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Hydroxyapatite as a Biomimetic Alternative to Fluoride in Toothpaste Formulations: A Review

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Abstract

Hydroxyapatite (HA) has gained increasing attention as a biomimetic active ingredient in toothpaste due to its structural similarity to dental enamel and dentin, especially amid concerns over excessive fluoride exposure. This review discusses the role of HA in caries prevention and enamel remineralization, covering its antibacterial activity, physicochemical properties, synthesis strategies, and toothpaste applications. Evidence from in vitro, in situ, and clinical studies demonstrates that HA particularly in nano and ion-substituted forms effectively promotes enamel remineralization, enhances acid resistance, reduces dentin hypersensitivity, and exhibits antibacterial activity comparable or superior to fluoride toothpaste. However, challenges remain regarding nanoparticle stability, formulation consistency, and limited long-term clinical data. For HA to replace fluoride, it should be engineered as a reactive, well-dispersed nano-apatite (≤100 nm) with moderate-to-high crystallinity (~69–75%), stoichiometric Ca/P ratio of 1.67, and appropriate ionic substitution. Overall, HA represents a safe, biocompatible, and promising material for advanced toothpaste formulations.

Keywords: Hydroxyapatite, toothpaste formulation, fluoride alternative, enamel remineralization, antibacterial activity

1 Introduction

Dental caries is a widespread oral health issue across all age groups [1]. According to the Indonesian Health Survey (SKI) 2023, 56.9% of the population aged ≥3 years experienced dental and oral health problems, with dental examinations revealing a high caries prevalence of 82.8% [2]. This condition is caused by the metabolic activity of bacteria in dental plaque, which leads to the demineralization of dentin and enamel. It gradually damages the hard tissue of the teeth [3]. Dental caries begins with the fermentation of dietary carbohydrates by oral bacteria, producing acids that demineralize enamel. This process is driven by oral microbiome dysbiosis, characterized by the predominance of acidogenic and acid-tolerant species such as Streptococcus mutans, Lactobacillus spp., Scardovia wiggsiae, and Actinomyces spp. [1,4,5]. Several determinants, such as nutritional habits, oral hygiene routines, access to dental care, and contact with fluoridated water, have a significant impact on oral health outcomes [6]. A multidisciplinary approach is often applied in caries prevention, with strategies focusing on modifying eating habits and strengthening host resistance, particularly through the use of fluoride toothpaste twice a day [7]. Concerns over the detrimental effects of excessive fluoride exposure on dental enamel, especially in children, have driven the development of fluoride-free oral care products [8]. These innovative formulations often

incorporate biomimetic agents, with biomaterials being the most prominent, due to their ability to inhibit caries progression and promote enamel remineralization [9,10].

The rapid growth in the demand for biomaterials has accelerated progress in biomedical applications, emphasizing the need for bioactive, biocompatible, and non-toxic materials [11]. Hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$) meets these requirements and has become one of the most studied compounds, evolving from a traditional biomaterial into an advanced functional material [12].

According to the Central Bureau of Statistics, chicken egg production in Indonesia in 2024 reached 6,342,705 tons, with high calcium carbonate contents ranging from 92 to 97% by weight [13]. Currently, HA is widely applied in oral health care, where it is particularly valued for its ability to remineralize tooth enamel and improve overall dental health, positioning it as a promising biomimetic agent in caries prevention and enamel repair [14,15].

Hydroxyapatite (HA) is increasingly explored as a biomimetic alternative for caries prevention and enamel remineralization amid rising concerns over the biocompatibility of high-concentration fluoride. This review examines the pathogenesis and prevalence of dental caries, the limitations of fluoride-based approaches, and the growing interest in HA as a safe and effective option. By evaluating its physicochemical characteristics, natural-source synthesis methods, and applications in oral care formulations, the review outlines the advantages, challenges, and future prospects of HA-based therapies. The findings and insights presented here are expected to be a valuable reference for researchers, clinicians, and industry stakeholders seeking innovative and sustainable solutions to improve oral health outcomes and reduce the global burden of dental caries.

