

Ferroptosis-Engineered Extracellular Vesicles Co-delivering siGPX4 and Iron Oxide Nanoparticles: *In Vitro* Evaluation of Ferroptosis Resistance Mechanisms in KG-1 Cells



Zahra Khoshnegah^{1,2}, Amin Golestani^{1,2}, Muhammad Hossein Ashoub^{1,2*}

¹ Department of Hematology and Medical Laboratory Sciences, Faculty of Allied Medicine,
Kerman University of Medical Sciences, Kerman, Iran

² Student Research Committee, Afzalipour Faculty of Medicine,
Kerman University of Medical Sciences, Kerman, Iran



INTRODUCTION

Acute myeloid leukemia (AML) remains a therapeutic challenge due to resistance mechanisms and limited treatment options. Ferroptosis, an iron-dependent form of regulated cell death, has emerged as a promising therapeutic strategy. However, cellular resistance mediated by antioxidant systems, particularly glutathione peroxidase 4 (GPX4), significantly limits ferroptosis-based therapies.

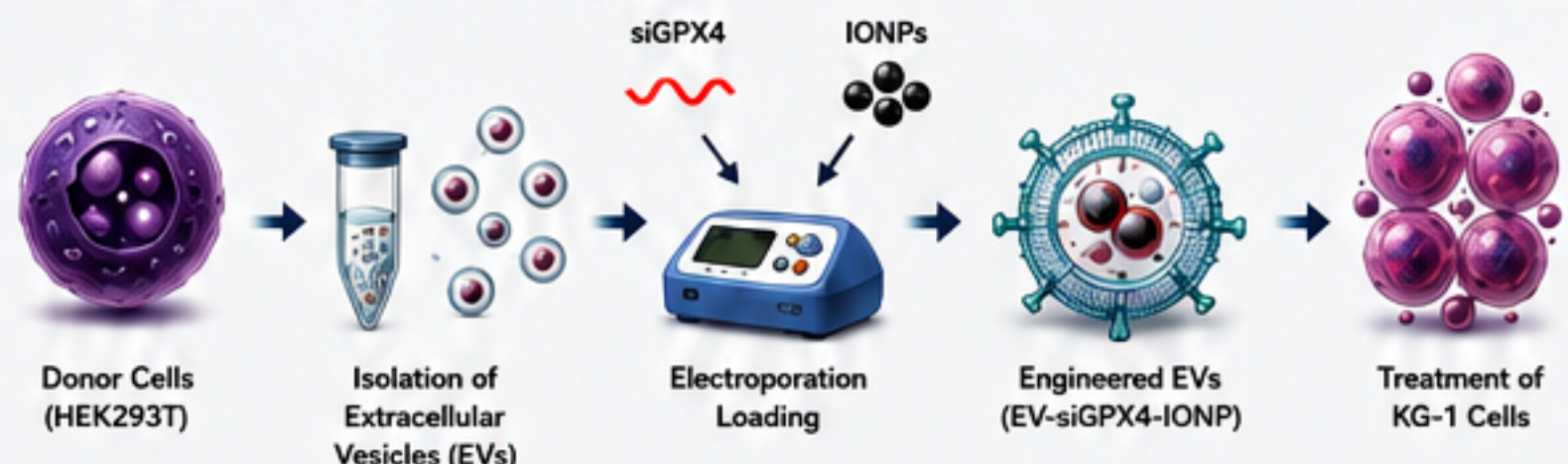


This study investigated the combined delivery of siGPX4 and iron oxide nanoparticles (IONPs) via engineered extracellular vesicles (EVs) to overcome ferroptosis resistance in the KG-1 AML cell line.



