing $MgO\text{-}CaO\text{-}SiO_2\text{-}P_2O_5\text{-}CaF_2$ glass beads with two other types of cement: AWC, containing apatite- and wollastonite-containing glass–ceramic (AW-GC) powder, and HAC, containing sintered HAp powder. The study revealed that GBC exhibited superior osteoconductivity compared to AWC and HAC, demonstrating its potential for orthopaedic applications. Nakashima et al. [127] developed a novel chelate-setting HAp cement based on the chelate bonding of inositol hexaphosphate (IP6). This chelate-setting HAp cement exhibited improved bioactivity, offering a promising option for bone regeneration applications.

Tsai et al. [128] utilized a soul-gel route and electrospinning technique to prepare HAp-CaO composite nanofibers that mimicked the three-dimensional structure of the natural extracellular matrix. The fabricated nanofibers exhibited enhanced bioactivity, making them suitable candidates for bone tissue engineering.

Sundarabharathi et al. [129] synthesized biocompatible and bioactive lanthanum (La^{3+})/strontium (Sr^{2+}) dual ion-doped HAp nanomaterials using a soul-gel method. The dual ion-doped HA showed improved bioactivity and cytocompatibility compared to undoped HA, suggesting their potential for use as bone substitutes[130].

Other noteworthy studies include Cho et al. [131] exploring the bioactivity and osteoconductivity of biphasic calcium phosphates and Nathanael et al. [132] investigating hydroxyapatite/titania bionanocomposites for their multifunctional properties. Both studies contribute valuable insights into the potential of these materials for bone tissue engineering applications.

Collectively, these studies underscore the significance of developing novel biomaterials and fabrication techniques to improve the bioactivity and osteoconductivity of bone tissue engineering materials. By tailoring their composition, structure, and properties, researchers can optimize their performance in bone regeneration and integration with host tissues.

3.4. Modifications to improve HAp properties

3.4.1. Doping

HAp, prized for its bioactivity and biocompatibility, finds extensive use in bone grafts and implants. However, its full potential remains untapped. Doping with various ions offers a promising avenue to elevate both its mechanical and biological performance.

This targeted manipulation can enhance HAp's biological properties, bolstering osteoconductivity, and simultaneously improve its mechanical robustness, increasing hardness and fracture toughness. Research efforts explore these possibilities. For instance, Li et al. [133] observed a reduction in hole mobility alongside decreasing pressure in doped materials. Furthermore, Wang et al. [133] investigated the crystallization and infrared radiation properties of iron ion-doped cordierite glass-ceramics in the $MgO\text{-}Al_2O_3\text{-}SiO_2$ system. They observed a change in the infrared radiation property upon doping with different contents of Fe_2O_3.

Beyond HAp, the impact of doping extends to other fields. Guo et al. [134] employed a duplex surface modification method to improve the surface and mechanical properties of porous poly(l-lactic acid) (PLLA) scaffold [135]. Zhao et al. [136] demonstrated that doping transition metal oxides (TMO) on organic semiconductors (OS) could form a two-layer structure, where interface mixing is minimized [156]. In contrast, doping OS on TMO resulted in a doping-layer structure due to the diffusion of TMO into the OS. Chen et al. reported a material with

excellent nonflammability, liquid repellency, high thermal stability, and self-cleaning properties [136]. In a study by Wang et al., doping layered double hydroxides (LDH) with high-valence state foreign metal provided a theoretical basis for enhancing the electrochemical oxygen evolution reaction (OER) activity [137]. Further prominent contributions in this realm include works by Shiraishi et al. [153], Huang et al. [138], and Xue et al. [139].

In conclusion, the strategic doping of HAp holds immense potential for significantly improving its mechanical and biological properties, rendering it an even more attractive material for diverse biomedical applications. However, meticulous optimization of doping concentration, ion type, and method remains crucial to achieve the desired performance enhancements.

3.4.2. Composite materials

Composite materials represent a cornerstone in enhancing the mechanical, tribological, and water absorption properties of HAp [140]. Researchers have explored diverse fabrication techniques and processing steps to improve the overall performance of HAp-based composites by combining HAp with various materials..

For evaluating load transmission, Pezzoli et al. [141] employed reflection photoelasticity, a valuable method for investigating distal-extension removable partial dentures that offers insights into the mechanical properties of HAp composites. Finite element analysis (FEA) has also proven instrumental in understanding the feasibility and shape control of these materials, as demonstrated by Wen et al. [142]. Through FEA, researchers can predict the structural behavior and shape control of HAp composites during manufacturing. Moving beyond static assessments, Blancas et al. [143] proposed the Differential Dynamic Index (DDI) for dynamic evaluation of HAp composites' sustainability. This method incorporates both static and dynamic components, enabling researchers to track the sustainability progress and compare it to other materials.

Understanding the consolidation mechanisms is crucial for rapid manufacturing of thermoplastic composites, as highlighted by Slange [144]. Their study emphasizes that the final quality of HAp composites depends on various factors throughout the entire processing chain. Addressing sustainability concerns, Vincent [145] proposed a recycling route for continuous-fibre thermoplastic composites, involving shredding, sieving, mixing, and compression moulding, potentially adaptable to HAp composites.

For broader insights into properties and production methods, Ayogwu et al. (2023) offer a comprehensive review of organic reinforced brake pad composites, which share similarities with HAp composites in terms of properties and applications [140]. In the context of information security, Fei et al. [146] utilized BAN logic for the access control solution of ndn, which can potentially be applied to protect sensitive information related to the development of HAp composites.

