JMBFS
Journal of Microbiology, Biotechnology and Food Sciences
International peer-reviewed scientific online journal
Published by Faculty of Biotechnology and Food Sciences

DEVELOPMENT AND APPLICATION OF ZINC NANOPARTICLES IN THE MEDICAL FIELD

Iveta Urban[1], Nikola Štefunková[1], Klaudia Jaszcza[2], Peter Massányi[1]*

Address(es):
[1] Slovak University of Agriculture in Nitra, Faculty of Biotechnology and Food Sciences, Institute of Applied Biology, Trieda Andreja Hlinku 2, 94976 Nitra, +421 37 641 4284.
[2] University of Agriculture in Krakow, Faculty of Animal Science, Department of Animal Physiology and Endocrinology, al. Mickiewicza 24/28, 30-059 Krakow, Poland.

*Corresponding author: nikola.stefunkova@uniag.sk

https://doi.org/10.55251/jmbfs.11061

ARTICLE INFO

Received 22. 2. 2024
Revised 23. 5. 2024
Accepted 27. 5. 2024
Published 1. 8. 2024

Review

OPEN ACCESS

ABSTRACT

Over the course of the last 10 years, there has been a significant amount of advancement in the subject of nanotechnology, which has demonstrated a great deal of potential not only in the realm of technological fields but also in the realm of medical research. It is possible to see a broad variety of uses for zinc oxide nanoparticles (ZnO-NPs) in the field of cancer research, which is being conducted using nanotechnology. Despite the fact that scientific knowledge is continually expanding in terms of its comprehension of the molecular foundation of cancer cells, the number of people who are diagnosed with cancer continues to rise. The World Health Organisation (WHO) forecasted that the number of cancer cases will rapidly rise over the following ten years.
ZnO-NPs have established themselves as a viable option for the treatment of cancer as a result of their capacity to trigger apoptosis in cancer cells. Due to the fact that ZnO nanoparticles have been shown to have anticancer, antibacterial, anti-diabetic, and anti-inflammatory activities, they have garnered a lot of interest in the field of biomedicine. The purpose of this study is to provide a summary of the recent research that have been conducted on the application of ZnO-NPS in the medical field.

Keywords: Zinc oxide, nanoparticles, cancer cells, research, medicine

INTRODUCTION

The domains of nanoscience and nanotechnology provide an immense amount of potential in an array of cancer research sectors, involving diagnostics, monitoring, and therapeutic solutions. It appears that the features of biosynthesis and the therapeutic potential of ZnO-NPs might pave the way for additional research on the creation of green synthesis agents for treatment, particularly in the area of nanomedicine, for the purpose of administering cancer treatment.
Nanotechnology offers the controlled synthesis of materials with at least one dimension of the structure that is fewer than 100 nanometers, which is one of the reasons why there is such a keen interest in this field of study. The size of these extremely small particles is equivalent to the proteins and biomolecules that exist naturally within the cell **(McNeil, 2005)**. Furthermore, it is far smaller than the normal diameter of many human cells, which is around 7 µm. Multiple cell lines have been subject to studies that have proven the beneficial impacts of nanoparticles made of ZnO, such as triggering cell death, oxidative stress, and genotoxicity **(Rasmussen *et al*, 2010)**. Zinc, known as a trace element that's essential to the body, can be found in all of the body's tissues and plays an essential role in the creation of proteins and nucleic acids, as well as in the process of hematopoiesis and neurogenesis. The nano-version of ZnO makes it easier for the human body to absorb zinc **(Ruszkiewicz *et al.*, 2017)**.

THE THERAPEUTIC VALUE OF NANOPARTICLES MADE OF ZINC OXIDE IN THE FIELD OF MEDICAL RESEARCH

Antimicrobial Activity of Zinc Oxide Nanoparticles

Through their ability to penetrate the cell membrane, ZnO-NPs have been shown to have antibacterial effects and to impede the replication of pathogens. The above is a fact that is properly acknowledged. Additionally, there is damage inflicted to DNA, lipids, carbohydrates, and proteins as a consequence of oxidative stress triggered by ZnO-NPs. There is an abundance of hypotheses explaining the mechanism through which ZnO-NPs are pathogenic (Fig. 1, **Mohd Yusof *et al.*, 2019**). They have been shown to have the ability to generate an excessive amount of reactive oxygen species (ROS), including superoxide anion, hydroxyl radicals, and hydrogen peroxide. This theory has been broadly accepted across the world of science **(Zhang and Xiong, 2015)**. There is also the possibility that ZnO-NPs may accumulate in the cytoplasm or the cell membrane, which will lead to the disintegration of the cell and the destruction of the proteins, eventually resulting in the death of the bacterial cells **(Shi *et al.*, 2014)**. The particular cytotoxic impact may be demonstrated in a wide range of gram-negative bacteria (such as *E. coli* and *Pseudomonas aeruginosa*) and gram-positive bacteria (such as *S. aureus and Bacillus subtilis*) **(Dutta *et al.*, 2013)**. There is a significant amount of continuing conversation over the processes that ZnO-NPs use to combat germs. The hypothesis that cytotoxicity is generated by affecting the membrane integrity through direct contact with the phospholipid layer is discussed in the study that was written by Jiang et al. **(2016)** The research additionally discusses the possibility that radical scavengers might be able to avoid the bactericidal activity of ZnO-NPs **(Reddy *et al.*, 2007)**.

