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Abstract

Cytotoxic Activity of Dendrimer Nanoparticles and Dendrimer Drugs Formulations on Human Neuroblastoma Cells: Our Recent Update †

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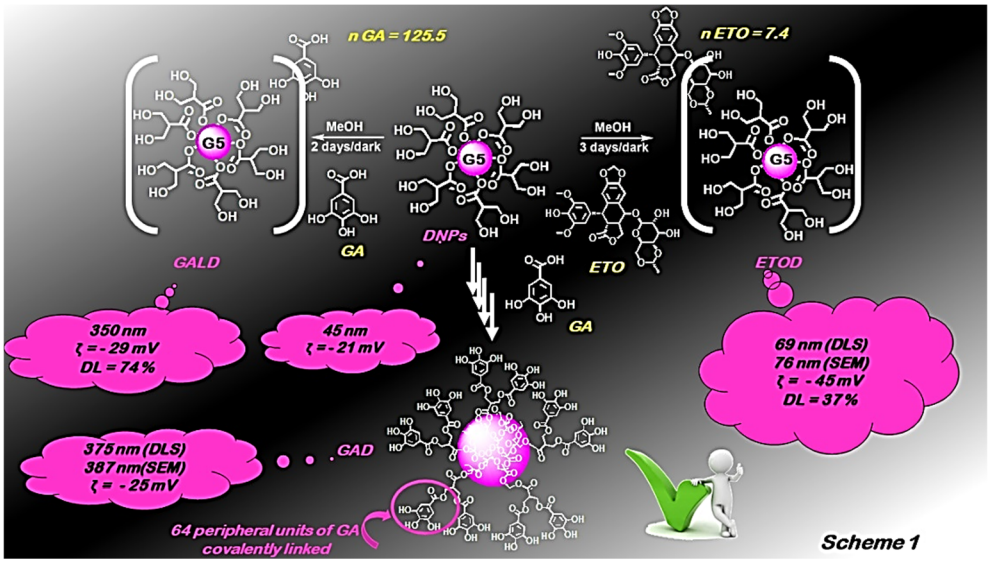
Human neuroblastoma (NB) is a pediatric tumor, which, after an initial response to therapy, usually develops resistance. Etoposide (ETO), which is a drug commonly used to clinically treat NB, exerts anticancer effects by increasing reactive oxygen species (ROS) generation [1,2]. Similarly, gallic acid (GA), although not specifically used in NB treatment, exerts pro-oxidant anti-cancer effects associated with low toxicity for healthy cells. Unfortunately, low stability, poor solubility, and unfavorable pharmacokinetics negatively influence ETO and GA efficacy [1,2]. To address GA and ETO issues, biodegradable dendrimer nanoparticles (DNPs) were prepared for entrapping ETO [2], as well as for encapsulating and covalently binding GA, obtaining the drugs-loaded dendrimers named ETO-dendrimer (ETOD), GA-loaded dendrimer (GALD), and GA-dendrimer (GAD) (Scheme 1) [1,2].



Scheme 1. Preparation of the drugs-loaded dendrimers named ETO-dendrimer (ETOD), GA-loaded dendrimer (GALD), and GA-dendrimer (GAD) [1,2].

The cytotoxic activity of DNPs, GA, ETOD, GALD, and GAD was tested on ETO-sensitive and ETO-resistant NB cells. Unexpectedly, DNPs were able to exert, per se, a ROS-mediated cytotoxic activity comparable to ETO on both cell populations. ETOD, combining DNPs and ETO, showed a synergistic action of the two molecules, a slow release of the drug and a significantly improved protracted bioactivity (Figure 1) [1,2].

