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GOLD NANOPARTICLES AND CHEMOTHERAPEUTIC AGENTS

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Abstract. *Gold nanoparticles (AuNPs) receive a great deal of attention for biomedical applications due to their unique properties to monitor intracellular delivery of therapeutic agents. Evidently, drug delivery is a compelling field of research due to the need of releasing medicine at specific locations in a controlled manner with a minimum amount of side effects. The present review focuses on the combination of AuNPs with different types of chemotherapeutic agents as potential drug delivery vehicles that can be used in cancer therapy.*

Keywords: gold nanoparticles, chemotherapeutic agents, cancer, drug delivery

1. Introduction

According to the World Health Organization (WHO), cancer is the second major cause of death at a global level, leading to a staggering 9.6 million deaths as of 2018 [1]. The war on cancer has led to intensive research in order to develop alternative methods that would increase the efficacy of antitumor medication while decreasing the potential side effects. Nanotechnology has proven to be a promising alternative to conventional therapies. As nanoparticles are much smaller in size than cells, they can readily and easily penetrate into the cell and interact with DNA, enzymes, proteins and different receptors [2]. Different nanoparticles, NPs, are being widely studied due to their large surface area, enhanced ability to interact with cancerous cells, and capability to be functionalized with specific medication [3].

Gold nanoparticles (AuNPs) are probably the most researched ones in regards to cancer therapy. The leaky tumour vasculature would allow AuNPs to

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easily accumulate, process that is known as the enhanced permeability and retention effect (EPR) [4]. They can be easily synthesized within a wide range of sized, from 1 to 100 nm, and a multitude of shapes (spheres [5-8], rods [9, 10], triangles [11-13], star-shaped [14-16]), are biocompatible and have the ability to be functionalized with several types of molecules [17-26].

Considering the unique properties of AuNPs and their potential applications there are already a great number of review papers tackling an in-depth study of synthesis methods and recent advances in cancer therapies and drug delivery [27-31]. However, a review regarding AuNPs and different types of chemotherapeutic agents has not yet been done, taking into account various models of nanoscale interactions. With this in mind, the present review focuses on gold nanoparticles loaded with different types of chemotherapy medicines, divided by class, with a brief attention on the types of methods that can be employed in the synthesis of such nanoparticles.

2. Synthesis of gold nanoparticles

While gold nanoparticles can technically be prepared by both 'top-down' and 'bottom-up' types of synthesis, this paper will focus on the latter, as this category permits a better control of properties and surface characteristics, such as size, size distribution, shape, zeta potential and nanoparticles charge analysis. Usually, the bottom-up methods refer to a chemical reduction of gold ions from a specific salt solution using a reducing agent followed by the stabilization of the gold nanoparticles with a capping agent.

2.1. Chemical synthesis routes

Chemical synthesis routes are probably the most popular methods for the synthesis of gold nanoparticles as they allow for a better control of properties in the final product [5, 6, 8, 17, 20, 22-24, 26, 32-46]. As a rule, this types of methods involve 2 steps, namely, a reduction through agents (citric acid, borohydrides, sugars, oxalic acids, hydrogen peroxide) followed by a stabilization process (with different agents such as trisodium citrate dihydrate, cetyltrimethylammonium bromide, nitrogen or oxygen based ligands). A summary of some studies employing chemical routes for synthesizing AuNPs is presented in Table 1 followed by some brief detail on two of the most recognizable chemical synthesis routes.

The classic Turkevich method is perhaps the most employed one in synthesizing gold nanoparticles. Originally reported by Turkevich [32], with later modifications by Frens [33] this method is based on the aqueous reduction of hydrogen tetrachloroaurate (III, $HAuCl_4$) by means of trisodium citrate. The citrate addition to a boiling aqueous solution of hydrogen tetrachloroaureate kept

under a vigorous stirring leads to a formation of a ruby-red colloidal suspension of gold. Here, citrate acts as both a reducing agent for Au(III) to Au(0) and a stabilizing one, preventing any possible aggregation. Of course, by variating the ratio of $HAuCl_4$ to citrate, temperature, and pH, gold nanoparticle falling within a wide range of size and degree of stability can be obtained. This synthesis method is widely used, either in its standard form [34-37] or with some variations [38].

Table 1. Chemical methods for the synthesis of AuNPs

Gold salt precursor	***Agents***	***AuNPs characteristics***	***Reference***
$AuCl_3$	Trisodium citrate, tannic acid, potassium carbonate	Spherical and ellipsoidal shapes average diameter, d: ~5 -7 nm	5, 8
$HAuCl_4$	Resveratrol	Spherical shape, d: ~20 nm	6
$Na_3Au(SO_3)_2$	Trisodium citrate	Spherical, elliptical, triangular, pentagonal or hexagonal, d: ~ 48 nm	22, 23
$HAuCl_4$	Trisodium citrate	Spherical or elliptical shape, d: ~14 nm	5, 20, 22, 24, 26
	Sodium citrate, ascorbic acid + UV rays	Various shapes, various sizes, d: ~ 40 nm	34
	Trisodium citrate	Mostly spherical, various sizes, d: < 32 nm	41
		Spherical, d: 5-10 nm	42
		Spherical, d: ~8-12 nm	43
$HAuCl_4$	Hydroquinone citrate	Spherical, d: 50-200 nm	44
	$NaBH_4$, citrate	Spherical, d: ~13 nm	45
	$NaBH_4$, TOAB ($N(C_8H_{17})_4Br$), dodecanethiol, toluene	Spherical, d: 2-4 nm	46

To put it briefly, the Brust-Schriffrin [39, 40] method employs a chemical reduction of gold ions ($HAuCl_4$ precursor) by means of borohydride in a water-toluene system, followed by an alkanethiol adsorption. Gold nanoparticles synthesized through this method are reported to be highly stable, of spherical shape and soluble in organic solvents.

