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Review article

Gold nanostructure-mediated delivery of anticancer agents: Biomedical applications, reversing drug resistance, and stimuli-responsive nanocarriers

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ABSTRACT

The application of nanoarchitectures in cancer therapy seems to be beneficial for the delivery of antitumor drugs. In recent years, attempts have been made to reverse drug resistance, one of the factors threatening the lives of cancer patients worldwide. Gold nanoparticles (GNPs) are metal nanostructures with a variety of advantageous properties, such as tunable size and shape, continuous release of chemicals, and simple surface modification. This review focuses on the application of GNPs for the delivery of chemotherapy agents in cancer therapy. Utilizing GNPs results in targeted delivery and increased intracellular accumulation. Besides, GNPs can provide a platform for the co-delivery of anticancer agents and genetic tools with chemotherapeutic compounds to exert a synergistic impact. Furthermore, GNPs can promote oxidative damage and apoptosis by triggering chemosensitivity. Due to their capacity for providing photothermal therapy, GNPs can enhance the cytotoxicity of chemotherapeutic agents against tumor cells. The pH-, redox-, and light-responsive GNPs are beneficial for drug release at the tumor site. For the selective targeting of cancer cells, surface modification of GNPs with ligands has been performed. In addition to improving cytotoxicity, GNPs can prevent the development of drug resistance in tumor cells by facilitating prolonged release and loading low concentrations of chemotherapeutics while maintaining their high antitumor activity. As described in this study, the clinical use of chemotherapeutic drug-loaded GNPs is contingent on enhancing their biocompatibility.

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1. Introduction

After heart disease, cancer has been highlighted as a life-threatening hazard (Park and Han, 2019; Heron, 2012). Although our knowledge and information about cancer biology have significantly improved, we still have a long way to go before curing cancer. Each cancer cell has unique properties distinct from normal cells, and such features can be targeted for the purpose of cancer therapy. Tumor cells display accumulation of genomic mutations during their progression, and some of the factors may increase their metastasis and reaching to a secondary site (Pastushenko and Blanpain, 2019). Furthermore, tumor cells show dysregulation of non-coding RNAs (Anastasiadou et al., 2018), and in spite of understanding the biological aspects of tumors, their cure is still a problem.

Nanoparticles are structures with a size in the range of nanometers (less than 100 nm), and throughout the past several decades, these carriers have opened a new window in the treatment of various diseases, particularly cancer. Nanomedicine is a growing field, and new discoveries in this field might considerably aid scientists in overcoming cancer, one of the most lethal and deadly diseases (Garbayo et al., 2020; Irvine and Dane, 2020). Because cancer is a complicated disease, it is unlikely for a single discipline to find a cure; thus, scientists have focused on merging biology, engineering, and other disciplines to make significant progress in cancer treatment (Dalpiaz et al., 2020; Venkatas and Singh, 2020). Furthermore, there are biological issues that can be resolved with nanotechnology and bioengineering. To date, nanoparticles have been fabricated for drug delivery (Ertas et al., 2021), gene delivery (Li et al., 2020), and the co-delivery of genetic tools and antitumor compounds (Yang et al., 2020a). One of the issues with cancer is the late detection in advanced stages, when cancer cells are no longer sensitive to therapies; thus, nanotechnology can play a crucial role by facilitating timely cancer diagnostics (Li et al., 2020; Alafeef et al., 2020; Abbasi et al., 2022). It is worth mentioning that nanocarriers have opened the way for the treatment of cancer patients (Khoobchandani et al., 2020). Finally, nanotechnology has found its way to precision cancer medicine (Adir et al., 2020).

For decades, chemotherapy has been the first option in the treatment of cancer patients, and it is generally preferred to surgery due to its minimally invasive nature and its efficacy in cancer elimination at advanced stages, when cancer cells have diffused to different organs of the body and it is impossible to use surgery. However, chemotherapy has its own issues, including side effects and chemoresistance (Wang et al., 2020; Shiokawa et al., 2020; Przanowski et al., 2020; Salehiabar et al., 2023; Hashemi et al., 2022a). Regardless of the negative consequences, drug resistance is a growing problem today and the leading cause of failure in cancer treatment (Davar et al., 2021). Although a variety of strategies have been developed for overcoming chemotherapy resistance, this condition is still causing a high rate of death among cancer patients, and novel tools should be considered in this way.

In the current review, we focus on using gold nanoparticles (GNPs) as one of the most well-known metal nanocarriers for delivery of chemotherapeutic agents in cancer therapy. First, we provide an overview of GNPs and their biomedical applications to demonstrate how these nanostructures have paved the way for disease treatment, with a focus on cancer. Then, currently applied chemotherapeutic agents—the most important ones—are discussed, and an overview of current problems with chemotherapy is provided. Drug resistance is the most important one. Then, we focus on the delivery of chemotherapeutic agents by GNPs. The co-delivery of chemotherapeutic agents with genetic tools or other antitumor compounds can be performed by GNPs. Stimuli-responsive devices based on GNPs have been developed for the targeted delivery of chemotherapeutic agents. Surface modification of GNPs by polymers has been conducted to enhance their selectivity towards cancer cells. Finally, theranostic potential and hybrid nanocomposites developed for delivery of chemotherapeutic agents are discussed to shed some light on the potential of GNPs as promising nanocarriers in cancer elimination.

2. Gold nanoparticles: an overview

GNPs are widely used for drug and gene delivery among inorganic nanomaterials because to their unique properties, including shape and size tunability, surface modification, and controlled release (Zhang et al., 2020a). GNPs have been found to possess high biocompatibility and biological inertia (Zhao et al., 2018; Connor et al., 2005a; Bhattacharya and Mukherjee, 2008; Kim et al., 2009). Typically, GNPs have a particle size in the range of 1–150 nm and can load drugs in their cavity or on their surface (Kim et al., 2009; Kong et al., 2017; You et al., 2010; Ajnai et al., 2014). Due to the high surface-to-volume ratio of GNPs, however, experiments favor conjugation of drugs on the surface of GNPs, resulting in the creation of pro-drugs (Biener et al., 2009). GNPs are being employed in a variety of sectors, including life sciences, analytical chemistry, genetic engineering, the food industry, medicine, and clinical therapy (Howes et al., 2014). To date, a variety of methods have been applied for the synthesis of GNPs, such as top-down and bottom-up techniques and physical techniques such as grinding and etching. However, physical techniques are not recommended due to their complexity and cost (Howes et al., 2014; Saha et al., 2012; Li and Yang, 2013; Zezin et al., 2020). Chemical methods and Brust-Schiffrin are other kinds of strategies that can be used for the synthesis of GNPs, both of which have drawbacks, including toxicity to the environment and biosystems (Panigrahi et al., 2004). In spite of different strategies to develop GNPs, there are still issues with their large-scale production due to the high cost of materials, chemicals, and energy, as well as the high use of organic solvents, necessitating the development of novel methods for their affordable synthesis with minimal environmental impact. For the synthesis of GNPs, an alternate procedure was utilized. This method relies on nature as a rich supply of molecules and substances with different properties useful for producing safe and inexpensive GNPs. Numerous methods, including one-pot hydrothermal chemical reduction, seed growth-assisted co-precipitation, microfluidic droplets, etc. have been proposed for the green synthesis of GNPs with low cost, high biocompatibility, and partial toxicity for environment and have recently been reviewed by Qiao and Qio (Qiao and Qi, 2020). Various forms of GNPs, such as spherical GNPs, gold nanorods, gold nanoshells, gold nanoclusters, GNP-liposomal hybrid nanocarriers, etc., have been produced for biomedical applications (Bromma and Chithrani, 2020). Each nanocarrier has its own advantages in disease therapy, but spherical GNPs are the most commonly used due to their ease of synthesis, affordable production, controlled size, and capacity of surface modification (Yeh et al., 2012; Stiufiuc et al., 2013). In cancer therapy, spherical GNPs can be used for antitumor drug administration or X-ray irradiation (Sztandera et al., 2019). As gold nanorods and gold nanoshells possess a high near-infrared (NIR) cross-section, they are favored over other types of GNPs for cancer hyperthermia (Huff et al., 2007; Rastinehad et al., 2019).

