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ORIGINAL PAPERS

GOLD NANOPARTICLES LOADED WITH DOXORUBICIN AND NATURAL COMPOUNDS TO TARGET CERVICAL CANCER CELLS: APOPTOSIS MECHANISMS

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Abstract. *The purpose of this study was to develop various combinations of natural compounds and create new drug delivery systems using gold nanoparticles and biomolecules in order to potentiate the anticancer capacity of doxorubicin used at its low dose, thus assuring its minimal negative effects on healthy cells. Resveratrol was used for the synthesis of gold nanoparticles, which were then multi-functionalized. The compounds containing low doses of doxorubicin, D, (2 μg/mL), piperine, P, resveratrol, R, and icariin, Ic, were tested on two cervical cancer lines: HeLa and CaSki cells. The determination of the cytotoxic activity of these compounds (carriers) on the cell lines was done using the MTT method. Our results are of major importance because the synthesized nanostructured carriers showed promising capabilities for the treatment of cervical cancer. Among the analyzed compounds, two of them are strongly evidenced. Thus, GNP_R1@DRPIc has a 3-fold higher activity on HeLa cancer cells compared to doxorubicin alone, at the same low dose, and GNP_R1@DIc manages to decrease the doxorubicin resistance of the CaSki cancer line. This research study displays the benefits of natural biomolecules in the functionalization of gold nanoparticles through the development of new nanocarriers and their possible applicability as anticancer agents against the two cell lines of cervical cancer. These results strengthen our idea that gold nanoparticles functionalized with natural compounds can enhance the therapeutic efficacy of doxorubicin against cervical cancer, being a safer alternative to classical doxorubicin therapy.*

Keywords: gold nanoparticles, multi-functionalized gold nanoparticles, drug delivery nanoparticles, doxorubicin, cervical cancer, HeLa cells, CaSki cells, cellular cytotoxicity

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INTRODUCTION

Cancer is one of the major global health concerns with a high occurrence and mortality rate, despite the availability of wide therapeutic options, particularly in chemotherapeutic treatment [1-4]. The majority of chemotherapeutic drugs have been synthesized based on recognized target genes or proteins associated with cancer cell survival or proliferation pathways. Phytochemical-derived nanomedicines represent an emerging strategy for the precise modulation of anticancer drugs, such as doxorubicin [1] (the main drug of choice), cisplatin, paclitaxel, or etoposide; most of these drugs have severe side effects due to cytotoxicity on normal non-target cells. In addition, cancer cells also have the capability to confer drug resistance due to increased expression of p-glycoprotein leading to increased efflux of these drugs [2,3]. The pharmacokinetic limitations of phytoconstituents, such as poor bioavailability, rapid metabolism, and diffuse systemic distribution, necessitate their integration into specialized nanocarriers [4-5].

Among these, liposomes (phospholipid bilayers) [6] provide high biocompatibility and allow the encapsulation of both hydrophilic and lipophilic compounds, being widely used for co-delivery of phytochemicals with chemotherapeutics, where they increase tumor accumulation and reduce systemic toxicity.

Polymeric micelles, self-assembled from amphiphilic block copolymers [7-9], ensure efficient solubilization of hydrophobic molecules and sustained drug release, making them suitable for long-term anticancer therapy. Dendrimers (branched macromolecules such as PAMAM) provide multiple functional sites for ligand conjugation [10], enabling active cellular targeting and combined transport of phytochemicals and conventional agents. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) offer prolonged release and enhanced physicochemical stability and have been investigated in formulations of curcumin and resveratrol [7, 11-14].

Cancer cells are abnormal cells that divide and grow uncontrollably, potentially invading and damaging surrounding tissues and spreading to other parts of the body. Unlike normal cells, they ignore signals that tell them to stop dividing or to die, and they can spread through the bloodstream or lymphatic system to form new tumors elsewhere in the body (metastasis) [15,16]. Cancer cells arise from normal cells that undergo genetic and epigenetic changes, leading to aberrant gene expression and altered cellular behaviors. These changes can result from mutations, gene amplification, changes in chromosome numbers, and other mechanisms. Cancer cells can be carcinomas, cancers that originate from epithelial cells, which line the body's surfaces (internal and external); sarcomas, cancers that develop in connective tissues like bone, cartilage, fat, and muscle; lymphomas, cancers of the lymphatic system; or leukemias, cancers that affect blood-forming cells in the bone marrow [17,18].

In addition, metallic and inorganic nanoparticles (e.g., gold, silica, iron oxide) can be functionalized with phytoconstituents for multimodal imaging and combined

therapy, although their long-term toxicity remains a concern [5,19]. A recent editorial highlights the convergence of these delivery platforms with molecular imaging, cellular biology, and pharmacology, outlining interdisciplinary opportunities for clinical translation of phytochemical-based nanomedicines [20]. A complementary approach involves the use of plant-derived extracellular vesicles (exosome-like nanoparticles, ELNs), which can be isolated through ultracentrifugation or microfiltration and exploited as natural drug delivery vehicles, offering advantages in terms of biocompatibility and intrinsic cellular uptake, though standardization and safety evaluation remain major challenges [21]. Ultimately, the in vivo performance of these nanomedicine systems is strongly influenced by their interactions with the immune system, including complement activation, recognition by macrophages and dendritic cells, and modulation of lymphatic trafficking, all of which dictate biodistribution, clearance, and therapeutic efficacy [17,18,22].

Monolayer and bilayer membranes are essential cellular structures, formed mainly by phospholipids. The monolayer membrane (or monolayer) is made up of a single layer of phospholipid molecules, in which the hydrophobic ends are oriented in a common direction, being rarely found in biological cells [23-30], but present on the surface of some lipid droplets [31-40]. In contrast, the bilayer membrane (or bilayer) is made up of two opposing layers of phospholipids, with the hydrophilic ends oriented outward (towards the aqueous environment) and the hydrophobic tails oriented inward, facing each other [41-49]. This type of membrane is characteristic of living cells, forming the basis of the plasma membrane and other cell membranes, giving them selective permeability, flexibility and protection [50-55]. Bilayer membranes are the basis for the formation of complex supramolecular structures, such as vesicles and liposomes, which are frequently used in research and medicine [56-59]. These spherical structures are composed of a phospholipid bilayer that encloses an aqueous compartment, mimicking cellular compartmentation [8,60]. Vesicles can occur naturally in cells (exocytosis, endocytosis), while liposomes are artificially formed and used as delivery systems for drugs, genes, or vaccines. The stability and functionality of these bilayers depend on the composition of the phospholipids, the environmental temperature, and the presence of other components, such as cholesterol, that carotenoids regulate membrane fluidity [61-70]. Thus, lipid bilayers not only separate compartments but also play an active role in processes such as membrane fusion, cell signaling, and molecular transport [71-81]. In nanomedicine, liposomes have become essential vectors for targeted drug delivery, as they can encapsulate both water-soluble molecules in the internal aqueous compartment and fat-soluble molecules in the lipid bilayer [82-91]. Due to their nanometric size and the possibility of functionalizing their surface (e.g. with antibodies or specific ligands), liposomes can be targeted to specific cells or tissues, reducing systemic toxicity and increasing therapeutic efficiency [92-99]. They are used in oncological treatments,

infectious diseases, or gene therapies, representing a versatile and promising platform in the development of new personalized therapies [100-112].

