The National University of Science and Technology

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Doctoral School of Chemical Engineering and Biotechnologies

PhD Thesis

COMPOSITE MATERIALS FOR THE TARGETED TREATMENT OF BONE CANCER

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CONTENTS

1. CURRENT STATE OF DEVELOPMENT IN THE FIELD

1.1. Bone Cancer: Clinical Perspectives, Therapeutic Approaches, and Innovative Solutions in Tissue Engineering

Bone is an active mineralized tissue involved in structural support, hematopoiesis, and mineral homeostasis. Osteosarcoma (Fig. 1) is the most common malignant bone tumor, with higher incidence in adolescents and the elderly, primarily affecting long bones. It is characterized by the production of malignant osteoid, localized pain, and risk of pathological fractures. Metastases frequently occur in the lungs, and the 5-year survival rate remains modest (~54%, and ~20% in metastatic cases). The high recurrence rate highlights the need for more effective and innovative therapies [1-4].

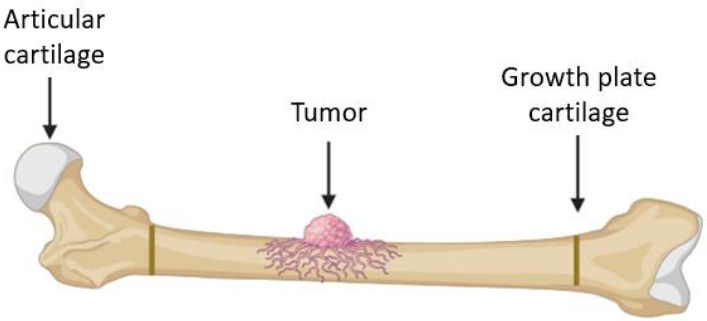


Figure 1. Schematic illustration of bone cancer (Image source: Created with BioRender)

Osteosarcoma treatment typically combines chemotherapy, surgical intervention, and radiotherapy. Systemic chemotherapy reduces tumor size but is limited by tumor cell resistance and side effects. Wide surgical resection ensures local control and is often followed by reconstruction using endoprostheses or bone grafts. Radiotherapy serves as an adjuvant or palliative treatment, especially for unresectable or metastatic tumors. Despite the effectiveness of conventional approaches, their limitations emphasize the need for safer and more efficient innovative therapies [5-7].

Bone is a composite material consisting of an inorganic phase (hydroxyapatite) and an organic phase (collagen), with the extracellular matrix regulating bone formation and remodeling.

Limitations of biological grafts have driven the development of biomaterials, including 3D scaffolds for tissue engineering, which support cell adhesion and differentiation. The structure and mechanical properties of scaffolds influence osteointegration and vascularization. Polymer–ceramic composites, such as collagen/hydroxyapatite or chitosan/hydroxyapatite, mimic natural bone and promote efficient bone tissue regeneration [8-11].

Chemotherapy involves agents such as doxorubicin (DOX), cisplatin, methotrexate, paclitaxel, and 5-fluorouracil, often incorporated into targeted delivery systems (scaffolds, nanoparticles) to increase efficacy and reduce side effects. Oxidative stress, through the accumulation of reactive oxygen species (ROS), plays a dual role in cancer: moderate levels promote tumor cell proliferation, migration, and survival, whereas high levels can induce cancer cell death. Natural polyphenols (curcumin, caffeic acid (CA), resveratrol) act as antioxidants, reducing harmful ROS and protecting DNA, but can also function as pro-oxidants in cancer cells, inducing apoptosis. Therefore, polyphenols can prevent cancer initiation by neutralizing excessive ROS and enhance chemotherapy effectiveness by selectively inducing oxidative stress in tumor cells [12-14].

2. ORIGINAL CONTRIBUTIONS

2.1. General and specific research objectives

The **main objective** was the development and characterization of innovative composite materials for the regeneration of bone tissue affected by malignant tumors and for localized treatment of bone cancer, through the incorporation of natural and synthetic compounds with synergistic effects.

Specific objectives:

1. **Preparation of chitosan–hydroxyapatite grafts** and their structural characterization (FT-IR, TG-DSC, SEM) as well as biological evaluation through biocompatibility and cytotoxicity testing.
2. **Synthesis of crosslinked collagen–hydroxyapatite composites** and assessment of water absorption, enzymatic stability, morphological and structural characterization (SEM, EDX, FT-IR, XRD, TG-DSC), mechanical testing, and antimicrobial activity evaluation.

3. **Development of collagen–hydroxyapatite grafts loaded with doxorubicin and caffeic acid** and their physicochemical characterization (water absorption, enzymatic degradation, SEM, EDX, FT-IR, XRD, TG-DSC) along with biological evaluation of biocompatibility and antitumor activity.

2.2. Materials and methods

Chitosan–Hydroxyapatite (CS/HAp) composite systems were obtained by dissolving chitosan in 1% acetic acid to form a 2% solution, followed by gradual addition of hydroxyapatite precursors ($Ca(OH)_2$ and $(NH_4)_2HPO_4$) for *in situ* synthesis. The resulting gel was freeze-dried to preserve the porous structure and characterized by FT-IR, TG-DSC, SEM, and biological tests for biocompatibility and cell viability.

Collagen–Hydroxyapatite (Coll/HAp) composites were synthesized in ratios of 3:1 (series I) and 1:1 (series II) by mixing 1% collagen gel with calcium and phosphate precursors to form *in situ* hydroxyapatite (Ca/P = 1.67). The gel was then crosslinked with glutaraldehyde, tannic acid, or genipin and freeze-dried to obtain sponge-like porous structures, which were subsequently structurally and morphologically characterized.

Finally, Coll/HAp 1:1 grafts were loaded with **doxorubicin (DOX)** and **caffeic acid (CA)** after genipin crosslinking (GP), using doxorubicin dissolved in water and caffeic acid dissolved in ethanol, resulting in the following samples: control GP, Coll/HAp/DOX – 7A, Coll/HAp/CA – 8A, Coll/HAp/DOX/CA – 9A. The porous matrices were designed to combine regenerative properties with antitumor activity.

2.3. Chitosan/Hydroxyapatite composite grafts for bone tissue engineering

The study aimed to develop CS/HAp composite systems for bone tissue regeneration, obtained via *in situ* hydroxyapatite synthesis and freeze-drying. FT-IR analysis (Fig. 2) confirmed the presence of characteristic groups for both the organic and inorganic components, indicating interactions between chitosan and HAp. The broad band in the 3125–3325 cm^{-1} region corresponds to N–H and O–H vibrations, while the bands at 2864 and 2922 cm^{-1} reflect C–H stretching. Peaks at 1541 and 1402 cm^{-1} correspond to amide II vibrations and C–H or carboxyl group deformations,

while the 1643 cm^{-1} band corresponds to amide I (C=O). The presence of hydroxyapatite is confirmed by phosphate-specific bands at 655, 615, 560, 960, and 1018 cm^{-1}.