GNPs have attracted much attention in the field of cancer therapy and diagnosis. Significant effort has gone into determining the true potential of these nanostructures in cancer eradication. GNPs can aid in the early detection of cancer in its early stages. It has been reported that ultrasmall gold quantum clusters have a low circulation time in blood and can effectively internalize at tumor site with low accumulation in reticuloendothelial system. In respect to producing contrast for fluorescence, X-ray computed tomography, and magnetic resonance imaging (MRI), and owing to their retention at tumor sites, they can be applied for the diagnosis of cancer (Yang et al., 2020b). Furthermore, radiolabeled GNPs have been developed for cancer diagnosis (Silva et al., 2020). Since GNPs can provide simultaneous cancer imaging and treatment, they have been extensively applied as theranostic agents. Decorating carbon nanotubes with magnetic and GNPs, for example, results in the preparation of therapeutic nanocarriers capable of imaging (MRI, for example) and providing thermotherapy to kill cancer cells

(Saghatchi et al., 2020). The next step in using GNPs in cancer therapy is making changes in their surface chemistry to enhance their selectivity towards cancer cells. It has been revealed that cancer cell membrane-coated GNPs can provide selective homotypic targeting of cancer cells (Sun et al., 2020). Different strategies, such as using polymers including chitosan, hyaluronic acid, alginate, fucoidan, aptamers, DNA linkers, etc. have been applied for surface modification of GNPs, and conjugating compounds on their surface (Zhang et al., 2020b; Khademi et al., 2020; Chen et al., 2020a; Manivasagan et al., 2019; Jacinto et al., 2020). Furthermore, GNPs can target molecular pathways that are responsible for cancer progression. Drug-conjugated GNPs suppress PI3K/Akt signaling to inhibit breast cancer viability and growth (Mahmoud et al., 2020). Taking everything together, GNPs are promising candidates in cancer therapy and diagnosis (Ding et al., 2020; Hao et al., 2020; Zhang et al., 2021; Fan et al., 2020; Chen et al., 2020b; Norouzi, 2020), and in the next section, we mechanistically discuss the role of these nanocarriers in cancer chemotherapy.

3. Chemotherapy: current status and promises

One of the foremost limiting factors in reaching a satisfactory level for the treatment of cancer patients is cancer drug resistance (Vasan et al., 2019). Importantly, cancer drug resistance shares many similarities with drug resistance during infections in that in both fields (cancers and infectious diseases), intrinsic and extrinsic aggressors participate in the emergence of drug resistance. When cancer cells develop resistance to therapy, cancer patients face another challenge: relapse and recurrence. One of the primary solutions for overcoming drug resistance in human cancers is to avoid single chemotherapy and instead use a variety of chemotherapy compounds with different action mechanisms; this is known as polychemotherapy. Important lessons have been learned from combination antimicrobial treatment (Crofton, 1959). However, this was not limited to hypothesis, and therefore, some empirical approaches were conducted in the therapy of lymphoma, breast cancer, and testicular tumors (DeVita et al., 1980; Bonadonna et al., 1976; Bosl et al., 1986). When it was believed that combination cancer therapy was beneficial in tumor suppression, complicated cancer therapy regimens were developed, resulting in the development of a new pattern in cancer elimination. Furthermore, some other approaches were developed to provide more insights and hope in cancer therapy, including various dose levels (Hryniuk and Bush, 1984), shorter-interval administrations of chemotherapy (Citron et al., 2003; Sternberg et al., 2001), and higher concentration levels of chemotherapy (Sternberg et al., 2001). Even in the process of polychemotherapy, there were different approaches; one of them was the combination of two chemotherapy compounds, and another was the combination of plant-derived natural products with synthetic drugs in cancer therapy. Both of these approaches have shown promising results in cancer therapy. For instance, resveratrol, as a natural product, is capable of suppressing the IL-6/STAT3 axis, which is beneficial in impairing M2 polarization of macrophages, enhancing the number of M1 polarized macrophages, and enhancing drug sensitivity (Cheuk et al., 2022). Furthermore, curcumin disrupts the PI3K/Akt/mTOR axis to increase the sensitivity of tumor cells to cisplatin chemotherapy (Kalinina et al., 2022). As a result, the chemotherapy process has been slightly improved in terms of tumor suppression. However, this is not the end of the story, and a new problem in cancer chemotherapy is multidrug resistance (MDR), which is defined as a process in which tumor cells obtain the ability to develop resistance to different kinds of chemotherapeutic agents that have various structures and mechanisms of action (Fojo et al., 1987). The interesting point is that tumor cells can not only obtain resistance to different chemotherapy compounds but also show such properties before exposure to these agents (Kaye, 1988).

The mechanisms of chemoresistance are categorized into two groups to make it easier to understanding the development of this process. Intrinsic and adaptive drug resistance are two major categories of chemoresistance that have been investigated in detail (Chatterjee and Bivona, 2019). If resistance is present before chemotherapy exposure, it is known as “intrinsic drug resistance,” and it is considered the capacity of treatment-naive tumors to survive in spite of exposure to chemotherapy that can result from genomic mutations or cell-state changes (Wu et al., 2008; Bivona et al., 2011; Ng et al., 2012; Konieczkowski et al., 2014). However, adaptive drug resistance occurs after the process of chemotherapy in which populations and colonies of tumor cells obtain genomic mutations or adaptations to the drug, and then some changes in growth mechanisms and other related pathways may occur, and these alterations lead to acquired drug resistance (Kobayashi et al., 2005; Yun et al., 2008; Cross et al., 2014; Thress et al., 2015; Paskeh et al., 2021).

Now, this question comes into mind: can specific mechanisms and pathways responsible for MDR be targeted to reverse this condition? The answer is yes, but MDR is a multifactorial condition, and it has been shown that hyperactivation of ABC transporters on the surface of tumor cells, epigenetic and genetic changes, apoptosis inhibition, autophagy modulation, DNA damage repair, and cancer stem cells are among the factors that can play a significant role in the process of MDR (Wu et al., 2014). When the concept of MDR was introduced, it caused some worry among physicians and those who work in the field of cancer therapy and overcoming chemoresistance. First of all, due to the presence of MDR, the strategy of combination cancer therapy may be compromised, and therefore, a new solution should be provided as a preventative measure. Moreover, although plant-derived natural compounds can be used along with chemotherapy agents, they have poor bioavailability and therapeutic index (Ashrafizadeh et al., 2020a). Hence, researchers focused on using gene therapy approaches to reverse chemotherapy resistance in tumor cells. The purpose and final aim of gene therapy are similar to those of polychemotherapy, but it is performed in a more specific way so that a certain pathway or mechanism that can lead to drug resistance is targeted by gene therapy, and then this can enhance the sensitivity of tumor cells to chemotherapy (Izquierdo, 2005; Mirzaei et al., 2022; Mahabady et al., 2022). With these descriptions, readers may consider that the problem of drug resistance has been solved completely. However, when it comes to practical work, these strategies demonstrate significant drawbacks that interfere with their therapeutic index. Both approaches, including polychemotherapy and gene therapy, suffer from a lack of specific delivery due to rapid metabolism of antitumor compounds, and their short half-lives, chemoresistance, and effectiveness in drug therapy still need to be addressed in cancer patients. Moreover, the problem in gene therapy is more tangible since genes can be degraded by RNase enzymes and they have an off-targeting feature. Moreover, low pH in the tumor microenvironment may negatively affect the structure and chemical activity of genetic tools. Therefore, nanostructures have been extensively utilized for the delivery of genetic tools to overcome the aforementioned problems in gene delivery and provide effective cancer therapy (Mirzaei et al., 2021a; Ashrafizadeh et al., 2021a; Chadar et al., 2021). According to these discussions, it can be highlighted that nanoparticles play a significant role in the process of cancer therapy, and one of their important functions is providing targeted delivery of drugs and genes in cancer therapy to protect them, increase their bioavailability, and internalize them in tumor cells in order to enhance the potential of tumor suppression by current therapeutic tools. The next sections specifically focus on the role of GNPs in providing cancer chemotherapy, their potential in drug delivery, and other benefits such as phototherapy in accelerating the process of tumor suppression. Table 1 summarizes use of GNPs in cancer therapy.

