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Recent Update on Various Ion-Doped Nanoparticles Applied in Biomedical: Challenges and Future Perspective

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Abstract

In recent years, there has been a significant increase in the utilization of nanoparticles (NPs) for dental applications. A wide range of ion-doped NPs are available for both research and clinical use. These NPs differ markedly from conventional materials due to their unique structures and physicochemical properties. However, the mechanisms underlying the distinctive functions of these nanoparticles remain incompletely understood. This review discusses the fundamental principles of NPs in material science, highlighting their advantages and limitations, based primarily on an analysis of the most cited scientific articles published in international peer-reviewed journals. To address the aims of the study, 22 articles from the MEDLINE (PubMed) database and 145 articles from the Scopus database were systematically screened by PRISMA method. Based on the selected literature, this review examines various aspects of ion doping in dental NPs, particularly focusing on the preparation methods and therapeutic applications of doped hydroxyapatite (HAP). A comprehensive understanding of the physical, chemical, and biological properties of NPs is essential to evaluate their potential benefits and inherent drawbacks. Despite their promising applications in dentistry, NPs do not inherently possess ideal characteristics, particularly regarding biocompatibility and long-term stability in biomedical fields. Further investigations are required to elucidate the cytotoxicity, ion release behavior, and surface modifications of NPs to enhance their clinical performance. Advances in synthesis technologies and characterization methods are expected to overcome current challenges and pave the way for safer and more effective nanoparticle-based dental therapies.

Keywords: *Bone remodeling; doped hydroxyapatite; ions-doped; nanoparticles; regenerative therapy*

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Dalam beberapa tahun terakhir, terjadi peningkatan signifikan dalam pemanfaatan nanopartikel (NPs) untuk aplikasi kedokteran gigi. Beragam nanopartikel yang didoping ion tersedia untuk keperluan penelitian maupun penggunaan klinis. Nanopartikel ini menunjukkan perbedaan yang nyata dibandingkan dengan material konvensional, terutama terkait struktur unik dan sifat fisikokimianya. Namun demikian, mekanisme yang mendasari fungsi khas dari nanopartikel tersebut masih belum sepenuhnya dipahami. Tinjauan ini membahas prinsip dasar nanopartikel dalam ilmu material, dengan menyoroti keunggulan serta keterbatasannya, berdasarkan analisis artikel ilmiah yang paling banyak disitasi dan diterbitkan di jurnal internasional bereputasi. Untuk memenuhi tujuan studi, sebanyak 22 artikel dari basis data MEDLINE (PubMed) dan 145 artikel dari basis data Scopus disaring secara sistematis menggunakan metode PRISMA. Berdasarkan literatur terpilih, tinjauan ini mengkaji berbagai aspek pendopingan ion pada nanopartikel untuk aplikasi kedokteran gigi, dengan

fokus khusus pada metode preparasi dan aplikasi terapeutik hidroksiapatit (HAP) yang didoping. Pemahaman yang komprehensif mengenai sifat fisik, kimia, dan biologis nanopartikel sangat penting untuk menilai potensi manfaat serta keterbatasan yang melekat. Meskipun nanopartikel menawarkan prospek yang menjanjikan di bidang kedokteran gigi, karakteristik ideal seperti biokompatibilitas dan stabilitas jangka panjang belum sepenuhnya tercapai. Penelitian lanjutan diperlukan untuk memahami sitotoksisitas, perilaku pelepasan ion, dan modifikasi permukaan nanopartikel guna meningkatkan performa klinisnya. Kemajuan dalam teknologi sintesis dan metode karakterisasi diharapkan dapat mengatasi tantangan yang ada dan membuka jalan bagi pengembangan terapi kedokteran gigi berbasis nanopartikel yang lebih aman dan efektif.

Kata Kunci: Doping ion; hidroksiapatit yang didoping; nanopartikel; pembentukan tulang Kembali; terapi regeneratif

INTRODUCTION

Nanoparticles (NPs) have unique and more superior characteristics compared to those of bulk forms. Their millimicron size is not are responsible for their advance nature, and it can be utilized further for assembling any diagnostic platform and treatment of the numerous disorders. NPs and their use in dental treatment have been fostered by the combined efforts of many different disciplines. In comparison to their conventional product, these advanced NPs will produce better results during the medical identification and treatment methods. This review describes the NPs that are available in dental medicine and their different compositions. NPs, which combine the fields of nanoscience and biotechnology, may be revolutionary in improving oral health by offering preventative and diagnostic procedures. They might even have therapeutic effects on repairing broken dental tissue [1].

Due to their tiny size and large surface area, NPs have unique physical and chemical properties. As a result, they have garnered a lot of attention for their potential use in various dental applications [2]. Finding composites that can restore the original dental appearance while simulating missing dentinal tissue is a challenge that most dentists face. Because of the development of sophisticated NPs, the use of an engineering-based bio-mimetic technique to replicate natural biomaterial has been seen as a more modern approach [3]. A great possibility for nano-dentistry can be done by preparing metals, polymers, and ceramics materials [4]. Numerous review papers on metal NPs-based life science have been published, and NPs have been the subject of substantial research [5]. Metal NPs, such as gold, silver, platinum, magnesium, strontium, selenium, manganese, silicon, copper, zirconium, aluminum, titanium, chromium, beryllium, boron, and zinc, were used to modify a variety of dental materials [6]. Among these different ions, there are a few that receive a lot of attention in pharmaceuticals due to their therapeutic effects. Recently, a number of promising candidates have gained widespread use due to their high safety and advantageous chemical properties. The subject of this article includes Se, Ag, Mn, Si, Sr, Zn, and Mg. The smart biocompatibility, high stability, low cost, and low toxicity of these substances have demonstrated their great promise in medical applications [7]. These ions will merely be produced using a variety of methods [8].

Even a small amount of doping in hydroxyapatite (HAP) will significantly modify characteristics, such as solubility, particle size, morphology, specific extent, porosity, and ratio [9]. These materials become multifunctional systems for the discharge of physiologically active ions since the doping components can eventually be released *in vivo* [10]. Given this complexity, it is to be noted that there is ongoing discussion regarding the mechanisms causing the purported alteration of biological characteristics [11]. Innovative approaches are currently being used for bone regeneration, including assisted bone affixation, which stimulates osteoblasts via biophysical and organic chemistry while also reducing the activities of bone cells. Additionally, HAP and ms-HAPs, imitating the composition of the most inorganic section of bone, are currently under research for a significant amount of graft biomaterials, preventing donor site injury. It is already known that biological HAP contains a variety of foreign ions, such as stable, nonradioactive Sr^{2+} ions with the atomic number 38 [12].

