



# Investigation of the antibacterial activity of synthesized hydroxyapatite Sr-doped nanocomposite

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## ABSTRACT

Hydroxyapatite is a mineral compound with a composition resembling the components found in human teeth and bones. Hydroxyapatite possesses osteoconductive, bioactive, and biocompatible characteristics. Nevertheless, hydroxyapatite has limitations, particularly its limited antibacterial activity. Therefore, this research uses the sol-gel method to synthesize and characterize strontium hydroxyapatite doped composites (HAp-Sr doped composites). The calcium precursor used in this research comes from the green mussel shells (*Perna viridis*); the main component is  $\text{CaCO}_3$ , which will later be converted into CaO compounds. HAp Sr-doped composites were synthesized by varying the concentration of Sr metal (5%, 10%, and 20% w/w), which aimed to determine its good antibacterial ability. The X-ray fluorescence analysis reveals that green mussel shells contain 97.261% calcium oxide (CaO). The X-ray diffraction analysis reveals that the pattern observed at an angle of  $2\theta$  corresponds to the hydroxyapatite standard from ICDD (No.96-101-1243), which possesses a hexagonal structure. The Fourier transform infrared spectroscopy spectra reveal the presence of  $\text{PO}_4^{3-}$  groups in the sample at wave numbers  $528\text{ cm}^{-1}$ ,  $604\text{ cm}^{-1}$ ,  $945\text{ cm}^{-1}$ , and  $1,018\text{ cm}^{-1}$ . The antibacterial activity of the HAp-Sr doped composite was evaluated against *Staphylococcus aureus* and *Escherichia coli* bacteria. The results indicated that the 5% HAp-Sr doped composite exhibited antibacterial activity. Therefore, it can potentially be utilized in bone grafts and implants.

## INTRODUCTION

Hydroxyapatite is a biomaterial with superior properties such as low toxicity, osteoconductive, high bioactivity, and biocompatibility [1]. Hydroxyapatite also has the same chemical properties as human bone so it can be used in bone implants [2-4]. Hydroxyapatite ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) is bioceramic obtained from calcium, phosphate, and hydroxide precursors [2]. Calcium precursors can be obtained using natural sources, namely shellfish [5], limestone [6], eggshell [7], and common cockle (*Cerastoderma edule*) shells [2]. This study employed the green mussel shells as precursors of synthesized hydroxyapatite due to high calcium oxide (CaO) content, around 97.261%. Previous research reported that using

shells as a biomaterial increases the strength and elasticity of the resulting product [8,9]. The limited antibacterial properties of hydroxyapatite mean that its potential in the implantation process cannot be utilized optimally [7]. Biofilm formation by *Staphylococcus aureus* and *Escherichia coli* bacteria on the implant surface can cause infection. It can cause clinical problems, the main problems in the bone implant process every year [10].

To overcome this problem, many researchers have synthesized hydroxyapatite materials composited or doped with other materials such as metals, polymers, or metal oxides to be applied more widely as biomedical materials. Some previous studies reported the synthesis of a biomedical material such as HAp/TiO<sub>2</sub> as antiviral/antibacterial material [11], NiFe<sub>2</sub>O<sub>4</sub>@HAp-Ag as a prompt antibacterial material against pathogenic strains [12], cytocompatibility of biodegradable Zn-3Fe-HAP composites which be promising material for bone repair [13], Vanadium and Strontium co-doped HAp for tissue engineering applications [14], metals (Al, Fe, Ni, and Zn) doping in nano-

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crystalline hydroxyapatite for efficient biomedical applications [15] and strontium-substituted hydroxyapatite-CaO-CaCO<sub>3</sub> nanofibers as drug delivery carriers [16].

In this study, the HAp-Sr doped was carried out to improve the antibacterial properties of HAp. The incorporation of strontium into bones occurs quickly (1–2 weeks). Strontium is also the main ingredient in the drug strontium ranelate, a drug currently being developed to treat cases of osteoporosis (bone fragility) [16]. *In vitro*, strontium is known to increase the number of osteoblasts (bone-forming cells) and can reduce the number of osteoclasts (bone-breaking cells) [17]. Strontium can also facilitate the process of bone resorption and stimulate bone formation [18]. Apart from that, strontium is also known to have good antibacterial properties because it can cause bacterial DNA to condense so that it loses its ability to replicate [19].

