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Original Article

Ormocarpum cochinchinense and Glutathione Enhanced Hydroxyapatite for Advanced Bone Graft Applications

Soundharya Manogaran, H. Tamilselvan, Ramya Ramadoss*, Radha Prabhu, K. Hemashree

Department of Oral Biology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamilnadu, India

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Bone tissue engineering is a promising approach to addressing bone defects and injuries. However, the development of an ideal bone graft with biocompatibility, osteoconductivity, and osteoinductivity remains a challenge. This study aimed to design and characterize a novel bone graft material incorporating hydroxyapatite (HA), Ormocarpum cochinchinese (OC) extract, and glutathione to enhance bioactivity and regenerative potential. Hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and a composite material containing HA, OC, and glutathione were synthesized. The physicochemical properties of the materials were analyzed using X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and energy-dispersive X-ray spectroscopy (EDAX). The antibacterial and antioxidant activities of the composite were also evaluated. XRD analysis confirmed that the incorporation of OC and glutathione did not significantly alter the crystal structure of HA. FTIR spectra indicated the presence of functional groups from OC and glutathione. SEM revealed a rough and porous surface morphology, which is beneficial for cell attachment and bone regeneration. The composite demonstrated enhanced antibacterial and antioxidant properties, suggesting its potential for improved bone healing. The HA-OC-glutathione composite presents a promising approach for bone graft applications, offering enhanced bioactivity and regenerative capabilities. The synergistic effects of its components contribute to improved osteoconductivity and biocompatibility. Further in vitro and in vivo studies are necessary to assess its clinical potential in bone tissue engineering.

Introduction

Bone defects and injuries resulting from trauma, tumors, infections, or congenital disorders present significant challenges in clinical orthopedics and maxillofacial surgery. While minor bone injuries can heal naturally, larger defects often require external intervention to facilitate proper regeneration. Traditional treatment strategies rely on bone grafting techniques, including autografts, allografts, and xenografts. However, each of these approaches has inherent limitations. Autografts, considered the gold standard, are limited by donor site morbidity and restricted availability. Allografts pose risks of immune rejection and disease transmission, while xenografts often lack the bioactivity necessary for effective bone regeneration. These challenges highlight the need for advanced synthetic bone graft materials with enhanced biological properties [1,2].

Among synthetic materials, hydroxyapatite (HA) has been widely utilized in bone tissue engineering due to its close resemblance to the mineral composition of natural bone. HA provides an excellent scaffold for bone cell attachment and proliferation, making it a preferred choice for bone regeneration application [3,4]. However, despite its advantages, HA has inherent brittleness and limited bioactivity, which can hinder its long-term success in clinical applications. To overcome these limitations, researchers have focused on functionalizing HA with bioactive compounds to improve its osteogenic, antimicrobial, and regenerative potential.

One promising approach to enhancing HA's biological performance is the incorporation of natural bioactive compounds derived from medicinal plants. In this context, *Ormocarpum cochinchinense* (OC), a medicinal plant known for its rich phytochemical composition, has gained research interest. OC contains flavonoids, alkaloids, and phenolic compounds, which exhibit anti-inflammatory, antimicrobial, and osteogenic properties. These bioactive molecules have the potential to improve the regenerative capability of bone graft materials by promoting osteoblast activity, reducing inflammation, and preventing microbial infections at the graft site

* *Coresponding author*
E-mail address: *drramya268@gmail.com* (*Prof. Dr. Ramya Ramadoss, B.D.S., M.D.S, PhD Department of Oral Pathology & Oral Biology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, 600077, India)*

[5,6] . Despite its known medicinal properties, OC has not been extensively explored in the field of bone tissue engineering, making it a novel candidate for inclusion in synthetic grafts.

