

## Carbonate Hydroxyapatite - A Multifunctional Bioceramics with Non-Medical Applications

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**Abstract.** Carbonate hydroxyapatite is the common derivative of hydroxyapatite found in living systems. It is the building block of most hard tissues, including the teeth and bones. A vast majority of the applications of this versatile material focus on its biomedical applications, which is attributable to its closeness to biological apatites. Hydroxyapatite is a strong precursor to carbonate apatite in nature, and many experiments show that both are similar in a few respects. A significant divergence point is carbonate's obvious impact on its physicochemical properties and concomitant applications. The inclusion of carbonate ions into the lattice of hydroxyapatite results in morphological and physicochemical changes that vary with the method of synthesis and extent of substitution. The unique crystal structure, improved surface area, and porous morphology of carbonate hydroxyapatites also make it useful for catalysis and environmental remediation as adsorbents for heavy metals. This review briefly examines carbonate hydroxyapatite, its synthesis, its modification, and its characterization. It also highlights its biomedical applications while drawing attention to its non-medical potential.

### Introduction

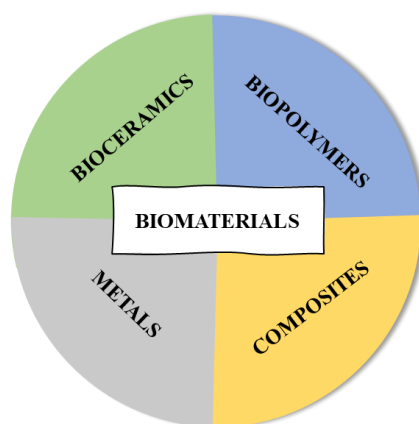
Biomaterials play a major role in modern medicine, facilitating the repair, replacement, and augmentation of damaged tissues and organs. Moreover, they are utilized to administer drugs and therapeutic materials to the body in a targeted and controlled manner [1, 2]. As the field of biomaterials continues to advance, innovative biomaterials are continuously being developed. One such material is hydroxyapatite and its derivatives, which are closely related to the calcium phosphate compounds found in living organisms. Carbonate hydroxyapatite, specifically, is present in the bones and teeth of vertebrates, as well as some marine organisms like corals and mollusks [3, 4]. Due to its bioactive properties and resemblance to biological apatite, it is a preferred material in hard tissue engineering and drug delivery. Additionally, carbonate hydroxyapatite has non-medical uses. This article will provide an overview of biomaterials, the synthesis, and the applications of carbonate hydroxyapatite in medicine and beyond.

### Biomaterials and their Classification

Over the years, the definition of biomaterials has evolved from its earliest mention in 1967 by Dr. Jonathan Cohen. His definition summed up biomaterials to include all materials except drugs and sutures [1]. Although his definition was limited by the knowledge and research available at that time and by his experience as a surgeon, it captured the essence of biomaterials. It also separates biomaterials from aesthetic and beauty-motivated structures [2]. Following recent technological advancements in research, biomaterials are no longer considered inert structures as previously conceived [5]. Modern biomaterials last longer and can be whole or partial replacements of tissues or organs in the body [6]. The success ratings of biomaterials have increased, and the risk of revision

surgeries and related complications has been reduced. Various types of biomaterials have been used to enhance the quality of life of patients on application [2, 7, 8].

The broadest system of classifying biomaterials is based on their chemical structure and mode of interaction with the living system. Under this classification, structurally, biomaterials can be bioceramics, polymers, metals, or composites (Fig. 1), then inert, bioactive, or bioabsorbable based on the mode of interaction [9]. An oversimplified classification focuses on their origin, that is, natural or synthetic [10, 11].



**Fig 1.** Classification of biomaterials

### **Bioceramics**

Due to their exceptional properties and versatility, bioceramics are a significant class of biomaterials [12]. Ceramic materials designed for biomedical use exhibit outstanding biocompatibility, chemical stability, and mechanical strength. Bioceramics can be credited with a significant portion of the boom in demand for biomaterials [13]. First-generation bioceramics were bioinert, while second-generation bioceramics are bioactive and can be loaded with therapeutic species for targeted treatment [14, 15]. Examples of bioinert bioceramics are alumina, zirconia, and pyrolytic carbon. Their bioactive counterparts include calcium phosphates, hydroxyapatite, bioactive glasses, and coralline [16]. Compatibility is a major concern when designing biomaterials [8, 15, 17]. The bioactivity of bioceramics drives the production of bone grafts, skeletal implants, and coatings that promote faster healing, thereby improving their performance and reducing recovery time [18, 19], and as carriers of drugs that provide precise and long-lasting delivery of therapeutic substances to target areas [20-22]. Since the 60s, interest in the use of calcium orthophosphate bioceramics has grown, especially hydroxyapatite and its derivatives [23].

### **Hydroxyapatite (HA) and apatites**

Biomineralization is a typical process in living systems in which bioactive minerals are crystallized and deposited in the form of specialized structures. Common biominerals include silica, calcium carbonate, and hydroxyapatite. Hydroxyapatite is the fundamental component of hard tissues found in vertebrates and is characterized by its hexagonal or monoclinic crystal structure with the main difference being the spatial arrangement of the hydroxyl groups relative to the other groups in the structure [24-26]. Hydroxyapatite crystals with hexagonal crystal structure confirmed through X-ray diffraction have been reported more than their monoclinic counterpart although, Korowash et al. and Prihanto et al. reported that monoclinic have better thermodynamic stability and are often found in nature being formed at lower temperatures and pH of between 5 to 7.5 [25, 27]. It has however been observed that the two crystal structures can coexist and possess a dynamic relationship depending on the conditions of synthesis and prevailing conditions [28, 29]. Apatites refer to a family of compounds that share similar structures, especially the hexagonal system and space group ( $P6_3/m$ ). Appreciable characterization of apatites began in the 18th century [30]. By 2019, 9.5 % of hydroxyapatite articles were focused on substituted hydroxyapatite, a steady rise from 3.3 % in 2010 [31]. Three main properties of hydroxyapatite include acidity, ion exchange property, and adsorption potential. These