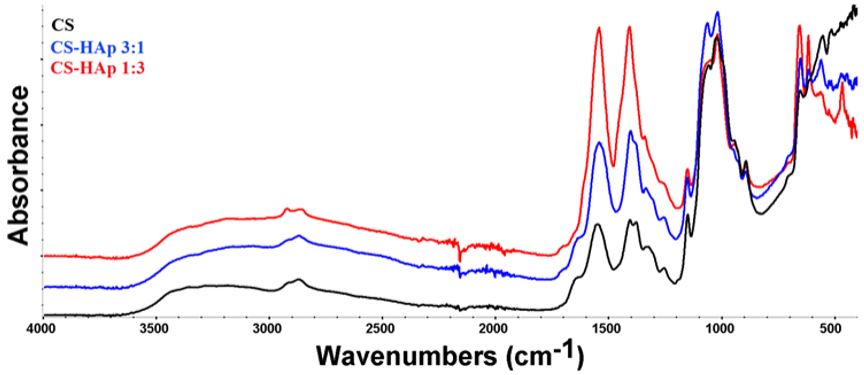


Figure 2. FT-IR spectra of CS (black), CS/HAp 1:3 (red), and CS/HAp 3:1 (blue)

Thermogravimetric characterization (Fig. 3) showed differences in thermal behavior depending on HAp content, indicating multiple degradation stages and interactions between chitosan and mineral components.

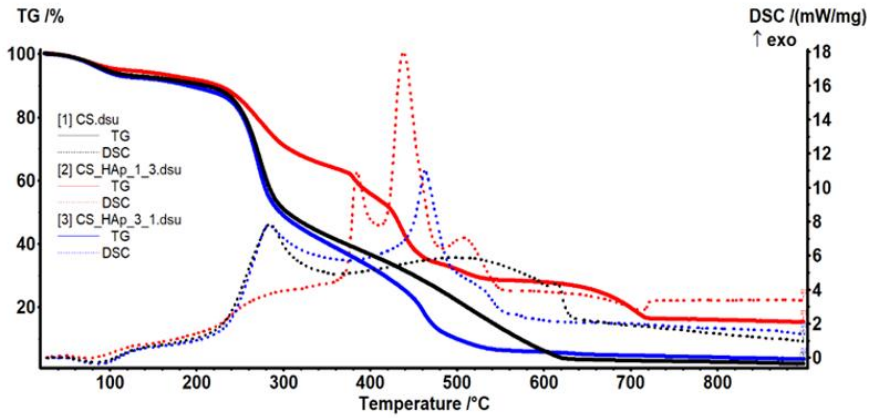
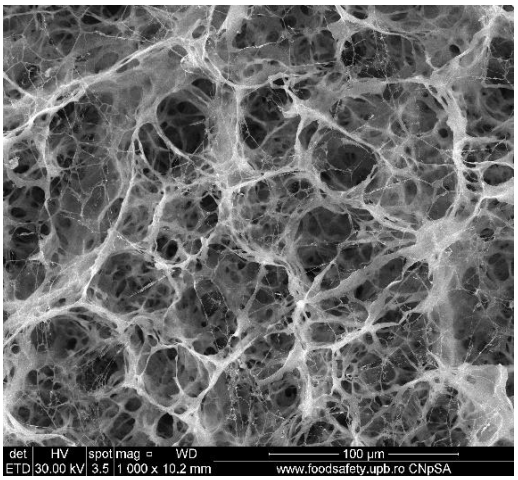
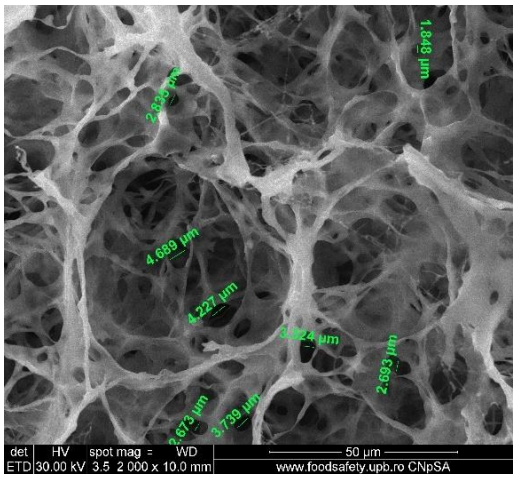


Figure 3. TG-DSC curves for CS and HAp-based composite systems

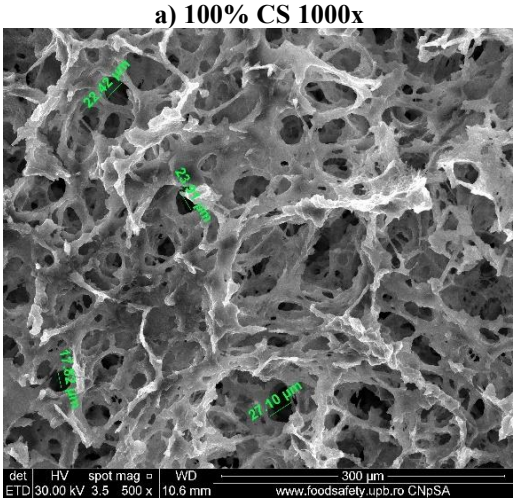
Scanning electron microscopy (SEM, Fig. 4) revealed the 3D porous structure of CS/HAp scaffolds, with interconnected pores allowing cell penetration and proliferation. Chitosan fibers, visible in unmineralized samples, became thicker and uniformly coated with the inorganic phase after mineralization. Nanorods and hydroxyapatite spheres (10–500 nm) were uniformly distributed along the fibers, providing a morphology suitable for interaction with osteogenic cells. This combination of porosity and mineral distribution suggests that the scaffolds can support tissue regeneration and serve as carriers for controlled release of active compounds.