4. Nanostructures in cancer chemotherapy: Beyond gold nanoparticles

The field of cancer chemotherapy has evolved due to the introduction of nanostructures for drug delivery of drugs. Before discussing function of GNPs in cancer chemotherapy and delivery of anticancer agents, it would be beneficial to give an introduction about the role of

Table 1
The application of GNPs for purpose of cancer therapy.

Nanoparticle	Cancer type	Remark	Ref.
Gold Nanoparticles and Graphene Oxide Flakes	–	Improving the phagocytosis of tumor cells	Al-Omar et al. (2021)
Gold Nanoparticles-MWCNT Based Aptasensor	Prostate cancer	Precise devices for diagnosis of tumor	Alnaimi et al. (2022)
Antibody-conjugated silica-coated gold nanoparticles	Cervical cancer	Apoptosis induction and targeted cancer therapy due to modification with aptamer	Yu et al. (2022)
Gold nanoparticles	–	Targeted delivery of epigallocatechin gallate for apoptosis induction	Cunha et al. (2022)
Gold nanoparticles	Ovarian cancer	Gold nanostructures target IGFBP2/mTOR/PTEN axis for suppressing cancer proliferation	Hossen et al. (2022)
Gold nanoparticles	Bladder cancer	Gold nanoparticles stimulate apoptosis and promote ROS generation	Daei et al. (2022)
pH-sensitive gold nanoparticles	–	Responsiveness to pH and mediating photothermal therapy	Park et al. (2019)
Genistein-loaded gold nanoparticles	Prostate cancer	High stability and reducing viability of tumor cells	Vodnik et al. (2021)
AS1411 aptamer-conjugated gold nanoparticles	Breast cancer	Exerting radio-sensitive activity	Mehrnia et al. (2021)
Gold nanoparticles	–	Suppressing cancer-associated fibroblasts and preventing the crosstalk of cancer and microenvironmental cells	Zhang et al. (2021)
PEGylated gold nanoparticles-ribonuclease	Colorectal cancer	Stimulation of oxidative damage and apoptosis	Akbarzadeh Khiavi et al. (2020)

nanoparticles in drug delivery and cancer chemotherapy, and then, potentials and benefits of GNPs are highlighted in the next sections. The polymeric nanostructures have always been used in the treatment of solid tumors, and they can be loaded with ICG and decitabine (DCT) to mediate cancer immunotherapy. They show high and preferential accumulation at the tumor site, and they have poor immunogenicity. Moreover, such polymeric nanostructures can stimulate pores in the cell membrane to enhance Ca2+ levels in the cytoplasm in cancer therapy (Zhao et al., 2020). ZnO@CuS nanoparticles are other candidates for use in cancer chemotherapy and phototherapy that show deep tumor penetration and can suppress cancer-associated fibroblasts in tumor microenvironment. Moreover, such nanoparticles enhance the production of ROS to mediate cell death (Deng et al., 2021). The ability of nanostructures in cancer chemotherapy can be improved, when they are modified with aptamers for selective and targeted delivery (Li et al., 2018). Lipid-based nanostructures have been introduced recently as novel types for purpose of cancer chemotherapy. In addition to high biocompatibility of such nanocarriers, they improve the pharmacokinetics of drugs and due to the presence of phospholipids and surfactants in their composition, it can lead to inhibition of P-glycoprotein, a drug efflux pump involved in chemoresistance (Ahmad et al., 2015). Furthermore, nanostructures can combine hyperthermia and chemotherapy in cancer suppression (Ohtake et al., 2017). Two important characteristics have made nanostructures promising structures in cancer chemotherapy: one of them is high encapsulation efficiency, and the other is the ability to control and prolong the release of drugs (Gogoi et al., 2014). In order to increase the potential of cancer chemotherapy, the blood circulation time of chemotherapy drugs should be improved, which can be obtained by nanostructures (Xu et al., 2021a). Importantly, even two different chemotherapy drugs can be loaded on nanostructures in combination cancer therapy (Rui et al., 2017), and all of the studies advocate the application of nanoparticles for cancer chemotherapy (Zhang et al., 2018; Zhao et al., 2022).

5. Nature-derived compounds for modification of gold nanoparticles in cancer therapy

One of the important advances in the field of cancer therapy is the modification, coating, and functionalization of GNPs with compounds derived from nature and the environment. There are several underlying reasons for using nature-derived compounds for coating GNPs, but it appears that improving the biocompatibility of GNPs and simultaneously, increasing their cytotoxicity against tumor cells are the most important reasons. Chitosan (CS) is a natural polysaccharide that can be isolated from chitin through deacetylation, and when the derived polymer is considered CS, the acetylation degree is less than 50%, and it shows solubility in acidic solutions (Akpan et al., 2020). CS has a cationic feature, which has resulted in its significant application. Furthermore, the mucoadhesive characteristic of CS is vital for the purpose of drug delivery (Yu et al., 2019). Both hydrophobic and hydrophilic drugs can be delivered by CS nanoparticles, and in addition to improving the stability of pharmaceutical compounds against enzymatic degradation, they can enhance the bioavailability and therapeutic index of drugs, and they can enhance the action mechanism of compounds (Shariatinia, 2019). In a recent study, GNPs were used to deliver tamoxifen in cancer therapy, and they were also modified with β-cyclodextrin (β-CD) and hyaluronic acid (HA)-CS. The nanocomposites demonstrated a particle size of 82.02 nm and a zeta potential of −23.6 mV, and their shapes were spherical, triangle, and irregular. Fluorescence microscopy demonstrated high internalization of GNPs in breast and colorectal tumor cells, and they displayed high cytotoxicity against tumor cells (Kahlous et al., 2022). Cervical and breast tumors are considered huge threats to the health of females around the world (Torre et al., 2015). The genomic mutations that occur in these cancers cause abnormal proliferation as well as cell death escape (Galluzzi et al., 2015). Surgical resection, immunotherapy, chemotherapy, radiotherapy, and hormonal therapies are considered the main tools in the treatment of cervical and breast tumors (Nosrati et al., 2022a, 2023; Rashidzadeh et al., 2023). However, there are adverse impacts associated with the aforementioned therapies, and due to genomic mutations in tumor cells, they can induce apoptosis resistance (Martinez-Torres et al., 2015; Taheriazam et al., 2023). CS/GNPs have been considered as interesting approaches in the treatment of cervical and breast tumors, and these nanoparticles are able to increase the generation of ROS to stimulate cell death in tumors (Martínez-Torres et al., 2018). This experiment adds to our understanding of cancer therapy: CS/GNPs have the ability to induce cell death, and when used for drug delivery, they can enhance the potential for tumor suppression.

Two important aspects regarding GNPs should be considered: A) if GNPs can be synthesized biologically, and B) if they can be modified with compounds from nature, these approaches are important in improving their characteristics, including preventing aggregation and others (Kalaivani et al., 2020). Biomimetic is defined as a field in which nanostructures are fabricated in a biological way (Wang and Wang, 2014), and different kinds of biological sources such as plant extracts, microorganisms, enzymes, starch, and biopolymers can be employed in this case. In recent decades, the synthesis and fabrication of nanostructures using marine sources have been of interest (Velusamy et al., 2016). However, marine resources have been mainly used for other applications, and their use for the synthesis of nanostructures is still at the beginning stage. Marine flora, fauna, and bioactive compounds can be utilized for nanostructure synthesis. Besides, biocompatible and biodegradable resources, including seashells, pearls, and fish bones,

have demonstrated great promise in nanoparticle synthesis (Jeevanandam et al., 2018). On the other hand, when modification of metal nanostructures with biopolymers is performed, their agglomeration can be avoided (Kalaivani et al., 2020). GNPs were prepared from squilla shell waste in a recent experiment, and their surface was then modified with CS. The synthesized nanostructures demonstrated a spherical shape with particle sizes in the range of 80–82 nm. Moreover, they were used against breast tumor cells and reduced their survival rate based on the results of MTT assay (Kalaivani et al., 2020).