2 Hydroxyapatite: Structure and Synthesis

Hydroxyapatite (HA), with the chemical formula $(Ca)_{10}(PO_4)_6(OH)_2$, is a widely utilized calcium phosphate material known for its broad availability in natural systems and its ability to be synthesized [16,17]. Generally, HA exhibits hexagonal and monoclinic crystal structures with a relative molecular mass (Mr) of 502.31 g/mol [12,18]. Renowned for its excellent chemical resistance and low solubility, being one of the most stable calcium phosphate-based bioceramics, with a Ca/P ratio of 1.67 [19]. HA is a bioceramic widely recognized for its excellent bioactivity, biocompatibility, and osteoconductive properties [20]. Consequently, HA has been extensively used in biomedical applications, particularly as a filling material and coating for bone and dental implants [21].

At room temperature, stoichiometric HA is predominantly described by a hexagonal structure with space group $P6_3/m$. A monoclinic structure (space group $P2_1/b$) can occur under specific conditions related to hydroxyl ion ordering, typically at lower temperatures. However, for dental applications, the hexagonal form is most relevant, as synthetic HA used in toothpaste formulations generally exhibits this structure. The monoclinic variant is rarely encountered under physiological or ambient conditions and thus is not discussed in detail here.

It is important to distinguish between stoichiometric HA and biological apatite found in dental enamel. Human enamel is not perfectly stoichiometric HA; rather, it is a carbonated, ion-substituted apatite with numerous crystallographic defects, including vacancies and substitutions (e.g., CO_3^{2-} replacing PO_4^{3-} or OH^-, and trace ions such as Mg^{2+}, Na^+, and F^-). Consequently, the efficacy of nano-hydroxyapatite in toothpaste does not rely solely on its structural similarity to ideal HA. Instead, its nanoscale size, surface defects, partial solubility, and ion-exchange capacity enable dynamic interaction with enamel surface defects, facilitating remineralization and ion exchange under oral conditions. The crystal structure of HA is shown in **Fig. 1**.

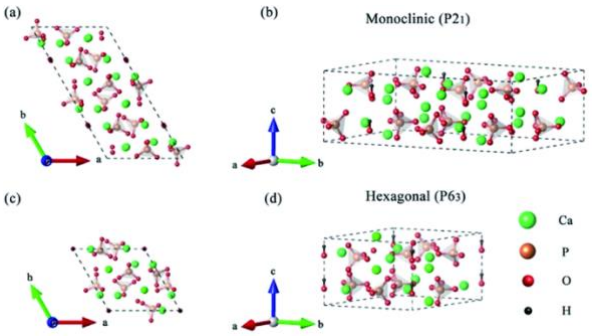


Figure 1. Crystal structures of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ in the low-temperature monoclinic *P21* phase (a) and (b), whereas panels (c) and (d) depict the high-temperature hexagonal P63 phase [22]. Copyright 2017 Royal Society of Chemistry.

The hydroxyl channels in the HA crystal structure do not directly enable replacement of

calcium and phosphate ions. Instead, ionic substitutions can occur at three distinct crystallographic sites: calcium (Ca^{2+}) sites (cationic substitution, e.g., by Sr^{2+}, Mg^{2+}), phosphate (PO_4^{3-}) sites (anionic substitution, e.g., by CO_3^{2-}, HPO_4^{2-}), and hydroxyl (OH^-) sites (e.g., by F^-, Cl^-, CO_3^{2-}). Understanding these distinct substitution mechanisms is essential for designing ion-substituted HA with enhanced bioactivity.

HA generally crystallizes in both hexagonal and monoclinic structures, although hexagonal structure predominates with lattice parameters $a = b = 9.432$ Å, $c = 6.881$ Å and $\gamma = 120°$ in the P63/m space group, whereas the monoclinic phase aligns with *P21/b* [23].