In addition to bioactive compounds, antioxidants play a critical role in bone healing and regeneration. Oxidative stress is known to impair bone formation by inducing inflammation and apoptosis in osteogenic cells. Glutathione (GSH), a naturally occurring antioxidant, helps neutralize reactive oxygen species (ROS) and protects bone cells from oxidative damage. The incorporation of glutathione into a bone graft composite could enhance cell viability, proliferation, and differentiation, thereby supporting the overall regenerative process. However, research on the synergistic effects of glutathione and HA in bone graft applications remains limited, warranting further investigation [7].

This study aims to design and characterize an advanced hydroxyapatite-based bone graft composite incorporating OC extract and glutathione. The primary goal is to evaluate whether this composite can enhance biocompatibility, osteoconductivity, and antibacterial properties while maintaining the structural integrity of HA. To achieve this, physicochemical characterization techniques such as X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and energy-dispersive X-ray spectroscopy (EDAX) was employed to analyze the crystal structure, functional groups, surface morphology, and elemental composition of the synthesized materials.

By integrating the osteogenic potential of HA, the bioactive properties of OC, and the antioxidant effects of glutathione, this study seeks to develop a novel bone graft material that offers superior regenerative potential. The combination of these components represents a unique and innovative approach in bone tissue engineering. This research not only addresses the limitations of current bone grafting techniques but also paves the way for the development of biofunctional graft materials that enhance bone healing and regeneration. Further *in vitro* and *in vivo* studies will be necessary to assess the clinical translation of this composite, potentially offering a new paradigm in bone repair strategies.

Materials and Methods

In this study, high-purity 95% ethanol was used as a solvent for the preparation and extraction processes. Calcium hydroxide (Ca(OH)) and calcium phosphate served as primary precursors for hydroxyapatite (HA) synthesis, ensuring the formation of a biocompatible mineral phase. Diammonium hydrogen phosphate ((NH)HPO) was utilized as a phosphate source to facilitate the precipitation of HA during the synthesis process. Ammonia (NH) was employed to control the pH of the reaction medium, optimizing conditions for HA formation. All chemicals were of analytical grade and were procured from Sigma-Aldrich, ensuring consistency and high quality for experimental procedures

Preparation of the plant extract

Preparation of the plant extract Healthy leaves of OC were collected from Ambur, Tamilnadu, India. The leaves were washed with double distilled water, dried under shade and powdered in an electric blender. The dried powder was extracted using 95% ethanol in a Soxhlet apparatus. Using rotary evaporator the extract was concentrated, stored at 4°C and the dried crude ethanolic extract was used for further study.

Synthesis of hydroxyapatite

HA was synthesized by modifying the procedure of Bouyer et al (9). An aqueous solution of 0.5 M calcium hydroxide was prepared and to this 0.3 M ortho phosphoric acid was added drop by drop until the pH reaches 12.5. The mixture was kept in continuous stirring for 24 h. The resultant was then centrifuged at 6000 rpm for 15 min. The precipitate was collected, rinsed with double distilled water and then dried at 100 °C for 7 h (Srividya et al) (10).

Synthesis of β-tricalcium phosphate

β-tricalcium phosphate (β-TCP) was synthesized by modifying the procedure of Krithiga et al [11]. An aqueous solution of diammonium hydrogen phosphate (25.76 g in 325 ml of double distilled water) was added to an aqueous solution of calcium nitrate tetra hydrate (69.675 g in 500 ml of double distilled water) under continuous stirring. To this, 16.5 ml of ammonia solution was added and stirred continuously for 2 h. The mixture was filtered, and the filtrate was rinsed with double distilled water (in order to remove the unreacted calcium and phosphate) and dried in the oven at 60°C for 24 h. The flakes were then powdered and calcinated in the furnace at 850°C for 12 h followed by cooling to obtain a white fluffy precipitate of single phase β-TCP (Srividya et al., 2014).