GPNs can be extensively used for the purpose of phototherapy, which will be discussed in detail in Section 5.4. However, it is worth mentioning that biopolymer-coated GPNs can be used for purposes of chemotherapy and phototherapy, and one of the reasons for using CS is to increase the safety profile of nanocarriers. A recent study has prepared folic acid-functionalized CS-coated GPNs for delivery of docetaxel and paclitaxel in cervical cancer therapy. It appears that the combination of phototherapy and drug delivery is of importance in suppressing tumor progression, but the important point is the function of CS, which not only improves features of GPNs but also can provide an anchor for surface modification with folic acid (Lee et al., 2022). Furthermore, the modification of gold nanorods with CS is advantageous for cancer chemotherapy or phototherapy (Duan et al., 2014). However, it should be noted that internalization of nanoparticles in cells depends on their shape (among other factors such as particle size and charge) (Makvandi et al., 2021), and future studies will compare which kinds of GPNs (spherical or rod shapes) are more efficacious in cancer therapy and drug delivery. Paclitaxel (PTX) is a common antitumor compound that has been utilized in the treatment of breast and ovarian tumors, but it suffers from low solubility and a poor therapeutic index (Lee et al., 2008; Tao et al., 2012). Different kinds of nanocarriers have been used for PTX delivery, and CS-based nanostructures are among them (Ashrafizadeh et al., 2020b). GNPs are promising carriers for targeted delivery of PTX in cancer therapy, but their stability is not satisfactory and can be improved by CS oligosaccharide. Then, CS-modified GNPs can be used for PTX delivery with a spherical shape and a particle size of 61.86 nm. These nanocarriers increased ROS generation and mediated the loss of mitochondrial potential to induce apoptosis in breast tumor cells (Fig. 1) (Manivasagan et al., 2016).

Xanthan gum (XG) is a natural exopolysaccharide gum that can be derived from the aerobic fermentation of glucose by Xanthomonas campestris (Garcıa-Ochoa et al., 2000). High availability, safety, affordability, and biodegradability are some of the features of XG (Rosalam and England, 2006). XG can be employed for the synthesis of GPNs using the heating method (Pooja et al., 2014). However, a recent experiment has synthesized GPNs using the microwave method, and they have been capped with XG. There are COO-groups on the surface of

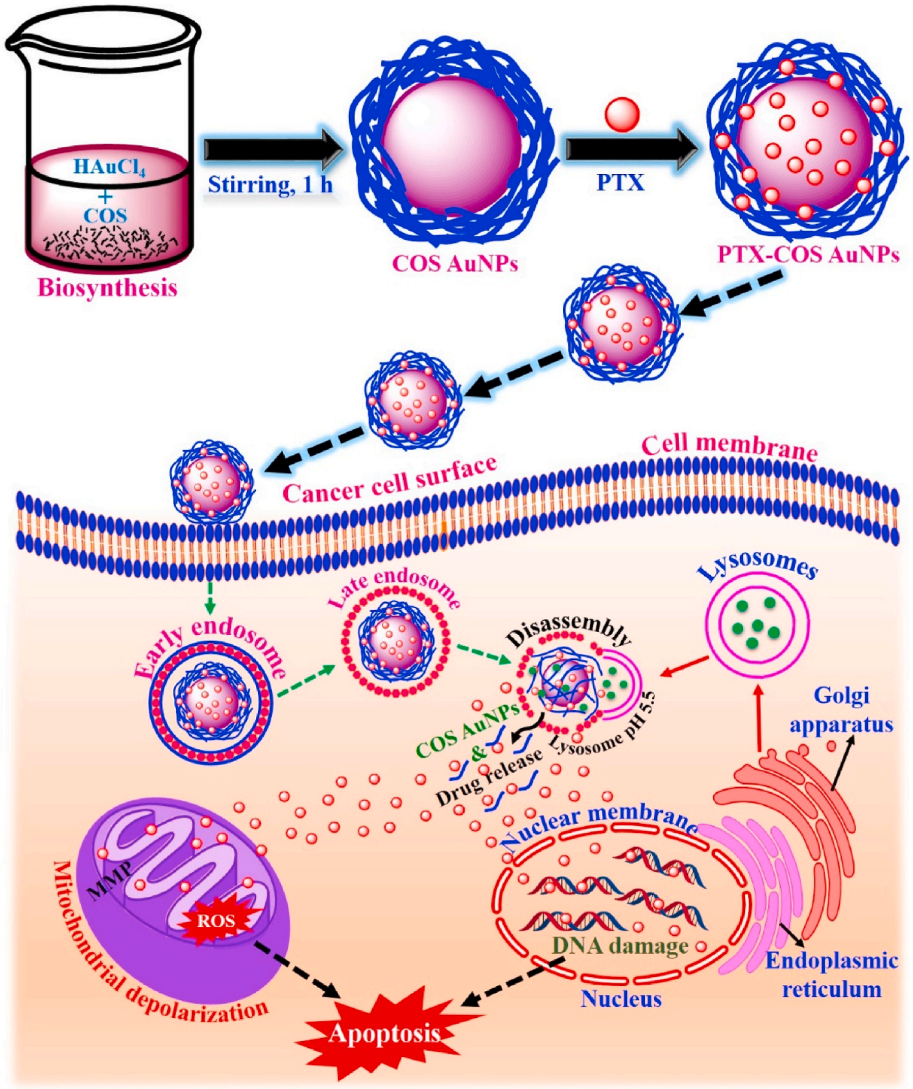

Fig. 1. The synthesis of gold nanoparticles, loading paclitaxel and subsequent mechanism of action in tumor cells to induce apoptosis via increasing ROS generation and impairing function of mitochondria. Reprinted with permission from Elsevier (Manivasagan et al., 2016).

XG-coated GNPs that can be used for conjugation with doxorubicin through electrostatic interaction. In acidic pH, doxorubicin was released from nanocarriers, but only partially in physiological pH. The nanostructures were internalized in tumor cells via endocytosis, and it was shown that they have higher cytotoxicity compared to free doxorubicin (4.6-fold higher) (Fig. 2) (Alle et al., 2020). According to these discussions, the compounds obtained from nature are promising candidates for surface modification of GNPs to improve their characteristics in cancer therapy (Fig. 3).

6. Gold nanoparticles and chemotherapeutic delivery

6.1. Co-delivery with antitumor agents

The drug resistance challenge has forced scientists to find new solutions. Combination cancer therapy appears to be a promising approach among various approaches for improving chemotherapy efficacy and overall survival of cancer patients. In this framework, antitumor agents, most of which are phytochemicals, are co-administered with chemotherapeutic agents to promote the sensitivity of tumor cells. This co-application exerts a synergistic impact and induces cell death and cell cycle arrest to prevent the proliferation of tumor cells. Although this strategy demonstrated promising results in cancer therapy, this life-threatening disease still has no absolute cure. Hence, more

