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Original Research Article

Reimagining Hydroxyapatite: Silver Doping for Antibacterial Precision

Kathryn Kiruba, Suganya Paneer Selvam*, Radha Gosla, Ramya Ramadoss, Sandhya Sundar

Department of Oral Biology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical And Technical Science University, Chennai, 600 077, Tamil Nadu, India

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Silver-doped hydroxyapatite (Ag-HA) has emerged as a promising biomaterial for antibacterial applications and bone regeneration. The incorporation of silver ions (Agz) into the hydroxyapatite (HA) lattice enhances its antimicrobial properties while maintaining biocompatibility. This study aims to synthesize and characterize Ag-HA composites using the ion exchange method and evaluate their structural, morphological, and antibacterial properties. Ag-HA was synthesized by replacing calcium ions in HA with silver ions through an ion exchange process. A reaction mixture of 0.5 M calcium nitrate and 0.3 M diammonium phosphate was maintained at pH 10 with ammonia, followed by the addition of silver nitrate. The mixture was stirred at room temperature for 24 hours. Characterization was conducted using Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM) to determine the chemical structure, crystallinity, and morphology. Antibacterial activity was assessed using inhibition zone assays against *Escherichia coli* and *Staphylococcus aureus*, while hemolysis studies evaluated biocompatibility. XRD analysis confirmed the hexagonal crystalline structure of HA, with characteristic peaks at 2è = 25.9°, 31.8°, 32.9°, and 34.1°. SEM images revealed a highly porous, clustered morphology at a 1 µm scale, characteristic of nanoparticle-based materials. Ag-HA demonstrated enhanced antibacterial activity, with inhibition zone diameters of 2.9 cm for *E. coli* and 1.2 cm for *S. aureus*, surpassing pure HA. Hemolysis tests showed 2.25% hemolysis, indicating good biocompatibility below the 5% threshold. The synthesized Ag-HA composite exhibited enhanced antibacterial activity and a porous morphology suitable for bone regeneration. With its low hemolysis rate, Ag-HA holds great potential as a biocompatible and antimicrobial biomaterial for biomedical applications.

Introduction

Silver-doped hydroxyapatite (Ag-HA) has recently emerged as a groundbreaking material in antibacterial applications and bone regeneration, representing a pivotal advancement in biomaterials research. Hydroxyapatite (HA), a naturally occurring mineral form of calcium apatite, is widely utilized in bone grafts due to its remarkable bioactivity and osteoconductivity, essential for promoting bone tissue growth and regeneration [1,2]. HA is thermodynamically stable under physiological conditions, such as temperature and pH. However, its unmodified form can be susceptible to bacterial colonization due to its surface properties and interactions with environmental factors and bacterial proteins [3].

The incorporation of silver ions into HA significantly enhances its antibacterial properties. Silver ions are known to inhibit bacterial efflux pumps, which bacteria use to expel toxic substances, thereby increasing the intracellular concentration of silver and boosting its antibacterial efficacy. Additionally, silver nanoparticles (AgNPs) exhibit a high surface area-to-volume ratio, promoting enhanced interaction with bacterial cells. Smaller nanoparticles demonstrate superior antimicrobial efficacy due to improved penetration and extensive contact with bacterial surfaces. By binding to bacterial proteins and DNA, AgNPs disrupt critical cellular functions, inhibit DNA replication and transcription, and ultimately induce cell death [4].

Numerous studies have underscored the dual benefits of Ag-HA materials in antibacterial activity and bone regeneration. Previous studies have shown that Ag-HA effectively inhibits the growth of *Pseudomonas aeruginosa* by damaging bacterial cells and disrupting essential proteins [5]. In addition, Ag-HA granules have demonstrated strong antibacterial efficacy against a range of bacterial strains while maintaining minimal cytotoxicity [6]. Similar findings also highlight the sustained antibacterial properties and excellent cytocompatibility of both Ag-HA and copper-doped HA over extended periods [7]. Furthermore, advancements in fabrication techniques, such as synthesising silver nanoparticles with biphasic calcium phosphate, have further enhanced the material's properties, making it well-suited for orthopaedic applications [7,8].