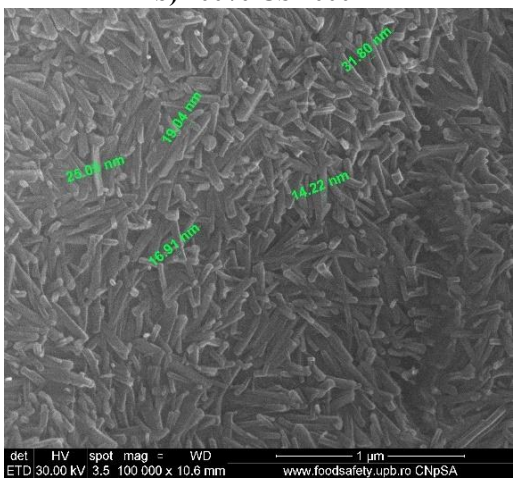
a) 100% CS 1000x



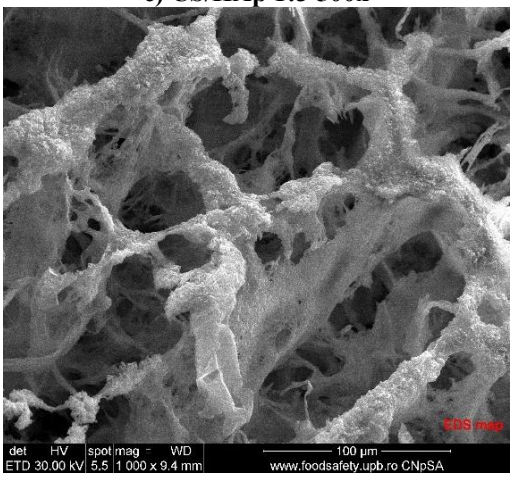
b) 100% CS 2000x



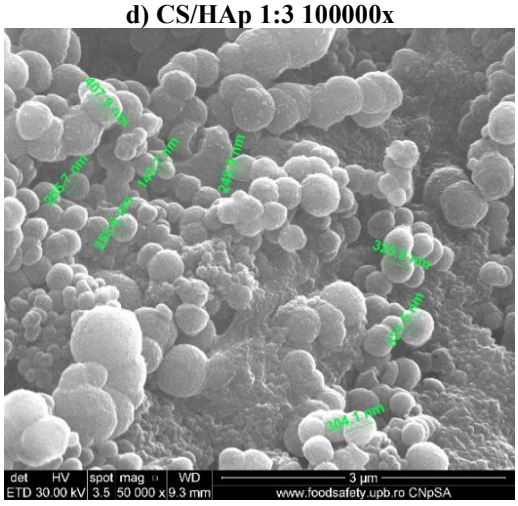
c) CS/HAp 1:3 500x



d) CS/HAp 1:3 100000x



e) CS/HAp 3:1 1000x



f) CS/HAp 3:1 50000 x

Figure 4. SEM images of chitosan and chitosan/hydroxyapatite structures

Biocompatibility and cytotoxicity tests (Fig. 5) indicated that CS/HAp composites support osteoblast proliferation and exhibit very low cytotoxicity, confirming their safety for bone tissue regeneration and potential use as drug delivery platforms.

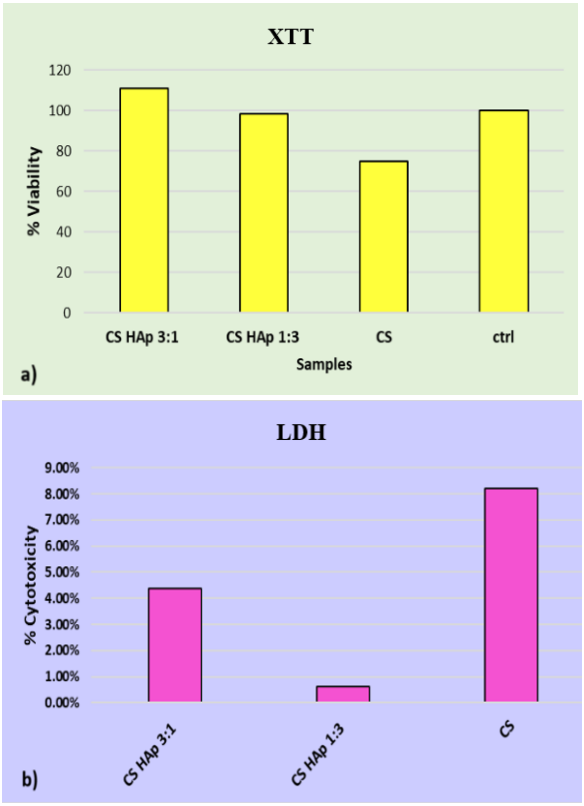


Figure 5. Osteoblast viability (a) and cytotoxicity of composite systems (b)

In conclusion, the CS/HAp systems developed represent promising candidates for bone tissue repair and for the development of platforms for controlled drug delivery.

2.4. The role of crosslinking agents in the development of collagen–hydroxyapatite composite materials for bone tissue engineering

The study focused on the development of crosslinked collagen/hydroxyapatite (Coll/HAp) scaffolds using three different crosslinking agents, obtained via freeze-drying after in situ synthesis of hydroxyapatite, for applications in bone tissue engineering. The water absorption was high for all samples, ranging between 23 and 40 g/g, and the presence of hydroxyapatite slightly reduced absorption, with no significant influence from the crosslinking agents. Enzymatic degradation in a collagenase solution (Fig. 6) showed that samples with lower HAp content degraded faster, while

those with higher HAp content exhibited slower degradation due to the protective effect of the mineral phase.

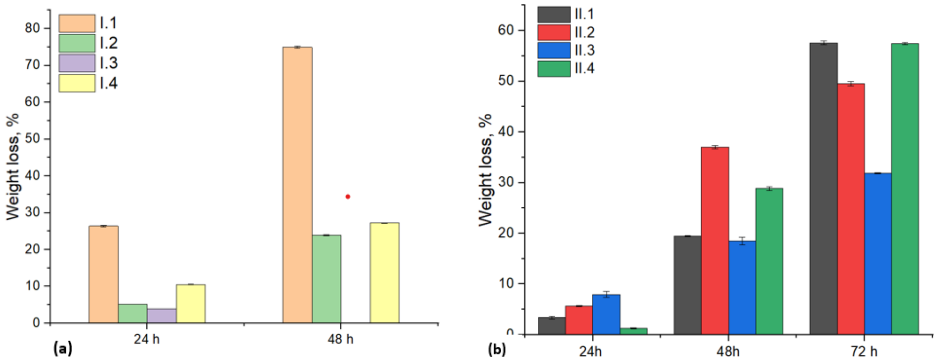
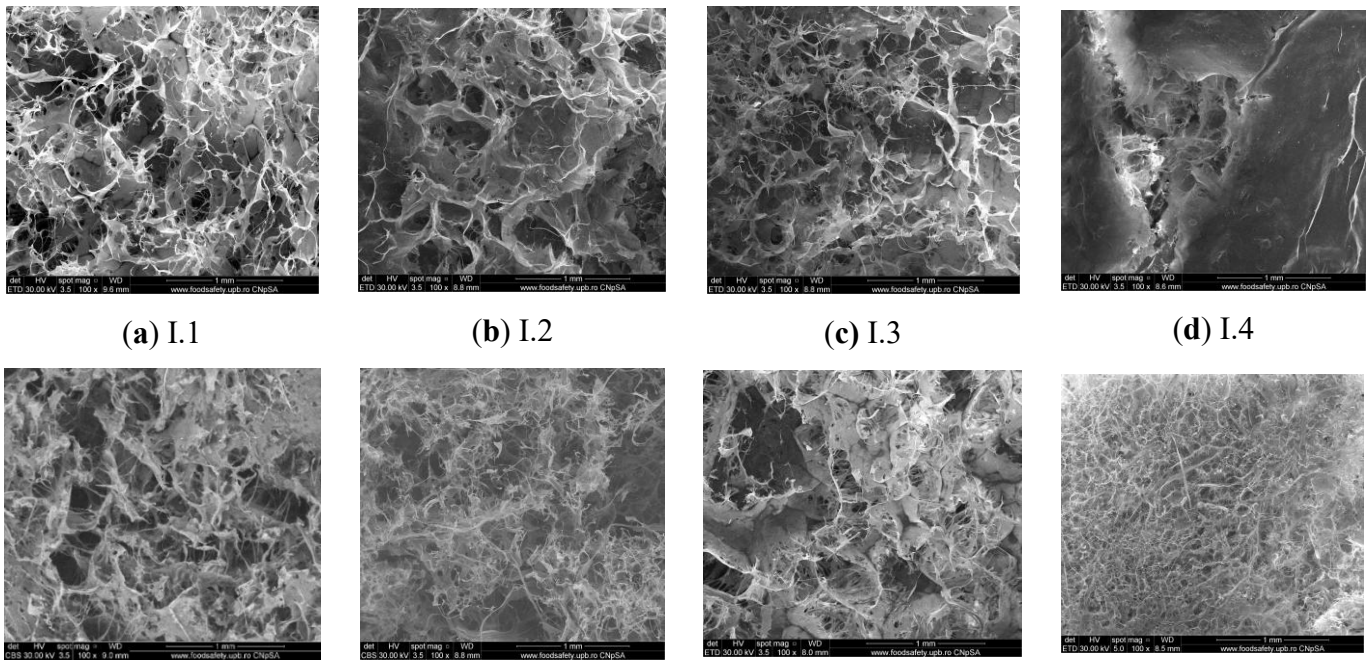


Figure 6. Enzymatic degradation of composite samples: **(a)** Series I; **(b)** Series II

Morphological analysis by scanning electron microscopy (SEM) (Fig. 7) revealed a spongy structure with interconnected pores of 50–300 µm, favorable for osteoblast migration and proliferation. Freeze-drying improved the morphology of the collagen matrix, and the genipin-crosslinked samples were more compact. The distribution of the inorganic phase was homogeneous, with aggregates ranging from 1 to 50 µm, and mineralization along collagen fibers was uniform.