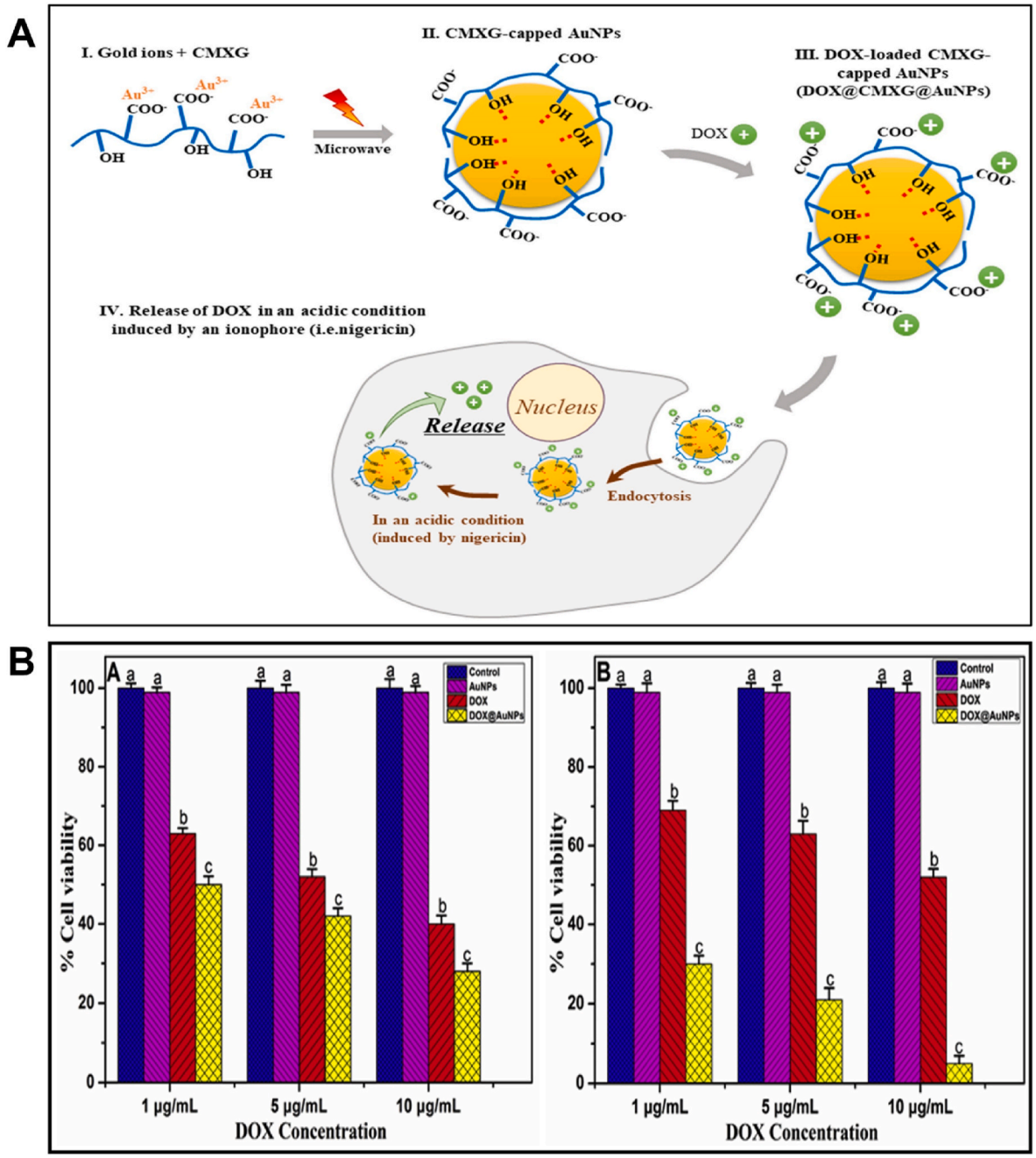

Fig. 2. A) The synthesis mechanism of gold nanoparticles, their endocytosis in tumor cells and their mechanism of action, B) the viability of tumor cells. Reprinted with permission from Elsevier (Alle et al., 2020).

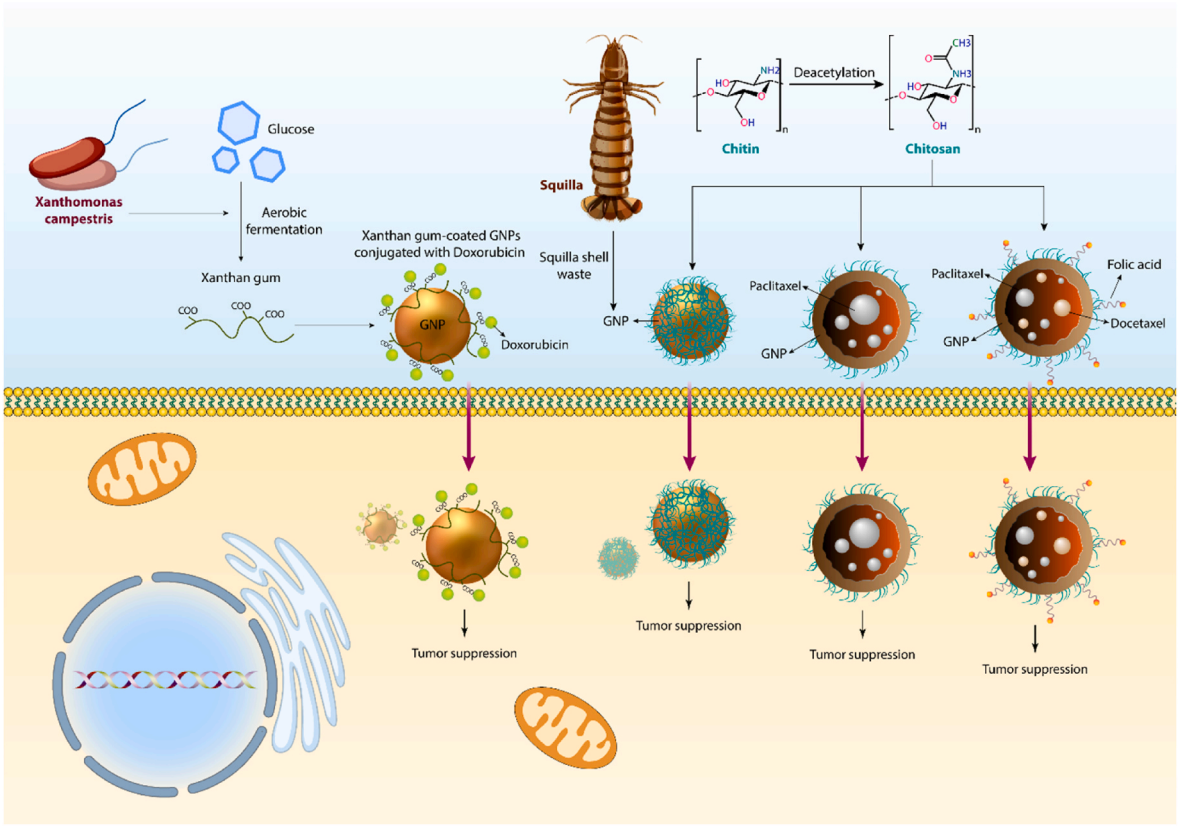

Fig. 3. Nature-modified GNPs in cancer therapy. The purpose of modifying GNPs with polymers and materials derived from nature, such as chitosan, is to improve their characteristics, and one of the most important reasons is improving biocompatibility.

advancement should be made in this case. It has been shown that the co-delivery of antitumor compounds and chemotherapeutic agents is advantageous in reversing drug resistance and suppressing cancer cell progression. Therefore, this section is allocated to understanding the potential of GNPs as nanocarriers for co-delivery and preventing tumor progression. A recent experiment has prepared GNPs for the co-delivery of 5-fluorodeoxyuridine (FUdR) and doxorubicin in breast cancer therapy. The surface of GNPs was decorated by hybrid DNA strands and then conjugated to FUdR using DNA solid-phase synthesis. At the next step, doxorubicin molecules were loaded into duplex regions. For selective targeting of breast cancer cells overexpressing HER2, affibody molecules were conjugated to DNA strands on the surface of GNPs. The finished nanoarchitecture is spherical in shape and has a high drug loading capacity. The in vitro experiment revealed the potential of GNPs for selectively targeting HER2-overexpressing breast cancer cells and suppressing their progression. Furthermore, there was a synergistic impact between FUdR and doxorubicin, improving the fight against breast tumor cells. This combination and the use of GNPs for co-delivery can effectively induce apoptosis in breast cancer cells (Zhang et al., 2020a). In addition to breast cancer therapy, GNPs have been used in the co-delivery of antitumor agents in pancreatic tumor treatment. In this case, PEGylated GNPs were prepared, and then doxorubicin and varlitinib were loaded. Such combination therapy and delivery of GNPs can elevate antitumor activity against pancreatic cancer cells while having high biocompatibility and being safe for healthy pancreatic cells.

Another study investigated the role of GNPs in co-delivery of cisplatin, doxorubicin, and capecitabine in hepatocellular carcinoma treatment. For the stabilization of GNPs, a monolayer of L-aspartate was utilized. The aforementioned antitumor drugs were conjugated to hydrophilic structures in GNPs. These antitumor drug-loaded GNPs are able to significantly diminish the progression and viability of tumor cells, demonstrating their capacity to provide chemosensitivity (Tomuleasa et al., 2012). To date, a few experiments have exploited GNPs for co-delivery of chemotherapeutic agents in tumor therapy. However, these studies obviously demonstrate the ability of GNPs to target tumor cells and promote the intracellular accumulation of antitumor compounds. There is still a long way to go in revealing the potential of GNPs in co-delivery and cancer treatment. For instance, doxorubicin and cisplatin, discussed above, use various pathways and mechanisms to exert their antitumor activity, such as apoptosis, autophagy, and DNA damage, among others (Mirzaei et al., 2021b, 2021c; Ashrafizadeh et al., 2020c, 2021b). The studies have ignored the molecular pathways and mechanisms that are affected by this co-delivery. Therefore, future studies should pay more attention to the underlying mechanisms responsible for drug resistance (Najafi et al., 2020; Ashrafizaveh et al., 2021) and their regulation of antitumor drug-loaded GNPs. Furthermore, surface modification of GNPs was overlooked, and there were a few efforts to improve the stability and biocompatibility of these nanoparticles.