2.2. Biological synthesis routes

While the chemical methods discussed previously are the preferred synthesis routes for gold nanoparticles, the use of potentially toxic substances severely restricts the range of applications. This is especially the case for biomedical applications. Thus, the needs to find more suitable alternatives to prepare gold nanoparticles have led to the development of biological routes that employ plants, biomolecules or microorganisms.

2.2.1. With the aid of plants

The synthesis of gold nanoparticles using various plant extracts is extensively researched and documented in scientific literature due to their reducing biomolecules and highly-stabilizing abilities [47-49]. These types of syntheses are particularly researched as they offer a low-cost, non-toxic and eco-friendly approach to classic chemical routes and involve mixing gold salts with plant extracts under various conditions (time, concentration, pH, temperature, stirring speed and time). Table 2 presents a selection of some of the more recent published works involving the synthesis of AuNPs by means of plant extracts [49-61].

Table 2. Plants used in synthesizing AuNPs

Plant	***AuNPs characteristics***	***Reference***
Angelica	Spherical or ellipsoidal d: 3 to 4 nm	49
Hypericum	Large aggregates, comprised of a large number of fractal-like shaped particles d: 7 nm	
Hamamelis	Various shapes (triangular, cubic, pentagonal, hexagonal, heart shaped), along with nearly spherical ones; fractions, 46 nm aggregates d: 4-8 nm; d: 8-12 nm.	
Rosa Rugosa (leaf)	Spherical, d: 11 nm	50
Ziziphus zizyphus (leaf)	Spherical, d: <30 nm	51
Corchorus olitorius (leaf)	Quasi-spherical, d: 35-50 nm	52
Mimosa tenuiflora (bark)	Diverse, d: 40-150 nm	53
Coffea arabica	Spherical, d: 15 nm	54
Chenopodium formosanum (shell)	Spherical, d: 8 nm	55
Ocimum sanctum (leaf)	Spherical, d: 12-20 nm	56
Sargentodoxa cuneata (plant)	Hexagonal, d: 15-30 nm	57
Periploca Aphylla (stem)	Spherical, d: 25-30 nm	58
Cistus incanus (leaves)	Popcorn, d: 45-85 nm Nanostars, d: 60 nm	59
Cymbopogon flexuosus (leaf)	Triangular, d: 12-30 nm	60
Stevia rebaudiana (leaf)	Octahedral, d: 8-20 nm	61

As it can be seen from Table 2, gold nanoparticles obtained through this type of method can be of different sizes and shapes. The plant extract is commonly obtained through a simple process of washing the different plant parts in use, boiling them and filtering the final broth. The extract is then used in combination with a gold salt at different working conditions to obtain the desired size and shape of nanoparticles. The phytochemicals (such as glutathione, tannins, polyphenols, ascorbates, terpenoids) present in the used extract act as the reducing agent here [62-65]. Following a change in colour of the solution, AuNPs were filtered out and washed either in purified water or ethanol.

2.2.2. With the aid of microorganisms

Various microorganisms, such as fungi, yeasts, algae and bacteria have recently been employed as mini laboratories for the fabrication of gold nanoparticles through enzymatic and non-enzymatic processes both intra and extracellular. The processes involved in this synthesis can be both enzymatic and non-enzymatic. When microorganism cells are treated with gold salts they tend to produce gold nanostructures. The colour of the microorganism supernatant can vary within a wide range, depending on the shape of AuNPs and the refractive index of the solution [66]. These latter nanostructures are then isolated and subjected to different techniques of purification to finally obtain AuNPs. Table 3 present a summary of some microorganisms employed for the synthesis of gold nanoparticles [67-79].

Table 3. Microorganisms used in synthesizing AuNPs

Microorganism	***Type***	***AuNPs characteristics***	***References***
Deinococcus radiodurans	Bacterium	Pseudo spherical, spherical, irregular shape, d: 43 nm	67
Bacillus cereus	Bacterium	Octagonal, spherical, hexagonal, d: 20-50 nm	66
Fusarium oxysporum	Fungi		
Marinobacter pelagius	Bacterium	Varied shapes, d: 2-6 nm	68
Brevibacillus formosus	Bacterium	Spherical, d: 5-12 nm	69
Pseudomonas fluorescens	Bacterium	Mostly spherical, d: 5-50 nm	70
Penicillium rugulosum	Fungi	Spherical, hexagonal, triangular, d: 20-80 nm	71
Aspergillus terreus IF0	Fungi	Elongated, triangular, rod shaped, d: 10-29 nm	72
Mariannaea sp. HJ	Fungi	Sphere, hexagon, irregular shape, d: 37 nm	73
Extremophilic yeasts	Yeast	Irregular shape, d: 30-100 nm	74
Phaffia rhodozyma	Yeast	Spherical, d: 4-7 nm	75
Magnusiomyces ingens LF-F1	Yeast	Spherical, hexagonal, triangular, pentagonal, irregular shape, d: 50 nm	76
Saccharomyces cerevisiae	Yeast	Spherical, d: 13 nm	77
Sargassum spp.	Algae	Hexagonal, truncated triangular, d: 50 nm	78
Turbinaria conoides	Algae	Spherical, pseudo-spherical, undefined shape, d: 6-10 nm	79

As can be observed in Table 3, microorganisms lead to the formation of gold nanoparticles in a wide range of sizes, depending on their type. Shapes are also varied, with many studies reporting a non-homogenous final product. This can of course be controlled by choosing the right type of microorganism and manipulating reaction parameters such as pH and temperature.

For bacteria, it is revealed that enzymes (such as cytochrome oxidase, NADPH-dependant reductase, sulphite reductase, hydrogenase) and defence pathways play a role in gold nanoparticle production while the exact mechanism is not as of yet known [80, 81]. In fact, enzymes, proteins and biomolecules play a similar role in the formation of gold nanoparticles for all microorganisms. In the case of algae, however, the synthesis of gold nanoparticles occurs at the extracellular level as algae cells are reported to be sensitive to metallic stresses and tend to die [29].