METHODS

EV Engineering and Experimental Workflow



Characterization

- Dynamic Light Scattering (DLS)
- Transmission Electron Microscopy (TEM)
- Zeta Potential Analysis

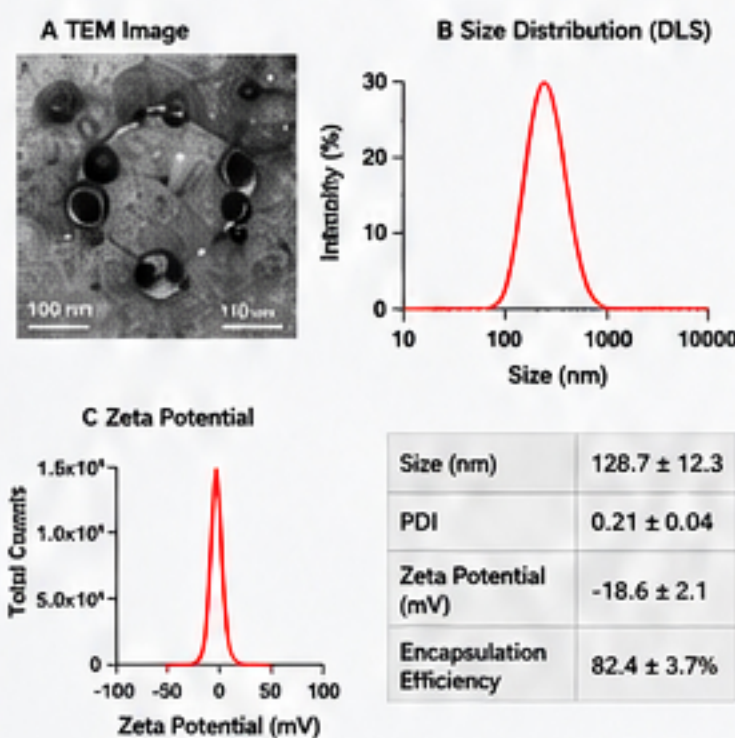
In Vitro Evaluation in KG-1 Cells

- Cellular uptake (confocal microscopy)
- GPX4 expression (qPCR)
- Intracellular iron (Fe^{2+}) measurement
- Lipid ROS (C11-BODIPY assay)
- Cell viability (MTT assay)
- Morphological assessment