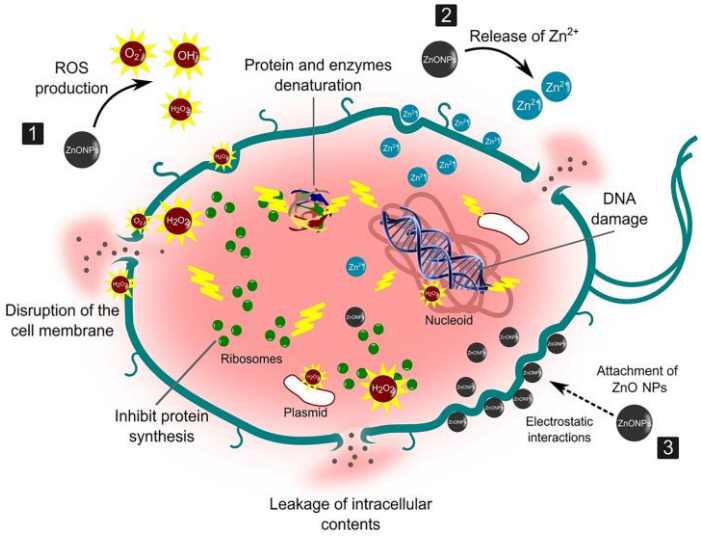

Figure 1 Schematic illustration of the antimicrobial mechanism of ZnO-NPs against bacterial cells. ZnO-NPs act as an antimicrobial agent through the following mechanisms: (1) the formation of reactive oxygen species (ROS), which induces oxidative stress and membrane and DNA damage, resulting in bacterial death; (2) dissolution of ZnO-NPs into Zn^{2+}, which interferes with enzyme, amino

acid, and protein metabolisms in bacterial cells; and (3) direct interaction between ZnO-NPs and cell membrane through electrostatic forces that damages the membrane plasma and causes intracellular content leaks (**Mohd Yusof *et al.*, 2019**)

The role of Zeno-NPs in cancer cells

It is common knowledge that cancer therapies are extremely challenging. With the help of nanoparticles, we are able to see enhanced efficacy of cancer treatments that are currently utilized, as well as improved bioavailability and drug stability, and an enhanced influence on the tissue **(Moghimi *et al.*, 2001; Fig. 2, Anjum *et al.*, 2021)**. ZnO-NPs have been proven to be one of the most effective agents since they are affordable to produce, they are non-toxic, and they have the capacity to release drugs in a programmed manner **(George *et al.*, 2019; Shetti *et al.*, 2019)**.

