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REVIEW

GOLD NANOPARTICLES: FROM SYNTHESIS THROUGH FUNCTIONALIZATION TO BIOMEDICAL APPLICATIONS

REVIEW

Madalina Anca UJICA[1], Cristina-Teodora DOBROTA[1,2], Gheorghe TOMOAIA[3,4], Aurora MOCANU[1], Cristina-Lavinia ROSOIU[2], Ionel MANG[1,3], Viorica RAISCHI[1,5], Maria TOMOAIA-COTISEL[1,4*]

[1] Research Center of Excellence in Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babeş-Bolyai University, 11 Arany Janos St., 400028 Cluj-Napoca, Romania;
[2] Department of Molecular Biology and Biotechnology, Faculty of Biology and Geology, Babeş-Bolyai University, 44 Republicii St., 400015 Cluj-Napoca, Romania;
[3] Department of Orthopedics and Traumatology, Iuliu Hatieganu University of Medicine and Pharmacy, 47 General Traian Moşoiu St., 400132 Cluj-Napoca, Romania
[4]Academy of Romanian Scientists, 3 Ilfov St., 050044 Bucharest, Romania [5]Institute of Physiology and Sanocreatology, State University of Moldova, Academy 1 St., Chișinău, Moldova 2028
*Corresponding author e-mail: *mcotisel@gmail.com*
maria.tomoaia@ubbcluj.ro

Abstract *This review presents a comprehensive analysis of current research on gold nanoparticles (GNPs), encompassing their synthesis, characterization and applications in cancer therapy. GNPs are synthesized through various chemical and biological methods, each contributing to their significance in diverse applications. Cytotoxicity plays a critical role in determining their practical utility, with distinct considerations depending on the context: in medical applications, high biocompatibility with living normal cells is essential, while in targeting pathogens and cancer cells, inducing apoptosis is desirable. Thus, optimizing the concentration of GNPs for each specific application is of paramount importance. Additionally, this review highlights the characterization techniques for GNPs, their functionalization using biomolecules, and their subsequent applications in cancer therapy, emphasizing their potential in advancing therapeutic strategies.*

Keywords: gold nanoparticles, synthesis, characterization, cancer cell lines

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1. INTRODUCTION

Nanoparticles ranging in size from 1 to 100 nm are primarily utilized for clinical and commercial purposes due to their extensive surface area and unique physicochemical, mechanical, and electrical properties [1,2]. Nanotechnology, the science focused on processes at the molecular scale, underpins these advancements [3-9]. It has rapidly integrated with disciplines such as physics and engineering [3], biomedicine [4-8], pharmaceutical sciences [7,8], and nanomedicine [9,10], with applications extending to molecular biology, biophysics, and bioengineering [9]. Additionally, the field of nanotoxicology examines the relationships between the physicochemical properties of engineered nanoparticles and their toxicological profiles [3,8,10]. Among nanoparticles, gold nanoparticles (GNPs) are particularly significant in biomedicine due to their distinctive optical and electronic properties [1-3,8,11,12].

The advantages of nanoparticles include reduced patient-to-patient variability, enhanced solubility, improved oral bioavailability, accelerated dissolution rates, increased surface area, reduced dosage requirements, and a faster onset of therapeutic effects [2,13-16]. As engineered nanoparticles become more ubiquitous, it is vital to study their physical and chemical properties [17-20], interactions with proteins [21,22], binding with anesthetic molecules [23], and interactions with amino acids [24-28]. These properties have paved the way for applications in chemical and biological sensing [29], biofunctionalization for nanomedicine [30], and interactions with biological structures [31,32], including antitumor efficacy against cancers such as breast, pancreatic, and prostate [33].

A key question arises: why is the interaction of GNPs with biological membranes so critical, compared to other cellular compartments? The answer lies in the protective role of cell membranes. Successful penetration of the membrane by nanoparticles can affect the internal cellular environment, a desirable outcome in specific cases such as drug delivery. To optimize these interactions, it is essential to understand the structure of each membrane type and their responses to various nanoparticles.

Gold nanoparticles are among the most extensively studied metal nanoparticles, especially for their diverse medical applications [1,2,10,12,13-17]. While hydroxyapatite is well-known for its role in joint replacements, its susceptibility to infections has prompted efforts to combine it with antibacterial agents such as gold and silver nanoparticles [17-20]. In surgical applications, the interaction between nanoparticles and commonly used anesthetics has shown promising results [23]. Furthermore, GNPs are crucial in nanotechnology and nanoscience due to their ability to interact with amino acids [24], such as cysteine [25,26], lysine [27], and arginine [28], as well as biomolecules like proteins [20-22]. These properties underscore their broad potential in advancing both therapeutic and diagnostic modalities.

2.GOLD NANOPARTICLES SYNTHESIS

Gold nanoparticles (GNPs) can be synthesized through a variety of methods, which are broadly categorized into "bottom-up" and "top-down" approaches. This review highlights the most prominent methods within these categories.

The **top-down** approach involves the decomposition of bulk materials into nanoparticles using physical techniques such as IR and UV irradiation, ion spraying, aerosol

technology, or laser ablation [5,7]. In contrast, the **bottom-up** approach starts at the atomic level, where gold atoms are chemically synthesized into nanoparticles of desired shapes and sizes. This process occurs in two key stages: reduction of a gold precursor and stabilization of the formed nanoparticles. Common reducing agents include trisodium citrate [34] and sodium borohydride [34,35], as well as organic molecules like trans-resveratrol (R) [16]. Stabilization is achieved by coating the nanoparticles with organic molecules [16,36], a method favored for its enhanced control over the resulting nanoparticles' properties.

Over the years, researchers have refined and improved GNPs synthesis methods, with three classic approaches credited to Turkevich, Brust, and Martin [34-36]. The **Turkevich method**, introduced in 1951, employs trisodium citrate to reduce gold ions (Au^{3+}) to gold atoms (Au^0), yielding spherical nanoparticles. In 1994, the **Brust method** enabled the synthesis of nanoparticles with small, well-controlled diameters (1.5–5.2 nm) using sodium borohydride and alkanethiol in a two-phase reaction. The **Martin method** further advanced the field by allowing the combination of GNPs with hydrophilic molecules through precise reactant ratio adjustments.

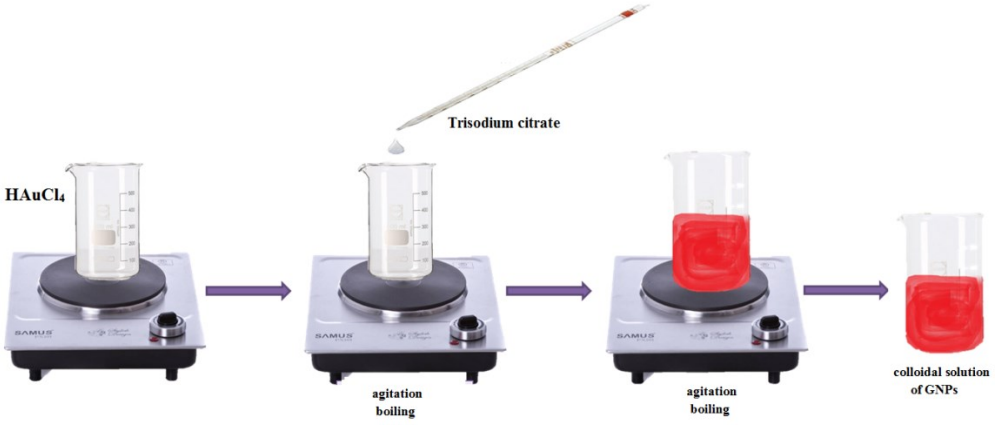

Fig. 1. GNPs synthesis with trisodium citrate procedure

In addition to chemical methods, recent years have seen a rise in eco-friendly synthesis techniques involving bacteria, plants, biomolecules, algae, and fungi. These methods offer economic and environmental advantages [37-44]. Notably, in 2015, our research group enhanced the trans-resveratrol reduction method to produce spherical nanoparticles approximately 20 nm in diameter [16].