Besides the highly important topic of cancer, nanomaterials have recently been of great interest in the field of dentistry; thus, recent advances in dental biomaterials research emphasize the role of biomimetic hydroxyapatite-based formulations in promoting enamel remineralization and antimicrobial protection. Clinical and in vitro studies have demonstrated that toothpastes enriched with substituted or nanoscale hydroxyapatite, particularly when combined with birch extract, significantly enhance the dynamics of enamel surface remineralization, restoring structural integrity and resistance to acid challenges [113-115]. These optimized formulations also exhibit broad-spectrum antibacterial activity, attributed both to hydroxyapatite–silver nanocomposites and to phytochemical constituents of birch extract, thereby reducing bacterial colonization and oral biofilm formation [116,117].

The biomimetic mechanism underlying remineralization is based on the physicochemical affinity of hydroxyapatite nanoparticles for demineralized enamel prisms, facilitating ion exchange and lattice repair, as confirmed by structural and morphological analyses [118,119].

Moreover, by restoring enamel integrity while reducing microbial load, such formulations provide a dual therapeutic benefit for daily oral care and preventive dentistry. Interestingly, parallels can be drawn with oncological nanomedicine, where nanoparticle–cell interactions can either promote cellular repair or, conversely, induce cytotoxic stress, as seen in autophagy's ambivalent role in cancer progression and suppression [120,121]. This highlights a broader translational significance of nanostructured biomaterials across biomedical fields.

In this work, we will analyze the interaction of multi-functionalized gold nanoparticles with doxorubicin, D, resveratrol, R, piperine, P, and icariin, Ic, with the cell membranes of HeLa and CaSki cells by a combination of advanced experimental techniques. We will also use cell viability assays to evaluate the therapeutic efficacy of doxorubicin-functionalized gold nanoparticles, GNP_R1@D and GNP_R1@DRPIc to identify potential differences in response between the two cell lines based on their molecular characteristics.

Through the multidisciplinary approach, this research study provides a detailed understanding of the interaction mechanisms between multi-functionalized gold nanoparticles and the cell membranes of cancer cells, contributing to the development of more effective and personalized therapeutic platforms for oncological treatments.

MATERIAL AND METHODS

Materials

For the synthesis of gold nanoparticles, there were used tetrachloroauric acid trihydrate ($HAuCl_4 \cdot 3H_2O$) 99.5% (Merck, Darmstadt, Germany), trans-resveratrol ≥ 99% (HPLC assay, from Sigma-Aldrich, Buchs, Switzerland), and NaOH reagent

grade ≥ 98% (Merck KGaA, Darmstadt, Germany) in aqueous solutions prepared with bi-distilled deionized water.
For the functionalization of GNPs there were used doxorubicin hydrochloride (about 98%) from Sigma-Aldrich Chemie GmbH (Munich, Germany), piperine ≥ 98% (HPLC assay) from AlfaAesar (Karlsruhe, Germany), and icariin, analytical standard (≥94%), from Sigma-Aldrich (Steinheim, Germany). Dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich (Schnelldorf, Germany).
Dulbecco's phosphate-buffered saline (PBS), without $CaCl_2$ and $MgCl_2$, (pH 7.4), was purchased from Alfa Aesar (Karlsruhe, Germany). MTT tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) ≥ 98% was acquired from Sigma-Aldrich (Buchs, Switzerland).

Synthesis of GNP_R and characterization
GNPs were synthesized by the green reduction of $HAuCl_4$ with resveratrol, similar to the method we used in Mocanu at al. 2025 [1]. In brief, a freshly prepared solution of 50 mg resveratrol in 20 mL 0.02 M NaOH was added to 200 mL 10^{-3} M $HAuCl_4$ in bi-distilled water, under steady stirring at 500 RPM for 10 min at room temperature. The gold nanoparticles, formed by reducing $HAuCl_4$ with resveratrol and noted as GNP_R, were obtained in the initial gold concentration of 0.91 mM (179 mg/L Au) in colloidal solution.

Synthesis of GNP_R1 and characterization
The GNP_R initially obtained (see the anterior paragraph) was centrifuged to eliminate the secondary reaction products obtained during their synthesis. Therefore, the gold nanoparticles obtained by synthesis were purified by centrifugation (at around 10,000 RPM) using a Hettich Universal 320R centrifuge, Beverly, MA, USA, in optimal experimental conditions for about 20 min at 5°C, with a relative centrifugation force, RCF, of 8000× g. These centrifuged GNP_R particles were washed with bi-distilled water of pH 5.6. Then, they were centrifuged again and redispersed in bi-distilled water to produce a final colloidal solution (referred to as GNP_R1) with the same gold concentration as in the initial solution of synthesized GNP_R, as confirmed by UV-VIS spectroscopy. This GNP_R1 colloidal solution was kept at 4°C, in the dark, to prolong its stability until use. This GNP_R1colloidal solution, through dilution with PBS (pH 7.4) or with cell culture media, such as DMEM (pH 7.2–7.4), was used in cancer cell culture media.
The obtained nanoparticles were characterized by the following methods: UV-VIS; TEM; high-resolution TEM (HR-TEM); atomic Force Microscopy, AFM; zeta (ξ-) potential; dynamic light scattering (DLS) and X-Ray Diffraction (XRD) [1,122].
Identification of surface functional group coating of GNPs was performed by Fourier transform infrared spectroscopy (FTIR) [122].

Preparation of GNP_R1@D, GNP_R1@DRPIc nanocarriers/ nanocomposites

The GNP_R1 colloidal solution was further used in the functionalization of GNP_R1 particles with selected natural compounds: resveratrol, piperine, and icariin (Table 1). Functionalization of resveratrol-covered gold nanoparticles, GNP_R1, with more resveratrol leads to ward the development of GNP_R1@R, which is primarily ruled by physical adsorption of R molecules within the R layer on gold nanoparticles. The high stability of this self-assembled R layer on Au surface is described through intermolecular hydrogen bonds and electrostatic interactions, without forming chemical bonds with the GNPs. This strategy to increase the number of biocompounds within the self-assembled R layer on Au surface proved successful. Further, GNP_R1 was functionalized with R, P, D, and Ic, resulting in GNP_R1@RPDIc.

To address these challenges, various solutions with different proportions of anticancer compounds, namely, doxorubicin hydrochloride, resveratrol, piperine, and/or icariin, as well as mixtures of these solutions, were added to GNP_R1 aqueous colloidal solution (0.91mM Au) at 25°C (or at room temperature), while thoroughly stirring, in the dark, for around 30 min.