Mg plays a crucial function in bone remodeling because it affects skeletal metabolism and bone formation by enhancing formative cell activity and preventing osteopenia and bone fragility. It has also been shown that Mg shortage is linked to pathology [13]. Similar to Sr, zinc was discovered to have a suppressing effect on osteoclasts in vitro while promoting bone growth [14]. In rats, zinc enhances deoxyribonucleic acid production and alkalic enzyme activity, promoting bone mineralization [15]. In order to benefit from zinc's positive effects on bone

formation, the synthesis of substituted HAP with zinc (HAP-Zn) has been distributed by using chemical precipitation methods for different zinc substitution levels within the HAP lattice [16]. It was discovered that silicon (Si) is necessary for the growth and development of bones [17]. This discovery has had a favorable effect on the creation of bioceramics supported by Si-substituted HAP (HAP-Si), especially when using precipitation processes [18]. Both *in vitro* and *in vivo* studies were done to determine how the HAP-Si biomaterial affected bone formation, mineralization, and transformation by increasing the bioactivity of human osteoblasts and encouraging bone regeneration. It was anticipated that some of the biological effects of HAP-Si biomaterials would be supported by the higher dissolution rates of HAP-Si compared to HAP [19].

As previously indicated, there are numerous experimental investigations on HAPs that have been mono-substituted with Sr, Mg, Zn, or Si, whereas there are few researches on HAPs that have been double-substituted with these components, such as HAP-Mg-Zn. It has been done to co-substitute Mg and Sr at HAp lattice intervals (HAp-Mg-Sr), which has increased biological response [20,21]. It was discovered that the Sr and Zn co-substituted HAP possessed magnificent osteoinductivity and therapeutic characteristics. Recently, Mg and Si were added to create another HAP that had two substitutions [22]. It is important to point out that a compensatory outcome was also established within the structural changes, which prevents both a destabilization of the HAP structure and a potential disintegration during the heat treatment using the oxidization procedure [23]. It is clear that different ions doped into HAP for use as dental field have great potential for the future. The purpose of this review is to critically examine the current update, challenges, and future directions of ion-doped HAP in detail and biomedical applications, providing insights in enhancing material properties for therapeutic applications.

MATERIALS AND METHODS

Materials

This paper provides a short overview of the numerous ions that can be used to dope HAP in regenerative dentistry. Although it is neither a systematic review nor a meta-analysis, the study was conducted using Cochrane's systematic review and the PRISMA methods (the recommended reporting item for systematic reviews and meta-analysis) as a framework [24,25].

Criteria for considering studies for this review

The potential for regeneration of dental tissue was examined in relation to the various ions doping HAP, which may encourage a suitable arrangement of composites for applications in tissue engineering and regenerative medicine. The retrieved information focuses on four main areas: technique, different types of ions used in HAP treatments, interpretation of research findings, and side effects of specific therapies. The data contained in this publication was taken from 4 previous research data to provide information regarding the formation of this review and show the strategy of the methods used to create a review.

Search strategy for identification of studies

An electrical search was conducted to indentify studies investigating the use of various ion-doped biomaterials combined with HAP scaffolds for bone regeneration in both medical and dental applications. The search was performed using the MEDLINE (Medical Literature Analysis and Retrieval System Online, via PubMed) and Scopus databases, with data retrieved up to and including September 2021. The search approach is restricted to English-language papers that contain certain keywords, including strontium, regeneration in dentistry, implantation, biomaterial or biocompatibility, and scaffold or bone graft. Case reports that mentioned earlier safety preclinical tests and systematic reviews were promptly incorporated.

Unpublished data and manual search.

To find unpublished data, search was done through the OpenGray database (www.opengrey.eu) which contains unpublished studies. A manual search was also conducted manually using the reference list from the chosen papers. Journal of Materials Science and Technology, Tissue Engineering, Biomaterials Advances, Advanced Engineering Materials, Journal of Materials Science, Materials Science and Engineering C, Journal of Biomaterials Science, Journal Inorganic Biochemistry, International Journal Molecule Science, Reviews on Advanced Materials Science, and Calcified Tissue International are just a few of the journals that were manually searched in the electronic databases for this review. Further, potential related research was identified in the listed papers' bibliographic references. The title, abstract, and full text of the search results are independently filtered by the author.

Study selection and data extraction.

The studies that satisfied the inclusion criteria underwent data extraction and validity assessments by the researchers. Data for regenerative dental therapies

are derived based on the content of each study report (for examples, ions doping, regenerative therapy, doped HAP, bone remodeling). According to Hooijmans *et al.* [26], the SYRCLE's risk of bias tool is used to assess the methodological quality of studies involving animals. No summary scores for the studies were included, as the tool is intended to evaluate individual domains rather than generate an overall score. Independent reviewers evaluated the study's quality. Consensus meetings were convened when there were conflicts about the evaluation data.

Data analysis

The initial search for data publishing included 22 titles from the MEDLINE (PubMed) databases and 145 titles from the Scopus database which published up to October 2022. After the initial screening of two publications' abstracts and keywords was done, four articles—three from PubMed and one from Scopus—were identified as having the potential to be used as criteria for constructing subjects. After the first screening, however, only 7 of the 15 titles were qualified while certain publications were not relevant to the main topics. The approach and use of different ions doping in combination with HAP in dentistry serve as the primary indicators in removing publications from the text selection.

The function and use of different ions doped with HAP in dentistry were consequently mentioned by the writers as being pertinent to this journal review. From bibliographic references and manual searching, no further articles were discovered as additional data sources in the journal. Although a lot of information about different ions doping applications was discovered, it has not been thoroughly studied. The studies selection process is depicted in the flowchart as shown in **Figure 1**.