Decision-making for HAp composite material allocation during emergencies can be aided by Fang et al.'s [147] time-series-based evidential reasoning approach for emergency material reserve location selection. Furthermore, Li et al. [148] introduced a novel graph contrastive learning method, GeomGCL, which utilizes molecule geometry across 2D and 3D views, potentially applicable to understanding HAp composite molecular structures and predicting their properties. Lastly, Guo et al. [149] studied learning constitutive models from microstructural simulations using a non-intrusive reduced basis method with geometrical parameterizations. This method can be employed to develop constitutive models for HAp composites, considering various geometrical factors.

In conclusion, composite materials significantly enhance the properties of HAp. By incorporating various materials, methods, and tools, researchers can optimize the performance of HAp composites for diverse applications, ensuring their sustainability and effectiveness.

4. Applications of hydroxyapatite in biomedical engineering

4.1. Orthopedic applications

4.1.1. Bone graft substitutes

Bone graft substitutes (BGS) have emerged as a valuable alternative to traditional autografts and allografts in orthopedics due to their ability to overcome limitations such as donor site morbidity and immune rejection [150]. HAp with its biocompatibility, osteoconductivity, and similarity to natural bone mineral, has been extensively studied and employed as a BGS material..

Recent research highlights the versatility and potential of HA-based substitutes:

- Growth factor application: Wang [151] demonstrated that exogenous basic fibroblast growth factor (bFGF) enhances bone formation in both traditional grafts and HAp substitutes, suggesting its potential to improve healing outcomes.
- Macroporous structures: Sepulveda et al. [152] successfully synthesized macroporous HAp structures that promote new bone formation in vivo, indicating their promise for clinical applications.
- Injectable composites: Low et al. [153] reviewed the advantages of calcium phosphate (CP)-based composites, including HAp, as injectable bone substitutes. These materials offer ease of application and adaptability to complex bone defects.
- Tailored properties: Adnen et al. [154] showed how calcination temperature significantly influences the properties of HAp derived from Setiu coral, emphasizing the importance of optimizing processing parameters for desired outcomes.
- Antibiotic incorporation: Oezel et al. [155] demonstrated that antibiotic-infused calcium sulfate/hydroxyapatite (CAS/HAp) promotes bone healing and reduces inflammation in an animal model, suggesting its potential to combat infection while promoting regeneration.

In summary, HAp has shown significant potential as a bone graft substitute in orthopaedic applications, owing to its biocompatibility, osteoconductivity, and ability to be tailored to various requirements. Further research and development in this area are expected to lead to the continued advancement of hydroxyapatite-based BGS materials and their successful integration into clinical practice.

4.1.2. Coatings for metallic implants

Metallic implants boast excellent mechanical properties and biocompatibility, making them crucial in orthopaedics. However, promoting osseointegration and preventing infections remain significant hurdles. HAp coatings have emerged as a promising solution due to their mimicry of natural bone's inorganic component, facilitating bone-implant interface formation [156]. Extensive research has explored the crystallinity and phase composition of plasma-sprayed HAp coatings, crucial for understanding their behavior and optimizing them for orthopaedic use [157]. An in-depth analysis of HAp-coated Ti6Al4V highlights film synthesis, mechanical testing, simulated body fluid assessments, and biocompatibility can be found here [156].

Magnesium (Mg) alloys, while highly biodegradable and possessing bone-like mechanical properties, suffer from rapid corrosion in physiological environments [158]. To address this, calcium phosphate coatings have been deposited using solution chemistry techniques, improving corrosion resistance and biocompatibility [158]. Similarly, a simple chemical conversion process applied to ZK60 Mg alloy substrates yielded HA coatings with enhanced in vitro corrosion resistance and cytocompatibility for orthopaedics [159]. Microwave-assisted coating technology has also been employed on Mg alloy AZ31 to improve corrosion resistance and biocompatibility by depositing calcium-deficient hydroxyapatite [160]. Furthermore, electrodeposition was used to prepare silver and zinc-modified bioactive calcium phosphate

layers on Ti6Al4V to enhance the implant's antimicrobial properties [161].

Various metallic biomaterials like stainless steel, cobalt-chromium alloys, and titanium alloys have been explored for plasma-sprayed HAp coatings [162]. Each material offers distinct advantages and disadvantages in terms of biocompatibility, mechanical properties, and corrosion resistance. Understanding the unique characteristics of each metallic biomaterial and their interactions with HA coatings is crucial for optimizing their performance in orthopaedic applications [162].

HAp coatings have demonstrated significant potential in improving osseointegration, corrosion resistance, and biocompatibility of metallic implants. Further research into advanced coating techniques, the use of composite coatings, and the incorporation of antimicrobial agents holds promise for further enhancing the performance of metallic implants in orthopaedic applications [163–165].

4.2. Dental applications

4.2.1. Dental implant coatings

The success of dental implants relies on osseointegration, which is the direct connection between living bone and the implant surface. Various coatings have been developed to improve the biocompatibility and osteoinductive properties of dental implants. This section focuses on the evolution and development of dental implant coatings and their impact on clinical outcomes.

Early studies focused on the influence of implant design, material, coating, diameter, and length on clinical performance and crestal bone height [166]. Meraw et al. [167] investigated the effects of locally applied alendronate sodium on guided bone regeneration around dental implants, demonstrating the potential of local drug delivery to enhance bone healing [168]. Lee et al. [169] evaluated the characteristics of ion beam-assisted deposition coatings on medical implants, confirming their viability for FDA approval [167]. Park et al. [170] developed HAp coating technique using aerosol deposition without post-heat treatment for titanium (Ti) dental implants [169]. The study compared the osteoinductive effect of this new technique with post-heat-treated HAp coatings and uncoated machined surfaces. The results indicated improved biocompatibility and osteoinductivity for the room temperature-coated implants.

