METALLIC NANOPARTICLES AND METAL OXIDE USED IN BIOMEDICAL APPLICATIONS

Rebecca Alexandra PUIU[1,†], Denisa Alexandra FLOREA[1,†], Alexandra-Cristina BURDUȘEL[1,†], Vasile-Adrian SURDU[1], Ecaterina ANDRONESCU[1,2,*]

Metallic nanoparticles reached great importance in the biomedical field due to their versatility, biocompatibility, anti-cancer properties, anti-inflammatory therapy, multiple synthesis routes, and the ability to be removed from an organism in a short period. Moreover, they present distinctive features over bulk materials due to their size which makes them optimal for various applications in the biomedical field including, but not limited to bioimaging, drug delivery systems, biosensors, photoablation therapy, etc. In general, metallic nanoparticles can be divided into four groups: metallic, bimetallic, metal oxides and magnetic nanoparticles, but here, we will focus on the applications and benefits of metallic and metal oxide nanoparticles..

Keywords: nanoparticles, nanomedicine, metallic nanoparticles, cancer therapy, tissue engineering

1. Introduction to Nanotechnology

Nanotechnology represents the control of materials with sizes between 1 and 100nm, which hold remarkable size-dependent properties as the United States National Nanotechnology Initiative affirm. The nanoscale materials' properties are different from those of bulk materials, mainly due to volume to surface area ratio, the quantum confinement effects, and chemical reactivity being changed. One remarkable property of them is their ability to be used in biotechnology, as their small size permits the entrance and transport of medicines in a targeted manner to specific structures in the human body. Nanomaterials are found very often in nature, under different forms since ancient times. Leon, Chung and Rinaldi [1].

Nanomedicine presents a great potential to anticancer therapy improvement, but unfortunately a reduced number of nanomedicines receive approval to be testet in clinical trials. Even so, potential in this area is immense, the clinical impact of nanomedicine requiring new perspectives and smart strategies. There are some

[1] Dept. of Science and Engineering of Oxide Materials and Nanomaterials, Faculty of Chemical Engineering and Biotechnologies, University POLITEHNICA of Bucharest, e-mail: rebecca_alexandra92@yahoo.com, denisa.florea94@yahoo.com, alexandra_burdu@yahoo.com.sg, adrian.surdu@upb.ro, ecaterina.andronescu@upb.ro
[2] Romanian Academy of Scientists, e-mail: ecaterina.andronescu@upb.ro
* Corresponding author's e-mail: ecaterina.andronescu@upb.ro
† These authors shared the first position and contributed equally to this work

important steps which need to be followed in order to prepare nano-drug formulations, like an organic or inorganic core, and surface properties like tuneable size of hydrophobicity can be modified to achieve the desired functions. In this way, nanoparticles, especially metallic ones represent an important candidate to fight against cancer disease [49], offering high stability, antimicrobial activity and ability to easily change surface properties [50].

Nanomaterials can be synthesized through a large variety of methods, including biological, physical or chemical routes. Because physical and chemical routes of synthesis are very expensive and need high energy consumption, green methods are mainly used, and offer a better purity of the final product [2].

In 2019, the European Commission stated that nanomaterials are 'materials which often have specific properties due to their small particle size'. De Jong and Borm described nanomaterials in 2008 as being a part of the nanotechnology industry, with at least one size in the range of 1- 100 nm [3].

2. Nanomaterials – a promising tool in biomedicine

Nanomaterials used in biotechnology often possess original physicochemical properties, which makes them suitable to be used in medical therapies. Also, nanomaterials represent an alternative for conventional science as they can be used as drug delivery systems, for an improved and targeted treatment, minimizing the risk of side effects or injury of other structures [4].

Nanomaterials are classified into organic, inorganic and metallic, depending on their chemical nature. The category of organic nanomaterials includes nanofibers, liposomes, polymeric nanoparticles, micelles and dendrimers, carbon-based materials etc.. By comparison, inorganic nanoparticles are metallic, magnetic nanoparticles, quantum dots etc. [5]. Nanoparticles can be synthesized using two different approaches: bottom-up, where nanoparticles are formed from the molecular level, and top-down, where the source is the bulk material that continues to decrease in size until nanoparticles are obtained [6].

Another area of interest for nanomaterials is regenerative medicine, which aims to repair damaged cells, tissues and organs, using tissue engineering, biomaterials, molecular biology and even stem cell science. The tissue engineering field consists of numerous disciplines combined, including but not limited to chemistry, physics and biology. Tissues can be regenerated through the stimulation of repairing mechanisms by delivering a scaffold which can be loaded with stem cells, growth factors or other molecules that can direct the cellular behaviour or induce a specific pathway in stem cells differentiation. There are many signs of progress in nanotechnology, mostly because of the nanoscale structure of human tissues, being able to imitate the structure of organs at nanoscale level [7].

US National Nanotechnology Initiative defined nanotechnology as "the understanding and control of matter at dimensions of roughly 1-100 nm, where unique phenomena enable novel applications." According to this quote, nanomaterials and nanotechnology have been included in a variety of research fields, such as drug delivery, tissue engineering, regenerative medicine, cancer therapy, and stem cell therapy [8].

At this moment, biofilm development and its related complications represent one of the hardest-to-solve challenges that healthcare systems are facing worldwide. Therefore, the use of nanotechnology in designing solutions that can overcome infection and its related complications is a must [9, 10]. Biofilms are well-known to survive in extremely difficult environmental conditions, like high temperatures, UV radiation, antibiotics and high salinity [11]. Due to the fact that biofilms possess the capacity to adapt to different conditions, it is assumed that they may also have developed mechanisms for self-protection, creating the right conditions for survival and growth [12]. There are plenty of studies in international literature which demonstrate that biofilms are a serious problem in public health, the bacteria present in biofilm being much more resistant to antibiotics than those in planktonic state [13]. Antibiotic resistance also appears because in biofilms, genes can be transferred among different microorganisms, having a large variety of connecting channels [14]. The role of nanoparticles in fighting biofilms and drug resistance is not only to destroy the biofilm, but also to reduce the dose of antibiotics required [15].

Cancer represents the biggest problem in medicine worldwide, and scientists are looking permanently for a sustainable treatment and a complete cure for the oncology area. The main objective of finding different approaches to prevent its progression is achieving personalized therapy by targeting molecular pathways. This field is very dynamic, with every discovery of drugs and therapies leading to a new perspective on cancer progression [16].

In the healthcare system, cancer represents a significant problem for society, taking second place in the world's causes of death. Cancer treatment is still an intensely studied subject, with different perspectives being applied in diagnosis and treatment procedures [16].

When a mutation appears in DNA, it can be irreparable. The gene and protein expression is controlled by epigenetic code and information. The appearance and progression of cancer can be caused by genetic mutations resulting from abnormalities in the genetic mechanism [16].

Because cancer cells do not resemble normal cells and have different biologic behaviour and composition, one of the different approaches used in cancer treatment is immune therapy. The principal forms of immunotherapy used against cancer are monoclonal antibodies, vaccines, T-cell therapy, immune checkpoint inhibitors and oncolytic virus therapy [16]. The monoclonal antibodies can induce

cytotoxicity antibody-dependent apoptosis by binding specific antigens to the surface of the membrane [17].

As shown in Fig. 1, different methods were used to cure cancer, such as immunotherapy, pharmacogenetics, epigenetic mechanism, drug delivery systems and targeted therapy [16].

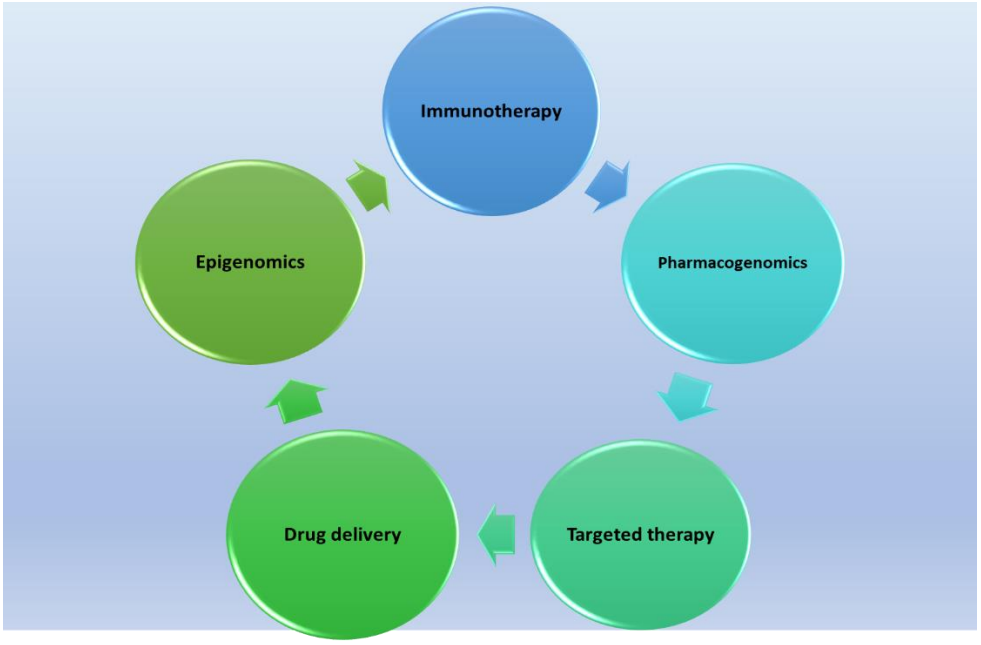


Fig. 1. Different therapies used in cancer treatment. Adapted from multiple sources [18-21].