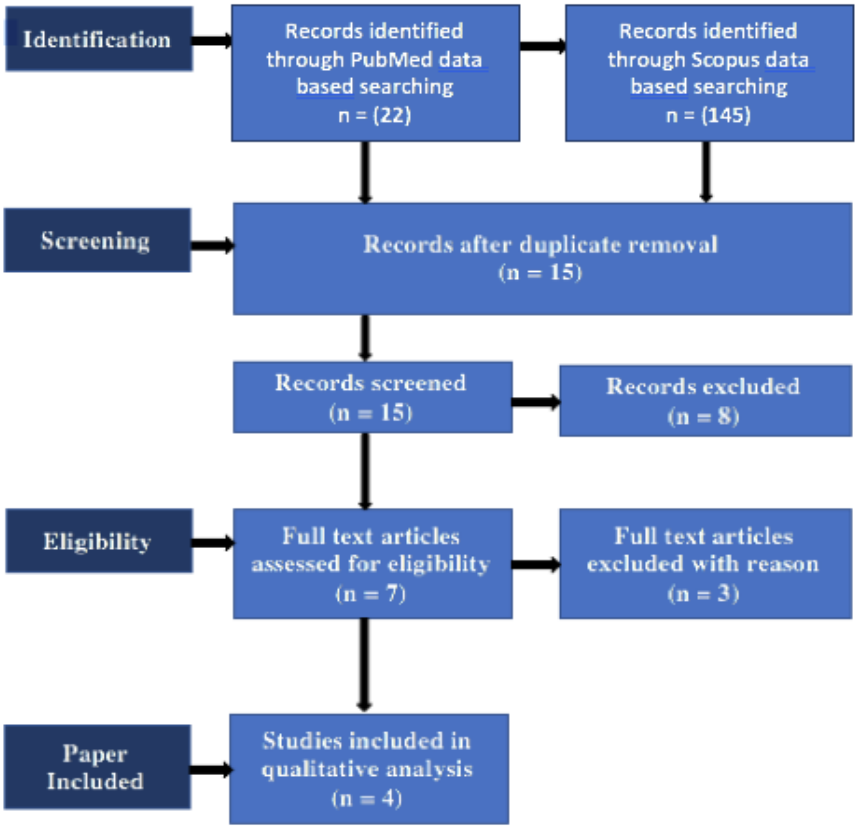

Figure 1. The studies selection process referred to the PRISMA flow diagram

It has been made known that 4 papers from this literature review were included for additional reading. The first review, Advanced Mg, Zn, Sr, and Si Multi-Substituted Hydroxyapatites for Bone Regeneration by Garbo *et al.* [27], was determined to be pertinent to this investigation. According to the study, compositional trade is getting a lot of attention in the development of advanced biomimetic NPs. The focus of this work was on advanced multi-substituted HAPs (ms-HAPs), which are similar to the inorganic component of bones and may have therapeutic potential for bone regeneration. Characterization techniques verified that all produced NPs had high integrative purity and a specific section of pure ratio HAP structure. The

doping components affected the crystallinity, lattice properties, crystal size, morphology, particle size and form a specific expanse, and body. In comparison to pure HAP, the results demonstrated a reduction in each NPs size and crystallinity level as well as an increase in the specific expanse of those advanced ms-HAP materials. The discharge of biologically necessary ions was demonstrated in several liquid mediums under static and simulated dynamic conditions. The four subbing components are unquestionably included in the HAP structure. Synthesized nanostructured ms-HAP materials may inherit the effects of substituting HAP's functional elements and properties for bone repair and regeneration. The findings demonstrated the application of a rational trading strategy in the synthesis of a new class of bioactive ms-HAPs that are attractive candidates for bone regeneration.

Additionally, the second study by Barot *et al.* [28] met the requirements for inclusion. Nanotechnology-based materials are discussed in this paper as developing trends in dental applications. This study is crucial in demonstrating the functions of NPs in dental applications. The study also demonstrated the special and superior characteristics of NPs, such as their high expanse and nanoscale size, which make them crucial for rapid illness diagnosis and treatment. Advanced NPs have been developed through collaborative efforts from many different fields, which have also made it possible for odontology to employ them. Compared to their conventional counterparts, these advanced NPs will provide more dazzling leads for identification and treatment processes. This overview describes the NPs that are available and used in odontology and might go on to explore the compositions and forms of various NPs. Dental restorative materials can incorporate NPs to help control and/or prevent degradation. They might even affect how damaged dental tissue heals.

The third study by Muthusamy *et al.* [29] focuses on the physiochemical, microstructural, and biological characterization of HAP nanophases enhanced with selenium and manganese ions for bone regeneration. Wet-co-chemical precipitation was used to create HAP nanopowders with completely different chemical components (Mn and Se). The findings showed that ion-substituted mineral components could be produced using clever crystallographic techniques with either Mn or Se doping. The combined evidence from qualitative analysis methods showed that Mn and Se ions were efficiently doped into nanocrystalline HAP. Mn and Se doped HAP samples possessed a rod- and needle-like morphology and a high propensity to aggregate. Mn and Se augmented HAP exhibits great blood compatibility and a potent therapeutic effect. Through biocompatibility testing, it was discovered that Mn and Se doped HAP increased osteoblast adhesion, migration, and proliferation in a manner that was extremely dose-dependent. The results of this work revealed that the doping quantity of each Mn and Se ion will confirm the scale and morphology of the final HAP product with satisfying microstructural, thermal, and biological qualities.

Research by Jiang *et al.* [30] was the fourth study in this review. One of the current problems in the fields of medicine and engineering is figuring out how to prevent infection from deep-seated bone replacements. This study set out to create an entirely original porous scaffold with adequate antibacterial activity for bone repair or regeneration. The in-place foaming approach was used to create porous nano-hydroxyapatite/polyurethane (n-HAP/PU) composite scaffolds with various concentrations of silver phosphate particles. Then, their preliminary cytocompatibilities, physicochemical characteristics, and antibacterial drug capabilities were assessed. According to the findings, n-HAP/PU scaffolds with Ag_3PO_4 incorporation did not significantly alter their porousness or mechanical properties when compared to those of n-HAP/PU scaffolds without Ag_3PO_4. Ag_3PO_4 sharing within the scaffolds and immersion time increased the Ag^+ discharge, which was time and concentration dependent. A perpetual release of Ag^+ will endure for about three weeks. According to antibacterial drug tests and cytocompatibility studies, the n-HAP/PU scaffolds with 3 weight percentage (wt.%) Ag_3PO_4 (n-HAP/PU3) exhibit higher antimicrobial effects as well as acceptable cytocompatibility. The n-HAP/PU3 scaffolds may have great promise for use in the field of bone regeneration, especially for the repair of infection-related bone defects.