(**a**) I.1 (**b**) I.2 (**c**) I.3 (**d**) I.4

(**e**) II.1 (**f**) II.2 (**g**) II.3 (**h**) II.4

Figure 7. SEM images of composite scaffolds (×100): (a) I.1, (b) I.2, (c) I.3, (d) I.4, (e) II.1, (f) II.2, (g) II.3, (h) II.4

EDX analysis confirmed the presence of elements characteristic of hydroxyapatite (Table 1), such as Ca, P, and O, with an atomic Ca/P ratio of 1.68, close to that of stoichiometric hydroxyapatite. The Na and Cl detected originate from the production process and are non-toxic.

Tabel 1. Elemental composition of sample II.4

Element	Weight %	Atomic %	Error %
C K	22.63	33.83	12.54
O K	43.26	48.55	11.18
Na K	3.03	2.37	14.86
P K	9.08	5.26	5.4
Cl K	2.17	1.1	7.23
Ca K	19.83	8.88	2

Overall, the presented samples combine optimal porosity, uniform mineral-phase distribution, and structural stability, making them suitable as bone scaffolds for tissue regeneration.

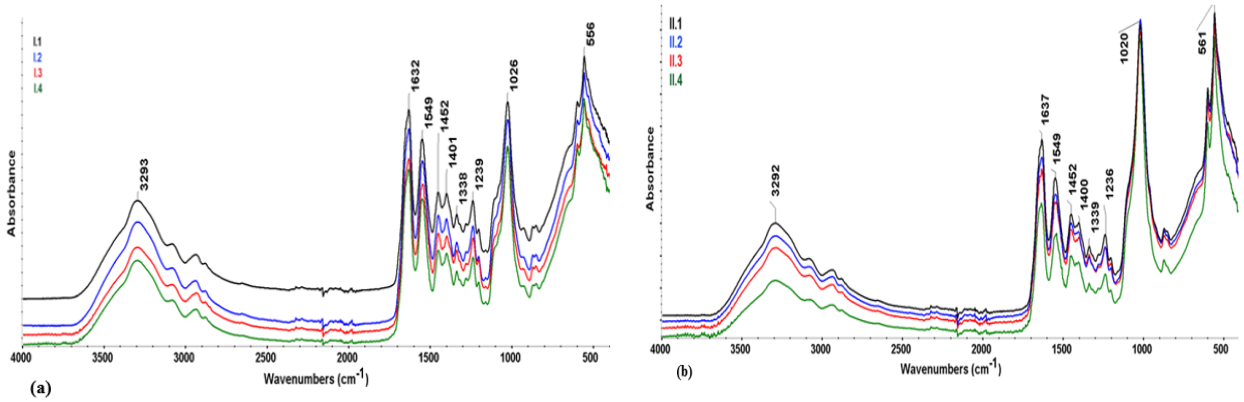


Figure 8. FT-IR spectra of composite materials: (a) Coll/HAp 3:1; (b) Coll/HAp 1:1

FT-IR analysis (Fig. 8) confirmed the presence of both organic and inorganic components in the Coll/HAp samples. Characteristic collagen bands were identified in the 3293–1239 cm^{-1} region, corresponding to amide groups and functional groups N–H, C–H, and C–N, while hydroxyapatite bands appeared at 1026, 556, and 615 cm^{-1}, with minor peaks at 950 cm^{-1} and 872 cm^{-1}, indicating brushite and carbonate presence. X-ray diffraction (XRD) revealed the formation of a more amorphous hydroxyapatite, similar to natural bone, with main peaks at $2\theta \approx 26°$ and 32° (Fig. 9).

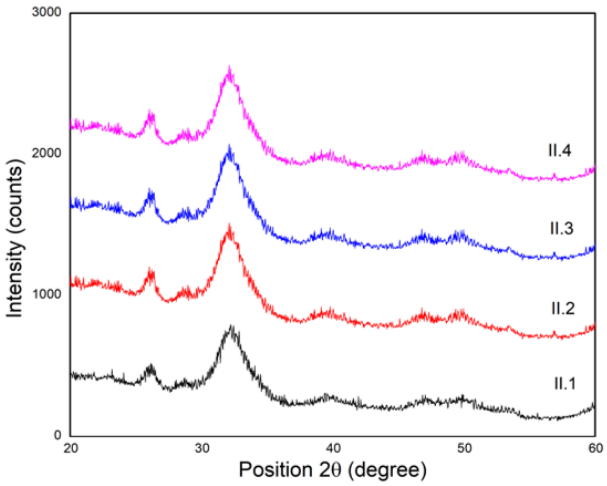


Figure 9. XRD diffractograms of Coll/HAp 1:1 scaffolds

Thermal analysis (TG-DSC) (Fig. 10) showed the loss of loosely bound water up to 135°C, followed by partial collagen denaturation and oxidation of fragments between 135 and 400°C, and oxidation of carbonaceous mass, HAp densification, and elimination of –OH groups above 400°C. The estimated HAp content was 19–22% for Coll/HAp 3:1 and 42–44% for Coll/HAp 1:1.

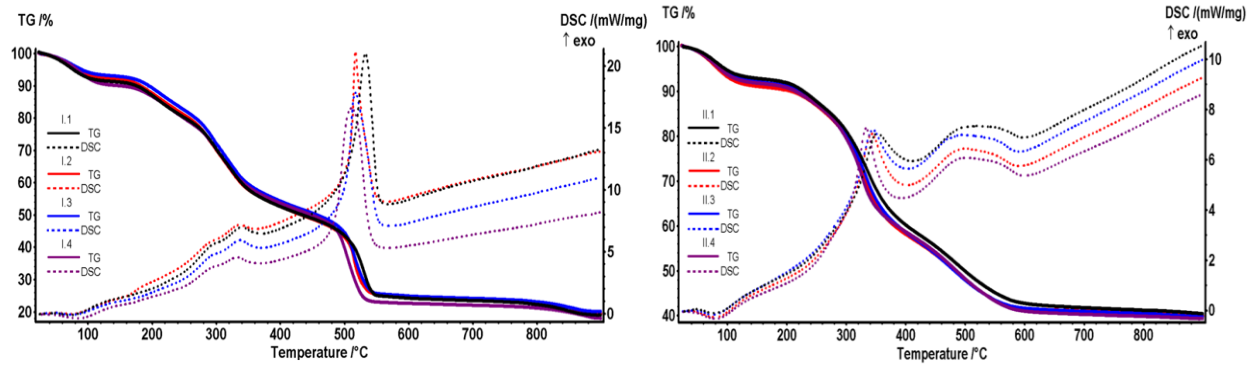


Figure 10. TG-DSC curves for Series I (Coll/HAp 1:3, left) and Series II (Coll/HAp 1:1, right)