Recent investigations have delved into the potential of doped HA composites, including the synthesis of zinc-silver doped mesoporous

*Coresponding authors - Dr. Suganya Paneer Selvam
E-mail address: suganresearch29@gmail.com

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HA using advanced methods like ultrasonic and sol-gel techniques, which have shown remarkable antibacterial properties [9,10]. Similarly, research on electrospun scaffolds, chitosan-incorporated bone scaffolds, and blends with copper or gold has expanded the clinical applications of Ag-HA, further underscoring its versatility and efficacy in combating infections and promoting bone regeneration [11]. This work aims to optimize Ag-HA composites, harnessing their synergistic antibacterial and osteoconductive properties. These findings provide a foundational proof-of-concept for developing next-generation dual-action medical devices designed to effectively address the challenges of deep bone infections and antimicrobial resistance.

Materials and Methods

Synthesis of silver doped hydroxyapatite

The synthesis of Ag-HAp was performed using the ion exchange method, a controlled process wherein calcium ions in the hydroxyapatite (HA) lattice are replaced with silver ions (Ag+), conferring antimicrobial properties to the material (Figure 1). To initiate the synthesis, 0.5 M calcium nitrate, and 0.3 M diammonium phosphate were mixed under controlled conditions. The reaction mixture was maintained at a calibrated pH of approximately 10 by the gradual addition of an ammonia solution, with continuous stirring. This step facilitated the formation of hydroxyapatite through a gradual chemical reaction, which served as the precursor for the silver-doped composite. The synthesized hydroxyapatite was then combined with a measured quantity of silver nitrate, the source of silver ions. The mixture was stirred continuously at room temperature for 24 hours to ensure the uniform incorporation of silver ions into the hydroxyapatite lattice. After the incubation period, the resultant Ag-HA composite was filtered to separate the solid product from the residual solvents and by-products. The material was washed thoroughly with deionized water to remove any impurities, yielding a pure Ag-HA composite. The final product was air-dried and prepared for subsequent characterization and testing.

Characterization of silver-doped hydroxyapatite

The synthesized Ag-HAp composite was characterized using Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM) to evaluate its chemical structure, crystalline nature, and surface morphology, respectively. X-ray diffraction (XRD) analysis provides comprehensive insights into the phase composition, crystalline structure, and orientation of materials while also detecting impurities by measuring the intensity of diffracted X-rays at specific 2è angles. The resulting diffraction pattern, a plot of intensity versus 2è, includes characteristic peaks representing specific crystalline phases and is compared with standard reference patterns from the International Centre for Diffraction Data (ICDD) database for confirmation. Fourier-transform infrared spectroscopy (FTIR) identifies functional groups, molecular composition, and structural vibrations by measuring the absorption of mid-infrared electromagnetic radiation (4000–400 cm{ ¹). The graphed spectra highlight the stretch vibrations of various functional group bonds, confirming the material's composition and bonding. Scanning electron microscopy (SEM), combined with energy-dispersive X-ray analysis (EDAX), captures high-resolution images of the material's morphology and determines its elemental composition. SEM imaging involves scanning the sample surface with an electron beam, while EDAX detects characteristic X-rays generated by electron interactions to identify and quantify elements. Together, SEM and EDAX provide detailed information on the material's surface features and elemental distribution.

Evaluation of antimicrobial activity

To evaluate the antimicrobial efficacy of the synthesized Ag-HA material, the Agar Disk Diffusion method was employed. This cost-effective technique assesses the ability of antimicrobial agents to inhibit bacterial growth, validating the material's potential as an antibacterial agent. The standardized bacterial strains, *E. coli* (Gram-negative) and *S. aureus* (Gram-positive), were used for the evaluation. The inoculum was prepared by cultivating the bacterial strains under optimal conditions until an adequate number of spores were obtained. Test samples and controls were carefully applied to agar plates to ensure proper dilution. After confirmation, the plates were inoculated with the bacterial strains and incubated under controlled conditions of temperature and humidity for a specific duration. Upon completion of the incubation period, the inhibition zones were measured, and the percentage of bacterial growth inhibition was calculated and compared with standard controls to assess the material's antibacterial activity. All experiments were performed in triplicate and expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA with significance set at $p < 0.05$.