RESULTS AND DISCUSSION

Subsection of results

According to the in vivo research, solid implantable devices (prosthetic stems, dental implants, fixation screws, etc.) made for bone replacement or fixation applications typically use HAP-based coatings to improve the bone adherence. Functionalized metal macroporous scaffolds 238 are an alternative to the existing alternative technique for treating bone deformities. These scaffolds must have the highest mechanical qualities and encourage the growth of new blood vessels and bones within their macroporous structure. For the regeneration of critical flaws in the bone, particularly in osteoporotic bones, both elements are crucial. The integration of the implant and the host bone is severely hampered by the poor rate of bone development in the vicinity of the implant. This highly

bioactive bioceramics' surface functionalization of the metal structure has emerged as a very intriguing substitute [31,32].

Dental and orthopedic implants might function better. Thanks to substituted HAP coatings which are a particularly eye-catching alternative. The different ionic replacements permitted by the HAP structure, together with the variety of production techniques, provide the commercially available plasma sprayed CaP coatings novel properties. As an illustration, Si-HAP coatings applied to porous auriferous implants have demonstrated excellent osteoinductive behavior of the soluble silicon dioxide species discharged from the coatings and magnificent bone regeneration capacities through the action of osteoconductive HAP. Sr^{2+}, Mg^{2+}, and Zn^{2+} are examples of alternate ionic substituents that promote bone healing, resulting in significant advancements in the treatment of osteoporotic fractures [33].

Table 1. Various ions-doped by HAp coatings and the enhanced biological function observed with in vitro studies.

Coating	Function	Method	Ref.
Zn-HAp	Osteoblast function	Plasma spraying	[34,35]
		Electrophoretic deposition	[36]
		Sol-gel spin coating	[37]
	Corrosion	Magnetron sputtering	[38,39]
	Resistance	Electrochemical deposition	[40]
		Hydrothermal coating	[41]
	Bactericidal	Pulse laser deposition	[42]
Mn-HAp	Mechanical properties	Pulsed laser deposition	[43,44,45]
	Corrosion resistance	Electrodeposition	[46]
Ag-HAp	Bactericidal	Plasma spraying	[47,48,49,50]
	Adhesion strength	Electrospraying	[51]
Mg-HAp	Osteoblast	Plasma spraying	[52]
		Electrochemical deposition	[53]
Sr-HAp	Osteoblast	Pulse electron	[54]
		Plasma electrolytic oxidation	[55]
	Osteoclast inhibition	Hydrothermal, electro deposition	[56]
	Corrosion	Radio frequency	[57]
	Resistance	Plasma spraying	[58]
Se-HAp	Osteoblast Antitumoral	Pulsed laser deposition	[59]
	Bactericidal	Biomimetic	[60]
Si-HAp	Osteoblast	Magnetron sputtering	[61,62,63,64]
	Osteoinduction	Pulsed laser	[65]
	Mechanical	Dip coating	[66]
		Spin coating	[67]
	Bonding strength	Electrochemical deposition	[68,69]
		CLVD/hydrothermal	[70]

As shown in **Table 1**, ions with antimicrobial properties have emerged as a key focus in research for developing new coatings. However, further evidence and a more detailed exploration of how these antimicrobial characteristics influence coating performance should be provided to substantiate this assumption. With certain microbe strains, substitutions with Ag^{+} have produced positive *in vitro* results. The lack of *in vivo* investigations, which may be attributed to the difficulty in developing in vivo infection models in bone, remains a notable challenge. For any advancement of those technologies, those models must be present. The integration of SeO_3^{2-} will result in additional biological activities like antitumoral activity. However, more *in vitro* and *in vivo* proof is required before being applied to clinical settings. The potential to accelerate bone regeneration in macroporous scaffolds or new bone formation at the peri-implant site is great when substituted HAP coatings are paired with biological agents. Recombinant human bone morphogenetic protein-2 (rhBMP-2) has demonstrated remarkable behavior in connection to Mg-substituted HAP, which led to superior bone growth among scaffolds. As more is learned about the interactions of substituted HAP with proteins, growth hormones, or microRNAs, it may one day be possible to create coatings that are specifically designed to address each unique clinical situation [71].

Roles of various ions doping in dentistry (Ag, Se, Si, Mg, Sr, Zn and Mn)

Silver, a non-essential metal that is not naturally found in the human body and does not play structural roles in cells or tissues, has gained significant attention in recent years for its incorporation as Ag+ ions into bioceramics, particularly in silver-substituted hydroxyapatite (Ag-HAP) coatings, due to its potent antibacterial properties, which make it an effective agent for preventing infections in medical devices and dental implantsilver-substituted hydroxyapatite (Ag-HAP) coatings. The ability of Ag^+ to bind to microbial substances, stop microbial replication, and interact with sulfhydryl teams of the metabolic enzymes in the microbial lepton transport chain would be related to its antimicrobial activity [72]. Ag-HAP coatings with proven medical effects are ready using PLD, co-precipitation, plasma spraying, thermionic tube sputtering, or sol-gel techniques [73-75]. Together, Ag^+ ions have a significant impact on bonding strength. According to Gokcekaya *et al.* [76], in the case of Ag-HAP onto Ti substrates, the presence of noble metal appears to increase the adhesion strength for electrosprayed deposited coatings. However, Yan *et al.* [77] found the opposite finding that the bonding strength for Ag-HAP coatings prepared by the same method had decreased. According to a theoretical reading, ions Ag^+ and Zn^{2+} fully affect the adhesion of HAP. Based on the estimated model's electronic structure analysis, doping with zinc or noble metals will increase the charge transfer to HAP, causing the HAP interface system to be very metal-like.

