Cyclo-(His-Phe) Complexes with Copper and Zinc Nanoparticles Have Targeted Anticancer Potential Against Osteosarcoma Cells

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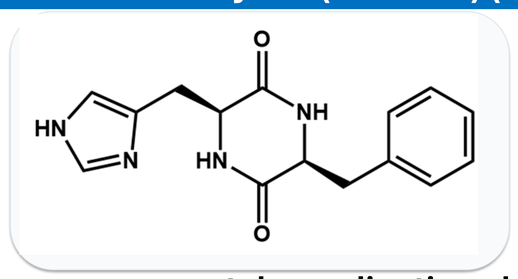
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OUTLINE

- The development of chemotherapy agents that exploit molecular carriers for controlled and targeted delivery in cancer cells is a crucial area in modern molecular medicine.
- Herein, we examined the potential of the cyclic peptide cyclo-(His-Phe) to chelate copper and zinc ions that have been recently proposed as therapeutic agents against osteosarcoma cells.
- The peptide self-assembled into amyloid-type fibrils; morphological and structural characterization following metal ion addition confirmed the formation of cHF–CuNPs and cHF–ZnNPs.
- We evaluated the optimal concentration of cHF–metalNP complexes with antimicrobial activity against *E.coli* and *S.aureus,* limited cytotoxicity to L929 fibroblasts and high cytotoxic effects against MG-63 osteosarcoma cells.

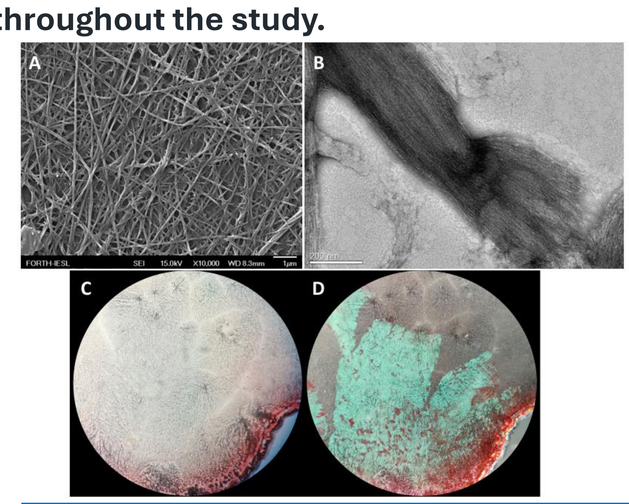
PEPTIDE DESIGN cyclo-(His-Phe) (cHF)



Histidine conveys metal coordination ability; the cyclic peptide backbone and the phenylalanine rin support self-assembly.

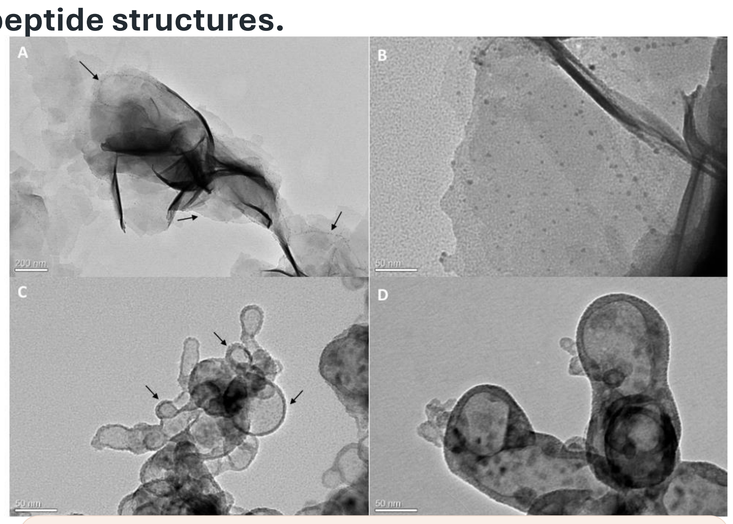
SELF-ASSEMBLY OF cHF in PBS

FESEM/TEM and CongoRed staining show fibrillar, amyloid-like cHF assemblies. The peptide concentration used was 5 mM throughout the study.



METAL ION COORDINATION

At 1 mM metal ion concentration, cHF-copper complexes form petal/flower-like structures, while cHF-zinc complexes form bubble-like spherical assemblies. TEM shows electron-dense nanoparticle dots templated on or within peptide structures.