HA exhibits two main crystal planes with different total charges. In its hexagonal structure, the a- and b-planes are rich in Ca^{2+} sites and are positively charged, while the c-plane is rich in PO_4^{3-} and OH^- groups and is negatively charged [24]. In these lattices, the hydroxyl groups are oriented along the c-axis, forming channels that enable the replacement of calcium and phosphate ions with various other cations (e.g., Sr^{2+}, Na^+, K^+, Mg^{2+}, Zn^{2+}, Ag^+) and anions (e.g., CO_3^{2-}, SiO_4^{4-}, SeO_3^{2-}, SeO_4^{2-}, F^-, Cl^-, Br^-) occur at their respective crystallographic sites [15,25].

The resulting properties of HA strongly dictate its bioactivity, mechanical performance, biological interactions, and adsorption efficiency. Therefore, understanding and controlling these properties through well-optimized synthesis techniques is essential for tailoring HA for advanced applications in biomedicine, materials science, and environmental engineering [26]. In recent years, increasing attention has been directed toward the use of natural and sustainable calcium-based precursors for HA synthesis, including avian and mammalian bones, horns, eggshells, fish scales and bones, algal biomass, mollusk shells (e.g. clams and mussels), and limestones [27]. These bio-derived resources not only provide an abundant calcium source but also align with environmentally friendly and cost-effective material development.

Each synthesis method uniquely affects HA properties relevant to toothpaste: wet precipitation produces nano-sized [27], low-to-moderate crystallinity HA with agglomeration; sol–gel yields high phase purity and high surface area but may leave carbon residues [28,29]; hydrothermal generates highly crystalline, well-defined morphology with minimal agglomeration [19,30]; sonochemical produces ultrafine particles with reduced agglomeration but potential metal contamination [31-33]; microwave-assisted synthesis offers rapid, uniform heating with controlled particle size and high phase purity [26-34]. Therefore, the selection of appropriate reagents, synthesis conditions, and processing parameters is essential, as these factors directly influence the crystallinity, morphologies, grain size, structure, porosity, and overall performance of HA.

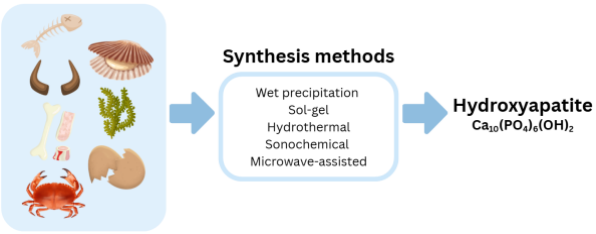


Figure 2. Bio-resource for HA synthesis

Across diverse synthesis strategies, pH consistently emerges as a central parameter controlling the physicochemical quality of HA. Kamieniak et al. (2018) demonstrated that although the crystal structure and overall morphology remain stable between pH 2 and 12, the textural properties respond strongly to pH variation [35]. In particular, pH 10 consistently yiels higher crystallinity, fewer secondary phases, and stronger antibacterial performance [36]. This trend is further supported by evidence showing that pH 10 promotes the formation of uniform needle-like particles with small crystallite sizes and stable stoichiometry due to optimal OH^- availability that regulates nucleation and growth [37]. Collectively, these findings identify pH 10 as the most favorable condition for producing HA with superior structural integrity, well-defined morphology, and enhanced functional attributes, which aligns with evidence that its antibacterial performance improves when synthesis conditions and composition are carefully controlled.

3 Application of Hydroxyapatite in Oral Care Toothpaste

Hydroxyapatite (HA) has been widely investigated as an antibacterial material due to its biocompatibility and structural similarity to dental hard tissues. HA exhibits a highly versatile

antibacterial profile, which can be significantly enhanced through controlled synthesis and compositional tuning.