Synthesis of hydroxyapatite Sr-doped was carried out using the sol-gel method. The sol-gel method is carried out at low temperatures but produces products with high purity with a phase change from colloidal suspension (sol) to liquid (gel). Apart from that, using little equipment and cost-effectiveness are also advantages of the sol-gel method [20]. This approach also provides the capability to achieve molecular mixing of chemical precursors. Compared to conventional solid-state, wet precipitation, and hydrothermal processes, it has the capability to generate nanosized particles and nanocrystalline powders. This approach comprises multiple phases: formulation of the precursor solution, hydrolysis to initiate gelation, maturation, desiccation, and sintering. The precursor may be either an inorganic or organometallic compound [21].

Thus, this study aimed to examine the antibacterial characteristics of HAp doped with Sr. Concentration variations of Sr were also conducted during the doping process to determine the effective concentration required to inhibit bacterial growth. The employing of Sr-doped HAp can effectively reduce the reliance on pharmaceuticals in the field of medicine.

## MATERIALS AND METHODS

### Materials

Green mussel shells (*Perna viridis*), nitric Acid (HNO<sub>3</sub>), ammonium hydroxide (NH<sub>4</sub>OH), anhydrous strontium nitrate (Sr(NO<sub>3</sub>)<sub>2</sub>), diammonium hydrogen phosphate ((NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>), and nutrient agar (NA).

### Methods

#### Calcium oxide preparation

The green mussel shells are cleansed of impurities, dried, and pulverized using a grinder. Subsequently, the material underwent calcination at a temperature of 900°C for 5 hours, producing powdered CaO. The CaO powder was subsequently analyzed using X-ray fluorescence (XRF) [20].

#### Synthesis of HAp by sol-gel method

CaO powder was weighed 4.2 g, dissolved in 75 ml of 2 M HNO<sub>3</sub>, and stirred at 250 rpm at 65°C for 15 minutes. Filtration is performed on the Ca(NO<sub>3</sub>)<sub>2</sub> solution. By adding an NH<sub>4</sub>OH solution and getting a Ca(OH)<sub>2</sub> sol, the Ca(NO<sub>3</sub>)<sub>2</sub> filtrate was

brought to pH 10. Then, dropwise 250 ml of 0.18 M diammonium phosphate ((NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>) was added and heated to 60°C for 5 hours while stirring. The hydroxyapatite sol formed was left for 24 hours until a gel formed. The gel obtained was filtered, dried at 110°C for 5 hours, then calcined at 600°C for 3 hours. The hydroxyapatite powder obtained was analyzed using X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) characterization.

#### Synthesis of HAp-Sr doped by sol-gel method

A weighed solution of CaO powder is then dissolved in 75 ml of 2 M HNO<sub>3</sub>, and the mixture is agitated with a stirrer at 65°C for 15 minutes at 250 rpm. After preparing and filtering a Ca(NO<sub>3</sub>)<sub>2</sub> solution, drop by drop of diammonium phosphate solution ((NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>) is added. A drop of 250 ml was added with NH<sub>4</sub>OH until a pH of 10 was obtained. A hydroxyapatite-strontium sol was formed by stirring Sr(NO<sub>3</sub>)<sub>2</sub> at concentrations of 5%, 10%, and 20% in a temperature-controlled environment at 60°C for approximately 5 hours. After being aged for 24 hours, the HAp-Sr sol turned into a gel. Filtered, dried for 5 hours in an oven at 110°C, and then calcined for 3 hours at 600°C. The composition of precursor solution HAp-Sr doped composite synthesis is shown below in Table 1.

#### Antibacterial assay

*Escherichia coli* and *S. aureus* bacteria were regenerated for a full day in a sealed chamber. Then, antibacterial testing was carried out by adding rejuvenated bacteria to the NA medium. Add 0.5 g of HAp and HAp-Sr doped composite powder to the disc ring in a sterile petri dish containing media and bacteria. Then, the incubation was carried out for 24 hours after the control (amoxicillin) was used.