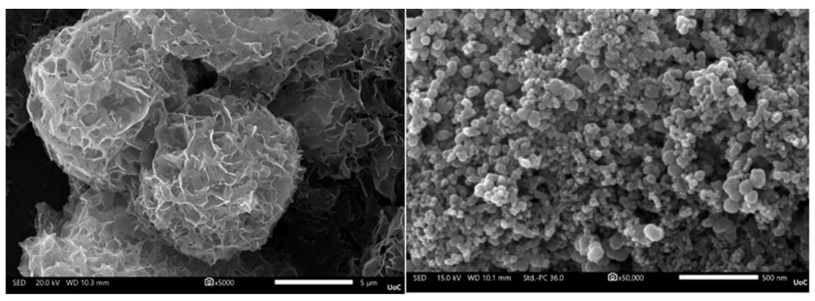


A,B =Cu^{2+} → flower-like / nanosheet-rich assemblies

C,D = Zn^{2+} → spherical / bubble-like assemblies

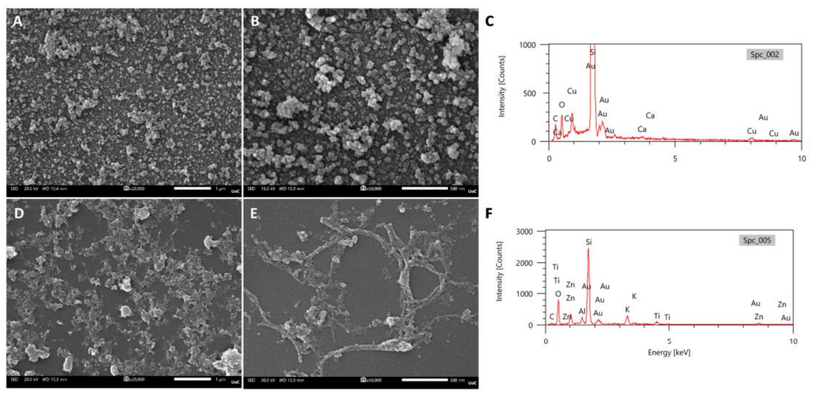
CHF ASSEMBLIES WITH COPPER and ZINC

Following **$NaBH_4$ reduction,** cHF in the presence of copper chloride forms flower-like spherical assemblies with diameters in the range of 10 μM (left), while in the presence of zinc chloride forms quasi-spherical assemblies at the nanoscale range (right).



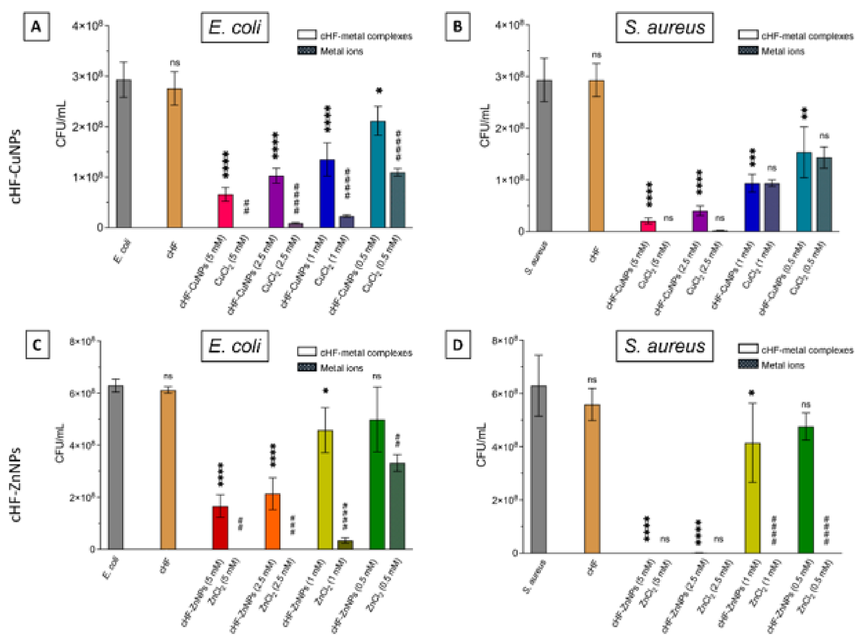
PH-RESPONSIVE STRUCTURAL CHANGE

At pH 6.4, the ordered peptide assemblies with Cu/Zn become smaller and more amorphous, with peptide fibrils reappearing—consistent with complex dissociation and metal ion release
A, B, C =copper, D, E,F =zinc.



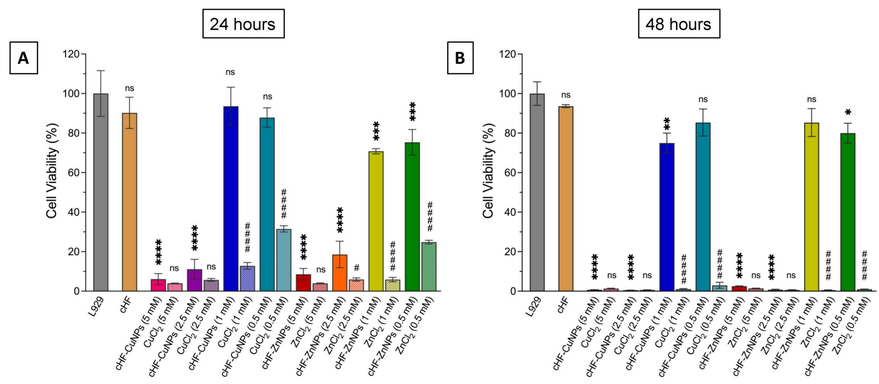
ANTIBACTERIAL ACTIVITY

- cHF alone (5 mM) showed no notable antimicrobial activity.
- Both complexes (cHF–CuNPs and cHF–ZnNPs) retained antimicrobial activity at 1 mM, with increasing effect at 2.5 and 5 mM, however, higher concentrations were more cytotoxic to mammalian cells (see “Fibroblast compatibility” graphs).