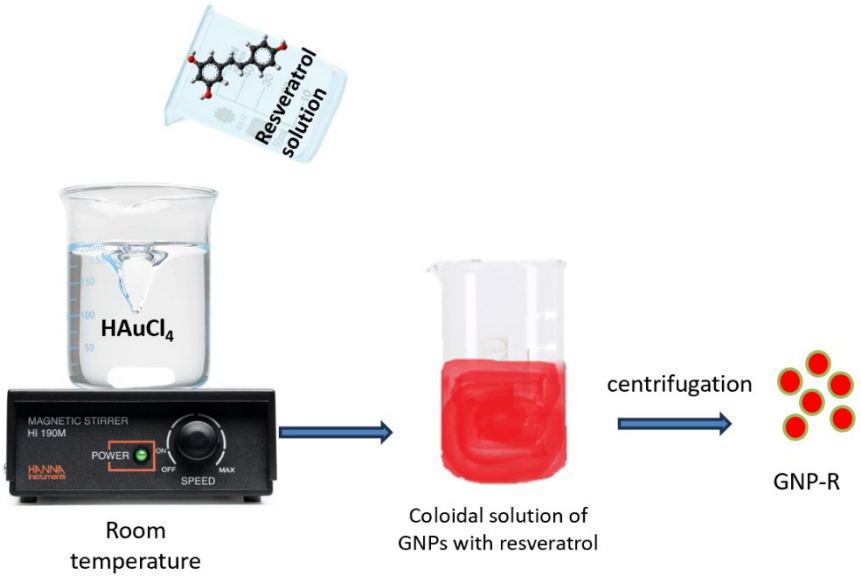

Fig. 2. GNPs synthesis with resveratrol procedure

Furthermore, GNPs synthesized through these methods exhibit unique and diverse properties, enabling functionalization with bioactive compounds such as resveratrol [45-48], piperine [49-51], and icariin for medical applications [52-59]. Table 1 summarizes various synthesis methods and the specific characteristics of the resulting nanoparticles.

Table 1. Methods of preparation of GNPs

No. crt.	*Type of synthesis*	*Reduction and capping agent*	*NP diameter*	*Observations*	*References no.*
1	Biological	plant extracts	4-8 nm	-Reducing chloroauric acid ($HAuCl_4$) with three different plant extracts (from *Angelica, Hypericum* and *Hamamelis*) -the Au (III) solution is reduced with a color change to black bluish	[37]
2		Cashew (*A. occidentale*) leaves extract	Around 10 to 40 nm	- Au source: chloroauric acid - The color changes from yellow to ruby red	[38]
3		phytochemicals from fruit extract of *Tribulus terrestris*	7nm and 55nm	reduction of chloroauric acid treated with the *T. terrestris* fruit extract	[39]

4		*Salacia Chinensis* (SC) extract	Around 80 nm	Gold (III) chloride hydrate with extract	[40]
5		bacterium *Rhodobacter sphaeroides*	5 to 8 nm	Bioreduction of Au (III) from chloroauric acid	[41]
6		extract of *Rhazya stricta decne*	Around 40 nm	color changes from light yellow to deep pink after the reaction between chloroauric acid and plant extract	[42]
7	Chemical	Trisodium citrate	Around 40 nm	citrate reduction of $HAuCl_4$	[43]
8			Around 14 nm	Preparation of colloidal gold solution by hydrogen tetrachloroaurate (III), $HAuCl_4$ reduction with trisodium citrate	[27]
9		9-borabicyclo (3.3.1) nonane (9-BBN)	Spherical Au-BSA bioconjugate of 7 nm average	Mild reduction of the diazonium gold (III) salt $[HOOC\text{-}4\text{-}C_6H_4N{\equiv}N]AuCl_4$ conjugated with bovine serum albumin (BSA)	[44]

3.GOLD NANOPARTICLES FUNCTIONALIZATION

Given the prominence of cancer as a major health challenge of the century, this section focuses on the anticancer properties of gold nanoparticles (GNPs). GNPs can be functionalized with various biomolecules to enhance their properties, with doxorubicin, piperine, resveratrol, and icariin being notable examples.

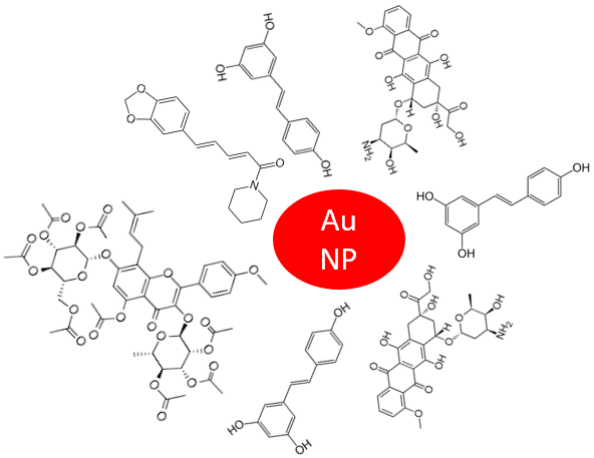

Fig. 3. GNPs functionalized with resveratrol, doxorubicin, piperine and icariin

3.1.Resveratrol

Resveratrol, chemically known as 3,4',5-trihydroxystilbene, is a natural phytoalexin produced by spermatophytes such as grapevines, often in response to injury. It is particularly abundant in red wine, as it is found in the skin of grapes rather than the pulp. Resveratrol's primary biological role is as an antioxidant, contributing to cardiovascular health by inhibiting platelet aggregation and the oxidation of low-density lipoproteins [45]. Beyond its antioxidant activity, resveratrol exhibits anticancer and anti-inflammatory properties, and it enhances the apoptotic effects of cytokines, γ-radiation, and chemotherapeutic agents [46]. Given these exceptional characteristics, functionalizing GNPs with resveratrol has garnered significant research interest.

Resveratrol serves not only as a biofunctional agent but also as a reducing agent for GNP synthesis. By reducing chloroauric acid with resveratrol, spherical GNPs are obtained with diameters ranging from 20 to 35 nm. These nanoparticles demonstrate good stability in saline, aqueous, and ethanolic solutions, making them suitable for various biomedical applications.

3.2.Piperine

Piperine, an alkaloid extracted from *Piper nigrum* (black pepper) seeds, also offers notable therapeutic benefits. Piperine inhibits the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), reducing inflammatory mediators such as prostaglandins in microglial cells and tumor necrosis factors [49]. Its anticancer properties make it an excellent candidate for functionalizing GNPs, further enhancing their therapeutic efficacy.

Piperine-functionalized GNPs are synthesized by boiling a solution of piperine in potassium hydroxide and adding gold chloride to the mixture [31]. These nanoparticles exhibit superior anti-inflammatory, antibacterial, antifungal, and anticancer effects compared to either GNPs or piperine used alone [31,50].

The functionalization of GNPs with biomolecules such as resveratrol and piperine represents a promising strategy to enhance their anticancer and therapeutic potential, demonstrating the value of integrating natural compounds with nanotechnology in modern medicine.

3.3.Icariin

Icariin, an 8-prenyl derivative of 3,7-O-diglucoside kaempferol, is a flavonoid with well-documented anticancer properties. It is a primary active component of the traditional Chinese medicinal herb *Epimedium grandiflorum* [51]. Icariin induces apoptosis in a variety of cancer cell types, including lung adenocarcinoma [52], ovarian cancer [53,54], pancreatic cancer [55], and cervical cancer [56,57]. One of its most significant advantages is its ability to induce the death of cancer cells at concentrations that are non-toxic to healthy cells.

In addition to its anticancer effects, icariin plays a role in modulating anti-inflammatory and immune responses in diseases such as multiple sclerosis, asthma, atherosclerosis, lupus nephritis, inflammatory bowel disease, rheumatoid arthritis, and cancer [58]. These multifaceted properties make icariin a promising candidate for synergistic use with gold nanoparticles (GNPs). Although research into icariin-functionalized GNPs is currently limited, this avenue holds considerable potential for future exploration.

3.4.Resveratrol and piperine

Building on the established bioactivities of resveratrol and piperine, a synergistic combination of these two biomolecules has been developed. Piperine has been shown to inhibit the glucuronidation of resveratrol, thereby slowing its metabolic elimination and enhancing its pharmacokinetic properties [59]. This combination produces improved therapeutic outcomes by sensitizing cancer cells and inducing apoptosis, representing a promising approach for cancer treatment [60].

The anticancer efficacy of the resveratrol-piperine complex has been particularly evident in studies on the breast cancer cell line MCF-7. This complex reduced the concentration of resveratrol required to achieve 50% cell death by 14-fold compared to resveratrol alone [61]. Additionally, in vivo studies on female mice with breast cancer demonstrated the therapeutic potential of this combination, though mild toxicity to healthy cells was observed as a limitation [62].

The synergistic effects of biomolecule-functionalized GNPs, such as those involving icariin, resveratrol, and piperine, underscore the immense potential of integrating traditional medicinal compounds with nanotechnology to create innovative and effective anticancer therapies.