#### Characterizations

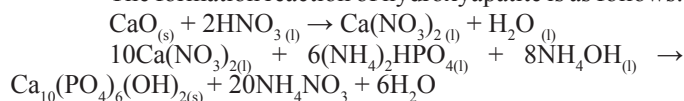
The determined element in the green mussel shell was analyzed using XRF (PANalytical type minimal 4). The functional group of the sample was analyzed using a Fourier Transform Infra-Red (Shimadzu IR Prestige-21) at a wavenumber of 4,000–500 cm<sup>-1</sup>. The structure properties of the HAp and HAp-Sr doped composite samples were analyzed using XRD (Bruker D8 Advance) at a 2θ value of 10°–90°.

## RESULTS AND DISCUSSION

#### Preparation of CaO from green mussel shells (*Perna viridis*)

Hydroxyapatite and strontium hydroxyapatite were synthesized using green mussel shells (*Perna viridis*). Calcination of green mussel shells aims to release substances in the form of carbonates and hydroxides into substances in the form of oxides. In the calcination stage, the decomposition process (breakdown) of calcium carbonate compounds (CaCO<sub>3</sub>) into calcium oxide (CaO) will occur above a temperature of 800°C [22]. However, if the sample is calcined above a temperature of 900°C, the CaO yield obtained will decrease because the CaO compound begins to change into other compounds [23].

The formation reaction of hydroxyapatite is as follows:



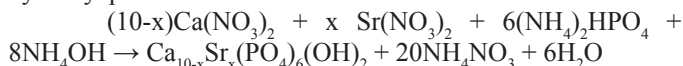
**Table 1.** Composition of precursor solution HAp-Sr doped composite synthesis.

No	Sample	CaO		$(\text{NH}_4)_2\text{HPO}_4$		$\text{Sr}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	
		gram	mol	gram	mol	gram	mol
1.	HAp	4.20	0.075	5.94	0.045	0.0000	0.0000
2.	HAp-Sr 5%	4.01	0.0732	5.94	0.045	0.3765	0.0018
3.	HAp-Sr 10%	4.00	0.0715	5.94	0.045	0.7530	0.0035
4.	HAp-Sr 20%	3.80	0.0679	5.94	0.045	1.5060	0.0071

**Table 2.** Composition of green mussel shells.

Compound	Composition %
CaO	97.261
MgO	0.089
$\text{Al}_2\text{O}_3$	0.337
$\text{SiO}_2$	0.277
$\text{P}_2\text{O}_5$	0.553
$\text{F}_2\text{O}_3$	0.311
$\text{Ag}_2\text{O}_3$	0.677
$\text{SrO}_2$	0.377

The reaction for the formation of strontium-hydroxyapatite is as follows:



#### Analysis of green mussel shell composition using XRF

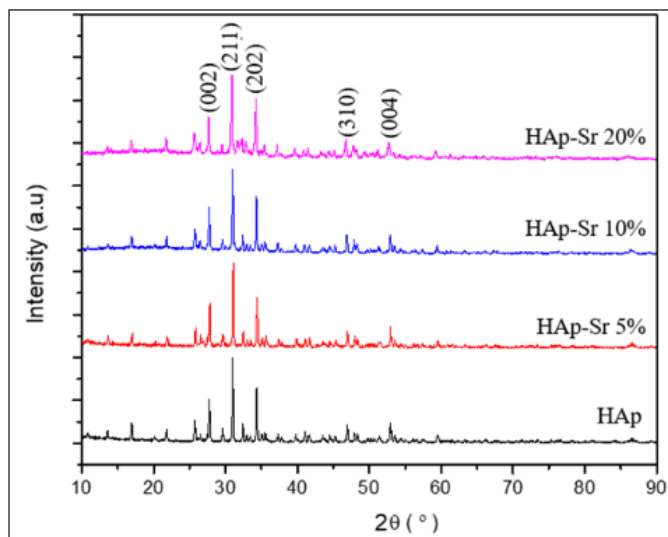
Green mussel shells are utilized as a calcium source due to their high calcium oxide content of 97.261%. The green mussel shells can serve as raw materials for synthesizing hydroxyapatite due to their significant calcium content. The chemical composition of green mussel shells that underwent calcination at a temperature of 900°C for 5 hours was determined using XRF and is presented in Table 2.

Based on the results of XRF characterization, the percentage of CaO was found to be 97.261%, so it can be concluded that green mussel shells can be used as a calcium precursor in the synthesis process of HAp and HAp-Sr doped composites. Apart from CaO, other oxide compounds such as MgO,  $\text{Al}_2\text{O}_3$ , and  $\text{SiO}_2$  were also found. However, the content of these compounds is small enough that when reacted with  $\text{HNO}_3$ , these compounds can dissolve and form a precipitate [23].