Characterization of the bone graft

Characterization of the bone graft The IR spectra of the prepared samples were read at 4000-400 cm^{-1} using Nicolet Impact 400 FTIR spectrophotometer using KBr pellet containing 1-2 mg of the sample. XRD analysis of the sample was done using an analytical X2Pert PRO alpha-1 with a RTMS X2Celerator detector. It utilizes Ni-filtered Cu Kα radiation over the 2θ range of 20-80° with a scan rate of 2.4°/min and at a sampling interval of 0.002° at 40 mA and 45 kV. The surface morphology was analysed with a Zeiss Gemini Supra 55, SEM and EDX with Oxford instrument X-act. The copper disc was pasted with carbon tape and the sample was dispersed over the tape. The disc was coated with gold in ionization chamber before microscopic analysis.

For the Antibacterial activity test, bacterial cultures were prepared by inoculating staphylococcus aureus and E. coli in nutrient broth and incubating at 37°C for 24 hours. The bone graft samples were placed on agar plates inoculated with bacterial cultures. Plates were incubated at 37°C for 24 hours and the zones of inhibition were measured to assess antibacterial activity by following the standard protocol.

A solution of DPPH in ethanol was prepared at a concentration of 0.1 mM. Samples of pure HA, Herbal-GSH Protein-HA composite, negative control (double distilled water), and positive control (diclofenac sodium) were immersed in the DPPH solution. The mixtures were incubated in the dark for 30 minutes. The absorbance was measured at 517 nm using a spectrophotometer for the antioxidant activity.

Results and Discussion

The XRD analysis of the pure hydroxyapatite (HA) sample reveals a pattern that aligns well with the standard JCPDS card, confirming the successful formation of HA nanoparticles. This alignment is indicative of the characteristic crystal structure of HA, which is crucial for its applications in biomedical fields [12]. The presence of well-defined peaks in the XRD pattern suggests high crystallinity, a desirable property for materials used in bone regeneration and other medical applications (figure 1) [13].

The incorporation of protein and herbal molecules into the HA matrix did not result in significant changes in the XRD pattern, indicating that these additions do not alter the fundamental crystal structure of HA. This finding is consistent with previous studies that have demonstrated the stability of HA's crystal structure even

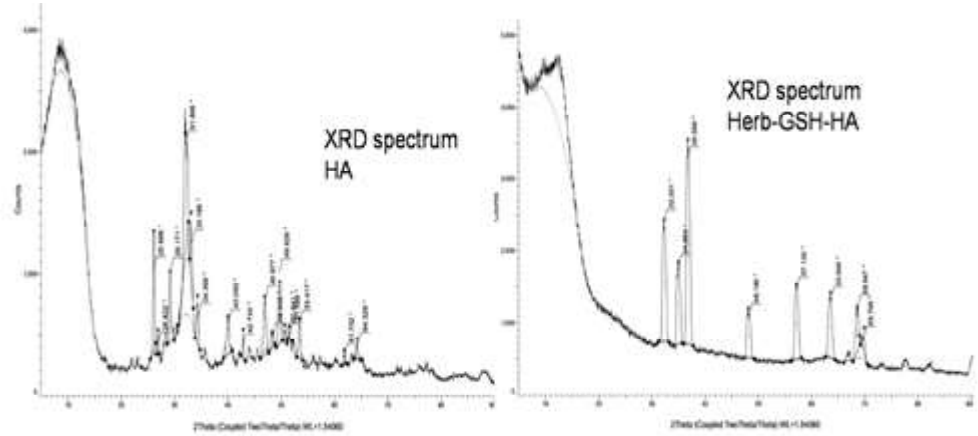

Figure 1: The X-ray difraction (XRD) analysis of synthesized samples

when combined with various bioactive molecules [14]. The ability to maintain the integrity of HA's crystal structure while incorporating additional bioactive components is advantageous, as it allows for the enhancement of the material's biological properties without compromising its structural characteristics. The stability of the HA crystal structure in the presence of protein and herbal molecules suggests that the composite material retains the beneficial properties of HA, such as biocompatibility and osteoconductivity, while potentially gaining additional therapeutic benefits from the incorporated molecules.