3.5.Doxorubicin

The chemotherapeutic agent doxorubicin, classified as an anthracycline, is widely utilized both as an anticancer drug and as a functionalization molecule in research to enhance the efficacy of other anticancer agents. Additionally, doxorubicin serves as a reference standard in cellular toxicity assays. Its anticancer activity is significantly enhanced when conjugated with hydrophilic nanoparticles, enabling deeper cellular penetration compared to the drug in its unbound form [63].

Functionalization of gold nanoparticles (GNPs) with doxorubicin has been successfully achieved, offering improved therapeutic potential. In 2011, Mirza demonstrated the conjugation of doxorubicin to gold nanoparticles through amino groups under slightly acidic conditions. The protonation of the amino groups facilitated the controlled binding of doxorubicin to the gold surface [64]. Four years later, this interaction was further elucidated, revealing a two-step binding mechanism. Initially, doxorubicin is attracted to the GNP surface through hydrophobic interactions. Subsequently, adsorption is stabilized through cation-π interactions and coordination between gold and carbonyl groups in the doxorubicin molecules [65].

These insights into the functionalization of GNPs with doxorubicin underscore the potential of nanoparticle-drug conjugates to enhance the efficacy and cellular uptake of established chemotherapeutic agents.

4.Characterization of gold nanoparticles

Characterization of gold nanoparticles (GNPs) employs a range of advanced physicochemical techniques to analyze their properties and structure. These methods include ultraviolet-visible spectroscopy (UV–Vis), X-ray diffraction (XRD) [66], energy-dispersive X-ray spectroscopy (EDX), Fourier-transform infrared spectroscopy (FT-IR) [67], atomic force microscopy (AFM) [68–70], transmission electron microscopy (TEM) [71], dynamic light scattering (DLS), X-ray photoelectron spectroscopy (XPS), and scanning electron microscopy (SEM) [72–79].

These characterization techniques provide critical insights into the properties of GNPs. For example, UV–Vis analysis identifies the characteristic surface plasmon resonance peak, indicative of nanoparticle formation. XRD [80] and EDX data confirm the crystalline structure and elemental composition of the nanoparticles. AFM [81], TEM, and DLS techniques provide detailed information on morphology, size, and particle distribution [73,75,76]. Furthermore, FT-IR analysis enables the identification of potential biomolecules involved in the reduction and capping processes [76,83,84].

In addition to these traditional techniques, researchers have explored in vitro permeability using membrane models to assess nanoparticle interaction with biological barriers [72]. Beyond immediate analysis, the long-term stability and properties of GNPs have also been evaluated, with some studies examining preparations stored for several months [85, 86]. Inductively coupled plasma atomic emission spectrometry (ICP-AES) is another valuable tool, particularly for quantifying the concentration of metal ions in biosynthesized nanoparticles [76].

These comprehensive characterization methods collectively enable the detailed analysis of GNPs, advancing their development for various biomedical and technological applications.

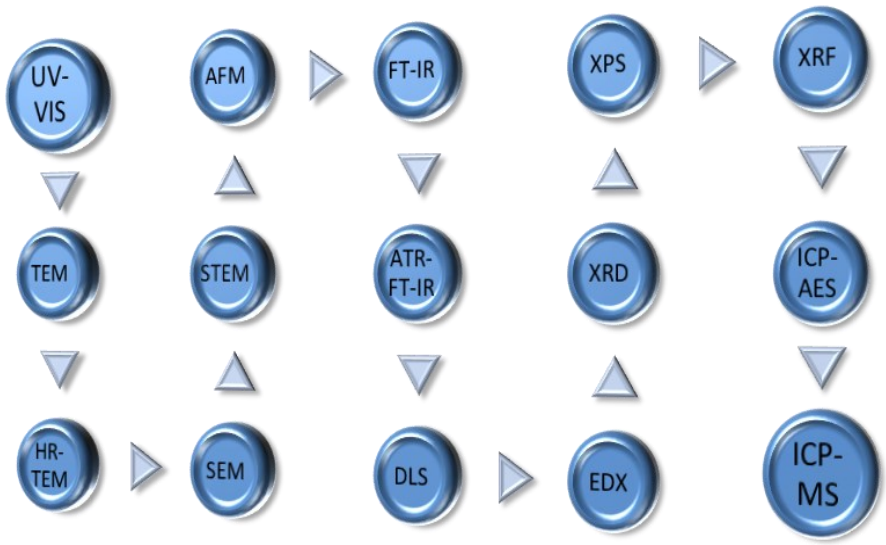

Fig. 4. The main characterization methods of GNPs

5.GNPs: biological membrane interactions and cytotoxicity

5.1.Biological membranes

All cellular membrane contains lipids and usually they are structured in two All cellular membranes are composed of lipids, typically arranged in a bilayer structure. A defining characteristic of these lipids is their amphipathic nature, consisting of a hydrophobic tail and a hydrophilic head group [86]. Cellular membranes play a crucial role in maintaining the cell integrity, providing both protection and facilitating essential cellular functions. [87] The interface between the cellular interior and the outer lipid layer serves as a dynamic site where lipids and proteins interact to drive various biochemical processes [88].

5.2.Langmuir monolayers

A Langmuir monolayer is a unique layer of atoms, molecules, or packed cells that is insoluble and typically forms a single-molecule-thick layer of an organic

material spread over an aqueous surface in a Langmuir-Blodgett trough. [89, 90, 91] These monolayers are composed of amphiphilic materials, which feature a hydrophilic headgroup and a hydrophobic tail. [92] Langmuir monolayers are formed at the air/water interface [93]. They can be made using L-α-dipalmitoyl phosphatidylcholine, either with or without procaine [91].

5.3.Liposomes

Liposomes are bidimensional spherical supramolecular lipidic structures. These structures self-assemble to form closed aqueous compartments enclosed by a lipid bilayer membrane. Various techniques are employed to produce liposomes, including sonication, solvent injection, hydration of a thin lipid film, and membrane extrusion. Liposomes are typically characterized by two key parameters: diameter and bilayer thickness. Their diameters generally range from 20 nm to 10 μm, while the bilayer thickness is approximately 4–5 nm. A notable advantage of this type of membrane is its capacity to allow precise control over composition, structure, and dynamic properties [94].

5.4.Lipidic bilayers

This type of membrane is similar with liposomes, but the difference is that if liposomes have spherical form, lipidic bilayers are planar. They are obtaining through deposition on solvents and with free solvent Langmuir based techniques [87].

5.5.Model membranes

Model membranes serve as simplified in vitro representations of biological membranes, offering the significant advantage of providing qualitative insights into the physicochemical properties of lipids. As such, they are invaluable tools in research [95-98]. These membranes are typically fabricated on solid supports and can be monolayers or bilayers. [99-102] They are usually flat bilayers but may also exist as suspended or deposited vesicular layers. Additional types include polymer-cushioned lipid bilayers, hybrid bilayers, and tethered lipid bilayers [93–103].

Various techniques are employed in the preparation of model membranes, including Langmuir-Blodgett and Langmuir-Schaefer methods, spin-coating, vesicle adsorption and fusion on support surfaces, direct spreading from water or organic solvents, self-assembly, spray-coating, and dip-coating [104–119].

Lipid membranes play a crucial role in cellular processes, acting as barriers and facilitating communication through the exchange of ions and molecules. They also have significant applications in biotechnology, where model membranes can be created by incorporating phospholipids modified with membrane proteins, such as channels, receptors, and transmitters. A notable example of a model membrane is stearic acid [120, 121].

5.6.Interactions and cytotoxicity

Many researchers posit that non-specific interactions between lipid components of eukaryotic cell membranes and nanoparticles play a critical role in modulating membrane

activity. Key processes involved in these interactions include substrate adhesion, complete or partial encapsulation of nanoparticles by the membrane, and potential nanoparticle clustering on lipid membranes. By studying these interactions in systems such as lipid bilayers deposited on solid supports derived from fluid lipid mixtures, as well as in free-standing membranes devoid of transmembrane proteins or raft-like domains, it becomes possible to predict nanoparticle-induced membrane activity

Metal nanoparticles interact with cells through multiple mechanisms to induce cytotoxic effects. They disrupt the integrity of the cell membrane, gaining entry via simple or facilitated diffusion or through active transport processes (Figure 5). Once inside the cell, these nanoparticles generate oxidative stress and impact various cellular compartments, leading to functional disruption and cellular damage (Figure 6).

