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ORIGINAL PAPERS

INTERACTION OF FUNCTIONALIZED GOLD NANOPARTICLES WITH BIOLOGICAL MEMBRANES

Madalina-Anca UJICA[1], Cristina-Teodora DOBROTĂ[2,a,b], Gheorghe TOMOAIA[3,c], Cristina-Lavinia ROȘOIU[4], Aurora MOCANU[5], Maria TOMOAIA-COTIȘEL[6,d]

[1]Chem. Eng., PhD student, Scientific Research Center of Excellence in Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, 11 Arany Janos St., 400028 Cluj-Napoca, Romania, (madalina.ujica@ubbcluj.ro).
[2]Assistant Professor, PhD, Scientific Research Center of Excellence in Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, 11 Arany Janos St., 400028 Cluj-Napoca, Romania;
[a]Department of Molecular Biology and Biotechnology, Faculty of Biology and Geology, Babeş-Bolyai University, 44 Republicii St., 400015 Cluj-Napoca, Romania,
[b]Academy of Romanian Scientists, 3 Ilfov St. 050044 Bucharest, Romania (cristina.dobrota@ubbcluj.ro)
[3]Prof., Habil., MD, PhD, Department of Orthopedics and Traumatology, Iuliu Hatieganu University of Medicine and Pharmacy, 47 General Traian Moşoiu St., 400132 Cluj-Napoca, Romania;
[c]Academy of Romanian Scientists, 3 Ilfov St., 050044 Bucharest, Romania, (tomoaia2000@yahoo.com).
[4]Student, Department of Molecular Biology and Biotechnology, Faculty of Biology and Geology, Babeş-Bolyai University, 44 Republicii St., 400015 Cluj-Napoca, Romania, (cristina.rosoiu@stud.ubbcluj.ro)
[5]Assistant professor, PhD, Scientific Research Center of Excellence in Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, 11 Arany Janos St., 400028 Cluj-Napoca, Romania, (mocanu.aurora@gmail.com).
[6]Prof., PhD, CS1, Scientific Research Center of Excellence in Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, 11 Arany Janos St., 400028 Cluj-Napoca, Romania;
[d]Academy of Romanian Scientists, 3 Ilfov St., 050044 Bucharest, Romania.
*Corresponding author e-mail: mcotisel@gmail.com, maria.tomoaia@ubbcluj.ro

Abstract. *The way gold nanoparticles, GNP, functionalized with various compounds, interact with cell membranes is of great interest for medical applications. The compounds used were trans-resveratrol, R, piperine, P, and icariin, Ic, with anticancer, antioxidant, and anti-inflammatory effects, as well as doxorubicin, D, with anticancer activity. Through the self-assembly mechanism, these compounds made a coating layer on the surface of gold, generating GNP@R/P/Ic/D nano drug carriers. They were developed to transport the active*

compounds into the cancer cell. The self-assembled layer on GNP was achieved through non-covalent interactions, including hydrogen bonds and electrostatic forces, which provide excellent stability to the functionalized nanoparticles and enhanced bioavailability of these compounds. Functionalized GNPs can interact with cell membranes and penetrate into cancer cells through various mechanisms, where they act on the DNA and might induce programmed cell death. Moreover, this study presents some interaction mechanisms of nanoparticles with cell membranes, such as cellular blebbing, which is an approach to destroy cancer cells. Thus, this study contributes to the understanding of action mechanisms of various anticancer compounds on cancerous membranes and cells.

Keywords: gold nanoparticles, cell membranes, cancer cells, doxorubicin, blebbing formation mechanism

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1.Introduction

Atmospheric and engineered nanoparticles have surrounded us, so it is very important to study their characteristics and more important, their interaction with biological membranes. Maybe it can be put the question why is so important the interaction with membranes and not with another cellular compartment, but the answer is simple: one of the main purposes of the biological membranes is to provide protection to cellular structure. So, if nanoparticles succeed in penetrating the biological membrane also the cellular content will be affected. There are cases when it is desirable that nanoparticles penetrate the biological membrane, and one example for this case is the nanoparticles used as drug carriers. To be able to know all these facts, it is necessary to know the structure of every single type of membrane and to research how they react in the presence of a specific type of nanoparticles.

The most well-known and studied metal nanoparticles are gold nanoparticles [1, 2]. One of the most important uses of gold nanoparticles is in the composition of various medicines for cancer treatment [3-6].

The interaction between gold nanoparticles (GNPs) and cellular membranes is a crucial area of research, particularly for drug delivery, cancer therapy, and nanomedicine. These interactions can significantly affect the behavior, efficacy, and safety of gold nanoparticles in biological systems.

Gold nanoparticles can interact with the lipid bilayer of the cell membrane [7]. Their size, surface charge, and surface chemistry influence how easily they penetrate the membrane [8]. In some cases, GNPs can passively diffuse through the membrane, while in others, they may be internalized via endocytosis or pinocytosis [9]. The most common route for GNP uptake into cells is through clathrin-mediated endocytosis, caveolae-mediated endocytosis, or macro-

pinocytosis, depending on their size and surface modification [10]. Once internalized, the nanoparticles can enter endosomes, where they may release their cargo, such as drugs, for targeted therapy [11].

To improve cellular uptake and targeting of specific cell types, GNPs are often functionalized with biomolecules like antibodies, peptides, or folate. These molecules can bind to specific receptors on the cell membrane, enhancing the nanoparticle's ability to recognize and enter cancer cells or other diseased cells. The surface charge (positive or negative) and hydrophobicity of GNPs also influence their interaction with the charged phospholipid bilayer [12,13].

High concentrations or improper surface functionalization of gold nanoparticles can cause membrane disruption, leading to cell damage or death [14]. GNPs may insert into the membrane, leading to local destabilization or changes in the membrane's integrity, which can result in cell lysis or apoptosis. The toxicity of GNPs depends on factors such as size, shape, surface charge, and exposure time. Some studies suggest that large nanoparticles or those with a high surface charge can induce more significant cytotoxic effects, including oxidative stress, inflammation, and cell membrane damage [15].

GNPs are often used to deliver therapeutic agents directly to cells. Their interaction with the cellular membrane is essential for controlled release, where the nanoparticles can deliver drugs, genes, or proteins. The ability to modify the surface of gold nanoparticles allows for tailoring the release rate and targeting the delivery to specific cells or tissues. Once inside the cell, GNPs can be used for controlled drug release by exploiting the acidic environment of endosomes or lysosomes. The interaction between GNPs and the membrane may trigger the release of the drug or cause a conformational change in the GNP that facilitates the release of the therapeutic agent [16].