properties have made them effective ion exchangers, sorbents, and carriers of biomolecules, also influencing their applications in many fields as shown in Table 1 [32-35]. Most hydroxyapatites are hydrated salts because water acts as both a stabilizer in their synthesis and ensures the stability of their crystals [36]. Hydroxyapatites, chemically represented as  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , play a vital role in the composition of mammalian hard tissues [37] and exist in natural phosphate mineral deposits [38]. Hydroxyapatites can be sourced from natural materials such as mammalian bones, shells, fish scales, and minerals [39-46]. Their crystal structure possesses two distinct planes [47, 48]. From a functional and evolutionary perspective, aquatic animals meet their phosphorus demands through the seawater around them; similarly, terrestrial animals depend on the apatites in their hard tissues as a store of phosphorus for metabolic activities. This makes apatite found in the bones and other hard tissues adaptational storage, providing and regulating calcium and phosphorus in the body [49, 50]. Biological apatites, while nonstoichiometric and calcium deficient, exhibit a range of Ca/P ratios from 1.5 to 1.69, which significantly impacts their biological and physical characteristics [51, 52]. The properties and amorphous behavior of these apatites are contingent upon the type of modification and the extent of substitution [53].

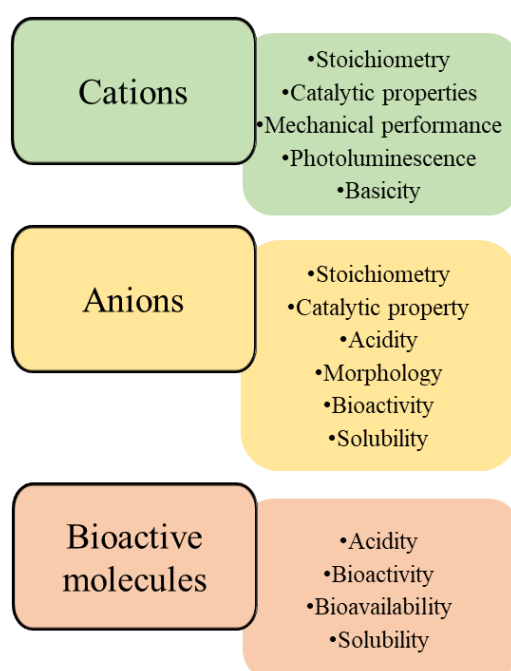
**Table 1.** Properties of hydroxyapatites and the influencing factors

Properties	Mechanisms and factors	References
Biocompatibility	Composed of ions, they are easily metabolized by the body. Adequate crystallinity and porosity Adaptable mechanical properties. Functional groups, functionalized surfaces, and high surface activity stimulate covalent bonding.	[54-57]
Bioactivity	Composed of ions that stimulate normal cell growth. Adequate surface area and porosity to support effective attachment of cells and flow of body fluid.	[54, 58]
Bioabsorbable	Slow degradation into Ions that are easily metabolized by the body.	[55, 56, 59]
Therapeutic	Inherent or incorporated ions Bioactive molecules incorporated into the structure.	[49, 57, 60]
Biostability/Biodegradability	Chemical composition, particle size, and purity.	[54, 58]
Ion exchange	High surface activity. Precipitation through complexation.	[54, 57, 61, 62]
Adsorption	Functional groups, functionalized surfaces, and high surface activity stimulate covalent bonding. Physical traps through nanopores.	[54, 57]

### Modifications and physicochemical properties

The structure, composition, and stoichiometry of hydroxyapatite have been successfully modified by the incorporation of other ions [63, 64]. Maximizing the ease of ion replacement in hydroxyapatites can improve their conductivity, crystallinity, solubility, and thermal stability, subsequently enhancing their applicability [65, 66]. The flexibility of hydroxyapatite crystal lattice encourages incorporating other ions to enhance their characteristics [49, 67]. Non-native ions found in the bone and tooth enamel hydroxyapatite include carbonate (~8 wt. %), sodium (~1 wt. %), magnesium, and trace amounts of other elements such as potassium, chloride, and fluoride [68]. Ince et al. [69] and Sridevi

et al. [70] reported that synthesized hydroxyapatite's morphology, stability, solubility, mechanical properties, and biological behavior are influenced by the type of ion, size, and charge. The hydroxyapatite lattice can accommodate ions larger in size than its native ions ( $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$ ), causing a marginal strain [49]. For example,  $\text{Ca}^{2+}$  could be replaced with alkali and alkaline earth ions, which alters its basicity, while  $\text{HPO}_4^{2-}$ ,  $\text{AsO}_4^{3-}$ ,  $\text{VO}_4^{3-}$ ,  $\text{SiO}_4^{4-}$ , and  $\text{CO}_3^{2-}$  can replace  $\text{PO}_4^{3-}$  to modify its acidity. Divalent ions like  $\text{Mg}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Ag}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$  have also been used to improve the mechanical performance of hydroxyapatite [67]. Sometimes bioactive organic molecules like citrate or other ions can adsorb functionally to the surface of apatites [49, 71]. Apatites doped with rare-earth elements have been used as biomarkers for tracking scaffolds in situ and other proteins [72–74]. Lanthanides replace  $\text{Ca}^{2+}$  in hydroxyapatite, yielding photoluminescent products, although Yttrium and Samarium have the potential to promote osteoblast adhesion. Rare elements take up selective positions in the calcium phosphate structure, which produces distinct properties in the products [34, 72, 73]. Fig. 2 summarizes the general effect of cations, anions, and bioactive molecules on hydroxyapatites.



**Fig. 2.** Properties affected by incorporating cations and anions into hydroxyapatite lattice.

### Carbonated hydroxyapatite (CHA)

CHA has become the important derivative of hydroxyapatite used in hard tissue engineering since natural bones are comprised of 60–70% by mass of carbonated, low-crystalline, calcium-deficient hydroxyapatites. It is the closest to the bioapatite found in bones and dental enamel. Pure stoichiometric hydroxyapatite is seldom found in nature whereas the presence of calcium-deficient hydroxyapatite combined with other ions are common [11, 75]. The introduction of carbonate ions ( $\text{CO}_3^{2-}$ ) into the crystal lattice structure of hydroxyapatite, which partially replaces hydroxyl ions or phosphate ions, imparts unique characteristics and complexities to the mineral [67, 76–78].