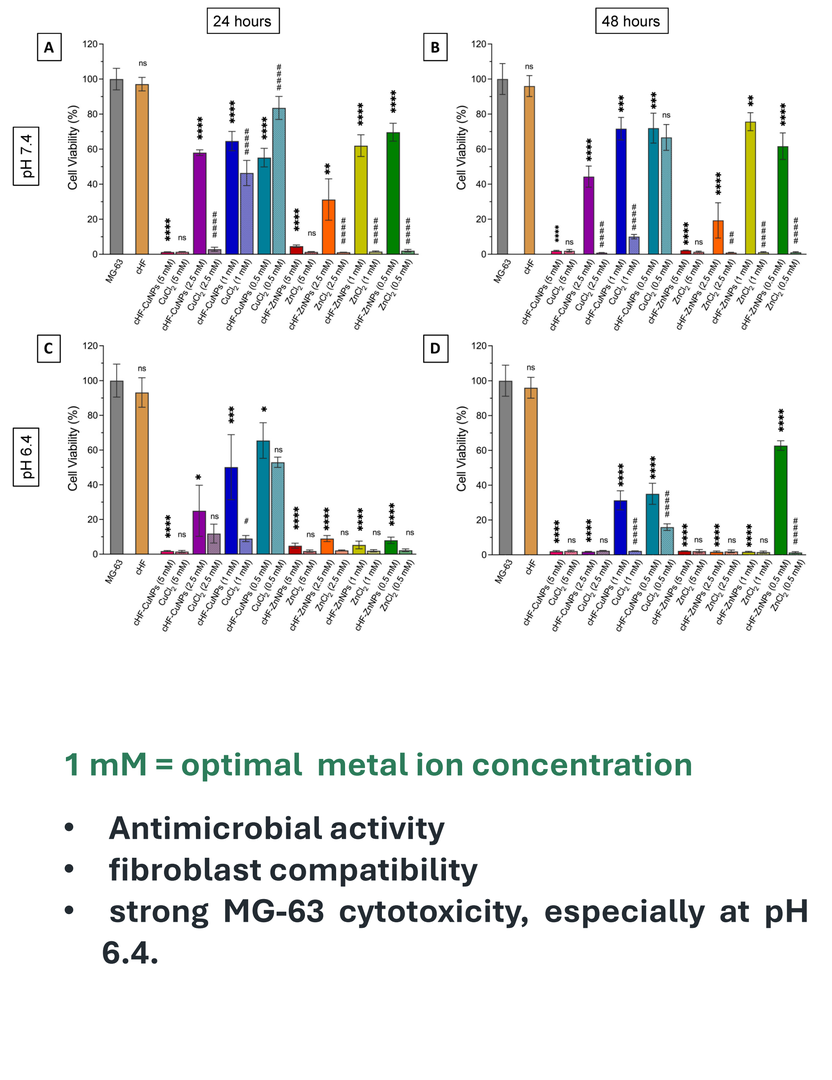
FIBROBLAST COMPATIBILITY

Peptide – metal ion complexes at metal concentrations 2.5–5 mM caused pronounced L929 fibroblast toxicity. Lower concentrations were substantially better tolerated.



ANTI-OSTEOSARCOMA ACTIVITY IS ENHANCED AT ACIDIC pH

- cHF alone (5 mM) remained essentially non-cytotoxic to osteosarcoma MG-63 cells.
- Both cHF–CuNPs and cHF–ZnNPs reduced MG-63 viability, with stronger effects at pH 6.4.
- At 1 mM, lowering pH from 7.4 to 6.4 produced an additional ~15% reduction in survival for cHF–CuNPs and ~50% for cHF–ZnNPs.



1 mM = optimal metal ion concentration

- Antimicrobial activity
- fibroblast compatibility
- strong MG-63 cytotoxicity, especially at pH 6.4.

CONCLUSIONS and OUTLOOK

- cHF fibrils efficiently chelates Cu^{2+} and Zn^{2+} and act as a structural/templating scaffold.
- Both complexes show concentration-dependent antibacterial activity against *E. coli* and *S. aureus*.
- Above 1 mM, mammalian-cell toxicity becomes a major limitation.
- At 1 mM, both complexes show the most attractive balance for further study, with stronger MG-63 effects under acidic pH.
- This work highlights the potential of cyclic peptides containing histidine as versatile carriers for the targeted delivery of metal ions against osteosarcoma treatment.
- Further optimization and combination with conventional anticancer drugs can be foreseen.

Reference

Apostolidou et al., Biomolecules 2026, 16, 284
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