Gold nanoparticles can also interact with specific membrane proteins, such as receptors or ion channels. This interaction can alter the function of these proteins, influencing cellular signaling pathways and affecting cell behavior. In the case of cancer cells, GNPs can potentially interfere with receptor-mediated signaling, enhancing the effectiveness of treatments. Functionalized GNPs can bind specifically to cell surface receptors involved in disease progression, such as epidermal growth factor receptors (EGFR) in cancer cells. This selective binding allows for targeted therapy, where GNPs deliver therapeutic agents directly to the diseased cells, minimizing damage to healthy cells [17].

Gold nanoparticles are often used in photothermal therapy to treat cancer. When GNPs accumulate in tumor cells, they can absorb light (especially near-infrared) and convert it to heat, which damages the tumor cells. The interaction of GNPs with the cancer cell membrane plays a key role in ensuring that

nanoparticles are selectively taken up by tumor cells, enhancing the effectiveness of the treatment [18].

Although gold is considered biocompatible, the interaction between GNPs and cellular membranes can still result in toxicity under certain conditions. Careful design of the size, shape, surface charge, and functionalization of the nanoparticles is crucial for minimizing unwanted effects. The long-term stability of gold nanoparticles in the bloodstream and their potential to accumulate in organs (such as the liver or spleen) due to membrane interactions are important factors to consider in designing GNP-based therapies [19].

The interaction between gold nanoparticles and cellular membranes is a fundamental aspect of their behavior in biological systems. These interactions determine their cellular uptake, therapeutic efficacy, and potential toxicity. By tailoring the surface properties of GNPs, it is possible to enhance their biocompatibility, improve targeted drug delivery, and optimize their use in cancer therapy, gene delivery, and immunotherapy. However, it is important to carefully consider factors like size, surface charge, and functionalization to minimize cytotoxic effects and maximize therapeutic outcomes.

2.Cell membrane

The cell membrane, also known as the plasma membrane, is a crucial structure that surrounds and protects the cell, separating its interior from the external environment [20]. It plays a vital role in maintaining the integrity of the cell and facilitating various cellular functions. Here’s an overview of the cell membrane's structure, functions, and importance.

2.1.Structure of the Cell Membrane

The fundamental structure of the cell membrane is a Langmuir monolayer or a Langmuir-Blodgett bilayer of oriented biomolecules, including lipids and phospholipids [21-35]. For instance, each phospholipid molecule has a hydrophilic (water-attracting) "head" and two hydrophobic (water-repelling) "tails". The hydrophilic heads face outward towards the aqueous environment, while the hydrophobic tails face inward, away from water, forming a semi-permeable barrier [36-42].

The membrane contains various proteins that are either embedded within the lipid bilayer (integral proteins) or attached to the surface (peripheral proteins). These proteins serve diverse functions, including transport, signaling, and structural support [43]. Carbohydrates are often attached to proteins (glycoproteins) or lipids (glycolipids) on the extracellular surface of the membrane. They play a key role in cell recognition, communication, and adhesion [44]. Cholesterol molecules are interspersed within the phospholipid bilayer,

contributing to membrane fluidity and stability. They help maintain membrane integrity, especially at varying temperatures [45].

2.2.Functions of the Cell Membrane

The cell membrane acts as a barrier that protects the cellular contents from the external environment and prevents the entry of harmful substances. It regulates the movement of substances into and out of the cell, allowing essential nutrients to enter while keeping out toxins and unwanted materials [46-56]. Membrane proteins facilitate communication between the cell and its environment through receptors that detect signaling molecules (ligands) such as hormones and neurotransmitters. Carbohydrates on the cell surface serve as recognition sites for other cells, facilitating processes such as immune response and tissue formation. The cell membrane contains proteins that help cells adhere to one another, forming tissues and maintaining structural integrity. The cell membrane facilitates various transport processes, including passive transport (diffusion, osmosis) and active transport (pumps, vesicular transport) [57-62].

The cell membrane is essential for maintaining homeostasis within the cell by regulating the internal environment and responding to changes in the external environment. The unique composition of lipids, vitamins, proteins, and carbohydrates in the membrane contributes to the identity of the cell, allowing it to interact appropriately with other cells and the extracellular matrix. The cell membrane's structure and properties are crucial for the proper functioning of the cell, influencing processes like metabolism, growth, and communication [63-68].

In summary, the cell membrane is a dynamic and essential structure that plays a critical role in protecting the cell, facilitating communication, and regulating transport, all of which are vital for the cell's survival and function.

3.Membrane models

Modeling cell membranes is an important approach in understanding their structure, function, and how they interact with various biological molecules. Cell membranes are complex structures, primarily composed of lipids, proteins, and carbohydrates. There are various methods and models used to simulate and study the behavior of cell membrane components at the molecular level [69-79]. Due to the complexity of biological membranes, it is first necessary to study the interaction of these complex nanoparticles with model cell membranes. Among the model membranes, frequently used are Langmuir lipid monolayers and Langmuir-Blodgett bilayers as well as liposomes; the interpretation of the experimental results is mainly based on the thermodynamic treatment of intermolecular interactions.

Certainly, the most common structures or methods used to model cell membranes are the following: lipid bilayer represents the fundamental structure of biological membranes, which consists of two layers of lipids with hydrophobic tails facing inward and hydrophilic heads facing outward. This structure provides a semi-permeable barrier. In this category we can speak about simplified lipid bilayer or monolayer models; these models focus on just the oriented biomolecules to study the basic properties of the membrane, like its fluidity, phase behavior, and permeability [80-84]. These models typically use phospholipids or other amphipathic molecules. Lipid bilayer in a water environment: more complex models include the surrounding water molecules, which interact with the hydrophilic heads of lipids. These models can be used to study the stability and dynamics of the membrane under different conditions [85, 86].

Molecular dynamics (MD) simulations are one of the most widely used techniques to model the behavior of cell membranes at the atomic level. In this approach, the positions of all atoms in the membrane and surrounding environment are tracked over time according to physical principles. These simulations can also incorporate membrane proteins, which can be embedded in the lipid bilayer. MD simulations are used to study how membrane proteins function, their conformational changes, and their interactions with lipids and other molecules (e.g., ions, drugs). MD simulations can reveal insights into membrane fluidity, protein-lipid interactions, membrane fusion, ion transport, and other membrane-associated processes [87].