One of the important problems with using GNPs in the field of drug delivery is their toxicity (Connor et al., 2005b; Goodman et al., 2004). Therefore, if the surfaces of GNPs are coated with biocompatible polymers, it is possible to improve their safety profile. On the other hand, the benefit of co-delivery is reducing the concentration of drugs, which decreases adverse impacts, avoids chemotherapy resistance, and improves the therapeutic index. Therefore, an experiment has developed PEGylated hybrid gold/nanogels for the co-delivery of doxorubicin and 6-mercaptopurine in cancer therapy. Because of the ERP effect and the presence of glutathione (GSH), these hybrid nanocarriers can increase accumulation at tumor tissue, resulting in cargo release in cancer cells. Furthermore, hybrid gold/nanogels are able to release drugs in response to pH due to the presence of disulfide bonds, and according to their high cytotoxicity, they can significantly decrease tumor growth (Fig. 4) (Ghorbani and Hamishehkar, 2018).

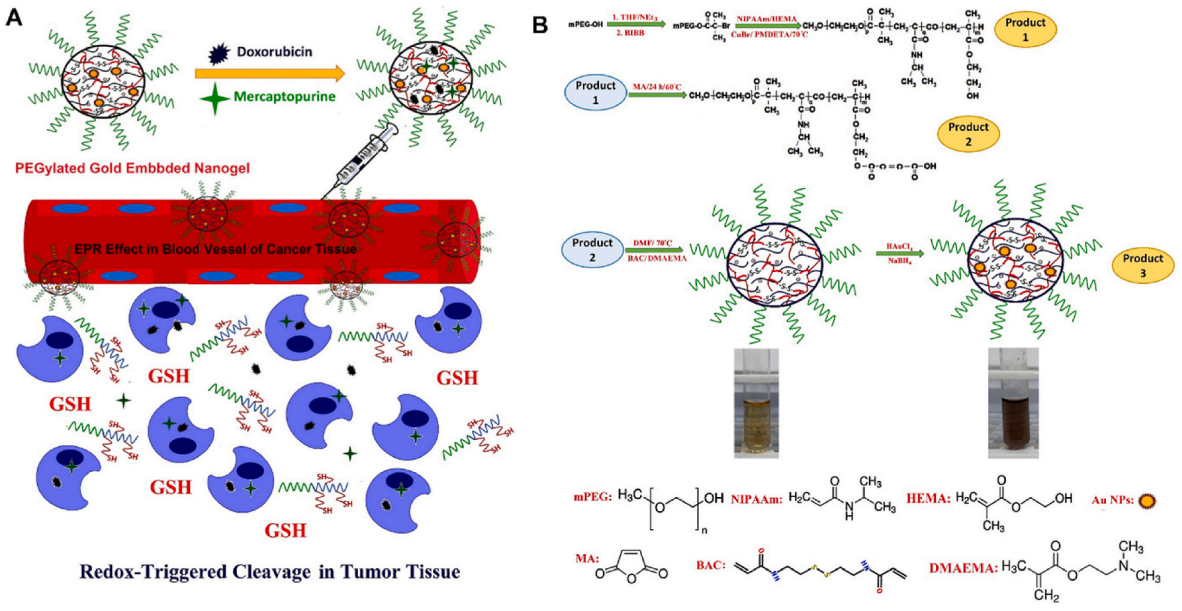

Fig. 4. A) The development of redox-responsive gold nanoparticles, B) The exact mechanism of synthesis. Reprinted with permission from Elsevier (Ghorbani and Hamishehkar, 2018).

Notably, since doxorubicin is widely used for the purpose of cancer therapy, there is a high chance for resistance development, which is why studies have focused on its delivery by nanoparticles and in cancer therapy (Mahabady et al., 2022; Hashemi et al., 2022b). Importantly, various kinds of nanoparticles, such as hyaluronic acid-based nano-architectures, have been shown to be advantageous in increasing doxorubicin's cytotoxicity and preventing drug resistance (Mirzaei et al., 2021a). In breast tumor cells, there is a high expression level of

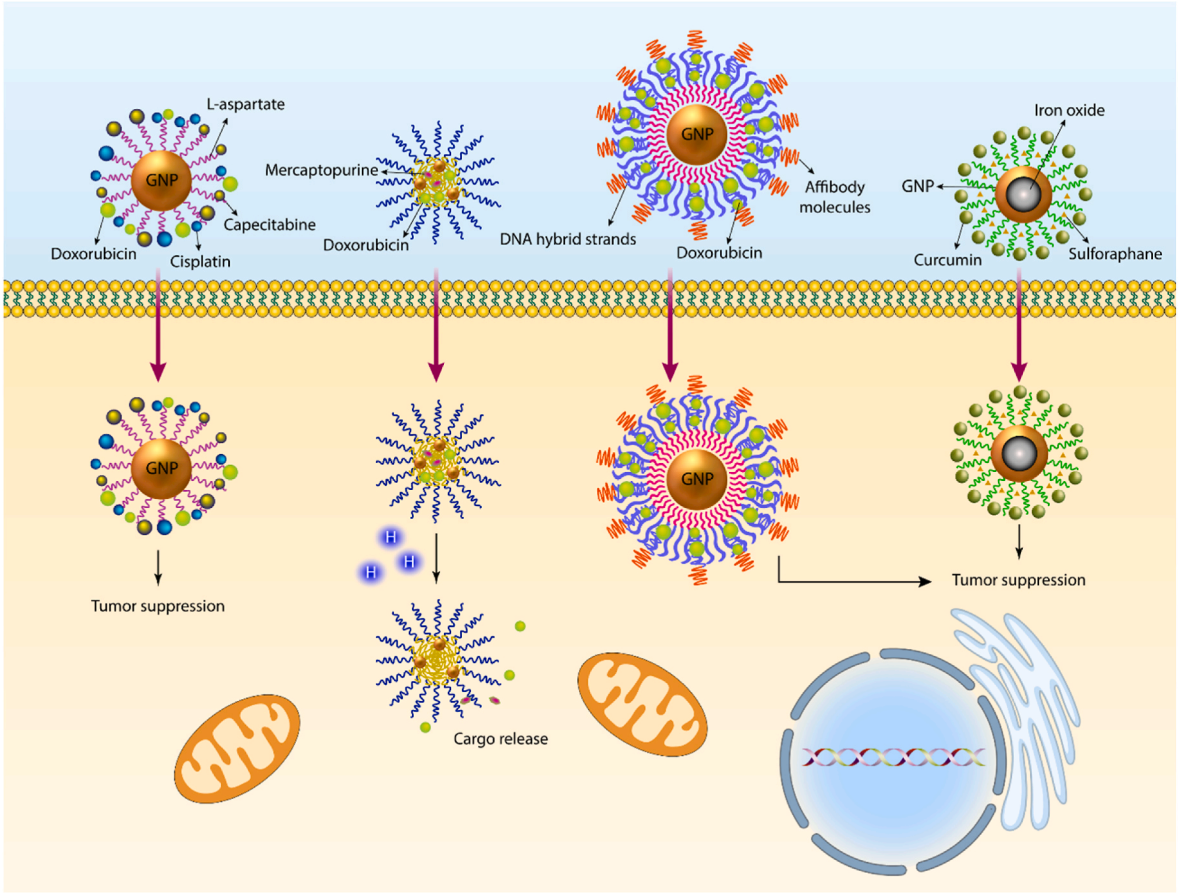

Fig. 5. The application of GNPs for purpose of co-delivery in cancer therapy. Combination cancer therapy has emerged as a promising approach in improving tumor cell elimination, and GNPs can encapsulate drugs in their core or on their surface.