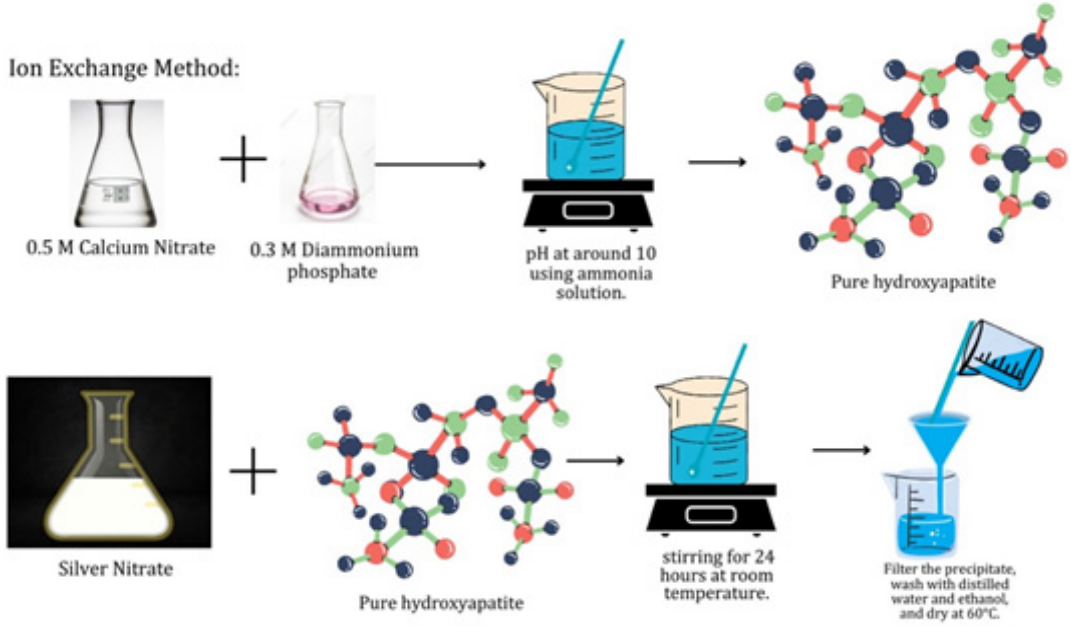


Figure 1: Synthesis of silver-doped hydroxyapatite by ion exchange method

Hemocompatibility assay

Assessing hemocompatibility is crucial to ensure the safe application of synthesized silver-doped hydroxyapatite when in contact with blood. The hemocompatibility assay evaluates the interactions between foreign materials and the various components of blood to identify any potentially harmful effects arising from exposure. Blood comprises cellular constituents such as red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes), each with intricate physical structures and biochemical mechanisms essential for maintaining normal hemostasis.

Results

FTIR of silver-doped hydroxyapatite

The Fourier-transform infrared spectroscopy (FTIR) results for silver-doped hydroxyapatite composites, as shown in Figure 2A, display characteristic absorption bands attributed to both hydroxyapatite and silver nanoparticles. Hydroxyapatite exhibits prominent bands in the range of 1030–1090 cm{ ¹ and 560–600 cm{ ¹, corresponding to phosphate (PO„ ³{) vibrations. Meanwhile, silver nanoparticles contribute absorption peaks between 1400–1600 cm{ ¹, associated with C=O and C-N stretching vibrations from organic components, as well as Ag-O stretching vibrations. The FTIR analysis confirms the successful integration of silver nanoparticles into the hydroxyapatite matrix, indicating enhanced antimicrobial properties while retaining the biocompatibility of hydroxyapatite.