The antibacterial efficacy of HA is strongly dependent on synthesis strategy and functional modification. In HA without additional antibacterial dopants, the measured reduction in bacterial viability against *Streptococcus mutans* ranges from 15.6% to 23.4%, while *Streptococcus sobrinus* displays a broader and, under certain conditions, markedly stronger response [38]. Microwave-assisted combustion at pH 10 yields HA with high crystallinity and reactive surface radicals, providing antibacterial activity for up to 720 hours while remaining biocompatible [39]. Ion and drug incorporation, such as Mg/Sr/ampicillin-modified HA via sol–gel, produces inhibition zones of 11–12 mm, surpassing tetracycline activity [40]. Green synthesis, exemplified by Zn-doped HA from spinach extract, forms rod-like particles that inhibit *Bacillus subtilis* and *Escherichia coli* with zones of 15 and 12 mm, respectively [41]. Bio-templated HA enriched with *Stephania pierrei* extract achieves the strongest effect, with inhibition zones up to 32 mm against *Bacillus cereus*, demonstrating selective antibacterial activity through extract–matrix interactions [42].

Representative studies on the antibacterial performance of HA-based materials are summarized in **Table 1**.

Table 1. Summary of antibacterial performance of HA-based materials.

Composition	Synthesis method	Antibacterial assay method	Material Characteristics	Antibacterial performance	Ref.
HA	Microwave-assisted combustion	Broth culture antibacterial viability assay (CFU method)	Ca/P ratio of 1.57, crystallinity of 75.42%, & crystallite size of 29.59 nm.	viability decreased by 15.6%, 18.7%, and 23.4% for *S. mutans;* viability decreased by 17.1%, 56.1%, and 98.6% for *S. sobrinus*	[38]
HA	Microwave-assisted combustion	Agar well diffusion	High crystallinity; reactive surface radicals	Sustained antibacterial activity up to 720 h	[39]
HA@Mg/Sr/Amp	Sol-gel	Agar well diffusion	Ca/P ratio of 1.67; crystallite size ~ 66 nm	Produces inhibition zones of 11–12 mm	[40]
ZnHANPs (spinach extract)	Wet-precipitation	Disk diffusion	Rod-shaped nanoparticles with a crystallite size of 100 nm	Inhibit *Bacillus subtilis* and *Escherichia coli* with zones of 15 and 12 mm	[41]
S. pierrei/BAM-HA	Sol-gel	Agar well diffusion	5 wt% BAM composite showed the highest surface area (17.59 m^2/g) and the smallest particle size (6.57 nm)	Inhibition zones up to 32 mm against *Bacillus cereus*	[42]

Hydroxyapatite is the main inorganic constituent of enamel and dentin. As a result, synthetic HA is widely applied in dental cements, restorative fillings, and oral care products, particularly toothpaste. Many commercially available toothpastes claim to provide protection against dental caries, periodontal disease, dentin hypersensitivity, tooth discoloration, and to promote the remineralization of dental hard tissues, including enamel and dentin [43]. In contrast to fluoride, which primarily promotes surface-level remineralization, hydroxyapatite particles can penetrate deeper into enamel lesions, enabling more effective structural repair [44]. HA-containing toothpastes have demonstrated high efficacy, as supported by numerous published studies encompassing both naturally derived and commercially manufactured hydroxyapatite formulations.

HA synthesized from various natural sources has been extensively investigated for toothpaste applications, as summarized in **Table 2**, which compiles studies employing different calcium sources, synthesis methods, and formulation strategies. Biological wastes such as fish bones, eggshells, snail shells, and fish scales have been utilized to produce HA with diverse physicochemical properties and functional performance in toothpaste formulations.Both conventional and composite HA formulations exhibit strong remineralization and antibacterial properties, with nano-engineered systems offering further enhancement. These findings support the potential of natural-source HA as a safe, biocompatible, and sustainable alternative to fluoride-based toothpaste formulations.

Table 2. Summary of included studies on HA synthesized from natural sources used in toothpaste.

