

Nanotechnology Applied to the Treatment of Bladder Cancer: Zinc Oxide and Innovation in Public Health

Nanotecnologia Aplicada ao Tratamento do Câncer de Bexiga: Óxido de Zinco e Inovação em Saúde Pública
Nanotecnología Aplicada al Tratamiento del Cáncer de Vejiga: Óxido de Zinc e Innovación en Salud Pública

RESUMO

Objetivo: Avaliar a atividade antitumoral seletiva de uma nanoestrutura de óxido de zinco contra o câncer de bexiga. **Método:** O nanomaterial foi sintetizado por coprecipitação e caracterizado morfológicamente por microscopia eletrônica de varredura e de transmissão. A citotoxicidade foi avaliada em linhagens celulares de carcinoma de bexiga humano (T24) e fibroblastos renais normais (Vero). O mecanismo de morte celular foi investigado por meio de análise morfométrica nuclear. **Resultados:** O nanomaterial apresentou morfologia laminar. O ensaio de MTT demonstrou citotoxicidade seletiva significativa contra as células T24, com redução de aproximadamente 65% na viabilidade celular a $200 \mu\text{g mL}^{-1}$, mantendo baixa toxicidade em células Vero. A análise morfométrica nuclear indicou que o nanomaterial induz morte celular predominantemente por apoptose. **Conclusão:** A nanoestrutura laminar de óxido de zinco demonstrou potencial terapêutico promissor, alta atividade antitumoral seletiva e baixa toxicidade, o que apoia seu uso no desenvolvimento de tratamentos mais acessíveis para o câncer de bexiga.

DESCRIPTORIOS: Nanoestruturas; Neoplasias da Bexiga Urinária; Saúde Pública.

ABSTRACT

Objective: To evaluate the selective antitumor activity of a zinc oxide nanostructure against bladder cancer. **Method:** The nanomaterial was synthesized by coprecipitation and morphologically characterized by scanning and transmission electron microscopy. Cytotoxicity was evaluated in human bladder carcinoma cell lines (T24) and normal renal fibroblasts (Vero). The mechanism of cell death was investigated through nuclear morphometric analysis. **Results:** The nanomaterial exhibited a laminar morphology. The MTT assay demonstrated significant selective cytotoxicity against T24 cells, with approximately 65% reduction in cell viability at $200 \mu\text{g mL}^{-1}$, while maintaining low toxicity in Vero cells. Nuclear morphometric analysis indicated that the nanomaterial predominantly induces cell death by apoptosis. **Conclusion:** The laminar zinc oxide nanostructure demonstrated promising therapeutic potential, combining high selective antitumor activity and low toxicity, which supports its use in the development of more accessible treatments for bladder cancer.

DESCRIPTORS: Nanostructure; Urinary Bladder Neoplasms; Public Health.

RESUMEN

Objetivo: Evaluar la actividad antitumoral selectiva de una nanoestructura de óxido de zinc frente al cáncer de vejiga. **Método:** El nanomaterial se sintetizó mediante coprecipitación y se caracterizó por microscopía electrónica de barrido y de transmisión. La citotoxicidad se evaluó en células T24 (carcinoma de vejiga humano) y en fibroblastos renales normales (Vero). El mecanismo de muerte celular se analizó mediante morfometría nuclear. **Resultados:** El nanomaterial mostró morfología laminar y una citotoxicidad selectiva significativa frente a las células T24, con una reducción del 65 % en la viabilidad celular a $200 \mu\text{g mL}^{-1}$, manteniendo baja toxicidad en células Vero. El análisis nuclear evidenció apoptosis como vía predominante de muerte celular. **Conclusión:** La nanoestructura laminar de óxido de zinc presenta un alto potencial terapéutico, combinando eficacia antitumoral selectiva y baja toxicidad, lo que la posiciona como una alternativa prometedora para el desarrollo de tratamientos más accesibles contra el cáncer de vejiga.

DESCRIPTORIOS: Nanoestructuras; Neoplasias de la Vejiga Urinaria; Salud Pública.

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INTRODUCTION

Bladder cancer is a significant global public health problem, with high incidence and mortality rates. Classified as the thirteenth most lethal neoplasm, it is responsible for approximately 213,000 deaths worldwide ¹ in 2020. This complex disease involves multiple genetic, environmental, and lifestyle factors, presenting particular therapeutic challenges due to its high recurrence rate and potential for progression. ² In Brazil, it is one of the most prevalent urological neoplasms, with a significant impact on both the public and private healthcare systems. ³ Given this scenario, the search for new, effective, and less invasive therapeutic approaches becomes crucial to improving patient prognosis.