In *coarse-grained models*, groups of atoms are treated as single interaction sites, which reduces computational complexity. This allows for the simulation of larger systems, such as entire membrane or larger structures like vesicles, over longer timescales. *Coarse-Grained Lipid Models*: for example, the *Martini model* is widely used to simulate lipid bilayers at a coarse-grained level. This model can simulate larger and longer systems while still providing insights into the behavior of lipids, proteins, and their interactions. Coarse-grained models allow researchers to study large-scale processes (e.g., membrane curvature, large protein complexes) without the computational cost of all-atom simulations [88].

Monte Carlo (MC) simulations use random sampling to calculate properties of a system, and in membrane modeling, this technique can be used to study lipid and protein distributions, membrane folding, and phase transitions. Unlike MD, Monte Carlo does not track atomic positions continuously but instead focuses on statistical properties [89].

Poisson-Boltzmann models are used to study electrostatic interactions in biological membranes. Since cell membranes often have an electrostatic potential due to the charged components of lipids and proteins, Poisson-Boltzmann models

help calculate how these charges influence the membrane's properties [89]. *Ion channel models* are particularly useful in understanding ion transport across the membrane, including the interactions of ions with membrane proteins like ion channels and pumps [90].

While computational models provide detailed insights, experimental techniques are also crucial for validating models of cell membranes. Cryo-Electron Microscopy (Cryo-EM) technique allows for the direct imaging of membrane structures at high resolution [91]. It has been instrumental in understanding the structure of membrane proteins and their interactions with lipids. Fluorescence Microscopy can be used to study membrane dynamics and protein localization in living cells. These experimental observations can be compared to computational predictions to validate membrane models [92]. Atomic Force Microscopy (AFM) can be used to study membrane properties like stiffness, surface morphology, and interactions at the nanoscale level [71, 93-95].

Hybrid models combine different simulation techniques (e.g., MD for the lipid bilayer and continuum models for the surrounding environment) to capture various aspects of membrane behavior across different scales. This can be useful for studying complex phenomena such as membrane fusion, vesicle formation, and interactions with other cellular components [96].

Understanding cell membranes is critical in various fields, including drug delivery, where membrane models help design drug delivery systems, including liposomes and nanoparticles, to ensure efficient drug transport across cell membranes. Studying how viruses interact with cell membranes can aid in the development of antiviral therapies. For example, understanding how viral proteins mediate fusion with host cell membranes is key to developing inhibitors. Membrane models can help study the mechanisms of ion channels, transporters, and pumps, which are essential in regulating cell function. Membrane models are used to study how cancer cells alter membrane properties for processes like metastasis, as well as how to target cancer cell membranes for therapy.

Cell membrane modeling is a powerful tool for understanding the complex interactions that govern cellular processes. Techniques like molecular dynamics simulations, coarse-graining, Langmuir monolayers and Langmuir-Blodgett supramolecular structures and experimental validation help provide detailed insights into the structure and behavior of cell membranes. These models play a crucial role in drug design strategies, studying disease mechanisms, and understanding cellular functions at the molecular level.

4.Cell membrane transport

Cell membrane transport refers specifically to the mechanisms by which substances move across the cell membrane, which is crucial for maintaining the

cell's internal environment and overall function. Transport through the cell membrane is of utmost interest because through it cells obtain essential nutrients and ions necessary for metabolic processes; cells expel waste products to maintain homeostasis; transport mechanisms are involved in signaling processes and communication with other cells and they are essential for processes like nerve impulse transmission and muscle contraction [97-98]. The cell membrane, also known as the plasma membrane, is a selectively permeable barrier composed of a lipid bilayer with embedded proteins. Across the cell membrane there are different types of transport processes [99].

4.1.Passive Transport

Passive transport does not require energy input from the cell. Substances move across the membrane down their concentration gradient (from high to low concentration) [100-103]. The passive transport options are:

- Simple diffusion: small, nonpolar molecules (e.g., oxygen, carbon dioxide) pass directly through the lipid bilayer [104].

- Facilitated diffusion: larger or polar molecules (e.g., glucose, ions) pass through specific transport proteins (channels or carriers) embedded in the membrane [105,106].

- Osmosis: the diffusion of water across a selectively permeable membrane. Water moves from an area of lower solute concentration to an area of higher solute concentration [107].

4.2.Active Transport

Active transport requires energy, usually in the form of ATP, to move substances against their concentration gradient (from low to high concentration) [108,109]. In this case we speak about:

- Primary Active Transport: direct use of ATP to transport molecules. An example is the sodium-potassium pump, which moves sodium ions out of the cell and potassium ions into the cell [110].

- Secondary Active Transport (Cotransport): uses the energy created by primary active transport to move other substances. This can be further divided into symport (both substances move in the same direction) and antiport (substances move in opposite directions (e.g., sodium and calcium)) [111,112].

4.3.Vesicular Transport

This involves the transport of large molecules or particles through vesicles and includes two main processes [113]:

- Endocytosis: the process by which cells engulf substances to bring them into the cell. The three types of endocytosis are: phagocytosis (engulfing large particles (cell eating)), pinocytosis (engulfing liquids (cell drinking)) and receptor-mediated endocytosis (specific uptake of molecules via receptors) [114].

- Exocytosis: the process by which cells expel materials in vesicles that fuse with the plasma membrane, releasing their contents outside the cell [115].

5.Cell blebbing

Cell blebbing refers to the formation of small, bubble-like protrusions from the cell surface, known as "blebs." This phenomenon can occur during various cellular processes and is associated with specific biological functions and pathologies. Blebs appear as rounded, membrane-bound extensions from the surface of the cell. They can vary in size and number depending on the cellular context. Blebs are generally transient structures that can form and retract rapidly [115-118].

5.1.Causes of Cell Blebbing

Blebbing is a hallmark of apoptosis, where cells undergo characteristic morphological changes. During apoptosis, the cell membrane begins to bulge outward, forming blebs as the cell breaks down. This process facilitates the eventual fragmentation and removal of the dying cell by immune cells [119-122].

Blebbing can occur in response to mechanical injury, oxidative stress, or exposure to toxins. In these situations, the integrity of the cell membrane is compromised, leading to the formation of blebs. Cells under stress may exhibit blebbing as a way to adapt to unfavorable conditions.