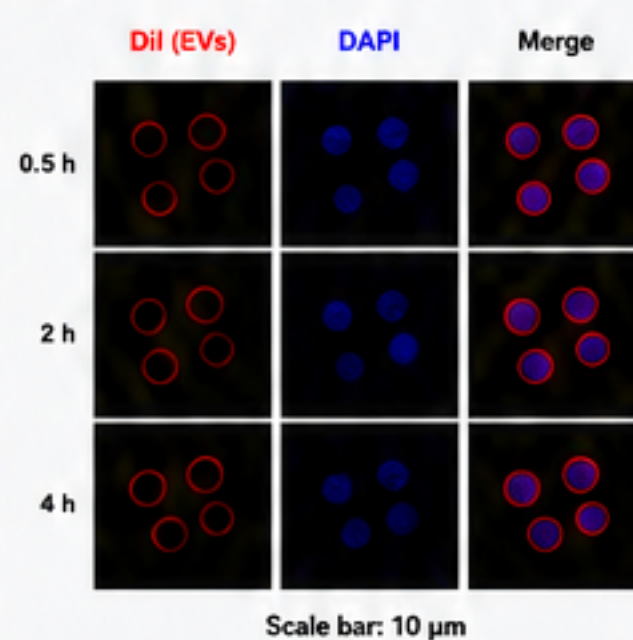


RESULTS

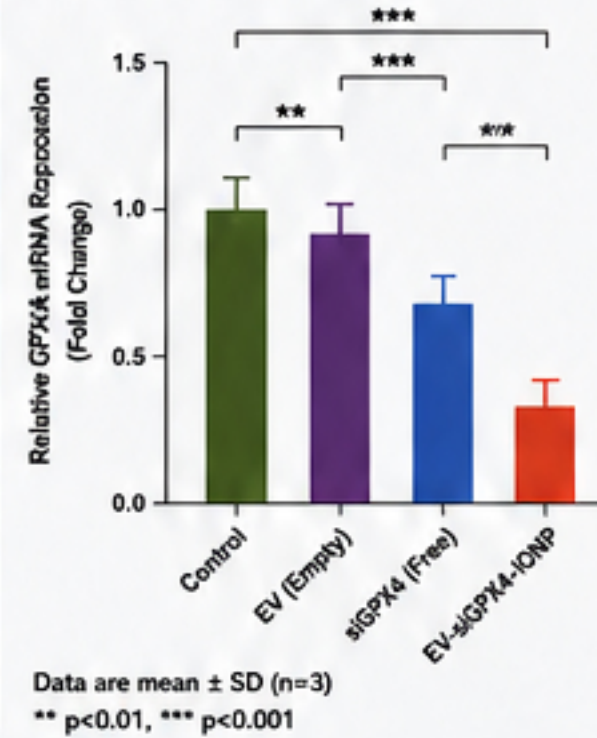
1 Characterization of Engineered EVs



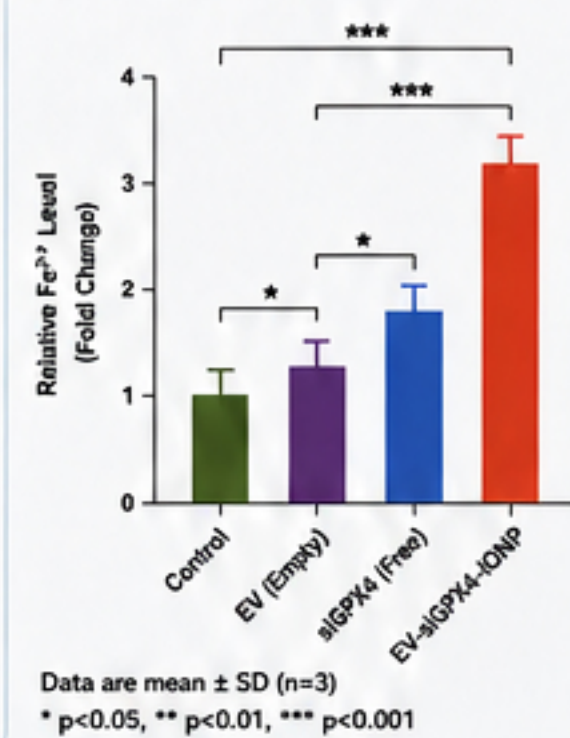
2 Cellular Uptake of EVs in KG-1 Cells



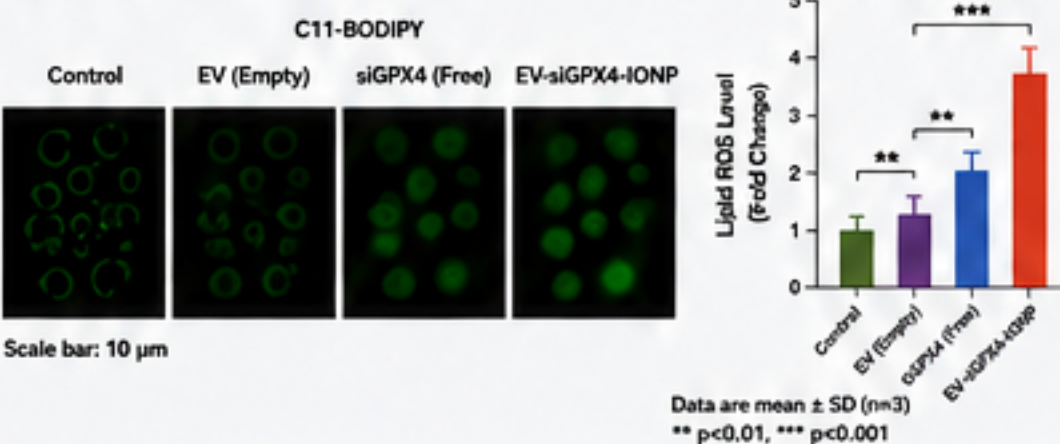
3 GPX4 mRNA Expression



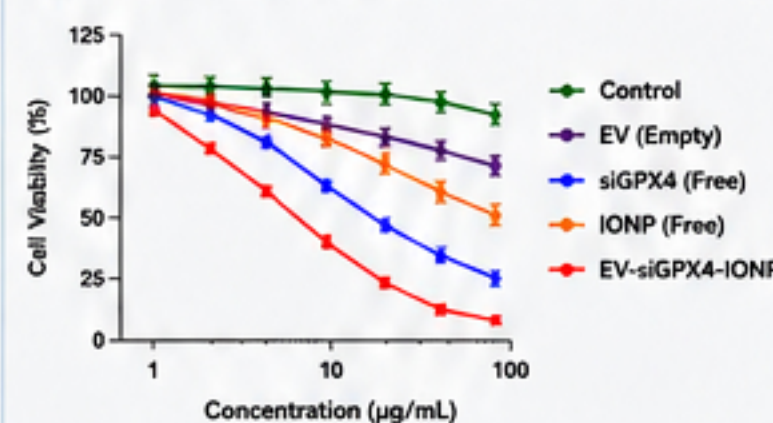
4 Intracellular Fe^{2+} Level



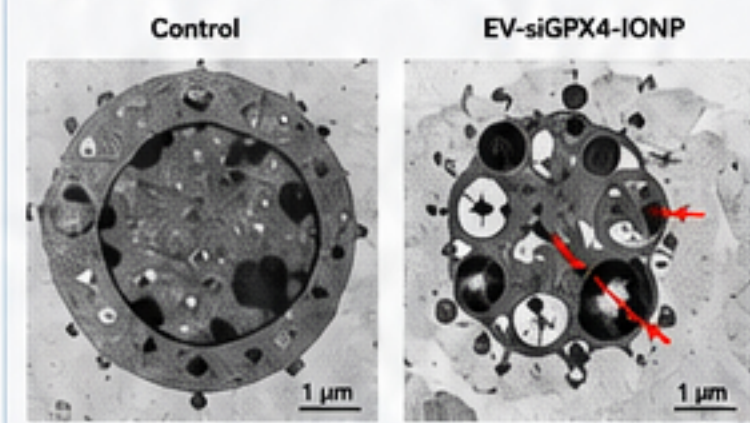
5 Lipid ROS (Lipid Peroxidation)



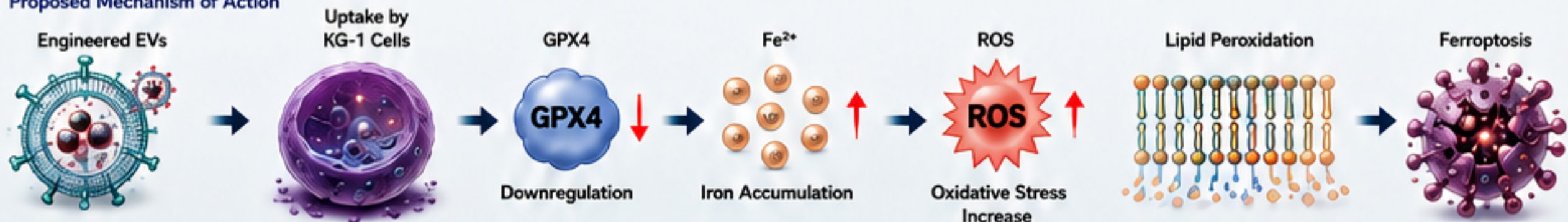
6 Cell Viability (MTT Assay)



7 Morphological Changes (TEM)



8 Proposed Mechanism of Action



CONCLUSION

EV-mediated co-delivery of siGPX4 and IONPs effectively overcomes ferroptosis resistance in KG-1 cells by simultaneously suppressing antioxidant defenses and enhancing oxidative stress, demonstrating potential as a novel therapeutic approach for AML treatment.



ACKNOWLEDGMENTS

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2. Ashoub, M.H., et al., pH-Sensitive Sulfasalazine Release from Green-Synthesized Mesoporous $\text{Fe}_3\text{O}_4/\text{SiO}_2$ Nanocomposites using *Opuntia ficus-indica* Extract. *Journal of Pharmaceutical Sciences*, 2025.
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