In this context, zinc oxide (ZnO) nanomaterials emerge as promising tools for cancer diagnosis and treatment. Their unique properties allow for functionalization to specifically target cancer cells, enabling both early detection and localized therapy. ⁴ The versatility of ZnO makes it viable for use in controlled drug delivery systems, increasing therapeutic efficacy and minimizing side effects ⁵, as well as in photodynamic therapy through the generation of reactive oxygen species. ⁶

Recent studies demonstrate that ZnO nanostructures exert selective toxicity against cancer cells, inducing apoptosis through multiple mechanisms. ⁷ This selectivity is attributed to its biocompatibility and ability to modulate specific biological responses. ⁸ Additionally, research with silver-doped ZnO ⁹ and functionalized with chitosan ¹⁰ have expanded their therapeutic potential.

The morphology of nanostructures is a critical factor for their biological activity. Different configurations, such as nanowires, nanoflakes, and nanotubes, exhibit distinctive properties that influence their interaction with biological systems. ¹¹ Zinc oxide nanowires stand out for their high surface area to volume ratio, making them ideal for biosensors and controlled release ¹², while nanoflakes exhibit an increased surface area, enhancing applications in photodynamic therapy. ¹³

Despite significant advances, a gap remains in the knowledge of how specific morphological variations in ZnO nanostructures influence their selective cytotoxicity in bladder cancer cells. Recent national and international studies point to the need for systematic investigations that correlate structure and biological activity for therapeutic optimization. ^{14,15}

Given this context, this study aims to evaluate the selective antitumor

activity of a zinc oxide nanostructure against bladder cancer.

METHOD

This is an *in vitro* experimental study for the development and biological evaluation of a zinc oxide (ZnO) nanostructure with selective antitumor activity against bladder cancer cells.

Synthesis and morphological characterization of the zinc oxide nanostructure:

The nanostructure was synthesized using a low-cost and scalable method, coprecipitation, following an adapted protocol with variations in parameters such as temperature and reaction time. ^{11,13} Morphological characterization was performed using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) ¹, allowing for the evaluation of particle shape, size, and distribution.

Cellular models and culture:

The T24 (human bladder carcinoma, ATCC) and Vero (African green monkey renal fibroblasts, ATCC) cell lines were used, cultured in RPMI and DMEM media, respectively, supplemented with 10% fetal bovine serum. The cells were maintained at 37 °C in a humidified atmosphere with 5% CO₂. ^{2,4}



Cytotoxicity assessment (MTT assay):

Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.^{5,6} T24 and Vero cells were seeded in 96-well plates and, after 24 h of adhesion, treated with ZnO-NB at concentrations of 25, 50, 100, and 200 $\mu\text{g mL}^{-1}$ for 24 h. The formazan crystals formed were solubilized with DMSO, and the absorbance was measured at 570 nm.

Analysis of the cell death mechanism (nuclear morphometry): To investigate the type of cell death, T24 cells treated with ZnO at concentrations of 25 and 50 $\mu\text{g mL}^{-1}$ for 24 h were fixed, stained with DAPI, and analyzed using a fluorescence microscope.^{7,10} As imagens foram processadas por software específico para quantificação de parâmetros morfométricos nucleares, permitindo classificar os núcleos como normais ou apoptóticos. The images were processed using specific software for quantifying nuclear morphometric parameters, allowing the nuclei to be classified as normal or apoptotic.