3. Gold nanoparticles and chemotherapy medicine

Cancer cells have the ability to proliferate at a faster than regular cells. Chemotherapy aims to kill cancer cells and stop proliferation by means of medicine that can target cancer cells at different stages of the cell cycle. At present, more than 100 different chemotherapy medicines are used to treat a variety of cancers, both by themselves or in combination. However, the balance between dealing with the disease by destroying the cancer cells and saving healthy ones has yet to be reached.

While still in progress, research for alternative delivery methods include the use of different nanoparticles as carriers of which gold nanoparticles are extensively studied due to nontoxic and bio inert. Fusing the potential of AuNPs with traditional drugs used in chemotherapy allows for a more personalized and targeted treatment of patients. In the following, this paper will address the different classes of chemotherapy medicine with a focus on the research regarding AuNPs.

Fig. 1 presents a schematic literature synthesis of the chemotherapy drugs researched on in relation to gold nanoparticles.

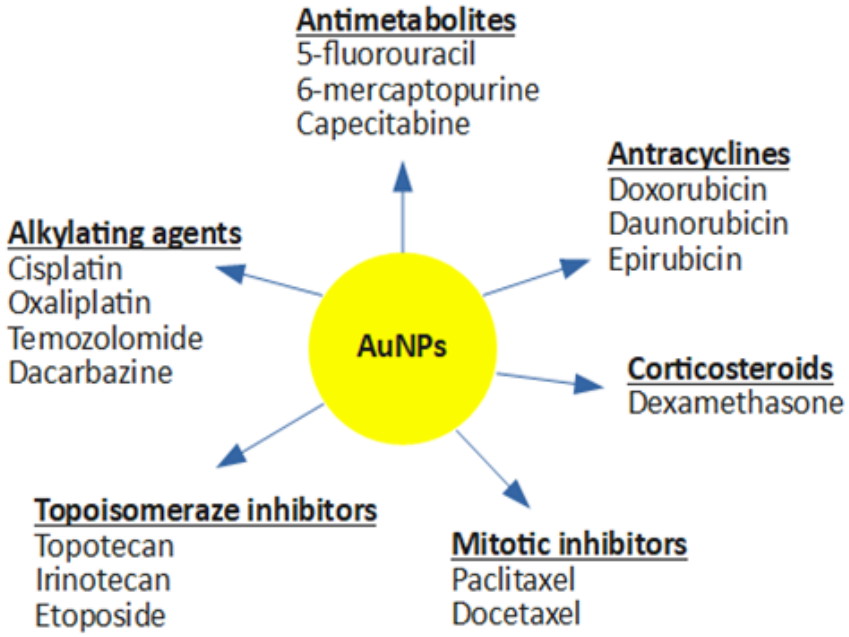

Fig. 1. Types of chemotherapeutic agent using AuNPs as carriers.

3.1. Alkylating agents

Drugs falling in the category of alkylating agents hinder cancer cells from reproducing through damaging DNA [82-84]. These types of medicine perform well in all phases of the cell cycle, being used to treat a variety of cancers (sarcoma, lymphoma, leukemia, myeloma, Hodgkin disease). Typical alkylating agents include, but are not limited to busulfan, lomustine, dacarbazine, and platinum compounds such as cisplatin, carboplatin, oxiplatin. Though research regarding the conjugation of cisplatin on gold nanoparticles is still in the beginning, there are some studies in literature that show promising results on the matter. Most of these studies involve platinum compounds (oxaliplatin, cisplatin, carboplatin) as the drug of choice.

Platinum compounds are reported to present a much lower risk of leading to leukemia (primarily Acute Myeloid Leukemia) as opposed to older alkylating agents that have a tendency to harm bone marrow [85-87]. As explained by Goodsell [88], these compounds have a platinum ion that is double charged and is surrounded by four ligands with the amine ones forming powerful bods with the platinum ion and the chloride or carboxylate compounds leaving moieties that permit the Pt ion to bond with DNA bases.

3.1.1. Cisplatin

Cisplatin is the most common compound used in studies correlation with AuNPs. Zhou et al. presented a cisplatin-conjugated gold nanocluster that showed an inhibition of tumour growth in a 4T1 murine breast tumour cell line [89]. Here, a folic acid alteration rapidly increased cell uptake and cytotoxicity, the conjugated nanoparticles being able to accumulate in the tumour in a selective manner. Another study [90] reported that gold nanoparticles have the ability to prevent cisplatin-induced chemo resistance, lead to tumour regression, while also increasing the sensitivity of ovarian tumours to a low dose of cisplatin in vivo. Gotov et al. [91] showed that a hyaluronic acid-coated, cisplatin-conjugated set of gold nanoparticle can suppress tumour growth in a mouse model injected with MCF-7 cells.

Coluccia et al. [92] studied the effect of AuNPs complexed with cell uptake peptides and cisplatin on GMB cell lines, leading to minimal to no tumour growth. Another group [93] presented the results of 11-mercaptoundecanoic acid (MUA) capped gold nanoparticles conjugated with cisplatin on a human lung carcinoma A549 cell line implanted in a mouse model. They found that gold nanoparticles lead to changes in the biodistribution of cisplatin, leading to them avoiding the organs where cisplatin typically accumulates and tends to be toxic.

Caballero et al. researched the assisted delivery of platinum drugs including cisplatin and the more bioavailable Pt(IV) pro-drugs by means of DNA-coiling AuNPs [94]. The experiment was performed on human ovarian carcinoma A2780 and human lung carcinoma A549 cell lines showing that the nanocarier with the Pt(IV) prodrug tends to enhance the activity of the drug alone. They also presented a dual possibility of drug delivery and imaging as the carriers can also support a fluorescent tag.