Source	Synthesis method	Objective	Result	Ref.
Mackerel bones	Wet-precipitation	45%, 50%, and 55% HA	Hydroxyapatite with a 77.47 nm crystallite size was formulated into toothpaste. The 45% concentration performed best despite minor agglomerates from incomplete mixing.	[45]
Egg shell	Wet-precipitation	4wt% HA	There was no statistically significant difference compared with the fluoride toothpaste ($p > 0.05$), although the resulting enamel microhardness tended to be lower, with a mean value of 1.980 ± 0.866 versus 2.840 ± 2.647.	[46]
Rice field snail shells	Microwave-assisted	5% and 10% nano-HA with 5% basil leaf extract	Nano-hydroxyapatite toothpaste from rice field snail shells with 5% basil extract enhances enamel hardness, reduces enamel microporosity more effectively than 1,450 ppm fluoride toothpaste, and maintains strong antibacterial activity with inhibition zones of about 24–25 mm and no significant differences among formulations.	[47]
Rice snail shells	Sol-gel	40%, 45%, and 50% HA-ZnO	HA–ZnO powder showed a crystallite size of 59.90 nm and 68.85% crystallinity. The 45% toothpaste formulation demonstrated good physical stability and produced a strong antibacterial effect against *Streptococcus mutans*, with an inhibition zone of 21.5 ± 0.707 mm.	[48]
Fish scale & poultry eggshell	Wet-precipitation	10%w/v HA	HA toothpaste restored enamel and reorganized tubules, with fish-scale (17.28 nm) and eggshell HA (17.20 nm) providing strong remineralization, higher calcium levels, and antibacterial effects, surpassing fluoride toothpaste.	[49]

Studies on the performance of commercial HA-based toothpastes are summarized in **Table 3**, encompassing a range of functional objectives including tooth whitening, stain removal, remineralization, and enamel protection. These studies evaluate HA formulations in comparison with conventional fluoride and non-fluoride toothpastes under both laboratory and clinical conditions. Toothpaste formulations prepared using commercial HA demonstrate strong performance across multiple oral care functions, including whitening, stain removal, remineralization, and enamel protection. HA- and nano-HA–based formulations consistently match or outperform fluoride-based toothpastes, particularly in enamel remineralization and resistance to erosive challenges, while maintaining good formulation stability. The incorporation of nano-scale HA, ion substitution, and natural calcium-based additives further enhances therapeutic efficacy. Overall, these findings support the use of commercially sourced hydroxyapatite as a safe, effective, and scientifically supported active ingredient in

advanced toothpaste formulations as alternatives to conventional fluoride systems.

Table 3. Summary of included studies on commercial HA used in toothpaste.

Formulation/Comparison	Result	References
20% HA vs Blue covarine	HA toothpaste showed higher stain-removing efficacy at 30 s (87.3 ± 2.1%) compared to blue covarine toothpaste (77.2 ± 7.3%), while both reached nearly identical efficacy after 180 s (~92%).	[50]
10 wt% & 1 wt% nHA	10 wt% nHA significantly improved tooth whitening, with △E increasing from 2.76 to 4.47 versus 1.62 to 2.55 in 1 wt% ($P < 0.05$). Whitening correlated with increased △L and decreased △a and △b, more pronounced at 10 wt%. Hydrodynamic shear reduced △E and △L ($P < 0.05$). SEM showed greater nano-HA coverage on enamel at 10 wt%, with partial removal of larger particles after shear.	[51]
$CaCO_3$, HA:$CaCO_3$, and HA	Calcium content increased from 21.10% in CaCO3 toothpaste to 27.03% in the HA:CaCO3 mix and 27.67% in the HA toothpaste. Spreadability ranged between 931.93 and 987.33 g·cm/s, with pH values from 8.3 to 8.9 and viscosity between 25 and 27.5 P.a. All formulations remained free of microbial contamination during storage.	[52]
$ZnCO_3$/nHA, 0.14 wt% amine fluoride, and 7 wt% nHA	Enamel and dentine lesions showed significant remineralization after treatment. Nano-hydroxyapatite (n-HA) and ZnCO3/n-HA toothpastes achieved similar or better remineralization than amine fluoride toothpaste ($p < 0.05$). No surface erosion was observed. These promising results warrant further clinical validation.	[53]
Zn-HA vs non-F and F	Zn-HA toothpaste showed the strongest protective effect with the lowest morphological score (1.3 ± 0.38; $p < 0.001$), along with visible surface deposits and minimal erosive changes in SEM images. Zn-HA demonstrated superior enamel protection against acidic erosion compared to fluoride and non-fluoride toothpastes.	[54]
10% nano-seashell, 10% nano-pearl, and 10% nHA vs F (850–1150 ppm sodium fluoride)	After 28 days, enamel microhardness rose most with nano-seashell (458.6%), followed by nano-pearl (406%), hydroxyapatite (286%), and fluoride toothpaste (207.8%). DIAGNOdent confirmed hydroxyapatite led to the greatest lesion improvement.	[55]