The inclusion of carbonate in the apatite structure has resulted in different morphological changes, which vary predominantly with the synthesis method. Generally, the inclusion of carbonate ions reduces crystallinity and increases solubility, thereby promoting biocompatibility, biomineralization, bioactivity, and reabsorption [77, 79–82]. CHA exhibits improved homogeneity and capacity, particularly when synthesized at the nanoscale [83]. Usually, when nanosized it offers better surface area, facilitating uniform distribution and interaction with its surrounding environment. However, nanosized apatites are preferred in drug delivery since they offer a higher surface area ratio, whereas bone graft and implant coatings use micro-sized apatite because they are bulkier [13].

The incorporation of carbonate ions into the apatite structure yields two types of CHA. B-type carbonation, characterized by substituting phosphate groups with carbonate ions, is notably present in young bones. B-type substitution results in CHA with a decrease in crystallinity and increased solubility [84]. B-type CHA mimics the chemical composition of natural bone constituents, though the carbonate content of bones is age-dependent. Interestingly, B-type CHA can be obtained from other sources besides humans [75, 85]. The A-type formed by substituting hydroxyl ions with carbonate is less polar, causing lower cell attachment to osteoblastic cells. Old tissues have been reported to contain more A-type CHA than younger ones [75]. A-type CHA compensates for charge through the loss of OH ions, whereas B-type CHA achieves compensation by the loss of  $\text{PO}_3^{4-}$  which is energetically favorable [86]. A-type CHA is represented as  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-2y}(\text{CO}_3)_y$ , ( $0 \leq y \leq 1$ ) and B-type is  $\text{Ca}_{10-x}(\text{PO}_4)_{6-x}(\text{CO}_3)_x(\text{OH})_{2-x}$ , ( $0 \leq x \leq 2$ ) [87, 88].

Depending on the extent and type of substitution, carbonates can influence the crystal lattice, crystallinity, morphology, and mechanical behavior of apatites [76, 78]. In a study, the incorporation of carbonate resulted in lower bending strength of single-crystal pure hydroxyapatite [89], which aligns with the findings that the elasticity of carbonated apatite increases [76]. The morphological transformation of CHA and their composites is proportional to the concentration of the carbonate included and attributed to the increase in disorder caused by introducing carbonate groups [90, 91]. Synthetic pure hydroxyapatite may be preferred because of its stability during sintering, but recent studies have improved the thermal stability of CHA, making it also available for medical applications [50].

The carbonate content in bone hydroxyapatite, which is about 7.4%, surpasses that in enamel and dentin which varies between 3.5% and 5.6% [92]. Variations in carbonate content exist both within a bone and among different bones in the body, reflecting composition-dependent functionality and this makes CHA a good substitute [93-95]. Spence et al. [96] and Ishikawa [96] confirmed this through in vitro studies on carbonated and pure hydroxyapatite. The study reported that carbonated hydroxyapatite stimulated collagen production in human osteoblasts when compared with pure hydroxyapatite [75, 97, 98]. An investigation into the implications of altered carbonate levels in bone diseases revealed connections between CHA and various pathological conditions. Comparative analyses of healthy bones and bones of patients with conditions such as osteoporosis or renal osteodystrophy revealed distinctive differences in carbonate content. Osteoporotic conditions result in elevated carbonate in bones which may correspond to impaired disruptions in mineralization processes and changes in bone mineral density. Furthermore, various pathological conditions and their extent of progress may be distinguished through comparisons of carbonate levels in the bones of patients [99, 100].

In physiological mediums, leaching is one of the series of processes that results in the formation of CHA and the incorporation of other ions into the apatite structure. The basic environment is formed by the migration of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Mg}^{2+}$  within the medium. As  $\text{Ca}^{2+}$  ions migrate to the surface, phosphates are formed, and eventually, crystallization occurs, and  $\text{OH}^-$  and  $\text{CO}_3^{2-}$  are incorporated to form carbonated apatite [101]. The altered crystal lattice due to carbonate substitution can lead to variations in bone load-bearing capabilities and resistance to fractures [102]. Simultaneous inclusion of  $\text{SiO}_4^{4-}$  and  $\text{CO}_3^{2-}$  increased its release potential. The replacement of Ca with Si resulted in lowered crystallinity and fine particle size [103]. Robin et al. [104] studied the mineralization process of CHA using micro-Raman spectroscopy and solid-state NMR. The process was initiated by the formation of amorphous calcium phosphate, which is then transformed into octacalcium phosphate and eventually into carbonated apatite.

### Synthesis methods and characterization

The ease of adjusting morphology and applications of apatites based on the choice of synthesis route has also favored apatites [13]. Popular biogenic sources of calcium for the synthesis of carbonate apatites include fish bones, shells, cow, and bovine bones [37]. Other standard reagents, such as  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{CaO}$ ,  $\text{CaCl}_2$ ,  $(\text{NH}_4)_2\text{HPO}_4$ ,  $\text{H}_3\text{PO}_4$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{CaCO}_3$ ,  $\text{K}_2\text{CO}_3$ , and  $\text{Na}_2\text{CO}_3$  are also used for the synthesis of CHA and its derivatives. The use of natural materials such as shells and salt