3.1.2. Oxaliplatin

Studies on oxaliplatin have also been reported in literature, while they are not as abundant. Tummala et al. [95] studied the effects of oxaliplatin gold nanoparticles conjugated with an antiDR5 antibody on colorectal carcinoma HTC-116 cell line. The results showed an inhibition in tumour growth. Brown et al. [96] reported on AuNPs functionalized with a monolayer of thiolated poly(ethylene glycol) (PEG) capped with a carboxylate group and tethered with oxaliplatin. The functionalized AuNPs presented a significantly better cytotoxicity in all cell lines (A549 lung epithelial cancer cell line and the colon cancer cell lines HCT116, HCT15, HT29, and RKO) when compared to that of oxaliplatin alone.

3.1.3. Temozolomide

Another chemotherapy drug that has been researched in relation with gold nanoparticle conjugation is *temozolomide*, with one group [97] reporting that gold nanostructures loaded with temozolomide are capable of reducing chemo-resistance. These structures are reported to have a greater effect on destroying cancer stem cells (82.7%) than the drug alone (42%). Another group of researchers [98] showed that temozolomide loaded onto AuNPs and liposome embedded AuNPs have promise in a BALB/c mouse model with urethane-induced lung cancer, showing a strong synergistic antitumor activity with the liposomes improving the distribution and penetration of temozolomide.

3.1.4. Dacarbazine

Dacarbazine has also started to gain attention in relation to gold nanoparticle-based drug delivery, with Zhang et al. [99] reporting that the presence of AuNPs could facilitate the binding of the drug to specific DNA bases, thus enhancing detection sensitivity of mismatches in the DNA helix. Shen et al. [100] also studied the effect of functionalized AuNPs on the binding of dacarbazine to DNA and DNA bases. These studies enhance the possibility of tumour-related biosensors which could provide a more rapid rate of detection.

3.2. Antimetabolites

This group of drugs take action by interfering with both RNA and DNA growth by substituting for their normal building blocks, damaging cancer cells when the chromosomes are being copied [101]. Antimetabolites are employed in the treatment of ovarian and breast cancers, among other types. Antimetabolite as chemotherapy drugs includes 5-fluorouracil, cytarabine, hydroxyurea, floxuridine and 6-mercaptopurine. There are quite a few studies that report on functionalized gold nanoparticles as carriers of some drugs in the antimetabolite family.

3.2.1. Fluorouracil

Fluorouracil (5-FU) is one of these drugs that have been extensively researched in order to improve upon its activity and limit its severe side effects. Safwat and his group [102] reported on how AuNPs can enhance the efficacy of fluorouracil in colorectal cancer with the drug release being pH-dependent and slow. The complex carrier induced apoptosis and managed to stop the progression of the cell cycle in colon cancer cells obtained from actual patients. The same group showed the effect of fluorouracil-loaded AuNPs for the treatment of skin cancer using a mouse skin cancer xenograft model (A431) [103] with the tumour line being lower after 8 days from application. Akinyelu and Singh [104] have presented some work on a folate-tagged chitosan-functionalized AuNPs on several assays, namely, human breast adenocarcinoma (MCF-7), hepatocellular

carcinoma (HepG2) and kidney cells (HEK293). The functionalized nanocarriers presented an enhanced cytotoxicity when compared to free 5-FU.

Chinnaiyan et al. [105] presented the results of 5-FU-loaded guar gum-capped gold nanoparticles (synthesized with Borassus flabellifer) for the in vitro treatment of some MiaPaCa-2 human pancreatic cancer cells. The results revealed an increase in apoptosis, with cancer cells having morphological changes after 24 hours. Another study worth mentioning is that of Nivethaa et al. [106] that deals with an in vitro cytotoxicity experiment of a chitosan/gold nanocomposite encapsulated with 5-fluorouracil on a MCF-7 cell line with a VERO control. The devised carriers exhibited a high cytotoxic effect on the MCF-7 cells (50% cell viability at a 31.2 $\mu g\ ml^{-1}$ sample concentration) without affecting the VERO ones. Mohamed et al. [107] also reports on the enhancement of 5-FU drug action on human colon cancer HTC-16 cell line, by loading it onto gold nanoparticles.

The more recent study of Ferreira Vilar et al. [108] is dealing with the effects of AuNPs on oral mucositis induced by fluorouracil in a hamster model. The gold nanoparticles prevented oral mucositis and improved upon inflammation parameters and oxidative stress. This is of particular importance as mucositis is a well-known side effect of chemotherapy against epithelial cells and confirms that the addition of AuNPs as a nanocarrier for 5-FU will prevent or at least limit potential negative side effects.

3.2.2. 6-Mercaptopurine

6-Mercaptopurine is another antimetabolite that has received attention in regards to gold nanoparticle drug delivery studies. One earlier study [109] paved the way by tackling the stabilization of AuNPs by monolayers of 6-mercaptopurine. On the other hand, Podsialdo et al. [110] discovered that AuNPs can enhance the anti-leukaemia (K569 cell line) action of 6-mercaptopurine making possible a reduction in drug concentration thus being clinically beneficial.

The toxicity and in vitro cytotoxicity of one such carrier (AuNPs-6-mercaptopurine) was studied by Ganeshkumar et al. [111] on a zebrafish embryo model and Hep-2 cell line. Here, both free 6-mercaptopurine and that loaded on AuNPs showed no embryo death. The carrier was observed to lead to a significant cytotoxic effect on Hep-2 cells after a period of incubation of 24 hours.

3.2.3. Capecitabine

The studies on capecitabine and gold nanoparticles as its carriers are still in the easily stages. However, one particular paper [112] tested the in vitro anti-tumour efficiency (HepG2 cells) of AuNPs conjugated with several drug including capecitabine. Here, the loaded gold nanoparticles lead to lower cell proliferation rates compared to capecitabine alone.