XRD analysis

The X-ray diffraction (XRD) results for silver-doped hydroxyapatite composites, as illustrated in Figure 2B, reveal characteristic peaks of hydroxyapatite at 2è values around 25.9°, 31.8°, 32.9°, and 34.1°, confirming its crystalline hexagonal structure. The incorporation of silver nanoparticles is evidenced by additional peaks at approximately 38°, 44°, 64°, and 77°, corresponding to the (111), (200), (220), and (311) planes of face-centered cubic silver. These XRD patterns validate the successful synthesis of silver-doped hydroxyapatite composites, demonstrating the coexistence of hydroxyapatite and silver nanoparticles within the material. The crystallite size was estimated from the most intense diffraction peak at 2è H" 31.8° using the Scherrer equation and was found to be approximately 28 ± 4 nm, confirming the nanocrystalline nature of the synthesized Ag-HA.

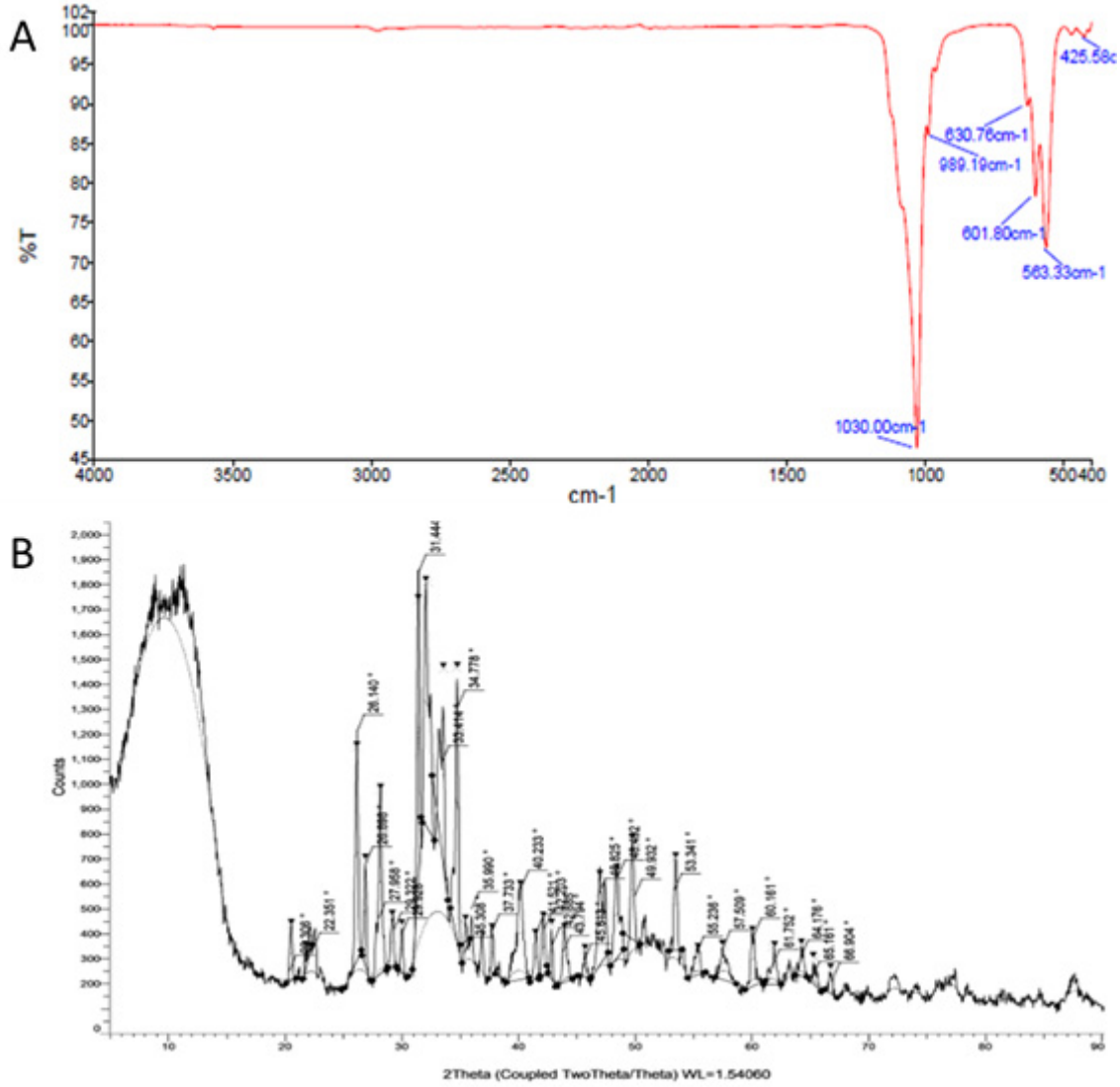


Figure 2: (A) FTIR pattern of silver-doped hydroxyapatite, (B) XRD analysis of silver-doped hydroxyapatite

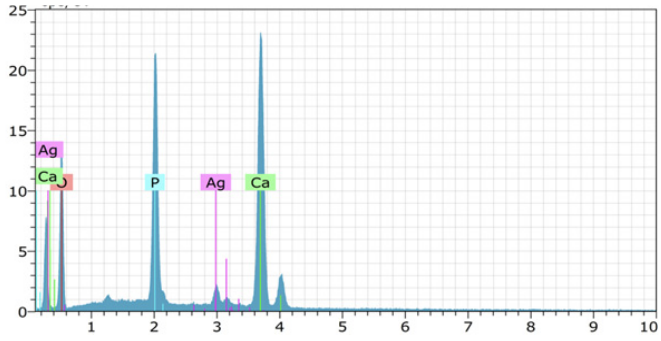


Figure 3: EDAX analysis of the Ag-HA complex

EDAX analysis

The Energy Dispersive X-ray Analysis (EDAX) spectrum, shown in Figure 3, reveals the elemental composition of the silver-doped hydroxyapatite (Ag-HAp) sample by detecting characteristic X-rays emitted when elements are excited by a high-energy electron beam. The X-axis represents wavelengths in nanometers (nm), while the Y-axis indicates the intensity of emitted X-rays, correlating to the elemental concentration. Prominent peaks in the spectrum include silver (Ag), with notable peaks around 0.5 nm and 3 nm, confirming its significant presence; calcium (Ca), with peaks at approximately 0.5 nm