Targeted therapy is part of precision medicine, inducing apoptosis of cancer cells without affecting the healthy ones. There is still one issue: identifying the target by determining the differences between normal and cancer cells. Various proteins are used to target cancer cells, like kinases, nuclear hormone receptors, ion channels, and G protein receptors [22].

Many drugs can be used as antitumor agents, but the risk is that they can be ineffective for cancer patients. Alfarouk et al. found out in 2015 that this problem can be fixed by increasing the time and dosage of drugs to streamline the effects of drugs on tumour cells [23]. Despite that, there are still two major problems in using this method of treatment: the transport directly to cancer cells and prevention of drug delivery [24].

Discovering new methods to control materials on a nanometer range led to visualizing a large variety of medical applications which had been seen only as an idea at the moment. The most studied cancer therapy approaches are those that involve nanoparticles which can target tumors to destroy them. Those techniques are based on the principle of differentiation of vessels that feed normal cells from

feed tumours. Nanoparticles are not able to penetrate normal blood vessels so they go with the blood flow. Therefore, nanoparticles can form agglomerations in the tumor due to slow lymphatic drainage from tumours [9].

The easiest method to destroy tumours is passive heating, in which nanoparticles are projected to absorb a specific wavelength of light are present in the blood stream. Gold is the most often used material for tumour heating, by infrared laser light [9].

Another possibility to heat tumours it through the magnetic method using nanoparticles made of biomaterials with magnetic characteristics, like iron oxide maghemite. Their unique properties offer the ability to heat rapidly when exposed to an alternating current magnetic field. When magnetic nanoparticles are exposed to AC magnetic field, the electromagnetic energy converts into termal energy through Brownian relaxation. In this way, the kinetic energy is dissipated and the tissue is surrounded by heat. Healthy tissue is not being affected because it does not contain any magnetic material [9].

Table 1 summarizes multiple categories of nanobiomaterials and their usage in biomedical applications.

Table 1

Categories of nanobiomaterials and their usage in biomedical applications

Nanobiomaterials category	Applicability	References
Metallic nanoparticles: silver nanoparticles, gold nanoparticles, iron oxide nanoparticles	Breast cancer, leukaemia, drug delivery systems, skin carcinoma, imaging	[25-28]
Carbon-based nanobomaterials: graphene, nanotubes, nanodiamonds	Drug delivery, photothermal treatment of tumours	[29-31]
Inorganic nanomaterials: hydroxyapatite, mesoporous silica, montomillonite	Bone repairment, drug delivery, intracellular treatment, regeneration	[32, 33]
Protein-peptide- based nanobiomaterials: albumin, gelatin, elastin	Brain infection treatment, infectious disease treatment	[34-36]
Polymeric nanomaterials: sodium alginate, hyaluronic acid, chitosan, polycaprolactone	Drug delivery, tissue regeneration	[37-40]

As stated before, the properties of nanomaterials are different from those of bulk materials, as follows [9]: The optical properties of nanomaterials are dependent on the size and morphology of nanoparticles. The colour characteristics of metallic nanoparticles are dramatically changed when the particle size is less than 100nm. The plasmon resonance frequency is higher when the particle size is decreasing. Additionally, the ratio becomes more important and the bonds between the nanoparticle and the atoms from the surface are more tense. Considering all these aspects, the use of nanoparticles in finding solutions to the most crucial problems in the healthcare systems has gained researchers' attention over the past decades.

3. Metallic nanoparticles in the biomedical field

The interest in using metallic nanoparticles in cancer therapy and biomedicine is increasing and has the main challenge of limiting the contact between their surface and the healthy cells to target only the cancerous cells and specific tissues. The current literature presents many studies regarding the production and optimization process of nanoparticles, which are divided into two categories: metallic (Au, Cu, Pt, Ag, etc.) and nonmetallic (polylactic-co-glycolic acid, carbon nanotubes, oxide nanoparticles, etc.) and can be obtained through three different methods; physical, chemical and based on microorganisms, green synthesis [41].

Cancer therapy is an area of interest in which nanoparticles are constantly used. An important aspect that may change cancer treatment is that cancer cells present resistance to a large variety of lipophilic drugs, causing drug resistance and the ineffectiveness of chemotherapy. Various studies reported that metallic nanoparticles with a highly reactive surface can induce apoptosis, which is considered the most effective method to eliminate cancer from organisms, due to their ROS ability [42].

It was shown in previous studies that transition metals have no cytotoxic effect on human use and have high therapeutic properties. When the nanoparticle is in contact with the cell, it releases metal ions, leading to ROS activation, leading to different pathways of programmed cell death, like necroptosis or autophagy [43].

Metallic nanoparticles can be designed in terms of size, charge and morphology, depending on their intended application. Recent studies focused on using nanoparticles as drug delivery systems due to improved retention and permeability by connecting them with tumour-targeting antibodies [44]. The most important advantage of metallic nanoparticles is the possibility to control their shape, charge, size, and surface modification very precisely [45]. Compared with non-metallic nanoparticles, metallic ones have a higher density and are easily taken up by cancer cells and can be used with success in immunotherapy because of their characteristic optical properties [46].

Metallic nanoparticles demonstrated major success in multiple applications, including tissue engineering, diagnostics, imaging, antimicrobial coatings, and many anti-cancer therapies, being used as delivery systems for antigens, cytokines, adjuvants, and also to induce antigen release. There is also a weak point, that these therapies are at the stage of clinical trials. However, their unique properties represent an opportunity to develop new cancer immunotherapy techniques or various products that can overcome the current obstacles encountered in clinical settings [44].

3.1. Silver Nanoparticles

Silver nanoparticles have been intensely used in the medical industry, mainly because of their antifungal, antiviral, and antibacterial properties. From all noble metals, it was found that silver has the most increased efficiency of plasmon excitation, leading to more substantial effects of physical activity [47]. Silver nanoparticles are very attractive in theragnostic platforms, suitable for surface conjugations with a large variety of therapeutic agents. Following the in vitro tests, it was observed that silver is more cytotoxic than gold, more likely at concentrations higher than 5 mg/mL; on tumour cells, they act through apoptotic mechanisms, the cytotoxic activity being dependent on the physicochemical characteristics [52].

With the help of unique properties, silver nanoparticles are an essential tool for cancer diagnosis. A study performed on the scattering efficiency and absorption rate of silver nanoparticles showed that they can be successfully used in imaging and thermal procedures, having a maximum efficiency of 20 nm in absorption and 30 nm for light scattering. One of many applications is the possibility of acting as biosensors in analyzing tumour markers, being cheaper than gold nanoparticles, and having a higher coefficient of molar extinction. One example is the determination of squamous cell carcinoma antigen, using surface plasmon resonance with AgNPs array [52].

Silver nanoparticles can be obtained through different synthesis techniques – physical, biological and chemical. Unfortunately, chemical methods can lead to secondary reaction products that manifest toxicity and are also expensive. The physical methods have the advantage that the nanoparticles obtained have an increased purity. When plant extracts are used to obtain silver nanoparticles, the reduction of Ag^+ ions is faster and the nanoparticles are more stable [53].

The benefits of silver nanoparticles are also seen in their ability to combine with other nanomaterials, like silica, gold, etc. providing superior properties in diagnostic procedures. Gold-silver core-shell nanoparticles can be used as biosensors, offering an accurate approximation of cancer antigens in ovarian cancer; the immunosensor was more sensitive when silver was added, being built by bonding amine-functionalized hybrid nanoparticles with anti-CA125 antibody [54].

A study made by Blanco et al. in 2016 [55] showed that AgNPs present a positive effect on human lung carcinoma, reporting a decrease of p53 tumour suppressor protein in two cases: after a low dosage under daily exposure or high dosage but administrated only once [55]. Administrating silver nanoparticles can also lead to ROS generation, which causes apoptosis and mitochondrial damage [56]. Researchers who studied silver nanoparticles' cytotoxicity level showed that it is highly dependent on capping material and tumour cell line. Using sodium alginate for capping silver nanoparticles, their antiproliferative activity has been

evaluated against human malignant melanoma. It was revealed the anti-cancer activity through necrosis and apoptosis [57].