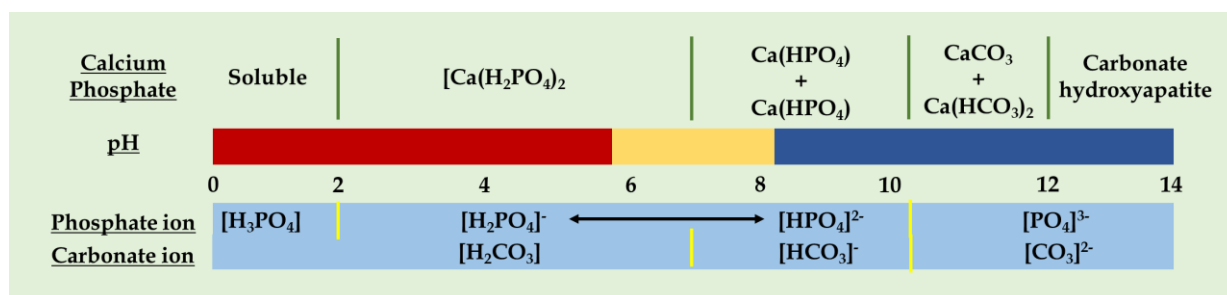
of sodium and potassium competitively includes magnesium, sodium, potassium or other elements in the carbonate apatite structure while optimizing the incorporation of carbonate through charge balance. Also, the products obtained from them imitate the natural bone CHA composition which is beneficial for bone tissue engineering [88, 105]. Similarly, halides are liberated when their salts are used. If pure undoped CHA is desired, ammonium and nitrates salts are mostly preferred because their residues are easily washed off after the reaction [106, 107]. Ultimately, the choice of reagents depends on the synthesis method and the desired properties of the hydroxyapatite nanoparticles. The synthesis route then, determines the morphology and size distribution, as shown in Table 2. The synthesis method also influences the mechanical properties, surface chemistry, purity, and bioproperties of the products [4, 108, 109]. Sometimes, nanosizing, nucleation and agglomeration of apatite nanoparticles is desired and facilitated using organic materials that serve as templates [110]. These organic modifiers uniquely influence the morphology and crystal structure of nanoparticles [111]. They are also beneficial in the chemical modification of hydroxyapatite nanoparticles' surface and are achieved through functionalization, which introduces functional groups that enhance the effective attachment of therapeutic materials, targeting, and release [112]. CHA synthesis methods can be grouped into two: wet and dry synthesis methods [4, 113-116].

**Table 2.** Synthesis methods, reagents, and morphology of carbonate hydroxyapatites.

Reagents	Synthesis method	Morphology	References
Ca(OH) <sub>2</sub> , (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> , CaCO <sub>3</sub> , (NH <sub>4</sub> )HCO <sub>3</sub>	Microwaved-assisted synthesis precipitation	Microcrystalline powders	[117]
CaO, (NH <sub>4</sub> ) <sub>3</sub> PO <sub>4</sub> , (NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	Microwave-assisted mechanosynthesis	Micro-sized granules	[118]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, (NH <sub>4</sub> ) <sub>3</sub> PO <sub>4</sub> , (NH <sub>4</sub> )HCO <sub>3</sub> , EDTA	Hydrothermal	Nanorods	[119]
CaCO <sub>3</sub> , CaHPO <sub>4</sub> .2H <sub>2</sub> O	Mechanosynthesis	Nanocrystalline powder	[120]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> , (NH <sub>4</sub> )HCO <sub>3</sub>	Nanoemulsion	Nanosized crystals	[121]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, (NH <sub>4</sub> )HCO <sub>3</sub> , (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub>	Nanoemulsion	Nanocrystalline	[122]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> , K <sub>2</sub> CO <sub>3</sub>	Wet precipitation	Nanocrystalline powder	[98, 123]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, KH <sub>2</sub> PO <sub>4</sub> , K <sub>2</sub> CO <sub>3</sub> , Urea	Hydrothermal	Nanorods	[124]
Calcium gluconate, Na <sub>2</sub> HPO <sub>4</sub> , Na <sub>2</sub> CO <sub>3</sub> , CaNO <sub>3</sub>	wet precipitation	Needle-like nanograins	[125]
Ca(NO <sub>3</sub> ) <sub>2</sub> .4H <sub>2</sub> O, (NH <sub>4</sub> ) <sub>3</sub> PO <sub>4</sub> , Na <sub>2</sub> CO <sub>3</sub>	Wet precipitation	Micro-sized solids	[107]

Dry methods are economically beneficial for the mass production of apatite powders. However, dry synthesis tends to contain impurities in the form of other phases and is therefore not always preferred for medical products [126]. Dry methods for synthesizing CHA include solid-state synthesis and mechanosynthesis [127-129]. Damayanti et al. [129] reported the synthesis of CHA through mechanosynthesis. The thoroughly milled mixture of hydroxyapatite and CaCO<sub>3</sub> produced predominantly B-type carbonate apatite. They observed that milling time is a major factor in the incorporation of the carbonate into the apatite structure through mechanosynthesis. Ito et al. [130] synthesized A-type carbonated hydroxyapatite by sintering pure hydroxyapatite in a CO<sub>2</sub> atmosphere at 900 °C for 15 hours. An alternative method reported by Nordström et al. [131], which yielded A-type CHA, involved immersing hydroxyapatite in a saturated CO<sub>2</sub> solution for up to two months.

Wet synthesis methods are particularly effective for tailoring the morphology and particle size of products [132]. For stoichiometric hydroxyapatite, a Ca/P ratio of 1.67 must be achieved during precipitation in wet synthesis. The inclusion of carbonate ion, however, increases the ratio up to 1.8, especially if it is B-type substitution [105]. All wet methods of CHA are carried out in an alkaline medium because at high pH levels, CHA is precipitated and remains stable, as shown in Fig. 3 [106, 127, 133-135]. Another important factor that increases the yield of wet methods, nanocrystallinity, and affects the percentage weight of incorporated carbonate is the aging period of the reaction system. This was explained by the increase in the number of phosphate ions replaced by carbonate ions [105]. Wet methods include sol-gel synthesis, hydrothermal synthesis, and wet precipitation (Fig. 4).



**Fig. 3.** Stability of calcium phosphate, phosphate ion, and carbonate ion at different pH [124].

*Sol-gel synthesis* involves the formation of a sol-gel of phosphate salt, carbonate salt, and calcium salt solution. The sol obtained must age properly at low temperature and then calcined at a higher temperature [136]. Sol-gel synthesis yields CHA nanoparticles with good homogeneity and biocompatibility [137]. Bang et al. [138] reported phase transformation of calcites prepared through sol-gel synthesis. The immersion of the initially prepared calcites into  $Na_2HPO_4$  solution produced nanosized needle-shaped carbonate apatites. Deptuła et al. [139] reported the synthesis of CHA through sol-gel synthesis using calcium acetate and phosphoric acid, calcining at 580 °C.

