

Comparative Effects of Ionic and Nanoparticulate Silver on Nematodes *C. elegans* and Mice

Daria N. Magazenkova^{1,2,3} , Mohammad Al Farroukh^{1,2,3} , Polina D. Samuseva^{1,2} ,
Aleksandra A. Mekhova-Caramalac³ , Tatyana P. Sankova³ , Anna D. Shchukina¹ ,
Sofia A. Baikina³, Ilya M. Sosnin¹ , Elvira V. Rozhina⁴ , Ludmila V. Puchkova^{1,2,3},
Ekaterina Yu. Ilyechova^{1,2,3} 

¹ Research Center of Advanced Functional Materials and Laser Communication Systems, ADTS Institute, ITMO University, St. Petersburg 197101, Russia

² Laboratory of Biochemical Genetics, Research Institute of Experimental Medicine, St. Petersburg 197022, Russia

³ Institute of Biomedical Systems and Biotechnology, Peter the Great St. Petersburg Polytechnic University, St. Petersburg 195251, Russia

⁴ Institute of Fundamental Medicine and Biology, Kazan Federal University, Kreml Uramı 18, Kazan 420008, Republic of Tatarstan, Russia

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Corresponding author: [Ekaterina Yu. Ilyechova](#)

Abstract. The increasing use of silver nanoparticles (SNPs) in various fields of human activity concerns about their potential toxicity, particularly for invertebrates that absorb substances through their body surface and for terrestrial mammals. This study focuses on the interference of abiogenic silver with copper metabolism. This is due to the fact that Ag^{1+} and Cu^{1+} are isoelectronic, silver ions can be recognized by copper transporters and erroneously incorporated into essential cuproenzymes, thereby impairing their function. We conducted a comparative analysis of the biological effects of ionic silver (from AgNO_3) and nanoparticulate silver (30–40 nm spherical SNPs) on both wild-type *Caenorhabditis elegans* and a mutant strain with impaired copper excretion, as well as on the copper status in the serum of laboratory mice. The results revealed that SNPs exert greater toxicity in nematodes, particularly in those with disrupted copper homeostasis, whereas ionic silver posed a higher potential risk to mice. The findings highlight the need for cautious evaluation of SNPs in biomedical applications.

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REFERENCES

- [1] T. Bruna, F. Maldonado-Bravo, P. Jara, N. Caro, Silver Nanoparticles and Their Antibacterial Applications, *Int. J. Mol. Sci.*, 2021, vol. 22, no. 13, art. no. 7202.
- [2] Z. Lu, K. Rong, J. Li, H. Yang, R. Chen, Size-dependent antibacterial activities of silver nanoparticles against oral anaerobic pathogenic bacteria, *J. Mater. Sci. Mater.: Med.*, 2013, vol. 24, no. 6, pp. 1465–1471.
- [3] A. Abbaszadegan, Y. Ghahramani, A. Gholami, B. Hemmateenejad, S. Dorostkar, M. Nabavizadeh, H. Sharghi, The Effect of Charge at the Surface of Silver Nanoparticles on Antimicrobial Activity against Gram-Positive and Gram-Negative Bacteria: A Preliminary Study, *J. Nanomater.*, 2015, vol. 2015, art. no. 720654.
- [4] T.P. Sankova, I.M. Sosnin, M.N. Karpenko, E.Yu. Ilyechova, Yu.A. Orlov, D.S. Polyakov, E.A. Skomorokhova, A.S. Sukhanova, N.A. Rozhkova, P.S. Babich, P.S. Kudryavtseva, M.R. Shafeev, A.E. Romanov, L.V. Puchkova, On the biological activity of silver nanoparticles, *Mater. Phys. Mech.*, 2015, vol. 24, no. 11, pp. 289–296.
- [5] E.Yu. Ilyechova, A.N. Saveliev, A.N. Skvortsov, P.S. Babich, Yu.A. Zatulovskaia, M.G. Pliss, D.E. Korzhenskii, N.V. Tsymbalenko, L.V. Puchkova, The effects of silver ions on copper metabolism in rats, *Metallomics*, 2014, vol. 6, no. 10, pp. 1970–1987.
- [6] A.N. Skvortsov, E.Yu. Ilyechova, L.V. Puchkova, Chemical background of silver nanoparticles interfering with mammalian copper metabolism, *J. Hazard. Mater.*, 2023, vol. 451, art. no. 131093.
- [7] L.V. Puchkova, M. Broggin, E.V. Polishchuk, E.Y. Ilyechova, R.S. Polishchuk, Silver ions as a tool for understanding different aspects of copper metabolism, *Nutrients*, 2019, vol. 11, no. 6, art. no. 1364.
- [8] E.A. Skomorokhova, T.P. Sankova, I.A. Orlov, et al., Size-dependent bioactivity of silver nanoparticles: antibacterial properties, influence on copper status in mice and the whole-body turnover, *Nanotechnol. Sci. Appl.*, 2020, vol. 13, pp. 137–157.
- [9] L.V. Puchkova, T.P. Sankova, D.N. Magazenkova, E.A. Skomorokhova, I.A. Orlov, E.I. Sakhenberg, I.M. Sosnin, M. Al Farroukh, A.E. Romanov, E.Yu. Ilyechova, Shape-dependent biological activity of spherical and quasi-spherical silver nanoparticles in *E. coli*, A549 cells and mice; *Environ. Sci.: Nano*, 2022, vol. 9, pp. 3581–3598.
- [10] D. Xiang, Y. Zheng, W. Duan, X. Li, J. Yin, S. Shigdar, M.L. O’Conner, M. Marappan, X. Zhao, Y. Miao, B. Xiang, C. Zheng, Inhibition of A/Human/Hubei/3/2005 (H3N2) influenza virus infection by silver nanoparticles in vitro and in vivo, *Int. J. Nanomed.*, 2013, vol. 8, no. 1, pp. 4103–4113.
- [11] L. Martín-Faivre, L. Prince, C. Cornu, B. Villeret, D. Sanchez-Guzman, F. Rouzet, J.-M. Sallenave, I. Garcia-Verdugo, Pulmonary delivery of silver nanoparticles prevents influenza infection by recruiting and activating lymphoid cells, *Biomaterials*, 2025, vol. 312, art. no. 122721.
- [12] I.V. Kiseleva, M. Al Farroukh, E.A. Skomorokhova, A.R. Rekstin, E.A. Bazhenova, D.N. Magazenkova, I.A. Orlov, L.G. Rudenko, M. Broggin, L.V. Puchkova, Anti-Influenza Effect of Nanosilver in a Mouse Model, *Vaccines*, 2020, vol. 8, no. 4, art. no. 679.
- [13] H. Almanza-Reyes, S. Moreno, I. Plascencia-López, et al., Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: In vitro and in vivo, *PLoS One*, 2021, vol. 16, no. 8, art. no. e0256401.
- [14] L. Wieler, O. Vittos, N. Mukherjee, S. Sarkar, Reduction in the COVID-19 pneumonia case fatality rate by silver nanoparticles: A randomized case study, *Heliyon*, 2023, vol. 9, no. 3, art. no. e14419.