Antibacterial effects of silver have generally been well known for hundreds of years. It has also been demonstrated to have antiviral and antifungal effects. The mechanism of action of silver ions results in the inactivation of enzymes, which prevents the replication of desoxyribonucleic acid and causes necrobiosis of microorganisms [78]. Researchers are very interested in studying silver's medicinal effects. Engineering research has expanded the potential uses of silver in the medical field. Silver's medicinal properties could be used in dental materials [79]. AgNPs have demonstrated strong medicinal capabilities as a filler in dental restorative materials in a number of recent articles [80]. When employed as a filler, AgNPs also provide better aesthetic outcomes without affecting the mechanical capabilities of the dental composite [81]. According to a recent study, using AgNPs in a dental composite significantly reduces the accumulation of biofilm and carboxylic acid on teeth, preventing secondary tooth decay [82]. AgNPs are used in a single-use capsule form of a dental sealer (Gutta-Flow Sealer) that contains gum powder and has demonstrated high medication potency [83]. AgNPs' potential to produce twin action qualities, such as remineralization and medicinal properties, with various bioactive substances is being investigated. AgNPs were recently used in dental composites, which exhibit a significant increase in strength as well as medicinal action [84]. According to a previous work, a gel containing AgNPs was utilized against an *Enterococci Faecalis* bio-film at extremely low concentrations, and it also demonstrated significant drug action [85]. In comparison to the dental composite material that is currently sold commercially, these twin action features have demonstrated outstanding mechanical capabilities, such as flexural strength and modulus.

The silver ions aren't focused within the native site when the scaffold is ingrained into the infected site, preventing a significant amount of Ag^+ unharnessed in a remarkably short period of time. The initial concentration of Ag^+ inside the scaffold may influence the discharge behavior. The unharness of the silver particle in deionized water may be a key achieving sufficient medicine efficacy with extremely little or no toxicity [86, 87]. Due to the composite scaffold's first rapid unharness rate in deionized water, it is a preferred choice for treating acute inflammation following surgery and applying emergency antibiotics after its implantation. Because of the ensuing persistent and ongoing unharness, it is ideally suited for long-term antibacterial treatment.

Zinc-substituted hydroxyapatite (Zn-HAP) coatings

The second most common necessary element in humans is zinc (Zn). At the nanoscale, zinc has powerful medicinal properties, significantly increasing the strength of their medications. A metallic element particle that comes into touch with a microorganism's plasma membrane attaches to the proteins and lipids, causing an imbalance in the diffusion that leads to membrane porosity and eventual death [88]. Zn plays a structural role in many proteins and is involved in cellular division, macromolecule replication, and factor transcription activities. Zn is therefore essential for all species' growth, development, and differentiation, especially for humans. Zn is merely a minor chemical element found in bone. But many researchers have been interested in the addition of Zn^{2+} cations to the HAP structure. Ca^{2+} is isoelectrically replaced by Zn^{2+}, which causes the lattice parameters to drop. Numerous researchers have stated explicitly that Zn activates osteoblast proliferation and differentiation to enhance bone formation [89,90].

Zn-HAP has simultaneously demonstrated therapeutic pharmacological effects. The bioactivity and drug-like characteristics of HAP doped with less than 1% of metallic element ions have been successfully demonstrated [91,92]. Vacuum tube sputtering, plasma spraying, EPD, sol-gel spin coating, and other processes are used to prepare Zn-HAP coatings [93]. Zn level as low as 1.3% was demonstrated by Webster *et al.* [94]. to increase formative cell responses. Indisputable evidence of enhanced bone apposition to the implant surface was provided by this substance. However, extensive research also demonstrated an expanded bone organic process within the medullar cavity region. These findings suggest that Zn^{2+} unharnessed from CaP can be used clinically just using minimal doses of Zn^{2+} or by carefully selecting implant sites without exposing bone marrow [95].

Magnesium-substituted hydroxyapatite (Mg-HAP) coatings

Mg is a significant substance that is widely present in organic structures. Mg plays a similar biological function to calcium in development of the skeleton and the stabilization of cell membranes in vertebrates. Mg is a crucial factor for phosphate cluster transfer processes and various non-oxidative supermolecule cleavage reactions by nucleases when it comes to protein function. Mg shortage has detrimental effects on the development as well as mental and physical capacities; this could be due to inadequate energy production brought on by abnormalities in phosphate transfer processes. Mg^{2+} ions prevent HAP from crystallizing, which subsequently prevents the growth of massive crystals and encourages the development of a lot of mineral nuclei. This action is particularly important for bone formation-resorption turnover which requires nanocrystalline bone apatite. Mg^{2+} deficiency impacts bone development, lowers bone density, and results in brittle bones [96]. These findings have motivated many teams to carry out the factitious production of Mg-HAP in a variety of forms, including coatings. Crystallinity decreases and a heterogeneous distribution with Mg content is seen in Mg-HAP coatings prepared by physical deposition and chemical methods, resulting in Mg-rich regions. *In vitro* cell culture experiments have demonstrated that osteoblasts concentrate, adhere, and develop preferentially in certain regions, demonstrating the beneficial effect of Mg on bone-forming cells. The characteristics of Mg-HAP coatings prepared by chemical deposition were similar to those determined for non-substituted HAP [97].

Strontium-substituted hydroxyapatite (Sr-HAP) coatings

Sr is considered a non-essential component. A typical adult human contains 0.14 g of Sr. Sr is mostly present in the mineral portion of bones, especially in areas where bone turnover is highly active [98]. Sr's inhibition effect on bone organic processes and the enhancement of bone growth in patients with osteoporosis have been the driving forces behind its integration into CaPs [99]. Numerous researches have demonstrated that Sr^{2+} by Ca^{2+} substitution in CaPs improved osteoblast activity and decreased osteoclast growth [100]. Sr^{2+} has a bigger ionic radius than Ca^{2+}, in contrast to Mg^{2+} and Zn^{2+}, which results in an expansion of the HAP unit and an increase in cell volume. Additionally, the inclusion of carbonate and HPO_4^{-2} is encouraged by this crystalline deformation because Sr^{2+} will completely replace Ca^{2+} in the HAP structure [102]. The incorporation of Sr ions into newly developed scaffolds for wound healing in dentistry, oral and maxillofacial regenerations, orthodontics treatment, dental implantology, and periodontal regeneration is awaiting to be studied to resolve problems in regenerative dentistry [101].

