




Hydroxyapatite for food packaging applications: translating evidence from biomedical and environmental research

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ABSTRACT

The increasing demand for sustainable, functional food packaging has heightened interest in bio-based additives that can enhance material performance while maintaining consumer safety. Hydroxyapatite (HA), extensively studied in biomedical and environmental contexts for its physicochemical stability, ion-exchange capacity, and biocompatibility, has recently been proposed as a prospective additive for food packaging systems. This review critically examines the feasibility of translating insights from biomedical and environmental studies to packaging applications by systematically analyzing peer-reviewed literature published between 2021 and 2025 following PRISMA guidelines. The synthesized evidence indicates that HA incorporation, typically at low filler loadings, has been reported to improve tensile strength and thermal stability, with polymer permeability improvements of up to several tens of percent observed in previous studies. Environmental studies further demonstrate HA's high adsorption capacity and ion-exchange behavior, whereas biomedical research provides indirect evidence of biological compatibility and controlled interaction with active agents. Nevertheless, direct experimental evidence in food packaging remains limited, including polymer–filler incompatibility, nanoparticle migration risks, and regulatory compliance. This review, therefore, positions hydroxyapatite as a prospective rather than validated packaging additive and outlines critical research priorities, including quantitative migration testing, formulation optimization, and regulatory evaluation, required to assess its practical feasibility in safe and sustainable food packaging applications.

1. Introduction

Global demand for sustainable, functional food packaging is growing due to environmental concerns and increased consumer awareness about food quality and safety. Traditional petroleum-based materials offer protection but pose ecological risks, including non-biodegradability and potential chemical migration into food. Bio-based materials (e.g., cellulose, PLA, PHA) have ecological benefits but often lack mechanical strength, barrier performance, and antimicrobial properties. These weaknesses hinder their widespread use (Huang et al., 2019; Noviyanti et al., 2024; Shouket et al., 2023).

Hydroxyapatite (HA), a calcium phosphate-based mineral with the chemical formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, is the primary inorganic component of hard tissues such as bone and teeth (Noviyanti et al., 2020). It has structural similarities to biological apatite and is widely used in

biomedical applications, such as bone regeneration, dental implants, and controlled drug delivery, due to its biocompatibility and bioactivity. (da Costa Brito et al., 2024; Malvano et al., 2022; Mehmood et al., 2025; Shouket et al., 2024; Sun et al., 2024). These domains illustrate HA's multifunctionality and provide insight into underlying mechanisms relevant to interaction with biological tissues as illustrated in Fig. 1.

Beyond biomedical use, HA has also shown significant potential in environmental applications. It has been effectively used for the adsorption of heavy metals, dyes, and organic pollutants from wastewater, thanks to its high surface area and ion-exchange capabilities (Amenaghawon et al., 2022; Hossain et al., 2023). Additionally, its role in controlled release systems and environmental remediation further demonstrates its multifunctionality (Ibrahim et al., 2020). These characteristics suggest that HA could be adapted for use in food packaging systems, particularly where contaminant adsorption, barrier

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enhancement, or antimicrobial action is desirable.

Despite these promising attributes, the application of HA in food packaging remains largely underexplored, with limited experimental studies directly assessing its performance within polymer matrices. Moreover, insights derived from biomedical and environmental studies cannot be directly extrapolated to food packaging systems, as critical challenges related to polymer-HA interfacial compatibility, nanoparticle migration, and regulatory compliance must be carefully addressed. Recent studies on nanomaterial migration into food simulants further underscore the need for material designed specifically to meet food-contact safety requirements. In this context, modern food packaging increasingly demands materials capable of responding to microbial contamination, absorbing harmful substances, and controlling gas and moisture transmission, which are increasingly sought after in modern food systems (Aziz et al., 2024; Singh et al., 2020; Zhang et al., 2025). Incorporating functional fillers or additives with proven biocompatibility and environmental relevance, such as HA, aligns with these objectives. Given its ion-exchange capacity, reported antimicrobial potential, and compatibility with polymer matrices under appropriate formulation strategies, HA represents a promising candidate for next-generation food packaging materials, though it still requires rigorous validation.

Although bio-based packaging has progressed considerably, the incorporation of inorganic additives remains relatively underexplored, primarily due to safety, compatibility, and regulatory compliance. HA, however, represents a unique and compelling case. Its biocompatibility, bioactivity, and multifunctional characteristics have been extensively validated in biomedical and environmental fields, its potential role in food packaging systems has not yet been systematically evaluated. To the best of our knowledge, there are no substantial experimental studies directly assessing the incorporation of HA into packaging matrices, highlighting a critical gap in the current literature. This gap is particularly significant, as insights from biomedical and environmental research offer valuable perspectives for the rational design of functional, safe, and sustainable packaging materials. While hydroxyapatite has been extensively studied in biomedical and environmental contexts, the direct transfer of findings from these domains to food packaging systems require careful interpretation. Accordingly, this review aims to address this gap by providing a cross-disciplinary synthesis that integrates the physicochemical characteristics of HA with evidence from biomedical and environmental studies, thereby establishing a theoretical foundation and research roadmap for future experimental investigations. Biological and aqueous environments differ fundamentally from solid polymer matrices in terms of mass transport mechanisms, exposure pathways, and material interactions. Therefore, in this review, evidence from biomedical and environmental studies is not treated as directly applicable to food packaging, but rather as a source of mechanistic

insight to inform material design, safety considerations, and performance expectations in packaging systems. This present work explicitly examines the interplay between HA properties and their implications for packaging functionality, safety, and regulatory considerations.

2. Method

This review used a Systematic Literature Review (SLR) approach based on PRISMA guidelines for transparency and rigor. We systematically analyzed peer-reviewed publications published between 2021 and 2025 about HA’s properties and their relevance to biomedical, environmental, and food packaging uses. The PRISMA flow diagram summarizes how studies were selected. We also show publication trends and themes to support the systematic method.

2.1. Literature search strategy

A systematic search was conducted across Scopus, Web of Science, PubMed, and ScienceDirect, covering publications between 2021 and 2025. Database-specific Boolean search strings were applied and adapted to each database’s indexing system. The primary search strings included: (“Hydroxyapatite” OR “HA”) AND (“food packaging”), (“Hydroxyapatite” OR “HA”) AND (“membrane”) AND (“biomedical application” OR “antibacterial”), (“Hydroxyapatite” OR “HA”) AND (“membrane”) AND (“environmental remediation” OR “water purification”). Only peer-reviewed research articles, review papers, and book chapters were considered. Conference proceedings, patents, and pre-prints were excluded to ensure the credibility and reliability of the sources. Duplicate records retrieved from multiple databases were identified and removed using reference management software, followed by manual verification of titles and author names to ensure accuracy, as summarized in Table 1.

2.2. Inclusion and exclusion criteria

The inclusion criteria comprised peer-reviewed English-language articles published between 2021 and 2025, focusing on hydroxyapatite

Table 1
Key steps in the systematic literature review workflow.

| Step | Description |
|------|--------------------------------|
| I | Formulating research questions |
| II | Search relevant studies |
| III | Evaluate study quality |
| IV | Summarize findings |
| V | Interpret results |

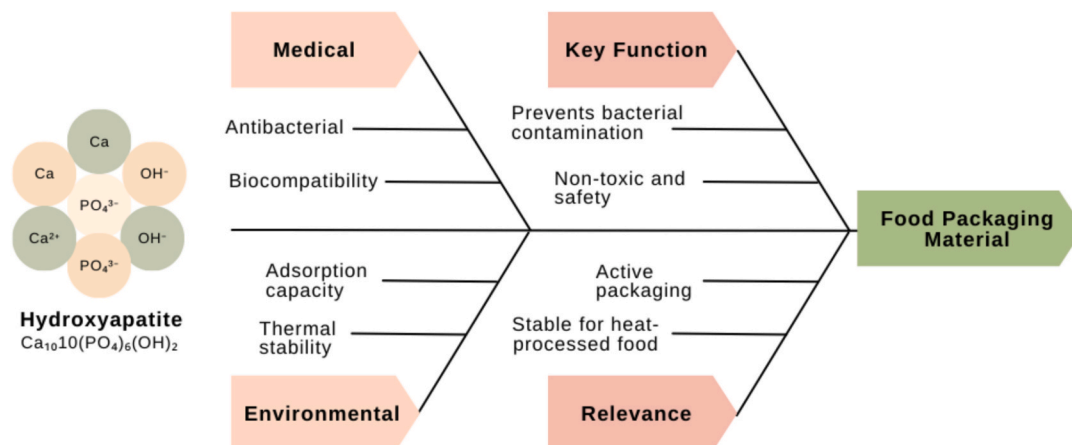


Fig. 1. Schematic diagram of HA properties in the biomedical and environmental field relevant to food packaging.

(HA) and its applications in biomedical, environmental, or polymer-based systems with potential relevance to food packaging. This time window was selected to highlight recent advances in HA synthesis, nanostructural modification, and biopolymer integration, all of which are directly applicable to next-generation packaging technologies. Foundational studies published before 2021 were cited only in the introduction section for background purposes and were explicitly excluded from the systematic screening and synthesis. Exclusion criteria included non-peer-reviewed sources, conference abstracts, and papers lacking direct relevance to HA composites. The selection of literature was based on predefined inclusion and exclusion criteria to ensure relevance and quality. Studies included discussion of physicochemical properties of HA relevant to food packaging applications, particularly its antibacterial activity, adsorption capacity, mechanical reinforcement, and biocompatibility. Research focusing on HA-polymer composites, especially in biopolymer matrices, was also considered. Conversely, studies solely addressing HA in bone regeneration, drug delivery, or dental applications, without relevance to key packaging properties, were excluded. Of the 296 records initially identified, 3 duplicates were removed, leaving 293 articles for title and abstract screening. Additionally, articles lacking experimental data or theoretical insights into HA's functional properties, as well as grey literature such as proceedings and technical reports, were excluded from this review.

Study selection and screening (PRISMA)

Study selection and screening were conducted following the PRISMA framework. After duplicate removal, retrieved records were screened in two stages: title-abstract screening to exclude clearly irrelevant studies, followed by full-text assessment using predefined inclusion and exclusion criteria focused on relevance to HA applications with potential implications for food packaging. The identification, screening, eligibility, and inclusion process is summarized in the PRISMA flow diagram (Fig. 2), while the thematic distribution of the selected studies across biomedical, environmental, and packaging-related domains is presented in Fig. 3.

2.3. Data extraction and synthesis

The relevant information from the selected studies was systematically extracted and organized into major thematic categories to provide a comprehensive perspective on the potential of hydroxyapatite (HA) as a food packaging additive. An initial pool of 293 articles was screened, focusing on four principal dimensions: (i) the physicochemical

characteristics of HA, such as composition, crystallinity, porosity, and stability; (ii) its biomedical applications, particularly concerning biocompatibility, cytotoxicity, and antimicrobial functions; (iii) its environmental applications, with emphasis on adsorption mechanisms, pollutant removal, and controlled release; and (iv) its prospective integration into food packaging, including effects on mechanical strength, barrier performance, and food safety. Following the screening process, 46 articles were retained for qualitative synthesis, which enabled the identification of research trends, knowledge gaps, and prospective directions. Ultimately, 21 of these articles were used as the primary references to establish a theoretical framework for further experimental investigations into HA-based food packaging materials. Given the narrative and cross-disciplinary nature of this review, a formal risk-of-bias assessment was not conducted; however, only peer-reviewed articles with clear methodological descriptions and relevant experimental or theoretical contributions were included.

3. Main discussion

This discussion synthesizes evidence from biomedical, environmental, and packaging-related studies to highlight key functional insights, unresolved limitations, and translational challenges associated with hydroxyapatite-based food packaging systems. The integration of hydroxyapatite (HA) into biopolymer-based material has been explored in various experimental studies to enhance the functional properties of food packaging applications (Thool et al., 2024). These studies aim to evaluate the effects of HA addition on thermal stability, antibacterial activity, mechanical strength, and barrier properties. Table 2 summarizes recent studies investigating HA-based composite systems proposed for food packaging applications. Rather than demonstrating uniform performance enhancement, the reported outcomes highlight the matrix-dependent and formulation-specific role of hydroxyapatite. Across different polymer systems, HA primarily functions as a reinforcing filler and structural modifier, enhancing tensile strength and rigidity by improving load transfer within the composite matrix. However, any reported improvements in

elongation at break or flexibility are more plausibly attributed to the synergistic effect of secondary additives, such as plasticizers or polyphenolic compounds, which enhance chain mobility and interfacial dispersion rather than to HA itself.