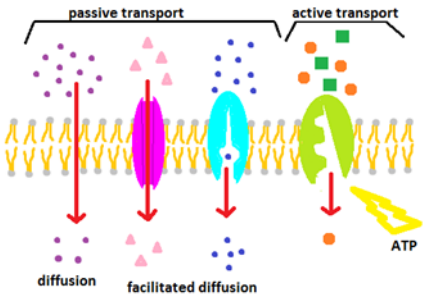

Fig. 5. Types of transportation of NP through the cell membrane

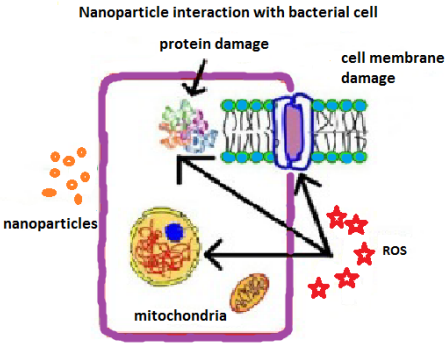

Fig. 6. Nanoparticles interaction with bacterial cell

5.7.Gold particles – biological membranes interaction

One of the notable properties of gold (Au) nanoparticles is their ability to target cancerous tissues through photothermal destruction. This effect arises from the thermal energy generated by light-absorbing structures within the nanoparticles [62]. Metallic nanoparticles, particularly gold-based ones, have gained significant attention in biomedicine for their applications in both therapeutics and diagnostics. Key features that make Au nanoparticles suitable for these purposes include their efficient conversion of light into heat, versatile surface chemistry, and, most importantly, their biocompatibility. Their optical properties are especially valuable in therapeutic interventions and biological detection, although these properties are highly sensitive to variations in nanoparticle structure and size [122, 123].

Au nanoparticles are typically stabilized by protected monolayers with well-defined molecular compositions. This structural stabilization is achieved through covalent bonding between the ligand shell and the nanoparticle surface via Au-S bonds [122, 124]. Due to their unique properties, gold nanoparticles are increasingly being applied in diverse fields, including dental implantology. Preliminary studies often focus on

assessing the biocompatibility of these nanoparticles with blood. Their excellent biocompatibility has also led to their use as drug carriers in treating various diseases, as illustrated in Figure 7.

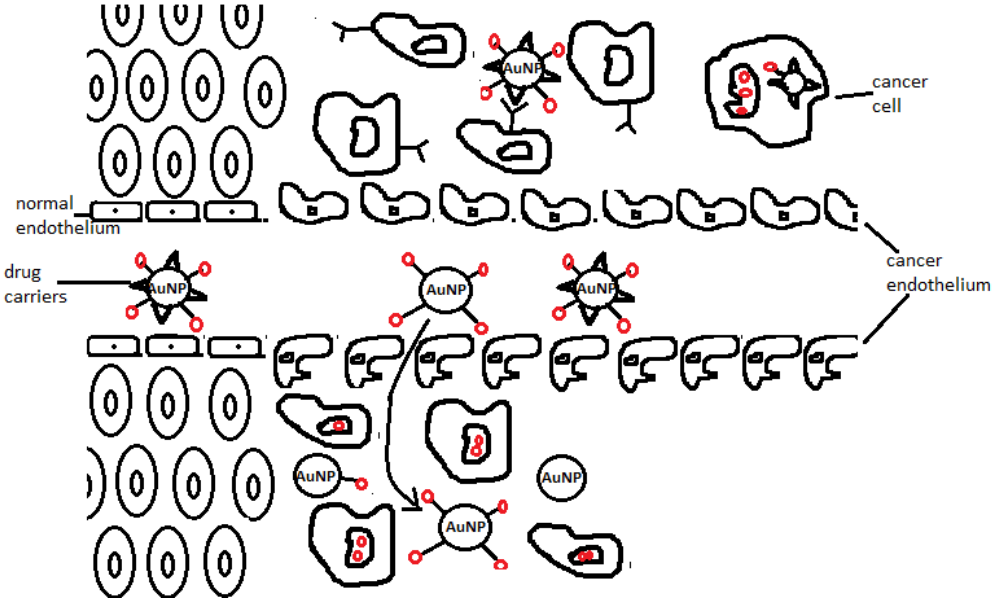

Fig. 7. Nanoparticles interaction

Gold nanoparticles (AuNPs) have demonstrated biocompatibility and are also reported to enhance cell viability, suggesting their osteo-inductive potential—a property that makes them suitable for use in dental implants [40]. Additionally, AuNPs serve as catalysts in the degradation of nitroaromatic compounds, extending their applications to environmental sustainability. Moreover, gold nanoparticles have been shown to prolong the lag phase during the growth of *Rhodobacter sphaeroides*, a gram-negative, purple bacterium known for its resistance to various environmental conditions and its reducing capabilities. This bacterium has been utilized for the ecological synthesis of gold nanoparticles via the reduction of Au(III) to Au(0) [41]. Its advantages include rapid growth, low cost, minimal safety requirements, and easily controlled growth conditions, making *R. sphaeroides* an excellent candidate for nanoparticle synthesis [41, 125–132].

One method for synthesizing gold nanoparticles involves the mild reduction of diazonium gold(III) salts. This approach has been employed to investigate interactions between gold-aryl nanoparticles and bovine serum albumin complexes with red blood cells. Promising results, including negligible hemolysis and an absence of morphological deformations, suggest that this complex is a strong candidate for hemocompatible nanoparticles [44]. Green synthesis methods, such as the use of plant extracts (e.g., *Rhazya stricta decne*), have also been explored for producing gold nanoparticles (Table 1).

Given the significance of nanoparticle effects, a key area of study is their antimicrobial activity against various microorganisms [42]. The versatility of AuNPs extends to oncology, where they are employed in the destruction of cancer cells. Complexes of gold nanoparticles with antibodies have been shown to significantly reduce the time and energy required for cancer cell eradication [43]. Additionally, AuNP-aptamer complexes offer a targeted approach to cancer treatment, as aptamers—short peptides or oligonucleotides—bind specifically to malignant cells, minimizing damage to healthy tissues. This therapeutic effect is primarily mediated by the energy generated when gold nanoparticles absorb light [122].

To ensure their effective use, gold nanoparticles must be thoroughly characterized. Techniques such as transmission electron microscopy (TEM), atomic force microscopy (AFM), Fourier-transform infrared spectroscopy (FTIR), and UV-VIS spectroscopy are commonly employed for this purpose [16, 37].

5.8.Cytotoxicity

Given their applications in the biomedical field, understanding the cytotoxicity of gold nanoparticles (AuNPs) is essential. This cytotoxicity can be advantageous, such as in targeting cancer cells, but undesirable for other uses. In terms of antibacterial activity, AuNPs have been shown to effectively destroy bacterial cells. For instance, studies by researchers from India and Korea demonstrated the efficacy of gold nanoparticles against Escherichia coli and Bacillus subtilis [38]. Furthermore, AuNPs with diameters of 7 nm and 55 nm have been found to exhibit activity against Heliobacter pylori [39].

In addition to their antibacterial properties, gold nanoparticles have potential as topical drug delivery agents due to their ability to penetrate the stratum corneum of the skin [133]. However, in some cases, gold nanoparticles require functionalization to enhance their transport capabilities. Functionalization with polyethylene glycol (PEG) has been explored to prevent the formation of a protein corona, thereby allowing the nanoparticle complex to evade detection by the immune system.

In cancer therapy, gold nanoparticles have also shown promise as carriers for anticancer drugs, such as curcumin, a natural phenolic antioxidant. Studies have demonstrated that AuNPs enhance the cytotoxicity of curcumin against cancer cells while sparing healthy cells [134]. This dual functionality highlights the versatility and potential of gold nanoparticles in therapeutic applications.

6.GNPs applications in cancer

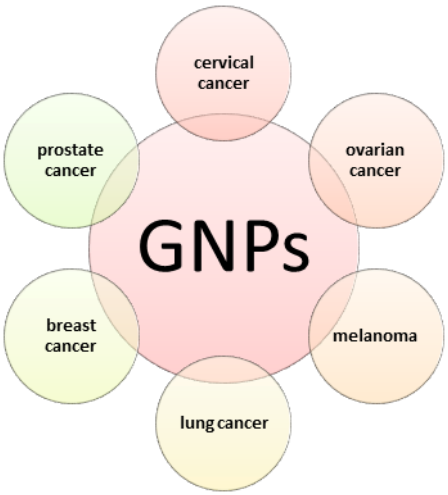

Fig. 8. Types of cancer that GNPs fight against

Cancer affects nearly all parts of the human body, necessitating treatments that are both diverse in approach and minimally toxic to healthy cells. A significant body of scientific research highlights the beneficial effects of gold nanoparticles (AuNPs), either in their native form or functionalized. Among these studies, particular attention has been given to AuNPs synthesized using trisodium citrate as a reducing agent. Key findings from these works have been organized and summarized in the table below.