Another important characteristic of silver nanoparticles is their antineoplastic activity, making them be used to treat a large variety of cancer forms. In the study performed by Ferreira et al., silver nanoparticles synthesized from Fusarium sp. showed time, and dose-dependent cytotoxicity. The tests performed in vitro and in vivo demonstrated that cell death is induced through apoptosis. Cell migration was also inhibited in bladder carcinoma, and a study on mice showed the antitumoral activity of silver nanoparticles against invasive bladder cancer–tumor regression with 57% at a dosage of 0.05 mg/mL AgNPs. In this case, the pharmacological options for bladder cancer treatment are expensive. AgNPs are a promising alternative, being cost-effective [58].

The antitumoral activity of silver nanoparticles is known to be realized by releasing silver ions and metallic silver, which can lead to DNA damage, membrane damage, oxidative stress and genotoxicity [59].

In literature, synthesized silver nanoparticles have sizes of more than 10nm. Because the parameters of chemical reactions are dependent on the shape and size of the particles, it is very likely that nanoparticles with smaller sizes to be less toxic for non-cancerous cells and target the cancer cells directly [60].

Silver nanoparticles can be successfully combined with various anti-cancer drugs, one of them being Paclitaxel. Kalındemirtas et al. [60] found a potent cytotoxic effect of AgNPs-PTX on osteosarcoma cell line (Saos-2), a fatal and very rare type of cancer, appearing more often in young adults and adolescents. Silver nanoparticles act as carriers, solving solubility and toxicity problems caused by Paclitaxel. The study also showed that the dosage of the drug known to have serious side effects can be reduced 10 times and cytotoxicity on normal cells is missing, indicating that the drug carried out by silver nanoparticles targets specifically the cancer cells [60].

The outstanding antimicrobial properties of silver nanoparticles were proved over the years by multiple studies against a diversity of pathogens. The antimicrobial activity of silver nanoparticles is confirmed in various studies, and it has a large spectrum of action. Besides Gram-negative and Gram-positive bacteria, they exhibit antibiofilm properties even on antibiotic-resistant strains. This can be associated with the fact that efficiency is dependent on size and concentration. In general, nanoparticles with an average diameter under 10 nm are the most effective ones [61]. The fact that at the nanoscale level, silver's antimicrobial efficiency has been significantly increased led to the investigation of silver nanoparticles for multiple applications in various industries: cosmetics, clothing industry, dental industry, food handling tools, biomedical devices (e.g. catheters), surgical products etc. In addition to their well-known antimicrobial properties, they also possess anti-inflammatory characteristics. Research suggested that silver nanoparticles altered

the expression of matrix metalloproteinase in animal models which are specific enzymes secreted in inflammatory and repair processes [61]. Considering all these aspects, the market potential has grown a lot in the past decades leading to a production of about 500 tons of silver nanoparticles yearly to supply the current demand of all industries [62]. However, specifically, in the biomedical field silver nanoparticles are used for a lot of applications, including, but not limited to: wound dressings, different formulations of antimicrobial gels for topical application, medical device coatings (e. g. catheters, implant surface, etc.), or medical textiles.

3.2. Gold nanoparticles

At the beginning of time, gold has been used in medical activities, mostly in China and India, and is linked to fertility and longevity. As time goes by, in modern times it has been used in syphilis and neurological affections treatment, and 20^{th} century for rheumatic affections and tuberculosis. Gold nanoparticles are made of a layer of organic ligands, which contain a gold core. Of all metallic nanoparticles available, gold nanoparticles are the least toxic and the safest for human organisms, having a large surface area and exceptional magnetic and optical properties [63].

Gold nanoparticles can be easily modified and loaded with different drugs to be used as a transporter for drug delivery. There are plenty of methods through which gold nanoparticles can be obtained. The most common is based on reducing HAuCl4 through a chemical method [63]. Different molecules or drugs can be easily attached to gold nanoparticles and can be targeted through two different methods: actively or passively. In active targeting, peptides or monoclonal antibodies act like ligands and are conjugated with nanoparticles. The ligands interact with specific biomarkers on tumor cells, allowing drug delivery. Passively, nanoparticles form accumulations in the tumour via enhanced retention and permeation effect, making the tumor's vascular path to be leaky [64].

Gold nanoparticles presented an anti-angiogenic effect in multiple studies, this being achieved by inflammatory cytokines deregulations or another molecular mechanism, inhibition of the vascular endothelial growth factor [65]. It was shown that gold nanoparticles helped reduce tumour vessel density and volume, normalized the vascularization, and reduced the anterior gradient 2 in mice inoculated with colorectal cancer cells [66].

In another study that combined both in vitro and in vivo experiments, gold nanoparticles were conjugated with quercetin, enhancing its therapeutic effect. Epithelial-mesenchymal transition, angiogenesis, and the growth of cancer cells were inhibited by targeting the epidermal growth factor receptor [67].

Another study performed in vivo combined photothermal therapy based on gold nanoparticles with anti-PD-L1 antibodies. The methods' effect was the activation of the immune system by photothermal effect, leading to the killing

cancer cells in distant tumours. Cancer cells become more vulnerable to immune cell killing action activated by nanoparticle photothermal therapy [68].

In another study performed by Liu et al. [69], photothermal effect and controlled drug release were combined by coating mesoporous silica on synthesized gold nanoparticles, being used as a drug delivery system for doxorubicin. Doxorubicin showed almost zero release at room temperature. The release was achieved at higher temperatures generated under near infrared irradiation [69].

Gold nanoparticles can be characterized in the visible and near-infrared region by light absorption, by its excellent optical properties. The absorption is low for small gold nanoparticles with a spherical shape, but increases for nanoshells and nanorods, being a better candidate for many cancer diagnosis methods [52].

Another important role of gold nanoparticles is the possibility of being used in nanosensor development to circulate cancer cell detection in an early stage and to monitor cancer evolution and treatment. A study performed by Ahmadzadeh-Raji et al. described the design of a detection system for colon cancer cells based on aptamers linked covalently on the surface of gold nanoparticles. Gold nanoparticles obtained with a diameter of approximately 32nm were used to catch cancer cells. These sensors record the limit of detection, translated into a number of trapped cells/mL [70].

The biomedical properties of gold nanoparticles are expanding, and the barriers of cancer nanotechnology are continuously changing. Owing to their high surface surface-to-volume ratio, surface chemistry and high atomic number, gold nanoparticles can be qualified to be used as radiosensitizers for RT enhancement [71]. More than that, gold nanoparticles can be used in the thermal ablation of tumour areas by generating localized heat due to their photothermal conversion ability [72].

Gold nanoparticles are ideal for drug delivery scaffolds due to their bioinert properties – a primary requirement for nanocarrier design. Cho et al. [73], demonstrated that in the case of positively charged gold nanoparticles, the cellular uptake was 5-10 times higher than negatively charged or neutral counterparts.

Radiotherapy represents a major cancer therapy component; almost half of the cancer patients are being treated as part of palliative treatment. Radiotherapy uses ionized radiation which interacts with the DNA or indirectly induces cellular damage by water radiolysis and free radicals. The main purpose of radiotherapy is to induce radiation damage to the tumour but keeping the toxicity of normal tissue as low as possible. Currently, techniques based on radiotherapy are not enough to destroy hypoxic tumors and advanced types of cancer [74]. An improvement of radiotherapy efficiency can be made by incorporating radiation sensitizers into the tumour. Gold nanoparticles are ideal candidates mostly because of their distinctive properties, including [75]: High atomic number (Z=79), which gives a larger photoelectric absorption cross-section and a higher possibility to emit secondary

radiations, suitable dimensions for passive accumulation in the tumour, ability to control morphological properties, capable of offering accurate diagnostic for image-guided radiotherapy, ability to be conjugated with ligands.

Another field in which gold nanoparticles are successfully used is imaging applications. For example, the MRI technique is non-invasive and has a high ability to differentiate soft tissues and possess an increased spatial resolution. CT, known as X-ray computed tomography, is a useful diagnostic method, that provides essential anatomical information, like location, shape, and size of tissues. Nanoparticles have been developed as contrast agents for these medical imaging techniques, defeating different problems like inflammation, short imaging times, renal toxicity, etc. Due to the high atomic number and increased X-ray absorption coefficients, gold nanoparticles are excellent candidates for a contrast agent in computer tomography. The space between gold nanoparticles is strongly electromagnetic charged. The intensity of fluorophores is enhanced, emitting fluorescence in the therapeutic window to enable tumour detection [76].