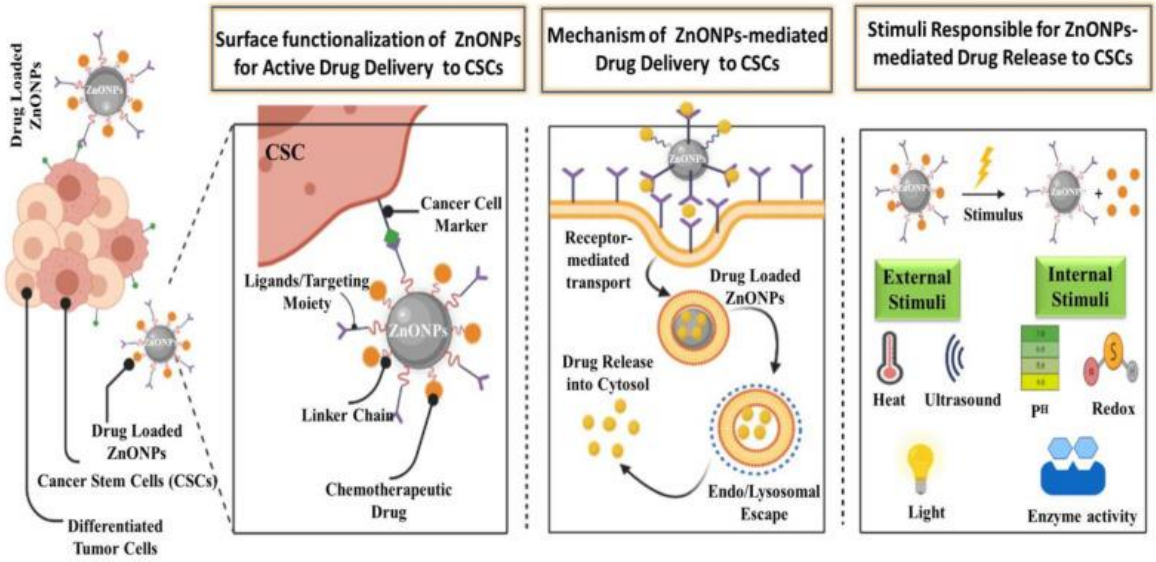

Figure 2 Graphical representation of the surface functionalization, mode of action, and various stimuli involved in the targeted delivery of anticancerous drugs to cancer stem cells (CSCs) via ZnO-NPs **, (Anjum *et al.*, 2021)**

Targeted drug therapy and the role of bioactive nanocomposites, green synthesis

A substantial number of studies are currently underway to explore new compounds in connection with ZnO-NPs. These studies aim to improve the efficacy of targeted treatment. Exploring the implications of conjugation of bioactive substances is one of the tasks that are being pursued. It was reported by Baskar et al. (2015) that treatment with ZnO-NPs conjugated with L-asparaginase led to a reduction of the viability of breast cancer cells to 35% **(Baskar *et al.*, 2015)**.

Green synthesized nanoparticles have demonstrated another thrilling potential. A study that was published by Namvar et al. (2016) demonstrated that the synthesis of ZnO-NPs via the algae *Sargasum muticum* and hyaluronan biopolymer provoked elevations in caspase 3/7 and cell cycle arrest in pancreatic, ovarian, and colorectal carcinoma. However, a non-pathological human lung fibroblast cell line did not exhibit any response or effect **(Namvar *et al.*, 2016)**.

Curcumin, a substance that is well-known for its potential impact on the treatment of various illnesses owing to its anti-inflammatory and anti-cancer effects, could offer a further chance for improvement in the field of medical research. Plain curcumin has unfavorable physical properties such as poor water solubility and bioavailability. Researchers Dhivya et al. **(2017)** developed a nanocomposite that was loaded with curcumin and ZnO-NPs. This nanocomposite was able to boost the bioavailability of curcumin in gastric cancer cells.

Nanotechnology has gained more attention due to its cutting-edge nature and wide-ranging applications in almost all fields of science and technology, including the biomedical sciences. In general, nanoparticles (NPs) are produced by several chemical and physical methods, which are quite expensive and pose a risk to the environment and human health (**Mahmoud *et al.*, 2019).**

A green and simple way to synthesize NPs using plants is becoming more and more popular; they facilitate the large-scale production of nanoparticles of different shapes and sizes. Using natural plant extracts is environmentally friendly, simple, and presents a cost-effective approach. There are many ongoing studies investigating the green synthesis of ZnO-NPs. Nail et al. **(2022)** reported the effectiveness of an aqueous extract of sea lavender, *Limonium pruinosum*, leading to the successful synthesis of ZnO-NPs showing significant antimicrobial activity compared to gentamicin and comparable antioxidant activity. In addition, NPs synthesized via the green route are biocompatible and do not contain toxic stabilizers compared to classical chemicals. Essentially, plant extracts contain various active biomolecules that help reduce and stabilize NPs **(Nilavukkarasi *et al.*, 2020)**.

Another antibacterial analysis revealed that ZnO-NPs synthesized from leaf extracts showed a significant ability to inhibit clinical pathogens compared to traditional drugs. In addition, some plant extracts are more effective than others in synthesizing NPs and their biological activities due to their diverse biochemical compositions (**Naseer *et al.*, 2020)**. Using ZnO-NPs biosynthesized with an aqueous solution of *Cymbopogon citratus* leaf extract, it showed significant antibacterial activity against both G(+) *S. aureus* and G(−) *P. aeruginosa* and excellent fungicidal activity against the plant pathogenic fungus *Aspergillus niger* **(Abdelbaky *et al.*, 2023)**. The green synthesis of ZnO-NPs using plant extracts as a capping and reducing agent shows promise for potential applications of these particles in biomedicine. However, toxicity evaluation is necessary to ensure the safety of humans and the environment. Several studies used zebrafish, thanks to their rapid embryonic development and similar physiological response to humans, to investigate the toxicity of ZnO-NPs **(Lee *et al.*, 2017)**. Research investigating negative assessments of ZnO-NPs in an in vivo study using the zebrafish model, observed embryo malformations, a lack of pigmentation, cardiotoxicity, and deformities **(Dmochowska *et al.*, 2020)**. The main pathophysiologic mechanism discussed is the production of ROS, leading to the induction of inflammatory cytokines and activation of macrophages and neutrophils **(Rosowski *et al.*, 2020)**. The impact of ZnO-NPs depends on many factors, such as size, exposure time, and concentration of particles. More investigation is needed to calculate and assess potential environmental hazards. There are a lot of unanswered questions due to increasing exposure and possible bioaccumulation, that need to be solved and the legal consequences have to be set.