The cytoskeleton, a network of protein filaments within the cell, is critical for maintaining cell shape and stability. Disruption of cytoskeletal components, such as actin filaments, can lead to blebbing. Changes in the actin cytoskeleton often promote bleb formation by allowing the membrane to extend outward.

During inflammation, immune cells can exhibit blebbing as part of their activation and response to pathogens [123, 124].

5.2.Mechanisms of Cell Blebbing

Blebbing is often associated with changes in membrane tension and cytoskeletal dynamics. When internal pressure increases or the cytoskeleton is disrupted, the membrane can bulge and form blebs. Certain signaling pathways, particularly those involving phospholipids like phosphatidylserine, can trigger blebbing by altering membrane properties and cytoskeletal interactions [116].

In the context of programmed cell death, blebbing is essential for ensuring that dying cells are efficiently removed by neighboring cells or immune cells, minimizing inflammation and damage to surrounding tissues. In cells experiencing stress, blebbing can serve as an early indicator of potential cell dysfunction or death, highlighting the need for investigation into underlying causes.

Understanding the mechanisms and consequences of blebbing has implications for various fields, including cancer research, neurobiology, and developmental biology, as alterations in blebbing may affect disease progression and treatment responses [121, 125].

Cell blebbing is a dynamic process that occurs in various biological contexts, particularly during apoptosis and in response to cellular stress. It reflects significant changes in cell shape and membrane integrity and plays a pivotal role in processes such as cell death and immune response [120-125].

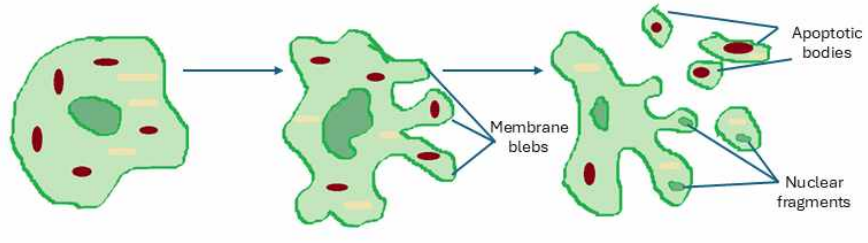

Fig. 1. Blebbing mechanism

6.Gold nanoparticles and cancer cell membrane

Since the mid-1900s, there has been great interest in the synthesis of gold nanoparticles. Classically, the Turkevich method [126] involves the reduction of Au3+ ions to atomic form using trisodium citrate as a reducing agent. Over time, this method has been improved in order to obtain gold nanoparticles with controlled shapes and sizes [127]. For this, not only the reagent conditions were modified, but various reducing agents, both chemical and biological, were introduced, and in 2015 we also managed to obtain spherical GNPs with a small diameter (20 nm), using resveratrol as a reducing agent [5].

Since gold nanoparticles have applications in the biomedical sphere, it is very important to know their cytotoxicity, which may be positive in the case of the fight against cancer cells, or undesirable for other uses. So, when we speak about its antibacterial activity it is very important to be able to destroy the bacterial cells, fact that was demonstrated by a group of researchers from India and Korea, who showed the activity of gold nanoparticles against Escherichia coli and Bacillus subtilis [128].

Plus, gold nanoparticles with 7 nm and 55 nm have activity against Helicobacter pylori [129]. Besides the antibacterial activity, it has been shown that gold nanoparticles can be used as topical transporters because they could cross the stratum corneum from the derma [130]. Sometimes gold nanoparticles need to be helped to transport active substances, so the idea of their function with polyethylene glycol appears has emerged that only avoids the formation of a corona protein and thus the complex is not detected by the immune system. Also, in the medical area we can speak about anticancer drugs, as curcumin (a natural phenolic antioxidant). It was proved that gold nanoparticles help curcumin in its job and increase the cytotoxicity against cancerous cells but not affecting the healthy cells [131].

Figure 2 presents the interaction of GNPs with the membrane of cancer cells. One of the most well-known methods for gold nanoparticles to cross the membrane of cancer cells is through endocytosis. This is allowed due to the increased porosity of cancer cells compared to healthy ones.

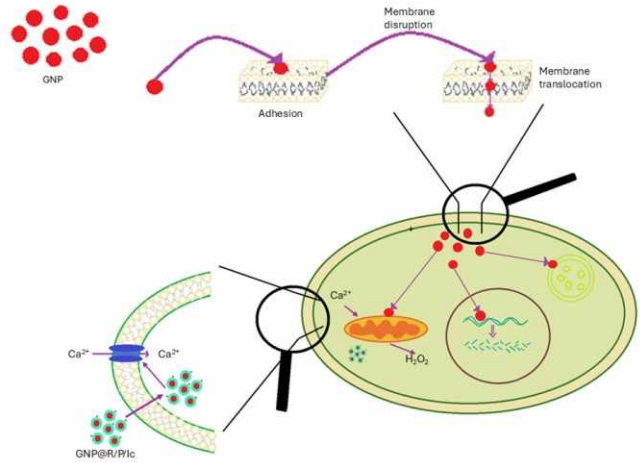

Fig. 2. Interaction of GNPs with the membrane of cancer cells.
Interaction of functionalized GNPs (e.g., GNP@R/P/Ic or GNP@R/P/Ic/D) with the biological membrane of cancer cells, symbolized by a membrane model as dipalmitoyl phosphatidyl choline, DPPC, bilayer with charged zwitterionic polar head groups. The kinetics of nanocarriers uptake: adhesion, direct translocation, endocytosis, or mixed entry into the cell.

Once inside the cell, gold nanoparticles act in several ways, attacking several cellular parts, in order to destroy the cancer cell. They attack the nucleus, having the ability to break the DNA double helix [132-134].

They will also attack cellular organelles such as lysosomes [135-140] and mitochondria [141-145]. In the case of gold nanoparticles functionalized with different biomolecules, such as resveratrol, piperine and icariin (GNP@R/P/Ic) and with doxorubicin, GNP@R/P/Ic/D, the phenomenon of oxidative stress

occurs. This happens because the nanoparticles cause the opening of calcium channels and thus, mitochondria are stimulated to generate oxidative stress [146] within the cell. Once inside the cell, the gold nanoparticles tend to associate in the form of clusters.