Pure HA composite

The FTIR spectrum of pure HA in figure 2A reveals a broad band from 1000 cm^{-1} to 1100 cm^{-1}, which is indicative of the phosphate groups in HA. This is consistent with previous studies that have identified similar spectral features as characteristic of HA [15]. The specific peaks at 962 cm^{-1}, 1029 cm^{-1}, and 1090 cm^{-1} correspond to the bending and stretching modes of the P-O bond, further confirming the presence of HA [16]. Additionally, the peaks at 564 cm^{-1} and 602 cm^{-1} are attributed to the bending character of the P-O-P bond, which is a hallmark of HA's crystalline structure [17].

Herb-GSH-HA composite

In the FTIR spectrum of the Herb-GSH-HA sample in figure 2B new peaks are observed, indicating the presence of herb and protein molecules in addition to HA. These new peaks suggest the successful incorporation of herbal extracts and GSH proteins into the HA matrix, which may enhance the composite's bioactivity and therapeutic potential. The presence of these additional components is likely responsible for the observed improvements in antioxidant and antibacterial activities, as discussed in previous sections.

The FTIR analysis thus confirms the structural integrity of HA while highlighting the successful integration of bioactive components in the composite. This structural characterization supports the potential applications of the Herb-GSH-HA composite in tissue engineering and regenerative medicine.

The antibacterial activity of the herbal-GSH protein-HA composite was evaluated by exposing it to bacteria for 24 hours. The pure HA did not exhibit any antibacterial effects. However, when the herbal-GSH protein-HA composite was tested, it was observed that it effectively impeded the growth rate of both E. coli and S. aureus bacteria. This suggests that the incorporation of herbal extracts and GSH proteins into the HA matrix enhances its antibacterial properties, making it a potential candidate for use in antimicrobial applications (table 1, figure 3).

This is consistent with previous studies that have demonstrated the antimicrobial potential of herbal extracts and bioactive proteins [18]. The ability of the composite to impede bacterial growth suggests a synergistic effect, where the combination of HA with