and 3.5 nm, characteristic of hydroxyapatite; and phosphorus (P), with a distinct peak near 2 nm, consistent with phosphate groups. The atomic percentage obtained from EDAX spectrum revealed Ca/P ratio of 1.05. The value deviates from the stoichiometric hydroxyapatite ratio of 1.67, indicating the formation of calcium-deficient hydroxyapatite due to partial substitution of $Ca^{2}z$ ions by Agz ions in the lattice. These findings validate the successful incorporation of silver ions or nanoparticles into the hydroxyapatite matrix, confirming the composite's structural and functional integrity.

SEM analysis

The Ag-HA composite exhibits a highly porous structure composed of aggregated clusters at a scale of 1 µm. The rough and irregular morphology indicates a sponge-like or networked configuration characteristic of nanoparticle-based materials (Figure 4A). The silver (Ag) nanoparticles appear embedded within or adhered to the hydroxyapatite (HA) matrix, contributing to the composite's structural integrity and functional properties. At a higher magnification (200 nm), the granularity and intricate details of the material are more apparent. The porous and rough structure is visible, with small particles forming aggregates (Figure 4B). These finer details highlight the potential range of particle sizes, with the Ag nanoparticles uniformly distributed within the HA matrix. This distribution and the material's surface characteristics suggest a high surface area, which is advantageous for enhancing reactivity and interactions with biological or chemical environments. The embedded silver nanoparticles are distinctly visible as small clusters, underscoring their role in imparting antimicrobial properties to the composite.