In some cases, GNPs do not cross this barrier alone, but they are functionalized with different biomolecules [137-154]. Following these conjugations and functionalization, the complexes formed pass together through the cell membrane. Among the most used biomolecules are curcumin, astaxanthin, piperine, resveratrol and icariin. Curcumin and gold nanoparticles have garnered significant attention in the field of cancer research due to their potential therapeutic applications. Curcumin, a polyphenol extracted from turmeric, a spice commonly used in cooking and traditional medicine, is known for its antioxidant, anti-inflammatory and anticancer properties and action on the central nervous system [155]. Curcumin exhibits cytotoxic effects on various cancer cell lines through multiple mechanisms, including induction of apoptosis (programmed cell death); inhibition of cell proliferation; modulation of multiple signaling pathways, including those involved in inflammation; suppression of angiogenesis. Encapsulation of curcumin in GNPs can enhance its stability, protecting it from degradation and improving its bioavailability [156-160]. Also, the combination of curcumin and gold nanoparticles can enhance the anticancer effects of both agents. GNPs can improve the delivery and effectiveness of curcumin while curcumin can enhance the cytotoxicity of gold nanoparticles. Studies have shown that curcumin-conjugated gold nanoparticles can effectively induce apoptosis in cancer cells, inhibit tumor growth, and enhance the efficacy of radiation therapy. Various formulations have been developed by incorporating curcumin and gold nanoparticles, demonstrating improved therapeutic outcomes in preclinical models of cancer. These nanocarriers can be designed to release curcumin in a controlled manner, thereby increasing its therapeutic potential and minimizing side effects [161-163].

Astaxanthin and gold nanoparticles have emerged as promising agents in cancer research due to their unique properties and potential synergistic effects in cancer treatment. Astaxanthin is a carotenoid pigment found in various algae and seafood, such as shrimp, salmon, and trout. It is known for its powerful antioxidant properties. It has garnered interest in cancer research due to its ability to scavenge free radicals and modulate cell signaling pathways. Astaxanthin is more potent than other antioxidants in protecting cells from oxidative stress, reducing inflammation, and preventing damage to cellular components [164, 165]. Astaxanthin has been shown to inhibit cancer cell proliferation and induce apoptosis in various cancer types, including breast, prostate, and colon cancers. It modulates signaling pathways such as NF-κB, MAPK, and PI3K/Akt, which are

involved in cell survival, growth, and differentiation. Astaxanthin can enhance the effectiveness of certain chemotherapy drugs and reduce their side effects. The combination of astaxanthin and gold nanoparticles can enhance the anticancer effects of both agents. GNPs may improve the delivery of astaxanthin to the target site, increasing its therapeutic efficacy while minimizing side effects. Preliminary studies have shown that astaxanthin-loaded gold nanoparticles can effectively inhibit cancer cell growth and induce apoptosis in various cancer cell lines. This combination has the potential to improve treatment outcomes when used in conjunction with other modalities, such as chemotherapy or radiation therapy [166-169].

Piperine, a bioactive compound found in black pepper, and GNPs are being explored in cancer research due to their potential synergistic effects in cancer treatment. Piperine has shown promise as a potential anticancer agent in several studies [170-175]. It has been found to possess anti-inflammatory, antioxidant and pro-apoptotic properties that may help in the treatment of various cancers. Piperine works by: inducing apoptosis (programmed cell death) in cancer cells; inhibiting cancer cell proliferation by affecting cell cycle regulators; modulating molecular pathways involved in cancer; enhancing the bioavailability of other anticancer drugs by inhibiting drug-metabolizing enzymes, which may improve the efficacy of conventional chemotherapy [176-179]. Combining piperine with gold nanoparticles could have a synergistic effect in cancer treatment. Piperine could enhance the uptake of gold nanoparticles into cancer cells, improving the efficacy of treatment. The combination may help in inducing apoptosis in cancer cells, while also modulating cancer cell signaling pathways and enhancing the effects of gold nanoparticles in targeting and killing cancer cells [180-184].

Resveratrol is a polyphenol produced by plants, such as grape skins, in response to infection or injury. It can form complexes with GNPs, whose biocompatibility has been demonstrated, making it a good candidate for drug potentiation [185-188]. Numerous studies have demonstrated the many beneficial effects that this phytoalexin has on the living organism, including anti-inflammatory action, modulation of lipid metabolism and inhibition of platelet aggregation [189-190]. Even alone, resveratrol has a mild anticancer action that manifests itself by sensitizing cancer cells [191], but it has been demonstrated that it reduces cellular oxidative stress and inflammation [127, 192] and modulates the activity of doxorubicin in cervical cancer cells, HeLa and CaSki, inducing cell death through apoptosis [30]. Resveratrol can decrease the side effects of doxorubicin, while also leading to protection against tumor initiation and development [193].

Icariin, a flavonoid compound found in Epimedium (commonly known as Horny Goat Weed), and gold nanoparticles are also being explored in cancer research for their potential therapeutic benefits. Both have demonstrated promising properties individually, and their combination is being studied for synergistic effects in cancer treatment. Icariin has shown potential as an anticancer agent through several mechanisms, including induction of apoptosis [194-198]. Icariin has been reported to promote apoptosis (programmed cell death) in various cancer cell lines, which is crucial for limiting cancer cell survival; inhibition of cancer cell proliferation: Icariin can block cell cycle progression in cancer cells, effectively slowing or stopping their division and growth. Icariin may help prevent cancer cells from spreading to other parts of the body by inhibiting factors involved in metastasis, such as matrix metalloproteinases (MMPs). Icariin can affect several molecular pathways involved in cancer, which are often upregulated in cancer cells and promote their survival and proliferation. Icariin has been shown to increase the sensitivity of cancer cells to chemotherapy drugs, potentially allowing lower doses of conventional chemotherapy agents to be more effective. The combination of icariin and gold nanoparticles is an exciting area of research in cancer therapy. Gold nanoparticles can be used as carriers for icariin, ensuring that the compound is delivered specifically to cancer cells. This targeted delivery could improve the drug's efficacy while minimizing toxicity to healthy tissues. Icariin can enhance the anticancer effects of gold nanoparticles. For instance, the combination could potentially improve the ability of GNPs to generate heat or promote apoptosis in tumor cells, leading to enhanced tumor destruction. Icariin has low bioavailability when taken orally, but by encapsulating it in gold nanoparticles, its bioavailability could be improved, leading to more effective treatment. Icariin may help overcome resistance to chemotherapy drugs by modulating drug resistance pathways. Combined with gold nanoparticles, this could enhance the overall therapeutic response of tumors that are resistant to conventional treatments. Icariin’s ability to inhibit cancer cell growth and promote apoptosis can be complemented by the photothermal properties of gold nanoparticles, which can offer a multi-pronged attack on cancer cells [199-201].