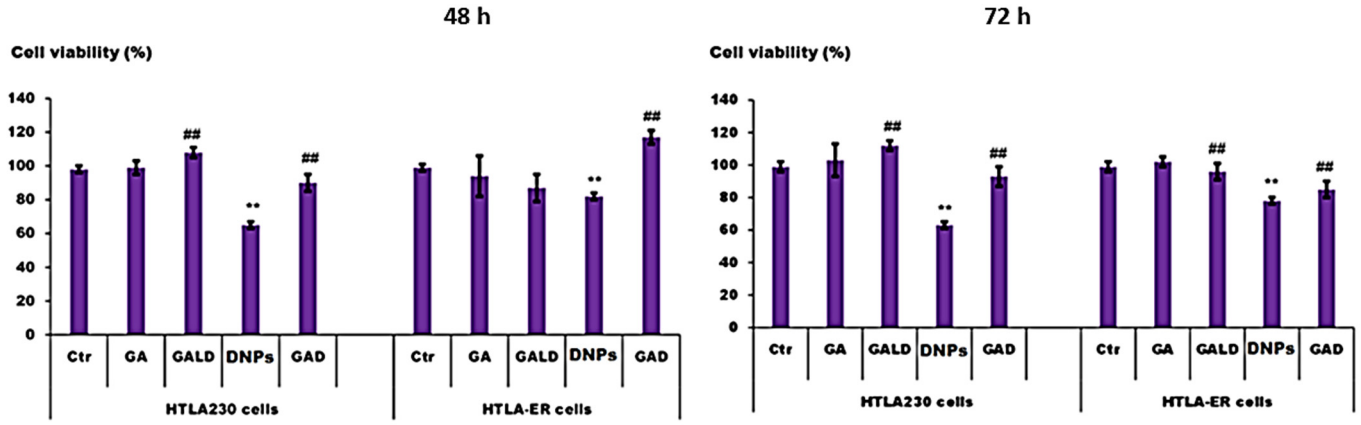


Figure 1. Viability (%) of HTLA-230 and HTLA-ER cells treated with DNPs, GA, GALD, and GAD. The analysis was performed by CellTiter 96® Aqueous One Solution Cell Proliferation Assay in HTLA-230 and HTLA-ER cells exposed to DNPs at the known active concentration (0.169 μM), GALD (in a dose capable of providing 0.169 μM DNPs), 21.20 μM GA (the dose provided by GALD used), and GAD in a dose capable to provide 21.20 μM GA for: 48 h (left panel); and 72 h (right panel). The bars graphs summarize quantitative data of the means ± S.E.M. of three independent experiments. ** $p < 0.01$ vs. Ctr cells; ## $p < 0.01$ vs. DNPs-treated cells.

In preliminary studies, free GA proved a dose-dependent ROS-mediated cytotoxicity on both cell populations, but at the dose provided by GALD of 21.20 μM was inactive. Intriguingly, when administered in dendrimer formulations at a dose not cytotoxic for NB cells, nullified any pro-oxidant activity of DNPs (Figure 2) [1].

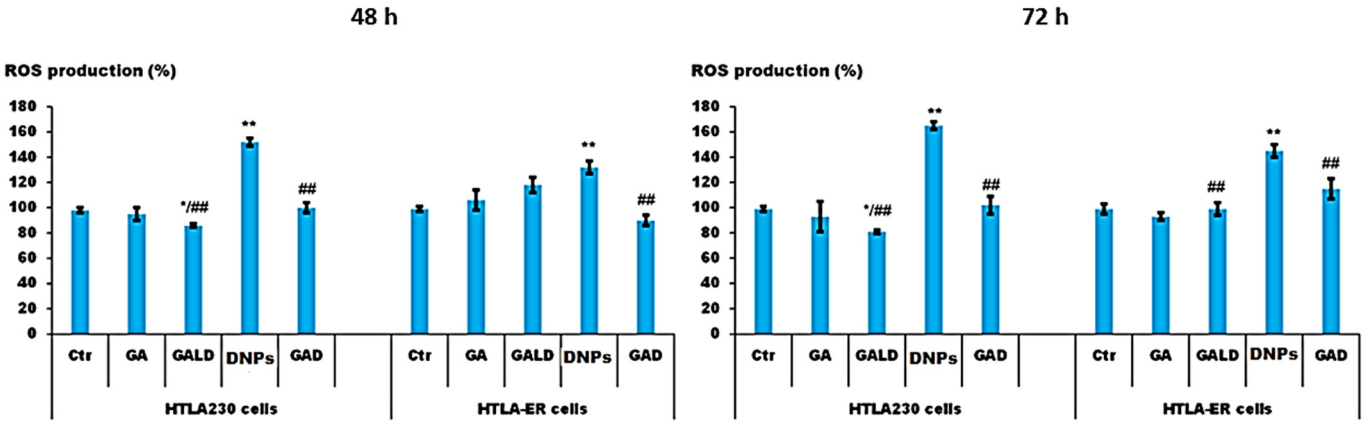


Figure 2. ROS levels in HTLA-230 and HTLA-ER cells treated with DNPs, GA, GALD, and GAD. ROS generation was analyzed in HTLA-230 and HTLA-ER cells exposed to DNPs at the known active concentration (0.169 μM), to GALD (in a dose capable of providing 0.169 μM DNPs) to 21.20 μM GA (the dose provided by GALD used), and GAD in a dose capable to provide 21.20 μM GA for: 48 h (left panel); and 72 h (right panel). The bars graphs summarize quantitative data of the means ± S.E.M. of three independent experiments. ** $p < 0.01$ vs. Ctr cells; ## $p < 0.01$ vs. DNPs-treated cells; * $p < 0.05$ vs. GA-treated cells.

Collectively, DNPs could represent a platform to develop novel devices against NB, while ETOD could be a biodegradable device for the efficient delivery of ETO into NB cells. GALD and GAD, due to the presence of GA, were inactive on NB cells, but GA resized in nanoparticles, and, at very low doses, has shown considerable ability in counteracting ROS production induced by DNPs, thereby exerting a possible protective action for healthy cells.

Data Availability Statement: More detailed data results are available in the articles cited in the following references list.

References

1. Alfei, S.; Marengo, B.; Zuccari, G.; Turrini, F.; Domenicotti, C. Dendrimer Nanodevices and Gallic Acid as Novel Strategies to Fight Chemoresistance in Neuroblastoma Cells. *Nanomaterials* **2020**, *10*, 1243.
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