According to Teng *et al.* [103], Sr-HAP coatings on Ti substrates increased wettability for a molar ratio of Sr^{2+}:Ca^{2+} of 0.12 whereas a molar ratio of Sr^{2+}:Ca^{2+} of 0.25 resulted in a significant decrease in wettability. Although Sr-HAP with a high Sr content has a low wettability and would provide excellent corrosion protection for gold substrates [104], osseointegration is heavily dependent on protein-surface interactions, which are controlled by hydrophilicity. In a very recent study, Wu *et al.* [105] demonstrated the beneficial effects of electrodeposited Sr-HAP coatings on the stability of Mg alloys, and might prevent corrosion as well as promote cell growth. However, a reduced expression of the osteogenic markers Col-1, Runx2, and mount was seen for coatings with the highest Sr concentration. These findings suggest that the Sr-HAP coating exhibits the best degree of substitution, which may result in the highest HAP concentration, hydrophilicity, and cell survival. It is obvious that the coating process has a significant impact on the optimal Sr/Ca quantitative relationship for *in vitro* cell response. Numerous studies using Sr-HAp reveal a questionable inhibition of osteoclastogenesis and a modest improvement in the function of osteoblasts that is reliant on the Sr concentration. Boanini et al [106] recently proposed an extremely intriguing variety of ions, which involved creating gradient coatings of Ca phosphates that were substituted with various cations. While a higher Sr-HAP concentration led to a

suppression of osteoclastogenesis without affecting osteoblast biocompatibility, zinc beta-TCP content increased osteoblast activity.

Other substituted hydroxyapatite coatings (Mn^{2+}, and Se^{2+})

An essential element with the most affinity for integrin binding is manganese [107]. While acting as Lewis' acid to accelerate hydrolytic reactions and as a reaction catalyst, Mn^{2+} could act as metalloenzymes. Numerous researches have attempted to use Mn to increase the osteoconductivity of Ti substrates due to its strong ability to promote cell adhesion [108]. By applying Mn-HAP coatings on ZnO-coated or unstained steel, these coatings generated a stronger cell response with improved viability, proliferation, and the activity in osteoblastic cells, as compared to those of Ti coat [109]. This bilayer coating enhanced *in vitro* bioactivity, biocompatibility, mechanical characteristics, corrosion resistance, and metal particle leach-out performance. Mn^{2+} does not always have benefits when it is combined with coatings other than metal phosphates. The effects of Mn inclusion into the titania coating on titanium were examined by Park et al [110]. These authors unquestionably demonstrate that Mn insertion reduced cellular attachment, spreading, proliferation, mountain activity, and bone-forming cell makeup organic phenomena in comparison to those of the Ti-free surface. It impaired cell behavior rather than offering biological advantages.

People have become interested in HAP doped with rare earths recently. Selenium, for instance, might be a trace element that is crucial for humans. A typical human contains about 15 milligrams of selenium. Selenium-doped HAP (Se-HAP) coatings can be prepared using a variety of procedures, such as PLD204, biomimetic methods, and selenite ions in SBF200. The osteogenic, anticancer, and antibacterial action of Se integrated as SeO3 2- anions into the HAP structure has been proposed by Rodriguez-Valencia *et al.* [111]. 2.7% Se-prone coatings had significant antiproliferative effects on malignant osteoblasts (MG63), significant osteogenic activity in MC3T3-E1 pre-osteoblasts, and antibiofilm capabilities against *S. epidermidis* and *S. aureus* microbial strains.

In order to demonstrate that nanocrystalline HAP was efficiently doped with Mn and Se ions within the lattice of HAP structure, FTIR, Raman, XRD, EPR, and ICP-OES investigations were performed. All of the examined samples were lacking in metals and they weren't hemolytic, showing a strong propensity to aggregate. Based on SEM and TEM investigations, Mn-HAP samples showed a predominately rod-like shape, while Se-HAP samples showed a needle-like morphology. Mn and Se HAP had an extremely dose-dependent potent bactericide effect against infectious pathogens. With the increase of culture time, the MG63 cells were highly cytocompatible and metabolically active for pure and Mn-doped materials. The Se doped HAP, on the other hand, demonstrated a significant drop in cell viability when the culture time was extended. It highlighted the constrictive effect caused by the release of Se ions into the culture media, causing MG63 cells to undergo programmed cell death. The doping quantity of both Mn and Se ions is the critical factor that controls the final HAP product's dimensions and morphology. As a result, Mn and Se HAP nanopowders with molar quantitative relation and no heat treatment will provide HAP with reasonable crystallographic alternatives and satisfy its morphological, thermal, and biological requirements. Future research is required to get better understanding of the potential benefits of these nanopowders for tissue regeneration and drug delivery applications, with a focus on more in-depth *in vitro* and *in vivo* experiments [113].

Silicon-substituted hydroxyapatites (Si-HAP) coatings.

Silicon is a crucial trace element for the majority of living things. Si-HAP has been proven to exhibit more physiological activity when compared to those of unsubstituted apatite [114]. Magnetron sputtering has been used to create the Si-HAP coating. Due to the extremely low Si substitution rate, HAP and Si are sputtered from separate targets rather than a single Si-HAP layer, resulting in a Si-HAP layer with a 0.7 m thickness and a Si content of around 0.8 wt.%. The Si-HAP thin layer demonstrates high biological activity and biological usefulness, according to *in vitro* cell culture tests. Human osteoblast-like (HOB) cells were seen to attach and develop during the culture process. Extracellular matrix production was higher on the coated titanium substrate than those on the uncoated titanium substrate. However, it was less stable than that of the pure HAP coating. HOB cells increase the coated surface's adherence and create a fully developed cytoskeleton with distinct actin stress fibers in the cell membrane [115].

However, the maximum degree of substitution Si-HAP increased the reactivity which in turn sped up dissolution and prevented early cell adhesion. Therefore, it was determined that 2.2 wt.% Si would be the ideal level of substitution. The microstructure properties of Si-HAP produced by magnetron sputtering were thoroughly examined by Surmeneva [116]. The mechanical characteristics of Si-HAP produced by magnetron sputtering will also be

impacted by silicon doping [117]. The relationship between Si content and the microstructure change brought on by silicon inclusion. Additionally, Si substitution has an impact on adhesion behavior. The poor cohesiveness of the unsubstituted HAP caused the coating failure. The Si-HAP with 1.2% of Si-HAP experiences plastic deformation without the development of cracks, while the Si-HAp coating with 4.6 atomic percentage (wt.%) Si exhibits mixed elastoplasticity. Additionally, Si-HAP coatings are successfully prepared via PLD, sol-gel chemistry, dip coating, spin coating, chemical science deposition, and electrolytes containing Na_2SiO_3 as a source of semiconducting material [118].