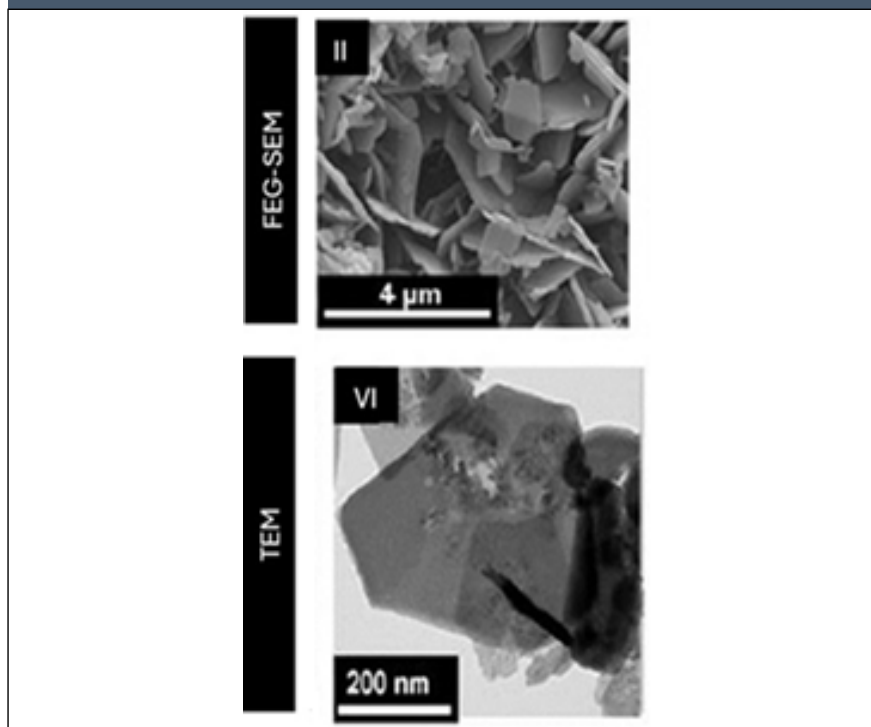
Statistical analysis:

All experiments were performed in independent triplicate. Data are presented as mean \pm standard deviation. Statistical analysis was conducted using one-way ANOVA, followed by Tukey's post-hoc test, considering p-values < 0.05 as statistically significant.

RESULTS

The morphological characterization of the nanomaterial obtained by FEG-SEM and TEM is presented in Figure 1. The nanostructure exhibited a sheet-like morphology with variable dimensions, confirming the formation of well-defined laminar structures.¹⁶

Figure 1. Representative micrographs of the zinc oxide nanostructure. Top image obtained by SEM (40,000 \times); bottom image obtained by TEM (35,000 \times).

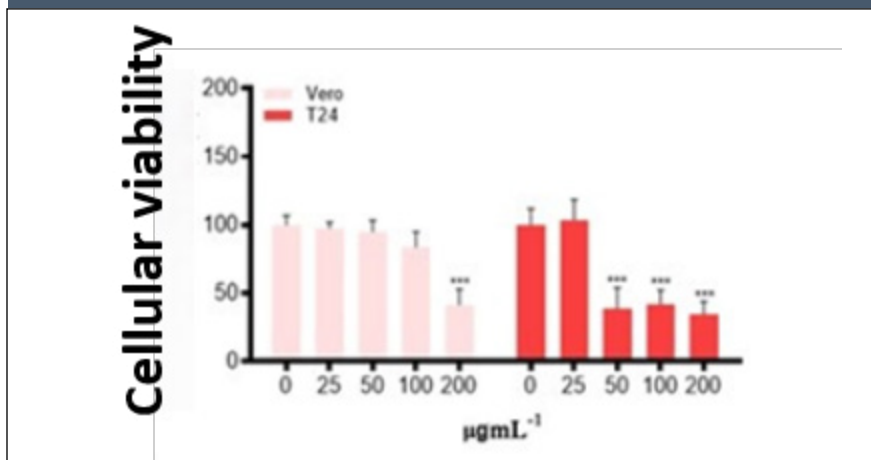


Source: prepared by the author.

The MTT assay (Figure 2) demonstrated that ZnO-NB exhibits selective cytotoxicity. In T24 (cancerous) cells, a significant and concentration-dependent inhibition of cell

viability was observed, reaching approximately 65% at 200 $\mu\text{g mL}^{-1}$. In contrast, toxicity to Vero (non-tumor) cells was significantly lower at the same concentration.^{17,18}

Figure 2. Effect of nanostructure on cell viability of Vero and T24 cell lines by MTT assay after 24 h. p < 0.05 (), p < 0.01 ().



Fonte: elaborada pela autora.