Yoo et al. [171] explored the application of recombinant human bone morphogenetic protein-2 (rhBMP-2) onto plasma-sprayed HAp implant surfaces, revealing a significant increase in bone apposition [170]. Wang et al. [172] aimed to deposit bioceramic calcium and phosphorus-containing coatings on sandblasted commercially pure titanium to enhance their bioactive performance [171]. Hashimoto et al. [173] studied the application of fluoridated hydroxyapatite thin film coatings using KrF pulsed laser deposition on titanium plates, providing a new method for preparing bioactive coatings [172]. Macha et al. [174] designed antibiotic-containing biocomposite thin films of polylactic acid (PLA) and coralline-derived HAp as controlled drug delivery systems for the treatment of dental, orthopaedic, and neural implant-related post-operative infections [173]. In a recent study, Łukaszewska-Kuska et al. [175] found that implant surface properties affected implant stability as determined by Osstell and Periotest measurements [174].

In conclusion, dental implant coatings have evolved significantly, with new materials and techniques aimed at improving osseointegration, biocompatibility, and antibacterial properties. Further research is needed to optimize these coatings and develop new strategies for better clinical outcomes.

4.2.2. Periodontal bone regeneration

Periodontal bone regeneration is an essential aspect of dental and oral health, which aims to restore the integrity and function of the periodontal tissues affected by diseases or trauma. Several biomaterials and techniques have been developed for this purpose, with a focus on hydroxyapatite, collagen, polymers, 3D scaffolds, guided bone and tissue regeneration, and bio adhesive gels [176].

Alendronate sodium has been shown to positively influence guided bone regeneration around dental implants [167]. Its local application has demonstrated promising results in *peri*-implant defect regeneration, suggesting potential applications in periodontal bone regeneration [167]. Biomimetic approaches based on enamel matrix proteins (EMPs) have been proposed for the remineralization of initial enamel caries, potentially leading to the development of bionics anti-cariogenic agents [177]. Hydroxyapatite-based bioactive scaffolds have been employed for periodontal tissue regeneration. Researchers have prepared and characterized hydroxyapatite microspheres (HAps), amoxicillin-hydroxyapatite composite (Amx-HAp), and collagen-hydroxyapatite composite (Col-HAp), demonstrating their potential for promoting dental pulp-derived mesenchymal stem cell growth [178].

Furthermore, cell-friendly chitosan-xanthan gum membranes incorporating hydroxyapatite have been designed for periodontal tissue regeneration, showing promise in guided tissue and guided bone regeneration [179]. Innovative peptide sequences have been identified from native proteins that can control hydroxyapatite biomineralization, potentially repairing damaged dental tissues [180]. Meanwhile, researchers have developed a standard stem cell procedure for bio-root regeneration to restore adult tooth function, representing a significant advance in periodontal bone regeneration [181]. Platelet-rich plasma (PRP) has been proposed for various applications in dental and oral surgery, including tooth extractions, periodontal surgery, soft tissues and bone tissue surgery, implant surgery, and bisphosphonate-related osteonecrosis of the jaw (BRONJ) surgery [182]. The use of PRP aims to enhance wound healing and bone maturation, showing promise for periodontal bone regeneration [182].

In conclusion, periodontal bone regeneration research has seen significant progress in recent years, with the development of various biomaterials, techniques, and biomimetic approaches. Hydroxyapatite, collagen, polymers, 3D scaffolds, guided bone and tissue regeneration, and bioadhesive gels have been extensively researched to treat periodontal and *peri*-implant diseases in both natural dentition and dental implants [36]. As our understanding of these materials and approaches deepens, the potential for periodontal bone regeneration continues to expand, offering promising therapeutic options for dental and oral health.

4.3. Drug delivery systems

4.3.1. HAp-based carriers for drug delivery

HAp has emerged as a promising biomaterial for drug delivery applications, owing to its excellent biocompatibility, bioactivity, and osteoconductivity [183]. HAp-based carriers have been extensively investigated for various biomedical applications, including orthopaedics and controlled drug release [184,185].

Govindan et al. [184] developed a gentamicin sulfate (GS) loaded phosphate glass/hydroxyapatite (PG/HA) nanocomposite for orthopaedic applications. The cylindrical-shaped nanocomposite demonstrated the potential for controlled drug release and could be a promising material for orthopaedic applications. HAp and its composites have been explored as anticancer drug carriers [183]. Saber-Samandari et al. [183] provided a comprehensive summary of recent studies focusing on HAp and its composites for anticancer drug delivery, highlighting the unique properties of HAp that make it an effective biomaterial for this application.

Nanostructured hydroxyapatite (nHAp) has also been investigated for controlled drug delivery, drug conjugation, and other biomedical treatments [185]. Mondal et al. [185] provided a historical background of nHAp development and its application potential, emphasizing the advantages of using nHAp in drug delivery systems. Iron oxide-hydroxyapatite (IO-HAp) nanocomposites have been synthesized and characterized for drug delivery applications [186]. Kermanian et al. [186] performed a characterization study of the IO-HAp nanocomposite

using various techniques, demonstrating its potential as a magnetic drug delivery system and for MR imaging. HAp-calcium ferrite (HAp-$CaFe_2O_4$) composites have been developed as drug carriers [187]. Khezerlou et al. [187] prepared a merit carrier consisting of HAp-$CaFe_2O_4$ via a convenient procedure and characterized it using several techniques. This composite showed promise for loading and sustainable release of antibiotics such as amoxicillin.

Other studies have explored the use of HAp-based carriers for drug delivery applications, including cellulose-based nano-biocomposite hydrogels [188], pH-responsive mesoporous HAp nanoparticles for intracellular controlled release of anticancer drugs [189], strontium-substituted HAp nanorods for protein delivery [182], and abalone shells derived biological mesoporous HAp microspheres for drug delivery [190].