Chemodynamic therapy

The complexity of treating oncological diseases presents new challenges leading to the demand for the development of innovative techniques, protocols, and technology. Chemodynamic therapy (CDT) is a compelling topic of modern research. Cancer cells frequently demonstrate a unique tumor microenvironment (TME) characterized by an acidic pH, increased levels of hydrogen peroxide, and dysregulation of growth factor and tumor repression genes. Chemodynamic therapy (CDT) is a tumor-specific, noninvasive treatment with low toxicity that is increasingly becoming incorporated into established therapeutic approaches like surgery, chemotherapy, or radiation. The presence of glutathione (GSH), a type of antioxidant, plays an essential role in cancer cells, which have significantly higher concentration levels of GSH than normal cells. Overexpression of GSH promotes tumor expansion, eliminates reactive oxygen species (ROS), and decreases the efficacy of chemotherapy drugs (CDT) **(Fu *et al.*, 2021; Xiong *et al.*, 2021)**. Dong et al. **(2023)** presented remarkable discoveries in the realm of CDT by creating a therapeutic drug using Zn-Cu nanoparticles (Zn-Cu-NPs). They demonstrated a decrease of GSH over-expression via reducing Cu^{2+} to Cu^{+} through contact with GSH in the tumor microenvironment (TME), demonstrating the capability to produce hydroxyl radicals (OH) from hydrogen peroxide (H_2O_2) through Fenton-like reactions. *In vivo* studies demonstrated the TME response to Zn-Cu-NPs, proving efficacy in applications such as suppressing lung cancer cells. Cost-effectiveness in synthesis, exceptional biocompatibility, and efficacy as an anti-cancer treatment were also highlighted.

The role of ZnO-NPs in targeting and sensitizing MDR cancer cells

Chemotherapy, a commonly used treatment for cancer patients, continues to face challenges in overcoming multidrug resistance (MDR), a major factor contributing to treatment failure, despite advancements in research. MDR creates a significant obstacle in cancer therapy. Pluchino et al. **(2012**) found that over ninety percent of treatment failures have been attributed to MDR in multiple ways. Plenty of researchers have a special interest in addressing the issue of "collateral damage" caused by chemotherapy. Various mechanisms of multidrug resistance (MDR) have been intensively debated over the years. These involve oncogene mutations, overexpression of transport proteins, alterations in drug metabolism, activation of anti-apoptotic proteins, and others. Robey et al**. (2018)** demonstrated that the ATP binding cassette operates as a transporter protein on the cell membrane, which leads to efflux drug resistance. The following occurs when ATP hydrolysis provides the energy to pump intracellular medicines out of the cell, resulting in decreased intracellular drug concentration.

In recent years, nanomedicine has demonstrated highly promising outcomes in oncological therapy. Utilizing nanoparticle-based drug delivery systems (NDDS) for tumor-targeted medication delivery is a novel method of drug administration. Chemotherapeutic medicines carried by the NDDS can enhance cellular absorption, prevent drug removal, and alter drug release by accumulating in cancer cells **(Liu *et al.*, 2022; Su *et al.*, 2022)**. Another benefit of using NDDS is to take advantage of the improved penetration and retention impact on certain tumor cells. A variety of nanoparticles are being explored for their role in the development of novel drug delivery systems. Zinc oxide nanoparticles possess potential in drug delivery, imaging, and treating various cancerous and non-cancerous diseases. Internal dissolution of ZnO-NPs leads to the release of Zn^{2+} ions, which can generate reactive oxygen species (ROS), disrupt mitochondrial function, increase oxidative stress, and ultimately trigger apoptosis **(Guo *et al.*, 2008)**.

Several obstacles are associated with the application of plain ZnO-NPs, such as their nonspecific distribution and their various interactions with cell membranes to emerge smart tumor-targeting. Zhou et al. (2023) showed promising results with developing matrix metalloproteinase 2 (MMP2) and pH dual-responsive ZnO-based particles using DOX against MDR cancer **(Fig. 3, Zhou *et al.*, 2023).** By targeting cancer cells that are susceptible to MMP2, it was possible to achieve increased cellular uptake, drug release within tumor cells, and success in overcoming the MDR. As a result, anticancer activity was increased, and the negative adverse effects of plain ZnO-NPs were reduced **(Zhou *et al.*, 2023)**.