3.3. Anthracyclines or anti-tumour antibiotics

Acting like antibiotics for tumours, anthracyclines hinder enzymes employed in copying DNA during a cell cycle therefore are used for a variety of cancer types. Anthracyclines include doxorubicin, daunorubicin, idarubicin and epirubicin. However, while effective, these types of drugs have the ability to permanently damage heart tissue if they are given in high doses. With this in mind, researchers have tried to find ways to minimize this negative side effect. One possible solution presents itself in the form of loading these drugs onto functionalized gold nanoparticles.

3.3.1. Doxorubicin

Doxorubicin is perhaps the most well-known drug in this family and there are thousands of papers in literature with results in relation to AuNPs as well as with other types of nanoparticles as delivery platforms. In the following, this paper will present a selection of the multitude of papers published on this interesting topic with a focus on stability, toxicity and how the devised doxorubicin-gold nanoparticles carriers interact in vitro or in vivo.

One particular study by Tomoaia et al. [6] reported results concerning the activity of doxorubicin mediated by gold nanoparticles and resveratrol in human cervical cancer HeLa and CaSki cell lines with excellent results in apoptosis.

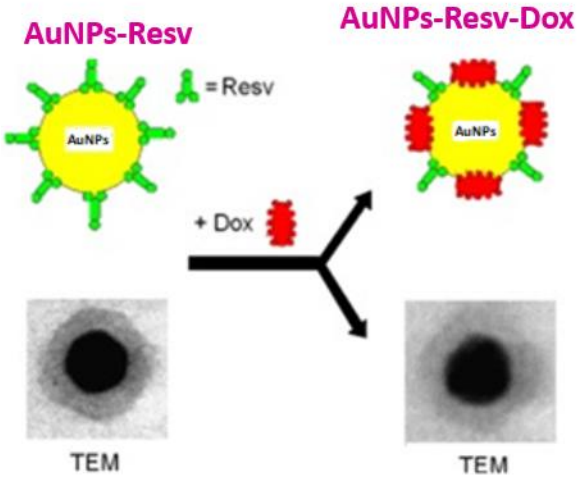

Fig. 2. Gold nanoparticles (AuNPs) functionalized with resveratrol (Resv) and doxorubicin (Dox) and the corresponding TEM images.

As can be seen in the TEM images, given in Fig. 2, resveratrol (Resv) or its oxidation products resulted from synthesis form a coating around AuNPs [17]. After functionalization with doxorubicin (Dox) the TEM image still presents a

single coating, showing that Dox molecules are entrapped in the initial Resv coating. Fig. 3 presents the cell responses for both resveratrol and doxorubicin alone and their mixtures, AuNPs alone, and AuNPs-Dox. Resveratrol alone only shows a mild response in CaSki cells (1), a response that intensifies when it is mixed with doxorubicin (2, 3). AuNPs-Resv (5) gives a response similar to the control while AuNPs-Resv-Dox (5, 6) has a more pronounced effect in the CaSki line. Of course, doxorubicin alone, at three all concentrations show the best cell response. However, these concentrations are quite high and therefore toxic.

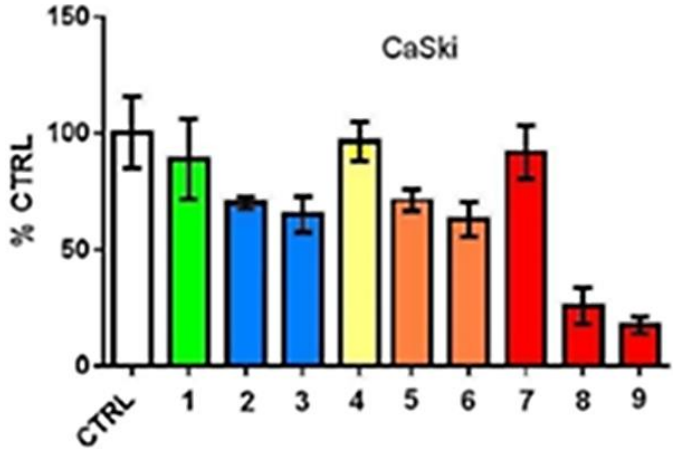

Fig. 3. CaSki cell response to Resv of 0.75 μg/mL (sample 1), Resv-Dox mixtures: 0.5 μg Resv /mL and Dox 0.1 μg /mL (2), and 1 μg Resv /mL and Dox 0.2 μg /mL (3), GNPs of 2.7 μg /mL (4), Dox-GNPs nanocomplexes, namely Dox 0.1 μg /mL and GNPs 1.3 μg /mL (5), and Dox 0.2 μg /mL and GNPs 2.7 μg /mL (6), and three Dox concentrations: 2.10 μg /mL (7), 6.25 μg /mL (8) and 12.5 μg /mL (9), after 24 h incubation. CTRL represents the control given by untreated cells. Cells viability was determined using MTT assay and it is given in % of CTRL. The bar values are the mean from at least three different experiments. Error bars represent the standard deviation (± SD).

To better convey this data, Fig. 4 presents the phase contrast microscopy on CaSki cells. It can be observed that while the cells present a resistance to a 2.1 μg/mL doxorubicin concentration they do show an excellent response to gold nanoparticles functionalized with a 21 times lower doxorubicin concentration, proving that the AuNPs synthesized in this study can be a good vehicle for the transport of chemotherapeutic agents. On the other hand, Du et al [113] synthesized 5 different doxorubicin analogues, two of which along with doxorubicin were conjugated to gold nanoparticles. The Dox-AuNPs showed a high stability in mouse models with no histopathological differences, the same as with the mouse models treated with saline solutions. On the other hand, simple doxorubicin leads to histopathological lesions.