One of the most interesting research categories in the cancer treatment area is applications based on drug delivery. Thambiraj et al. considered gold nanoparticles conjugated with docetaxel to be a possible option for therapy. Gold nanoparticles were obtained through chemical reduction and conjugated with docetaxel by a non-covalent method. Docetaxel is an anticancer drug, produced by plants of Texus family. Treatment based on docetaxel represents a viable option for patients suffering from hormone-refractory lung cancer. The system formed of gold nanoparticles and docetaxel showed a decrease in cell survival of almost 50%, compared to control, being a promising nanocarrier in treating different cancer categories [77].

3.3. Platinum-based nanomaterials

Lately, nanomaterials presenting numerous characteristics in cancer therapy are becoming more and more popular. Platinum is part of the pure metals category, with a light-absorbing in biological range and antioxidant properties in some specific concentrations. Latest studies showed that using nanoparticles as a therapeutic agent in cancer treatment - reduces the side effects and improves the patients' lifetime [78].

Researchers did not focus so much on platinum nanoparticles studies because of their toxic effect on cancer cells but there are many papers which show that in a small concentration, platinum nanoparticles are biologically stable and present a high tolerance [79].

The effect of platinum nanoparticles in small concentrations was studied in photothermal therapy. It was demonstrated that the size of nanoparticles influences therapy effectiveness. There were synthesized two types of nanoparticles, of 2 and 80 nm and morphology changes have been shown in colon cell lines, which were

irradiated by lasers of 650 and 808nm, compared with controls. There were some differences in cell mortality, of 15%, in both nanoparticles' sizes. More than that, when platinum nanoparticles were used for laser irradiation, a connection between the cytotoxicity effect and nanoparticle size could be observed. The mortality of cancer cells was higher in the presence of platinum nanoparticles with a size of 2nm than in the presence of nanoparticles with 80nm dimensions. The conclusion of the study performed by Depciuch et al. [79] was that platinum nanoparticles are a promising tool to be used in both diagnostic and therapeutic techniques in cancer therapy, their remarkable physicochemical properties making them suitable as photosensitizers in photothermal therapy [79].

The standard treatment for advanced non-small cell lung cancer is known to be chemotherapy based on platinum nanoparticles, followed by a chemotherapeutic agent. In this case, it was used as a natural antioxidant named curcumin, which showed significant anti-inflammatory, and anti-cancer properties without causing any damage to the kidney or liver. Following this idea, Chen et al. synthesized a complex of Platinum and curcumin to maintain anti-cancer efficacy while drug solubility is improved [80].

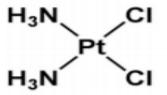
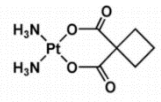
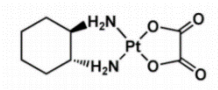
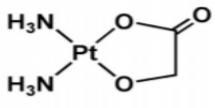
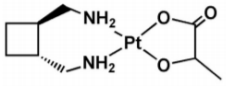
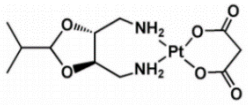
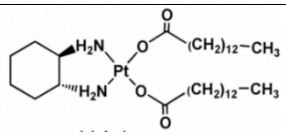
Platinum nanomaterials have many atoms and represent an essential candidate for biomedical applications, especially in computed tomography. Another essential property of platinum nanomaterials is the ability to convert laser energy into heat and catalyze hydrogen peroxide, improving in this way tumour hypoxia. Recently, a new type of agent opportune for tumour treatment is mesoporous platinum nanoparticles, which have many pores that can be filled with molecules. Usually, to improve treatment, both hyperthermia and chemotherapeutic are transported to tumour sites [81].

Platinum nanoparticles are also used in breast cancer because is localize the tumour and prevent tumour recurrence [48]. Moreover, combining platinum drugs with imaging agents, allows the monitoring of drug-loaded nanoparticles in real-time. Combining platinum nanoparticles with irradiation causes DNA damage. By encapsulating platinum nanoparticles in liposomes, DNA damages are threefold greater than using Cisplatin or Platinum-based nanoparticles alone in breast cancer cells [82].

In testicular cancer, the principal clinical treatment is also based on platinum anti-cancer agents, with cure rates exceeding 95% since cisplatin has been introduced into the treatment regimen [83]. There are three main drugs based on Platinum, used worldwide in cancer treatment: cisplatin, carboplatin and oxaliplatin. Carboplatin has been used for ovarian cancer treatment since 1988 and oxaliplatin has been mainly used for colorectal cancer in combination with folinic acid since 2002 (Table 2) [84].

Table 2

Platinum-based drugs used in different types of cancer

Pt-based drug	Chemical formula	Type of cancer	References
Cisplatin		Testicular cancer, lung cancer, bladder cancer	[85-87]
Carboplatin		Ovarian cancer	[88]
Oxaliplatin		Colorectal cancer	[89]
Nedaplatin		Small cell lung cancer, head and neck cancer, esophageal cancer, non-small cell lung cancer	[90-93]
Lobaplatin		Chronic myelogenous leukemia, small cell lung cancer, inoperable metastatic breast cancer	[94-96]
Heptaplatin		Gastric cancer	[97]
Miriplatin		Hepatocellular carcinoma	[98]

The mechanism of action of cisplatin can be done in two different ways: active transport helped by membrane proteins and passive diffusion. Active transport is more advantageous because it can play an important role in combating cisplatin resistance [83].

The effect of platinum-based drugs has been studied also for malignant bone tumours by Zhou et al. [99], fabricating complexes made of phytic acid capped with platinum nanoparticles. It was shown to have a great photothermal effect and they can be easily eliminated by the body due to their ultrasmall size. The complex presented a high affinity to hydroxyapatite by in vitro studies. The therapeutic results demonstrated that this combination reduced osteolysis and eliminated bone tumours [99].

Despite the above-mentioned findings in cancer therapy, the unique properties of platinum nanoparticles are the basis of their applicability in multiple biomedical applications such as: drug delivery, biosensors or MRI contrast agents. Moreover, multiple studies conducted over the last decades proved their efficiency

as antimicrobial agents as well. For instance, studies confirmed their efficiency against *Candida albicans, Aspergillum flavus, E. coli, P. aeruginosa, Salmonella choleraesuis* and *Klebsiella pneumonia* [100].

3.4. Copper based nanomaterials

Copper nanoparticles gained a particular interest in the biomedical field due to their low cost, availability and most importantly, their similar characteristics with noble metals. An important property is that under NIR laser irradiation, copper nanoparticles can be used in imaging to transform the light into heat [101]. Copper also represents a trace element, the daily intake being about a maximum of 10mg. It is involved in the functions of immune cells responsible for defeating pathogens. Additionally, it has antioxidant properties and is involved in the synthesizing of neuropeptides [102].

It has a monoclinic structure, being intensively used in the biomedical area, as drug delivery, anti-fungal, antimicrobial, anti-cancer, antioxidant, etc. There are different approaches used in copper oxide nanoparticle fabrications. However, the disadvantages are the increased cost, the release of toxic elements into the environment, and high consumption of energy [103]. Green chemistry became a popular method for nanoparticle fabrications, synthesising homogenous nanoparticles with high crystallinity and purity at a lower cost.

Copper oxide nanoparticles can be obtained through various chemical, physical and biological methods, like precipitation, chemical reduction, hydrothermal method, sol-gel, and green chemistry [104]. These synthesis routes can be divided into: bottom-up, in which nanoparticles are assembled from smaller atomic size particles, and top-down, where large molecules are converted to smaller ones [105].

Nagajyothy et al. discovered the cytotoxic effect produced by copper oxide nanoparticles against cervical cancer, the cellular death being possible by ROS intracellular initiation [106]. Similarly, copper oxide nanoparticles could be synthesized using aqueous leaf extracts of different plants, like Murraya koenigii, Tamarindus indica, Tamarindus indica, Azadirachta indica, which showed toxicity in different types of cancer: lung cancer cells, breast cancer, epithelioma, cervical cancer. The best value for IC50 was gained by Tamarindus indica, even if the morphology of nanoparticles was similar [43].

Copper sulfide is another example of promising cancer therapy agents, because of their therapeutic potential and multifunctional properties. Compared with other inorganic materials, these nanoparticle presents low cost and toxicity together with higher biocompatibility. Copper sulfide nanoparticles can be easily adapted to be used as nanocarriers, photothermal agents, or as adjuvant in different cancer therapies, such as immunotherapy, chemotherapy or radiotherapy [107]. From various types of nanoparticles, copper sulfide can be removed easily from the

organism, being an exceptional candidates for cytotoxic drug delivery into cancer cells [108].