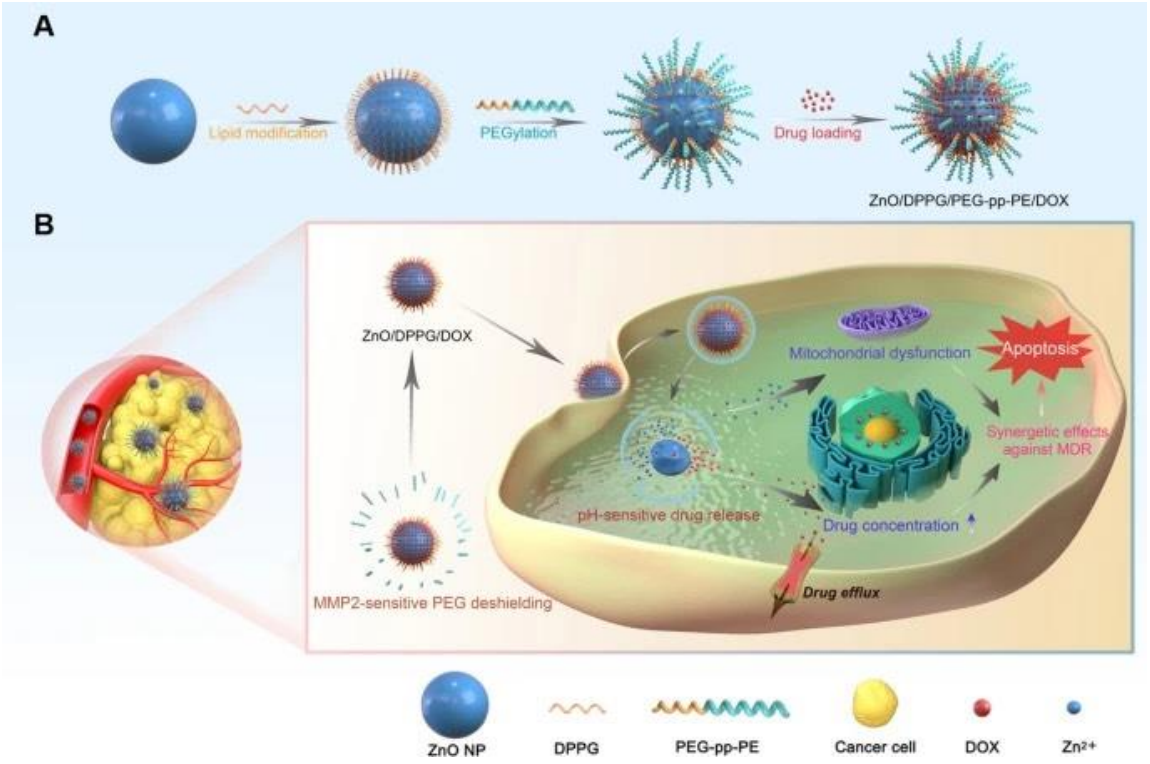

Figure 3 A Preparation of the ZnO/DPPG/PEG-pp-PE/DOX NPs. B Schematic illustration of the MMP2 and pH dual-responsive ZnO-based polymer-lipid hybrid nanoparticles for tumor-targeted drug delivery and MDR cancer treatment (**Zhou *et al.*, 2023).**

Tumor imaging

When it comes to the subject of tumor imaging, nanotechnology is also bringing forward new possibilities. Several cancer-specific modalities have evolved and become more successful, but the remaining trouble is the detection of early-stage cancer. Diagnostic techniques that are applied nowadays, such as magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET), are effective methods for diagnosing cancer **(Antoch *et al.*, 2003)**. A large number of scientists have taken an interest in the optimal physical characteristics of NPs. Promising results in tumor tracking using NPs have been reported, which can be attributed to the unusual size, structure, biocompatibility, and luminescence of the material **(Chen *et al.*, 2013)**. An increasing number of experiments are being carried out in the field of biomedical research to investigate luminous NPs. As a result of their exceptional physical qualities, which include great photostability and minimal toxicity, they are regarded as the most effective instruments for bioimaging. Wanas et al. (2023) have successfully synthesized a nanocomposite consisting of graphene, folic acid, and zinc oxide (GN/FA-ZnO) that exhibits dual-mode emissions, including down-conversion and up-conversion. Improvements in electron transfer and conductivity were made possible as a result of the interaction between ZnO-NPs and GN, which led to the development of an optical transfer capability for application in bioimaging applications **(Ebnalwaled *et al.*, 2019)**. *In vivo*, bioimaging experiment with tumor-bearing mice, Swiss albino mice inoculated with diluted Ehrlich ascites carcinoma tumor cells, demonstrated that the position of fluorescence was found in the tumor cells in the mice-group that was injected with GN/FA-ZnO nanocomposite **(Fig. 4, Wanas *et al.*, 2023)**. This finding lends support to the concept of using GN-FA-ZnO nanocomposites for *in vivo* tumor targeting.