Icariin, which is not soluble in water, was solubilized in dimethyl sulfoxide (DMSO, 11mg/10mL), and then 100mL PBS was added to the solution. The mixtures were then maintained at the chosen temperature while thoroughly stirring, in the dark, until used in physicochemical research or in cellular treatment (up to 1h).

Table 1. Samples prepared and used

Samples (COMP)	Concentration, μmol/L					Mole Ratios
Concentration, μg/mL	Au	D	R	P	Ic	
1 – D 2 μg/mL	-	3.68	-	-	-	-
2 – R 0.2 μg/mL, D2 μg/mL	-	3.68	0.88	-	-	D/R 4.18
3 – P 0.5 μg/mL, D 2 μg/mL	-	3.68	-	1.75	-	D/P 2.10
4 – R 0.5 μg/mL, P 0.5 μg/mL, D 2 μg/mL	-	3.68	2.19	1.75	-	D/R 1.67; D/P 2.10; R/P 1.25
5 – Ic 1 μg/mL, D 2 μg/mL	-	3.68	-	-	1.48	D/Ic 2.49
6 – GNP_R1 4.8 μg/mL, D 2 μg/mL	24.4	3.68	-	-	-	Au/D 6.63
7 – GNP_R1 4.8 μg/mL, R 0.2 μg/mL, D 2 μg/mL	24.4	3.68	0.88	-	-	Au/D 6.63; Au/R 27.7; D/R 4.18
8 – GNP_R1 4.8 μg/mL, P 0.5 μg/mL, D 2 μg/mL	24.4	3.68	-	1.75	-	Au/D 6.63; Au/P 13.9; D/P 2.10

9 – GNP_R1 4.8 µg/mL, Ic 1 µg/mL, D 2 µg/mL	24.4	3.68	-	-	1.48	Au/D 6.63; Au/Ic 16.5; D/Ic 2.49
10–GNP_ R1 3.6 µg/mL, R 0.14 µg/mL, P 0.35 µg/mL, Ic 0.7 µg/mL, D 2 µg/mL	18.3	3.68	0.61	1.23	1.03	Au/D 4.97; Au/R 30.0; Au/P 14.9; Au/Ic 17.8; D/R 6.03; D/P 2.99; D/Ic 3.57; R/P 0.50; R/Ic 0.59; P/Ic 1.19

Cell lines

Certified cell lines of HeLa and CaSki cervical carcinoma cells were used in this study. Cell lines were provided by the European Collection of Authenticated Cell Cultures (ECACC) and purchased from Sigma-Aldrich.

HeLa cells were cultivated with Dulbecco's modified Eagle (DMEM) medium, low glucose, supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine, 1% antibiotic, and 1% non-essential aminoacids (NEAs) at 37°C in 5% CO_2 humidified air; for CaSki cells, the cultivation medium was RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine, and 1%antibiotic; all Sigma-Aldrich reagents, all Sigma-Aldrich reagents.

Statistical analysis

The data are presented, from triplicate experiments, as mean ± standard deviation. Statistical analysis was performed with the GraphPad Prism 5 program, using two statistical analysis methods: one-way ANOVA followed by the "Dunnett's Multiple Comparison Test" posttest for the comparison of the treated cells with the control sample without treatment, setting the p-value at $p < 0.05$ (statistically significant).

RESULTS AND DISCUSSIONS

Assessment of doxorubicin cytotoxic activity

To perform the MTT test, the cells were trypsinized and counted with a hemocytometer and seeded on 96-well plates at a density of 1 × 104 in 200 µL complete medium/well. After 24 h, during which HeLa and CaSki cells adhered to the surface of the plates, treatments with functionalized gold nanoparticles and biocompounds and/or doxorubicin were applied, with a dilution of 1/20.

Increasing concentrations of doxorubicin were used to compare the effects of nanoparticles with standard treatments in the human clinic as follows: 2.1 µg/mL and two higher concentrations of 6.25 µg/mL and 12.5 µg/mL. The experiments were performed in triplicate.

The viability of cells was evaluated after 24h and 48h by an MTT assay that uses a tetrazolium salt (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide). MTT salt is enzymatically reduced by viable cells into formazan.

After 24 and 48 h of exposure to treatments, the medium was extracted from the wells, 100 µL of MTT solution was added, and the plates were incubated for 1 h at 37°C in the dark. The MTT solution was discarded from the wells, and 150 µL of DMSO/well was added to solubilize the formazan crystals from the cells.
Optical density readings were performed at 492 nm using a BioTek Synergy 2 microplate reader (Winooski, VT, USA). The cytotoxic effect of doxorubicin and/or of biomolecules, such as resveratrol, was expressed as the relative viability (% control).
The calculation of IC50 of doxorubicin, D, necessary to produce 50% inhibition of cell growth for *HeLa cancerous cells* was calculated from the linear equation of the survival fraction curve, and the result shows that it takes about 9.8 µg/mL of doxorubicin to kill 50% of the cells (Figure 1).

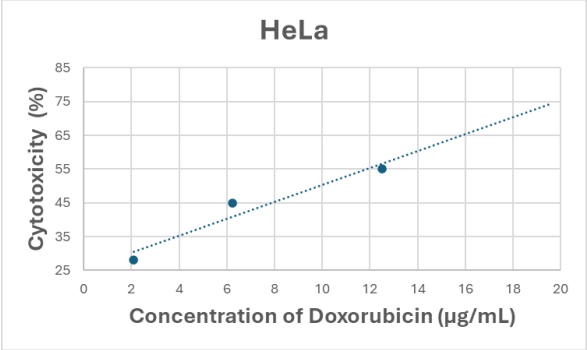

Figure 1. Cytotoxicity of doxorubicin alone, y, versus doxorubicin concentration, x, on HeLa cancerous cell line at 24h inhibition time. The equation of the line: y=2.5166x+25.176; R=0.9316.

Doxorubicin exhibits a wide range of cytotoxicity across cancer cell lines, with IC_{50} values highly dependent on cell type and drug resistance status. In breast cancer cells, IC_{50} values were reported as ~0.05 µM for MCF-7, 0.69 µM for MCF-7 in another study, and markedly higher (13.99 µM) in the resistant MCF-7/ADR line [123,124].
Triple-negative breast cancer subtypes also displayed variable sensitivity, ranging from 2.72 nM in DU4475 to 96.6 nM in HCC1143 [125]. Other breast cancer lines included BT-474 (1.14 µM), T-47D (8.53 µM), and MDA-MB-231 (3.16 µM).
In hematological malignancies, IC_{50} values were ~0.30 µM for HL-60 and 0.03 µM for K562 leukemia cells [1]. Colon adenocarcinoma HT-29 showed high sensitivity (0.04 µM), while lung carcinoma A549 exhibited intermediate values between 0.58 and 0.69 µM. Osteosarcoma 143B cells had an IC_{50} of 0.4 µM, which increased drastically to 75 µM in a doxorubicin-resistant subline [126]. Additional reports indicate IC_{50} values of 0.085–0.17 µM in epidermoid carcinoma A-431 [127].
A broader 24-cell panel confirmed variability, with values spanning from low micromolar in MCF-7 (2.5 mM) and HeLa (2.9 mM) to millimolar resistance in Huh7, VMCUB-1, A549, and HK-2 cells (>20 mM) [128].