In summary, HAp-based carriers offer numerous benefits for drug delivery applications, such as biocompatibility, bioactivity, and controlled release. Various HAp-based composites and nanostructures have been investigated for diverse applications, including orthopaedics, anticancer drug delivery, and antibiotic release. Further research and development in this area will likely lead to the advancement of HAp-based drug delivery systems for various biomedical applications.

4.3.2. HAp coatings for localized drug release

HAp coatings have garnered significant attention in recent years due to their ability to provide localized drug release for various applications, such as dental, orthopaedic, and neural prostheses [174,191]. HAp coatings can be employed as drug carriers, enabling controlled release and minimizing side effects associated with systemic drug administration [192].

One example of a HAp-based drug delivery system is the ionic immobilization of dexamethasone (DEX)-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres on HAp scaffold surfaces, as demonstrated by Son et al. [193]. This system combines the biocompatibility and osteoconductivity of HAp with the controlled release capabilities of PLGA microspheres, providing a promising approach for bone tissue regeneration. Another study by Dubnika et al. examined the use of HAp scaffolds coated with sodium alginate and chitosan for controlled drug delivery, specifically for lidocaine release [192]. The composite materials displayed promising results for dental applications, with potential for other biomedical uses as well.

Additionally, Zhao et al. developed a multifunctional nanocomposite composed of a magnetite nanocrystal core and a mesoporous silica shell (Fe_3O_4@$mSiO_2$), end-capped with pH-stimuli-responsive HAp nano valves for pH-responsive drug release [194]. This system demonstrates the versatility and potential of HAp coatings in targeted drug delivery. Macha et al. designed and tested antibiotic-containing biocomposite thin films of polylactic acid (PLA) and coralline-derived HAp for controlled drug delivery, targeting dental, orthopaedic, and neural implant-related post-operative infections [195]. The combination of PLA and HAp exhibited promising antibacterial properties while maintaining biocompatibility. In a recent study, Karacan et al. evaluated the in vitro efficacy of poly-lactic acid coating incorporating antibiotic-loaded coralline bio-ceramics on Ti6Al4V implants against Staphylococcus aureus [196]. The coating successfully reduced S. aureus biofilm formation while promoting the growth and proliferation of adipose-derived stem cells (ADSCs), demonstrating its potential for use in dental and orthopaedic applications.

Overall, HAp coatings for localized drug release offer multiple advantages, such as biocompatibility, osteoconductivity, and controlled drug delivery [195]. However, further research is needed to optimize these systems and address potential drawbacks, such as drug loading capacity, release kinetics, and long-term stability. Nevertheless, HAp coatings hold great promise for revolutionizing drug delivery in various biomedical applications, with numerous influential studies providing a solid foundation for future research and development [197–200].

4.4. Tissue engineering scaffolds

4.4.1. Porous HAp scaffolds

Porous HAp scaffolds have garnered significant attention for their potential applications in bone tissue engineering and orthopaedic drug delivery systems [201]. In this section, we discuss various methods, materials, and strategies used to create HAp-based scaffolds, evaluating their advantages and disadvantages.

Zhang et al. [202] successfully fabricated a 3-D porous scaffold of surface-grafted hydroxyapatite/poly(lactide-co-glycolide) (g-HAP/PLGA) using the solvent casting/particulate leaching method. The resultant scaffold demonstrated improved interface compatibility, mechanical properties, and biocompatibility, making it an attractive candidate for bone fixation materials. However, the solvent casting/particulate leaching method can be time-consuming and may involve hazardous solvents.

To develop a HAp coated genipin-chitosan conjugation scaffold (HGCCS) with a well-defined HAp nanostructured surface, Wang et al. [203] introduced a simple and controllable approach, which allowed for the construction of a two-level, three-dimensional (3D) networked structure. This scaffold design achieved desired mechanical function and mass transport properties, including permeability and diffusion. Maheshwari et al. [204] fabricated a polymer-ceramic bilayer nanocomposite scaffold based on electrospun polycaprolactone (PCL) / polyvinyl alcohol (PVA) bilayer nanofibers blended with HAp nanoparticles. Electrospinning offers excellent control over fibre diameter and morphology; however, it can be limited by the need for specialized equipment and potential clogging of the spinneret.

Xu et al. [205] developed Ag-loaded strontium hydroxyapatite (SrHAP)/chitosan (CS) porous scaffold (Ag-SrHAP/CS) using freeze-drying and deposition of Ag nanoparticles. This scaffold exhibited enhanced biocompatibility, osteoinductivity, and antibacterial activity, crucial properties for the reconstruction of large bone defects and prevention of implant-associated infections. However, the freeze-drying method may not be suitable for all materials and may require optimization for different composite systems. He et al. [206] prepared composite scaffolds made of polycaprolactone (PCL), and HAp using near-field electrospinning and tested their effectiveness in cell culture with mouse pre-osteoblast cells (MC3T3-E1). Near-field electrospinning allowed for the creation of a novel layer-structured scaffold with large pore sizes suitable for 3D cell culture. However, this method also requires specialized equipment and expertise.

Ofudje et al. [207] explored a novel application of pig bone waste for the synthesis of HAp via heat treatment between 600 and 1000 °C. This approach provided an environmentally friendly and cost-effective method for HAp synthesis, making it an attractive option for large-scale production. However, the use of animal-derived materials may raise concerns about disease transmission and immunogenicity. Zhang et al. [208] used silk fibroin (SF), carboxymethyl chitosan (CMCS), cellulose nanocrystals (CNCs), and strontium substituted hydroxyapatite (Sr-HAp) to prepare biocomposite scaffolds. These scaffolds showed promising biocompatibility and potential for bone tissue engineering applications. However, the development and optimization of composite scaffolds can be complex due to the numerous materials and interactions involved.