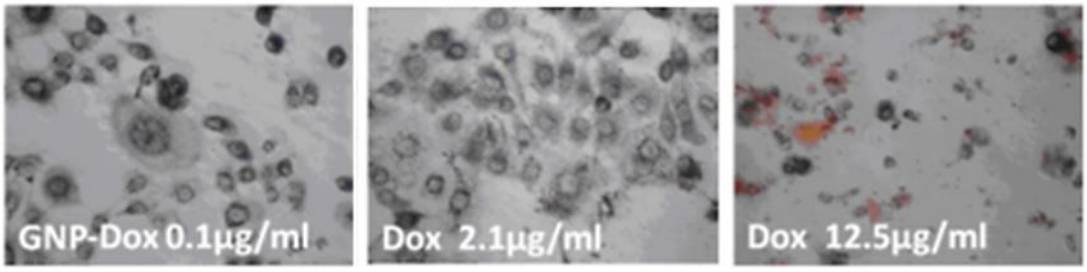

Fig. 4. Phase contrast optical microscopy images of CaSki cells treated with Dox alone, at two different concentrations, and Dox-GNPs nanocomplex (Dox 0.1 µg /mL and GNPs 1.3 µg /mL). The same concentrations and symbols were used as in Fig. 3. Magnification× 400.

One other study [114] deals with chemically induces fibrosarcoma in mouse models. The developed doxorubicin-AuNPs carriers were proven to be non toxic and cell compatible while also exhibiting a higher therapeutic efficacy (81%) compared to that of free doxorubicin (48%) at the same concentrations. Further, Ramalingam et al. [115] stabilized gold nanoparticles with polyvinylpyrrolidone and conjugated them with doxorubicin (Dox@PVP-AuNPs) and used them in regards to lung cancer. The results showed an in vitro cytotoxic effect that inhibited the growth of lung cancer cells and induced intrinsic apoptosis.

Wu and his team [116] tried to understand the effects on the size of the gold core (10, 20, 60 nm) on the performance of gold nanoparticles conjugated with doxorubicin, both in vitro and in vivo. Here, the 10 nm-core conjugate displayed the highest efficacy in liver cancer models, regardless of the fact that it loaded fewer drugs. Conversely, Curry et al. [117] present both factual and theoretical evidence concerning the adsorption of doxorubicin on gold nanoparticles, where hydrophobic forces steer doxorubicin towards the nanoparticle surface followed by a surface adsorption by means of gold-carbonyl coordination and cation π-interactions. This study revealed that glutathione and serum albumin helped the enhancement of desorption of drug molecules from gold nanoparticles at physiological concentrations.

3.3.2. Daunorubicin

Another anthracycline, namely, daunorubicin has also been studied with Danesh et al. [118] reporting on its delivery by an aptamer-modified gold nanoparticle to T-cell acute lymphoblastic leukemia. The Apt-Dau-AuNPs complex showed promising results on U266 (B lymphocyte human myeloma, non-target) and Molt-4 (target) cell lines – the complex being able to selectively target Molt-4 cells while being less toxic for U266 ones. Another similar study by the same group [119] worked on polyvalent aptamers-modified AuNPs loaded

with daunorubicin (PT-Dau-AuNPs) showing that this drug delivery system could decrease cytotoxic effects of daunorubicin.

3.3.3. Epirubicin

Some other studies deal with the improvement of targeting and decrease in toxicity of another major anthracycline, namely epirubicin**.** In this case, Chen et al. [120] discuss the epirubicin-loaded marine carrageenan ligosaccharide capped AuNPs. This type of carrier significantly releases epirubicin in a simulated acidic cancer environment while the release in a normal environment is negligible. Also, it induced a higher apoptosis in HCT-116 and HepG2 cell lines when compared with the free drug. Another study by Meng et al. [121] confirms the suppression of a hepatocellular carcinoma xenograft in a mouse model by means of epirubicin-AuNPs.

A tumour specific delivery and release experiment by Kunjiappan et al. [122] involved liposome encapsulated epirubicin-AuNPs and showed a stop in proliferation of MCF-7 breast cancer cell line with the apoptosis being dependant on time and dose. Another paper worth mentioning is that by Devi et al. [123] that present the effects of some gum arabic capped gold nanoparticles (Fa-E-GNPs) on a A549 cell line of human lung adenocarcinoma. Here, the Fa-E-GNPs had an improved cytotoxic effect on the cell lines when compared to the free epirubicin. Senthil Kumar et al. reported on a plant-synthesized (Limonia acidissima) gold nanoparticle attached with epirubicin and its effects on a MCF-7 cell line [124]. The number of cancer cells that were nonviable increased dramatically after treatment with the epirubicin-AuNPs.

3.4. Topoisomerase inhibitors

Used predominantly to treat different types of leukemia, topoisomerase inhibitors hinder topoisomerase enzymes, thus interfering with the copying of DNA [125]. This group includes irinotecan and topotecan (which are topoisomerase I inhibitors) and teniposide and etoposide (which are topoisomerase II inhibitors).

3.4.1. Topotecan

While of high interest and the focus of many studies regarding cancer, topotecan (TOPO), a camptothecin compound, has been investigated very little in regards to its interactions with gold nanoparticles. One study found by the authors [126] presented a glutathione-triggered delivery of topotecan from AuNPs in vitro and in vivo by subcutaneous administration using a mouse model. The results suggest that the AuNPs-TOPO delivery system can be utilized as a controlled drug release system with low toxicity. Li et al. [127] examined the loading and delivery of various chemotherapy medicines (one of them being topotecan

hydrochloride) from a novel polysaccharide-gold nanocluster supramolecular conjugate. This delivery system was discovered to be pH-responsive, the best results regarding drug release being at a mildly acidic pH. Here, the encapsulation efficiency (34.65 ± 3.31 %) and loading efficiency (5.04 ± 0.87 %) of topotecan were significantly lower than other drugs in the experiment, with doxorubicin having the highest values.