Collectively, these findings highlight that doxorubicin's efficacy is both cancer-type specific and significantly modulated by mechanisms of drug resistance.

Assessment of GNP_R1@D, GNP_R1@DRPIc effects

Beneficial effects of functionalized GNPs were examined using an investigation on HeLa and CaSki cell viability in response to GNP_R1 functionalized GNPs with resveratrol, piperine, icariin and doxorubicin.

In this study, the effects on cervical carcinoma cells' viability were investigated as a response to cells' treatment with ten compositions (Figures 2 and 3), including D alone and functionalized GNP_R1, following 24 h (Figure 2) and 48 h (Figure 3) of exposure. The concentration of doxorubicin in the compositions was 2 µg/mL, as shown in Table 1.

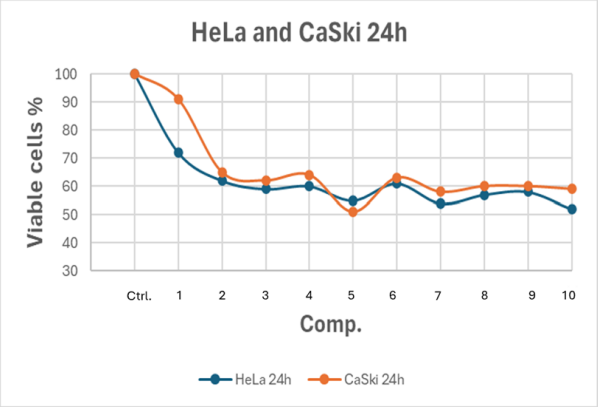

Figure 2. Viability cells HeLa and CaSki versus composition at 24h incubation time.

The differences between the compounds used were statistically evaluated and the interpretation are the following. Treatment of HeLa cancer cells with 2 µg/ml doxorubicin for incubation time 24 h, either alone (cytotoxicity about 28%) or with the smart delivery system, such as GNP_R1@DRPIc (sample 10 on HeLa cells, with cytotoxicity about 48%), increased the D cytotoxicity, for at least 3 times corresponding to a composition of approximate D 6.25 µg/ml doxorubicin alone with cytotoxicity of about 45%.

The most effective composition we found is sample 10, which contains 3.6 µg/mL gold nanoparticles, 0.14 µg/mL resveratrol, 0.35 µg/mL piperine, 0.7 µg/mL icariin and 2 µg/mL doxorubicin. In the case of the HeLa cell line, after 24 hours a value close to the IC_{50} was obtained, and after 48 hours this value was exceeded.

Treatment of CaSki cancer cells with 2 µg/ml doxorubicin for incubation time 24 h, either alone (cytotoxicity about 5%) or with the smart delivery system, such as GNP_R1@DIc (sample 9 on CaSki cells, with cytotoxicity about 40%), increased the D cytotoxicity, for at least 9 times.

Recent studies demonstrate that the minimal effective concentration of doxorubicin varies significantly depending on the cancer cell type, with values reported as low as 0.03 µM in K562 leukemia cells and approximately 0.05 µM in MCF-7 breast cancer cells, while resistant sublines such as MCF-7/ADR exhibit markedly higher IC_{50} values exceeding 13 µM [123,124].

To enhance therapeutic efficacy and overcome multidrug resistance, multi-functionalized gold nanoparticles have been explored as carriers for combined delivery of doxorubicin with natural bioactive molecules such as piperine, resveratrol, and icariin. Piperine has been shown to inhibit P-glycoprotein efflux pumps and increase intracellular accumulation of chemotherapeutics, resveratrol contributes to pro-apoptotic and anti-oxidative signaling pathways, while icariin exerts anti-proliferative effects and modulates PI3K/Akt and NF-κB pathways, collectively sensitizing cancer cells to doxorubicin.

Gold nanoparticle conjugation provides additional advantages, including improved cellular uptake, controlled drug release, and potential photothermal synergy, resulting in reduced IC_{50} values compared to free doxorubicin and enhanced cytotoxicity against resistant cancer phenotypes [129-132].

Thus, multi-functionalized gold nanocarriers represent a promising strategy for lowering the minimum effective dose of doxorubicin while simultaneously mitigating systemic toxicity and overcoming resistance mechanisms.

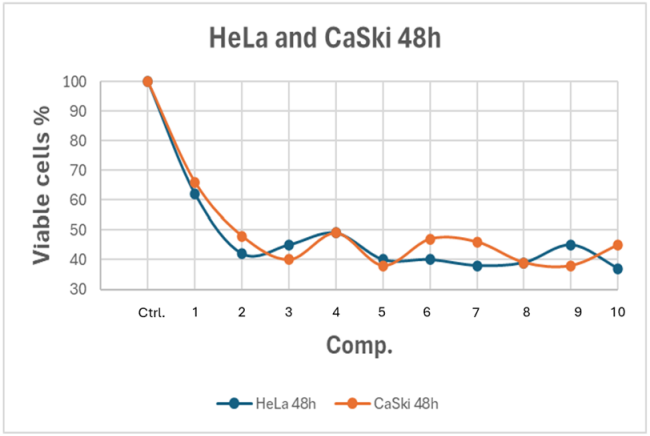

Figure 3. Viability cells HeLa and CaSki versus composition at 48h incubation time.

The statistical analysis of data from Figure 3 showed that at incubation time 48 h, comparing sample 10, on HeLa cells, with cytotoxicity about 63%, with doxorubicin alone at 24h incubation time (cytotoxicity about 28%) the D cytotoxicity increased for at least of 9 times (corresponding to D 18 µg/ml doxorubicin alone at 24 h.

In the same time, comparing sample 9, which contain GNP_ R1 4.8 μg/ml; Ic 1 μg/ml; D 2 μg/ml on CaSki cells, with cytotoxicity about 62%, with doxorubicin alone at 24 h (cytotoxicity about 5%) the D cytotoxicity increased exponentially.
Following the MTT assay, after 48 hours of exposure, it is easily observed that the 2μg/mL dose of doxorubicin decreases cell viability to 62% of the HeLa cell line and to 66% of the CaSki cell line. This shows that HeLa cells are slightly more sensitive to doxorubicin than CaSki cells.
From the 24-hour graph, it can be easily seen that the CaSki cell line is resistant to doxorubicin alone (cytotoxicity around 10%), but with the help of the compounds obtained by us, a reduction of this resistance was achieved. For example, the compounds 7 (GNP_R1 4.8 μg/mL, R 0.2 μg/mL, D 2 μg/mL), 8 (GNP_R1 4.8 μg/mL, P 0.5 μg/mL, D 2 μg/mL), 9 (GNP_R1 4.8 μg/mL, Ic 1 μg/mL, D 2 μg/mL) and 10 (GNP_ R1 3.6 μg/mL, R 0.14 μg/mL, P 0.35 μg/mL, Ic 0.7 μg/mL, D 2 μg/mL) increased cytotoxicity from approximately 40% in the case of 24-hour incubation to 60% at 48 hours of incubation time.