Many studies were performed on copper nanoparticles to demonstrate their applicability in anti-cancer therapy. In a study, Karlsson et al. discovered that copper oxide nanoparticles lead to almost 100% cell death in only 18 h from the administration. Another study about the copper oxide anticancer effect showed that in human lung cells, it generated a toxic effect 24 hours after exposure [109].

One of the other important characteristics of Cu/CuO nanoparticles is that they enter easily in the human body through the respiratory system and skin. A study performed by Fahmy et al. evaluated its genotoxicity and cytotoxicity in lung cells. It demonstrated that cell viability decreases in 72h after treatment, the decrease being dose-dependent [109].

4. Conclusions

Due to limitations imposed by conventional diagnostic and treatment methods, and the limitations to detect cancer in an early stage, nanotechnology gained more and more attention over the past years. Nanotechnology puts together information from many related fields, like medicine, materials science, biochemistry, imaging, physics, and diagnostics. Nanoparticles gained a lot of interest in nanomedicine, being used in drug delivery systems, design of antimicrobial coatings, hydrogels, encapsulation of various molecules, creation of nanostructured multifunctional systems, etc.

Specifically, metallic nanoparticles have a broad range of applications in many industries, including, but not limited to: medical devices coating (implants, prosthesis, catheters etc.), gene therapy, drug screening, imaging, medical textiles, gels for topical applications, wound dressings, cosmetic formulations, construction industry, tissue engineering, cell labeling.

Multiple side effects and poor bioavailability which are linked with currently available medicines lead to the idea that nanotechnology might overcome these issues and contribute in the creation of efficient drug delivery systems. Currently, the advancements in this area permitted the encapsulation and targeted delivery of an active substance at a specific site. Delivery systems based on metallic nanoparticles presents important properties like biocompatibility, less degradation when meeting blood circulation, tumour targeting, and not least, reduced side effects. Formulations based on metallic nanoparticles can be functionalized with different therapeutic agents due to their dense surface and can be used in therapeutic methods based on heat or optical effect.

Nowadays, multiple synthesis routes have been developed and tested and they can be successfully used to obtain a variety of metallic nanoparticles. Moreover, a novel approach in this regard is to use green synthesis routes that are

both effective and friendly with the environment. The success of such methods has been proved over the past years, so they represent a promising tactic for future research.

Acknowledgement:
This work was supported by the grant POCU/993/6/13-153178, co-financed by the European Social Fund within the Sectorial Operational Program Human Capital 2014–2020.

REFERENCES

[1] *L. Leon, E.J. Chung and C. Rinaldi*, A brief history of nanotechnology and introduction to nanoparticles for biomedical applications, in Nanoparticles for Biomedical Applications, 2020, pp. 1-4.
[2] *S.M. Alsharif, S.S. Salem, M.A. Abdel-Rahman, A. Fouda, A.M. Eid, S. El-Din Hassan, M.A. Awad and A.A. Mohamed*, Multifunctional properties of spherical silver nanoparticles fabricated by different microbial taxa, in Heliyon, **vol 6**, 2020.
[3] *A.W.K. Yeung, E.B. Souto, A. Durazzo, M. Lucarini, E. Novellino, D. Tewari, D. Wang, A.G. Atanasov and A. Santini*, Big impact of nanoparticles: analysis of the most cited nanopharmaceuticals and nanonutraceuticals research, in Current Research in Biotechnology, **vol. 2**, 2020, 53-63.
[4] *R. Kumar, K.R. Aadil, S. Ranjan, and V.B. Kumar*, Advances in nanotechnology and nanomaterials-based strategies for neural tissue engineering, in Journal of Drug Delivery Science and Technology, **vol. 57**, 2020.
[5] *P.G. Jamkhande, N.W. Ghule, A.H. Bamer and M.G. Kalaskar*, Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications, in Journal of Drug Delivery Science and Technology, **vol. 53**, 2019.
[6] *P. Sensharma, G. Madhumathi, R.D. Jayant and A.K. Jaiswal*, Biomaterials and cells for neural tissue engineering: Current choices, in Mater Sci Eng C Mater Biol Appl, **vol. 77**, 2017, pp. 1302-1315.
[7] *Y. Yang, A. Chawla, J. Zhang, A. Esa, H.L. Jang and A. Khademhosseini*, Applications of Nanotechnology for Regenerative Medicine, in Healing Tissues at the Nanoscale, Principles of Regenerative Medicine, 2019, pp. 485-504.
[8] *R.A. Meyer and J.J. Gree*n, Shaping the future of nanomedicine: anisotropy in polymeric nanoparticle design, in Wiley Interdiscip Rev Nanomed Nanobiotechnol, **vol. 8**, 2016, pp. 191-207.
[9] *P. Davidovits*, Nanotechnology in Biology and Medicine, in Physics in Biology and Medicine, 2019, pp. 293-305.
[10] *T.G. Vladkova, A.D. Staneva, I.A. Avramova, I.A. Ivanova, and D.N. Gospodinova*, Fucoidan-Containing, Low-Adhesive Siloxane Coatings for Medical Applications: Inhibition of Bacterial Growth and Biofilm Development, **vol. 16,** 2023, pp. 3651.
[11] *W. Yin, Y. Wang, l. Liu, and J. He*, Biofilms: The Microbial "Protective Clothing" in Extreme Environments, **vol. 20**, 2019, pp. 3423.
[12] *R. Mirghani, T. Saba, H. Khaliq, J. Mitchell, l. Do, l. Chambi, K. Diaz, T. Kennedy, K. Alkassab, T. Huynh, M. Elmi, J. Martinez, S. Sawan, and G. Rijal*, Biofilms: Formation, drug resistance and alternatives to conventional approaches, in AIMS Microbiology, **vol. 8**, 2022, pp. 239-277.
[13] *M.E. Olson, H. Ceri, D.W. Morck, A.G. Buret, and R.R. Read*, Biofilm bacteria: formation and comparative susceptibility to antibiotics, in Canadian journal of veterinary research = Revue canadienne de recherche veterinaire, **vol. 66**, 2002, pp. 86-92.
[14] *S. Singh, S.K. Singh, I. Chowdhury, and R. Singh*, Understanding the Mechanism of Bacterial Biofilms Resistance to Antimicrobial Agents, in The open microbiology journal, **vol. 11**, 2017, pp. 53-62.