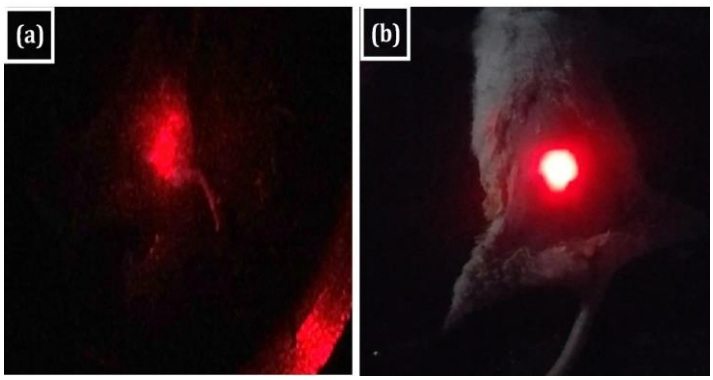

Figure 4 *In vivo* bioimaging of mice at 630 nm excitation wavelength: (a) bioimaging of control group; (b) bioimaging using 10% GN/FA-ZnO nanocomposite (**Wanas *et al.*, 2023).**

CONCLUSION

New anti-cancer drugs that have a greater capacity for attacking cancer cells while preserving normal cells and tissues have to be developed as soon as possible.
Recent years have seen a rise in the focus placed on nanomaterials and the effective application of these materials in cancer treatment regimens. ZnO and other metal oxide nanoparticles are starting to show their potential, and this realization is only beginning. The use of nanomedicine, including utilizing ZnO-NPs, has a great deal of future potential in this area. ZnO-NPs are thought to possess highly promising features as novel anticancer agents. On the other hand, many questions remain unanswered about the mechanism by which ZnO-NPs cause cytotoxicity.
The dual-responsive ZnO-based nanomedicine shows potential for targeted drug delivery and therapy of multidrug-resistant (MDR) cancer. To improve the therapeutic efficiency of CDT, metal-based nanoparticles (NPs) with pH-responsive ZnO-NPs exhibit high biocompatibility and durability. Furthermore, *in vivo* experiments indicated that Zn-Cu-NPs could successfully prevent the growth of tumors.

Acknowledgments: This research was funded by Scientific Agency of the Slovak Republic VEGA No. 1/0083/21, VEGA No. 1/0207/23, by the Slovak Research and Development Agency Grant APVV-21-0168, APVV-20-0218, APVV-19-0243, APVV-16-0289 and by the Cultural and educational grant agency KEGA023SPU-4/2022.