HER2, and if GNPs are decorated with ligands targeting HER2, the ability of nanostructures to suppress tumors is significantly enhanced. For this purpose, GNPs have been modified with affibody-DNA hybrid strands, and then 5-fluorodeoxyuridine was conjugated to these strands via DNA solid-phase synthesis. Furthermore, doxorubicin was embedded into duplex regions of DNA strands on the surface of GNPs. The GNPs were stable with a spherical shape, and they showed high tumor suppressor activity against HER2-overexpressing breast tumor cells, and due to co-delivery, synergistic cancer suppression was provided (Zhang et al., 2020a). The essential part of co-delivery is that this strategy can also be used for the co-delivery of two antitumor agents that have been derived from nature. In previous studies, doxorubicin and other chemotherapy compounds have been utilized in cancer therapy, but since plant-derived natural products suffer from poor bioavailability, using GNPs can be beneficial in improving their therapeutic index in cancer therapy. Sulforaphane (SNF) suppresses the Akt/mTOR axis to reduce the growth and invasion of bladder tumor cells (Xie et al., 2022); furthermore, it reduces MMP-9 levels to decrease the metastasis of gastric cancer (Li et al., 2022). Curcumin, on the other hand, is a naturally occurring compound with a high potential for reducing tumor cell sensitivity to chemotherapy (Abadi et al., 2022; Ashrafizadeh et al., 2020d; Wei et al., 2022). PEGylated iron oxide-gold core shell nanostructures were prepared for the co-delivery of curcumin and SFN. The prepared nanostructures demonstrated an 80.57 nm particle size and a zeta potential of −15.4 mV. The loading efficiency for curcumin and SFN was 17.32% and 16.74%, respectively. Furthermore, the encapsulation efficiencies for curcumin and SFN in nanostructures were 83.72% and 81.2%, respectively. The cytotoxicity of these antitumor drugs increases after delivery by nanostructures, and they are able to suppress metastasis and stimulate apoptosis and necrosis (Fig. 5) (Ashrafizadeh et al., 2022).

6.2. Combined gene therapy and chemotherapy

In Section 3, the challenges in the field of chemotherapy were discussed, and it was noted that the drawbacks and limitations of chemotherapy, such as resistance, can also be solved with the help of gene therapy. More importantly, the application of gene therapy has its own problems, such as a lack of appropriate internalization in tumor cells and targeted delivery, that can be solved by nanostructures. The use of GNPs has been shown to be promising in terms of providing synergistic gene- and chemotherapy. The dendrimer-entrapped GNPs have been shown to be beneficial for the co-delivery of miR-21 inhibitors and gemcitabine in pancreatic tumor suppression. The resulting nanocarriers can be internalized in tumor cells, and interestingly, their cellular uptake can be improved by ultrasound-targeted microbubble destruction (UTMD) to elevate cell permeability. Furthermore, this co-delivery led to a reduction in the IC_{50} value of gemcitabine, and in vivo, it caused a decrease in tumor growth and volume and enhanced blood perfusion in xenograft models (Lin et al., 2018). Since miR-21 functions as an oncogene in cancer chemotherapy, its delivery by GNPs has been tried in various studies (Ren et al., 2016). Upregulation of miR-21–5p leads to down-regulation of PTEN and TIMP3 and induces doxorubicin resistance in gastric cancer (Chen et al., 2018a). Silencing miR-21 inhibits prostate tumor cell growth and increases doxorubicin sensitivity (Zhao et al., 2021). Therefore, miR-21 inhibitor delivery by nanostructures and their combination with doxorubicin improve the potential of cancer chemotherapy (Raniolo et al., 2021). In NIR-responsive hollow GNPs, both doxorubicin and miR-21 inhibitor have been loaded, and at the first step, the release of miR-21 inhibitor occurs to enhance drug sensitivity, and then NIR leads to the collapse of GNPs to release doxorubicin in effective cancer chemotherapy. This co-delivery exerts synergistic impact and promotes antitumor capacity by 50-fold. Moreover, upon intravenous administration of cargo-loaded hollow GNPs, they accumulated at the tumor site and reduced tumor progression (Fig. 6) (Ren et al., 2016). Therefore, co-delivery of miRNAs and chemotherapy agents by GNPs is beneficial in cancer therapy, and one of the limitations is the lack of significant focus on the molecular pathways that are affected after this co-delivery in cancer chemotherapy.

Although GNPs have shown good efficacy in miRNA delivery, most emphasis in experiments is on the co-delivery of siRNA and

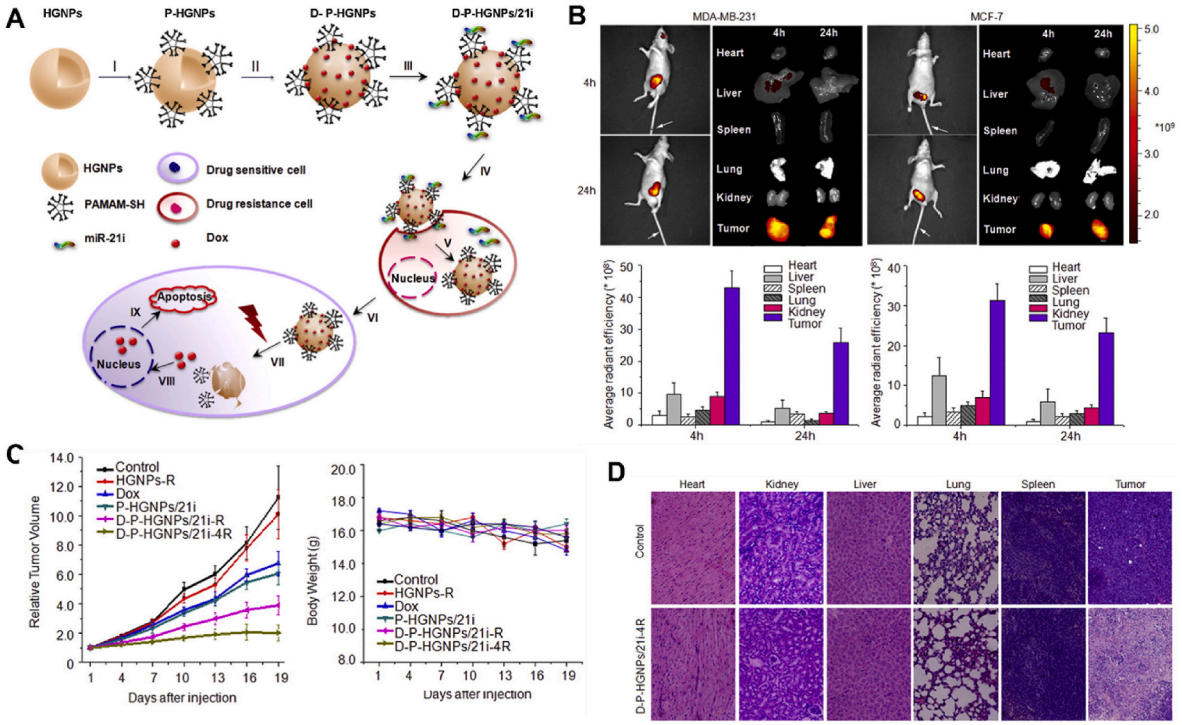

Fig. 6. A) The synthesis of nanoparticles and their mechanism of action upon entrance into tumor cells, B) Antitumor activity in vivo in animal model, C) Tumor volume and weight upon administration of nanoparticles, D) Histopathological profile of tissues. Reprinted with permission from Elsevier (Ren et al., 2016).

chemotherapy agents in cancer therapy. STAT3 pathway has been considered oncogenic in various human cancers due to its function in modulating proliferation, metastasis, and therapy response as well as its potential in interaction with other pathways (Garg et al., 2021; Ashrafizadeh et al., 2020e). Targeting STAT3 with nanoparticles has been shown to be beneficial in cancer therapy. On the other hand, STAT3 plays a significant role in melanoma progression, and its inhibition by luteolin can enhance melanoma suppression (Li et al., 2022). Furthermore, STAT3 increases glycolysis in melanoma via upregulation of PKM2 (Zhang et al., 2022). An experiment has focused on the co-delivery of STAT3-siRNA and imatinib in melanoma therapy. This co-delivery by GNPs decreased protein levels of STAT3 to impair tumorigenesis in melanoma, and based on in vivo results, it significantly reduced tumor weight and volume (Labala et al., 2017). However, focus has been placed on the co-delivery of doxorubicin and siRNA by GNPs in cancer therapy. The reason is the high popularity of doxorubicin in cancer chemotherapy, and its action mechanism is based on topoisomerase II suppression to reduce DNA replication. However, due to the presence of doxorubicin resistance, interest has been directed towards using nanoparticles for the delivery of doxorubicin in cancer suppression. The octreotide-conjugated gold nanorods have been applied for the co-delivery of doxorubicin and siRNA in effective cancer therapy, and in addition to demonstrating uniform size distribution, these nanostructures also demonstrate pH-sensitive release of cargo. The conjugation with octreotide enhances the internalization of gold nanorods in tumor cells, and they suppress proliferation (Xiao et al., 2012).