3.4.2. Irinotecan

As with its counterpart, there are a few studies that pursue the nanocarrier drug delivery approach to irinotecan using carriers, mostly biodegradable polymers. However, the study of Li et al. [127] examined the loading and delivery of irinotecan hydrochloride from a novel polysaccharide-gold nanocluster supramolecular conjugate. The results presented an encapsulation efficiency of 45.16 ± 4.51 %, and a loading efficiency of 7.35 ± 0.74 %, values higher than those of topotecan.

3.4.3. Etoposide

Gold nanoparticles loaded with etoposide have only recently been gaining attention, namely, through the study of Ali et al. from 2020 [128] that proposed different formulations based on different variables such as nanoparticle size, experimental temperature, etoposide load. The in vitro cytotoxicity assay on NHI-H69 cancer cell line and BEAST-B2 normal cell line showed that the developed system has a high selectivity towards the first.

3.5. Mitotic inhibitors

This class of compounds are mainly derived from plants, stopping cellular division as well as stopping enzymes from producing proteins needed for cell reproduction, thus damaging them [129]. Some examples of mitotic inhibitors include Paclitaxel, Docetaxel, Vinblastine and Vinorelbine.

3.5.1. Paclitaxel (Taxol)

Paclitaxel-loaded gold nanoparticles have been the focus of several studies, with a variety of papers and patents being published on this matter. An earlier work of Gibson et al. [130], describe the first instance of gold nanoparticles (2 nm) functionalized with paclitaxel focusing on the processes that occur. Paciotti et al [131] have worked on several paclitaxel thiolated analogues and their release from AuNPs. Several analogues were biologically evaluated using a human ovarian A2780 cancer cell line with two formulations being found to be more potent than the actual paclitaxel. One analogue was tested in tumour bearing mouse models with a 50% reduction within 9 days which is very promising. Heo et al. [132] reported on a paclitaxel-loaded AuNP and biotin

receptor and their interactions with different cell lines – HeLa (human breast cancer), MG63 (human osteosarcoma) and A549 (human lung carcinoma). Here, glutathione enhanced the release of paclitaxel to 71% in 24 h, compared to 21% in the absence of glutathione. The experimental carrier has an affinity towards cancerous cells while not affecting healthy ones. On the other hand, Alhalili et al. [133] investigated the pH dependent cytotoxicity of AuNPs loaded with paclitaxel against a breast cancer cell line (T47D). It was found that the viability of cells decreased in a significant manner at a pH value of 6.5. Meanwhile, Asar et al. [134] investigated the effects of AuNPs-paclitaxel on oral squamous cell carcinoma that was induced in Syrian hamsters with those treated with the medicine loaded on AuNPs showing beter results than those treated with rhe drug alone.

3.5.2. Docetaxel

Docetaxel-loaded gold nanoparticles have raised interest with several researched groups. Francois et al. [135] reported on docetaxel encapsulated in PEGylated AuNPs and its effect on HTC15 human colon carcinoma and MCF7 human breast cancer cell lines. While standalone gold nanoparticles presented absolutely no cytotoxic effects, the carrier was found out to be 2.5 times more efficient than the drug alone. Another paper [136] studied the cytotoxicity of AuNPs loaded with docetaxel against a H520 lung cancer cell line with an observed decrease in cell survival. It is reinforced again that a gold-based nanocarrier loaded with chemotherapy medicine is more effective than the free drug. The effect of such carrier on another type of cancer, namely human prostate LNCaP, was studied by Oliveira et al. [137]. In this case, the gold nanoparticle functionalized with PEG (550 and 2000) and loaded with docetaxel produced a durable cytotoxic effect while the unloaded AuNPs were without any effect.

On the other hand, Wan and his team [138] employed apatite as a carrier for docetaxel and gold nanoparticles. In vitro tests on HepG2 human liver cancer cell lines demonstrated the high cytotoxicity of the devised carrier.

3.6. Corticosteroids

Corticosteroids, natural hormones or hormone-like drugs, are considered chemotherapy drugs when used as integral part of a cancer treatment. Probably the most well-known types of corticosteroids are prednisone and methylprednisolone. The research on the delivery of corticosteroids by means of gold nanoparticles as the carriers is still in the early stages. However, one article [139] does address this issue by analysing the release of *dexamethasone* (glucosteroid drug) from functionalized AuNPs (AuNP-3MPS/DXM). An in vitro assay was performed on HeLa (human cervix carcinoma), EG.7-OVA murine lymphoma and Karpass 422 human B cell non-Hodgkin’s lymphoma cell lines at different concentrations of

the developed compound. It was found that tumour cell proliferation was hindered at a AuNP-3MPS/DXM concentration of 8.4 ng mL^{-1}.

4. Safety concerns in using AuNPs as drug carriers

Gold nanoparticles show promising results in improving pharmacokinetics [140] thus leading to a reduction in known side effects of chemotherapy agents and potentially allowing higher doses to reach cancer cells. However, the cytotoxicity of AuNPs needs to be taken into account especially considering all surface adjustments in regards to drug delivery. The size of gold nanoparticles is another important parameter, with AuNPs of 10 nm being able to circulate through the blood stream for more than 24 hours in animal models [141] and can accumulate in organs. Also, immune responses that can be potentially triggered should also be taken into account.

5. Future trends: AuNPs loaded onto inorganic biomimetic compounds

A more recent trend in gold nanoparticle research is their binding to other types of materials, specifically biomimetic ones such as calcium phosphates. Synthetic hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, is highly biocompatible and has been the focus of a wide range of studies regarding biomedical applications [142-159]. While both hydroxyapatite and calcium phosphates are generally believed to be used more in bone implants, they can act as effective drug delivery systems. Nontoxic by nature, phosphate nanoparticles can be readily dissolved in an acidic environment of around pH 4.5 acidity that can be found in humoral tissues and lysosomes after uptake. Literature exhibits a few studies on gold nanoparticles loaded on calcium phosphates. Cha et al. [160] reported on a pH sensitive nanocarrier of AuNPs coated with calcium phosphate and loaded with doxorubicin (PEGylated Dox-AuNP@CaP).