#### XRD analysis

XRD characterization was used to determine the structure of the synthesized samples. The samples analyzed on XRD consisted of HAp, HAp-Sr doped composite 5%, 10%, and 20%, as shown in Figure 1.

Based on the XRD graph in Figure 1, the spectra are conformed to ICDD standards (No. 96-101-1243). It can be concluded that Sr has succeeded in replacing or partially substituting Ca because no new peaks were found on the graph. Sr ions have a greater ion radius than Ca, which can be used as a substitute ion or ion to replace  $\text{Ca}^{2+}$ . The  $\text{Sr}^{2+}$  ion is known to have an ionic radius of 1.18 Å. Meanwhile, the  $\text{Ca}^{2+}$  ion

**Figure 1.** XRD pattern HAp and HAp-Sr doped composite.

has an ionic radius of 1.00 Å<sup>32</sup>. The three prominent peaks of hydroxyapatite found at  $2\theta$  with values of 27.65°, 31.17°, and 34.50° have Miller indices of (002), (211), and (112), indicating that hydroxyapatite does not crystallize well [24]. In addition, XRD analysis was also used to determine the sample size through Scherer calculation.

$$D = \frac{k\lambda}{\beta \cos \theta}$$

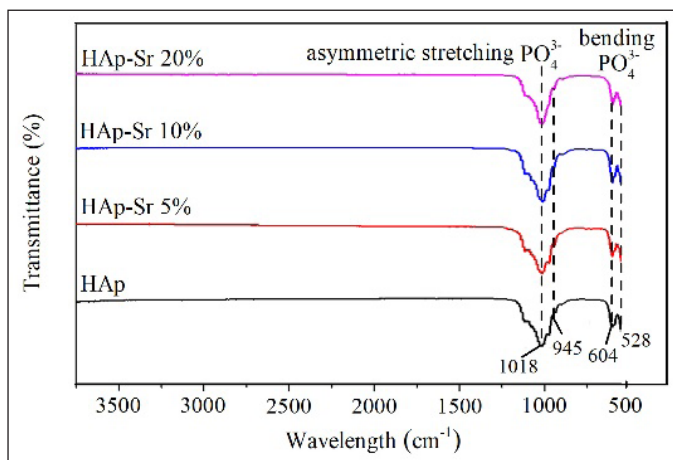
where  $D$  = crystal size (nm),  $k$  = constant (0.9),  $\lambda$  = X-ray wavelength,  $\beta$  = FWHM (Full Width at Half Maximum) at  $2\theta$  ( $\pi$  180), and  $\theta$  = Bragg angle. Based on Table 3, the crystallite size of HAp, HAp-Sr 5%, HAp-Sr 10%, and HAp-Sr 20% is 0.85 nm. It shows no change in the crystal size after doping with Sr. From the XRD data, it is known that the synthesized compounds are hydroxyapatite and hydroxyapatite-strontium composites.

#### Fourier transform infra-red

The synthesis results were analyzed using FT-IR to identify functional groups in absorption peaks and molecular interactions that play a role in the HAp and HAp-Sr doped composite synthesis process [25]. FT-IR analysis was carried out at wave numbers 3,500–500  $\text{cm}^{-1}$ . The FT-IR absorption of HAp and HAp-Sr doped composite is shown in Figure 2 as follows.

**Table 3.** The crystallite size of HAp and HAp-Sr doped sample.

Sample	Peak 2θ (°)	FWHM	Crystal size (nm)
HAp	31.17	0.17	0.85
HAp-Sr 5%	31.34	0.17	0.85
HAp-Sr 10%	31.17	0.17	0.85
HAp-Sr 20%	31.17	0.17	0.85