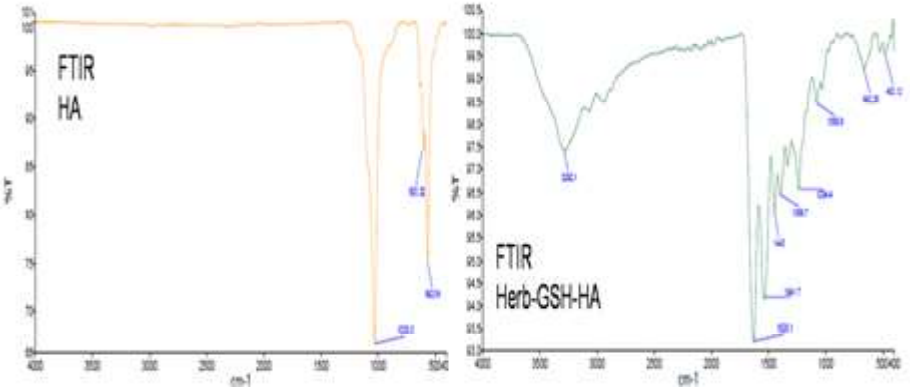

Figure 2: The FTIR spectra of pure and composite bone graft materials

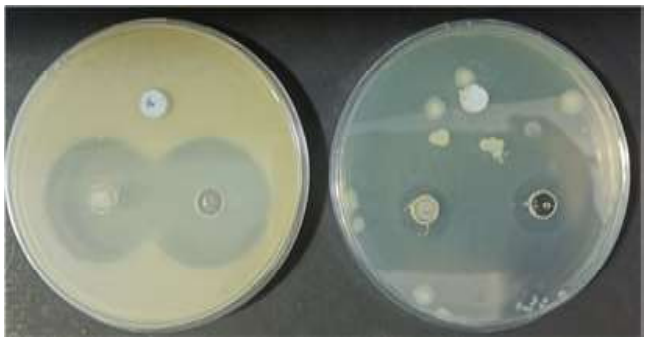

Figure 3: Antibacerial activity of pure HA and HA-OC-GSH composite

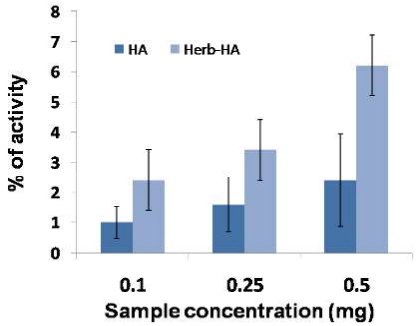

Figure 4: Antioxidant activity of synthesized bone graft materials

herbal and protein components results in a material with enhanced antimicrobial properties. Such composites are increasingly being explored for their potential to prevent infections in biomedical applications, particularly in implantable devices and wound healing [19].

In this study, a negative control of double distilled water and a positive control of diclofenac sodium were used to assess the anti-inflammatory activity of both pure HA and Herbal-GSH protein-HA composite demonstrated improved antioxidant activity compared to pure HA, suggesting that the incorporation of herbal extracts and GSH proteins enhanced the antioxidant properties of the composite.

In this figure 4 the improved antioxidant activity of the herbal-HA composite compared to pure HA is particularly noteworthy. The presence of herbal extracts and GSH proteins likely contributes to this enhancement, as these components are known for their antioxidant properties [20]. This finding is supported by literature that emphasizes the importance of antioxidants in reducing oxidative stress and promoting healing in biomedical applications [21]. These findings highlight the potential of the herbal-HA composite as a promising candidate for anti-inflammatory and antioxidant applications.

The SEM images A, B of Hydroxyapatite (HA) reveal a surface morphology that is highly desirable for biomedical applications. The left image shows a rough and porous structure formed by the clustering of smaller particles into irregular clusters. This roughness and porosity provide a high surface area, making it ideal for bone tissue engineering as it promotes cell attachment and tissue integration. The right image, at a higher magnification, exhibits