*Hydrothermal synthesis* is carried out under high pressure and temperature usually in an autoclave and can produce carbonate hydroxyapatite, which is adequate for biomedical applications. The closed synthesis system eliminates the need for calcination after synthesis [119, 140, 141]. Hydrothermal method was used to synthesize 5% and 13% hydroxyapatite-carbonate composites from corals. The hydroxyapatite-carbonate composites obtained on application initiated rapid bone differentiation within a year as evidence of the viability of synthetic carbonate apatites [142]. Organic templates have been used to mediate the hydrothermal synthesis of CHA [119, 140].

*Wet precipitation* is usually carried out with calcium, phosphate, and carbonate salts in alkaline medium at ambient or slightly elevated temperatures. To improve the homogeneity of the products, reaction conditions and material purity must be taken into consideration [141, 143]. Safarzadeh et al. [98] and Furko et al. [125] carried out wet synthesis of CHA using carbonate salts. In another research, Nowicki et al. [144] used a two-step approach to synthesize CHA. The first involves wet precipitation of pure hydroxyapatite followed by sintering in dry  $CO_2$ .



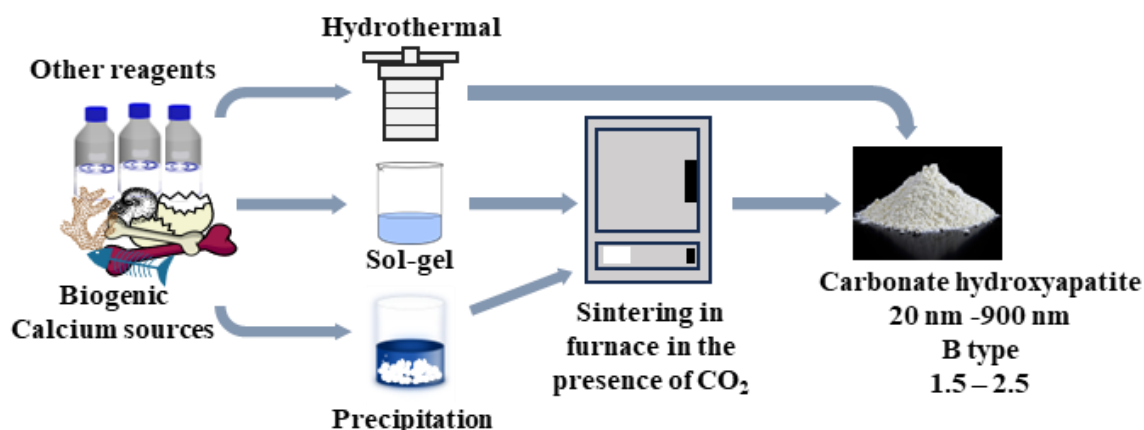


Fig. 4. Scheme for common CHA wet synthesis routes [145-147].

Other methods for the synthesis of CHA that are derived from wet precipitation include *microwave-assisted* synthesis, *nanoemulsion* synthesis and sometimes a combination of two methods. CHA obtained from *microwave-assisted synthesis* were reported to be less thermally stable although their bioactivity increased [148]. Ezekiel et al. [122] also concluded that CHA prepared through *nanoemulsion* exhibits a similar level of crystallinity and chemistry to biological apatites. After the incorporation of  $Mg^{2+}$ ,  $Co^{2+}$ , and  $Sr^{2+}$  separately and together by *nanoemulsion* route into CHA, the product remained amorphous and retained its phase purity. However, unlike their initial spherical shapes, the particles became more needle-like [84]. An example of the combination was carried out by Liu et al. [106]. They conducted a two-step process to synthesize CHA. For the first step, they performed stoichiometric synthesis of hydroxyapatite using  $KH_2PO_4$  and  $Ca(NO_3)_2$ . Subsequently, they employed a hydrothermal process for biomimetic CHA synthesis at 200 °C for 24 h using KOH as a mineralizer and  $K_2CO_3$  as the carbonate source. Interestingly, carbonation resulted in a reduction in the length of the rod-like hydroxyapatite nanoparticles as the carbonate concentration increased.

*Sintering* also known as thermal treatment, improves mechanical performance, stability, porosity, osteoclastic properties, and granular structure of CHA [17, 75]. It can be carried out at 900 °C upwards in a dry  $CO_2$  atmosphere [149]. Thermal stability is attributed to the concentration and type of carbonates used in the synthesis, though there is always significant decomposition of CHA with onset from 800 °C. Sintering time, temperature, and atmosphere affect carbonate substitution [150].