Antibacterial assay

The antibacterial assay of silver-doped hydroxyapatite (Ag-HA) composites demonstrated clear zones of inhibition against bacterial strains, whereas pure hydroxyapatite (HA) showed no inhibition. As depicted in Figure 5 A&B, the Ag-HA composites exhibited significantly greater antibacterial activity, with inhibition zone diameters of 2.9 ± 0.12 cm (n = 3) for *Escherichia coli* and 1.2 ± 0.08 cm (n = 3) for *Staphylococcus aureus*, surpassing the performance of pure HA and control (Amoxycillin). This highlights the enhanced antimicrobial efficacy of Ag-HA composites compared to undoped hydroxyapatite.

Hemocompatibility assay

Hemocompatibility is essential for materials interacting with blood, as high hemolysis can cause complications such as inflammation, clotting, or immune reactions. In this evaluation, the percentage of hemolysis (% RBC lysis) indicates the material's effect on red blood cells (RBCs). Silver-doped hydroxyapatite (Ag-HA) exhibited 2.25% hemolysis at a low erythrocyte concentration, which is slightly higher than 5 pure HA but remains below the 5% threshold for biocompatibility (Figure 5C). This demonstrates that Ag-HA maintains good blood compatibility while showing reduced hemolytic activity compared to less compatible materials. This improved hemocompatibility is attributed to the controlled release of silver ions, minimizing adverse effects on RBCs while retaining strong antibacterial properties.

Discussion

In our study, the silver-doped hydroxyapatite (Ag-HA) composites demonstrated a range of beneficial properties that align with and extend findings from previous research. FTIR analysis revealed characteristic peaks associated with hydroxyapatite, including phosphate and hydroxyl vibrations, alongside peaks corresponding to silver nanoparticles. The calculated Ca/P ratio was lower than the theoretical stoichiometric value (1.67), confirming the formation of calcium-deficient hydroxyapatite (CDHA). Such deviation occurs due to substitution of $Ca^{2}z$ by Agz ions and lattice vacancies created to maintain charge neutrality. Calcium-deficient hydroxyapatite is known to exhibit higher solubility and bioresorbability compared to stoichiometric HA, which favors controlled ionic release and enhances antibacterial action. However, excessive deficiency may reduce long-term structural stability. In the present study, the moderate reduction suggests a balance between structural integrity and therapeutic ion release, making the material suitable for biomedical

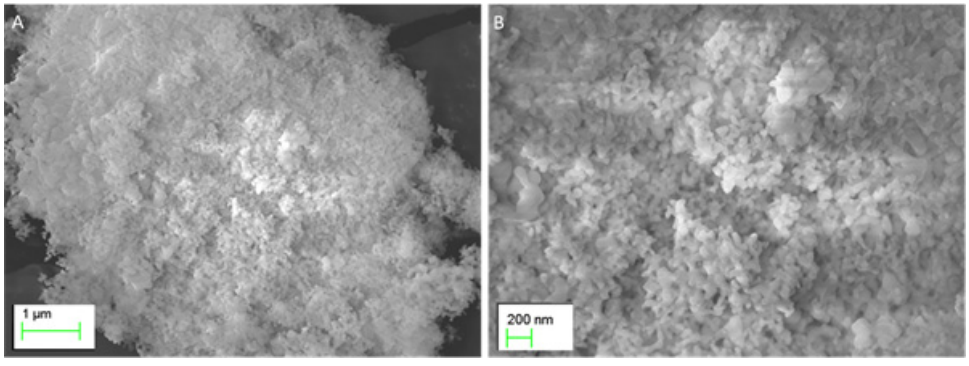
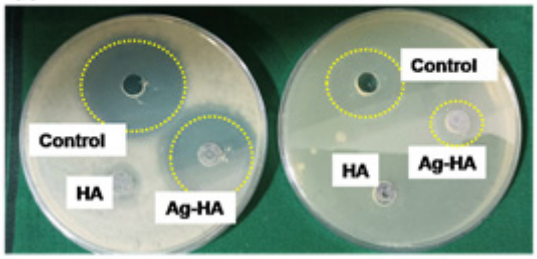