Table 2. Citrate capped GNPs (GNP-Ci or GNP-C) effects on cells

Cell line	*Cell line type*	*Ref.*	*GNPs size (nm)*	*Apoptosis determination method*	*Details*
HeLa	Cervical cancer	[135]	20	Alamar Blue	- GNPs have a weak cytotoxic effect on healthy cells, compared to other sizes, but they have a good effect on cancer cells. - Most sensitive (IC50) at 2.1µg/mL.
		[136]	12–14	MTT	- IC50 at 34 µg/mL Cit AuNPs
MDA-MB-231	Triple negative breast cancer	[137]	25-30	MTT	IC50 at 720 µg/mL. They attacked the cytoplasm and mitochondria
		[138]	4-22	MTT	They produce apoptosis
MDA-MB-468	Triple negative breast cancer	[137]	25-30	MTT	IC50 at 348,35µg/mL

MCF-10A	Human mammary epithelium	[137]	25-30	MTT	30% cell death at 1mg/mL
SKOV-3	Ovarian cancer	[138]	4-22	MTT	They produce apoptosis
B16	Melanoma	[139]	9-18	MTS	<10µg/mL nontoxic >10µg/mL have a slight effect
L929	Mouse fibroblasts	[139]	9-18	MTS	<10µg/mL non-toxic >10µg/mL have a slight effect
L02	Normal human liver cells	[140]	56.2 33.3 15.5	MTT	It does not affect them, so they are safe to use
A431	Epidermoid carcinoma model cells	[141]	15	LDH cytotoxicity assay kit	Ci-AuNPs conjugated with cancer-specific anti-EGFR antibody, destroyed cancer cells through ROS-mediated apoptosis by intensifying caspase-3 activity
CF-31	Human dermal fibroblasts	[142]	14	Microscopy	They can cross the cell membrane and accumulate in vacuoles. It affects the actin filaments and the extracellular matrix. They reduce cell proliferation, adhesion and motility.
A549	Human lung carcinoma cells	[143]	5–10	MTT	It induces apoptosis
HDMEC	Human dermal microvascular endothelial cells	[144]	10 11 25	MTS	The higher amount of Ci on the surface of the particles resulted in a greater impairment of cell viability
hCMEC-D3	Human cerebral microvascular endothelial cells				
Human erythrocytes	Human red blood cells	[135]	20	Alamar Blue	Toxic
NIH3T3	Murine fibroblasts		20	Alamar Blue	Toxic
B16F10	Melanoma		10	Alamar Blue	Produce apoptosis
BHK	Normal fibroblasts	[136]	12–14	MTT	IC50 at 45 µg/ml

Gold nanoparticles (AuNPs) are promising nanocarriers for cancer treatment and diagnosis due to their effective biocompatibility [145, 146], ease of surface modification with various agents [147, 148], and strong light-scattering properties [149, 150]. One notable application of AuNPs is in prostate cancer treatment, where studies have shown complete tumor regression with minimal cytotoxic effects on healthy prostate cells [151]. Similarly, AuNPs have demonstrated the ability to induce apoptosis in breast tumor cell lines, such as MCF-7 [152, 153].

Cervical cancer cell lines, including HeLa and CaSki, are also of significant interest as model systems for studying the effects of gold nanoparticle-based compounds [16]. Beyond their role as anticancer agents, AuNPs have been employed in the detection of physiological functions, including antigen-antibody interactions and blood glucose monitoring [154,155].

Conclusions

The concept of "nano" has become increasingly prominent, serving as a "gateway" to future advancements. This literature review addresses the topic of metallic nanoparticles, with a particular focus on gold nanoparticles (AuNPs). These particles, which may originate from atmospheric dispersion or be synthesized chemically or via biogenic methods, are poised to play a significant role in various fields. Their importance lies in their unique properties at the nanoscale, making them highly versatile for applications in medicine, technology, biology, and beyond.

For their effective use, it is essential to understand methods of synthesis and characterization, as well as to determine the specific properties of each nanoparticle type. These properties directly influence their potential applications. With the recent integration of AuNPs into medical preparations and devices, cytotoxicity studies have become crucial. Such studies aim to clarify how these nanoparticles interact with cellular membranes, both in model systems and in vivo. Investigating their interactions with cell membranes is particularly important, as membranes regulate the substances entering cells and play a critical role in cellular function.

Currently, metallic nanoparticles represent a significant area of interest, with extensive research aimed at transitioning them from experimental to practical applications. Given this trajectory, nanoparticles are expected to achieve even greater prominence in nanoscience and everyday life in the near future.

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REFERENCES

[1] W. A. Arcos Rosero, A. Bueno Barbezan, C. Daruich de Souza, M. E. Chuery Martins Rostelato, Pharmaceutics **16**, 255 (2024).

[2] K. Sztandera, M. Gorzkiewicz, B. Klajnert-Maculewicz, Mol. Pharmaceutics **16**, 1 (2019).

[3] G. Tomoaia, O. Soritau, M. Tomoaia-Cotisel, L.-B. Pop, A. Pop, A. Mocanu, O. Horovitz, L.-D. Bobos, Powder Technol. **238**, 99 (2013).

[4] G. Furtos, M.-A. Naghiu, H. Declercq, M. Gorea, C. Prejmerean, O. Pana, M. Tomoaia-Cotisel, J. Biomed. Mater. Res. B Appl. Biomater. **104**(7), 1290 (2015).

[5] S. Kargozar, S. Mollazadeh, F. Kermani, T. J. Webster, S. Nazarnezhad, S. Hamzehlou, F. Baino, J. Funct. Biomater **13**, 100 (2022).

[6] M. A. Naghiu, M. Gorea, E. Mutch, F. Kristaly, M. Tomoaia-Cotisel, J. Mater. Sci. Technol. **29**(7), 628 (2013).

[7] Al. N. Al-Thani, A. G. Jan, M. Abbas, M. Geetha, K. K. Sadasivuni, Life Sci. **352**, 122899 (2024).

[8] G. Tomoaia, A. Mocanu, I. Vida-Simiti, N. Jumate, L.-D. Bobos, O. Soritau, M. Tomoaia-Cotisel, Mat. Sci. Eng. C-Mater. **37**, 37 (2014).

[9] C. R. Martin, Nanomedicine **1**(1), 5 (2006).

[10] A. R. Ribeiro, P. E. Leite, P. Falagan-Lotsch, F. Benetti, C. Micheletti, H. C. Budtz, N. R. Jacobsen, P. N. Lisboa-Filho, L. A. Rocha, D. Kuhnel, D. Hristozov, J. M. Granjeiro, Nanoimpact **8**, 59 (2017).

[11] G. Rossi, L. Monticelli, Biochim. Biophys. Acta, Biomembr. **1858**(10), 2380 (2016).

[12] M. Tomoaia-Cotisel, G. Tomoaia, E. Indrea, L.D. Bobos, O. Horovitz, A. Mocanu, J. Optoelectron. Adv. M. **2**(1), 125 (2010).

[13] A. Mocanu, O. Horovitz, C. P. Racz, M. Tomoaia-Cotisel, Rev. Roum. Chim. **60**(7-8), 721 (2015).

[14] R. D. Tilley, S. Saito, Langmuir **19**(12), 5115 (2003).

[15] Y. Xiao, H.-X. Ju, H.-Y. Chen, Anal. Chim. Acta **391**, 73 (1999).

[16] G. Tomoaia, O. Horovitz, A. Mocanu, A. Nita, A. Avram, C. P. Racz, O. Soritau, M. Cenariu, M. Tomoaia-Cotisel, Colloids Surf. B Biointerfaces **135**, 726 (2015).

[17] M. Tomoaia-Cotisel, *Multifunctional nanostructure formed of gold or silver nanoparticles and different biomolecules with medical applications* (Cluj University Press, Cluj-Napoca, Romania, 2016).

[18] G. Furtos, M. Tomoaia-Cotisel, C. Garbo, M. Senila, N. Jumate, I. Vida-Simiti, C. Prejmerean, Particul. Sci. Technol. **31**(4), 392 (2013).