Cell imaging

Phase-contrast microscopy has been widely employed to assess morphological alterations in cervical cancer cell lines such as HeLa and CaSki following chemotherapeutic treatment. Exposure of these cells to doxorubicin induces characteristic cytotoxic changes, including cell shrinkage, membrane blebbing, and reduced confluence, consistent with apoptosis and loss of proliferative capacity [133,134].
Incorporation of gold nanoparticles (GNPs), particularly when functionalized with bioactive molecules or co-loaded with doxorubicin, significantly enhances these effects by improving intracellular uptake and promoting localized drug accumulation [129,135].
Comparative phase-contrast imaging has revealed that HeLa and CaSki cells treated with GNP–doxorubicin conjugates display more pronounced morphological disruption and detachment compared to cells treated with free doxorubicin, indicating synergistic enhancement of cytotoxicity [133,135,136].
These findings underscore the potential of gold nanoparticle–based delivery systems to potentiate the therapeutic response in cervical cancer while allowing detailed, non-invasive visualization of cellular dynamics under phase-contrast microscopy.
Phase contrast microscopy of cells treated with these compounds for 48 hours (Figures 4 and 5) showed, first, a less intense staining, suggesting defects in the reduction of MTT dye to formazan due to mitochondrial dysfunction, and a drastic decrease in cell number with important changes in cell morphology, increased cell volume, and adhesion surface, suggesting alterations in the cellular cytoskeleton.

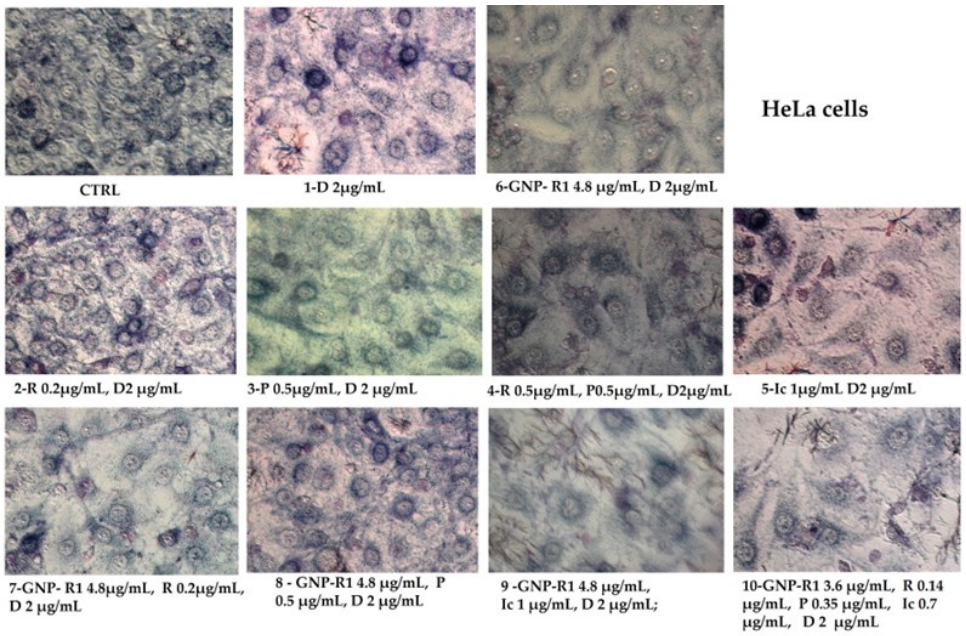

Figure 4. Phase contrast microscopy images of HeLa cells stained with MTT after 48 hours of exposure to various compositions developed in this research study (x40 magnification objective).

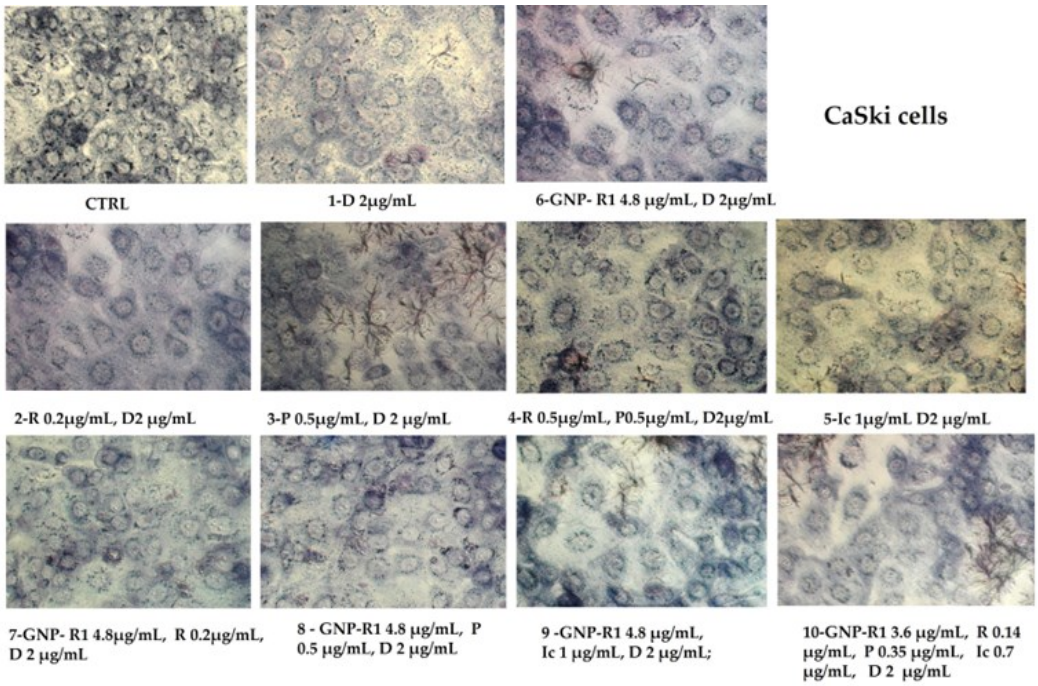

Figure 5. Phase contrast microscopy images of MTT-stained CaSki cells after 48 hours of exposure to various compositions developed in this research study (x40 magnification objective)

Ballooning and detached cells with cell shrinkage were also observed in the treated samples (Figures 4 and 5). Cellular uptake of doxorubicin alone, as shown in composition 1 in Figure 4, for HeLa, and of doxorubicin-functionalized GNP_R1, e.g., GNP_R1@D in composition 6, Figure 5, exemplifies a late apoptosis morphology (e.g., membrane blebbing).