Figure 4: SEM image of the Ag-HA complex (A - 1µm & B – 200 nm)

A



B

Sample	E. Coli ZOI (cm)	S. aureus ZOI (cm)
Control	3.8	3.2
HA	Nil	Nil
Ag-HA	2.9	1.2

C

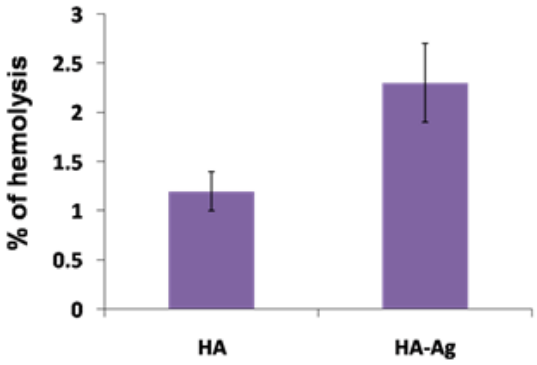


Figure 5: (A&B) Antibacterial assay of pure HA & Ag-HA complex against E.coli and S.aureus (A&B), (C) Hemocompatibility of pure HA & Ag-HA complex

coatings and regenerative applications. This observation aligns with the findings of Iqbal et al., who reported that low silver content (up to 0.3 wt%) did not alter the HA structure, while higher concentrations caused significant changes in OH and PO4 groups, indicating structural modification and â-TCP formation [12]. Similarly, our FTIR results corroborate the studies by Lim et al. and SL Bee et al., confirming the successful incorporation of silver nanoparticles without forming new impurity phases, thereby preserving the structural integrity of the HA matrix [13,14].

The XRD analysis in our study confirmed the incorporation of silver nanoparticles into the hydroxyapatite (HA) lattice, with distinct peaks at 38° and 44° corresponding to face-centered cubic silver, in agreement with prior findings [15,16]. Notably, our XRD results exhibited increased intensity of the silver peaks, indicating a refined synthesis process promoting effective nanoparticle dispersion within the matrix. The nanoscale crystallite size increases the surface-to-volume ratio, facilitating enhanced ionic exchange and antibacterial activity due to improved Agz ion interaction with bacterial membranes. This enhanced dispersion highlights the material's potential for superior antimicrobial activity, as higher concentrations of well-dispersed silver nanoparticles were linked to more substantial inhibition zones in antimicrobial assays.

The antibacterial assessment using the disk diffusion method revealed significant inhibition zones for E. coli (2.9 cm) and S. aureus (1.2 cm), surpassing the results reported by previous studies where the inhibition zones were approximately 18 mm and 17 mm, respectively [17,18]. This indicates that our synthesized Ag-HA composites possess enhanced antibacterial efficacy, likely due to a controlled release of silver ions that disrupt bacterial cell membranes more effectively. Although only a 24-hour antibacterial assay was performed, the sustained antimicrobial activity of Ag-HA can be attributed to the gradual dissolution of calcium-deficient hydroxyapatite and controlled release of Agz ions from lattice substitution rather than surface adsorption. Future studies will include quantitative ion-release kinetics over extended periods to validate long-term antimicrobial performance.

Hemocompatibility testing revealed a hemolysis ratio of 2.25% for the synthesized Ag-HA, indicating excellent blood compatibility, well below the 5% threshold for biocompatibility. Compared to studies such as Chen et al., which highlighted the challenges of optimizing silver content to balance antimicrobial efficacy and hemocompatibility, our results demonstrate a successful synthesis process that achieves this balance [18,19]. Notably, the hemolysis ratio in our study is significantly lower than the 9.3% reported for 5% Ag-HA in other research, emphasizing the advantage of our optimized silver concentration.