7.Functionalized gold nanoparticles and cancer cells

7.1.Doxorubicin and cancer cells

Doxorubicin (DOX) is a widely used chemotherapeutic agent that is particularly effective against various types of cancer, such as breast cancer, lymphoma, and leukemia. The drug works by targeting cancer cells through several mechanisms [202]. Here's an overview of how doxorubicin targets and kills cancer cells:

- DNA Intercalation: doxorubicin primarily exerts its cytotoxic effects by intercalating (inserting) itself between the base pairs of DNA. This disrupts the normal structure of the DNA helix, inhibiting the ability of cancer cells to replicate or transcribe their DNA. As a result, the cell cannot produce the necessary proteins for growth and division. The aromatic rings in the doxorubicin molecule intercalate between the DNA base pairs, causing structural distortion and preventing the action of key enzymes like DNA polymerase and RNA polymerase. This leads to a halt in DNA replication and transcription [203].

- Inhibition of Topoisomerase II: doxorubicin also inhibits the action of topoisomerase II, an enzyme that is essential for DNA replication. Topoisomerase II makes temporary cuts in the DNA strands to relieve torsional stress during replication and transcription. When doxorubicin interferes with topoisomerase II, it prevents the enzyme from resealing the DNA breaks, leading to double-stranded DNA breaks that ultimately trigger cell death via apoptosis. By stabilizing the complex between topoisomerase II and DNA, doxorubicin prevents the proper repair of DNA breaks, causing permanent damage to the cancer cells [204].

- Generation of Reactive Oxygen Species (ROS): doxorubicin induces the formation of reactive oxygen species (ROS), which are highly reactive molecules that can damage cellular components such as lipids, proteins, and DNA. The accumulation of ROS causes oxidative stress, which further contributes to DNA damage and disrupts cell function. Doxorubicin undergoes redox cycling, where it gets reduced and re-oxidized in the cell, generating ROS in the process. These ROS can lead to cellular damage and induce cell death pathways like apoptosis [205].

- Apoptosis Induction: when doxorubicin induces significant DNA damage, the cell's repair mechanisms are overwhelmed, leading to activation of apoptotic pathways (programmed cell death). The cancer cells essentially self-destruct to prevent the spread of DNA damage, although some may become resistant to this process. Doxorubicin activates several pro-apoptotic proteins, including p53, BAX, and caspases, which orchestrate the death of the cancer cell. It can also increase the expression of pro-apoptotic genes and decrease the expression of anti-apoptotic proteins [206].

- Cell Cycle Arrest: doxorubicin can also cause cell cycle arrest, particularly in the G1 and S phases of the cell cycle. By inhibiting DNA replication and causing DNA damage, it prevents the cell from progressing through the cell cycle. This arrest gives the cell time to repair the damage, but in cancer cells, the damage is often too severe to repair, leading to cell death. The activation of checkpoint kinases such as ATM and ATR causes cell cycle arrest by activating tumor suppressor proteins like p53 [207].

- Targeting Tumor Vascularity: in some cases, doxorubicin can also target the blood vessels supplying the tumor. Doxorubicin can penetrate the blood vessel walls of the tumor more effectively because tumor vasculature is often irregular and leaky. This allows the drug to accumulate at higher concentrations in the tumor tissue. Tumor blood vessels lack the integrity of normal blood vessels, which facilitates the extravasation of doxorubicin into the tumor microenvironment [208].

- Drug Resistance Mechanism: while doxorubicin is effective, many tumors eventually develop resistance mechanisms that reduce its effectiveness. These mechanisms include: efflux pumps (e.g., P-glycoprotein) - these pumps actively transport doxorubicin out of the cancer cells, reducing its intracellular concentration [209].

- Altered DNA repair pathways: cancer cells may enhance their DNA repair capacity, allowing them to repair the damage caused by doxorubicin [210].

- Altered apoptotic pathways: mutations or changes in the regulation of apoptotic proteins can allow cancer cells to survive even in the presence of doxorubicin [211].

Doxorubicin is typically administered intravenously and is often used in combination with other chemotherapeutic agents to enhance its therapeutic effect. While effective against cancer cells, doxorubicin is also toxic to normal, rapidly dividing cells, such as those in the bone marrow, gastrointestinal tract, and heart. One of the most concerning side effects is cardiotoxicity, which can lead to heart failure in some patients, especially at higher cumulative doses [212].

Efforts are being made to improve the specificity of doxorubicin for cancer cells to minimize damage to healthy cells. Some strategies include: nanoparticle-based delivery - encapsulating doxorubicin in nanoparticles or liposomes to increase its accumulation at the tumor site; targeted delivery: attaching antibodies or ligands to the doxorubicin molecule that specifically bind to receptors overexpressed on cancer cells, thereby enhancing drug delivery to the tumor [213, 214].

7.2.Resveratrol and cancer cells

Resveratrol is a naturally occurring polyphenolic compound found in certain plants, most notably in the skin of red grapes, and is also present in other foods like berries, peanuts, and dark chocolate. It has garnered significant attention in cancer research due to its potential anticancer properties. Resveratrol has been shown to influence a variety of cellular mechanisms that can help inhibit cancer cell growth, induce apoptosis (programmed cell death), and prevent metastasis [215]. Here's a closer look at how resveratrol targets cancer cells:

- Antioxidant Activity: resveratrol is a potent antioxidant that can scavenge reactive oxygen species (ROS) and free radicals, which are known to cause DNA damage, oxidative stress, and promote cancer development. By neutralizing ROS, resveratrol can help prevent the initiation and progression of cancer. Resveratrol inhibits the formation of ROS and regulates the activity of antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby reducing oxidative stress in cells. In cancer cells, this can help prevent DNA mutations and damage to critical tumor suppressor genes [216].