As shown in Table 2, incorporating hydroxyapatite generally enhances tensile strength and thermal stability across various biopolymer matrices, reflecting its rigid mineral structure and its ability to improve stress transfer within composite systems. Moreover, the incorporation of

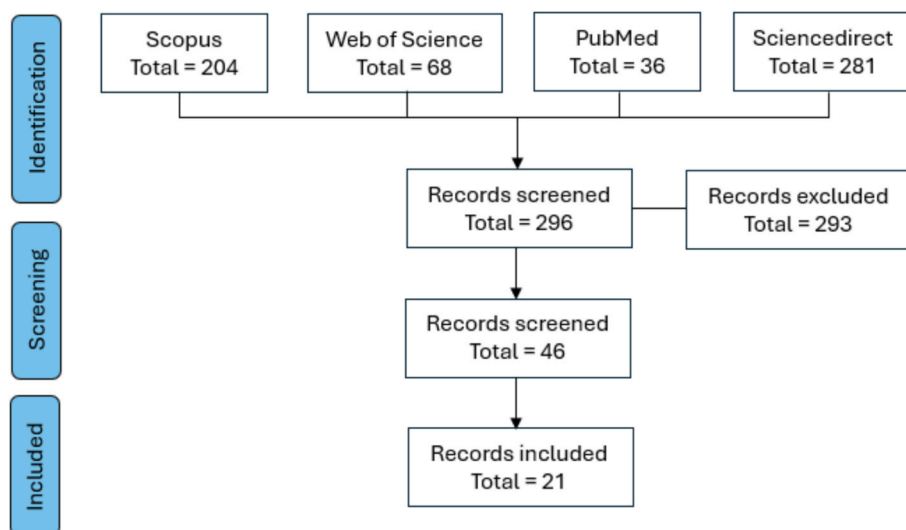


Fig. 2. Illustrative PRISMA outline of the systematic literature review methodology.

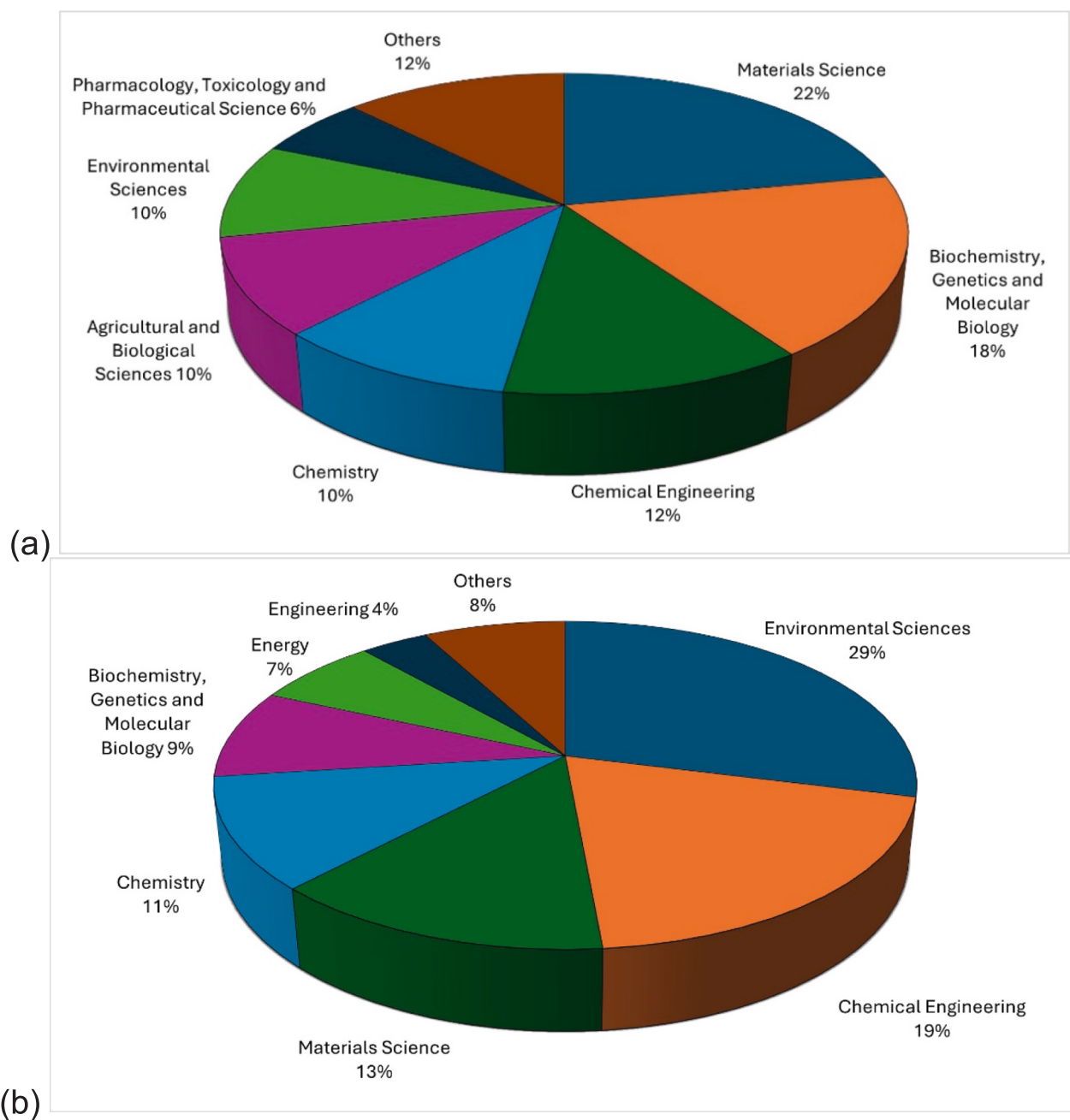


Fig. 3. Temporal published research analysis trend on Scindirect (2025 – 2021) of hydroxyapatite in (a) biomedical and (b) environmental applications.

HA into chitosan film has been reported increase with higher glass transition (141 to 155 T_g with 1% HA addition) and delayed weight loss temperature by 60% from 374 °C for neat CS to 383 °C and 404 °C for CS-HA 1% and 3%, respectively) (Thool et al., 2024; Upadhyay & Ullah, 2024). According to (Qiu et al., 2024), HA also improved the thermal stability of pure chitosan film with a higher residual weight ratio from 32.18% for pure CS film and 34.25% for CS-HA film). Nevertheless, this mechanical reinforcement is frequently accompanied by reduced ductility, particularly in formulations lacking flexible or plasticizing components. Such behavior is consistent with established composite mechanics, where the inclusion of inorganic fillers increases stiffness at the expense of elongation at break (Y. Wang et al., 2023).

Improvements in antibacterial performance reported in several studies should also be interpreted with caution. In most cases, effective antibacterial activity arises from composite formulations containing additional bioactive agents, such as plant-derived polyphenols or

essential oils, rather than from HA alone. Within these systems, HA primarily serves as a structural scaffold or carrier that facilitates the dispersion and stabilization of antibacterial compounds, rather than acting as a dominant antibacterial agent (Qiu et al., 2024; Y. Wang et al., 2023). Nevertheless, HA itself may exhibit modest antibacterial activity through surface-mediated interactions and ionic exchange mechanisms (Malvano et al., 2022). As reported by (Adzkiya et al., 2026), the incorporation of HA into the cellulose acetate matrix activated the antibacterial properties, as evidenced by increased inhibition zones against *Bacillus subtilis* (from 0 to 1.27 mm) and *Pseudomonas aeruginosa* (from 0 to 1.14 mm). It may be activated, but the activity still remains weak. However, this intrinsic effect is generally insufficient for robust antibacterial performance, thereby justifying the incorporation of complementary bioactive agents to achieve effective antibacterial functionality.

Similarly, reductions in water vapor or gas permeability observed in HA-based composites are better attributed to increased diffusion

Table 2
The effects of HA incorporation into the composite in food packaging applications.

| Composite | Form | Advantages on application | Mechanical strength Thermal stability | Antibacterial | Elasticity | Permeability | Ref. |
|---|---------|---|--|---|---|---|--------------------------|
| Hydroxyapatite porous microspheres (HPMS)-Polyvinyl alcohol (PVA)-sesbania gum (SG)-tea tree oil(TTO) | Film | Provided theoretical basis for bio-based packaging with 2% loaded TTO-HPMS | TTO-HPMS enhanced thermal stability | Increased bacteriostatic efficiency and inhibition zone against <i>S.aureus</i> and <i>E. coli</i> from 6.86 mm to 9.70 mm | Decreased elongation at break from 437% to 286% | Highest WVP reached with 1.5% TTO-HPMS | (Y. Wang et al., 2023) |
| Chitosan-hydroxyapatite (CS-HA) | Film | Signified potential of film in food packaging | Higher glass transition (141 to 155 T _g with 1% HA addition) and improved thermal stability (delayed weight loss temperature by 60% from 374 °C for neat CS to 383 °C and 404 °C for CS-HA 1% and 3%, respectively) | – | 61.54% increased in tensile strength with incorporated 3% HA | WVP decreased by 52% with the addition of HA compared to neat CS film | (Upadhyay & Ullah, 2024) |
| Chitosan-nano hydroxyapatite-tea polyphenol (CS-HA-TP) | Film | Demonstrated excellent performance in the preservation of semi-dried fish product (prolonged the product by > 7 days) | Improved thermal stability (higher residual weight ratio; 34.25% for CS-HA film than CS film 32.18%) | Delayed increases in the microbial proliferation (lower total viable count from 7.47 log CFU/g to 6.53 log CFU/g) | Increased tensile strength by 126.22% and elongation at break by 67.87% | Reduced 29.78% WVP | (Qiu et al., 2024) |
| Hydroxyapatite/Quercetin-sodium alginate (HA/QUE-SA) | Coating | Prolong the quality of fresh chicken fillet during the storage period of 11 days (prolonged 3 days) | No significant difference after cooked at high temperature | Inhibit bacterial growth against <i>Pseudomonas spp.</i> and <i>Enterobacteriaceae</i> (with 7–8 CFU/g bacteria at 11 days; 3 days later compared to control) | – | – | (Malvano et al., 2022) |
| Cassava starch-nano hydroxyapatite | Film | Demonstrated the efficient HA (with 0.8% concentration) incorporation in cassava starch film as biodegradable packaging | – | – | Improved tensile strength from 12.5 MPa to 16.10 MPa and elongation at break from 1.55% to 6.87% | Reduction of WVTR by 42% | (Thool et al., 2024) |
| Poly(lactic acid) / hydroxyapatite | Film | Exhibited higher stabilization efficiency for biodegradable package | Better thermal resistance (increased filler content from 2 to 10 wt%) | – | – | – | (Zaharescu et al., 2020) |
| Alginate/starch beads with hydroxyapatite | Beads | HA incorporation increased stability to prolong food quality | Exhibited higher thermal stability (decreased weight loss from 67% to 60–37%; with HA content varying from 2 to 10% w/v) | – | – | – | (Kongthong et al., 2025) |
| Carboxymethyl cellulose (CMC) / sodium alginate / nano-hydroxyapatite / tea polyphenols | Film | Reduces food (tomato) weight loss (9.04% to 7.52%) and extends shelf life | – | – | Exhibited improved tensile strength (45.19 MPa to 63.58 MPa) and elongation (52.56% to 82.45%) | Excellent oxygen permeability (1.841 x 10 ⁻³ g/m ² s) | (Z. Wang, 2025) |
| Cellulose acetate / hydroxyapatite (CA/HA) | Film | Highlighted potential of CA/HA film as food packaging material | Increased thermal stability (decreased weight loss from 5.93% for pure CA film to 5.07 for CA with 20% HA content) | Activated the antibacterial properties via increased inhibition zone against <i>Bacillus subtilis</i> (from 0 to 1.27 mm) and <i>Pseudomonas aeruginosa</i> (from 0 to 1.14 mm) | Increased compressive strength (from 0.207 to 0.749 kgf) and tensile strength (from 0.206 to 0.397 kgf) | Lower WVTR value than pure CA film approximately by 45% | (Adzkiya et al., 2026) |

tortuosity and microstructural modification of the polymer matrix, rather than to direct adsorption phenomena. These findings underscore that HA's functional contribution in food packaging systems is highly dependent on formulation design, polymer compatibility, and filler dispersion. Consequently, performance enhancements reported across different studies are not directly comparable and should not be

generalized without careful consideration of matrix-specific interactions and trade-offs.