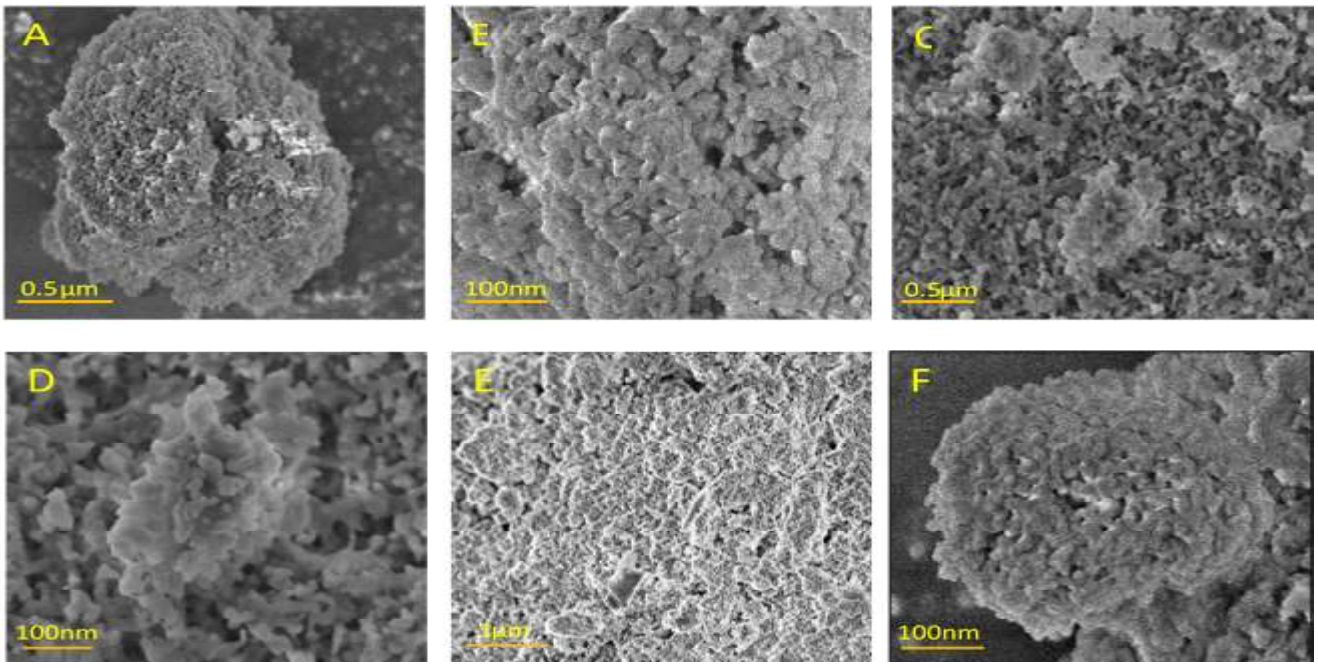

Figure 5: Surface morphology (SEM) analysis of synthesized materials. (A, B) Pure HA showing porous, rough morphology. (C, D) HA-OC composite revealing irregular clusters with organic integration. (E, F) HA-OC-GSH composite exhibiting highly porous, cauliflower-like morphology with rugged texture and organic inclusions

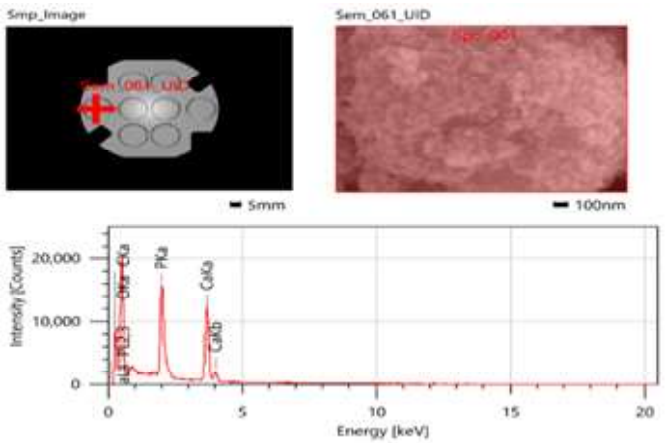

Figure 6: EDAX analysis of HA-OC-GSH composite. Spectrum showing elemental peaks of calcium (Ca) and phosphorus (P) confirming the HA phase, along with oxygen (O) and carbon (C) peaks indicating the presence of organic components from OC and glutathione

even smaller particles and a more intricate surface texture, which increases the material's surface area and enhances its interaction with biological tissues. This fine-scale structure is particularly advantageous in drug delivery systems, where efficient drug adsorption and release require a high surface area. In conclusion, the morphology of this HA sample suggests that it is well-suited for medical applications that require both high surface area and porosity.

The images C, D reveal a composite material consisting of hydroxyapatite (HA) and OC, a plant known for its medicinal properties. The composite exhibits a rough and heterogeneous surface, suggesting the presence of both HA particles and organic matter from OC. Clusters of HA particles are visible, indicating uneven distribution and potential aggregation within the matrix. This rough surface morphology is typical of a composite material, where the combination of natural organic components with inorganic HA enhances the material's bioactivity and therapeutic potential. At a higher magnification, the image shows fine and irregularly shaped particles, likely resulting from the interaction between HA and the organic compounds from OC. The composite maintains a porous structure, which is essential for biomedical applications as it promotes cell attachment, nutrient flow, and efficient drug delivery. The presence of OC within the HA matrix may provide additional benefits such as antioxidant and anti-inflammatory properties. This composite material shows promise for multiple applications in tissue engineering and regenerative medicine.