**Figure 2.** Spectrum HAp and HAp-Sr doped composite.

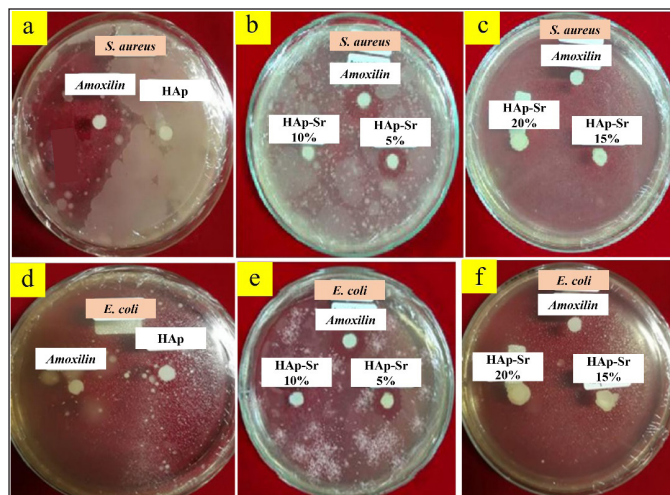
**Table 4.** Inhibition zone of HAp and HAp-Sr doped composite.

Bacteria	Inhibition zone (mm)				
	HAp	HAp-Sr 5%	HAp-Sr 10%	HAp-Sr 20%	Control (Amoxicillin)
<i>Staphylococcus aureus</i>	0	0.2	0	0	0.8
<i>Escherichia coli</i>	0	0.2	0	0	0.8

There is a typical peak in the FT-IR spectrum of hydroxyapatite, namely the  $PO_4^{3-}$  group peak. At wave numbers  $604\text{ cm}^{-1}$  and  $528\text{ cm}^{-1}$ , it is the vibrational bending of  $PO_4^{3-}$ . The peak at wave number  $1,018\text{ cm}^{-1}$  is vibrational stretching (asymmetry) of the  $PO_4^{3-}$  group. Meanwhile, wave number  $945\text{ cm}^{-1}$  is vibrational stretching (symmetry) of the  $PO_4^{3-}$  group. Identifying the  $PO_4^{3-}$  group and the  $OH^-$  group, functional groups found in hydroxyapatite, suggests that the sample contains Hap [26].

**Antibacterial assay**

Antibacterial tests were carried out on samples of HAp, HAp-Sr 5%, HAp-Sr 10%, and HAp-Sr 20% using amoxicillin as a control as shown in Figure 3. In this antibacterial test, two types of bacteria are used: the Gram-positive bacteria *S. aureus* and the Gram-negative bacteria *E. coli*. Inoculum was prepared from fresh culture after incubation for 24 hours at  $37^\circ\text{C}$ . Antibacterial activity was observed using the disc ring method, measuring the minimum inhibition zone in millimeters. Inhibition Zone of HAp and HAp-Sr doped composite is shown in Table 4.



**Figure 3.** Antibacterial activity of HAp-Sr doped composite against *S. aureus* bacteria (a–c) and *E. coli* (d–f).

The test results found that the antibacterial activity of HAp-Sr 5% had an inhibition zone compared to HAp, HAp-Sr 10%, and HAp-Sr 20%. The more Sr is added, the less antibacterial activity it becomes. Therefore, the Sr added to the sample must be in a certain amount. Previous research revealed that strontium-hydroxyapatite will have good bioactivity if the level of Sr added in hydroxyapatite doping is 3%–7% [27]. When the added Sr exceeds the specified level, it can be toxic in the body. These data show that HAp-Sr 5% has an inhibition zone value and can act as an antibacterial. It proves that doping strontium ions on hydroxyapatite can increase the bioactivity of hydroxyapatite [28]. Nagyné-Kovács *et al.* [29] reported that In vitro cytotoxicity tests of HAp-doped revealed evident antibacterial activity compared to pure HAp against *E. coli* bacteria [29].

**CONCLUSION**

The HAp-Sr doped composites have been successfully synthesized using the sol-gel method. The XRD and FTIR analysis results show that HAp-Sr doped has been appropriately synthesized. HAp-Sr doped with several Sr concentration variations (5%, 10%, 20%) showed different antibacterial activities. Only HAp-Sr 5% has antibacterial activity, while HAp-Sr 10% and HAp-Sr 20% have no antibacterial activity. The overall characterization and tests implied that HAp-Sr 5% has antibacterial activity, so it can be applied to biomedical materials such as bone grafts.

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**AUTHOR CONTRIBUTIONS**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising

it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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#### CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

#### ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

#### DATA AVAILABILITY

All data generated and analyzed are included in this research article.

#### USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

#### PUBLISHER'S NOTE

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