- Cell Cycle Arrest: resveratrol has been shown to induce cell cycle arrest in various types of cancer cells, particularly at the G1/S and G2/M checkpoints. By halting the cell cycle, resveratrol prevents the proliferation of cancer cells and gives them time to repair DNA damage or undergo programmed cell death. Resveratrol can upregulate the expression of cell cycle inhibitors such as p21 and p53 while downregulating the expression of cyclins and cyclin-dependent kinases (CDKs), which are necessary for cell cycle progression. This leads to cell cycle arrest and inhibition of cancer cell division [217].

- Induction of Apoptosis: one of the keyways resveratrol exerts anticancer effects is by promoting apoptosis (programmed cell death) in cancer cells. This is critical because many cancer cells evade apoptosis, allowing them to grow uncontrollably. Resveratrol activates multiple apoptotic pathways, including both intrinsic (mitochondrial) and extrinsic (death receptor) pathways: intrinsic pathway - resveratrol induces mitochondrial membrane potential collapse and activates pro-apoptotic proteins like BAX and caspases (particularly caspase-9 and caspase-3). This leads to DNA fragmentation and cell death; extrinsic pathway - resveratrol can also upregulate death receptors such as Fas and TRAIL, activating the extrinsic apoptotic pathway that involves caspase-8 activation [218].

- Inhibition of Tumor Growth and Angiogenesis: resveratrol has been shown to inhibit angiogenesis, the process by which new blood vessels are formed to supply growing tumors. By blocking angiogenesis, resveratrol can reduce the tumor's ability to receive nutrients and oxygen, thereby limiting its growth. Resveratrol suppresses the expression of vascular endothelial growth factor (VEGF), a key pro-angiogenic factor. It also inhibits signaling pathways like PI3K/Akt and MAPK, which are involved in angiogenesis and tumor survival. This can reduce tumor vascularization and impair cancer cell growth [219].

- Inhibition of Metastasis: resveratrol has been reported to reduce the metastatic potential of cancer cells by affecting key signaling pathways involved in cell migration, adhesion, and invasion. Metastasis is a major cause of cancer-related deaths, so blocking this process is crucial for cancer treatment. Resveratrol

suppresses the expression of matrix metalloproteinases (MMPs) and chemokines, which play critical roles in the degradation of extracellular matrix (ECM) components and facilitate tumor cell invasion into surrounding tissues. Resveratrol also inhibits NF-κB, a key transcription factor involved in metastasis [220].

- Inhibition of Inflammatory Pathways: chronic inflammation is closely linked to cancer development. Resveratrol has anti-inflammatory properties that can help reduce the inflammatory environment that supports tumor growth and progression. Resveratrol inhibits the NF-κB pathway, which regulates the expression of pro-inflammatory cytokines like TNF-α and IL-6. By blocking this pathway, resveratrol reduces inflammation and the potential for cancer initiation and progression [221].

- Epigenetic Modulation: resveratrol can also influence epigenetic modifications such as DNA methylation and histone modifications, which regulate gene expression without altering the underlying DNA sequence. These modifications can impact tumor suppressor genes and oncogenes. Resveratrol has been shown to inhibit histone deacetylases (HDACs), which leads to increased acetylation of histones and activation of tumor suppressor genes. Additionally, resveratrol can modulate the expression of genes involved in DNA repair, apoptosis, and cell cycle regulation through epigenetic mechanisms [222].

- Modulation of Key Signaling Pathways: resveratrol interacts with several important molecular signaling pathways that regulate cell growth, survival, and differentiation. Some of these include: I3K/Akt pathway - resveratrol inhibits the PI3K/Akt signaling pathway, which is often dysregulated in cancer cells and promotes cell survival, growth, and resistance to apoptosis. MAPK/ERK pathway - resveratrol downregulates the MAPK/ERK pathway, which is involved in cell proliferation and differentiation. This contributes to the inhibition of cancer cell growth and migration. SIRT1 activation: - resveratrol activates SIRT1, a NAD+-dependent deacetylase that plays a role in regulating DNA repair and apoptosis. SIRT1 activation has been linked to the regulation of tumor suppressor proteins like p53 [223].

- Synergistic Effects with Other Therapies: resveratrol has been studied for its potential to enhance the effects of conventional cancer treatments such as chemotherapy and radiation therapy. It may increase the sensitivity of cancer cells to these therapies by sensitizing them to apoptosis or reducing drug resistance mechanisms. Resveratrol can potentiate the effects of chemotherapy drugs by modulating multidrug resistance (MDR) proteins like P-glycoprotein and improving the accumulation of chemotherapeutic agents inside cancer cells [224, 225].

A growing body of preclinical studies has demonstrated the anticancer effects of resveratrol in vitro (in cell cultures) and in vivo (in animal models). However, the clinical evidence in humans is still emerging, with some early-stage trials suggesting that resveratrol may have potential as an adjunctive therapy in cancer treatment, particularly due to its ability to modulate various signaling pathways [226]. The bioavailability of resveratrol is relatively low, which has been a limitation in translating preclinical findings into effective human therapies. Research is ongoing to develop methods to improve its absorption and stability, such as using resveratrol-loaded nanoparticles or combining it with other compounds to enhance its efficacy.

7.3.Gold nanoparticles with doxorubicin and resveratrol in cancer therapy

The functionalization of gold nanoparticles (GNPs) with resveratrol and doxorubicin (DOX) has emerged as a promising strategy in cancer therapy, combining the unique properties of gold nanoparticles with the therapeutic benefits of resveratrol and doxorubicin [227, 228]. This approach aims to enhance the delivery and efficacy of the drugs, improve their bioavailability, and reduce side effects by targeting cancer cells more specifically [229]. Let's explore how each component contributes to this strategy and how functionalization works in cancer therapy.

Gold nanoparticles have unique optical, electronic, and chemical properties that make them attractive candidates for drug delivery systems in cancer therapy [230]. Their small size, biocompatibility, and ease of functionalization allow for precise control over the delivery of therapeutic agents [231]. Some key advantages of GNPs in cancer therapy include: enhanced stability - gold nanoparticles are stable in biological environments, which helps in maintaining the integrity of the attached drugs (resveratrol and doxorubicin); surface modification -the surface of GNPs can be easily modified with various molecules (e.g., peptides, antibodies, or small molecules like resveratrol and doxorubicin) to enable targeted delivery to specific cells or tissues; surface charge - the surface charge of GNPs can be adjusted to optimize cellular uptake via endocytosis, enhancing drug accumulation inside cancer cells; biocompatibility - gold is biocompatible and non-toxic, making it an ideal platform for drug delivery, with minimal side effects compared to conventional therapies [232-234].