[19] A. Mocanu, G. Furtos, S. Rapuntean, O. Horovitz, C. Flore, C. Garbo, A. Danisteanu, G. Rapuntean, C. Prejmerean, M. Tomoaia-Cotisel, Appl. Surf. Sci. **298**, 225 (2014).

[20] E. Indrea, S. Dreve, I. Bratu, G. Mihailescu, L. Olenic, G. Tomoaia, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, NSTI-Nanotech **4**, 461 (2007).

[21] O. Horovitz, G. Tomoaia, A. Mocanu, T. Yupsanis, M. Tomoaia-Cotisel, Gold Bull. **40**(4), 295 (2007).

[22] A. Mocanu, R.-D. Pasca, G. Tomoaia, A. Avranas, O. Horovitz, M. Tomoaia-Cotisel, J. Nanosci. Nanotechnol. **12**, 8935 (2012).

[23] O. Horovitz, A. Mocanu, G. Tomoaia, M. Crisan, L.-D. Bobos, C. Racz, M. Tomoaia-Cotisel, Stud. UBB Chem. **52**(3), 53 (2007).

[24] I. Petean, G. Tomoaia, O. Horovitz, A. Mocanu, M. Tomoaia-Cotisel, J. Optoelectron. Adv. M. **10**(9), 2289 (2008).

[25] A. Mocanu, I. Cernica, G. Tomoaia, L.-D. Bobos, O. Horovitz, M. Tomoaia-Cotisel, Colloids Surf. A: Physicochem. Eng. Asp. **338**, 93 (2009).

[26] O. Horovitz, A. Mocanu, G. Tomoaia, L. Bobos, D. Dubert, I. Daian, T. Yupsanis, M. Tomoaia-Cotisel, Stud. UBB Chem. **52**(1), 97 (2007).

[27] O. Horovitz, G. Tomoaia, A. Mocanu, T. Yupsanis, M. Tomoaia-Cotisel, Gold Bull. **40**(3), 213 (2007).

[28] G. Tomoaia, P. T. Frangopol, O. Horovitz, L.-D. Bobos, A. Mocanu, M. Tomoaia-Cotisel, J. Nanosci. Nanotechnol. **11**, 7762 (2011).

[29] K. Saha, S. S. Agasti, C. Kim, X. Li, V. M. Rotello, Chem. Rev. **112**(5), 2739 (2012).

[30] J. Conde, J. T. Dias, V.Grazu, M. Moros, P. V. Baptista, J. M. de la Fuente, Front. Chem. **2**, 48 (2014).

[31] B. G. Anand, D. S. Shekhawat, K. Dubey, K. Kar, ACS Biomater. Sci. Eng. **3**(6), 1136 (2017).

[32] A. Chaudhary, C. Dwivedi, A. Gupta, C. K. Nandi, RSC Adv. **5**, 97330 (2015).

[33] V. C. Thipe, K. Panjtan Amiri, P. Bloebaum, A. Raphael Karikachery, M. Khoobchandani, K. K. Katti, S. S. Jurisson, K. V. Katti, Int. J. Nanomedicine **14**, 4413 (2019).

[34] J. Turkevich, P. C. Stevenson, J. Hiller, Discuss. Faraday Soc. **11**, 55 (1951).

[35] S. Ehlert, S. M. Taheri, D. Pirner, M. Drechsler, H.-W. Schmidt, S. Forster, ACS Nano **8**(6), 6114 (2014).

[36] E. C. Dreaden, A.M. Alkilany, X. Huang, C. J. Murphy, M. A. El-Sayed, Chem. Soc. Rev. **41**(7), 2740 (2012).

[37] R.-D. Pasca, A. Mocanu, S.-C. Cobzac, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Particul. Sci. Technol. **32**(2), 131 (2014).

[38] V. Sunderam, D. Thiyagarajan, A. V. Lawrence, S. S. S. Mohammed, A. Selvaraj, Saudi J. Biol. Sci. **26**, 455 (2019).

[39] V. Gopinath, S. Priyadarshini, D. MubarakAli, M. F. Loke, N. Thajuddin, N. S. Alharbi, T. Yadavalli, M. Alagiri, J. Vadivelu, Arab. J. Chem. **12**, 33 (2019).

[40] K. Jadhav, H. R. Rajeshwari, S. Deshpande, S. Jagwani, D. Dhamecha, S. Jalalpure, K. Subburayan, D. Baheti, Mat. Sci. Eng. C-Mater. **93**, 664 (2018).

[41] F. Italiano, A. Agostiano, B. D. Belviso, R. Calandro, B. Carrozzini, R. Comparelli, M. T. Merillo, E. Mesto, G. Tempesta, M. Trotta, Colloids Surf. B Biointerfaces **172**, 362 (2018).

[42] A. Ahmad, Y. Wei, S. Ullah, S. I. Shah, F. Nasir, A. Shah, Z. Iqbal, K. Tahir, U. A. Khan, Q. Yuan, Microb. Pathog. **110**, 304 (2017).

[43] I. H. El-Sayed, X. Huang, M. A. El-Sayed, Cancer Lett. **239**, 129 (2006).

[44] M. K. Hameed, I. M. Ahmady, H. Alawadhi, B. Workie, E. Sahle-Demessie, C. Han, M. M. Chehimi, A. A. Mohamed, Colloids Surf. A: Physicochem. Eng. Asp. **558**, 351 (2018).

[45] L. Fremont, Life Sci. **66**(8), 663 (2000).

[46] B. B. Aggarwal, A. Bhardwaj, R. S. Aggarwal, N. P. Seeram, S. Shishodia, Y. Takada, nticancer Res. **24**, 2783 (2004).

[47] R. K. Mohanty, S. Thennarasu, A. B. Mandal, Colloids Surf. B Biointerfaces **114**, 138 (2014).

[48] M. Fadel, K. Kassab, T. Youssef, A. I. El-Kholy, Drug Dev. Ind. Pharm. **45**(6), 937 (2019).

[49] S. Benayad, H. Wahnou, R. El Kebbaj, B. Liagre, V. Sol, M. Oudghiri, E. M. Saad, R. E. Duval, Y. Limami, Cancers **15**, 5488 (2023).

[50] S. Srivastav, B. G. Anand, M. Fatima, K. P. Prajapati, S. S. Yadav, K. Kar, A. C. Mondal, ACS Chem. Neurosci. **11**(22), 3772 (2020)

[51] S. Bawazeer, I. Khan, A. Rauf, A. S. M. Aljohani, F. A. Alhumaydhi, A. A. Khalil, M. N. Qureshi, L. Ahmad, S. A. Khan, Green. Process. Synth. **11**, 11 (2022).

[52] C. He, Z. Wang, J. Shi, Adv. Pharmacol. **87**, 179-203 (2020).

[53] S. Di, C. Fan, Y. Yang, S. Jiang, M. Liang, G. Wu, B. Wang, Z. Xin, W. Hu, Y. Zhu, W. Li, Y. Zhou, X. Li, X. Yan, Apoptosis **20**(9), 1229 (2015).

[54] J. Li, K. Jiang, F. Zhao, Oncol. Rep. **33**, 2829 (2015).

[55] Y. Fu, H. Liu, M. Long, L. Song, Z. Meng, S. Lin, Y. Zhang, J. Qin, Front. Oncol. **12**, 940926 (2022).

[56] X. Zheng, D. Li, J. Li, B. Wang, L. Zhang, X. Yuan, C. Li, L. Cui, Q. Zhang, L. Yang, X. Wang, Biomed. Pharmacother. **118**, 109275 (2019).

[57] S. Huang, T. Xie, W. Liu, J. Buon. **24**(3), 990 (2019).

[58] B. Li, M. Xia, R. Zorec, V. Parpura, A. Verkhratsky, Brain Res. **1752**, 14723 (2021).

[59] Z. Bi, W. Zhang, X. Yan, Biomed. Pharmacother. **151**, 113180 (2022).

[60] J. J. Johnson, M. Nihal, I. A. Siddiqui, C. O. Scarlett, H. H. Bailey, H. Mukhtar, N. Ahmad, Mol. Nutr. Food Res. **55**, 1169-1176 (2011).

[61] J. K. Tak, J. H. Lee, J.-W. Park, BMB Rep. **45**(4), 242 (2012).

[62] P. Jadhav, C. Bothiraja, A. Pawar, RSC Adv. **6**, 112795 (2016).

[63] M. J. AlHur, N. Barakova, W. H. Talib, Pharmacia **71**, 1 (2024).

[64] S. A. Kumar, Y.-A. Peter, J. L. Nadeau, Nanotechnology **19**, 495101 (2008).