[15] *P. Das, and V.S. Karankar*, New avenues of controlling microbial infections through anti-microbial and anti-biofilm potentials of green mono-and multi-metallic nanoparticles: A review, Journal of microbiological methods, **vol. 167**, 2019, pp. 105766.
[16] *G.T. Ulu, Y. Kiraz, and Y. Baran*, Personalized biomedicine in cancer: from traditional therapy to sustainable healthcare, 2020, pp. 441-457.
[17] *K.W. Phelan, and A.S. Advani*, Novel Therapies in Acute Lymphoblastic Leukemia, in Current hematologic malignancy reports, **vol. 13**, 2018, pp. 289-299.
[18] *L.M. Lafave, R.E. Savage, and J.D. Buenrostro*, Single-Cell Epigenomics Reveals Mechanisms of Cancer Progression, **vol. 6**, 2022, pp. 167-185.
[19] *F. Diniz, P. Coelho, H.O. Duarte, B. Sarmento, C.A. Reis, and J. Gomes*, Glycans as Targets for Drug Delivery in Cancer, **vol. 14**, 2022, pp. 911.
[20] *L. Kraehenbuehl, C.-H. Weng, S. Eghbali, J.D. Wolchok, and T. Merghoub*, Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways, in Nature Reviews Clinical Oncology, **vol. 19**, 2022, pp. 37-50.
[21] *B.T. Scandolara, B.R. Barreto Pires, B. Vacario, I.S.S. de Amorim, B.P. Siqueira, M.J. Serpeloni, L.A. Mencalha, R.C. Bonvicino, and C. Panis*, An Overview Regarding Pharmacogenomics and Biomarkers Discovery: Focus on Breast Cancer, in Current topics in medicinal chemistry, **vol. 22**, 2022, pp. 1654-1673.
[22] *K.S. Bhullar, N.O. Lagaron, E.M. McGowan, I. Parmar, A. Jha, B.P. Hubbard, and H.P.V. Rupasinghe*, Kinase-targeted cancer therapies: progress, challenges and future directions, Molecular cancer, **vol. 17**, 2018, pp. 48.
[23] *K.O. Alfarouk, C.M. Stock, S. Taylor, M. Walsh, A.K. Muddathir, D. Verduzco, A.H. Bashir, O.Y. Mohammed, G.O. Elhassan, S. Harguindey, S.J. Reshkin, M.E. Ibrahim, and C. Rauch*, Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp, in Cancer cell international, **vol. 15**, 2015, pp. 71.
[24] *B. Bahrami, M. Hojjat-Farsangi, H. Mohammadi, E. Anvari, G. Ghalamfarsa, M. Yousefi, and F. Jadidi-Niaragh*, Nanoparticles and targeted drug delivery in cancer therapy, in Immunology Letters, **vol. 190**, 2017, pp. 64-83.
[25] *E. Mostafavi, A. Zarepour, H. Barabadi, A. Zarrabi, l.B. Truong, and D. Medina-cruz*, Antineoplastic activity of biogenic silver and gold nanoparticles to combat leukemia: Beginning a new era in cancer theragnostic, in Biotechnology reports (Amsterdam, Netherlands), **vol. 34**, 2022, pp. e00714.
[26] *M. Anisuzzman, V. komalla, M.A.M. Tarkistani, and V. Kayser*, Anti-Tumor Activity of Novel Nimotuzumab-Functionalized Gold Nanoparticles as a Potential Immunotherapeutic Agent against Skin and Lung Cancers, **vol. 14**, 2023, pp. 407.
[27] *Y. Chen, and S. Hou*, Recent progress in the effect of magnetic iron oxide nanoparticles on cells and extracellular vesicles, in Cell Death Discovery, **vol. 9**, 2023, pp.195.
[28] *L. Tao, X. Chen, J. Sun, and C. Wu*, Silver nanoparticles achieve cytotoxicity against breast cancer by regulating long-chain noncoding RNA XLOC_006390-mediated pathway, in Toxicology research, **vol. 10**, 2021, pp. 123-133.
[29] *E. Perevedentseva, Y.C. Lin, and C.L. Cheng*, A review of recent advances in nanodiamond-mediated drug delivery in cancer, in Expert opinion on drug delivery, **vol. 18**, 2021, pp. 369-382.
[30] *P. Mckernan, N.A. Virani, G.N.F. Faria, C.G. Karch, R. Prada Silvy, D.E. Resasco, L.F. Thompson, and R.G. Harrison*, Targeted Single-Walled Carbon Nanotubes for Photothermal Therapy Combined with Immune Checkpoint Inhibition for the Treatment of Metastatic Breast Cancer, in Nanoscale Research Letters, **vol. 16**, 2021, pp. 9.
[31] *G. Cellot, A. Franceschi Biagioni, and l. Ballerini*, Nanomedicine and graphene-based materials: advanced technologies for potential treatments of diseases in the developing nervous system, in Pediatric Research, **vol. 92**, 2022, pp. 71-79.
[32] *G.C. Carvalho, R.M. Sábio, T. de Cássia Ribeiro, A.S. Monteiro, D.V. Pereira, S.J.L. Ribeiro, and M. Chorilli*, Highlights in Mesoporous Silica Nanoparticles as a Multifunctional Controlled Drug

Delivery Nanoplatform for Infectious Diseases Treatment, in Pharmaceutical Research, **vol. 37**, 2020, pp. 191.

[33] *F. Fendi, B. Abdullah, S. Suryani, I. Raya, D. Tahir, and I. Iswahyudi*, Hydroxyapatite based for bone tissue engineering: innovation and new insights in 3D printing technology, in Polymer Bulletin, 2023.

[34] *X. Shi, D. Chen, G. Liu, H. Zhang, X. Wang, Z. Wu, Y. Wu, F. Yu, and Q. Xu*, Application of Elastin-like Polypeptide, in Tumor Therapy, **vol. 14**, 2022, pp. 3683.

[35] *S. Kirar, N. thakur, J. laha, J. Bhaumik, and U. Banerjee*, Development of Gelatin Nanoparticle Based Biodegradable Phototheranostic Agents: Advanced System to Treat Infectious Diseases, in ACS Biomaterials Science & Engineering, **vol. 4**, 2018.

[36] *H.K. Ma, and J.F. Bebawy*, Albumin Use in Brain-injured and Neurosurgical Patients: Concepts, Indications, and Controversies, in Journal of neurosurgical anesthesiology, **vol. 33**, 2021, pp. 293-299.

[37] *R. Pawar, A. Pathan, S. Nagaraj, H. Kapare, P. Giram, and R. Wavhale*, Polycaprolactone and its derivatives for drug delivery, N/a.

[38] *T. Sukpaita, S. Chirachanchai, A. Pimkhaokham, and R.S. Ampornaramveth*, Chitosan-Based Scaffold for Mineralized Tissues Regeneration, in Marine drugs, **vol. 19**, 2021.

[39] *J. Li, S. Guan, J. Su, J. Liang, L. Cui, and K. Zhang*, The Development of Hyaluronic Acids Used for Skin Tissue Regeneration, in Current drug delivery, **vol. 18**, 2021, pp. 836-846.

[40] *S.R. Dalal, M.H. Hussein, N.E.-A. El-naggar, S.I. Mostafa, and S.A. Shaaban-Dessuuki*, Characterization of alginate extracted from Sargassum latifolium and its use in Chlorella vulgaris growth promotion and riboflavin drug delivery, in Scientific Reports, **vol. 11**, 2021, pp. 16741.

[41] *B. Skora, K.A. Szychowski, and J. Gminski*, A concise review of metallic nanoparticles encapsulation methods and their potential use in anticancer therapy and medicine, in European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, **vol. 154**, 2020, pp. 153-165.

[42] *A. Abdal Dayem, M.K. Hossain, S.B. Lee, K. Kim, S.K. Saha, G.M. Yang, H.Y. Choi, and S.G. Cho*, The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles, in Int J Mol Sci, **vol. 18**, 2017.

[43] *P. Vaid, P. Raizada, A.K. Saini, and R.V. Saini*, Biogenic silver, gold and copper nanoparticles - A sustainable green chemistry approach for cancer therapy, in Sustainable Chemistry and Pharmacy, **vol. 16**, 2020, pp. 100247.

[44] *E.R. Evans, P. Bugga, V. Asthana, and R. Drezek*, Metallic Nanoparticles for Cancer Immunotherapy, Materials today, **vol. 21**, 2018, pp. 673-685.

[45] *S. Salatin, S. Maleki Dizaj, and A. Yari Khosroushahi*, Effect of the surface modification, size, and shape on cellular uptake of nanoparticles, in Cell biology international, **vol. 39**, 2015, pp. 881-890.

[46] *L.T. Nguyen, and P.S. Ohashi*, Clinical blockade of PD1 and LAG3--potential mechanisms of action, in Nature reviews. Immunology, **vol. 15**, 2015, pp. 45-56.

[47] *L.Marinescu, D.Ficai, O.Oprea, A. Marin, A. Ficai, E. Andronescu, A.M.Holban,* Optimized Synthesis Approaches of Metal Nanoparticles with Antimicrobial Applications, Journal of Nanomaterials, 2020

[48] *C-H.Yang, W-T. Wang, A.M.Grumezescu, K-S Huang, Y-S.Lin,* One-step synthesis of platinum nanoparticles loaded in alginate bubbles, Nanoscale Research Letters, **Vol.9**, 2014, pp.277

[49] *Spoială, A.; Ilie, C.-I.; Motelica, L.; Ficai, D.; Semenescu, A.; Oprea, O.-C.; Ficai, A.* Smart Magnetic Drug Delivery Systems for the Treatment of Cancer. Nanomaterials , **vol.13**, 2023, *876.*

[50] *M. Boboc, F. Curti, A.M. Fleacă, M.L. Jianu, A-M Roşu, C. Curutiu, V. Lazar, M. C. Chifiriuc, A. M. Grumezescu,* Chapter 14 - Preparation and Antimicrobial Activity of Inorganic Nanoparticles: Promising Solutions to Fight Antibiotic Resistance, Nanostructures for Antimicrobial Therapy, 2017, pp. 325-340

[51] *S. Zanganeh, G. Hutter, R. Spitler, O. Lenkov, M. Mahmoudi, A. Shaw, J.S. Pajarinen, H. Nejadnik, S. Goodman, M. Moseley, L.M. Coussens, and H.E. Daldrup-Link,* Iron oxide nanoparticles inhibit

tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues, in Nature nanotechnology, **vol. 11**, 2016, pp. 986-994.

[52] *C. Soica, Pinzaru I., Trandafirescu, C., Andrica, F., Danciu, C., Mioc, M., and Dehelean, C.* , Silver-, gold-, and iron-based metallic nanoparticles, in Design of Nanostructures for Theranostics Applications, 2018.

[53] *S. Rajawat, and M.M. Malik*, Anticancer Activity of Green Silver Nanoparticles against He-La Cervical Cancer Cell Lines, in Materials Today: Proceedings, **vol. 18**, 2019, pp. 841-847.