4 Limitation and Future Perspectives

Despite the promising performance of nano-hydroxyapatite (nHA) in toothpaste formulations, several limitations must be considered. The physicochemical instability of nanoparticles, including agglomeration, surface oxidation, and variability in size and morphology, can affect formulation homogeneity, biological response, and long-term efficacy. In addition, differences in synthesis methods, nHA concentrations, and toothpaste compositions across studies introduce substantial methodological heterogeneity, limiting reproducibility and the strength of clinical evidence. Most available studies rely on short-term in vitro or in situ models, which do not fully reflect the complexity of the oral environment or long-term exposure conditions.

Future research should therefore prioritize the development of cost-effective, scalable, and environmentally sustainable synthesis strategies for nHA, particularly those derived from natural calcium sources. Advanced surface modification techniques should be further explored to enhance nanoparticle stability while minimizing potential

toxicity. Equally important is the need for long-term, well-designed randomized clinical trials with standardized formulations and outcome measures to reliably assess durability, safety, and clinical relevance. Integrating regulatory considerations, life-cycle assessment, and cost–benefit analysis at earlier stages of product development will also be essential. By addressing these limitations, nanotechnology-based HA toothpastes can more realistically transition from promising laboratory systems into safe, effective, and widely accepted clinical solutions for modern oral care.

5 Conclusions

Hydroxyapatite (HA) and its nano-structured derivatives represent promising active ingredients for toothpaste formulations, offering advantages in caries prevention, enamel remineralization, and oral health improvement. Based on the studies reviewed, HA particles with nanoscale dimensions (≤100 nm), near-stoichiometric Ca/P ratio (~1.67), moderate-to-high crystallinity (~69–75%), good dispersion stability, and tunable surface chemistry appear particularly promising for toothpaste applications as alternatives to fluoride. When antibacterial enhancement is required, ionic substitution or composite strategies (e.g., Zn-HA or Mg/Sr-modified systems) are advantageous. However, these parameters should be viewed as observational trends from selected studies rather than universal formulation standards. Overall, HA represents a safe, biocompatible, and promising material for advanced toothpaste formulations.

Nevertheless, several challenges remain, including variability in physicochemical properties arising from different synthesis routes, nanoparticle agglomeration, formulation stability, and the need for standardized concentrations and particle sizes. Economic constraints, scale-up limitations, and regulatory requirements for nano-enabled products further hinder widespread adoption. Future research should therefore focus on cost-effective and sustainable synthesis strategies, improved nanoparticle stabilization and formulation design, and long-term randomized clinical trials to confirm safety, durability, and clinical effectiveness across diverse populations. Addressing these challenges will support the broader implementation of HA-based toothpaste formulations as reliable, safe, and sustainable alternatives or complements to conventional fluoride systems in modern oral care.

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