The SEM images E, F depict the surface characteristics of a composite material comprised of hydroxyapatite (HAP), OC, and glutathione. At a lower magnification, the image reveals a rugged and grainy surface with cracks and potential organic fibres, indicating the integration of OC and glutathione within the HAP matrix. This irregular texture, along with the observed roughness and porosity, is advantageous for biomedical purposes such as tissue engineering as it promotes cell adhesion and proliferation. At a higher magnification, the image presents a more detailed view of the composite's structure, exhibiting highly porous particles resembling cauliflower, suggesting a substantial surface area. This unique structure is particularly beneficial for drug delivery applications due to its efficient drug loading and release capabilities. The combined attributes of HAP, glutathione's antioxidant properties, and OC therapeutic benefits result in a composite material with enhanced bioactivity, potentially suitable for bone regeneration and the development of effective drug delivery systems.

The SEM images of the composite material consisting of Hydroxyapatite (HA) and OC reveal a rough and heterogeneous surface morphology, indicative of the integration of inorganic and organic components. This structural characteristic is consistent with findings from previous studies, which emphasize the role of surface roughness in enhancing the bioactivity of composite materials [22]. The presence of clusters of HA particles suggests an uneven distribution, a common occurrence in composites that can influence mechanical properties and biological interactions [23].

The rough surface and porous structure observed in the SEM images are crucial for biomedical applications. Porosity is known to facilitate cell attachment, nutrient flow, and efficient drug delivery, making such composites highly suitable for tissue engineering [24]. The incorporation of OC, a plant with known medicinal properties, into the HA matrix may provide additional benefits, such as antioxidant and anti-inflammatory effects, which are advantageous for promoting healing and reducing inflammation in regenerative medicine [25] (figure 5).

At higher magnifications, the fine and irregularly shaped particles likely result from the interaction between HA and the organic compounds from OC. This interaction can enhance the composite's mechanical strength and bioactivity, as supported by studies demonstrating the synergistic effects of combining natural organic materials with inorganic scaffolds [26].

The EDAX spectra in figure 6 reveal the presence of crucial elements in the bone graft synthesis materials. Calcium is a major component of hydroxyapatite, a critical material for bone grafting due to its similarity to human bone mineral. The peaks corresponding to phosphorus align with the presence of hydroxyapatite, which contains both calcium and phosphorus. The presence of oxygen and carbon suggests the incorporation of organic components, likely derived from OC and glutathione. The quantitative analysis confirms a high content of hydroxyapatite in the sample, as indicated by the significant amounts of calcium and phosphorus. This composition suggests that the bone graft formulation has favourable bone mineral characteristics.

The synthesis of bone grafts using a combination of OC, hydroxyapatite, and glutathione is innovative. Hydroxyapatite is well-documented for its osteo conductivity and similarity to human bone mineral [27]. The inclusion of OC, could introduce beneficial organic compounds that might enhance the bioactivity of the graft [28]. Glutathione, a powerful antioxidant, could potentially reduce oxidative stress in the grafting site, promoting better integration and healing [29].

Conclusion

In conclusion, the formulation and characterization of a novel bone graft material integrating OC extract, hydroxyapatite (HA), and glutathione protein show promising potential for the treatment of large bone defects. The combination of these components offers a unique approach to enhance bone regeneration through natural growth factors and therapeutic agents. However, several limitations need to be addressed, including the limited availability of the extract, the need for standardized extraction and purification processes, and the need for extensive in vitro and in vivo studies to validate its effectiveness.

Additionally, further research is required to optimize the composition, explore controlled release strategies, utilize advanced fabrication techniques, and evaluate the long-term stability and degradation of the graft material. Future preclinical studies in animal models and subsequent clinical trials are necessary to assess the safety, effectiveness, and long-term outcomes of this novel bone graft material. Overall, while there is still work to be done, this formulation offers a promising avenue for the treatment of large bone defects and holds potential for advances in regenerative medicine.

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