Modulation of doxorubicin cytotoxicity through natural compounds and GNPs composites

The study of the interaction of DOX-functionalized gold nanoparticles with the cell membranes of HeLa and CaSki cancer cells is based on the fundamental importance of this process in the effectiveness of oncological treatment. HeLa cells, derived from a cervical adenocarcinoma, are among the most studied cell lines in oncological research due to their rapid proliferation capacity and resistance to various types of chemotherapeutic treatment [1]. HeLa cells are a line of cervical cancer cells that have been continuously cultured since their isolation in 1951 from a patient named Henrietta Lacks.

These cells, derived from an adenocarcinoma of the cervix, were the first human cells to be successfully grown indefinitely in the laboratory. They have been crucial in various scientific research areas, particularly in virology, cancer biology, and human genetics. HeLa cells are known to contain human papillomavirus 18 (HPV-18), a virus linked to cervical cancer [137,138].

On the other hand, the CaSki cell line, also derived from cervical carcinoma, is notable for containing the HPV type 16 viral genome, an essential factor in the development of cervical carcinoma [139]. This molecular difference between the two cell lines makes them relevant models for investigating differences in behavior in response to doxorubicin-functionalized gold nanoparticles [140].

Regarding the interaction mechanisms, recent studies suggest that gold nanoparticles can interact with cell membranes through several mechanisms, including passive adsorption, receptor-mediated endocytosis, and pinocytosis, each of which has direct implications for drug delivery efficiency [141,142].

The size, surface charge, and morphology of nanoparticles significantly influence the type of interaction with cell membranes. Smaller nanoparticles tend to be more easily internalized by endocytosis mechanisms, while larger nanoparticles can interact with membranes through direct physical interaction, favoring “lipid raft”-type absorption or by modifying membrane curvature [10,143-150].

To understand how the size and shape of gold nanoparticles influence this process, it is essential to study in detail the physicochemical parameters of GNPs. In the literature, it has been observed that spherical nanoparticles tend to be internalized more efficiently than irregularly shaped ones, and changes in surface charge, such as the addition of functional groups (e.g., thiol acid, amino groups), can modulate their affinity for target cells [151-155].

These characteristics are highly relevant in the context of doxorubicin delivery, as the drug is often unable to efficiently cross cell membranes without an appropriate transport system [156-168]. Functionalization of nanoparticles with DOX allows for controlled release and direct delivery to tumor cells, thus minimizing side effects on healthy tissues.

Apoptosis mechanism and blebbing

Cell death occurs through distinct, genetically and biochemically regulated pathways that are characterized by specific molecular and morphological features (Figure 6).

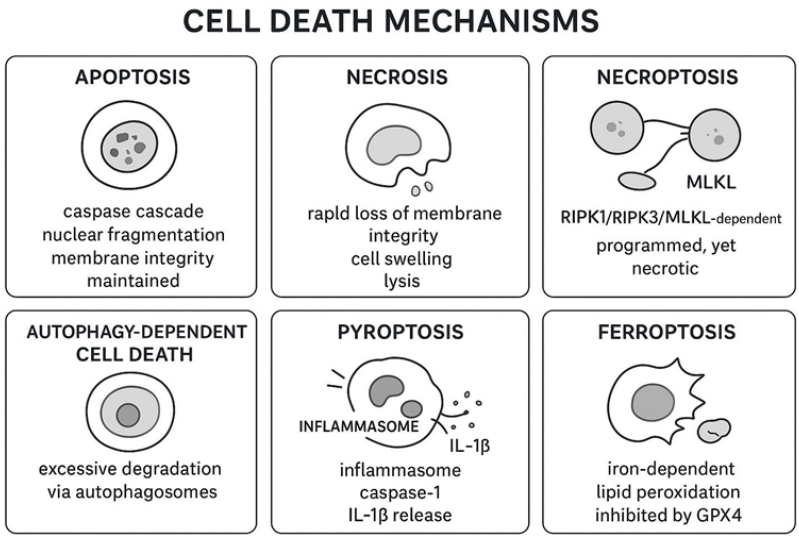

Figure 6. Cell death mechanisms

Apoptosis is an energy-dependent process driven by caspase activation, nuclear condensation, and DNA fragmentation, while maintaining plasma membrane integrity (Figure 6). In contrast, necrosis involves uncontrolled cellular swelling, plasma membrane rupture, and subsequent release of intracellular content. Necroptosis represents a programmed form of necrosis mediated by the RIPK1–RIPK3–MLKL signaling axis, leading to membrane permeabilization.

Autophagy-dependent cell death arises from excessive self-digestion through autophagosome formation and lysosomal degradation (Figure 6). Pyroptosis is an inflammatory mode of cell death triggered by inflammasome activation, caspase-1 cleavage, and gasdermin-mediated pore formation with release of IL-1β. Finally, ferroptosis is an iron-dependent process characterized by uncontrolled lipid peroxidation due to impaired glutathione peroxidase 4 (GPX4) activity. Together, these mechanisms illustrate the diversity of cellular demise and their distinct physiological and pathological implications [169-171].

A kit was used to determine apoptosis by flow cytometry. Thus, cells were incubated for 24 hours and 48 hours with the selected compounds, and then the cells were collected by trypsinization, the cell suspensions were washed with cold PBS and resuspended in 100 µL of binding buffer. 5 µL of Annexin V-FITC and 1 µL of propidium iodide working solution (100 µg/mL) were added to each sample. The next step was incubation for 15 minutes in the dark and then analysis with a flow cytometer (BD FACSCantoTMII, purchased from BD Biosciences, San Jose, CA, USA).

Fluorescence was detected using specific filters for annexin and propidium iodide. The analysis was performed using FACSDiva 6.1.2 software. Depending on the observed staining, the cells were divided into four categories, as follows: positivity for Annexin V-FITC alone indicates an early stage of apoptosis, double staining (Annexin V-FITC/PI) indicates late apoptosis (a more advanced stage), cells stained with PI alone are considered necrotic, and unstained cells are considered alive [122].

Apoptosis, a form of programmed cell death, is triggered by DNA damage through various pathways. DNA damage can activate both the extrinsic (death receptor) and intrinsic (mitochondrial) pathways of apoptosis [172]. This process involves the activation of caspases, enzymes that dismantle the cell, leading to DNA fragmentation and other characteristic apoptotic changes [173-177]. Caspases are a family of proteases crucial for apoptosis, a form of programmed cell death. They exist as inactive zymogens and are activated during apoptosis, initiating a cascade of proteolytic events that dismantle the cell. These enzymes cleave specific proteins at aspartate residues, leading to the characteristic morphological changes of apoptosis. In essence, caspases are the executioners of apoptosis, dismantling cells in a controlled manner through a cascade of proteolytic events, ultimately leading to the removal of damaged or unwanted cells [178-182].