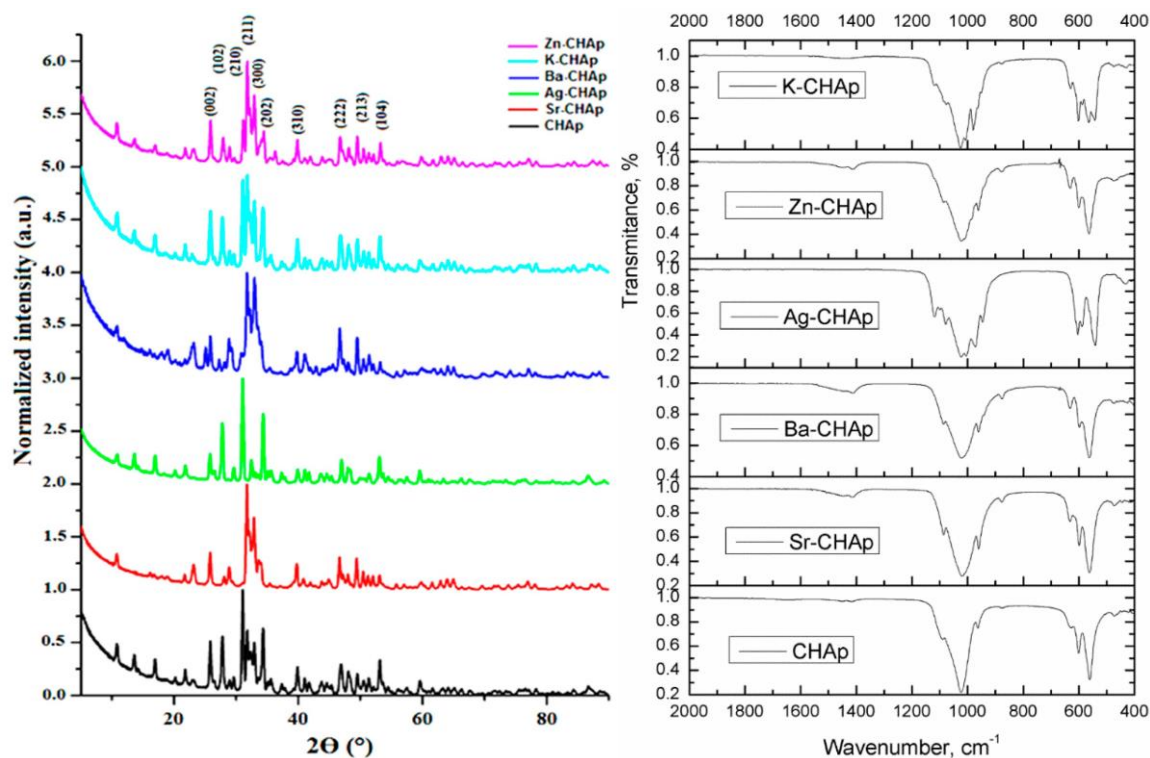
During thermal treatment, the carbonate content of apatites reduces. However, functional CHA must contain the average carbonate content of bones after sintering. To solve this challenge, Landi et al. [75] proposed residue-controlled sintering or sintering in a controlled atmosphere. Muhammad Syazwan et al. [84] observed that furnaces wear out easily when wet  $CO_2$  is used for carbonation during sintering. Their proposed alternative was to carry out an intermittent supply of wet  $CO_2$  during the sintering or to use sintering aids. CHA prepared with sintering aids ( $Mg(OH)_2$ ,  $Ca(OH)_2$ , NaOH, KOH, and  $K_2CO_3$ ) produced samples with improved morphology and better strength [151]. During thermal treatment, B-type CHA may form alongside various other phases, and at extreme temperatures,  $\beta$ -tricalcium phosphate is formed [86]. Lovón-Quintana et al. [133] noted that thermal treatment in  $CO_2$  atmosphere at high temperatures above 1000 °C yields A-type CHA while lower temperature gives B-type. However, they noted that the synthesis route of CHA also influences the type of sintered CHA obtained [149].

X-ray diffraction (XRD) studies serve as a tool to elucidate shifts in the lattice parameters and the position of carbonate ions within the apatite structure. From observation, an increase in the amorphous phase due to the inclusion of carbonate results in broader peaks with lower intensity [88, 119, 152, 153]. Also, Verma et al. [154] explained that the slight shift in  $2\theta$  to higher values was connected to a compressive microstrain in the lattice structure. This strain leads to the extension of the c-axis and shortening of the a-axis, a characteristic of B-type carbonation of hydroxyapatites. In the study of the effect of ammonium carbonate on the formation of calcium-deficient hydroxyapatite, lower levels of carbonation still maintained the sharper peaks and crystalline structure of



hydroxyapatite. As the degree of carbonation increased, the peaks became broader, and crystallinity reduced [152, 155-157]. Generally, peaks between  $20^\circ$  and  $28^\circ$  represent the (002) plane while those between  $31$  and  $50^\circ$  represent 211, 213, 222, 300 and 310 planes of apatites (Fig. 5) [41, 119, 154, 158, 159].

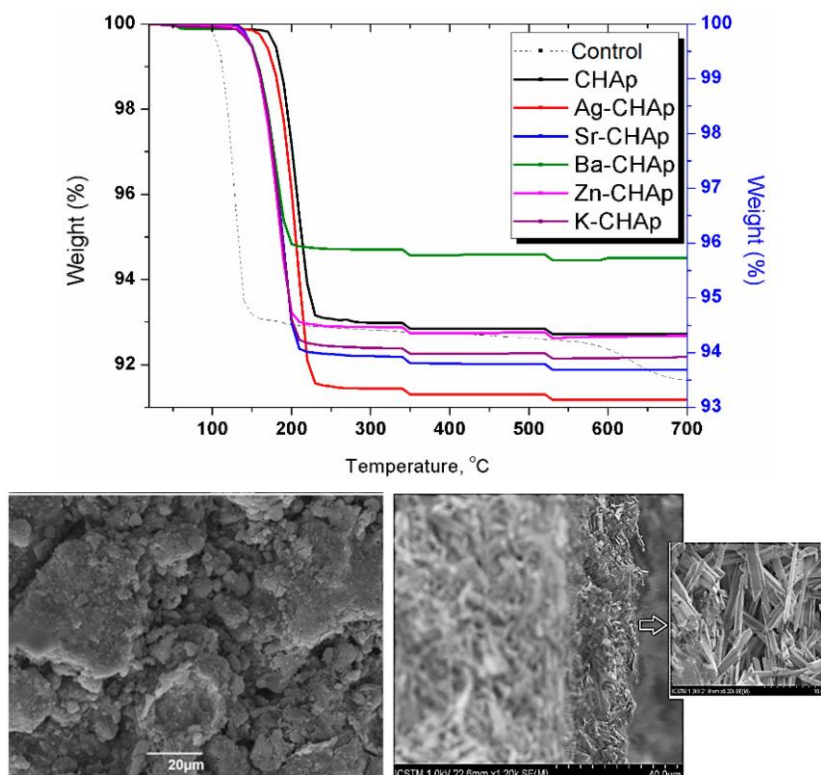
Although X-ray diffraction patterns can identify the hydroxyapatite phase, the presence of hydroxyl, phosphate, and carbonate groups is easily confirmed through FTIR [160]. Typically, FTIR spectra of CHA have broad  $\text{OH}$  absorption around  $3446.6\text{ cm}^{-1}$  and  $962.4\text{ cm}^{-1}$ , and absorption around  $472.5\text{ cm}^{-1}$  representing the  $\text{PO}_4^{3-}$   $\nu_1$  and  $\nu_2$ , respectively. Sharp peaks for  $\text{PO}_4^{3-}$   $\nu_4$  are recorded at around  $603.7\text{ cm}^{-1}$  and  $565.1\text{ cm}^{-1}$ . The bands at  $1458.1\text{ cm}^{-1}$  and  $1400.2\text{ cm}^{-1}$  are attributed to  $\text{CO}_3^{2-}$  absorption [160, 161]. Usually, the replacement of  $\text{PO}_4^{3-}$  or  $\text{OH}^-$  by the incorporated ion weakens the intensity peaks for the corresponding ion but according to stoichiometry, the O-H stretching band is usually weaker when compared with P-O (Fig. 5) [161-163].