Collagen/hydroxyapatite composites exhibited Shore A hardness values between 21 and 30 (Fig. 11(a)) and a Young's modulus ranging from 37.5 to 98.5 kPa (Fig. 11(b)), characteristics specific to soft and porous structures. These properties make them suitable as scaffolds for early-stage bone regeneration, especially in spongy bone. Increasing hydroxyapatite content improves stiffness and compressive strength, but the values remain moderate, adequate for regions with low mechanical demands. The low Young's modulus favors essential cellular processes such as adhesion, proliferation, and osteoblast differentiation by creating a biomechanical

microenvironment comparable to natural bone. These scaffolds also allow efficient nutrient diffusion and bone-specific mechanical signaling. To further improve mechanical properties, additional mineralization of the scaffolds through immersion in biomimetic solutions (SBF) before implantation is a viable strategy.

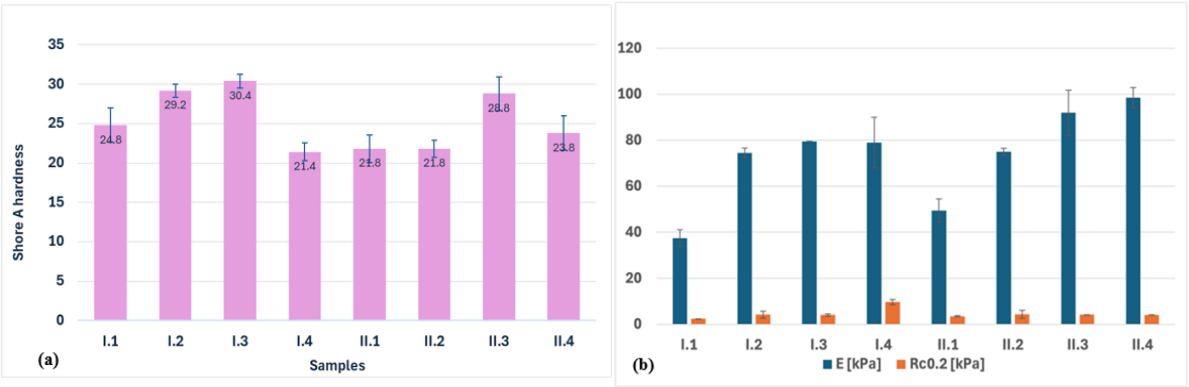


Figure 11. (a) Shore A hardness and (b) Young's modulus and compressive strength of composite scaffolds

Coll/HAp composites demonstrated antimicrobial activity against *E. coli* and *S. aureus*, with inhibition zones ≥20 mm for crosslinked samples. Samples with higher hydroxyapatite content showed slightly enhanced effects due to ion release and local pH changes. The strong activity is attributed to the crosslinking agents and phenolic compounds, which affect bacterial cell walls, enzymes, and DNA, being more pronounced against *S. aureus*, a common pathogen in bone graft infections (Fig. 12).

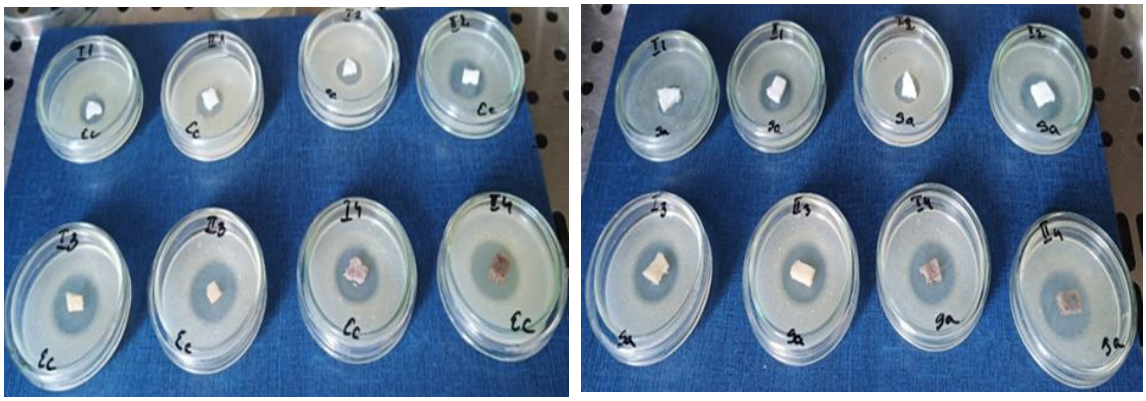


Figure 12. Antibacterial effect of Coll/HAp samples against *E. coli* (left) and *S. aureus* (right)

This chapter highlighted the development of crosslinked collagen–hydroxyapatite composites obtained via freeze-drying, with three different crosslinkers, exhibiting interconnected porosity suitable for bone regeneration. Hydroxyapatite formed *in situ* and was uniformly distributed, while samples crosslinked with natural agents (tannic acid and genipin) demonstrated strong antibacterial activity against *E. coli* and *S. aureus*. Although mechanical properties require optimization for mechanically stressed applications, the most promising results were obtained for crosslinked samples with higher hydroxyapatite content (Series II), which will be further evaluated for cytocompatibility and subsequently loaded with antitumor agents for potential use in bone cancer treatment..

2.5. Localized combination therapy using collagen–hydroxyapatite bone grafts for simultaneous bone cancer inhibition and tissue regeneration

The study aimed to develop multifunctional collagen–hydroxyapatite scaffolds loaded with doxorubicin and caffeic acid for the treatment of osteosarcoma, combining bone regeneration with tumor inhibition. Analysis of water absorption capacity (Fig. 13) showed values ranging from ~23–32 g/g, with rapid water uptake and stabilization after 24 hours. Sample 9A exhibited slightly higher absorption, attributed to the hydrophilicity conferred by the active compounds, while the GP control showed lower values, likely due to increased density and the hydrophobic nature of genipin. Statistical differences among the samples were evident during the first hours but diminished after reaching equilibrium, except for 9A, which maintained higher absorption.

Enzymatic degradation of Coll/HAp composites loaded with doxorubicin and caffeic acid (Fig. 13) revealed superior stability compared to the GP control, which was completely degraded after 6 days. Samples 7A and 9A initially exhibited negative values, explained by collagenase inhibition by doxorubicin, an effect enhanced in 9A by the presence of caffeic acid. Among all formulations, 9A demonstrated the greatest enzymatic resistance, with ~40% mass loss after 7 days, suggesting a synergistic stabilizing effect of the two compounds. Statistical analysis showed significant differences compared to GP from 2 hours onward, and after 144 hours all loaded matrices exhibited significantly reduced degradation, confirming the role of active agents in enhancing structural stability.