To improve the mechanical qualities of dental restorative materials, silicon dioxide NPs are added as a filler. In traditional medicine, fine silicon oxide powder is used as a polishing agent to smooth down the rough surface of the teeth in order to prevent food collection or plaque formation. SiO_2 NPs, also known as silicon dioxide or oxide, is most frequently found in nature as quartz and is an oxide of silicon with the chemical formula SiO_2. SiO_2 NPs are being used increasingly in a variety of dentistry and specialist medical applications. SiO_2 NPs can hold a variety of medicinal compounds. Due to their size, extent, biocompatibility, low toxicity, tenuity, and sorption capacity, SiO_2 NPs play a significant role in medicine [119]. Mesoporous SiO_2 can be utilized to treat the dentinal tubules, which become hypersensitive when exposed [120]. When silicon oxide NPs HA NPs are combined, the resulting completely demineralized dentin demonstrates a native increase in the concentration of orthophosphate compounds and a recovery of the mineral volume [121].

Every fundamental component of calculated and measured content has an incredibly logical connection. For all samples, the mole quantitative relationship between the total amount of cations (Ca^{2+}, Mg^{2+}, Zn^{2+}, and Sr^{2+}) and the total amount of anions (PO_4^{3-} and SiO_4^{4-}) is very close to the predicted value (1.67) for ratio of the HAP structure. The ICP-OES analysis cannot detect any contaminants (such as Mg or Sr traces) in the HAP samples or in the raw materials used in their manufacture [122]. Therefore, even though the substitution ions have completely different charges or sizes, they will make it easier for this particular composition to construct a stable isostructural lattice. Furthermore, it revealed that the optical phenomena peaks for ms-HAPs were larger than those of pure ratio HAP. The multi-ionic replacement at intervals HAP lattice resulted in a very low degree of crystallinity for the ms-HAP materials. Similar data for co-substituted HAPs with Si and Sr (HAP-Si-Sr) support this result [123]. In structural changes brought on by multielement doping, a stabilizing effect is clearly elicited that prevents both an instability of the HAP structure and a potential disintegration during the heat treatment through the oxidation procedure.

In comparison to pure HAP, the substituted HAP released a greater amount of each substituted component. The solubility of doped HAP will therefore undoubtedly rise in the presence of the work components. The behavior of HAPs will be distinguished in terms of competitive processes, particle unharness, dissolution, and particle surface assimilation, just like HAP precipitation [124,125]. For instance, the precipitation process, specifically the atomic number 20 and phosphate precipitate to create the HAP layer, will be blamed for the drop in Ca^{2+} particle concentration. For the creation of a HAP layer, the opposing ions may serve as nucleation sites. Therefore, multi-substituted HAPs could serve as a simple source of ions that are important to biological processes. Additionally, HAP-Mg-Sr-Zn-Si, as produced ion-doped HAPs, may have interesting applications as bone/tooth materials, mainly due to the trace unharness of therapeutically active ions. For instance, it is widely known that administering atomic number 14 and Sr at low doses can improve bone mass and strength by reducing bone resorption and promoting bone formation [126,127]. Undoubtedly, a localized unharnessing of those trace elements—Sr, Mg, Zn, and Si—from coatings on bronze implants in a very small, unquantifiable amount may promote bone regeneration and have a significant positive effect on clinical applications. The current study provides evidence for triple- and four-substituted HAPs as powders. It may include the effects of co-doping with completely different components (such as Mg, Zn, Sr, and Si) at intervals of HAP lattice, on physical and chemical properties, such as nanostructure, crystallization size, crystallinity degree, morphology, NPs size, lattice parameters, specific extent, body, and particle unharness. The combined action of ions free of ms-HAPs may promote scaffolds containing msHAPs with better biological characteristics compared to those of pure HAP scaffolds [128].

Roles of hydroxyapatite in bone remodeling

Over the past few decades, bone tissue engineering has become one of the most essential methods for treating bone injuries. By utilizing a combination of biomaterials and cells to accelerate bone regeneration, this method offers an affordable and secure alternative to autografts and allografts. A ceramic biomaterial of HAP may be able to replicate

the mineral makeup of vertebrates' bones and teeth. It is not surprising that HAP, which has been produced artificially by numerous methods throughout the years, has reasonable bioactivity, biocompatibility, and osteoconductivity both *in vitro* and *in vivo*. HAP has been used in combination with many composites to create biocomposite implants. This has improved the mechanical properties of the implants and improved their overall performance the compound used to make the biocomposite. This paper provides an overview of recent and historical developments in the "ideal" biomaterial scaffold for bone regeneration, HAP biocomposite implants [129].

The phosphate ceramic mineral HAP ($Ca_{10}(PO_4)_6(OH)_2$) may be one of them. Tricalcium phosphates and bioglass ceramics are other members of this class and are frequently employed as bone substitutes. Because of its structural and functional similarities to the mineral makeup of bones and teeth, HAP is preferred over other Ca phosphates. HAP makes up to 70% of the human bone, along with 5% water and 25% organic matter [130,131]. Because of HAP's inherent bioactivity and biocompatibility as well as its ease of manufacture, it is a suitable implant material [132,133]. The solid scaffolds with varying porosities that are preferred for cell attachment, migration, and bone formation include a range of solid scaffolds with HAP. Additionally, HAP is pulverized into nanoscale powders that can be combined with other biomaterials to increase bone mineralization [134,135]. Additionally, there is evidence that HAP coatings can improve the integration of implants with the host bone [136]. This has led to the extraction of HAP from a wide range of sources, including animal bones, eggshells, marine mollusk shells, and even plants that produce affordable and environmentally friendly bone substitute. Analysis has, however, only been performed using small animal models, with varying degrees of success. It remains to be observed if the biocomposites would live up to their potential once incorporated into human major bone lesions. However, given the ongoing technological developments, biocomposites are anticipated to play a crucial role in encouraging bone regeneration [137,138].

In the other study, HAP might be a phosphate (CaP) that is typically made into coatings, layers, or thin films and applied to the surface of prosthetic devices to hasten bone repair at the time of early implantation. The coating should be bioactive, osteoconductive, and biocompatible to achieve this goal [139]. However, biocomposites require a number of qualities, such as the presence of a dominant crystalline part to prevent rapid dissolution of the layer, the presence of an amorphous part to promote early osteointegration without disturbing the stability in the form of programmed dissolution. This requires an elemental composition that is compatible with the bone mineral part, and strong implant adhesion to prevent mechanical failure [140,141].