SEM and EDAX analyses confirmed the porous and nanostructured morphology of the Ag-HA composite, with uniform dispersion of silver nanoparticles within the HA matrix. The high surface area observed in SEM images is advantageous for applications requiring biocompatibility and antimicrobial activity, such as bone regeneration and implant coatings [20]. The elemental composition revealed by EDAX corroborates the successful incorporation of silver, calcium, and phosphorus, essential for the material's structural and functional performance. Unlike prior studies, our work highlights the uniform dispersion and optimal synthesis parameters, which enhance the composite's biomedical applicability [21-23].

Pure hydroxyapatite (HA) exhibits significant antibacterial properties, making it a promising material for clinical applications, particularly infection control. The antibacterial effects stem from ionic interactions between HA and bacterial cell membranes, disrupting bacterial integrity and inhibiting colonization. Studies have shown that pure hydroxyapatite (HA) possesses intrinsic antibacterial properties, effectively inhibiting the growth of common bacterial strains such as *Staphylococcus aureus* and *E. coli*, while also demonstrating excellent biocompatibility [24,25]. Although incorporating nanoparticles like silver (Ag) or zinc into HA can enhance its antibacterial activity—such as silver-loaded HA composites exhibiting a minimum inhibitory concentration (MIC) as low as 2.5 μg/mL—the results are highly dependent on nanoparticle type and concentration. For example, zinc-doped HA shows improved antibacterial potential with increased zinc content but still does not consistently outperform pure HA [26]. Moreover, these nanoparticle-infused composites often face challenges related to cytotoxicity and reduced efficacy against certain bacterial strains, compromising the delicate balance between antimicrobial activity and biocompatibility [27,28]. In contrast, silver-hydroxyapatite (Ag-HA) composites offer a more favorable alternative. They maintain the biocompatibility of pure HA while providing superior antibacterial performance. This makes Ag-HA composites a more balanced and effective option for biomedical applications, mainly where long-term safety and efficacy are critical.

The study has several limitations that warrant further investigation. While the incorporation of silver enhances antimicrobial properties, optimizing its concentration is crucial to balance antibacterial efficacy and biocompatibility, as excessive silver may cause cytotoxic effects. The antimicrobial activity was evaluated against only two bacterial strains, necessitating testing against a broader range of microbes, including fungi and drug-resistant strains. The findings are limited to in vitro analyses, requiring in vivo studies to confirm further safety and efficacy.

Strength and Limitations

The study presents a successful synthesis of silver-doped hydroxyapatite (Ag-HA) via a simple and cost-effective ion exchange method, offering potential for scalability. Comprehensive characterization using FTIR, XRD, and SEM confirmed the material's chemical structure, crystallinity, and porous nanoparticle morphology. Notably, Ag-HA demonstrated enhanced antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, along with good biocompatibility as indicated by a hemolysis rate of 2.25%, well below the accepted 5% threshold. These results high-

light the material's potential for biomedical applications. However, the study is limited by the absence of in vitro or in vivo bone regeneration assays, despite the material's intended application in bone-related fields. Moreover, the antibacterial evaluation in this study was limited to two bacterial strains, which, while indicative, may not fully represent the material's broad-spectrum efficacy. Although the hemolysis assay demonstrated favorable short-term biocompatibility, further in-depth cytotoxicity studies are required to evaluate the material's safety for biomedical use comprehensively.

Conclusion

The study successfully developed silver-doped hydroxyapatite (Ag-HA) composites with promising applications in biomedical fields. Characterization techniques like FTIR and XRD confirmed the effective incorporation of silver nanoparticles without altering the structural stability of hydroxyapatite. SEM imaging revealed a porous and nanostructured morphology, while EDAX confirmed the presence of silver, calcium, and phosphorus. Antibacterial assays demonstrated potent activity against Gram-positive and Gram-negative bacteria, attributed to the controlled release of silver ions. Hemocompatibility tests showed minimal hemolysis, confirming the material's biocompatibility. These findings highlight the potential of Ag-HA composites for use in medical applications such as implant coatings and bone tissue engineering.

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