Certain cell surface receptors, like Fas, trigger apoptosis upon binding to their respective ligands (e.g., FasL). This pathway can be activated by DNA damage through various mechanisms, leading to the formation of a death-inducing signaling complex (DISC) and caspase activation. DNA damage can also induce apoptosis through the mitochondrial pathway. This pathway involves the release of cytochrome c from the mitochondria, which activates caspases and ultimately leads to cell death. A network of proteins, including NBS1, ATM, and ATR, sense DNA damage and initiates signaling cascades that can lead to apoptosis. These pathways often involve the activation of p53, a tumor suppressor protein, which can induce apoptosis by regulating the expression of genes involved in cell cycle arrest and apoptosis [183-192].

Apoptosis also involves the targeted degradation of mRNA. This mRNA decay is a rapid and early event during apoptosis, preceding other hallmarks like DNA fragmentation. The process is initiated by mitochondrial outer membrane permeabilization and is further amplified by caspase activation. Specific enzymes,

including terminal uridylyl transferases (TUTases) (ZCCHC6 and ZCCHC11) and the 3' to 5' exonuclease DIS3L2, are involved in creating and degrading uridylated mRNA fragments during this process [193-195].

Blebbing is a cellular process characterized by the formation of "bubbles" or extroflections of the plasma membrane, which occur as a result of dynamic changes in the structure of the cellular cytoskeleton [196-198].

This phenomenon can be observed in various physiological and pathological conditions, including the processes of apoptosis, necrosis, tumor metastasis and responses to cellular stress, such as exposure to chemotherapeutic agents or nanoparticles [199-202] (Figure 7).

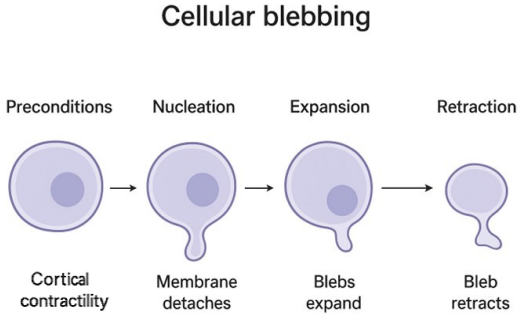

Figure 7. Cellular blebbing

During blebbing, the actin structure of the cytoskeleton is reorganized, leading to localized separation of the plasma membrane from the rest of the cell, and this process can be accompanied by an accumulation of fluid inside the formed "bubbles" [203,204].

Blebbing is considered a sign of cellular instability and may be an indicator of a cell's self-defense reaction against various stress factors, but also a mechanism for inducing cell migration, especially in the context of tumor metastasis. In nanomedicine studies, blebbing is often associated with the interaction of tumor cells with nanosystems (e.g., gold nanoparticles or other types of functionalized nanoparticles), which can cause changes in the integrity of the cell membrane, thus favoring drug or particle internalization, but also inducing cytotoxic effects [205-207].

At 48 hours, cells undergoing programmed cell death, such as apoptosis, show significant morphological changes and activation of specific molecular pathways. These changes include DNA fragmentation, chromatin condensation, and activation of caspases, which are enzymes that dismantle the cell from within. Cells may also exhibit features of other programmed cell death pathways like autophagy, where cellular components are digested by lysosomes, or necrosis, characterized by cell swelling and rupture [208-215].

Gold nanoparticles (GNPs) have emerged as a versatile system in nanomedicine due to their exceptional physicochemical properties [216,217], including biocompatibility, the ability to carry biomolecular molecules [218], and the possibility of being chemically modified to align with various therapeutic and diagnostic applications [219-230]. In the context of oncology therapy, the use of GNPs for the controlled delivery of chemotherapeutic agents has been intensively studied due to the possibility of addressing the limitations of conventional chemotherapy approaches, such as systemic toxicity and drug resistance [231-242].

Recent studies highlight the potential of nucleus-targeting nanomaterials as advanced oncological therapeutics. Gold nanoparticles (GNPs) and functionalized nanocomposites demonstrate the ability to penetrate the nuclear envelope, either directly or via translocation peptides such as Tat, thereby enabling precise nuclear delivery of therapeutic cargos [243,244].

Direct visualization experiments confirmed the intimate interactions of GNPs with nuclear structures, revealing their capacity to bind DNA and disrupt replication machinery, which has been validated through combined computational and experimental approaches [245,246]. Moreover, nanoparticles exert profound effects on the cell cycle by inducing DNA damage, mitotic arrest, and apoptosis, indicating a strong correlation between nuclear targeting and cytotoxic outcomes [247,248].

Importantly, GNP-bound DNA exhibits enhanced stability against enzymatic, chemical, and physical degradation, which supports their use as robust carriers in harsh intracellular environments [249]. Furthermore, GNPs act as radiosensitizers and chemosensitizers, significantly amplifying DNA damage when combined with conventional anticancer drugs or ionizing radiation, thereby potentiating therapeutic efficacy [250]. Collectively, these findings establish nuclear-targeted nanoparticles as powerful tools for disrupting cancer cell proliferation through synergistic physical, chemical, and biological mechanisms [251,252].

Doxorubicin (DOX), a broad-spectrum chemotherapeutic agent used in the treatment of various types of cancer, is often associated with severe side effects and the development of multidrug resistance (MDR) [253-256]. In this regard, the functionalization of gold nanoparticles with doxorubicin presents itself as an innovative strategy for targeted and controlled drug delivery, with the aim of maximizing therapeutic efficacy and reducing systemic adverse effects [5,257].

DOX-functionalized gold nanoparticles offer a number of technical advantages: (i) the possibility of controlling the size and shape of the nanoparticles, essential parameters for the interaction with biological cells and cell membranes; (ii) their chemical stability and biocompatibility, which allow safe administration in body, and (iii) the ability to release doxorubicin in a controlled manner, depending on the local conditions in the tumor microenvironment.

At the molecular level, the interaction between functionalized gold nanoparticles and cell membranes represents an essential aspect in the drug internalization process and

in the final therapeutic effects. In particular, the interaction mechanisms vary significantly depending on the physicochemical characteristics of the nanoparticles, the typology of the cell membrane and the presence of certain receptors or biomolecules on the cell surface [2,258].