[54] *R. Raghav, and S. Srivastava*, Core–shell gold–silver nanoparticles based impedimetric immunosensor for cancer antigen CA125, in Sensors and Actuators B: Chemical, **vol. 220**, 2015, pp. 557-564.

[55] *J. Blanco, D. Lafuente, M. Gomez, T. Garcia, J.L. Domingo, and D.J. Sanchez*, Polyvinyl pyrrolidone-coated silver nanoparticles in a human lung cancer cells: time- and dose-dependent influence over p53 and caspase-3 protein expression and epigenetic effects, in Archives of toxicology, **vol. 91**, 2017, pp. 651-666.

[56] *B. Zhu, Y. Li, Z. Lin, M. Zhao, T. Xu, C. Wang, N. Deng*, Silver Nanoparticles Induce HePG-2 Cells Apoptosis Through ROS-Mediated Signaling Pathways, in Nanoscale research letters, **vol. 11**, 2016, pp. 198.

[57] *P. Netchareonsirisuk, S. Puthong, S. Dubas, T. Palaga, and K. Komolpis*, Effect of capping agents on the cytotoxicity of silver nanoparticles in human normal and cancer skin cell lines, in Journal of Nanoparticle Research, **vol. 18**, 2016.

[58] *L.A.B. Ferreira, F. Garcia-Fossa, A. Radaic, N. Durán, W.J. Fávaro, and M.B. De Jesus*, Biogenic silver nanoparticles: In vitro and in vivo antitumor activity in bladder cancer, in European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, **vol. 151**, 2020, pp. 162-170.

[59] *T. Ishida*, Anticancer activities of silver ions in cancer and tumor cells and DNA damages by Ag+ - DNA base - pairs reactions, in MOJ Tumor Research, **vol. 1,** 2017.

[60] *F. Danışman-Kalındemirtaş, İ.A. Kariper, C. Hepokur, and S. Erdem-Kuruca*, Selective cytotoxicity of paclitaxel bonded silver nanoparticle on different cancer cells, in Journal of Drug Delivery Science and Technology, **vol. 61**, 2021, pp. 102265.

[61] *S.P. Singh, C. Bhargava, V. Dubey, A. Mishra, and Y. Singh*, Silver nanoparticles: Biomedical applications, toxicity, and safety issues.

[62] *T. Bruna, F. Maldonado-Bravo, P. Jara, and N. Caro*, Silver Nanoparticles and Their Antibacterial Applications, **vol. 22**, 2021, pp. 7202.

[63] *M. Yafout, A. Ousaid, Y. Khayati, and I.S. El Otmani*, Gold nanoparticles as a drug delivery system for standard chemotherapeutics: A new lead for targeted pharmacological cancer treatments, in Scientific African, **vol. 11**, 2021.

[64] *S.K. Golombek, J.N. May, B. Theek, L. Appold, N. Drude, F. Kiessling, and T. Lammers*, Tumor targeting via EPR: Strategies to enhance patient responses, in Advanced drug delivery reviews, **vol. 130**, 2018, pp. 17-38.

[65] *S.R. Satapathy, A. Nayak, S. Siddharth, S. Das, D. Nayak, and C.N. Kundu*, Metallic gold and bioactive quinacrine hybrid nanoparticles inhibit oral cancer stem cell and angiogenesis by deregulating inflammatory cytokines in p53 dependent manner, in Nanomedicine: nanotechnology, biology, and medicine, **vol. 14**, 2018, pp. 883-896.

[66] *F. Pan, W. Yang, W. Li, X.Y. Yang, S. Liu, X. Li, X. Zhao, H. Ding, L. Qin, and Y. Pan*, Conjugation of gold nanoparticles and recombinant human endostatin modulates vascular normalization via interruption of anterior gradient 2-mediated angiogenesis, in Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine, **vol. 39**, 2017.

[67] *S. Balakrishnan, F.A. Bhat, P. Raja Singh, S. Mukherjee, P. Elumalai, S. Das, C.R. Patra, and J. Arunakaran*, Gold nanoparticle-conjugated quercetin inhibits epithelial-mesenchymal transition, angiogenesis and invasiveness via EGFR/VEGFR-2-mediated pathway in breast cancer, in Cell proliferation, **vol. 49**, 2016, pp. 678-697.

[68] *Y. Liu, P. Maccarini, G.M. Palmer, W. Etienne, Y. Zhao, C.T. Lee, X. Ma, B.A. Inman, and T. Vo-Dinh*, Synergistic Immuno Photothermal Nanotherapy (SYMPHONY) for the Treatment of Unresectable and Metastatic Cancers, in Scientific reports, **vol. 7**, 2017, pp. 8606.

[69] *J. Liu, C. Detrembleur, M.C. De Pauw-Gillet, S. Mornet, C. Jerome, and E. Duguet*, Gold nanorods coated with mesoporous silica shell as drug delivery system for remote near infrared light-activated release and potential phototherapy, Small, **vol. 11**, 2015, pp. 2323-2332.

[70] *M. Ahmadzadeh-Raji, E. Ghafar-Zadeh, and G. Amoabediny,* An Optically-Transparent Aptamer-Based Detection System for Colon Cancer Applications Using Gold Nanoparticles Electrodeposited on Indium Tin Oxide, and Sensors, **vol. 16**, 2016, pp. 1071.

[71] *J. Beik, M. Khateri, Z. Khosravi, S.K. Kamrava, S. Kooranifar, H. Ghaznavi, and A. Shakeri-Zadeh*, Gold nanoparticles in combinatorial cancer therapy strategies, in Coordination Chemistry Reviews, **vol. 387**, 2019, pp. 299-324.

[72] *H. Ghaznavi, S. Hosseini-Nami, S.K. Kamrava, R. Irajirad, S. Maleki, A. Shakeri-Zadeh, and A. Montazerabadi*, Folic acid conjugated PEG coated gold-iron oxide core-shell nanocomplex as a potential agent for targeted photothermal therapy of cancer, in Artificial cells, nanomedicine, and biotechnology, **vol. 46**, 2018, pp. 1594-1604.

[73] *J.X. Eun Chul Cho, Patricia A. Wurm, and Younan Xia*, Understanding the Role of Surface Charges in Cellular Absorbtion versus Internalization by Selectively Removing Gold Nanoparticles on the Cell Surface with a I2/KI Etchant, 2009.

[74] *J.W. Bergs, M.G. Wacker, S. Hehlgans, A. Piiper, G. Multhoff, C. Rodel, and F. Rodel*, The role of recent nanotechnology in enhancing the efficacy of radiation therapy, in Biochimica et biophysica acta, **vol. 1856**, 2015, pp. 130-143.

[75] *S. Thambiraj, S. Hema, and D. Ravi Shankaran*, Functionalized gold nanoparticles for drug delivery applications, in Materials Today: Proceedings, **vol. 5**, 2018, pp. 16763-16773.

[76] *S. Taghizadeh, V. Alimardani, P.L. Roudbali, Y. Ghasemi, and E. Kaviani*, Gold nanoparticles application in liver cancer, Photodiagnosis and photodynamic therapy, **vol. 25**, 2019, pp. 389-400.

[77] *S. Thambiraj, S. Shruthi, R. Vijayalakshmi, and D. Ravi Shankaran*, Evaluation of cytotoxic activity of docetaxel loaded gold nanoparticles for lung cancer drug delivery, in Cancer treatment and research communications, **vol. 21**, 2019, pp. 100157.

[78] *W. Cheng, J. Nie, N. Gao, G. Liu, W. Tao, X. Xiao, L. Jiang, Z. Liu, X. Zeng, and L. Mei*, A Multifunctional Nanoplatform against Multidrug Resistant Cancer: Merging the Best of Targeted Chemo/Gene/Photothermal Therapy, in Advanced Functional Materials, **vol. 27**, 2017, pp. 1704135.

[79] *J. Depciuch, M. Stec, B. Klebowski, A. Maximenko, E. Drzymala, J. Baran, and M. Parlinska-Wojtan*, Size effect of platinum nanoparticles in simulated anticancer photothermal therapy, in Photodiagnosis and photodynamic therapy, **vol. 29**, 2020.

[80] *Y. Chen, C. Chen, X. Zhang, C. He, P. Zhao, M. Li, T. Fan, R. Yan, Y. Lu, R.J. Lee, M.W. Khan, M. Sarfraz, X. Ma, T. Yang, and G. Xiang*, Platinum complexes of curcumin delivered by dual-responsive polymeric nanoparticles improve chemotherapeutic efficacy based on the enhanced anti-metastasis activity and reduce side effects, in Acta pharmaceutica Sinica. B, **vol. 10**, 2020, pp. 1106-1121.