**Fig. 5.** XRD diffractograms and FTIR spectra of carbonated hydroxyapatites [163].

Scanning Electron Microscopy (SEM) reveals the transition in morphology as chemical composition changes or modification occurs with the inclusion of carbonate ions (Fig. 6). The morphology of CHA as confirmed by SEM showed that an increase in carbonation increased amorphous characteristics leading to the formation of “featureless” structures from the previous rod-like shapes of the hydroxyapatite [152]. Moore et al. [157] also confirmed the amorphous structure of carbonate hydroxyapatite prepared through low-temperature precipitation. Frank-kamenetskaya et al. [164] compared the morphology of CHA prepared by precipitation and hydrothermal routes. The hydrothermal route produced more crystalline CHA than the precipitation route although the amorphous characteristics generally increased in both cases as degree of carbonation increased.

Thermal behavior of materials studied through thermogravimetric analysis is crucial to determining the behavior of materials in mild and extreme temperatures (Fig. 6). Usually, CHA obtained from biogenic materials undergoes a refinement in the structure after calcining. This is due to the volatilization of organic matter, resulting in a loss of mass at about  $700^\circ\text{C}$  [162]. Thermogravimetric analysis of CHA obtained through sol-gel synthesis [165] revealed a loss of mass resulting from the water below  $150^\circ\text{C}$  and a loss of mass from  $600^\circ\text{C}$  due to the release of  $\text{CO}_2$  [74, 166, 167].



**Fig. 6.** TGA spectra [163] and SEM of granular [168] and rod-like [163] CHA.

### Biomedical applications and biomaterial design

CHA has significant relevance in biomedical applications due to its distinctive properties derived from carbonate substitution within the hydroxyapatite lattice (Fig. 7). It is a better substitute for pure synthetic hydroxyapatite [17]. Hard tissues in orthopedics and dentistry have been repaired or replaced using CHA [169]. The porous microstructure obtained after sintering CHA confers osteoconductive, osteoinductive, and osteointegrative properties [170]. The context of application determines whether CHA is used in its pure form or as a composite with other materials or bioactive molecules. Carbonate apatite products can be incorporated into living systems as a solid body with low porosity, porous structures, sponges, or alloy and metal implant coatings [49, 171, 172].

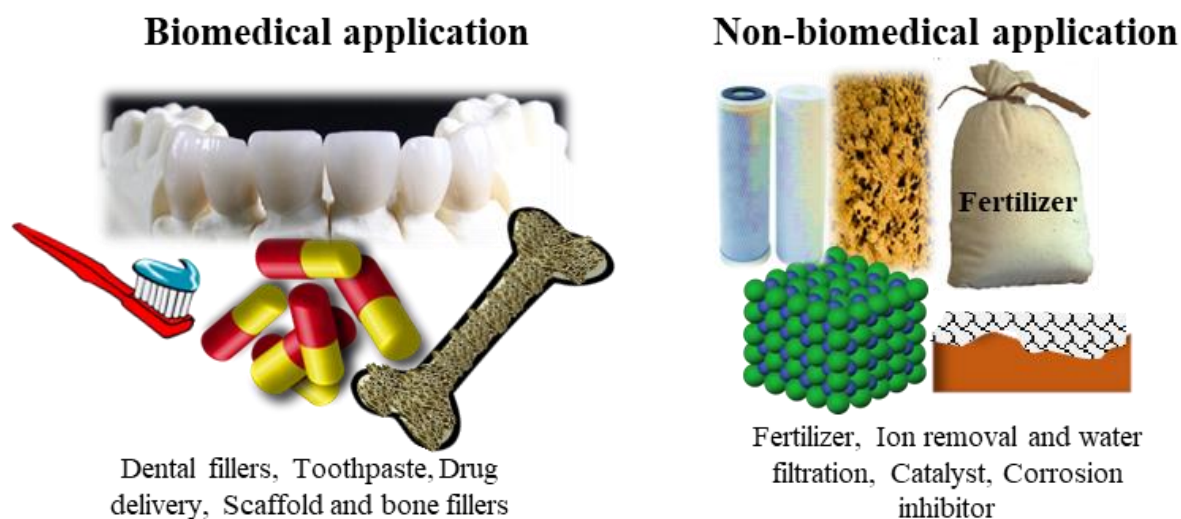
Studies have demonstrated that CHA nanoparticles surpass their micron-sized counterparts in terms of mechanical properties [102]. The CHA layer formed on the surface of implants facilitates the attachment of the implant to the living bone and the surrounding tissues [173]. The dense network formed by the porous CHA allows the diffusion of cells responsible for the deposition of bone tissue (osteoconduction), ultimately improving biointegration and mechanical stability. These pores are interconnected and have dimensions ranging from 100 μm to 500 μm [174]. CHA also works as a scaffold that supports biomineralization [82]. Porous scaffolds made through CHA incorporated into sponges are like those found in bones. The best scaffolds are made through optimal slurry concentration and sintering conditions. Porous bodies of B-type CHA prepared by impregnating cellulose sponge with CHA are usually sintered in air and CO<sub>2</sub> to determine their thermal stability. Compared with pure hydroxyapatite, the CHA-based materials displayed good osteoconductive and biosorption properties [75]. Sintered CHA coatings are effective anti-corrosion materials [100]. Hiromoto et al. (2020) asserted that insoluble materials with good osteoclastic resorption have good anti-corrosion properties. Upon examination, the CHA coating dissolved in the presence of osteoclasts, which makes it a possible bioabsorbable material for corrosion control of biodegradable Mg alloys.