The conceptual framework of this review is illustrated in Fig. 4, which outlines the interrelationships between hydroxyapatite's physicochemical properties and its demonstrated functions in biomedical and environmental fields, providing a foundation for its prospective

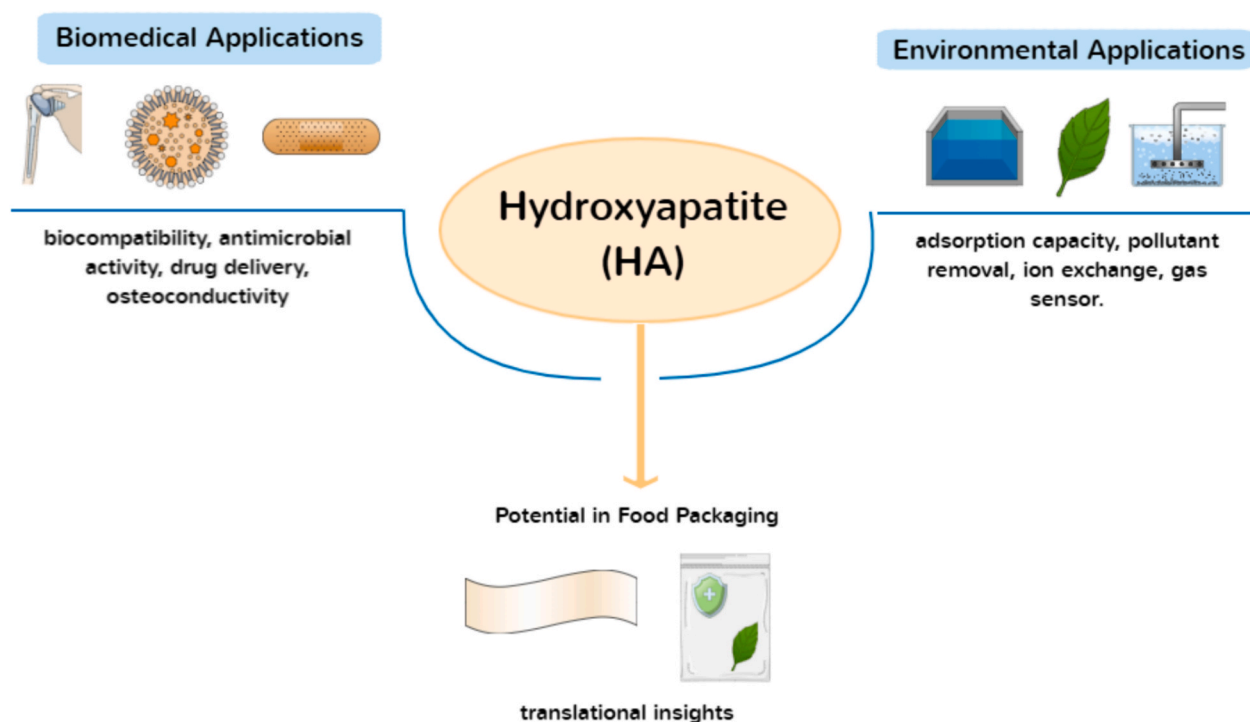


Fig. 4. Schematic conceptual framework insights from biomedical and environmental applications of hydroxyapatite can be translated into prospective functions in sustainable food packaging.

application in food packaging systems. In this review, biomedical and environmental studies are not discussed as independent application domains, but rather as reference systems to elucidate the physicochemical mechanisms of hydroxyapatite that may be relevant to food packaging performance. Specifically, biomedical studies provide insight into biocompatibility, interfacial interactions, and controlled release behavior, while environmental applications highlight adsorption mechanisms, ion exchange, and stability under complex conditions. These mechanisms are critically evaluated in the context of solid polymer matrices to assess their potential transferability to food packaging systems.

3.1. Fundamental physicochemical properties of hydroxyapatite

As previously discussed, hydroxyapatite (HA) possesses a wide array of physicochemical properties, including biocompatibility, bioactivity, porosity, and ion-exchange capacity, that have been successfully applied in biomedical and environmental fields. These properties also position HA as a highly promising additive in food packaging systems, where functionality beyond basic containment is increasingly demanded. Specifically, HA can play multiple functional roles in packaging matrices, including enhancing barrier performance, providing antibacterial activity, and supporting active or intelligent packaging mechanisms. As outlined in Table 3, these potential roles highlight HA's versatility and underscore the importance of further research to optimize its integration into biopolymer-based packaging materials.

While hydroxyapatite is widely recognized for its porous structure and large surface area, the relevance of these features differs substantially across biomedical, environmental, and packaging contexts. In composite systems, such characteristics primarily influence interfacial interactions with polymer and biopolymer matrices, contributing to biocompatibility and structural compatibility rather than acting as standalone functional agents. Consequently, hydroxyapatite represents a promising candidate for the development of composite material (Voskanyan et al., 2024; Zaharescu et al., 2020). Its biocompatible characteristics exhibit value in the medical field, particularly for bone

Table 3
Summary of Functional Features of Hydroxyapatite Relevant to Food Packaging.

| Functional Feature | Description | Relevance to Packaging | Ref. |
|------------------------|--|--|--|
| Biocompatibility | Non-toxic and safe | Indicates safety and compatibility of the contact from migration of material to food product | (Voskanyan et al., 2024) |
| Antibacterial activity | Inhibit growth of gram-positive and gram-negative bacteria | Prevents microbial contamination in packaging and prolong the product quality | (Qiu et al., 2024; Y. Wang et al., 2023) |
| Adsorption capacity | Ability to adsorb gases, moisture, and toxins | Suitable for active packaging applications | (Shafiq et al., 2023) |
| Thermal stability | Stable at high processing temperatures | Enables use in heat-processed packaging systems | (Kongthong et al., 2025; Qiu et al., 2024) |

and teeth implants, thereby indicating safety and a non-toxic profile for the human body (Ielo et al., 2022). Beyond biomedical applications, this biocompatibility also supports its use in environmental contexts, especially as an adsorbent for heavy metals in wastewater treatment, where material safety and minimal ecological impact are essential (Voskanyan et al., 2024). In packaging composites, HA primarily enhances barrier performance by increasing the tortuosity of the gas and vapor diffusion pathways within the polymer matrix. Although its polar surface groups may interact with certain small molecules, such effects are secondary compared to its role in physically obstructing diffusion. Therefore, HA's barrier improvement mechanism arises mainly from diffusion-mediated processes rather than true bulk adsorption, distinguishing it from the adsorption behavior observed in environmental remediation systems (Lara-Ochoa et al., 2021; Qiu et al., 2024).

While HA has demonstrated promising reinforcing and barrier-enhancing capabilities, the inherent interfacial incompatibility

between its hydrophilic surface and hydrophobic polymer matrices (e.g., PLA or PVA) poses a significant challenge. Unmodified HA particles tend to aggregate and form interfacial voids, which may hinder stress transfer and degrade mechanical performance. To overcome these limitations, surface functionalization is essential. Techniques such as silane coupling, surfactant coating, and polymer grafting have been shown to improve dispersion, reduce interfacial tension, and strengthen interfacial adhesion (Akindoyo et al., 2017; Farkas et al., 2022; Gapsari et al., 2025; Morsy, 2024; Subramaniyan et al., 2024). These modifications enable effective load transfer within the composite and ensure uniform filler distribution, key factors. Hence, surface modification is a crucial step toward achieving reliable and scalable HA-based food packaging materials.

Microbial activity caused by food spoilage bacteria is a primary factor in the degradation of various food products, often resulting in reduced quality, accelerated spoilage, and substantial economic losses (Ben Lagha et al., 2020). To address this issue, antibacterial agents have been employed in food preservation to inhibit the growth of pathogenic bacteria. In line with increasing health and environmental awareness, consumers are increasingly preferring natural and safe preservatives (Yuliana et al., 2022). HA also has inherent antibacterial properties, which are particularly beneficial in minimizing bacterial contamination. This activity is attributed to its surface characteristics and interaction with bacterial cell walls, which can hinder bacterial adhesion and growth (Ain et al., 2019; Seyedmajidi et al., 2018). Hence, it should still be noted that the intrinsic antibacterial activity of pristine HA is generally mild, and stronger antibacterial effects reported in composite systems are often associated with synergistic interactions with secondary bioactive agents or polymer matrices (Malvano et al., 2022; Qiu et al., 2024).

In addition to physical and microbiological safety, the potential for chemical migration from packaging materials into food remains a critical consideration. Such migration may involve additives or residual synthesis compounds that can leach into food under certain storage or temperature conditions. Although hydroxyapatite (HA) is generally recognized as chemically stable and safe, careful assessment is still required to ensure that all incorporated additives comply with established safety thresholds. HA is widely recognized for its biocompatibility and low toxicity; however, these characteristics are not universal across all forms and applications. Importantly, biocompatibility demonstrated in biomedical applications does not automatically translate into safety for food-contact materials, as exposure routes, contact durations, and regulatory evaluation criteria differ substantially between biological tissues and food packaging systems. The safety profile of HA is strongly influenced by its source, synthesis method, degree of crystallinity, particle size, and surface modification. In particular, nano-sized HA particles may raise additional concerns related to cellular internalization and oxidative stress, necessitating careful evaluation of potential migration behavior in food-contact applications. Consequently, prospective use of HA in food packaging requires thorough migration testing and regulatory compliance prior to commercialization. According to (European Commission, 2025), regulations on plastic materials intended for food contact specify migration limits (SMLs) are defined to safeguard consumer health. In parallel, the European Food Safety Authority (EFSA) emphasizes the importance of assessing long-term exposure, particularly from emerging biodegradable or bio-based materials. While HA, composed of calcium and phosphate ions, is classified as a GRAS substance and generally exhibits minimal migration risk in its conventional bulk form (Adzkie et al., 2025). This designation does not necessarily extend to nano-scale HA, which may require separate regulatory evaluation depending on its physicochemical characteristics and intended application.

Regulatory compliance is a decisive factor in determining the feasibility of hydroxyapatite (HA) for food-contact applications. Under EU Regulation No. 10/2011 and EFSA guidance, mineral-based fillers are required to undergo migration testing using standardized food simulants

(aqueous, acidic, and fatty) to assess substance release and compliance with specific migration limits (SMLs) as summarized in Table 4. Similarly, the U.S. Food and Drug Administration (FDA, 21 CFR 177) mandates compositional analysis and extractive testing for indirect food additives. At present, hydroxyapatite-based nanocomposites do not possess explicit regulatory authorization for use in food packaging applications. Consequently, despite promising laboratory-scale performance, regulatory approval remains a critical challenge for industrial translation and must be addressed through systematic migration, toxicological, and exposure assessments.

When benchmarked against authorized inorganic fillers such as calcium carbonate (CaCO_3) and titanium dioxide (TiO_2), HA offers a comparable chemical stability and a lower cytotoxicity profile. However, its regulatory status in food packaging applications remains preliminary, primarily due to the limited availability of migration, toxicokinetic data, and long-term exposure data, particularly for nano-scale formulations. For industrial implementation, HA-based packaging systems must therefore demonstrate not only adequate physicochemical performance, but also strict compliance with regulatory requirements, including migration limits, toxicological safety, and long-term exposure assessments under internationally recognized frameworks. Despite its mineral origin, systematic data regarding the gastrointestinal fate, bioavailability, and cumulative exposure of HA, especially in nano-sized forms, remain scarce. This limitation highlights the necessity for application-specific safety evaluations before HA can be established as a regulatory-compliant additive in sustainable food packaging.

Although hydroxyapatite is widely regarded as safe in its bulk form, nanoscale HA (<100 nm) introduces specific regulatory and toxicological considerations when applied in food-contact materials. Under the EU Regulation No. 10/2011, migration testing into aqueous and fatty food simulants required to evaluate the potential release of nanoparticles. Migration behavior is strongly influenced by particle size, morphology, surface charge, and dissolution kinetics, all of which affect gastrointestinal exposure and biological interaction. While the intrinsic chemical composition of HA ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) suggests low inherent toxicity, nanoscale formulations may exhibit altered bioavailability and enhanced interaction with biological tissues compared to bulk materials (J. Han et al., 2023; M. Han et al., 2024). Consequently, nano-hydroxyapatite is subject to heightened regulatory scrutiny, increased surface area, and modified dissolution behavior, which may influence cellular uptake, accumulation, and long-term exposure, factors that are not fully captured by conventional bulk-material safety evaluations. Therefore, the safe implementation of HA nanocomposites in food packaging requires a comprehensive evaluation of migration dynamics, cytotoxicity, and long-term exposure effects in accordance with EFSA and EU safety guidelines. In this context, the suitability of hydroxyapatite for food packaging applications should be regarded as prospective rather than conclusive until supported by systematic toxicological and migration studies.

To establish the novelty of hydroxyapatite (HA) in food packaging applications, it is essential to compare its performance potential with that of other commonly employed fillers in biopolymer-based systems. Existing reinforcement agents, such as nanostructured montmorillonite, cellulose nanofibers, and metallic nanoparticles (e.g., AgNPS and ZnO), have been widely used to enhance the mechanical, barrier, and antimicrobial properties of packaging materials. However, each of these additives presents distinct advantages and limitations, particularly regarding safety, biocompatibility, and environmental persistence. As shown in Table 5, HA offers a unique balance of functional performance and safety credentials, positioning it as a sustainable alternative with cross-disciplinary potential derived from biomedical and environmental research.