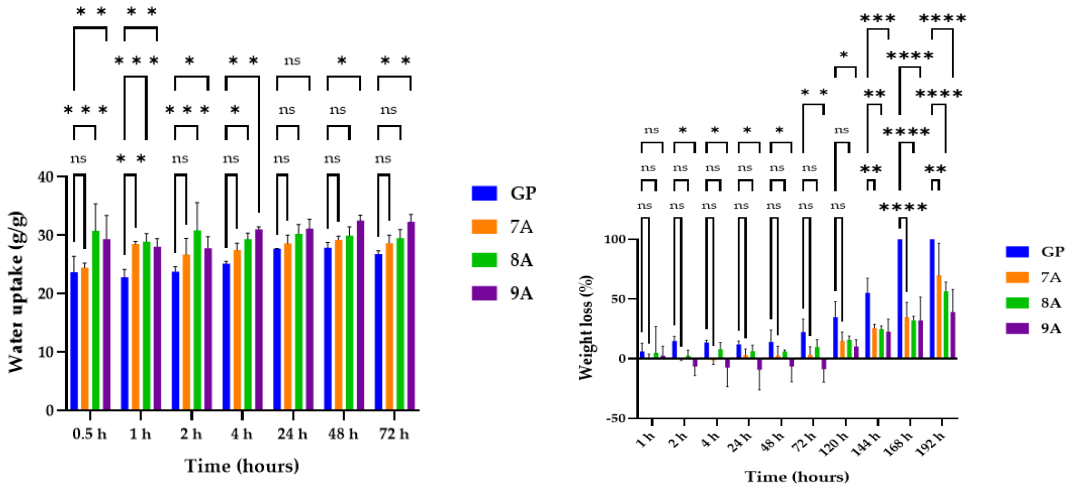
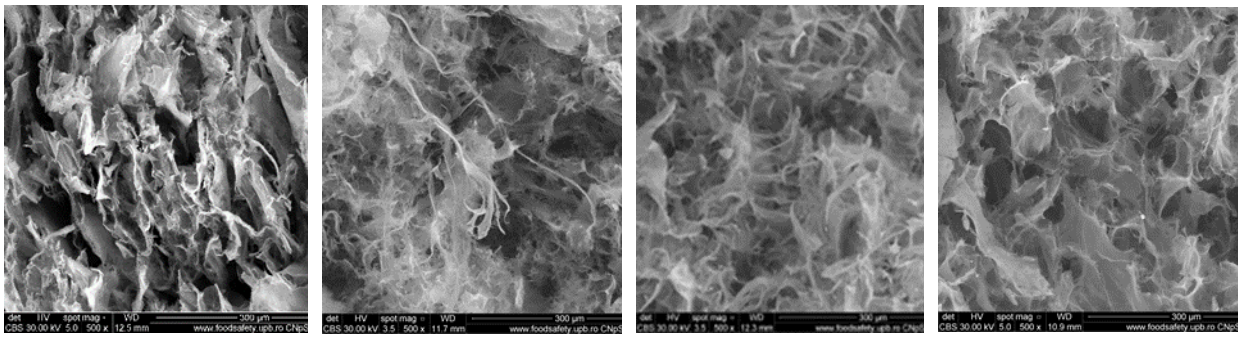


Figure 13. Water absorption (left) and enzymatic degradation (right) for matrices 7A, 8A, 9A, and GP. Results are not statistically significant (ns) for $p > 0.05$; statistically significant results are: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

The microstructure of the collagen/hydroxyapatite composite scaffolds loaded with doxorubicin and caffeic acid was analyzed by scanning electron microscopy (SEM) (Fig. 14), showing a sponge-like architecture with high porosity and interconnected pores ranging from 20 to 250 µm, favorable for osteoblast migration and nutrient diffusion. The collagen fiber structure was well preserved, and the inorganic phase (hydroxyapatite) was uniformly distributed with nanometric dimensions.



(**a**) 7A (**b**) 8A (**c**) 9A (**d**) GP

Figure 14. Microstructure of loaded composite scaffolds (x500): (a) 7A, (b) 8A, (c) 9A, (d) GP

FT-IR spectroscopy confirmed the presence of collagen and hydroxyapatite in the loaded scaffolds, with characteristic bands at 3294, 1636, 1541, 1448, and 1237 cm^{-1} for collagen, and 1025, 1103, 559, and 601 cm^{-1} for hydroxyapatite (Fig. 15). Partial band overlap in the regions 3100–3400 cm^{-1} and 1400–1636 cm^{-1} suggests molecular interactions, such as hydrogen bonding or electrostatic interactions, between the organic matrix and inorganic phase. The presence of doxorubicin, caffeic acid, and genipin could not be definitively detected due to their low concentrations and overlap with collagen bands.

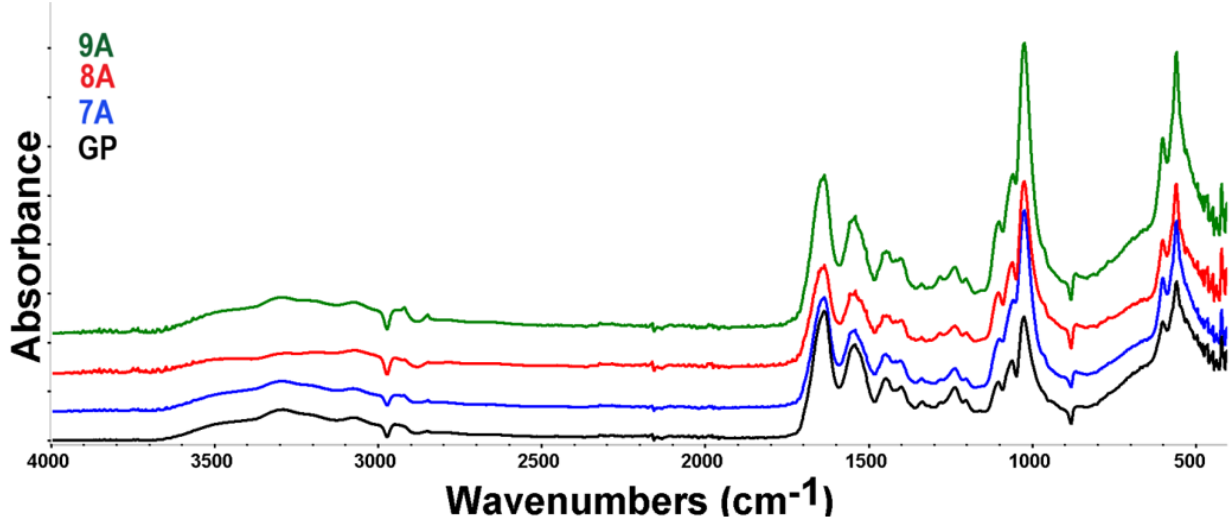


Figure 15. FT-IR spectra for samples 7A, 8A, 9A, and GP

TG-DSC analysis (Fig. 16) showed loss of free water up to 200°C (8–9%), followed by degradation and oxidation of organic components between 200–540°C (50–52%), with exothermic peaks at 329–339°C and 465–475°C. Beyond 540°C, mass loss was minimal (~4%), corresponding to the inorganic phase. The final residual mass was 34–38%, slightly lower in samples loaded with doxorubicin or caffeic acid, indicating good thermal stability and controlled material degradation.