4.4.2. HAp-based composite scaffolds

HAp has long been recognized as a promising material for bone tissue engineering due to its biocompatibility, osteoconductivity, and similarity to the inorganic components of natural bone. However, the brittleness and low fracture toughness of HAp have limited its use in load-bearing applications. To overcome these drawbacks, researchers have developed HAp-based composite scaffolds, which combine HAp with various types of bioactive polymers, to improve mechanical properties and biocompatibility while maintaining its osteoconductive potential [209–211].

Zhang et al. [212] fabricated a 3D porous scaffold of surface-grafted HAp (g-HAp) and poly(lactide-co-glycolide) (PLGA) using the solvent casting/particulate leaching method1. This g-HAp/PLGA composite scaffold exhibited improved interface compatibility, mechanical properties, and biocompatibility, making it suitable for bone fixation and tissue engineering applications. Another approach to creating HAp-based composite scaffolds is the combination of nanocrystalline HAp (nHAp) with various bioactive polymers [210]. Sun et al. [210] characterized the biodegradability and biocompatibility of these scaffolds through in vitro and in vivo tests, demonstrating their potential for osteoconduction in orthopaedic surgery.

Pallela et al. [213] prepared a novel scaffold containing chitosan (Chi), HAp derived from Thunnus obesus bone, and marine sponge (Ircinia fusca) collagen (MSCol) using freeze-drying and lyophilization methods. This Chi-HAp-MSCol composite scaffold showed promising biophysical and chemical properties for bone tissue engineering applications [240]. Zhang et al. [212] studied the preparation and characterization of bionic bone structure chitosan/hydroxyapatite scaffolds for bone tissue engineering. They prepared three-dimensional oriented chitosan (CS)/hydroxyapatite (HAp) scaffolds via an in situ precipitation method, which mimicked the natural bone structure [241]. Li et al. [211] developed a PLGA nanofiber scaffold with enhanced biocompatibility by incorporating gelatin/nano-hydroxyapatite bone biomimetics. The composite scaffold, with diameters ranging from nano- to micrometres, was fabricated using the electrospinning technique [211].

In a recent review, Sun et al. [210] summarized the various rapid prototyping (RP) methods used to fabricate nanoscaled HAp-based scaffolds with high porosity for bone regeneration. These methods offer a variety of options for designing HAp-based composite scaffolds with tailored properties for specific applications in bone tissue engineering.

In conclusion, HAp-based composite scaffolds have demonstrated considerable potential for bone tissue engineering applications. Various fabrication methods, such as solvent casting/particulate leaching, freeze-drying, and electrospinning, have been employed to create scaffolds with tailored properties and structures [202,211,213]. Each method has its advantages and drawbacks, and the choice of an appropriate technique depends on the desired scaffold properties, material compatibility, and application requirements. Further research is needed to optimize scaffold fabrication, biocompatibility, mechanical properties, and the potential use of animal-derived materials in HAp-based composite scaffolds.

4.5. Emerging applications

4.5.1. Cancer therapy

Cancer therapy is an area that has greatly benefited from advancements in biomaterials, organic chemistry, bio-engineering, and materials science. The development of novel drug delivery systems, targeted treatments, and combination therapies has opened new avenues for combating cancer more effectively. In this section, we will discuss recent advancements in cancer therapy through the use of biomaterials and their potential applications [214–216].

Magnetic hydroxyapatite nanoparticles have been investigated for their potential in cancer hyperthermia therapy. Hou et al. [214] conducted an in vivo study using a mouse model to assess the performance of these nanoparticles, demonstrating promising results for cancer treatment. Polysulphone/nanohydroxyapatite (PSu/nHAp) composite nanofibers have been fabricated via electrospinning techniques with varying concentrations of HAp (0–8 %) [215]. These nanofibers were found to be effective in vitro as bioactive and biocompatible implants for the post-surgical therapy of gastric cancer [215].

Mengxia et al. [217] developed a dual drug delivery system for the co-release of two anticancer drugs, doxorubicin hydrochloride (DOX) and hydroxy camptothecin (CPT). The PLGA composite nanofiber embedded with DOX@MSNs and CPT@HANPs demonstrated enhanced antitumor efficacy, showcasing the potential of biomaterials in cancer therapy [217]. Enriquez-Navas et al. [218] reviewed treatment methods that aimed to understand and exploit intratumoral evolution to prolong response to therapy [208]. This approach offers a new perspective on how biomaterials and bioengineering can contribute to the development of more effective cancer treatments.

Selenium-doped hydroxyapatite nanoparticles have been investigated for their potential application in bone tumour therapy [219]. Barbanente et al. [219] studied the incorporation and release of selenite ions (SeO) in hydroxyapatite nanoparticles and demonstrated their potential for treating bone tumours. Sun et al. explored the use of ent-kaurane diterpenoids to induce apoptosis and ferroptosis in cancer cells, targeting redox resetting to overcome cisplatin resistance [220]. This approach highlights the potential of utilizing biomaterials for cancer drug resistance management.

In conclusion, biomaterials have paved the way for innovative cancer therapies, with new drug delivery systems, targeted treatments, and combination therapies showing great promise. Further research and development in this area will undoubtedly lead to more effective and personalized cancer treatments, improving patient outcomes and quality of life.

4.5.2. Biosensors

The burgeoning field of biosensors has witnessed significant advancements in recent years, driven by groundbreaking developments in materials science, engineering, and biotechnology. These advancements have culminated in biosensors with enhanced performance, sensitivity, and selectivity, offering new avenues for diagnosing and monitoring diverse medical conditions and environmental factors.