Table 5 provides a comparative overview of commonly employed fillers in biopolymer-based food packaging, highlighting their functional roles, advantages, and inherent limitations. Established fillers, such as cellulose nanofibers (CNF), are widely recognized for their mechanical

Table 4
Potential chemical substances from packaging materials and relevant migration limits.

| Substance | Possible Source | SML (mg/kg food) | Regulatory References |
|---------------------|--|--|--|
| Formaldehyde | Adhesives, crosslinkers | 15.0 | EU Reg. 2025 amending No. 10/2011 |
| Phosphate ions | Natural component of HA | Not regulated (GRAS) | EFSA |
| Calcium | Natural component of HA | Not regulated (GRAS) | EFSA |
| Hydroxyapatite (HA) | Multifunctional additive for reinforcement, adsorption, and antimicrobial protection | Biocompatible, bioactive, GRAS-certified, stable, and non-toxic; enhances mechanical, barrier, and safety properties | Limited experimental validation in packaging; dispersion challenges in polymer matrices |
| | | | Represents a sustainable and safe alternative with cross-functional potential derived from biomedical and environmental insights |
| | | | Malvano et al., 2022; Qiu et al., 2024; Thool et al., 2024 |

Table 5
Comparison of Common Fillers Used in Biopolymer-Based Food Packaging and Their Key Functional Attributes.

| Filler Type | Main Function in Packaging | Advantages | Limitations | Relevance to HA-Based Applications | Ref. |
|------------------------------------|---|---|---|---|---|
| Cellulose Nanofibers (CNF) | Structural reinforcement and biodegradability enhancement | Renewable, biodegradable, and good mechanical performance | Hydrophilic nature may compromise moisture resistance; limited antimicrobial activity | HA can complement CNF's reinforcement with additional antimicrobial and adsorption capabilities | (Kwak et al., 2025) |
| Silver Nanoparticles (AgNPs) | Antimicrobial agent | Strong broad-spectrum antibacterial activity | Potential cytotoxicity, migration concerns, and regulatory restrictions | HA provides safer antimicrobial functionality with GRAS status and lower migration risk | (Plaeyao et al., 2025; Sitisan et al., 2024) |
| Zinc Oxide Nanoparticles (ZnO-NPs) | UV-blocking and antimicrobial activity | Good antimicrobial and photocatalytic effects | Possible toxicity and particle migration; limited biodegradability | HA offers comparable antibacterial potential with better environmental compatibility | (Hendrawati et al., 2023; Saleh et al., 2024) |

reinforcement and biodegradability; however, their hydrophilic nature often compromises moisture barrier performance and provides limited antibacterial functionality (Hamad et al., 2020; Kwak et al., 2025). In contrast, metal-based fillers such as silver and zinc oxide nanoparticles offer strong antibacterial or UV-blocking effects but raise persistent concerns regarding cytotoxicity, nanoparticle migration, and regulatory restrictions (Hendrawati et al., 2023; Plaeyao et al., 2025; Saleh et al., 2024; Sitisan et al., 2024). Within this context, HA occupies an intermediate functional position. Unlike AgNPs and ZnO, HA is intrinsically biocompatible and chemically stable, with GRAS status for bulk or food-related formulations, thereby substantially reducing safety-related barriers for food-contact applications. However, this designation still requires independent migration and toxicological evaluation (Adzka et al., 2025; J. Han et al., 2023; M. Han et al., 2024). However, its antibacterial activity is comparatively mild and formulation-dependent, often requiring combination with bioactive agents or surface modification to achieve performance levels comparable to conventional antibacterial fillers (El Fawal et al., 2019; Y. Wang et al., 2023). Nevertheless, this moderate antibacterial performance, combined with its superior safety profile and multifunctionality, positions HA as a promising complementary filler rather than a direct replacement for highly active antimicrobial nanoparticles in food packaging systems.

From a structural perspective, HA primarily functions as a reinforcing filler and tortuosity enhancer, improving mechanical stiffness and reducing gas permeability rather than acting as a standalone active agent (Thool et al., 2024; Upadhyay & Ullah, 2024). Nevertheless, challenges related to dispersion, interfacial compatibility with polymer matrices, and limited experimental validation in real packaging systems remain significant constraints. Therefore, rather than replacing existing fillers, HA should be viewed as a complementary additive whose value lies in balancing moderate multifunctionality with superior safety and environmental compatibility. In this context, understanding HA's long-established behavior in biological systems becomes essential for evaluating its safety profile and functional limitations prior to food-contact applications.

3.2. Biomedical Perspectives: Biocompatibility, Safety, and functional behavior

Growing interest has focused on developing green antibacterial agents that minimize the risk of resistance while offering broad-spectrum activity. In this context, hydroxyapatite has emerged as a promising material for biomedical applications (Yi et al., 2024). In biomedical and pharmaceutical research, such materials are crucial for improving drug efficacy, enabling targeted treatment approaches, and advancing regenerative medicine. Among various candidates explored, HA demonstrated such significant potential (Noviyanti et al., 2024).

Hydroxyapatite has a long way to go in being utilized in the biomedical field due to its remarkable characteristics, namely its unique biocompatibility, bioactivity, osteoconductive, and functional versatility, as stated in Table 6. These properties are included not as direct evidence for food packaging performance, but as a mechanistic reference framework to understand HA-matrix interactions, surface

Table 6
Biomedical-Inspired Functionalities of Hydroxyapatite for Food Packaging.

| Application Area | Key Function | Relevance to Packaging | Ref. |
|---------------------------|---|--|---|
| Bone implants | Biocompatibility, bioactivity, low toxicity | Ensures safety and compatibility with food contact | (Iwanami-Kadowaki et al., 2021; Kotak & Devarajan, 2020) |
| Drug delivery and carrier | Controlled release, carrier role, increasing adsorption capacity | Enables potential for smart or active packaging systems | (Asghar et al., 2022; Farkas et al., 2021; Wan et al., 2022) |
| Drug release | Controlled release, biocompatibility | Ensures safety and compatibility with food contact | (El-Habashy et al., 2021; Levingstone et al., 2021) |
| Wound dressing | Antimicrobial, regenerative, enhanced mechanical properties and thermal stability | Suggests microbial protection capabilities and flexibility of material | (Cunha et al., 2020; Tabassum et al., 2024; Q. Wang et al., 2024) |

reactivity, and material stability. Importantly, differences in exposure conditions, contact media, and performance requirements between biomedical and packaging systems necessitate careful reinterpretations of these findings (Munir et al., 2021). To avoid conceptual overlap, biomedical and environmental evidence are discussed separately before being translated into packaging implications. Moreover, HA also serves as a carrier in drug delivery and release systems, illustrated in Fig. 5. This figure is not intended to represent a direct packaging system but rather to illustrate the adsorption-release principles that may inspire active packaging design. It has the capability to control the release of active substances, a trait that may be repurposed for smart or active packaging solutions (Rial et al., 2021). Drug carriers are made up of many binding agents (e.g., hydrogels, xerogels, or biodegradable polymers) that release the medication for various uses, namely anesthetic effects first, followed by anti-inflammatory protection and bone growth stimulation (Loca et al., 2015). Its antimicrobial and regenerative properties, commonly harnessed in wound healing applications, further reinforce HA's potential to enhance food safety by preventing microbial contamination (Lamkhao et al., 2019). Such features suggest that HA may also be safe and effective in having contact between food and bioplastic materials.

Although biomedical studies consistently demonstrate HA's biocompatibility, chemical ability, and surface functionality, these attributes do not directly guarantee suitability for food-contact applications. In packaging systems, HA is embedded within solid polymer matrices, where gas and vapor transport, mechanical reinforcement, and migration behavior are governed by diffusion kinetics, interfacial adhesion, and composite morphology rather than biological interactions (Adzkie et al., 2025; Lara-Ochoa et al., 2021). Consequently, biomedical data should be regarded as supportive but indirect evidence, highlighting mechanisms rather than performance benchmarks.

Despite persistent skepticism regarding the safety of inorganic materials, hydroxyapatite (HA) provides strong evidence that not all inorganic compounds pose risks to human health (Lara-Ochoa et al., 2021). As bone tissue research advances, synthetic materials that can replicate natural apatite for bone repair and regeneration are being developed. This substitute material is utilized to repair diseased and damaged areas of human bone, caused by various factors (Singh et al., 2020). HA's

exceptional biocompatibility, close mineral resemblance to human bone, and low toxicity make it a reliable material, particularly for critical biomedical applications such as bone implants. Beyond its role in structurally reinforcing the bone matrix, HA also exhibits osteogenic properties that promote bone regeneration and enhance the regenerative capacity of bone tissue (Iwanami-Kadowaki et al., 2021; Kotak & Devarajan, 2020). To serve as an effective bone repair material, the mechanical properties of HA must be enhanced to match those of natural bone, while maintaining its inherent biocompatibility (Hench, 1991; Singh et al., 2020). Table 7 compares the mechanical properties of HA and natural bone tissue as reported in biomedical literature. This comparison is not intended to suggest equivalence with food packaging materials but to provide contextual insight into HA's intrinsic stiffness and load-bearing characteristics, which underpin its role as a reinforcing filler in polymer composites.

In food packaging applications, mechanical performance is governed by the composite architecture rather than HA's intrinsic properties alone. While bone-related mechanical data illustrate the structural robustness of HA, the relevance to packaging must be interpreted cautiously, as polymer flexibility, filler dispersion, and interfacial bonding ultimately determine tensile behavior, elongation, and toughness. Therefore, these biomedical comparisons serve as qualitative reference points rather than quantitative predictors of packaging performance.

Given that an ideal bone repair material must support osteogenesis, ensure biosafety, remain cost-effective, and possess appropriate mechanical strength to achieve optimal bioadaptability, HA clearly fulfills these multifaceted requirements. Furthermore, HA can be combined with various biopolymers to further optimize its functional properties and mechanical adaptability for bone repair applications (Liang et al., 2024). To maximize properties, HA functionalized with quercetin (Forte et al., 2016), cellulose (Liang et al., 2024; Tabaght et al., 2021), collagen (Iwanami-Kadowaki et al., 2021), and chitosan (Muzzarelli, 2009).

According to recent research, HA has been extensively investigated in biomedical research as a carrier for drug delivery systems; primarily due to its biocompatibility, low toxicity, controllable physicochemical characteristics, and porous structure that enables adsorption and controlled release of therapeutic agents (Singh et al., 2020). Furthermore, the porous architecture of HA, combined with its capacity to adsorb and gradually release therapeutic agents, enables precise modulation of drug release kinetics, potentially enhancing treatment efficacy and patient adherence (Lara-Ochoa et al., 2021; Noviyanti et al., 2024). While HA's osteoconductive behavior and affinity for certain bioactive molecules support tissue integration and localized therapeutic action (Asghar et al., 2023; Higino & Franca, 2022). Collectively, these biomedical functions highlight HA's capacity to interact safely and predictably with active substances, providing indirect but relevant insights into its potential role as a functional additive in food packaging systems.

The function of HA as a carrier in drug delivery and drug release applications has been demonstrated to enable effective controlled release, resulting in optimal therapeutic outcomes. This capability also enhances its capacity to adsorb bioactive substances at the intended target site (Asghar et al., 2023; Farkas et al., 2022; Rial et al., 2021; Wan et al., 2022). Because of its low solubility at physiological pH, HA is also

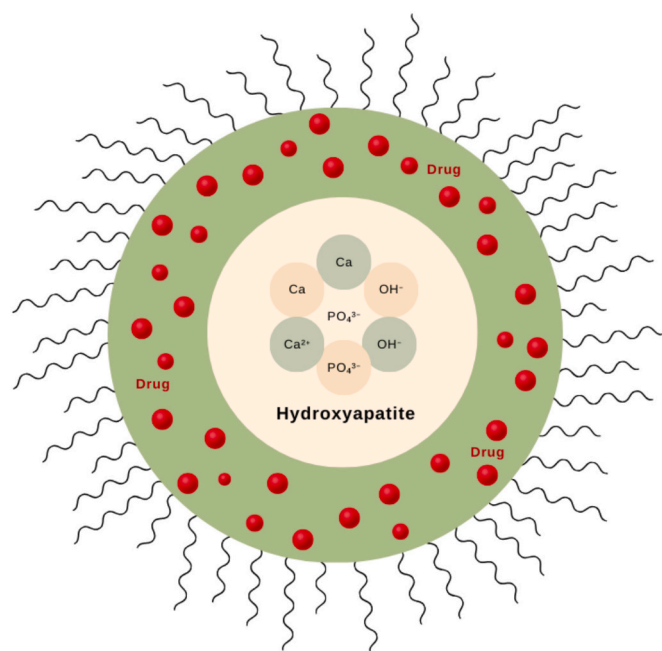


Fig. 5. Conceptual illustration of hydroxyapatite (HA)-mediated adsorption and controlled release mechanisms, as extensively demonstrated in biomedical delivery through drug-loaded hydroxyapatite.

Table 7

Properties comparison between HA and natural bone (Hench, 1991; Singh et al., 2020).

| Mechanical Properties | HA | Natural bone |
|--|-----------|--------------|
| Compressive strength (MPa) | 300 | 10 – 230 |
| Bending strength (MPa) | 110 – 200 | 200 |
| Fracture toughness (MPa/m ^{1/2}) | < 1 | 2 – 12 |
| Young's modulus (GPa) | 40 – 120 | 7 – 30 |
| Poisson's ratio | 0.27 | 0.30 |

utilized as a carrier for local drug delivery via injection and surgical implantation. Three essential kinds of HA can be employed primarily for this purpose (Lara-Ochoa et al., 2021):

- (1). Drugs placed onto or coupled with implanted HA scaffolds;
- (2). Porous HA or nano-HA granular particles;
- (3). HA or nano-HA particles coated with polymers.

Due to their ability to penetrate cellular membranes and biological barriers, hydroxyapatite (HA) nanoparticles smaller than 100 nm can deliver therapeutic agents to otherwise inaccessible sites. Porous HA, when loaded with antibiotics, has been used as an implantable drug-delivery system for sustained release to target specific diseases. Microporous structures of HA can function as effective (Ain et al., 2019). The integration of drugs into the microporous structure facilitates sustained release over extended periods. Compared to dense scaffolds, microporous HA scaffolds exhibit significantly higher drug-loading capacity and prolonged release profiles. The presence of fine pores enables both high adsorption and extended release duration (Loca et al., 2015). Initially, drug molecules adhered to the surface of HA particles are rapidly released, creating a burst effect. Subsequently, as the HA matrix gradually degrades, the release becomes more controlled and continuous (Singh et al., 2020). Many studies have reported that HA exhibited excellent controlled release and sustained dosage of drugs that can adjust the limitation of toxicity (El-Habashy et al., 2021; Levingstone et al., 2021; Singh et al., 2020). Thus, this proves that HA has its own high potential as a low-toxic material to apply in the food area due to its safety and biocompatibility with food.