The combination of doxorubicin with natural bioactive compounds such as resveratrol, piperine, and icariin has emerged as a promising strategy to enhance anticancer efficacy while mitigating systemic toxicity [259-263]. Doxorubicin, although highly effective against a broad spectrum of malignancies, is limited by cumulative dose-dependent cardiotoxicity, multidrug resistance (MDR), and nonspecific cytotoxicity [264-269]. Resveratrol, a polyphenolic stilbene, exerts antioxidant, anti-inflammatory, and pro-apoptotic effects, and has been shown to sensitize cancer cells to doxorubicin by downregulating efflux transporters (e.g., P-glycoprotein) and modulating apoptotic pathways, thereby overcoming MDR [122, 270-283]. Piperine, an alkaloid derived from Piper nigrum, acts primarily as a bioavailability enhancer by inhibiting cytochrome P450 enzymes and drug efflux pumps, prolonging systemic exposure to doxorubicin and synergistically enhancing its intracellular accumulation [284-286]. Icariin, a prenylated flavonol glycoside, exhibits both anti-proliferative and anti-angiogenic activity, and has been reported to attenuate doxorubicin-induced cardiotoxicity through modulation of oxidative stress and mitochondrial pathways, while simultaneously exerting direct cytotoxic effects on tumor cells [287]. When integrated into nanocarrier-based co-delivery systems (e.g., liposomes, polymeric nanoparticles, or lipid–polymer hybrid carriers), these phytochemicals can achieve spatiotemporal co-localization with doxorubicin in the tumor microenvironment, enhancing tumor selectivity, reducing off-target toxicity, and potentiating apoptosis through synergistic mechanisms [9,288,289]. Collectively, the rational co-delivery of doxorubicin with resveratrol, piperine, and icariin represents a multifaceted therapeutic approach that addresses the limitations of conventional chemotherapy by combining cytotoxic potency with chemo-sensitization, bioavailability enhancement, and cardio-protection [132, 290-293].

From a molecular point of view, the internalization process of DOX-functionalized gold nanoparticles is dependent on the interactions between lipids in the cell membrane and the gold nanoparticles [294-298]. For example, recent studies have shown that the phospholipid lipids of the membrane, especially those that form micro-grooves or lipid domains, can significantly influence the ability of nanoparticles to attach to the cell surface. In addition, specific receptors present on cell membranes can mediate the recognition and internalization of nanoparticles. This interaction is essential not only for the internalization of nanoparticles but also for the controlled release of doxorubicin [299].

Recent studies have highlighted significant advancements in the synthesis, structural characterization, and biomedical applications of bioactive compounds, nanomaterials, and their complexes [300-309]. Curcumin’s bioavailability and physicochemical

behavior have been improved through various strategies, including its complexation with proteins and nanoparticles [310,311]. Spectroscopic analyses, such as IR, Raman, and FT-Raman, have been extensively used to characterize metal complexes and biomolecules, providing insights into molecular interactions and conformational dynamics [312-316]. The incorporation of silicon and other elements into nano calcium phosphates enhances their biocompatibility with human osteoblasts, while gold and silver nanoparticles functionalized with amino acids or anesthetics exhibit controlled assembly and interaction with proteins [317-327]. Xanthophyll and lipid monolayers at the air/water interface have been investigated to elucidate their structural dynamics, which informs drug penetration studies and the design of bioactive films [328-335]. Hydroxyapatite-based materials, nanostructured phosphates, collagen, chitosan composites, and forsterite biocomposites demonstrate promising mechanical properties, bioactivity, and potential for heavy metal removal or medical applications [336-338]. Cyclodextrin inclusion complexes with antioxidants like α-lipoic acid and the structural characterization of starch granules further expand the scope of functional biomaterials [313,339]. Overall, the integration of nanomaterials, bioactive compounds, and advanced spectroscopic techniques provide a robust framework for the design of novel therapeutics, drug delivery systems, and biomedical scaffolds [340-345].

Thus, the acidic pH characteristic of the tumor microenvironment may facilitate the dissolution of the bonds between DOX and nanoparticles, releasing the chemotherapeutic agent inside the tumor cell. The functionalization of gold nanoparticles (GNPs) with doxorubicin, resveratrol, piperine, and icariin represents an advanced multimodal strategy in oncological nanomedicine [60,346-349]. GNPs provide a stable and biocompatible platform with tunable size, surface charge, and plasmonic properties, enabling both targeted drug delivery and theranostic applications. Conjugation of doxorubicin to GNPs enhances its tumor accumulation via the enhanced permeability and retention (EPR) effect while reducing systemic cardiotoxicity. The incorporation of resveratrol synergistically modulates apoptotic signaling and downregulates drug resistance pathways, whereas piperine improves intracellular uptake by inhibiting efflux transporters [350-357]. Icariin, when co-delivered on GNPs, exerts anti-proliferative and cardioprotective roles, further mitigating doxorubicin-induced toxicity [358-364].

Collectively, GNP-based co-delivery systems potentiate anticancer efficacy by integrating cytotoxic activity with chemo-sensitization, bioavailability enhancement, and protective modulation of adverse effects, while also offering opportunities for image-guided therapy through GNPs' intrinsic optical properties [365-367].

The polyunsaturated fatty acids are also important for opening the blood brain barrier for nanostructured carriers of drugs to the brain. Specifically, it is revealed that the docosahexaenoic acid/poly-L-lysine conjugates bind to the cerebrovascular endothelium [368]. Moreover, it is shown that docosahexaenoic acid plays a

unique role in facilitating the vital functions of astrocytes in the brain. Thus, the docosahexaenoic acid might be used as the adjuvant agent, in future innovative strategies, for increasing the efficacy of these nanostructured carriers of drugs for the treatment of brain cancer.

CONCLUSIONS

In this research study, it was demonstrated that the compounds under discussion, at a constant concentration of doxorubicin (2 μg/mL) with resveratrol and piperine and/or icariin, gradually decreased the viability of HeLa and CaSki cells at 24 hours, an activity that was further potentiated after 48 hours. In this way, the anticancer effect of the three biocompounds that support the anticancer activity of D, even increasing it, is clearly evident.

The study highlighted two main active compounds, one for each cell line under consideration. Thus, GNP_R1@DRPIc, which contains 3.6 μg/mL GNP_R1, 2 μg/mL D, 0.14 μg/mL R, 0.35 μg/mL P and 0.7 μg/mL Ic dramatically decreased HeLa cell viability at 24 hours, with an increase in the effect after 48 hours of incubation; and GNP_ R1@DIc, which contains 4.8 μg/mL GNP_R1, 2 μg/mL D and 1 μg/mL Ic, demonstrated the ability to decrease doxorubicin resistance of the CaSki cell line, also with a potentiation of the effect at 48 hours of incubation.

These results highlight the importance of multifunctional GNPs, as a general platform for doxorubicin delivery with the major advantage of reducing the negative effects on the heart that doxorubicin at higher concentrations causes.

The nanoparticles used for drug delivery were realized through a combinatorial strategy as well as multi-functionalized, GNP_R1@RPIc, opening a new strategy for designing future combination therapies against tumor tissues. The proposed strategy of synergistic drug delivery and chemical treatment of cancer cells, GNP_R1@DRPIc, improved the cytotoxicity and efficacy of doxorubicin on cervical cancer cells, offering advantages over treatment with doxorubicin or resveratrol, or other individual natural compounds.

The potentiation of the anticancer activity of doxorubicin through the interaction with gold nanoparticles and the natural biomolecules, resveratrol, piperine, and icariin could have clinical applications.

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