In healthcare, biosensors hold immense potential for disease monitoring and diagnosis. Notably, Rubin [221] explored their potential role in improving patient outcomes following eye surgeries, highlighting their future value in clinical settings. Additionally, a comprehensive review by Zhang et al. [222] sheds light on the diverse applications of biosensors in medical diagnostics and environmental monitoring, showcasing their widespread potential..

Beyond healthcare, biosensors are finding exciting applications in diverse fields. For example, amperometric biosensors with platinum-printed electrodes and immobilized enzymes like alcohol oxidase are revolutionizing wine analysis by enabling rapid and accurate quality assessment [223]. For cyanide detection, hydroxyapatite nanowire array (HANWA) biosensors offer a simple and biocompatible approach [224]. The simplicity and biomolecular-friendly protocol for fabricating these sensors with spatial positioning, large surface area, and abundant adsorbing sites make them suitable for a wide range of applications.

Aptamers and sensors have been developed for pharmaceutical detection, focusing on environmental applications [225]. Yamanaka et al. [226] described the fabrication and surface modification of printed electrodes for sensitive and selective detection of targeted DNA sequences, as well as integration with reverse transcription-polymerase chain reaction (RT-PCR). Carbon nanomaterials have been widely employed in the development of biosensors for pesticide detection [227]. The use of graphene, carbon nanotubes, carbon dots, and other carbon nanomaterials with enzyme and enzyme-free biosensing approaches have shown great potential for improving sensitivity and selectivity.

The future of biosensors is bright, with constant advancements in material science, engineering, and biotechnology fueling the development of even more diverse applications. Key research in this area includes the work of Song et al. [223], Scheller et al. [228], and Viswananthan et al. [229] provides a glimpse into the immense potential of these groundbreaking technologies.

5. Challenges and future perspectives

Despite the substantial promise of HAp in biomedical applications,

particularly dentistry, Table 2 sheds light on potential challenges and limitations that may arise in the coming years. The table also proposes promising techniques to mitigate these limitations and ensure HAp's continued success in this field.

5.1. Limitations of current HAp-based biomaterials

Despite its numerous advantages, HAp utilization in biomedicine faces several challenges. A critical limitation lies in the inherent brittleness and fracture susceptibility of HAp under load-bearing conditions [230]. Hence, enhancing toughness without compromising bioactivity and osteoconductivity remains a crucial objective.

Another challenge lies in the limited availability of natural bone grafts. Ethical concerns have spurred the development of biomimetic synthetic substitutes using calcium-phosphate powders [233]. While these offer promising alternatives, they only partially replicate the healing responses observed with patient-derived autografts, and complete replacements remain elusive. Similar limitations apply to dental implants, where metallic alloys outperform pure HAp coatings in long-term performance. Composite options improve coating durability without compromising protective or biocompatible properties, offering a potential solution [234].

Scaffolds hold immense promise for promoting tissue regrowth after major injuries/surgeries, surpassing traditional replacements like tooth dentures (lasting ~ 20 years) and fusion/welding techniques. However, controlling humidity gradients within scaffolds remains challenging, necessitating design updates, particularly when used internally within the body's interconnected circulatory system. Maintaining sensitive equilibrium balances between oxygen/nutrient uptake through blood vessels is crucial [234].

Drug release remains a critical question for HAp-based scaffolds and coatings, despite their appeal in controlled drug delivery [235]. Studies have shown that morphology (size, shape, porosity) and surface area significantly impact release rates, with porous structures like scaffolds exhibiting higher absorption propensity. This has significant implications for dosage timing, particularly in localized/guided bone-regenerating agents used in orthopedic or maxillofacial surgery, where precise growth factor placement is crucial [236,237]. Predicting and optimizing in vivo kinetics is crucial to ensure targeted drug delivery to specific tissues or organs within defined treatment protocols [238,239].

Additional limitations arise from the biodegradation rates of these scaffolds [240]. While controlled, slow degradation appears promising for long-term healing due to the sustained release of growth factors and mineral formation; inadequate cleaning can lead to adverse effects [241–243]. These include mobilization of heavy metal ions, allergic reactions, and disruption of biological feedback mechanisms [244]. This underscores the need for multidisciplinary collaboration involving chemists, material engineers, and scientists to develop advanced purification methods at the atomic level, without compromising integration [245].

Beyond their potential to promote tissue regeneration after major injuries and surgeries, compared to traditional approaches like dentures (lasting 20 years), scaffolds still face challenges in managing humidity gradients and tissue integration. This necessitates design improvements, especially for internal applications within the body's complex circulatory system, where blood vessels require precise oxygen and nutrient exchange balance [237].

Therefore, cross-disciplinary teams combining engineering and biological expertise are crucial to developing intermediate devices for nanomedicine and therapy advancement. These efforts should involve upgrades in manufacturing platforms like additive processing, focusing on optimizing strength, cell adhesion, degradation rates, and other parameters to create novel breakthrough therapies that overcome current limitations in effective medical delivery [240]. Ultimately, patient-specific needs should guide implant design to ensure stability and success.

Broader adoption of HAp in biomedical applications hinges on cost-effectiveness analyses, particularly for surgical procedures and regenerative treatments [246]. However, cost considerations must not compromise therapeutic efficacy or safety. Despite its advantages, HAp faces limitations. Mechanical properties are a major hurdle, as HAp can be brittle and fracture under load [230]. Enhancing toughness without sacrificing bioactivity or osteoconductivity remains a challenge.

Table 2
Challenges and limitations of HAp.