Wound dressings are critical tools in clinical care, traditionally used to absorb exudates, keep wounds dry, and prevent infection. However, recent research indicates that a moist and warm environment significantly improves healing outcomes. Modern dressings are therefore designed to retain moisture, support oxygen flow for tissue regeneration, and limit bacterial growth (Q. Wang et al., 2024). The addition of HA to certain main matrix films enhanced many properties. As reported by (Cunha et al., 2020), the incorporation of HA powder has activated the antibacterial activity against Gram-negative strain, *Escherichia coli*, and Gram-positive strain, methicillin-resistant *Staphylococcus aureus*. At the same time, the film is also non-cytotoxic. Thus, they stated that this material is very suitable for wound dressing, due to its properties that could reduce bacterial contamination. Moreover, HA can enhance the mechanical properties of the main matrix biopolymer film, making it a promising component for advanced wound care applications (Q. Wang et al., 2024). The favorable mechanical properties of HA are also accompanied by improved thermal stability, as demonstrated through Thermo-Gravimetric Analysis (TGA), as reported by (Tabassum et al., 2024) in Fig. 6. The TGA curve comparison indicates that HA exhibits the highest thermal stability, with two distinct stages. The first stage (35 – 145 °C) corresponds to the evaporation of surface-adsorbed water, while the second stage (145 – 500 °C) is associated with the vaporization of crystallization water.

In addition to its antibacterial properties, the incorporation of HA into biomedical scaffolds can serve as a reservoir for calcium ions at the site of injury. These ions play a crucial role in stimulating the formation of fibroblasts and keratinocytes during the wound healing process, while also mitigating acidic inflammatory responses. In contrast to traditional materials, nanoscale HA offers favorable surface characteristics, including grain size, porosity, and wettability—enabling better regulation of protein interactions and prolonged functional performance (Sahmani et al., 2019; Tabassum et al., 2024). The ability of HA to release calcium ions and interact with biomolecules can be leveraged to develop antimicrobial or controlled-release packaging systems, enhancing food safety and extending shelf life. However, it is important to note that biocompatibility, antibacterial, and other functional performance in biological systems do not directly equate to food-contact safety, and additional considerations, such as migration behavior and

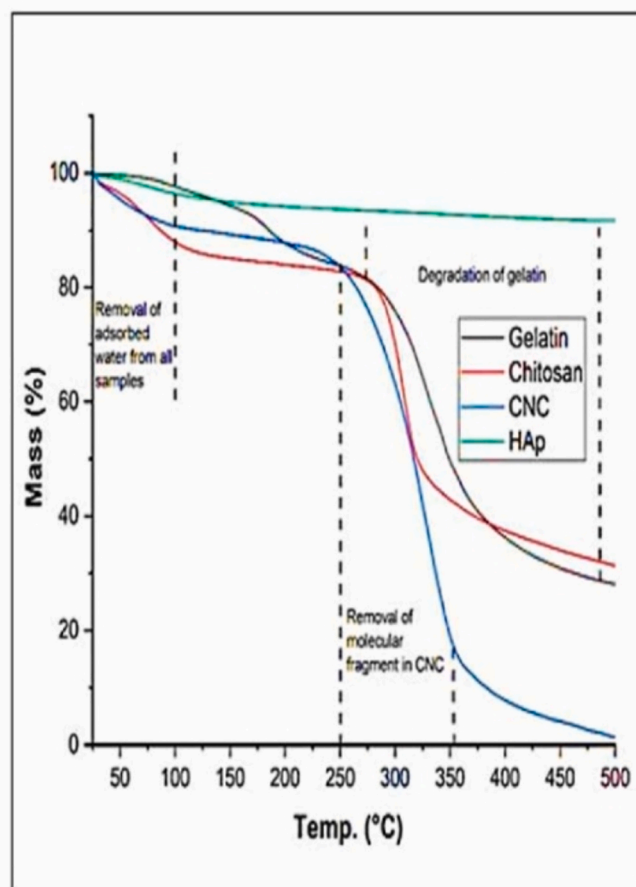


Fig. 6. TGA curve comparison of gelatin, chitosan, CNC, and HA. Reprinted with permission from Elsevier (Tabassum et al., 2024).

long-term exposure, must be evaluated in packaging applications. Beyond biomedical systems, the adsorption capacity and surface chemistry of HA have also been exploited in environmental applications, further demonstrating its multifunctional potential.

3.3. Environmental Perspectives: Adsorption, ion Exchange, and remediation sensor

In environmental applications, hydroxyapatite has been extensively investigated for its strong affinity toward various contaminants, including heavy metals, volatile organic compounds (VOCs), and microbial agents. HA's unique ability to be assimilated within physiological environments offers a significant advantage in facilitating interactions with biological molecules (Noviyanti et al., 2024). Its adsorption and ion exchange capabilities have been widely exploited in wastewater treatment, soil remediation, and environmental sensing, demonstrating its effectiveness in immobilizing and stabilizing hazardous substances. While these functions are predominantly validated in aqueous and soil-based systems, they provide indirect insights into how HA may contribute to advanced food packaging concepts. Rather than acting as a direct adsorbent within polymer matrices, HA's environmental performance highlights its chemical stability, surface reactivity, and safety profile, which are relevant to the design of active or smart packaging materials, as summarized in Table 8. Furthermore, HA's application in air filtration technologies, particularly in removing microbes and airborne contaminants, suggests an extended use for antimicrobial food packaging, contributing to prolonged shelf life and improved food hygiene.

Environmental pollution arising from industrial, domestic, urban

Table 8
Environmental Utility of Hydroxyapatite and Its Relevance to Food Packaging.

| Application Area | Key Function | Conceptual Relevance | Ref. |
|-----------------------|--|--|--|
| Wastewater treatment | Adsorption of heavy metals, cationic dyes, surfactants | Demonstrates conceptual relevance for toxin mitigation strategies in active packaging and biocompatibility to ensure food safety | (Saha Chowdhury et al., 2025; Shafiq et al., 2023; Voskanyan et al., 2024; Wen et al., 2024) |
| Soil remediation | Ion exchange and stabilization | Indicates capability for neutralizing harmful compounds | (Jia et al., 2024; Xiao et al., 2024; Yan et al., 2025) |
| Environmental sensors | Sensor environmental contaminants | Sensor material to detect contaminants or spoilage through ion-sensitive responses as smart packaging | (Arnau et al., 2024; Hu et al., 2025; Taha et al., 2020) |

runoff, and agricultural activities has resulted in the release of cationic dyes (methylene blue and methyl violet) (Shafiq et al., 2023), non-ionic surfactants (Voskanyan et al., 2024), and heavy metals (Saha Chowdhury et al., 2025; Wen et al., 2024) into water systems. In this context, the relevance of HA lies not in direct contaminant uptake but in its potential to influence barrier performance, surface interactions, and smart-sensing functionalities when appropriately integrated into packaging materials (Shafiq et al., 2023; Voskanyan et al., 2024). These considerations reinforce the need for packaging-specific experimental validation.

In the application of HA for the removal of methylene blue (MB) dye, the adsorption mechanism involves several interactions. Adsorption scheme of hollow mesoporous HA (HM-HA) reported by (Shafiq et al., 2023). To illustrate the adsorption mechanisms of HA in environmental systems, Fig. 7 presents a schematic representation of MB dye adsorption

on the HA surface. This example is included to elucidate the fundamental interaction mechanisms, such as hydrogen bonding, electrostatic attraction, and ion exchange, that govern HA-contaminant interactions in aqueous environments. At the surface of HM-HA, hydrogen bonding forms between the dye's hydroxyl ($-OH$) and amine ($-NH_2$) functional groups, resulting in strong molecular affinity. Electrostatic interactions also occur, driven by attractive and repulsive forces between charged dye molecules and the ionic sites on HM-HA. Furthermore, ion-exchange processes occur, primarily involving phosphate groups (PO_4^{3-}) within the HA matrix. These mechanisms not only demonstrate HA's effectiveness in removing cationic dyes like methylene blue but also highlight its versatility as a functional material for pollutant adsorption.

These environmental studies provide valuable mechanistic insights that may inform the design of HA-filled packaging systems, particularly in understanding filler-matrix interactions and potential indirect barrier-enhancing effects. Other than wastewater contaminated with heavy metals, soil contamination also increased significantly over the years due to the rapid growth of agricultural activities and industrial emissions. The infiltration of heavy metals into soil may lead to their accumulation in living organisms through the food chain, posing serious and often irreversible health risks due to their persistence, and resistance to biodegradation. Moreover, the remediation of such contaminants from soil environments is typically a prolonged and challenging process (Jia et al., 2024; Xiao et al., 2024). To address this issue, hydroxyapatite presents a sustainable solution due to its strong capacity to bind heavy metals (Yan et al., 2025). Moreover, HA has slow-release properties (Singh et al., 2020) that can facilitate the gradual immobilization of contaminants, particularly advantageous in soil remediation, as it ensures prolonged effectiveness in reducing pollutant mobility (Xiao et al., 2024). Calcium ions, along with phosphate and hydroxyl groups present in hydroxyapatite, can immobilize heavy metals through mechanisms such as ion exchange, surface complexation, and precipitation (Cui et al., 2016).

HA have been developed by many researchers as gas sensor due to its unique capability to be sensitive of certain ions, so it is generally considered to be an ionic conductor that can perform proton transfer before the surface hydroxyl groups, and is often used for ammonia (Hu et al., 2025), carbon dioxide (Arnau et al., 2024), and alcohol (Taha et al., 2020). These gases have increased enormously in recent years due to industry emissions, livestock, and poultry farming (Arnau et al., 2024). The environment being highly polluted causes several cases of poisoning, accidents, and even deaths. However, gas detection systems are not common in public areas due to their high maintenance and high power consumption. Henceforth, the development of new gas sensor materials has a large response amongst researchers (Noviyanti et al., 2025). Due to its unique ability to exchange ions, HA has great potential as a raw material for gas sensors (Amenaghawon et al., 2022).

As illustrated by (Hu et al., 2025) in Fig. 8, through reactions between ammonia adsorption and desorption processes in porous hydroxyapatite fiber monolith (PHFM) and oleic acid. Selective physical adsorption is one of the key factors influencing charge transfer through HA. The hydroxyl and phosphate groups on the HA surface act as hydrophilic adsorption sites, initially forming hydrogen bonds with water molecules in the environment. Moreover, the oleic acid on the surface of hydroxyapatite fibers prepared by the oleic-acid assisted method exists in the form of a bilayer, and the carboxylic acid groups at the end of the chain of the oleic acid molecule also exhibit excellent hydrophilicity. These sites subsequently continue to physically adsorb water molecules through single hydrogen bonding, ultimately forming multilayers of water molecules on the HA surface.

Insights from environmental applications have highlighted HA's capacity for adsorption, ion exchange, and pollutant immobilization in aqueous systems. While these properties provide valuable mechanistic understanding, their relevance to food packaging must be interpreted with caution. In polymer-based packaging materials, HA is not expected to function as a direct adsorbent, but rather to influence gas and vapor

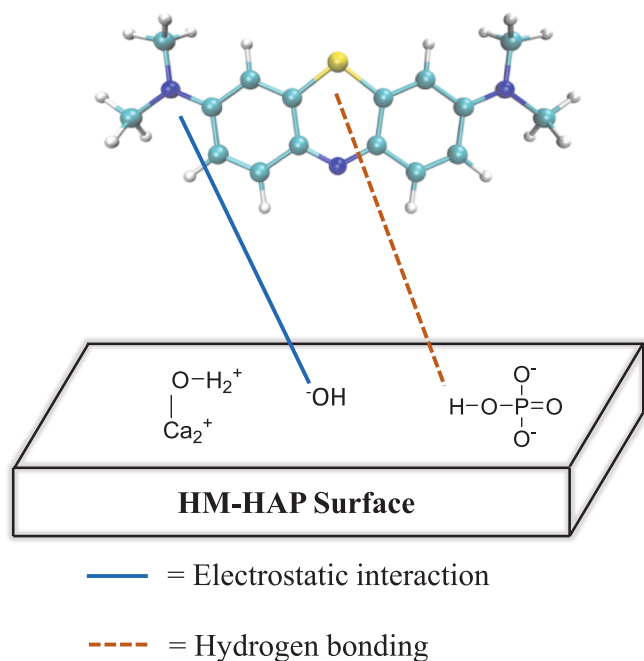


Fig. 7. Schematic illustration of the adsorption mechanism of methylene blue (MB) dye on the surface of hollow mesoporous hydroxyapatite (HM-HA), involving hydrogen bonding, electrostatic interactions, and ion exchange. Reprinted with permission from Elsevier (Shafiq et al., 2023). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

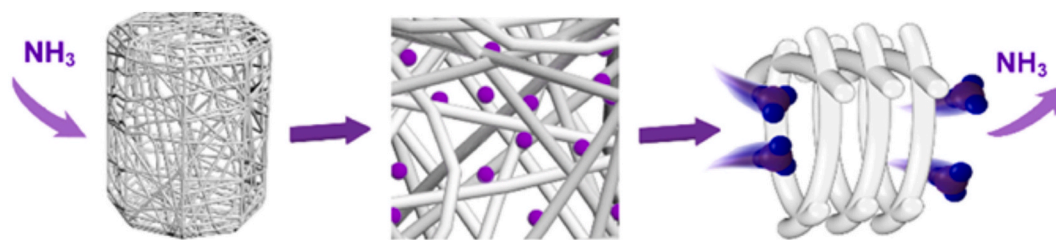


Fig. 8. Schematic illustration of the HA sensing mechanism. Reprinted with permission from Elsevier (Hu et al., 2025).

transport indirectly through diffusion control and increased tortuosity. Nevertheless, these environmental studies offer important conceptual guidance for the design of active and sustainable packaging systems, particularly regarding material safety, environmental compatibility, and functional stability. Accordingly, the adaptation of HA from remediation contexts to food packaging applications requires translating of mechanisms rather than directly extrapolating performance.