REFERENCES

Abdelbaky, A.S., Mohamed, A.M.H.A., Sharaky, M. et al. (2023) Green approach for the synthesis of ZnO nanoparticles using Cymbopogon citratus aqueous leaf extract: characterization and evaluation of their biological activities. Chem. Biol. Technol. Agric. 10, 63 https://dx.doi.org/10.1186/s40538-023-00432-5
Anjum, S.; Hashim, M.; Malik, S.A.; Khan, M.; Lorenzo, J.M.; Abbasi, B.H.; Hano, C. (2021). Recent Advances in Zinc Oxide Nanoparticles (ZnO NPs) for Cancer Diagnosis, Target Drug Delivery, and Treatment. *Cancers*, 13, 4570. https://dx.doi.org/10.3390/cancers13184570
Antoch, G., Vogt, F.M., Freudenberg, L.S., Nazaradeh, F., Goehde, S.C., Barkhausen, J., Dahmen, G., Bockisch, A., Debatin, J.F., Ruehm, S.G. (2003). Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. *Jama* 290, 3199–3206. http://dx.doi.org/ 10.1001/jama.290.24.3199
Baskar G., Chandhuru J., Fahad K.S., Praveen A., Chamundeeswari M., Muthukumar T. (2015). Anticancer activity of fungal L-asparaginase conjugated with zinc oxide nanoparticles. *J. Mater. Sci. Mater. Med*.;26:43. http://dx.doi.org/10.1007/s10856-015-5380-z
Chen, H., Zhen, Z., Todd, T., Chu, P. K. & Xie, J. (2013). Nanoparticles for improving cancer diagnosis. *Mat. Sci. Eng. R.* 74, 35–69. http://dx.doi.org/ 10.1016/j.mser.2013.03.001
Dhivya R., Ranjani J., Bowen P.K., Rajendhran J., Mayandi J., Annaraj J. (2017). Biocompatible curcumin loaded PMMA-PEG/ZnO nanocomposite induce apoptosis and cytotoxicity in human gastric cancer cells. *Mater. Sci. Eng. C. 80:59–68.* http://dx.doi.org/10.1016/j.msec..05.128
Dmochowska A., Czajkowska J., Jędrzejewski R., Stawiński W., Migdał P., Fiedot-Toboła M. (2020). Pectin based banana peel extract as a stabilizing agent in zinc oxide nanoparticles synthesis. Int J Biol Macromol. 165:1581–1592. http://dx.doi.org/10.1016/j.ijbiomac.2020.10.042
Dong, Z. Z., Yang, C., Wang, Z., Zhong, Z., Wong, M.S., Li, H.W. (2023). Tumor microenvironment-responsive Zn/Cu nanoparticles for enhanced chemodynamic therapy, *Smart Materials in Medicine*, Volume 4, Pages 286-293, ISSN 2590-1834, https://dx.doi.org/10.1016/j.smaim.2022.11.002
Dutta, R. K., Nenavathu, B. P., Gangishetty, M.K., Reddy, A.R. (2013). Antibacterial effect of chronic exposure of low concentration ZnO nanoparticles on E. coli. *Journal of Environmental Science and Health: Part A, vol. 48, no. 8, pp. 871–878.* http://dx.doi.org/10.1080/10934529.2013.761489
Ebnalwaled A., Abu El-Fadl A., Tuhamy M. (2019). Synthesis and characterization of reduced graphene oxide/zinc oxide nanocomposite. *Assiut Univ. J. Phys*. 48(2), 45–69. http://dx.doi.org/ 10.21608/AUNJ.2019.221107
Fu, L., Wan, L., Qi, C., He, J., Li, C., Yang, C., Xu, H., Lin, J.,Huang, P. (2021). Nanocatalytic theranostics with glutathione depletion and enhanced reactive oxygen species generation for efficient cancer therapy *Adv. Mater., 33* (7) , Article 2006892. https://dx.doi.org/10.1002/adma.202006892
George D., Maheswari P.U., Begum K.M.S. (2019). Synergic formulation of onion peel quercetin loaded chitosan-cellulose hydrogel with green zinc oxide nanoparticles towards controlled release, biocompatibility, antimicrobial and anticancer activity. *Int. J. Biol. Macromol. 132:784–794.* http://dx.doi.org/10.1016/j.ijbiomac.2019.04.008
Guo, D., Wu, C., Jiang, H., Li, Q., Wang, X., Chen, B. (2008). Synergistic cytotoxic effect of different sized ZnO nanoparticles and daunorubicin against leukemia cancer cells under UV irradiation. *J Photochem Photobiol B, Biol* 93(3):119–126. http://dx.doi.org/10.1016/j.jphotobiol.2008.07.009
https://dx.doi.org/10.1016/j.ijbiomac.2020.10.042
Jiang, Y., Zhang, L., Wen, D., Ding, Y. (2016). Role of physical and chemical interactions in the antibacterial behavior of ZnO nanoparticles against E. coli. *Materials Science and Engineering: C, vol. 69, pp. 1361–1366.* https://dx.doi.org/10.1016/j.msec.2016.08.044
Lee KY, Jang GH, Byun CH, Jeun M, Searson PC and Lee KH: Zebrafish models for functional and toxicological screening of nanoscale drug delivery systems: Promoting preclinical applications. Biosci Rep. 37(BSR20170199)2017. https://dx.doi.org/10.1042/BSR20170199
Liu, Y., Zhang, J., Tu, Y., Zhu, L. (2022). Potential-independent intracellular drug delivery and mitochondrial targeting. *ACS Nano* 16(1):1409–1420. http://dx.doi.org/10.1021/acsnano.1c09456
Mahmoud, A.E.D. ,Fawzy, M. (2021) Nanosensors and nanobiosensors for monitoring the environmental pollutants. Top. Min. Metallurg. Mater. Eng. https://doi.org/10.1007/978-3-030-68031-2_9
McNeil, SE. (2005). Nanotechnology for the biologist. *J Leukoc Biol.Sep;78(3):585-94.* http://dx.doi.org/ 10.1189/jlb.0205074