[81] *B. Fu, M. Dang, J. Tao, Y. Li, and Y. Tang*, Mesoporous platinum nanoparticle-based nanoplatforms for combined chemo-photothermal breast cancer therapy, in Journal of colloid and interface science, **vol. 570**, 2020, pp. 197-204.

[82] *C. Enrico*, Nanomedicine strategies for chemoresistance breast cancer theranostics, 2020, pp. 175-189.

[83] *S. Zhang, X. Wang, and Z. Guo*, Rational design of anticancer platinum(IV) prodrugs, **vol. 75**, 2020, pp. 149-182.

[84] *R.G. Kenny, S.W. Chuah, A. Crawford, and C.J. Marmion*, Platinum(IV) Prodrugs - A Step Closer to Ehrlich's Vision?, in European Journal of Inorganic Chemistry, 2017, pp. 1596-1612.

[85] *G. De vries, X. Rosas-Plaza, M.A.T.M. Van Vugt, J.A. Gietema, and S. De Jong*, Testicular cancer: Determinants of cisplatin sensitivity and novel therapeutic opportunities, in Cancer Treatment Reviews, **vol. 88**, 2020, pp. 102054.

[86] *M. Ashrafizadeh, A. Zarrabi, K. Hushmandi, F. Hashemi, E.R. Moghadam, M. Owrang, F. Hashemi, P. Makvandi, M.A.S.B. Goharrizi, M. Najafi, and H. Khan*, Lung cancer cells and their sensitivity/resistance to cisplatin chemotherapy: Role of microRNAs and upstream mediators, in Cellular Signalling, **vol. 78**, 2021, pp. 109871.

[87] *J. Schardt, B. Roth, and R. Seiler*, Forty years of cisplatin-based chemotherapy in muscle-invasive bladder cancer: are we understanding how, who and when?, in World journal of urology, **vol. 37**, 2019, pp. 1759-1765.

[88] *L.R. Boyd, and F.M. Muggia*, Carboplatin/Paclitaxel Induction in Ovarian Cancer: The Finer Points, in Oncology (Williston Park, N.Y.), **vol. 32**, 2018, pp. 418-420, 422-414.

[89] *J.-F. Lin, P.-S. Hu, Y.-Y. Wang, Y.-T. Tan, K. Yu, K. Liao, Q.-N. Wu, T. Li, Q. Meng, and J.-Z.J.S.T. Lin*, T. therapy, Phosphorylated NFS1 weakens oxaliplatin-based chemosensitivity of colorectal cancer by preventing PANoptosis, **vol. 7**, 2022, pp. 54.

[90] *C.-H. Li, M.-Y. Liu, W. Liu, D.-D. Li, and L.J.A.P.J.O.C.P. Cai*, Randomized control study of nedaplatin or cisplatin concomitant with other chemotherapy in the treatment of advanced non-small cell lung cancer, **vol. 15**, 2014, pp. 731-736.

[91] *Q. Wu, C. Zhu, S. Zhang, Y. Zhou, and Y.J.F.I.O. Zhong*, Hematological toxicities of concurrent chemoradiotherapies in head and neck cancers: comparison among cisplatin, nedaplatin, lobaplatin, and nimotuzumab, **vol. 11**, 2021, pp. 762366.

[92] *H. Ohnuma, Y. Sato, N. Hayasaka, T. Matsuno, C. Fujita, M. Sato, T. Osuga, M. Hirakawa, K. Miyanishi, and T.J.C.S. Sagawa*, Neoadjuvant chemotherapy with docetaxel, nedaplatin, and fluorouracil for resectable esophageal cancer: a phase II study, **vol. 109**, 2018, pp. 3554-3563.

[93] *C. Li, X.-E. Huang, and Y.J.A.P.J.C.P. Li*, Phase II trial of irinotecan plus nedaplatin (INP) in treating patients with extensive stage small cell lung cancer, **vol. 12**, 2011, pp. 487-490.

[94] *M.-H. Yan, F. Liu, B.-L. Qu, B.-N. Cai, W. Yu, and X.-K.J.W.J.O.G.O. Dai*, Induction chemotherapy with albumin-bound paclitaxel plus lobaplatin followed by concurrent radiochemotherapy for locally advanced esophageal cancer, **vol. 13**, 2021, pp. 1781.

[95] *H. Zhang, R. Chen, X. Wang, H. Zhang, X. Zhu, J.J.F.I.O. Chen*, Lobaplatin-induced apoptosis requires p53-mediated p38MAPK activation through ROS generation in non-small-cell lung cancer, **vol. 9**, 2019, pp. 538.

[96] *Q.-Q. Deng, X.-E. Huang, L.-H. Ye, Y.-Y. Lu, Y. Liang, and J.J.A.P.J.O.C.P. Xiang*, Phase II trial of Loubo®(Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes, **vol. 14,** 2013, pp. 413-417.

[97] *J.-H. Ahn, Y.-K. Kang, T.-W. Kim, H. Bahng, H.-M. Chang, W.-C. Kang, W. kim, J.-S. lee, and J.-S.J.C.C. Park*, , Nephrotoxicity of heptaplatin: a randomized comparison with cisplatin in advanced gastric cancer, in Pharmacology, **vol. 50**, 2002, pp. 104-110.

[98] *M. Ikeda, M. Kudo, H. Aikata, H. Nagamatsu, H. Ishii, O. Yokosuka, T. Torimura, M. Morimoto, K. Ikeda, and H.J.J.O.G. Kumada*, Transarterial chemoembolization with miriplatin vs. epirubicin for unresectable hepatocellular carcinoma: a phase III randomized trial, **vol. 53,** 2018, pp. 281-290.

[99] *Z. Zhou, T. Fan, Y. Yan, S. Zhang, Y. Zhou, H. Deng, X. Cai, J. Xiao, D. Song, Q. Zhang, and Y. Cheng*, One stone with two birds: Phytic acid-capped platinum nanoparticles for targeted combination therapy of bone tumors, in Biomaterials, **vol. 194**, 2019, pp. 130-138.

[100] *M. Jeyaraj, S. Gurunathan, M. Qasim, M.-H. kang, and J.-H. Kim*, A Comprehensive Review on the Synthesis, Characterization, and Biomedical Application of Platinum Nanoparticles, **vol. 9**, 2019, pp. 1719.

[101] *M. Zhou, M. Tian, and C. Li*, Copper-Based Nanomaterials for Cancer Imaging and Therapy, in Bioconjugate chemistry, vol. 27, 2016, pp. 1188-1199.

[102] *A. Waris, M. Din, A. Ali, M. Ali, S. Afridi, A. Baset, and A. Ullah Khan*, A comprehensive review of green synthesis of copper oxide nanoparticles and their diverse biomedical applications, Inorganic in Chemistry Communications, **vol. 123**, 2021, pp. 108369.

[103] *S.S. Foad Buazar, Mohammad Badri, and Feisal Kroushawi*, Biofabrication of highly pure copper oxide nanoparticles using wheat seed extract and their catalytic activity: a mechanistic approach, in Green Process Synth, **vol. 8,** 2019, pp. 691-702.

[104] *J. Sackey, A.C. Nwanya, A.K.H. Bashir, N. Matinise, J.B. Ngilirabanga, A.E. Ameh, E. Coetsee, and M. Maaza*, Electrochemical properties of Euphorbia pulcherrima mediated copper oxide nanoparticles, in Materials Chemistry and Physics, **vol. 244**, 2020, pp. 122714.

[105*] I. Khan, K. Saeed, and I. Khan*, Nanoparticles: Properties, applications and toxicities, in Arabian Journal of Chemistry, **vol. 12**, 2019, pp. 908-931.

[106] *P.C. Nagajyothi, P. Muthuraman, T.V.M. Sreekanth, D.H. Kim, and J. Shim*, Green synthesis: In-vitro anticancer activity of copper oxide nanoparticles against human cervical carcinoma cells, in Arabian Journal of Chemistry, **vol. 10**, 2017, pp. 215-225.

[107] *K. Poudel, M. Gautam, S.G. Jin, H.G. Choi, C.S. Yong, and J.O. Kim*, Copper sulfide: An emerging adaptable nanoplatform in cancer theranostics, in International journal of pharmaceutics, **vol. 562**, 2019, pp. 135-150.

[108] *L. Han, Y. Zhang, X.W. Chen, Y. Shu, and J.H. Wang*, Protein-modified hollow copper sulfide nanoparticles carrying indocyanine green for photothermal and photodynamic therapy, in Journal of materials chemistry. B, **vol. 4**, 2016, pp. 105-112.

[109] *H.M. Fahmy, N.M. Ebrahim, M.H. Gaber*, In-vitro evaluation of copper/copper oxide nanoparticles cytotoxicity and genotoxicity in normal and cancer lung cell lines, in Journal of Trace Elements in Medicine and Biology, **vol. 60**, 2020.