3.5. Translational implications for food packaging applications

Building on insights gained from biomedical and environmental research, this section does not assume direct applicability but critically evaluates how these findings can inform packaging-specific design considerations under fundamentally different physicochemical conditions. The integration of hydroxyapatite (HA) into food packaging systems is an emerging interdisciplinary field of exploration. Although direct experimental validation remains limited, existing evidence provides a strong theoretical rationale for utilizing HA as a functional additive or reinforcing filler in biodegradable packaging matrices. Through its physicochemical stability, adsorption capacity, and antimicrobial potential, HA could contribute to improved mechanical strength, enhanced barrier performance, and active protection against microbial contamination. Consequently, translating HA's established roles in biocompatible and environmentally responsive systems into food packaging applications offers a promising direction toward safer and more sustainable materials. In this context, biomedical findings on controlled release and environmental data on adsorption and ion exchange have been reinterpreted as packaging-relevant mechanisms, particularly for diffusion control, active compound release, and food-contact safety.

Although hydroxyapatite is often regarded as environmentally benign due to its biocompatibility and compositional similarity to natural minerals, its sustainability largely depends on the synthesis approach. Conventional methods such as sol-gel and hydrothermal processing are energy-intensive and generate chemical waste, whereas emerging biogenic synthesis routes using natural or waste-derived precursors (e.g., eggshells, fish bones, coral) can substantially reduce energy demand and reagent consumption (Dewi et al., 2024; Kuśnieruk et al., 2016; Noviyanti et al., 2020). However, quantitative life-cycle assessments (LCAs) comparing HA with other fillers, such as nanocellulose or clay, remain scarce (Jose et al., 2025; Okeke et al., 2024). Consequently, while HA shows promise for integration into sustainable packaging systems, its environmental benefits should be considered potential rather than confirmed, pending comprehensive cradle-to-grave evaluations in future studies.

While pure HA demonstrates minimal intrinsic antibacterial activity, its use in composites has shown effective bacterial inhibition due to its function as a carrier or stabilizing matrix for antimicrobial agents such as silver, zinc, or bioactive plant-derived compounds. In such systems, HA enhances the dispersion and sustained release of these agents, contributing indirectly to antibacterial performance in food packaging applications. Incorporating reinforcing agents or fillers is a common strategy to enhance the performance of bioplastic matrices (Hendrawati et al., 2023; Morsy, 2024; Ruíz-Baltazar et al., 2018; Silva-Holguín &

Reyes-López, 2020). The reduction in oxygen and moisture permeability observed upon HA incorporation can be explained by fundamental transport and thermodynamic mechanisms. HA particles increase the tortuosity of diffusion pathways, thereby lowering the effective diffusion coefficient within the polymer matrix. Additionally, their polar surface and high crystallinity can alter gas polymer partitioning at the interfacial region, leading to reduced solubility of permeating molecules. This combined effect, governed by Fickian diffusion and Henry's law partitioning, results in lower overall permeability. Temperature-dependent permeability behavior may also follow Arrhenius-type kinetics, reflecting the thermally activated nature of diffusion processes (Lara-Ochoa et al., 2021; Qiu et al., 2024; Uskoković, 2020; Yue et al., 2024). Together, these mechanisms rationalize the barrier enhancement observed in HA-filled composites.

HA demonstrates the potential to contribute to multiple functional improvements in biopolymer-based packaging systems; these effects are often interdependent and governed by compositional balance. For instance, increasing HA loading can enhance tensile strength and barrier performance by reducing polymer free volume but may also induce brittleness or loss of elongation due to particle agglomeration (Liu et al., 2024; Shafiq et al., 2023; Tingting et al., 2012; Zaharescu et al., 2020). Similarly, incorporating doped or bioactive HA to improve antibacterial activity can influence surface polarity and potentially impact food sensory properties if not carefully controlled (da Costa Brito et al., 2024; Silva-Holguín & Reyes-López, 2020). Hence, achieving multifunctionality requires strategic optimization of HA concentration, dispersion, and interfacial modification, rather than assuming linear enhancement across all properties. This nuanced understanding is crucial for translating HA's laboratory-scale potential into a practical, safe, and industrially viable packaging system.

These materials are intended to improve various properties of the matrix, including its degradability, mechanical strength, and barrier effectiveness against oxygen and water vapor (Marta et al., 2022). Based on its multifunctional characteristics demonstrated across biomedical and environmental applications, hydroxyapatite holds considerable promise as an additive material in food packaging. Its unique physicochemical properties enable it to serve multiple roles when incorporated into biopolymer-based packaging systems. These roles address key challenges in sustainable packaging, such as barrier protection, bacterial inhibition, and mechanical integrity. As outlined in Table 9, HA can be projected to fulfill various functional purposes that are essential to

Table 9
Potential Roles of Hydroxyapatite in Food Packaging Systems.

| Functional Role | Description | Remarks |
|----------------------------|--|---|
| Barrier enhancer | Improves resistance to oxygen and moisture | Performance depends on dispersion and concentration |
| Antibacterial agent | Inhibits the growth of foodborne pathogens | Can be enhanced via metal doping |
| Active packaging component | Absorbs gases or releases functional agents | Requires further migration analysis |
| Mechanical reinforcement | Enhances the strength and flexibility of biopolymer films or membranes | Effect varies with formulation |

modern food packaging composites.

The table shows that HA is not limited to a single function but provides various benefits depending on how it is formulated and applied. While its effectiveness as a barrier enhancer or mechanical reinforcer depends on factors such as dispersion and compatibility with the polymer matrix, its antibacterial inhibition potential may be further tailored through surface modifications. However, to fully optimise these roles for commercial food packaging, further research is needed to assess migration safety, material stability, and performance under real storage conditions. Rather than reiterating individual study outcomes, this discussion emphasizes the critical trade-offs, evidence gaps, and design constraints that must be addressed before hydroxyapatite can be reliably translated into food packaging applications.

4. Conclusion

Hydroxyapatite (HA) has demonstrated versatile functionality across biomedical and environmental domains, attributed to its biocompatibility, ion-exchange capacity, and structural stability; however, its relevance to food packaging remains largely conceptual and indirect. In biomedicine, HA supports bone regeneration, drug delivery, and wound healing through its bioactivity and compositional similarity to natural apatite, while in environmental systems, it functions as an effective adsorbent for contaminant immobilization. These applications provide valuable mechanistic insights; however, they do not directly validate HA performance or safety in food-contact materials. Despite these promising cross-disciplinary insights, the integration of HA into food packaging systems remains insufficiently validated, with limited experimental evidence addressing migration behavior, polymer compatibility, and long-term exposure safety. Particular uncertainty persists for nano-sized HA, where particle migration, altered bioavailability, and regulatory classification present unresolved safety and compliance challenges. Hence, while HA presents meaningful theoretical potential as a sustainable packaging additive, its suitability for real-world food packaging applications should be considered prospective rather than conclusive until supported by systematic migration testing, toxicological evaluation, and regulatory approval.

4.1. Future roadmap and research Outlook

Although hydroxyapatite demonstrates theoretical promise as a functional additive in food packaging, several critical scientific, regulatory, and engineering challenges remain unresolved. Addressing these issues is crucial to translating its theoretical advantages into practical, safe, and scalable applications. The following roadmap summarizes key research priorities and future directions for advancing HA-based packaging systems. To advance hydroxyapatite (HA) from conceptual potential to practical application in food packaging, several engineering pathways must be prioritized. Future studies should prioritize optimization of HA/polymer composite formulations, particularly through surface modification (e.g., silane coupling or organic acid treatment) to improve dispersion, interfacial adhesion, and mechanical consistency in biopolymer matrices such as PLA, PVA, or CA. Standardized characterization protocols, including dynamic mechanical analysis (DMA), oxygen and water vapor permeability, and migration testing in accordance with FDA or EFSA guidelines, are necessary to establish reproducible benchmarks for performance and safety. At the translational level, techno-economic analysis, life cycle assessment, and regulatory feasibility studies must accompany material development to assess cost efficiency, scalability, and environmental impact under realistic industrial processing conditions. Finally, collaboration among academic researchers, regulatory bodies, and packaging industry will be essential to bridge laboratory-scale discoveries with real-world implementation. This roadmap highlights the need for coordinated cross-disciplinary efforts to bridge laboratory-scale findings with regulatory-compliant, industrially viable HA-based food packaging systems.

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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.

References

- Adzka, Q.A.A., Noviyanti, A.R., Cahyana, Y., Rukayadi, Y., Ogino, C., Putra, F.J.N., 2026. Sustainable antibacterial films from cellulose acetate and hydroxyapatite: a green approach to food packaging. *Results Chem.* 20. <https://doi.org/10.1016/j.rechem.2025.102973>.
- Adzka, Q. A. A., Noviyanti, A. R., Cahyana, Y., Torres-Giner, S., & Rukayadi, Y. (2025). Cellulose/hydroxyapatite composite as an innovative sustainable material for food packaging applications. In *Green Chemistry Letters and Reviews* (Vol. 18, Issue 1). Taylor and Francis Ltd. Doi: 10.1080/17518253.2025.2535392.
- Ain, Q.U., Munir, H., Jelani, F., Anjum, F., Bilal, M., 2019. Antibacterial potential of biomaterial derived nanoparticles for drug delivery application. *Mater. Res. Express* 6 (12). <https://doi.org/10.1088/2053-1591/ab715d>.
- Akindoyo, J.O., Beg, M.D.H., Ghazali, S., Heim, H.P., Feldmann, M., 2017. Effects of surface modification on dispersion, mechanical, thermal and dynamic mechanical properties of injection molded PLA-hydroxyapatite composites. *Compos. A Appl. Sci. Manuf.* 103, 96–105. <https://doi.org/10.1016/j.compositesa.2017.09.013>.
- Amenaghawon, A., Anyalewechi, C., Darmokoesomo, H., Kusuma, H., 2022. Hydroxyapatite-based adsorbents: applications in sequestering heavy metals and dyes. *J. Environ. Manage.* 302, 113989. <https://doi.org/10.1016/j.jenvman.2021.113989>.
- Arnau, M., Sans, J., Turon, P., Alemán, C., 2024. Establishing ultraporous permanently polarized hydroxyapatite as a green and highly efficient catalyst for carbon dioxide conversion in continuous flow under mild conditions. *RSC Sustainability*. <https://doi.org/10.1039/d4su00305e>.
- Asghar, M.S., Ghazanfar, U., Idrees, M., Irshad, M.S., Haq, Z., Javed, M.Q., Hassan, S.Z., Rizwan, M., 2023. In vitro controlled drug delivery of cationic substituted hydroxyapatite nanoparticles; enhanced anti-chelating and antibacterial response. *Kuwait Journal of Science* 50 (2), 97–104. <https://doi.org/10.1016/j.kjs.2023.02.014>.
- Aliz, T., Li, Z., Naseeb, J., Sarwar, A., Zhao, L., Lin, L., & Al Samari, F. (2024). Role of bacterial exopolysaccharides in edible films for food safety and sustainability. Current trends and future perspectives. In *Italian Journal of Food Science* (Vol. 36, Issue 4, pp. 169–179). Exon Publications. Doi: 10.15586/ijfs.v36i4.2690.
- Ben Lagha, O.M., Zakaria, M.P., Ismail, I.S., Nor-Khaizura, M.A.R., Rukayadi, Y., 2020. Antibacterial activity of nutmeg (*Myristica fragrans* houtt.) extract against foodborne pathogens on raw beef during chilled and frozen storage. *Food Res.* 4 (2), 380–388. [https://doi.org/10.26656/fr.2017.4\(2\).280](https://doi.org/10.26656/fr.2017.4(2).280).
- Cui, X., Fang, S., Yao, Y., Li, T., Ni, Q., Yang, X., He, Z., 2016. Potential mechanisms of cadmium removal from aqueous solution by Canna indica derived biochar. *Sci. Total Environ.* 562, 517–525. <https://doi.org/10.1016/j.scitotenv.2016.03.248>.
- Cunha, C.S., Castro, P.J., Sousa, S.C., Pullar, R.C., Tobaldi, D.M., Piccirillo, C., Pintado, M.M., 2020. Films of chitosan and natural modified hydroxyapatite as effective UV-protecting, biocompatible and antibacterial wound dressings. *Int. J. Biol. Macromol.* 159, 1177–1185. <https://doi.org/10.1016/j.ijbiomac.2020.05.077>.
- da Costa Brito, S., Pereira, V.A.C., Prado, A.C.F., Tobias, T.J., Paris, E.C., Ferreira, M.D., 2024. Antimicrobial potential of linear low-density polyethylene food packaging with Ag nanoparticles in different carriers (Silica and Hydroxyapatite). *J. Microbiol. Methods* 217–218, 106873. <https://doi.org/10.1016/j.mimet.2023.106873>.
- Dewi, N., Rahmadella, A., Hatta, I., Apriasari, M.L., Putri, D.K.T., 2024. Antibacterial activity of nano-hydroxyapatite paste of snakehead fish bone against *S. mutans*: an in vitro study. *Padjadjaran. J. Dent.* 36 (1), 9. <https://doi.org/10.24198/pjd.vol36no1.51018>.
- El Fawal, G.F., Omer, A.M., Tamer, T.M., 2019. Evaluation of antimicrobial and antioxidant activities for cellulose acetate films incorporated with Rosemary and Aloe Vera essential oils. *J. Food Sci. Technol.* 56 (3), 1510–1518. <https://doi.org/10.1007/s13197-019-03642-8>.
- El-Habashy, S., Eltahir, H., Gaballah, A., Mehanna, R., El-Kamel, A.H., 2021. Biomaterial-based nanocomposite for osteogenic repurposing of doxycycline. *Int. J. Nanomed.* 16, 1103–1126. <https://doi.org/10.2147/IJN.S298297>.
- European Commission. (2025). *Commission Regulation (EU) 2025/351 of 21 February 2025 amending Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.*
- Farkas, N.I., Marincas, L., Barabás, R., Bizo, L., Ilea, A., Turdean, G.L., Toşa, M., Cadar, O., Barbu-Tudoran, L., 2022. Preparation and Characterization of Doxycycline-Loaded Electrospun PLA/HAP Nanofibers as a Drug delivery System. *Materials* 15 (6). <https://doi.org/10.3390/ma15062105>.
- Forté, L., Torricelli, P., Boanini, E., Gazzano, M., Rubini, K., Fini, M., Bigi, A., 2016. Antioxidant and bone repair properties of quercetin-functionalized hydroxyapatite:

- an in vitro osteoblast-osteoclast-endothelial cell co-culture study. *Acta Biomater.* 32, 298–308. <https://doi.org/10.1016/j.actbio.2015.12.013>.
- Gapsari, F., Kartikowati, C.W., Madurani, K.A., Harmayanti, A., Sulaiman, A.M., 2025. Enhanced PVA-bioplastic membranes with nanocellulose and hydroxyapatite derived from blood clam shells. *Environmental Nanotechnology, Monitoring and Management* 23. <https://doi.org/10.1016/j.enmm.2024.101035>.
- Hamad, A.A., Hassouna, M.S., Shalaby, T.I., Elkady, M.F., Abd Elkawi, M.A., Hamad, H. A., 2020. Electrospun cellulose acetate nanofiber incorporated with hydroxyapatite for removal of heavy metals. *Int. J. Biol. Macromol.* 151, 1299–1313. <https://doi.org/10.1016/j.ijbiomac.2019.10.176>.
- Han, J., Tong, X.Y., Rao, C.Y., Ouyang, J.M., Gui, B.S., 2023. Size-Dependent Cytotoxicity, Adhesion, and Endocytosis of Micro-/Nano-hydroxyapatite Crystals in HK-2 Cells. *ACS Omega* 8 (50), 48432–48443. <https://doi.org/10.1021/acsomega.3c08180>.
- Han, M., Zhu, T., Liang, J., Wang, H., Zhu, C., Lee Binti Abdullah, A., Rubinstein, J., Worthington, R., George, A., Li, Y., Qin, W., & Jiang, Q. (2024). Nano-plastics and gastric health: Decoding the cytotoxic mechanisms of polystyrene nano-plastics size. *Environment International*, 183. Doi: 10.1016/j.envint.2023.108380.
- Hench, L.L., 1991. Bioceramics: From Concept to Clinic 74 (7), 1487–1510. <https://doi.org/10.1111/j.1151-2916.1991.tb07132.x>.
- Hendrawati, Liandi, A. R., Ahyar, H., Maladi, I., Azhari, A., & Cornelia, M. (2023). The influence of the filler addition of rice husk cellulose, polyvinyl alcohol, and zinc oxide on the characteristics of environmentally friendly cassava biodegradable plastic. *Case Studies in Chemical and Environmental Engineering*, 8. Doi: 10.1016/j.csee.2023.100520.
- Higino, T., França, R., 2022. Drug-delivery nanoparticles for bone-tissue and dental applications. *Biomedical Physics and Engineering Express* 8 (4). <https://doi.org/10.1088/2057-1976/ac682c>.
- Hossain, M.S., Hossain, M.M., Khatun, M., Hossain, K.R., 2023. Hydrogel-based superadsorbents for efficient removal of heavy metals in industrial wastewater treatment and environmental conservation. *Environmental Functional Materials* 2 (2), 142–158. <https://doi.org/10.1016/j.efmat.2024.01.001>.
- Hu, Y., Ma, T., Ji, Y., Gao, L., Qi, J., Jin, Q., Hu, Y., Wang, K., 2025. Flexible self-supporting porous hydroxyapatite fiber monolith for sensitive microwave ammonia detection. *Sens. Actuators B* 432. <https://doi.org/10.1016/j.snb.2025.137468>.
- Huang, T., Qian, Y., Wei, J., & Zhou, C. (2019). Polymeric Antimicrobial food packaging and its applications. In *Polymers* (Vol. 11, Issue 3). MDPI AG. Doi: 10.3390/polym11030560.
- Ibrahim, M., Labaki, M., Giraudon, J. M., & Lamonier, J. F. (2020). Hydroxyapatite, a multifunctional material for air, water and soil pollution control: A review. In *Journal of Hazardous Materials* (Vol. 383). Elsevier B.V. Doi: 10.1016/j.jhazmat.2019.121139.
- Ielo, I., Calabrese, G., De Luca, G., Conoci, S., 2022. Recent advances in Hydroxyapatite-based Biocomposites for Bone Tissue Regeneration in Orthopedics. *Int. J. Mol. Sci.* Vol. 23, Issue 17, MDPI. <https://doi.org/10.3390/ijms23179721>.
- Iwanami-Kadowaki, K., Uchikoshi, T., Uezono, M., Kikuchi, M., Moriyama, K., 2021. Development of novel bone-like nanocomposite coating of hydroxyapatite/collagen on titanium by modified electrophoretic deposition. *Journal of Biomedical Materials Research - Part A* 109 (10), 1905–1911. <https://doi.org/10.1002/jbm.a.37182>.
- Jia, L., Zhou, Y., Su, Y., Zhao, P., Zhang, J., Fan, W., Yang, S., Long, G., 2024. Coupling raw material cultivation with nano-hydroxyapatite application to utilize and remediate severely Cd-containing soil. *Process Saf. Environ. Prot.* 184, 96–104. <https://doi.org/10.1016/j.psep.2024.01.098>.
- Jose, D., Sivakumar, R., Agarwal, M., Arshad, N., Gundupalli, M. P., Thiagamani, S. M. K., Venkatachalam, P., Amornraksa, S., & Sriariyanun, M. (2025). A comprehensive review of conversion of rice biomass into sustainable products: A green approach toward a circular economy. In *Sustainable Chemistry for Climate Action* (Vol. 6). Elsevier B.V. Doi: 10.1016/j.scca.2025.100069.
- Kongthong, K., Champoochana, N., Kaewtatip, K., 2025. Preparation of alginate/starch beads with hydroxyapatite for curcumin loading and application as a colorimetric pH label. *Int. J. Biol. Macromol.* 309. <https://doi.org/10.1016/j.ijbiomac.2025.143005>.
- Kotak, D.J., Devarajan, P.V., 2020. Bone targeted delivery of salmon calcitonin hydroxyapatite nanoparticles for sublingual osteoporosis therapy (SLOT). *Nanomed. Nanotechnol. Biol. Med.* 24. <https://doi.org/10.1016/j.nano.2020.102153>.
- Kuśnierk, S., Wojnarowicz, J., Chodara, A., Chudoba, T., Gierlotka, S., Lojkowski, W., 2016. Influence of hydrothermal synthesis parameters on the properties of hydroxyapatite nanoparticles. *Beilstein J. Nanotechnol.* 7 (1), 1586–1601. <https://doi.org/10.3762/bjnano.7.153>.
- Kwak, H., Jung, H., Park, S.-A., Park, S.B., Shin, G., Choi, S., Kim, H.J., Jeon, H., 2025. Balancing performance and eco-friendliness: Esterified cellulose nanofiber films for next-generation food packaging. *Carbohydr. Polym.* 360, 123612. <https://doi.org/10.1016/j.carbpol.2025.123612>.
- Lamkhao, S., Phaya, M., Jansakun, C., Chandet, N., Thongkorn, K., Rujijananagul, G., Bangrak, P., Random, C., 2019. Synthesis of Hydroxyapatite with Antibacterial Properties using a Microwave-Assisted Combustion Method. *Sci. Rep.* 9 (1). <https://doi.org/10.1038/s41598-019-40488-8>.
- Lara-Ochoa, S., Ortega-Lara, W., Guerrero-Blétrán, C.E., 2021. Hydroxyapatite nanoparticles in drug delivery: Physicochemistry and applications. In *Pharmaceutics* (vol. 13, Issue 10), MDPI. <https://doi.org/10.3390/pharmaceutics13101642>.
- Levingstone, T., Ali, B., Kearney, C., Dunne, N., 2021. Hydroxyapatite sonosensitization of ultrasound-triggered, thermally responsive hydrogels: an on-demand delivery system for bone repair applications. *Journal of Biomedical Materials Research - Part B Applied Biomaterials* 109 (10), 1622–1633. <https://doi.org/10.1002/jbm.b.34820>.
- Liang, Q., Dong, J., Ren, J., Xiao, C., Deng, C., 2024. Intensified cross-linking dramatically improved the mechanical properties of hydroxyapatite and cellulose composites for repairing bone segmental defects. *Mater. Adv.* 5 (6), 2556–2569. <https://doi.org/10.1039/d3ma00974b>.
- Liu, L., Xu, Y., long, Liu, J. xin, Wang, S., & Zhu, Q. xia. (2024). Preparation and characterization of high flux cellulose acetate/hydroxyapatite composite ultrafiltration membranes for water treatment. *Desalination and Water Treatment*, 317, 100309. Doi: 10.1016/j.dwt.2024.100309.
- Loca, D., Locs, J., Dubnika, A., Zalite, V., & Berzina-Cimdina, L. (2015). Porous hydroxyapatite for drug delivery. In *Hydroxyapatite (Hap) for Biomedical Applications* (pp. 189–209). Elsevier. Doi: 10.1016/b978-1-78242-033-0.00009-2.
- Malvano, F., Montone, A.M.I., Capuano, F., Colletti, C., Roveri, N., Albanese, D., Capparelli, R., 2022. Effects of active alginate edible coating enriched with hydroxyapatite-quercetin complexes during the cold storage of fresh chicken fillets. *Food Packag. Shelf Life* 32, 100847. <https://doi.org/10.1016/j.fpsl.2022.100847>.
- Marta, H., Wijaya, C., Sukri, N., Cahyana, Y., Mohammad, M., 2022. A Comprehensive Study on Starch Nanoparticle potential as a reinforcing Material in Bioplastic. In *Polymers Vol. 14, Issue 22, MDPI.* <https://doi.org/10.3390/polym14224875>.
- Mehmoed, A., Aziz, T., Al-Asmari, F., Shami, A., Haiying, C., Xu, J., Lin, L., 2025. Insight Into the Recent Advances in the Development of Antimicrobial Edible Films for Food Packaging. *Packag. Technol. Sci.* 38 (6). <https://doi.org/10.1002/pts.2895>.
- Morsy, R., 2024. Development and characterization of antibacterial 3D porous hydroxyapatite-gelatin-PVA scaffolds containing zinc oxide nanoparticles. *Mater. Chem. Phys.* 314. <https://doi.org/10.1016/j.matchemphys.2023.128831>.
- Munir, M. U., Salman, S., Javed, I., Bukhari, S. N. A., Ahmad, N., Shad, N. A., & Aziz, F. (2021). Nano-hydroxyapatite as a delivery system: overview and advancements. In *Artificial Cells, Nanomedicine and Biotechnology* (Vol. 49, Issue 1, pp. 717–727). Taylor and Francis Ltd. Doi: 10.1080/21691401.2021.2016785.
- Muzzarelli, R.A.A., 2009. Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone. In *Carbohydrate Polymers* (vol. 76 (2), 167–182. <https://doi.org/10.1016/j.carbpol.2008.11.002>.
- Noviyanti, A. R., Aini, Q., Adzka, A., Novella, I., Kurnia, I., Suryana, S., Bin, A., Amor, M., & Irwansyah, F. S. (2024). *Hydroxyapatite as Delivery and Carrier Material: Systematic Literature Review with Bibliometric Analysis*. Doi: 10.17509/xxxx.xxxx.
- Fauziah, R. P., & Risdiana. (2020). A novel hydrothermal synthesis of nanohydroxyapatite from eggshell-calcium-oxide precursors. *Heliyon*, 6(4). Doi: 10.1016/j.heliyon.2020.e03655.
- Noviyanti, A.R., Muhammad, N.M., Hartati, Y.W., Permana, M.D., Takei, T., Ma'amor, A., 2025. Synthesis and characterizations of hydroxyapatite-lanthanum strontium cobalt ferrite (HA-LSCF) for improving gas sensing performance of carbon dioxide. *J. Indian Chem. Soc.* 102 (1). <https://doi.org/10.1016/j.jics.2024.101484>.
- Okeke, F.O., Ahmed, A., Imam, A., Hassanin, H., 2024. Study on agricultural waste utilization in sustainable particleboard production. *E3S Web of Conferences* 563. <https://doi.org/10.1051/e3sconf/202456302007>.
- Plaeyao, K., Talodthaisong, C., Yinguen, W., Kaewbundit, R., Tun, W.S.T., Saenchoopa, A., Kayunkid, N., Wiwattananukul, R., Sakulsombat, M., Kulchat, S., 2025. Biodegradable antibacterial food packaging based on carboxymethyl cellulose from sugarcane bagasse/cassava starch/chitosan/gingerol extract stabilized silver nanoparticles (Gin-AgNPs) and vanillin as cross-linking agent. *Food Chem.* 466. <https://doi.org/10.1016/j.foodchem.2024.142102>.
- Qiu, D., Zhou, J., Feng, Q., Ren, K., Zhang, H., He, Y., Li, C., Liu, J., Mai, N.T.T., 2024. Functionality, physicochemical properties, and applications of chitosan/nano-hydroxyapatite- γ -tea polyphenol films. *Food Chem.: X* 24. <https://doi.org/10.1016/j.fochx.2024.101762>.
- Rial, R., Hassan, N., Liu, Z., Ruso, J.M., 2021. The design and green nanofabrication of noble hydrogel systems with encapsulation of doped bioactive hydroxyapatite toward sustained drug delivery. *J. Mol. Liq.* 343. <https://doi.org/10.1016/j.molliq.2021.117598>.
- Ruiz-Baltazar, Á. de J., Reyes-López, S. Y., Silva-Holguin, P. N., Larrañaga, D., Estévez, M., & Pérez, R. (2018). Novel biosynthesis of Ag-hydroxyapatite: Structural and spectroscopic characterization. *Results in Physics*, 9, 593–597. Doi: 10.1016/j.rinp.2018.03.016.
- Saha Chowdhury, S., Mishra, D.P., De, S., 2025. Synthesis of sulfonated metal-substituted hydroxyapatite and its polymeric composite for sequestration of lead and cadmium from water: batch and column study. *Sep. Purif. Technol.* 362. <https://doi.org/10.1016/j.seppur.2025.131822>.
- Sahmani, S., Saber-Samandari, S., Khandan, A., Aghdam, M.M., 2019. Influence of MgO nanoparticles on the mechanical properties of coated hydroxyapatite nanocomposite scaffolds produced via space holder technique: Fabrication, characterization and simulation. *J. Mech. Behav. Biomed. Mater.* 95, 76–88. <https://doi.org/10.1016/j.jmbmm.2019.03.014>.
- Saleh, A.K., Hussein, A.S., Ray, J.B., Elzaref, A.S., 2024. Comparative versatility and diverse biological applications of eco-friendly zinc oxide and cobalt oxide nanoparticles using *Punica granatum* L. peel extract. *Nano-Structures and Nano-Objects* 38. <https://doi.org/10.1016/j.nanos.2024.101174>.
- Seyedmajidi, S., Rajabnia, R., Seyedmajidi, M., 2018. Evaluation of antibacterial properties of hydroxyapatite/bioactive glass and fluorapatite/bioactive glass nanocomposite foams as a cellular scaffold of bone tissue. *Journal of Laboratory Physicians* 10 (03), 265–270. <https://doi.org/10.4103/jlp.jlp.167.17>.
- Shafiq, F., Liu, C., Zhou, H., Chen, H., Yu, S., Qiao, W., 2023. Adsorption mechanism and synthesis of adjustable hollow hydroxyapatite spheres for efficient wastewater cationic dyes adsorption. *Colloids Surf A Physicochem Eng Asp* 672. <https://doi.org/10.1016/j.colsurfa.2023.131713>.
- Shouket, S., khurshid, S., Khan, J., Batoool, R., Sarwar, A., Aziz, T., Alhomrani, M., Alamri, A.S., Sameeh, M.Y., Zubair Filimban, F., 2023. Enhancement of shelf-life of food items via immobilized enzyme nanoparticles on varied supports. A sustainable