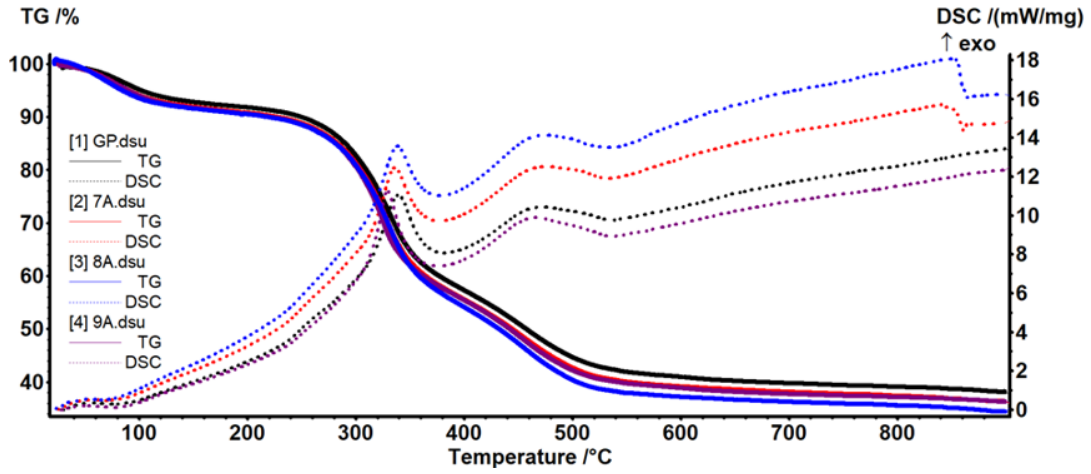


Figure 16. TG-DSC curves for samples 7A, 8A, 9A, and GP

X-ray diffraction of the antitumor composites showed diffraction peaks corresponding to the main planes of hydroxyapatite: (002) at 2θ = 25.88°, (120) at 2θ = 28.92°, (121) at 2θ = 31.76°, (112) at 2θ = 32.19°, (030) at 2θ = 32.89°, and (222) at 2θ = 46.69°, with a hexagonal structure (Fig. 17). Peak broadening indicates nanometric hydroxyapatite crystallites, suggesting the formation of a nanostructured phase. Crystallite size, determined via Rietveld refinement, was ~3 nm for all analyzed samples. This nanometric size is essential for the bioactive properties of bone. The crystallinity of the samples was ~30–31%, indicating a more amorphous, biomimetic structure similar to natural bone, known to enhance bioactivity and resorbability, thereby promoting osteointegration and bone tissue regeneration.

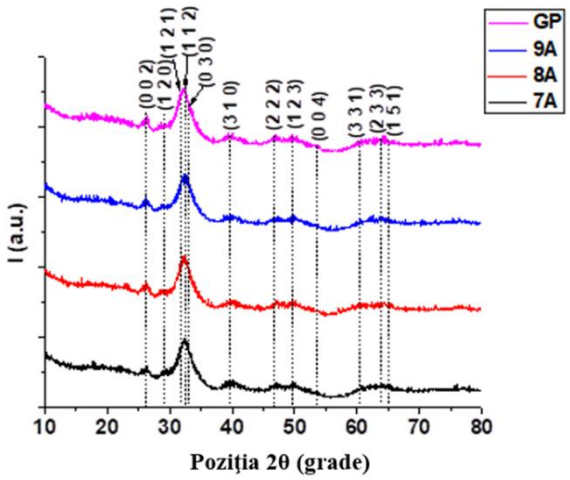


Figura 17. XRD diffractograms of antitumor composites – 7A, 8A, 9A, and GP

In vitro tests evaluated the cytotoxic effect of extracts from 7A (loaded with DOX), 8A (loaded with CA), and 9A (loaded with DOX/CA) on MG63 osteosarcoma cells and BMSC mesenchymal stem cells. After 24 hours, no significant LDH release was observed, and cell viability was generally similar to the control. Sample 7A reduced viability below 70%, while 8A showed a slightly protective effect, and 9A maintained BMSC viability at ~94%, while affecting MG63 (~51%) (Fig. 18).

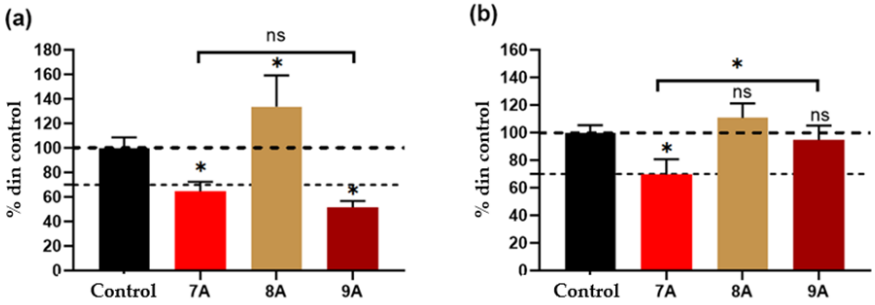


Figure 18. Cell viability of MG63 (a) and BMSC (b) cells cultured with 100% extracts from each sample for 1 day. Complete growth medium was used as control. The dashed line indicates the 70% threshold for cytotoxicity. Results are expressed as mean ± SD (n≥3, independent samples, *p<0.05)

After 3 days, extracts from 7A and 9A significantly reduced MG63 viability (<7% and 20%, respectively), while 9A maintained higher BMSC viability (~17%), suggesting a selective protective effect of caffeic acid (Fig. 19).

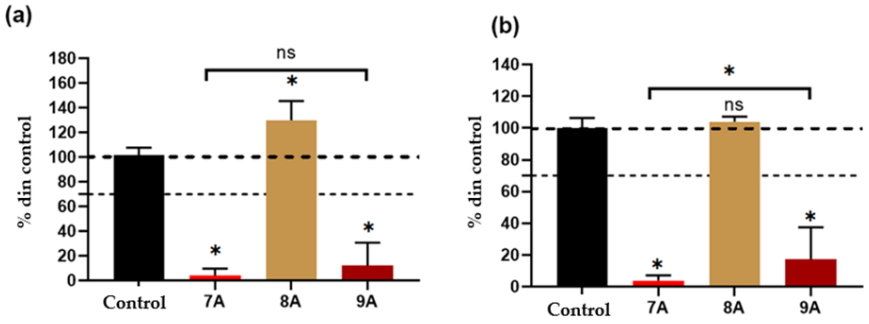


Figure 19. Cell viability of MG63 (a) and BMSC (b) cells cultured for 3 days with 100% extracts from each sample. Results expressed as mean ± SD (n≥3, independent samples, *p<0.05)

The DOX–CA combination inhibits osteosarcoma proliferation while maintaining stem cell compatibility. The selective effect of CA may be attributed to its antioxidant properties and

the natural defense mechanisms of BMSC. Scaffold 9A represents a promising candidate for combinatorial anti-osteosarcoma therapies, although further dose–response and mechanistic studies are required. The results highlight the potential of these scaffolds as a localized combinatorial therapy, providing both anticancer activity and support for bone regeneration, and recommend continuation of *in vivo* studies to optimize drug loading and release.

3. CONCLUSIONS

3.1. General conclusions

The thesis focused on the development and characterization of composite scaffolds for bone regeneration and localized treatment of osteosarcoma, using biomimetic materials based on chitosan or collagen and hydroxyapatite, loaded with synthetic and natural active compounds (doxorubicin and caffeic acid).