Sl. No.	Challenges and Limitations	Physical Modification Techniques	Chemical Modification Techniques	Desired Properties	Strategies to Overcome Challenges	References
1	Limited natural bone graft sources	Pore size control	Biomimetic synthesis methods	Bioactivity, osteo-conductivity	Innovations in biomimetic synthesis methods with better precision at the atomic scale	[3,4,8]
2	Control of biodegradation rates	Porosity optimization	Degradable nanophased compound 3D-Printed scaffolds	Controlled biodegradation, efficient drug delivery	Sophisticated machine learning algorithms in tandem with empirical laboratory observations	[5,6]
3	Drug release rate from HAp carriers	Timed-release systems, spatial control of drug-loaded structures	Controlled drug release	Optimized drug delivery, patient-specific dosing	Development of highly porous scaffold systems with controlled degradation/release rates	[11]
4	Inadequate osteointegration	Surface topography modification	Surface functionalization with biomolecules	Enhanced osseointegration	Improve surface properties to promote cell adhesion and bone growth	[13,14]
5	Infection risk at the implant site	Incorporation of antimicrobial agents	Incorporation of antimicrobial agents	Reduced infection rates	Develop HAp materials with antimicrobial properties to reduce infection risk	[16]
6	Hydroxyapatite resorption kinetics	–	Controlled resorption kinetics	Customized degradation rates	Design HAp materials with tunable resorption kinetics for specific applications	[32,231]
7	Thermal stability of HAp materials	Heat treatment	Dopant addition	Enhanced thermal stability	Develop HAp materials with improved thermal stability for various applications	[15,232]
8	Cytotoxicity of HAp-based materials	–	Surface functionalization with biocompatible molecules	Reduced cytotoxicity	Design HAp materials with reduced cytotoxicity to improve biocompatibility	[33,34]
9	Insufficient angiogenesis	Surface topography modification	Incorporation of angiogenic factors	Enhanced angiogenesis	Develop HAp materials that promote angiogenesis to improve tissue integration	[17,18]

5.2. Strategies to overcome challenges

This paper addresses the aforementioned challenges in hydroxyapatite biomaterials by proposing innovative strategies with clinically relevant implications (see Fig. 1). These strategies prioritize a wise balance between enhancing benefits, maximizing convenience, reducing costs, and ensuring patient satisfaction throughout the hospitalization period.

One promising approach involves advanced particle fabrication and modification techniques. These techniques enable the incorporation of additives, ionic substitutions, and organic molecules, leading to real-world functional changes and desirable responses. This allows for tailoring properties to specific applications without compromising initial advantages or hindering scalability for larger production volumes.

Another path forward lies in biomimetic synthesis methods with enhanced atomic-level precision. Creative approaches to mechanical and chemical manipulation might yield novel materials that retain their biological performance while exhibiting improved toughness. However, replicating nature's intricate chemistry and architecture remains a challenge. Researchers are exploring advanced machine learning algorithms in conjunction with real-world laboratory observations to accelerate progress in this area.

Further improvements could stem from degradable nanophased compounds, 3D-printed porous scaffolds, and loaded therapeutic agents. This includes commercially available antibiotics, bone morphogens, proteins, and hemocompatible polymers. Such systems can optimize drug delivery through timed release, strategic placement, and fine-tuned structures. These structures predict degradation and release rates, dynamically respond to adjacent cell signaling networks, and control biodegradation velocity – all crucial factors for implant retention efficiency and avoiding secondary surgeries.

Various innovative strategies have been proposed to address the challenges facing hydroxyapatite biomaterials. The primary objective is to optimize clinical efficacy, improve patient convenience, minimize costs, and maximize patient satisfaction throughout the hospitalization period. This analysis draws upon established literature to outline five promising tactics:

1. Advanced Particle Fabrication and Modification: Sophisticated techniques are being developed to incorporate additives, ionic substitutions, metals, and organic molecules into hydroxyapatite. These advancements lead to tailored material properties for specific applications while preserving initial advantages and enabling scalable production.
2. Enhanced Biomimetic Synthesis: Research efforts are focused on improving biomimetic synthesis methods for enhanced atomic-level precision. Creative approaches to mechanical and chemical manipulation offer the potential to develop novel materials with improved toughness while maintaining their biological effectiveness. However, replicating nature's intricate architecture remains a challenge. Advanced machine learning algorithms combined with real-world laboratory observations are being explored to accelerate progress in this area.
3. Degradable Nanophased Scaffolds and Drug Delivery: Highly porous scaffold systems fabricated using degradable nanophased compounds and 3D-printing technology offer significant promise. These scaffolds can be loaded with various therapeutic agents, such as antibiotics, bone morphogenetic proteins, and hemocompatible polymers. This facilitates optimized drug delivery through controlled release via strategically designed structures. Tailored degradation and release rates dynamically respond to adjacent cell signaling networks, influencing implant retention efficiency and potentially reducing the need for secondary surgeries.
4. Understanding Biodegradation Mechanisms: Further exploration of factors influencing biodegradation velocity, including the role of intermediates, is crucial for optimizing implant longevity. A deeper understanding of these mechanisms will inform the development of biomaterials with improved retention efficiency, potentially reducing the need for secondary interventions.
5. Collaborative Research Efforts: The success of these strategies hinges upon collaborative research efforts. The synergy between material scientists, clinicians, and computational scientists is essential for effectively addressing the challenges and realizing the full potential of hydroxyapatite biomaterials.