- approach towards food safety and sustainability. *Food Res. Int.* 169. <https://doi.org/10.1016/j.foodres.2023.11294>.
- Shouket, S., khurshid, S., Khan, J., Nadeem, A.A., Sarwar, A., Aziz, T., Alotaibi, N.M., Alamri, A.S., Alhormani, M., Sameeh, M.Y., 2024. Biosynthetically produced glucose oxidase immobilized silver nanoparticle bioconjugate treatment improves the shelf life of mango fruit: an innovative method towards food safety and sustainability. *Biomass Convers. Bioref.* 14 (24), 31357–31368. <https://doi.org/10.1007/s13399-023-04753-1>.
- Silva-Holguin, P.N., Reyes-López, S.Y., 2020. Synthesis of Hydroxyapatite-Ag Composite as Antimicrobial Agent. *Dose-Response* 18 (3). <https://doi.org/10.1177/1559325820951342>.
- Singh, G., Singh, R. P., & Jolly, S. S. (2020). Customized hydroxyapatites for bone-tissue engineering and drug delivery applications: a review. In *Journal of Sol-Gel Science and Technology* (Vol. 94, Issue 3, pp. 505–530). Springer. Doi: 10.1007/s10971-020-05222-1.
- Sitisan, K., Sukthavorn, K., Nootsuwan, N., Jariyasakoolroj, P., Veranitisagul, C., Laobuthee, A., 2024. Development of Dielectric Biocomposite and Biaxially Oriented Films from Poly(Lactic Acid) and Nano-silver Coated Microcrystalline Cellulose. *J. Polym. Environ.* <https://doi.org/10.1007/s10924-024-03222-8>.
- Subramanian, M., Karuppan, S., Helaili, S., Ahmad, I., 2024. Structural, mechanical, and in-vitro characterization of hydroxyapatite loaded PLA composites. *J. Mol. Struct.* 1306. <https://doi.org/10.1016/j.molstruc.2024.137862>.
- Sun, H., Qiu, X., Li, X., Wang, H., 2024. Eco-friendly, pH-sensitive curcumin-loaded sodium alginate/hydroxyapatite/quaternary ammonium chitosan microspheres with enhanced antibacterial and antioxidant activities for fruit preservation. *Int. J. Biol. Macromol.* 279. <https://doi.org/10.1016/j.ijbiomac.2024.135297>.
- Tabaght, F.E., Azzaoui, K., Elidrissi, A., Hamed, O., Mejdoubi, E., Jodeh, S., Akartasse, N., Lakrat, M., Lamhamdi, A., 2021. New nanostructure based on hydroxyapatite modified cellulose for bone substitute, synthesis, and characterization. *Int. J. Polym. Mater. Polym. Biomater.* 70 (6), 437–448. <https://doi.org/10.1080/00914037.2020.1725758>.
- Tabassum, M., Shahruzzaman, M., Mukta, N.A., Biswas, S., Khan, M.N., Kader, M.A., Haque, P., 2024. Hydroxyapatite and cellulose nanocrystals loaded gelatin-chitosan based electrospun nanofibrous mats for rapid wound healing. *Heliyon* 10 (4). <https://doi.org/10.1016/j.heliyon.2024.e25871>.
- Taha, S., Begum, S., Narwade, V.N., Halge, D.I., Dadge, J.W., Mahabole, M.P., Khairmar, R.S., Bogle, K.A., 2020. Development of alcohol sensor using TiO₂-Hydroxyapatite nano-composites. *Mater. Chem. Phys.* 240. <https://doi.org/10.1016/j.matchemphys.2019.122228>.
- Thool, O.K., Sasiidharan, A., Krishna, B.M., Sabu, S., Navaf, M., Sunooj, K.V., 2024. Nano-hydroxyapatite (n-HAP) from Pangasius bone side streams and its application as a reinforcing agent in biodegradable food packaging films. *Sustainable Food Technol.* <https://doi.org/10.1039/d4fb00264d>.
- Tingting, D., Yang, X., Hua, L., Zhewei, H., Jiao, S., 2012. Effect of Particle size of Hydroxyapatite Nanoparticles on its Biocompatibility. *IEEE Trans. NanoBiosci.* 11. <https://doi.org/10.1109/TNB.2012.2190418>.
- Upadhyay, P., Ullah, A., 2024. Enhancement of mechanical and barrier properties of chitosan-based bionanocomposites films reinforced with eggshell-derived hydroxyapatite nanoparticles. *Int. J. Biol. Macromol.* 261. <https://doi.org/10.1016/j.ijbiomac.2024.129764>.
- Uskoković, V. (2020). Ion-doped hydroxyapatite: An impasse or the road to follow? In *Ceramics International* (Vol. 46, Issue 8, pp. 11443–11465). Elsevier Ltd. Doi: 10.1016/j.ceramint.2020.02.001.
- Voskanyan, L., Syukkalova, E., Glavinskaya, V., Osmolowsky, M., Voznesenskiy, M., Bobrysheva, N., Osmolovskaya, O., 2024. Eco-friendly, high-effective, and biocompatible sorbent based on specially designed hydroxyapatite nanoparticles for wastewater treatment from non-ionic surfactants. *Surf. Interfaces* 55. <https://doi.org/10.1016/j.surfin.2024.105441>.
- Wan, W., Li, Z., Wang, X., Tian, F., Yang, J., 2022. Surface-Fabrication of Fluorescent Hydroxyapatite for Cancer Cell Imaging and Bio-Printing applications. *Biosensors* 12 (6). <https://doi.org/10.3390/bios12060419>.
- Wang, Q., Sun, X., Basem, A., Hussam, Ibe S., Baghaei, Sh., & Rezaei, R. (2024). Evaluating mechanical and biological responses of bipolymeric drug-chitosan-hydroxyapatite scaffold for wound created during sport training: Fabrication, characterization, and finite element analysis. *Burns*. Doi: 10.1016/j.burns.2024.07.011.
- Wang, Y., Cheng, M., Yan, X., Zhao, P., Wang, K., Wang, Y., Wang, X., Wang, J., 2023. Preparation and characterization of an active packaging film loaded with tea tree oil-hydroxyapatite porous microspheres. *Ind. Crop. Prod.* 199. <https://doi.org/10.1016/j.indcrop.2023.116783>.
- Wang, Z., 2025. Nacre-like structural carboxymethyl cellulose dual-layered film with a combination of high strength, elongation, and UV-blocking for food packaging. *Int. J. Biol. Macromol.* 306, 141692. <https://doi.org/10.1016/j.ijbiomac.2025.141692>.
- Wen, J., Dan, Y., Liu, X., Li, H., 2024. Promoting microalgal biofilm formation by crushed oyster shell-hydroxyapatite layer on micropatterned aluminum coating for heavy metal ions removal. *Colloids Surf. B Biointerfaces* 243. <https://doi.org/10.1016/j.colsurfb.2024.114168>.
- Xiao, S., Ding, S., Gao, W., Qi, X., 2024. Hydroxyapatite self-doped biochar with MgO modification immobilizes heavy metal and alters soil microbial community. *J. Environ. Chem. Eng.* 12 (6). <https://doi.org/10.1016/j.jece.2024.114283>.
- Yan, Y., Du, M., Song, Z., Li, Q., Faheem, M., Zhang, X., Cao, Y., Zhang, Z., Zhang, Z., Zhou, S., 2025. Exploring the potential of green-synthesized hydroxyapatite for cadmium remediation in paddy soils. *Ecotoxicol. Environ. Saf.* 297, 118267. <https://doi.org/10.1016/j.ecoenv.2025.118267>.
- Yi, X., Bao, F., Fu, S., Yang, Y., Xu, Y., 2024. Preparation of mesoporous silica/hydroxyapatite loaded quercetin nanoparticles and research on its antibacterial properties. *Med. Eng. Phys.* 126. <https://doi.org/10.1016/j.medengphy.2024.104160>.
- Yue, S., Zhang, T., Wang, S., Han, D., Huang, S., Xiao, M., & Meng, Y. (2024). Recent Progress of Biodegradable Polymer Package Materials: Nanotechnology Improving Both Oxygen and Water Vapor Barrier Performance. In *Nanomaterials* (Vol. 14, Issue 4). Multidisciplinary Digital Publishing Institute (MDPI). Doi: 10.3390/nano14040338.
- Yuliana, T., Hayati, F., Rialita, T., Cahyana, Y., 2022. Partial purification of bacteriocin from lactobacillus pentosus strain 124-2 isolated from “dadih. Pak. J. Biol. Sci. 25 (9), 796–802. <https://doi.org/10.3923/pjbs.2022.796.802>.
- Zaharescu, T., Tardei, C., Răpă, M., Iordoc, M., 2020. Size particle effects on the thermal stability of poly(lactic acid) / hydroxyapatite hybrids for biodegradable package. *Ceram. Int.* 46 (6), 7288–7297. <https://doi.org/10.1016/j.ceramint.2019.11.223>.
- Zhang, X., Dai, J., Aziz, T., Al-Asmari, F., Shami, A., Al-Joufi, F.A., Cui, H., Lin, L., 2025. Advances in Green Preparation and Functionalized Applications of Cellulose Aerogels Derived from Agricultural Waste for Food Packaging Vol. 165. <https://doi.org/10.1016/j.tifs.2025.105352>.