- [15] S. Lutsenko, S. Roy, P. Tsvetkov, Mammalian copper homeostasis: physiological roles and molecular mechanisms, *Physiol. Rev.*, 2025, vol. 105, no. 1, pp. 441–491.
- [16] A. Członkowska, T. Litwin, P. Dusek, P. Ferenci, S. Lutsenko, V. Medici, J.K. Rybakowski, K.H. Weiss, M.L. Schilsky, Wilson disease, *Nat. Rev. Dis. Primers*, 2018, vol. 4, art. no. 21.
- [17] F. Catalano, T.J. O'Brien, A.A. Mekhova, et al., A new *Caenorhabditis elegans* model to study copper toxicity in Wilson disease, *Traffic*, 2024, vol. 25, no. 1, art. no. e12920.
- [18] V.A. Ohse, L.O. Klotz, J. Priebs, Copper Homeostasis in the Model Organism *C. elegans*, *Cells*, 2024, vol. 13, no. 9, art. no. 727.
- [19] E.J. Ge, A.I. Bush, A. Casini, et al., Connecting copper and cancer: from transition metal signalling to metalloplasia, *Nat. Rev. Cancer*, 2022, vol. 22, no. 2, pp. 102–113.
- [20] D.N. Magazenkova, E.A. Skomorokhova, M. Al Farroukh, M.S. Zharkova, Z.M. Jassem, V.E. Rekina, O.V. Shamova, L.V. Puchkova, E.Y. Ilyechova, Influence of Silver Nanoparticles on the Growth of Ascitic and Solid Ehrlich Adenocarcinoma: Focus on Copper Metabolism, *Pharmaceutics*, 2023, vol. 15, no. 4, art. no. 1099.
- [21] C.A. Owen, H. Smith, Detection of ceruloplasmin after zone electrophoresis, *Clin. Chim. Acta*, 1961, vol. 6, no. 5, pp. 441–444.
- [22] Y. Choi, H.A. Kim, K.W. Kim, B.T. Lee, Comparative toxicity of silver nanoparticles and silver ions to *Escherichia coli*, *J. Environ. Sci.*, 2018, vol. 66, pp. 50–60.
- [23] A. Wamuch, J. Unrine, J. May, O. Tsyusko, Global DNA Adenine Methylation in *Caenorhabditis elegans* after Multigenerational Exposure to Silver Nanoparticles and Silver Nitrate, *Int. J. Mol. Sci.*, 2023, vol. 24, no. 7, art. no. 6168.
- [24] C.L. Schultz, A. Wamuch, O.V. Tsyusko, J.M. Unrine, A. Crossley, C. Svendsen, D.J. Spurgeon, Multigenerational exposure to silver ions and silver nanoparticles reveals heightened sensitivity and epigenetic memory in *Caenorhabditis elegans*, *Proc. R. Soc. B: Biol. Sci.*, 2016, vol. 283, no. 1832, art. no. 20152911.
- [25] P.S. Babich, A.N. Skvortsov, P. Rusconi, N.V. Tsymbalenko, M. Mutanen, L.V. Puchkova, M. Brogini, Non-hepatic tumors change the activity of genes encoding copper trafficking proteins in the liver, *Cancer Biol. Ther.*, 2013, vol. 14, no. 7, pp. 614–624.
- [26] C. Recordati, M. De Maglie, S. Bianchessi, et al., Tissue distribution and acute toxicity of silver after single intravenous administration in mice: nano-specific and size-dependent effects, *Part. Fibre Toxicol.*, 2016, vol. 13, art. no. 12.
- [27] A. Sibiya, N. Gopi, J. Jeyavani, S. Mahboob, K.A. Al-Ghanim, S. Sultana, A. Mustafa, M. Govindarajan, B. Vaseeharan, Comparative toxicity of silver nanoparticles and silver nitrate in freshwater fish *Oreochromis mossambicus*: A multi-biomarker approach, *Comp. Biochem. Physiol. C: Toxicol. Pharmacol.*, 2022, vol. 259, art. no. 109391.