Resveratrol has been found to enhance the sensitivity of cancer cells to chemotherapy drugs, like doxorubicin. By incorporating resveratrol onto gold nanoparticles, it may potentiate the anticancer effects of doxorubicin while reducing resistance mechanisms in the cells.

Resveratrol can be conjugated to the surface of gold nanoparticles via covalent bonding (using thiol groups or other functional groups) or non-covalent

interactions (like π-π stacking or hydrophobic interactions). The gold nanoparticles may be coated with a layer of resveratrol either alone or as part of a mixed polymeric or ligand system, enhancing the biocompatibility and targeted delivery properties [235].

Cancer cells have an increased tendency to internalize nanoparticles compared to normal cells. By conjugating doxorubicin to gold nanoparticles, the drug can be delivered directly to the tumor cells, improving its therapeutic efficacy. Gold nanoparticles can be engineered to release doxorubicin in a controlled manner at the tumor site. This controlled release minimizes systemic toxicity while ensuring a high concentration of the drug at the target site. Doxorubicin and resveratrol, when delivered together through gold nanoparticles, may work synergistically to induce greater cancer cell death through multiple mechanisms (e.g., apoptosis, cell cycle arrest, oxidative stress) [236, 237].

Doxorubicin can be attached to gold nanoparticles via thiol groups, amine groups, or disulfide bonds. The doxorubicin is typically conjugated to a linker molecule that is capable of being cleaved in the tumor environment (e.g., by acidic pH or by enzymatic activity), thereby releasing the drug in a controlled fashion. Doxorubicin is often conjugated to nanoparticles with a pH-sensitive linker, allowing the drug to be released specifically in the acidic environment of the tumor or inside cancer cells (via endocytosis and lysosomal degradation) [238-240].

The functionalization of both resveratrol and doxorubicin on the same gold nanoparticle is a highly promising strategy for improving cancer therapy. Here's how these two agents can work together: synergistic action - resveratrol and doxorubicin target different aspects of cancer cell survival. Doxorubicin induces DNA damage and apoptosis, while resveratrol can modulate cancer cell signaling, reduce drug resistance, and enhance the sensitivity of cancer cells to chemotherapy. By encapsulating both resveratrol and doxorubicin in gold nanoparticles, the overall side effects of each drug can be reduced. The drugs are delivered specifically to cancer cells, minimizing damage to healthy tissues. Resveratrol can help overcome doxorubicin resistance by inhibiting efflux pumps like P-glycoprotein (MDR), which is responsible for pumping chemotherapy drugs out of cancer cells. This increases the intracellular concentration of doxorubicin, improving its effectiveness [241].

The gold nanoparticles loaded with resveratrol and doxorubicin can be engineered to release the drugs in a targeted and controlled manner: the acidic environment of the tumor (pH ~ 6.5–7.0) or the acidic lysosomal compartments of cancer cells (pH ~ 4.5–5.0) can trigger the release of doxorubicin [242]. Resveratrol, being a small molecule, can also be released in a similar fashion, or

its release may be more gradual. Certain linkers between the nanoparticles and the drugs can be cleaved by tumor-specific enzymes, ensuring that drug release happens specifically at the tumor site. Gold nanoparticles have unique optical properties and can be heated upon exposure to near-infrared (NIR) light. This can be used to trigger the controlled release of doxorubicin or resveratrol from the nanoparticles.

Functionalized GNPs can target cancer cells more precisely due to the use of targeting ligands (e.g., folic acid, antibodies) or the inherent affinity of resveratrol for tumor cells. By using gold nanoparticles as carriers, both resveratrol and doxorubicin can be delivered directly to the tumor, reducing their exposure to healthy tissues and thus minimizing side effects such as cardiotoxicity (from doxorubicin). The combination of resveratrol's anticancer effects with doxorubicin's and another anticancer drug's chemotherapeutic effects [243, 244] and/or with various bioactive composites [245-247] could lead to a more potent therapeutic response through synergistic therapy [127].

The functionalization of gold nanoparticles with resveratrol and doxorubicin represents a novel and promising strategy for cancer therapy, combining the unique properties of nanoparticles with the therapeutic benefits of two potent anticancer agents [244]. This approach holds the potential for improving the targeting, efficacy, and safety profile of conventional chemotherapies, while reducing side effects and overcoming drug resistance. However, more research is needed to optimize formulation and delivery systems for clinical application.

Conclusions

Currently, metal nanoparticles, and especially gold nanoparticles, are of great interest in the fight against cancer. In order for this fight to be waged, it is absolutely necessary to study their interactions on model membranes and then on living cancer cells.

Although gold nanoparticles are generally biocompatible, their long-term toxicity, especially after repeated administration, is still under investigation. Their proper surface coating and functionalization with doxorubicin are crucial to enhance drug toxicity on cervical cancer cells. For this approach to be clinically viable, there will need to be extensive testing for safety, pharmacokinetics, and long-term effects. Manufacturing gold nanoparticles with consistent quality, functionality, and drug loading is a challenge that must be addressed for large-scale clinical applications.

This study presents the possible interactions of gold nanoparticles, either alone or functionalized with doxorubicin, D, (a drug with anticancer activity), as GNP@D nanoparticles with biological membranes of cervical cancer cells. Also,

GNPs was multi-functionalized with natural biomolecules, such as resveratrol, R, piperine, P, and icariin, Ic, (as adjuvant compounds with demonstrated anticancer activity, antioxidants and anti-inflammatory effects) resulting in GNP@R/P/Ic nanoparticles. Moreover, these carriers were functionalized with doxorubicin resulting GNP@R/P/Ic/D nanoparticles, which were used in interaction with biological membranes and with cervical cancer cells. Whether we are talking about the modes of transport through biological membranes or the mechanisms of membrane disruption, such as the blebbing phenomenon, all these membrane effects are of great interest to enhance the cytotoxicity of these carriers against cancer cells, having a minimal effect on healthy tissue and normal cells.

Most prior studies on metal nanoparticles and membrane interactions used simplified model membranes. In contrast, biological membranes are highly complex [248] containing thousands of lipid species, carbohydrates and proteins [249] that, significantly affect membrane structure, dynamics, and elasticity. They also exhibit lateral organization, which plays key functional roles as suggested by the raft concept [250], although not forming stable macrodomains as in model systems.

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