Nuclear morphometric analysis of T24 cells treated with ZnO (Figure 3) revealed a significant increase in the proportion of small and regular nu-

clei (73.8% at 50 $\mu\text{g mL}^{-1}$ vs. 2.6% in the control), a typical characteristic of apoptosis.³

velopment of accessible and effective nanotherapies against bladder cancer, aligning technological innovation and social impact.¹⁵

CONCLUSION

This study demonstrated that controlling morphology in the synthesis of zinc oxide nanostructures is an effective strategy for optimizing selective antitumor activity.¹⁶ The laminar nanostructure demonstrated a remarkable ability to induce apoptosis in bladder carcinoma cells (T24), while maintaining low toxicity in healthy cells (Vero).¹²

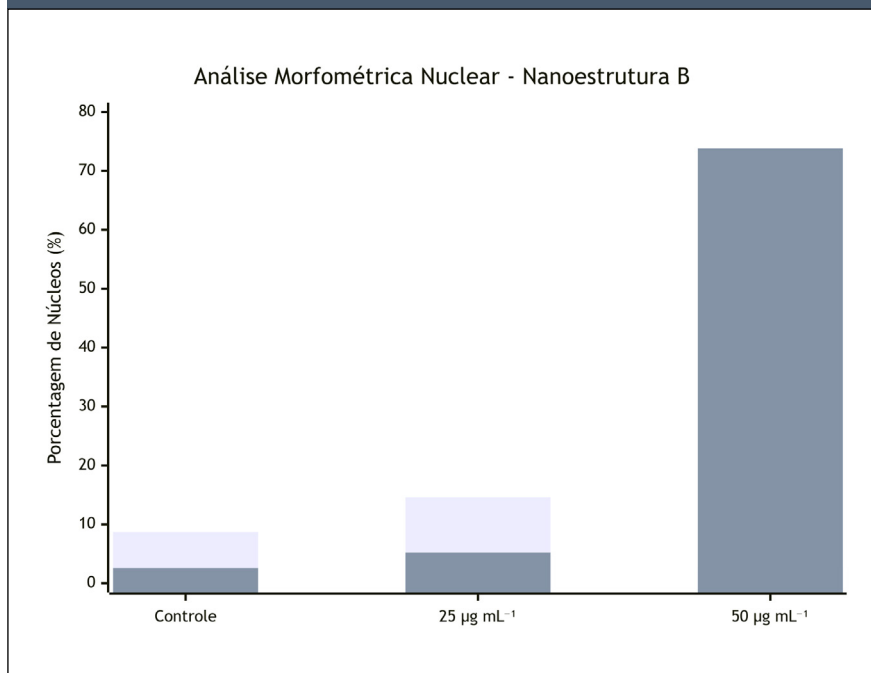
The results obtained validate the potential of the nanomaterial as a promising tool for the development of accessible nanotechnology therapies against bladder cancer.⁰⁶ The combination of antitumor efficacy, safety profile, and scalable synthesis method¹⁵ It reinforces its applicability in public health scenarios.

As future perspectives, it is recommended to validate the results in animal models and conduct cost-effectiveness studies to support the implementation of the technology in health systems, especially in middle- and low-income countries, where the impact of bladder cancer is more significant.^{7,8}

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Figure 3. Nuclear morphometric analysis of T24 cells treated with ZnO.



Source: prepared by the author.

DISCUSSION

The synthesis strategy employed proved effective in obtaining nanostructures with controlled architectures, confirming morphology as a determining factor in biological activity.¹⁶ The nanostructure with laminar morphology stood out for its superior cytotoxic selectivity profile, corroborating previous results that associate laminar shapes with greater interaction with biological systems and a better therapeutic response.¹²

Nuclear morphometric analysis reinforced the biological mechanism of selectivity by indicating apoptosis as the predominant pathway of cell death.⁰⁹ This finding is clinically relevant, since apoptosis is a process of programmed cell death that reduces unwanted inflammatory responses,

promoting better therapeutic tolerability.¹⁰

From a public health perspective, the nanomaterial presented a set of advantageous attributes: selective antitumor efficacy, low toxicity profile, and feasibility of synthesis using low-cost methods.⁰⁸ These factors are especially relevant in resource-limited settings, where bladder cancer imposes a high economic and social burden.⁰⁷

One limitation is the *in vitro* nature of the experiments, reinforcing the need for *in vivo* studies to evaluate systemic toxicity, pharmacokinetics, and biodistribution.¹⁴ Furthermore, cost-effectiveness analyses will be essential to estimate the feasibility of large-scale implementation.

Taken together, the findings of this study support the potential of nanotechnology as a basis for the de-

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