[65] A. Z. Mirza, H. Shamshad, Eur. J. Med. Chem. **46**, 1857 (2011).

[66] D. Curry, A. Cameron, B. MacDonald, C. Nganou, H. Scheller, J. Marsh, S. Beale, M. Lu, Z. Shan, R. Kaliaperumal, H. Xu, M. Servos, C. Bennett, S. MacQuarrie, K. D. Oakes, M. Mkandawirea, X. Zhang, Nanoscale **7**, 19611 (2015).

[67] C.-P. Racz, G. Borodi, M. M. Pop, I. Kacso, S. Santa, M. Tomoaia-Cotisel, Acta Crystallogr. B. **68**, 164 (2012).

[68] P. T. Frangopol, A. Mocanu, V. Almasan, C. Garbo, R. Balint, G. Borodi, I. Bratu, O. Horovitz, M. Tomoaia-Cotisel, Rev. Roum. Chim. **61**(4-5), 337 (2016).

[69] M. Tomoaia-Cotisel, C. Prejmerean, G. Tomoaia, A. Mocanu, M. Trif, A. Badanoiu, T. Buruiana, A. Hosu, J. Optoelectron. Adv. M. **10**(4), 937 (2008).

[70] G. Tomoaia, V.-D. Pop-Toader, A. Mocanu, O. Horovitz, D.-L. Bobos, M. Tomoaia-Cotisel, Stud. UBB Chem. **52**(4), 137 (2007).

[71] C. Prejmerean, M. Tomoaia-Cotisel, E. Vasile, G. Furtos, L. Pop, M. Moldovan, C. Sarosi, I. Petean, Int. J. Nano Biomater. **3**(4), 344 (2011).

[72] G. Tomoaia, M. Tomoaia-Cotisel, L.-B. Pop, A. Pop, O. Horovitz, A. Mocanu, N. Jumate, L.-D. Bobos, Rev. Roum. Chim. **56**(10-11), 1039 (2011).

[73] W. R. Rolin, M. T. Pelegrino, B. de Araujo Lima, L. S. Ferraz, F. N. Costa, J. S. Bernardes, T. Rodrigues, M. Brocchi, A. B. Seabra, Appl. Surf. Sci. **463**, 66 (2019).

[74] N. M. Khalil, M. N. Abd El-Ghany, S. Rodriguez-Couto, Chemosphere **218**, 477 (2018).

[75] M. K. Choudhary, J. Kataria, S. Sharma, J. Clean. Prod. **198**, 882 (2018).

[76] A. Daphedar, T. C. Taranath, Toxicol. Rep. **5**, 910 (2018).

[77] A. Ahmad, Y. Wei, F. Syed, K. Tahir, R. Taj, A. U. Khan, M. U. Hameed, Q. Yuan, Microb. Pathog. **99**, 271 (2016).

[78] O. Horovitz, N. Cioica, N. Jumate, M. Pojar-Fenesan, A. Balea, V. Liteanu, A. Mocanu, M. Tomoaia-Cotisel, Stud. UBB Chem. **LVI**(1), 211 (2011).

[79] M. Tomoaia-Cotisel, C. Cota, A. Mocanu, O. Horovitz, Mater. Plast. **47**(4), 426 (2010).

[80] F. Goga, E. Forizs, A. Avram, A. Rotaru, A. Lucian, I. Petean, A. Mocanu, M. Tomoaia-Cotisel, Rev. Chim. **68**(6), 1193 (2017).

[81] M. A. Naghiu, M. Gorea, F. Kristaly, M. Tomoaia-Cotisel, Ceram.-Silik. **58**(4), 303 (2014).

[82] C. Prejmerean, G. Tomoaia, M. Tomoaia-Cotisel, A. Mocanu, O. Horovitz, M. Moldovan, D. Dudea, G. Voicu, I. Petean, J. Optoelectron. Adv. Mat. **10**(3), 597 (2008).

[83] C.-P. Racz, S. Santa, M. Tomoaia-Cotisel, G. Borodi, I. Kacso, A. Pirnau, I. Bratu, J. Incl. Phenom. Macrocycl. Chem. **76**(1-2), 193 (2012).

[84] C. Garbo, M. Sindilaru, A. Carlea, G. Tomoaia, V. Almasan, I. Petean, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Part. Sci. Technol. **35**(1), 29 (2015).

[85] M. Gorea, M-A. Naghiu, M. Tomoaia-Cotisel, G. Borodi, Ceram.-Silik. **57**(2), 87 (2013).

[86] M. Tomoaia-Cotisel, E. Chifu, J. Zsako, A. Mocanu, P. J. Quinn, M. Kates, Chem. Phys. Lipids. **63**(1-2), 131 (1992).

[87] U. V. Zdrenghea, G. Tomoaia, D. V. Pop-Toader, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Comb Chem High Throughput Screening. **14**(4), 237 (2011).

[88] P. L. Yeagle, *The membranes of cells* (Academic Press, Connecticut, USA, 2016) Vol. 3, pp. 27-56.

[89] J. Zsako, M. Tomoaia-Cotisel, E. Chifu, J. Colloid Interface Sci. **102**(1), 186 (1984).

[90] M. Tomoaia-Cotisel, J. Zsako, E. Chifu, Ann. Chim. (Rome) **71**(3-4), 189 (1981).

[91] P. T. Frangopol, D. A. Cadenhead, G. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, Rev. Roum. Chim. **60**(2-3), 265 (2015).

[92] M. E. Orczyk, J. Samoc, M. Swiatkiewicz, N. Manickam, M. Tomoaia-Cotisel, P. N. Prasad, Appl. Phys. Lett, **60**(23), 2837 (1992).

[93] G. Tomoaia, M. Tomoaia-Cotisel, A. Mocanu, O. Horovitz, L. D. Bobos, M. Crisan, I. Petean, J. Optoelectron. Adv. Mat. **10**(4), 961 (2008).

[94] M. Tomoaia-Cotisel, I. W. Levin, J. Phys. Chem. B **101**(42), 8477 (1997).

[95] Y.-H. M. Chan, S. G. Boxer, Curr. Opin. Chem. Biol. **11**(6), 581 (2007).

[96] E. T. Castellana, P. S. Cremer, Surf. Sci. Rep. **61**, 429 (2006).

[97] M. Edidin, Annu. Rev. Biophys. Biomol. Struct. **32**, 257 (2003).

[98] I. Cojocaru, A. Tomoaia-Cotisel, A. Mocanu, T. Yupsanis, M. Tomoaia-Cotisel, Rev. Chim. **68**(7), 1470 (2017).

[99] M. Tomoaia-Cotisel, E. Chifu, J. Colloid Interface Sci. **95**(2), 355 (1983).

[100] P. Joos, A. Tomoaia-Cotisel, A. J. Sellers, M. Tomoaia-Cotisel. Colloids and Surfaces B: Biointerfaces, 37(3-4), 83 (2004).

[101] M. Tomoaia-Cotisel, A. Mocanu, Rev. Chim. (Bucharest) **59**(11), 1230 (208).

[102] M. Rappolt, H. Amenitsch, J. Strancar, C. V. Teixeira, M. Kriechbaum, G. Pabst, M. Majerowicz, P. Laggner, Adv. Colloid Interface Sci. **111**, 63 (2004).

[103] G. Pompeo, M. Girasole, A. Cricenti, F. Cattaruza, A. Flamini, T. Prosperi, J. Generosi, A. Congiv Castellano, Biochim. Biophys. Acta. **1712**, 29 (2005).

[104] C. Rossi, J. Chopineau, Eur. Biophys. J. **36**(8), 955 (2007).

[105] J. Gunster, R. Souda, Langmuir **22**, 6939 (2006).

[106] B. Cross, A. Steinberger, C. Cottin-Bizonne, J.-P. Rieu, E. Charlaix, Europhys. Lett. **73**(3), 390 (2006).

[107] Y.-L. Lee, C.-Y. Chen, Appl. Surf. Sci. **207**, 51 (2003).

[108] E. Chibowski, L. Holysz, M. Jurak, Colloids Surf. A: Physicochem. Eng. Asp. **321**, 131 (2008).

[109] M. Jurak, E. Chibwski, Appl. Surf. Sci. **256**(21), 6304 (2010).

[110] M. Jurak, E. Chibowski, Colloids Surf. B. Biointerfaces **75**(1), 165 (2010).

[111] M. Li, M. Chen, E. Sheepwash, C. L. Brosseau, H. Li, B. Pettinger, H. Gruler, J. Lipkowski, Langmuir **24**, 10313 (2008).