At the moment, only phosphate bioceramics created by plasma spraying are clinically certified for use as bone coverings and are commercially available. A very promising alternative to conventional CaP coatings is substituted HAP coatings. The goal of ionic substitutions is to provide HAP additional features like osteoinduction or antibacterial action. Therefore, modified HAP coatings would be developed for a variety of pathological conditions, including infection, in addition to quick biomechanical fixing. The subject of substituted HAP coatings is currently an area of research that is constantly expanding, largely because of the variety of components and ions that have been discovered to have therapeutic benefits during the past fifty years [142]. Additionally, the crystalline structure of HAP just allows ions to be included by substitutive and opening mechanisms. These facts have created new scenarios where coatings actively treat diseases while also accelerating bone healing in the early post-implantation period. Substituted HAP coatings are expanding the therapeutic applications of bimetallic implants beyond their standard substitutive functions towards bone regeneration functions in conjunction with the recently discovered additive factory-made bimetallic scaffolds. Recently, new opportunities in the realm of coatings for orthopaedic uses have also emerged due to the combination of substituted HAP and nanostructures [143].

Challenges for regenerative therapy

Incorporating quick prototyping techniques as a fresh approach for coatings production is known to be essential in this industry. Micro-dispensing techniques enable coating modification by dispensing completely new replacement HAP at the micrometer scale. These methods also provide fresh resources for integrating and controlling the release of medication from the coating into the local environment. However, until previously built *in vivo* animal models of osteoporosis, infection, malignancies, etc., these prospects are dispensed with success [144].

It may be difficult to transition new medical equipment from the workplace to clinical settings. As a rough estimate, one technology initiative out of every ten results in a medical device that is put through the clinical testing stage [87]. Technology is frequently at the forefront of innovation in the biomaterials sector,

but it is always done to address unmet clinical needs. In this regard, the vast body of scientific literature demonstrates that research on novel coatings is strongly backed by technological advancement. The ability to create substituted HAP coatings with satisfactory *in vitro* behavior can be achieved through a variety of manufacturing techniques.

Undoubtedly, increasing coating adherence and lowering the costs associated with industrial upscaling can be seen as the primary obstacles to the widespread application of new coatings [145]. Although quick early bone-implant integration and the prevention of prosthesis infection remain unmet clinical needs that must also be improved, the variety of production procedures and compositions should be important in bringing innovative replacement of HAP coatings to the clinical setting. But in most ways, this circumstance is different from that. Only a few numbers of CaP bioceramics created by plasma spraying are readily available on the market. There are a number of factors that could be the root of this lack of product translation. Firstly, there is very little *in vivo* research on substituted HAP coatings, which is partly due to a lack of suitable animal models. Avoiding prosthetics infection is one of the most important clinical goals. Hence, various ion replacements are added to HAP coatings. However, only a few body covering models are predicted, and it doesn't appear that any *in vivo* studies or a bone infection model have been done to test these devices.

The second difficulty is the stringent procedures for market approval. In this sense, new replacements for HAP coatings that are unreal with different technologies to plasma spraying are regarded as products that don't exist anywhere else. Pre-market approval (PMAs) is required in these situations, which adds to the cost and time compared to products with comparable ones already on the market. This fact would make innovative coatings less appealing to investors, especially since the biggest obstacle will arise during the clinical trials, which come at the very end of the process and after a significant portion of the investment has already been made [144].

Future perspective

Those biomaterials' chemical doping and topographic characteristics, particularly their nanostructure, useful crystallinity, and relatively large specific area, are unquestionably responsible for the *in vitro* response. In particular, the development of artificial HAPs for bone regeneration, a deeper knowledge of the specific integrative impact of doping components on the HAP structure and physical properties of ms-HAPs is of great interest. In this regard, ms-HAPs made of completely distinct physiological components like Mg, Zn, Sr, and Si (e.g., HAP-Mg-Zn-Si and HAP-Mg-Zn-Sr-Si) may have a strong chance of being effective in bone regeneration [64].

On the basis of *in vitro* prior investigations, a rational technique was chosen to style ms-HAPs for the purpose of this work [78]. For the coincidental multi-doping with Mg, Zn, Sr, and Si in HAP structure, a wet chemical precipitation method was used. It has not yet been possible to report on how this type of doping affects the physical and chemical properties of ms-HAPs. The newly created NPs are primarily used in paste (precipitate) and nano powder applications, such as carriers for native drug delivery [42], injectable gels, or as novice (non-sintered) NPs for staging in cell culture [79], as well as chemical coating onto gold-bearing implants for bone regeneration and healing [54]. In other words, technology is not the only factor influencing the commercial conversion of alternative HAP coatings. To lower the chance of failure during clinical trials, evidence-based definitions of unmet clinical needs and preclinical research employing suitable animal models are essential. In order for new HAP goods to be sold, regulatory filings and successful marketing techniques are also necessary [144].

CONCLUSION

The synthesized NPs represent a fertile addition to the world, and their ideal composition was designed to obtain a novel multi-doped HAP section of terribly high purity for all ms-HAP biomaterials developed during the study. These findings are supported by the studies discussed in this review. These innovative biomaterials are also compatible for medical specialty applications in bone regeneration because they may have the therapeutic effects and the features of HAP for bone formation. In addition to implants or coatings on argentiferous implants, our study clearly identified a reasonable trade technique for the search of a new generation of multi-substituted bioactive HAPs as viable candidates for bone regeneration and bone replacement applications.

Dentistry and engineering science working together would raise the bar for present treatment methods. It will provide a cutting-edge approach for the production of dental materials, enhancing treatment effectiveness, precision, and speed while lowering costs. Some development of modern methods for the early detection and treatment of bone defects will significantly benefit from material engineering research. Research on this field combined with antimicrobial materials also has the potential to

advance the medical dentistry. The development of highly sophisticated, restorative NPs requires extensive analysis in order to be successful in odontology. Before using new material in a clinical setting, it is crucial to have sufficient clinical knowledge. The potentials and capacities of engineering science within the dentistry discipline are highlighted in this critical review.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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