Moghimi S.M., Hunter A.C., Murray J.C. (2001). Long-circulating and target-specific nanoparticles: Theory to practice. *Pharmacol. Rev. 53:283–318.*
Mohd Yusof, H., Mohamad, R., Zaidan, U.H. et al. (2019). Microbial synthesis of zinc oxide nanoparticles and their potential application as an antimicrobial agent and a feed supplement in animal industry: a review. *J Animal Sci Biotechnol 10, 57,* https://dx.doi.org/10.1186/s40104-019-0368-z
Naiel, B., Fawzy, M., Halmy, M.W.A. et al. (2022) Green synthesis of zinc oxide nanoparticles using Sea Lavender (Limonium pruinosum L. Chaz.) extract: characterization, evaluation of anti-skin cancer, antimicrobial and antioxidant potentials. Sci Rep 12, 20370 https://dx.doi.org/10.1038/s41598-022-24805-2
Namvar F., Azizi S., Rahman H.S., Mohamad R., Rasedee A., Soltani M., Rahim R.A. (2016). Green synthesis, characterization, and anticancer activity of hyaluronan/zinc oxide nanocomposite. Oncotargets Ther.;9:4549. https://dx.doi.org/10.2147/OTT.S95962
Naseer, M., Aslam, U., Khalid, B. et al. (2020) Green route to synthesize Zinc Oxide Nanoparticles using leaf extracts of Cassia fistula and Melia azadarach and their antibacterial potential. Sci Rep 10, 9055 https://dx.doi.org/10.1038/s41598-020-65949-3
Nilavukkarasi M., Vijayakumar S., Prathipkumar S. Capparis zeylanica mediated bio-synthesized ZnO nanoparticles as antimicrobial photocatalytic and anti-cancer applications. Mater. Sci. Technol. 2020;3:335–343 https://dx.doi.org/10.1016/j.mset.2019.12.004
Pluchino, K.M., Hall, M.D., Goldsborough, A.S., Callaghan, R., Gottesman, M.M. (2012). Collateral sensitivity as a strategy against cancer multidrug resistance. Drug Resist Updat 15(1–2):98–10513. https://dx.doi.org/10.1016/j.smaim.2022.11.002
Rasmussen JW, Martinez E, Louka P, Wingett DG. (2010) Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. *Expert Opin Drug Deliv. Sep;7(9):1063-77.* http://dx.doi.org/10.1517/17425247.2010.502560
Reddy, K. M., Feris, K., Bell, J., Wingett, D.G., Hanley, C., Punnoose, A. (2007). Selective toxicity of zinc oxide nanoparticles to prokaryotic and eukaryotic systems. *Applied Physics Letters, vol. 90, no. 21, article 213902* http://dx.doi.org/10.1063/1.2742324
Robey, R.W., Pluchino, K.M., Hall, M.D., Fojo, A.T., Bates, S.E., Gottesman, M.M. (2018). Revisiting the role of ABC transporters in multidrug-resistant cancer. Nat Rev Cancer 18(7):452–464. http://dx.doi.org/10.1038/s41568-018-0005-8
Rosowski E.E: (2020). Determining macrophage versus neutrophil contributions to innate immunity using larval zebrafish. Dis Model Mech. 13(dmm041889). https://dx.doi.org/10.1242/dmm.041889
Ruszkiewicz, J.A., Pinkas, A., Ferrer, B., Peres, T.V., Tsatsakis, A., Aschner, M. (2017). Neurotoxic effect of active ingredients in sunscreen products, a contemporary review. *Toxicology Reports, vol. 4, pp. 245–259.* http://dx.doi.org/10.1016/j.toxrep.2017.05.006
Shetti N.P., Malode S.J., Nayak D.S., Bagihalli G.B., Kalanur S.S., Malladi R.S., Reddy C.V., Aminabhavi T.M., Reddy K.R. (2019). Fabrication of ZnO nanoparticles modified sensor for electrochemical oxidation of methdilazine. *Appl. Surf. Sci 496:143656.* http://dx.doi.org/10.1016/j.apsusc.2019.143656
Shi, L.E., Li, Z.H., Zheng, W., Zhao, Y.F., Jin, Y.F., Tang, Z.X. (2014). Synthesis, antibacterial activity, antibacterial mechanism and food applications of ZnO nanoparticles. *Food Additives and Contaminants: Part A, vol. 31, no. 2, pp. 173–186.* http://dx.doi.org/10.1080/19440049.2013.865147
Su, Z., Dong, S., Zhao, S.C., Liu, K., Tan, Y., Jiang, X., Assaraf, Y.G., Qin, B., Chen, Z.S., Zou, C. (2022) Novel nanomedicines to overcome cancer multidrug resistance. *Drug Resist Updat* 58:100777. http://dx.doi.org/ 10.1016/j.drup.2021.100777
Wanas, W., Abd El-Karaem, S.A., Ebrahim, S. et al. (2023) Cancer bioimaging using dual mode luminescence of graphene/FA-ZnO nanocomposite based on novel green technique. Sci Rep 13, 27, https://dx.doi.org/10.1038/s41598-022-27111-z
Xiong, Y., Xiao, C., Li, Z., Yang, X. (2021).Engineering nanomedicine for glutathione depletion-augmented cancer therapy. *Chem. Soc. Rev.*, 50 , pp. 6013-6041. http://dx.doi.org/10.1039/d0cs00718h

Zhang, Z.Y., Xiong, H.M. (2015). Photoluminescent ZnO nanoparticles and their biological applications. *Materials, vol. 8, no. 6, pp. 3101–3127.* http://dx.doi.org/10.3390/ma8063101
Zhou, Q., Zhang, L., Li, Y. et al. (2023). Targeting and sensitizing MDR cancer by an MMP2 and pH dual-responsive ZnO-based nanomedicine. *Cancer Nano* 14, 56. http://dx.doi.org/10.1186/s12645-023-00205-7