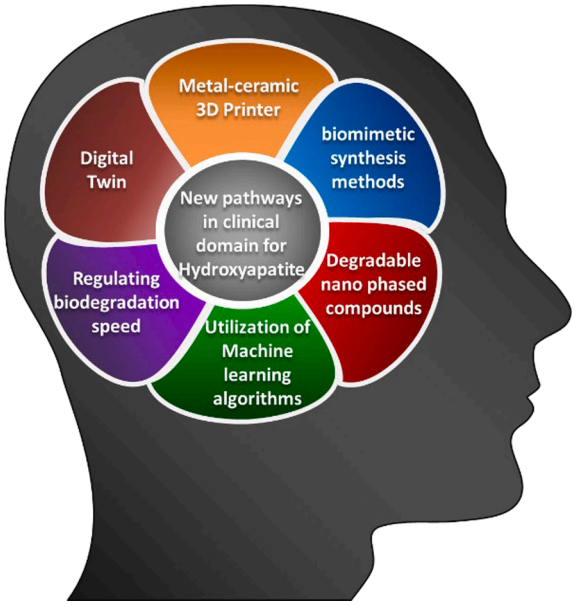

Fig. 1. New pathways in clinical implication for hydroxyapatite.

Conquering the challenges faced by hydroxyapatite biomaterials demands the development and execution of innovative strategies. Recent advancements in advanced particle fabrication techniques, biomimetic synthesis methods, machine learning applications, and the creation of degradable 3D-printed scaffold systems have demonstrated significant potential in enhancing the efficacy of these materials.

By pursuing these avenues, researchers can develop hydroxyapatite biomaterials that are not only clinically effective but also cost-effective, convenient, and patient-centric, ultimately leading to better healthcare outcomes. However, the full potential of hydroxyapatite biomaterials in regenerative medicine and tissue engineering hinges on sustained interdisciplinary collaboration and research.

5.3. Future directions in HAp research and development

The future of HAp research holds immense promise for both academic institutions and industry leaders. Ongoing collaboration and innovation can overcome current limitations and unlock novel functionalities for medical devices and regenerative medicine strategies.

Key areas of advancement include:

- Gene editing refinement: Precise bone regeneration using gene editing techniques could offer improved control over tissue responses after trauma or cancer treatment. Understanding zinc transport and enhancing metalloproteinase activity hold promise for efficient tissue remodeling after cell death. Additionally, incorporating effective free radical scavengers, with careful evaluation of benefits and risks, could enable treatments with positive hypoxic responses.
- Bioengineered constructs: Recent collaborations between academia and industry have led to breakthroughs in merging surface

modification techniques with synthetic genes encoding biomolecules. This has enabled the development of bioengineered tissue patches and "bioprinted scaffolding," paving the way for complex translational therapies using emerging HAp technologies.

- Interdisciplinary teams: Assembling diverse teams of experts from microbiology, genetics, cell biology, material sciences, and physics can facilitate comprehensive research efforts toward developing clinical-grade products. Encouraging commercialization strategies and identifying potential partnerships within the biomedical field can further accelerate the growth of the HAp-based materials industry.

Despite the remaining challenges, researchers are actively exploring innovative approaches to fully realize the potential of HAp-derived materials for medical applications. The rapidly evolving field demonstrates significant progress in enhancing physical transduction properties, opening doors for broader integration of HAp-based materials into routine medical procedures and ultimately benefiting global healthcare.

6. Conclusion

As we conclude our exploration of hydroxyapatite (HAp), a hopeful landscape unfolds. This remarkable biomaterial, with its exceptional bioactivity and biocompatibility, holds transformative potential across various biomedical applications. Diverse synthesis methods, including co-precipitation, sol–gel, mechanochemical, and biomimetic approaches, highlight the multifaceted nature of HAp.

Of particular interest is the needle-like structure of HAp produced through hydrothermal synthesis. This unique morphology introduces a novel approach to synthetic bone creation due to its robust mechanical grip. This distinct feature is reshaping the landscape of biomedical materials, challenging established norms, and revealing new insights into biological mechanisms such as osteoclast attachment and implant osseointegration.

Furthermore, HAp is venturing into uncharted territory in the fight against prostate cancer. The possibility of utilizing nanoscale carriers and enzyme pro-drugs for targeted chemotherapy holds significant promise. These advancements could offer improved and, importantly, more tolerable therapeutic outcomes, protecting healthy cells while focusing on malignant ones.

HAp's potential extends beyond promoting bone growth and enhancing cell adhesion. It exhibits immense promise in pharmaceutical delivery systems and cancer treatment advancements. Early-stage HAp-based implementations showcase promising safety and efficacy profiles, offering renewed hope in the relentless battle against cancer.

However, despite these exciting applications, challenges remain. Key hurdles include balancing mechanical support and biocompatibility in HAp-based scaffolds, maintaining quality control during scale-up, and navigating complex regulatory landscapes. These challenges, however, also illuminate the path forward, emphasizing the need for innovative solutions and continuous research.

The future beckon us to delve deeper into HAp's morphologies and properties, necessitating the use of cutting-edge tools like machine learning algorithms. Implementing these technologies could unveil previously hidden mechanisms, leading to unprecedented precision in medical treatment and delivery.

To unlock the full potential of HAp, a collaborative approach is required from all stakeholders in bioengineering, including manufacturers, academic institutions, hospitals, and governmental agencies. As we embark on this exciting journey, we stand at the precipice of groundbreaking advancements, ranging from augmenting bone growth to revolutionizing cancer therapies. Our unwavering commitment to researching and utilizing HAp not only propels us towards a healthier world but also bestows upon us a future brimming with optimism and possibility.

CRediT authorship contribution statement

Tajammul Hussain M. Mysore: Conceptualization, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. **Arun Y. Patil:** Conceptualization, Data curation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Chandrashekhar Hegde:** Funding acquisition, Investigation, Methodology, Project administration. **M.A. Sudeept:** Investigation, Methodology, Project administration, Software, Visualization. **Raman Kumar:** Data curation, Formal analysis, Resources, Validation, Visualization. **Manzoore Elahi M. Soudagar:** Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **I.M.R. Fattah:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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