[112] G. Zhavnerko, G. Marletta, Mater. Sci. Eng. B. **169**(1-3), 43 (2010).

[113] I. Reviakine, A. Brisson, Langmuir **16**(4), 1806 (2000).

[114] Z. V. Leonenko, A. Carnini, D. T. Cramb, Biochim. Biophys. Acta **1509**(1-2), 131 (2000).

[115] Z. V. Leonenko, E. Finot, H. Ma, T. E. S. Dahms, D. T. Cramb, Biophys. J. **86**(6), 3783 (2004).

[116] I. Reviakine, A. Simon, A. Brisson, Langmuir **16**, 1473 (2000).

[117] A. Charrier, F. Thibaudau, Biophys. J. **89**(2), 1094 (2005).

[118] T. Spangenberg, H. F. de Mello, T. B. Creczynski-Pasa, A. A. Pasa, H. Neihus, Phys. Status Solidi A **201**(5), 857 (2004).

[119] M. Jurak, E. Chibowski, Langmuir **22**(17), 7226 (2006).

[120] J. Zsako, M. Tomoaia-Cotisel, E. Chifu, A. Mocanu, P. T. Frangopol, Biochim. Biophys. Acta - Biomembr. **1024**(2), 227 (1990).

[121] M.Tomoaia-Cotisel, J. Zsako, A. Mocanu, M. Lupea, E. Chifu, J. Colloid Interface Sci. **117**(2), 464 (1987).

[122] C. Montis, V. Generini, G. Boccalini, P. Bergese, D. Bani, D. Berti, J. Colloid Interface Sci. **516**, 284 (2018).

[123] M. Singh, D. C. C. Harris-Birtill, S. R. Markar, G. B. Hanna, D. E. Elson, Nanomed.: Nanotechnol. Biol. Med. **11**(8), 2083 (2015).

[124] K. Salorinne, T. Lahtinen, S. Malola, J. Koivisto, H. Hakkinen, Nanoscale **6**(14), 7823 (2014).

[125] H. Hakkinen, Nat. Chem. **4**(6), 443 (2012).

[126] F. Italiano, A. Buccolieri, L. Giotta, A. Agostiano, L. Valli, F. Milano, M. Trotta, Int. Biodeterior. Biodegradation **63**(7), 948 (2009).

[127] F. Italiano, G. M. D'Amici, S. Rinalducci, F. De Leo, L. Zolla, R. Gallerani, M. Trotta, L. R. Ceci, Research in Microbiology, 162(5), 520 (2011)

[128] B. D. Belviso, F. Italiano, R. Caliandro, B. Carrozzini, A. Costanza, M. Trotta, Biometals **26**(5), 693 (2013)

[129] C. D. Calvano, F. Italiano, L. Catucci, A. Agostiano, T. R. I. Cataldi, F. Palmisano, M. Trotta, Biometals **27**(1), 65 (2014).

[130] M. Volpicella, A. Costanza, O. Palumbo, F. Italiano, C. Leoni, A. Placido, E. Picardi, M. Carella, M. Trotta, L. R. Ceci, FEMS Microbiol. Ecol. **88**(2), 345 (2014).

[131] M. Bebien, J.-P. Chauvin, J.-M. Adriano, S. Grosse, A. Vermeglio, Appl. Environ. Microbiol. **67**(10), 4440 (2001).

[132] F. Italiano, S. Rinalducci, A. Agostiano, L. Zolla, F. De Leo, L. R. Ceci, M. Trotta, Biometals **25**(5), 939 (2012).

[133] E. J. Hong, Y.-S. Kim, D. G. Choi, M. S. Shim, J. Ind. Eng. Chem. **67**, 429 (2018).

[134] P. F. Hsiao, H.-C. Tsai, S. Peng, A. Prasannan, T.-C. Tang, H.-M. Chang, Y.-S. Cheng, S.-Y. Lin, G.-H. Hsiue, Mater. Chem. Phys. **224**, 22 (2019).

[135] N. Amanlou, M. Parsa, K. Rostamizadeh, S. Sadighian, F. Moghaddam, Mater. Chem. Phys. **226**, 151 (2019).

[136] I. C. D. Vechia, B. T. Steiner, M. L. Freitas, G. dos Santos Pedroso Fidelis, N. C. Galvani, J. M. Ronchi, J. C. Possato, M. I. Fagundes, F. K. Rigo, P. E. Feuser, P. H. Hermes de Araujo, R. A. Machado-de-Avila, J. Nanopart. Res. **22**, 133 (2020).

[137] M. M. Fathy, A. A. Elfiky, Y. S. Bashandy, M. M. Hamdy, A. M. Elgharib, I. M. Ibrahim, R. T. Kamal, A. S. Mohamed, A. M. Rashad, O. S. Ahmed, Y. Elkaramany, Y. S. Abdelaziz, F. G. Amin, J. I. Eid, Sci. Rep.**13**, 2749 (2023).

[138] S. K. Surapaneni, S. Bashir, K. Tikoo, Sci. Rep. **8**, 12295 (2018).

[139] M. M. Khalaf, F. F. El-Senduny, H. M. A. El-Lateef, H. Elsawy, A. H. Tantawy, S. Shaaban, J. Mol. Liq. **340**, 117202 (2021).

[140] A. Boldeiu, M. Simion, I. Mihalache, A. Radoi, M. Banu, P. Varasteanu, P. Nadejde, E. Vasile, A. Acasandrei, R. C. Popescu, D. Savu, M. Kusko, J. Photochem. Photobiol. B **197**, 111519 (2019).

[141] J.-J. Shen, P. Zhang, F. Zheng, H. Chen, W. Chen, Y. Ding, X.-H. Xia, ACS Appl. Nano Mater. **1**(5), 2120 (2018).

[142] V. Raji, J. Kumar, C. S. Rejiya, M. Vibin, V. N. Shenoi, A. Abraham, Exp. Cell Res. **317**, 2052 (2011).

[143] N. Pernodet, X. Fang, Y. Sun, A. Bakhtina, A. Ramakrishnan, J. Sokolov, A. Ulman, M. Rafailovich, Small **2**(6), 766 (2006).

[144] J. C. Mohan, G. Praveen, K. P. Chennazhi, R. Jayakumar, S. V. Nair, J. Exp. Nanosci. **8**(1), 32 (2015).

[145] C. Freese, C. Uboldi, M. I. Gibson, R. E. Unger, B. B. Weksler, I. A. Romero, P.-O. Couraud, C. J. Kirkpatrick, Part. fibre toxicol. **9**, 23 (2012).

[146] S. Pinho, T. Ferreira-Goncalves, J. M. P. Coelho, J. Lopes, M. M. Gaspar, M. Neves Amaral, C. Pinto Reis, Int. J. Mol. Sci. **25**, 4488 (2024).

[147] S. Siddique, J. C. L. Chow, Appl. Sci. **10**(11), 3824 (2020).

[148] P. Sakore, S. Bhattacharya, S. Belemkar, B. G. Prajapati, C. M. Elossaily, Results in Chem.**7,** 101264 (2024).

[149] F. Wang, Y.-C. Wang, S. Dou, M.-H. Xiong, T.-M. Sun, J. Wang, ACS Nano **5**(5), 3679 (2011).

[150] G. Deng, H. Zha, H. Luo, Y. Zhou, Front. Bioeng. Biotechnol. **11**, 1118546 (2023).

[151] M. A. A. Maki, M. S. Teng, K. F. Tan, P. V. Kumar, OpenNano **13**, 100182 (2023).

[152] A. B. Barbezan, W. A. A. Rosero, D. P. Vieira, M. E. Z. Rigo, G. D. da Silva, A. A. Rodrigues, L. F. de Almeida, F. F. A. da Silva, A. G. Rivera, N. G. da Silva, E. S. Bernardes, C. A. Zeituni, M. E. C. M. Rostelato, Nanotheranostics **8**(1), 112 (2024).

[153] Y. Bustanji, J. Taneera, M. H. Semreen, E. Abu-Gharbieh, W. El-Huneidi, M. A.-I. E. Faris, K. H. Alzoubib, N. C. Soares, B. Albustanji, A. Y. Abuhelwa, R. Abu-Zurayk, M. A.Y. Alqudah, H. S. Alkatib, OpenNano **12**, 100164 (2023).

[154] A. S. Abed, Y. H. Khalaf, A. M. Mohammed, Results in Chem. **5**, 100848 (2023).

[155] C.-H. Li, M.-H. Chan, Y.-C. Chang, M. Hsiao, Molecules **28**, 364 (2023)