Carbonate ions and other ions in the CHA structure influence the formation and growth of hydroxyapatite crystals within the bone tissue by maintaining the acid-base balance needed to ensure uninterrupted metabolic processes. Additionally, carbonate ions enhance the absorption of Ca<sup>2+</sup> and other cations to maintain the balance of ions within the apatite structure [49]. Calcium ion is released

through the breakdown of apatites in living systems, a factor known to induce apoptosis in tumor cells, contributing to their efficiency in tumor treatment [175]. The inherent cancer-inhibitory attributes of CHA [112] further support its use as a vehicle for drug delivery, dental enamel repair [176], and injectable bone cement [177]. CHA has been used in the presence of organic phases, for example, CHA-chitosan membranes and their microporous surface aided adhesion to living tissue when used as coatings for  $\text{Ti}_6\text{Al}_4\text{V}$  exoskeletons. The organic phase (chitosan) also aided agglomeration and biocompatibility of the composite membrane [178]. Biomimetic mineral coatings made of CHA can be used as alternatives to typical fluoride compounds. When applied, nanocrystalline CHA acts as a self-distributing filler for the surface dents and scratches in enamels [179] and when doped with specific cations, controls the growth of some microbes. On its own, carbonated hydroxyapatite (CHA) exhibits limited antimicrobial inhibitory properties, with a minimum inhibitory concentration of 200 mg/ml which supports its doping with ions with known antimicrobial properties [119, 154, 180]. Aziz et al. [107] reported the use of Ag-doped CHA for the inhibition of bacterial growth on peri-implants.

### Non-Biomedical Applications of CHA Nanoparticles

The tunable surface chemistry of CHA nanoparticles allows for modifications that increase their selectivity toward specific contaminants, making them versatile tools for addressing environmental pollution (Fig. 7) [181]. The high surface area-to-volume ratio of nanosized CHA enhances their adsorption capacity, making them effective in removing heavy metal ions from polluted water and soil [182]. The dispersal leading to toxicity of Au, Ag, and graphene nanoparticles when used in water treatment is a limitation [183]. Asimeng et al. [184] reported the use of CHA synthesized from snail shells as nontoxic  $\text{Fe}^{2+}$  removal material from wastewater. An efficiency of 45.87 mg/g was reported compared with 2.39 mg/g for pure hydroxyapatite [185]. Sometimes CHA forms insoluble phosphates with toxic ions when used in water treatment [109]. CHA is very effective in water treatment because of its adsorption affinity, ion exchange, complexation, and coprecipitation properties [186, 187]. CHA removes lead ions from contaminated water through adsorption and dissolution-precipitation models [188]. Liao et al. [160] determined the uptake of lead (II) ion by CHA as a pseudo-second-order reaction and takes place optimally at pH 6. Xing et al. [189] also reported rapid adsorption of  $\text{Cd}^{2+}$  by CHA flakes synthesized through ureolytic bacteria. The nanomaterial had large adsorption capacity (270 mg/g). Municipal wastewater is known to be rich in phosphorus, and phosphorus is removed through precipitation as part of the purification process [190]. Struvite is the major precipitate obtained in the anaerobic process. However, Sarria et al. [61] and Castro et al. [62] observed that other forms of hydroxyapatite including carbonated apatite can be obtained through pH adjustments in the purification process.



**Fig. 7.** Biomedical and non-biomedical application of CHA

Moore et al. [157] exploited the affinity of selenite for Ca-based materials to remediate soils polluted with selenium using CHA. Smart spongy fertilizers were synthesized using CHA. The eco-friendliness was verified by application on water spinach plants, and it had no adverse effect on their growth. Also, the cationic exchange properties of apatites come into play in their use as fertilizers [109]. CHA also simultaneously adsorbs organic pollutants like glyphosate and radionuclides [191]. Nanofertilizers doped with bioorganic molecules and ions can perform better due to increased surface area, porosity, and easy degradability [192]. A surface coating for stonework made of CHA doped with zinc, strontium, and magnesium increased their mechanical strength and decreased water absorption, ultimately improving their surface durability [193].

Catalysis is important in many processes because it reduces cost in terms of energy and time. With rising awareness of the impact of unfettered consumption of energy on the environment, studies to diversify and obtain efficient catalysts have not spared the use of hydroxyapatite [194]. Ethanol is one of the major additives in gasoline and could become an alternative energy source. CHA is being investigated as an alternative catalyst with better results in the synthesis of ethanol and biodiesel and the detection of glucose and hydrogen peroxide [115]. Some defects in B-type CHA microstructure have been reported to promote its catalytic performance in ethanol-to-hydrocarbon conversion. Ethanol was also successfully synthesized using CHA as a catalyst. The acid-basic sites of CHA make it a potential bifunctional catalyst. [133]. The unique chemical composition and surface morphology of CHA nanoparticles make them potential candidates for heterogeneous catalysis [109]. Active surface sites on these nanoparticles can participate in various catalytic reactions, including biodiesel production through transesterification [195]. The presence of carbonate groups enhances acidity and modifies the electronic structure of the apatite, thereby influencing its catalytic activity [72]. Apatite catalysts are produced through anionic and cationic modifications.

The catalytic properties of apatites and their use as detectors have also been enhanced by introducing various transition metals, such as nickel [196] or iron [64]. When preparing doped apatites for catalytic or ion exchange purposes, it is necessary to recognize the nature of the mechanism of the surface reaction. In the case of doped or impregnated apatite, catalyst synergistic effect is a common phenomenon [109].

Self-hardening cement was made from a mixture of  $\text{Ca}_3(\text{PO}_4)_2$ ,  $\text{CaCO}_3$ ,  $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$  and  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ . When the CHA component was increased, the rate of resorption increased. An increase in acidity of the environment also increases the ease of absorption of the cement [197].

## Conclusion

Carbonate hydroxyapatite (CHA) is a common derivative of hydroxyapatite, with a morphology and properties that can be tailored through the choice of synthesis method and conditions. CHA can be synthesized via dry methods like mechanosynthesis and solid-state synthesis; however, when nanosized CHA is desired, wet methods such as hydrothermal, precipitation, and microwave-assisted synthesis are preferred. CHA is a versatile ceramic with increased porosity compared to stoichiometric hydroxyapatite, resulting in a high surface area. CHA has been extensively exploited in various medical applications, including use as a scaffold, bone filler, biomarker, and drug delivery material. Doping CHA with specific biogenic ions like strontium and silver has further enhanced its antibacterial and anticancer properties for biomedical applications. Beyond medicine, CHA has the potential to be used as a catalyst, fertilizer, and water purifier. As research progresses, additional non-medical applications of CHA are likely to emerge.

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