The CS/HAp and Coll/HAp materials were obtained via *in situ* hydroxyapatite synthesis and lyophilization, exhibiting porous structures with interconnected pores (17–300 μm), a uniformly dispersed nanostructured inorganic phase, and thermal and mechanical properties suitable for bone regeneration. FT-IR, XRD, SEM-EDX, and TG-DSC analyses confirmed the uniform integration of organic and inorganic phases, formation of nanocrystalline hydroxyapatite, and enhanced thermal stability, particularly in samples with higher HAp content.

Coll/HAp scaffolds demonstrated high water absorption capacity (~23–40 g/g), enzymatic resistance proportional to HAp content, significant antibacterial activity, Shore A hardness between 21–30, and Young's modulus between 37.5–98.5 kPa—values characteristic of soft, porous, biomimetic materials.

Samples loaded with DOX and CA (especially 9A) efficiently combined anticancer activity with stem cell protection: DOX reduced MG63 osteosarcoma cell viability to <7–20%, while CA maintained BMSC viability (~17%). The scaffolds exhibited enhanced structural stability, water retention, and uniform distribution of nanometric hydroxyapatite, providing an optimal support for bone tissue regeneration.

In conclusion, these multifunctional composite materials show both therapeutic and regenerative potential, offering a localized drug delivery system that can increase the efficacy of osteosarcoma treatment and reduce systemic toxicity, opening new perspectives for tissue engineering and orthopedic cancer therapy.

3.2. Original contributions

Within this doctoral thesis, a series of original contributions were made regarding the development of composite drug delivery systems used in the therapy of bone cancer.
The following elements of originality can be highlighted:

- **Determination of the role of different crosslinking agents** in the development of collagen–hydroxyapatite composite systems for bone tissue engineering.
- **Development of a novel type of bone graft based on collagen and hydroxyapatite**, obtained via freeze-drying, which simultaneously incorporates two active substances — doxorubicin (a synthetic chemotherapeutic agent) and caffeic acid (a natural compound with antioxidant and anticancer effects).
- **A combined approach for osteosarcoma treatment and bone regeneration**, a concept less explored in the specialized literature, using both a cytotoxic agent and a natural protective compound simultaneously.
- **Investigation of the synergistic effect of combining caffeic acid with doxorubicin**, which demonstrated high cytotoxicity against MG63 osteosarcoma cells while partially protecting mesenchymal stem cells (BMSC), likely due to the antioxidant properties of caffeic acid.

3.3. Future developments

The results obtained in this doctoral thesis for the presented composite materials highlight their therapeutic and regenerative potential, while also offering new directions and opportunities for future research, such as:

- **Optimization of the material composition** to improve both mechanical properties and biological performance.

- **Extensive *in vitro* testing** to evaluate the behavior of the composites under complex biological conditions and to confirm their efficiency in bone regeneration, as well as ***in vivo*** evaluation of scaffold performance; deeper exploration of the DOX–CA interactions in the tumor microenvironment, and optimization of drug loading and release; advanced optimization of the individual content of each active compound and their ratio.
- **Development of Coll/HAp materials with other active substances exhibiting synergistic effects**.
- **Long-term analysis of biodegradability and bioactivity** to determine degradation rates and how the material interacts with bone tissue over time.
- **Exploration of adapting biomaterials for other clinical applications**, including personalized treatments and combinations with additional therapeutic agents (antibiotics, growth factors).
- **Scaling up the manufacturing process** for industrial production while ensuring compliance with regulations required for clinical approval

PUBLICATIONS

1. **Vladu, A.F**.; Ficai, D.; Ene, A.G.; Ficai, A. Combination Therapy Using Polyphenols: An Efficient Way to Improve Antitumoral Activity and Reduce Resistance. *Int. J. Mol. Sci.* **2022**, *23*, 10244. https://doi.org/10.3390/ijms231810244, IF – 5.2/2022

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3. **Vladu, A.F**.; Motelică, L.; Oprea, O.C; Truşcă, R.D.; Iordache, F.; Ficai, D.; Ficai, A. Chitosan/Hydroxyapatite composite grafts for bone tissue engineering. *U.P.B. Sci. Bull., Series B.* **2025**, Series B, Vol. 87, Iss. 3, IF – 0.3/2025

4. **Vladu, A.F.**; Albu Kaya, M.G.; Ficai, A.; Ficai, D.; Tutuianu, R.; Motelica, L.; Surdu, V.A.; Oprea, O.-C.; Truşcă, R.D.; Titorencu, I. Localized Combination Therapy Using Collagen–Hydroxyapatite Bone Grafts for Simultaneous Bone Cancer Inhibition and Tissue Regeneration. *Polymers* **2025**, *17*, 2239. https://doi.org/10.3390/polym17162239, IF – 4.9/2025

PARTICIPATION IN INTERNATIONAL CONFERENCES

1. **Alina Florentina Vladu**, Anton Ficai, "Polyphenols: a natural alternative for cancer therapy", International Scientific Conference "Applications of chemistry in nanosciences and biomaterials engineering", online, June 2021, oral presentation.
2. **Alina Florentina VLADU**, Anton FICAI, Alexandra ENE, Ecaterina ANDRONESCU, Ionela Andreea NEACSU, "Composite Drug Delivery Systems for Bone Cancer Treatment", International Scientific Conference "Applications of chemistry in nanosciences and biomaterials engineering", online, November 2021, poster.
3. **Alina Florentina Vladu**, Ludmila Motelica, Alexandra Ene, Ecaterina Andronescu, Ionela Neacsu, Anton Ficai, "Chitosan/Hydroxyapatite Based Composite Structures for Bone Cancer Treatment", International Scientific Conference "Applications of chemistry in nanosciences and biomaterials engineering", online, June 2022, poster
4. **Alina Florentina Vladu**, Ludmila Motelica, Roxana Trusca, Anton Ficai, "Composite Systems for Bone Tissue Regeneration", International Scientific Conference "Applications of chemistry in nanosciences and biomaterials engineering", online, November 2022, poster
5. **Alina Florentina Vladu**, Ludmila Motelica, Roxana Trusca, Florin Iordache, Anton Ficai, Preparation and Characterization of Composite Bone Substitutes, Virtual International Scientific Conference on "Applications of Chemistry in Nanosciences and Biomaterials Engineering" NanoBioMat 2023 – Summer Edition 28-30 June 2023, online, poster.
6. **Alina Florentina Vladu**, Ludmila Motelica, Ovidiu Cristian Oprea, Roxana Doina Trușcă, Florin Iordache, Denisa Ficai, Anton Ficai, Freeze-Dried Chitosan/Hydroxyapatite Based Composite Systems For Bone Tissue Regeneration, 7th International Conference On Emerging Technologies In Materials Engineering, 30-31 October 2024, Bucharest, Romania, poster

Awards

1. **Alina Florentina Vladu**, Anton Ficai, "Polyphenols: a natural alternative for cancer therapy", International Scientific Conference "Applications of chemistry in nanosciences and biomaterials engineering", online, June 2021, Best Paper Award.
2. **Alina Florentina Vladu**, Ludmila Motelica, Roxana Trusca, Florin Iordache, Anton Ficai, Preparation and Characterization of Composite Bone Substitutes, Virtual International Scientific Conference on "Applications of Chemistry in Nanosciences and Biomaterials Engineering" NanoBioMat 2023 – Summer Edition 28-30 June 2023, Best Poster Award

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