Cell viability tests performed using HeLa showed that cellular viability was 19% after a period of incubation of 24 hours. Also, the release of doxorubicin from the said carrier in a lysosomal fluids environment (pH 4.5) reaches 78%. Another study by Ito et al. [161] deals with the preparation of a DNA/AuNPs encapsulated in calcium phosphate with the DNA being released by immersion of the carrier in an acetate buffer. Moreover, Liang et al. [162] reports on hydroxyapatite composites loaded with AuNPs that are able to guide osteogenic differentiation from human bone marrow-derived mesenchymal stem cells by means of a WNT/β catenin signalling pathway. Possessing similar bioactive/ biocompatible properties to those of phosphates and hydroxyapatite, forsterite (Mg_2SiO_4) is another promising candidate for gold nanoparticles loading/ drug delivery research. Its bioactivity relies on the content of Mg and Si that are

essential minerals that are known to contribute to the mineralization of young bone and skeletal mass gain respectively [163-169]. There is an increased demand for more effective drug delivery systems that are both nontoxic in nature and are able to decrease the toxicity of certain medications while maintaining/ increasing their potency. With this in mind, the use of such inorganic, biocompatible materials as HAP and forsterite in combination with gold nanoparticles and medicine would provide a new pathway towards a more sustainable patient treatment with few to none side effects.

6. Nanoscale interactions

As is given throughout this review, the nanoscale interaction is a non-explored area, despite the fact that the anti-neoplastic drugs need to cross blood brain barrier, BBB [170-174], to treat brain cancer. Also, the AuNPs functionalized with anti-tumour agents have to cross cell membranes to approach the cell nucleus [175-181] to treat cancer in the body. Definitely, the knowledge of nanoscale interactions obtained at the level of self-assemblies of different organic molecules, like lipids, lecithin and proteins, as monolayers [182-230], bilayers [231-233] or liposomes, as well as Langmuir-Blodgett layers [234-239] is important (Fig. 5).

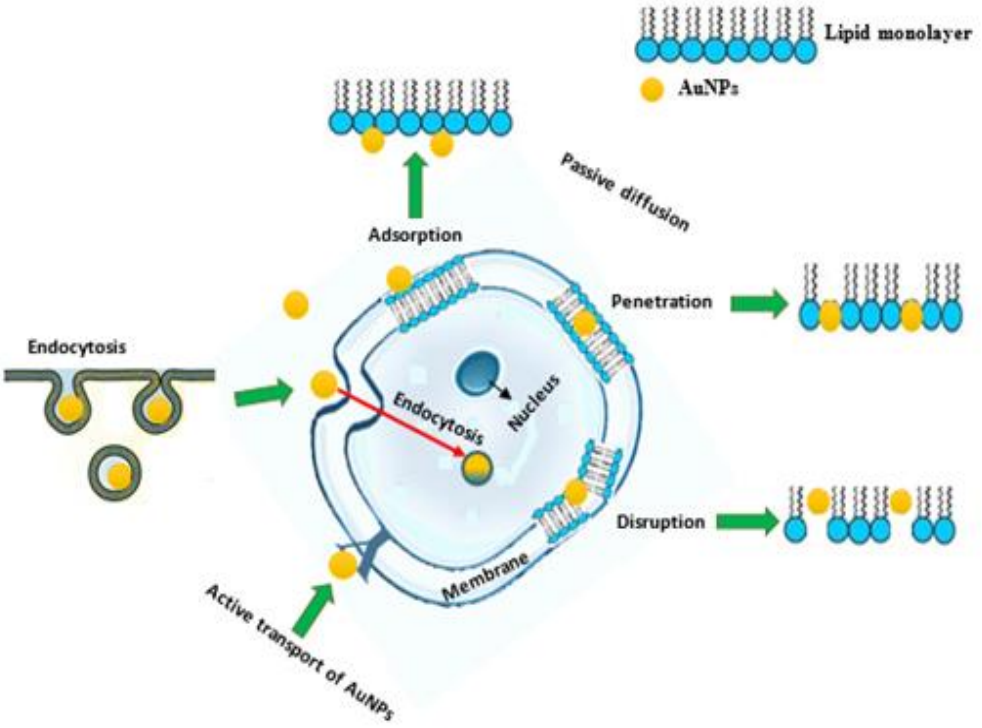

Fig. 5. Models for nanoscale interactions.

The understanding of the importance of nanoscale interaction is enriched by using the said self-assemblies known as models of cell membranes and of different compartments in cytoplasm, like cell organelles called lysosomes. Lysosomes hold enzymes that digest all materials that are taken into the cell and also recycle intracellular materials. The AuNPs functionalized with anti-tumour agents can cross the cell membranes [240-243] by passive diffusion and endocytosis or by active transport through binding to a cell membrane receptor. Considering the complexity of these interactions, it is reasonable to suggest the use of self-assemblies of organic molecules, like monolayers, bilayers, Langmuir-Blodgett layers to explore nanoscale interaction in these systems, which remains a major challenge (Fig. 5). Nanoscale interaction effects are also seen in various phenomena as opening and closing of ion channels, which are known to be important in cell signalling. Future studies should attempt an understanding of the role of nanoscale interactions and how their effects can influence cell membrane properties, DNA synthesis, and eventually gene expression in cancer treatment.

Conclusions

Gold nanoparticles can be employed in cancer therapy due to their unique properties as well as to their physical, chemical and biological characteristics. Combining AuNPs with classic cancer drugs can improve pharmacokinetics and potentially lead to a more efficient treatment with fewer side effects. Most studies reviewed showed an improved effect at decreased drug concentrations when gold nanoparticles were the carriers. Moreover, AuNPs-drug complexes were cytotoxic particularly to cancer cells. Additionally, it was demonstrated that AuNPs can diminish or dismiss the side effect of chemotherapeutic agents.

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