Doxorubicin is a popular agent in pancreatic cancer therapy, but since resistance has been developed, there have been attempts to increase drug sensitivity. Autophagy inhibition by danthron impairs pancreatic cancer progression and elevates doxorubicin sensitivity (Chen et al., 2019). Moreover, deguelin has been associated with autophagy inhibition and enhanced doxorubicin sensitivity (Xu et al., 2017). One of the promising strategies is the combination of siRNA and doxorubicin and delivery by GNPs in pancreatic cancer therapy. Gold nanorods have been utilized in the co-delivery of doxorubicin and siRNA in pancreatic cancer chemotherapy, and exposure to 665 nm light leads to reducing tumor growth by 90%. Moreover, co-delivery by gold nanorods leads to down-regulation of K-Ras to induce cycle arrest in pancreatic tumor cells and by combining gene-/chemo-therapy, it decreases tumor progression (Yin et al., 2015). These studies highlight the fact that when it comes to understanding the biological mechanisms involved in increasing the progression of tumor cells and decreasing the potential of chemotherapy, siRNA and co-delivery with antitumor compounds can provide promising results in cancer therapy, such as what has been observed in the delivery of EGFP-siRNA and erB2-siRNA with doxorubicin using GNPs in cancer therapy (Kotcherlakota et al., 2017; Kumar et al., 2017). Fig. 7 provides a summary of gene and drug co-delivery by GNPs in cancer therapy.

6.3. Combined phototherapy and chemotherapy

Phototherapy is the use of light as a tool to halt tumor cell progression. Phototherapy is categorized into two groups, including photothermal therapy (PTT) and photodynamic therapy (PDT), that have their own distinct features (Zhen et al., 2019; Thangudu and Su, 2021; Jan et al., 2022). Phototherapy, as a minimally invasive therapeutic

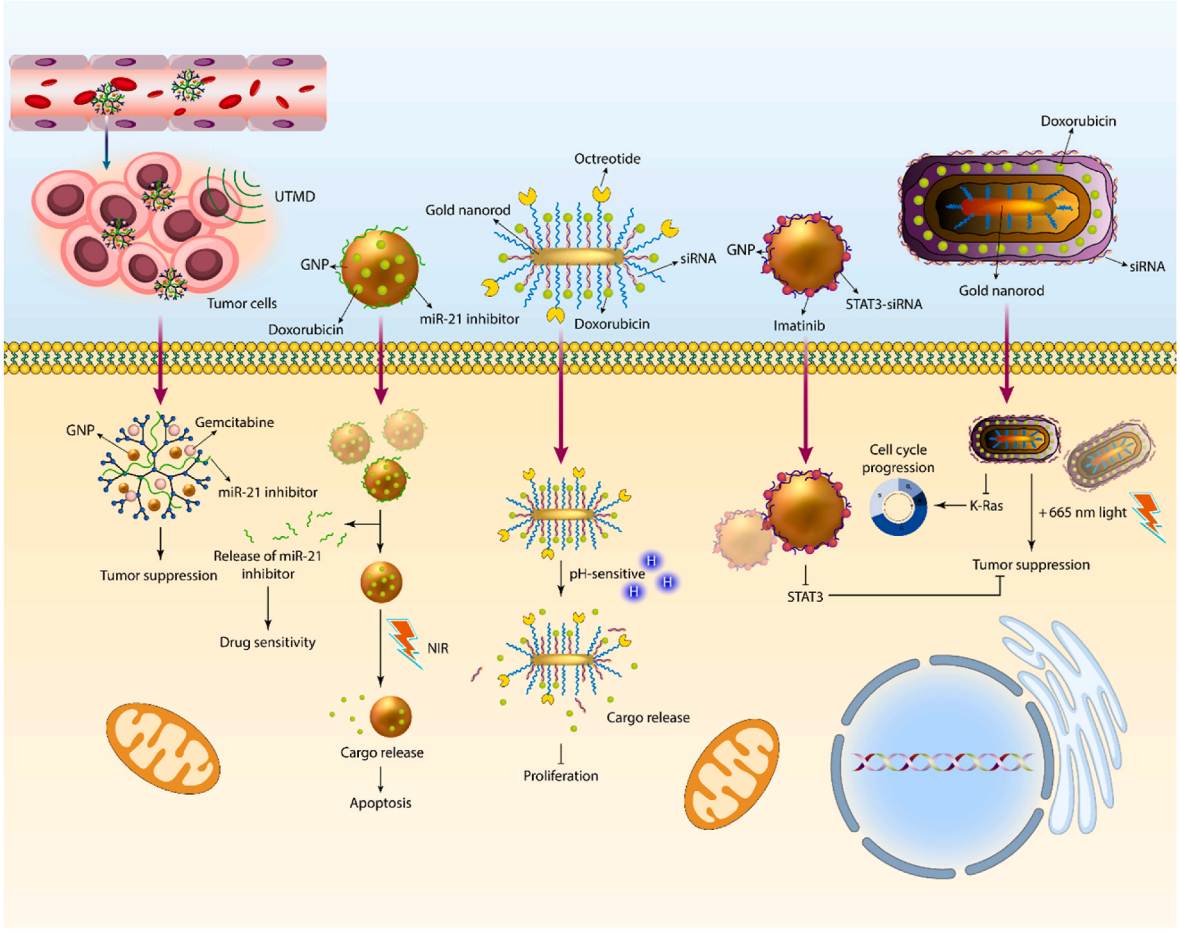

Fig. 7. The ability of GNPs in co-delivery of drugs and genes in cancer therapy. The genes can be degraded by enzymes during bloodstream circulation, but by loading in GNPs, they can be protected, and they regulate gene expression levels with high efficiency.

approach, focuses on the use of photo-responsive factors to apply irradiation for the elimination of tumor cells with minimal side effects on normal and healthy tissues (Luo et al., 2016). The functions of PDT and PTT in triggering cancer cell death are a little different. In PTT, a photo-absorbing compound is utilized that, under NIR irradiation, causes heat generation and induces tumor ablation (Jiang et al., 2018). In PDT, the used photosensitizers generate reactive oxygen species (ROS) under a specific wavelength that can be utilized for oxidizing biomolecules and suppressing tumor progression (Xu et al., 2017; Lucky et al., 2015; Shen et al., 2016). The current section aims to accelerate cancer chemotherapy by using GNP-mediated PDT and PTT (Fig. 8). A question may come into mind: if the problem related to lack of specific delivery and low accumulation of tumor cells in cancer tissues can be solved using nanostructures, what is the necessity of using PDT or PTT along with nanoparticle-mediated chemotherapy? The answer is similar to the goal of co-delivery of drugs and genes in cancer therapy in that a combination of chemotherapy and phototherapy can improve the potential of cancer therapy. For instance, paclitaxel is one of the chemotherapeutic agents used in cancer therapy. However, increasing evidence has revealed that dysregulation of molecular mechanisms can lead to the development of paclitaxel resistance in tumor cells (Wang et al., 2022a; Ren et al., 2022; Wu et al., 2022). For increasing the potential of paclitaxel in cancer therapy, paclitaxel-loaded GNPs were first prepared, and then they were modified with a polydopamine layer to increase their stability. The resulting nanocarriers demonstrated high biocompatibility and cellular uptake, and they were able to induce apoptosis and decrease the expression level of P-gp. Moreover, exposure to NIR irradiation led to the release of paclitaxel, and by providing PTT, it caused mitochondrial damage, oxidative stress, DNA injury, and upregulation of pro-apoptotic proteins including caspase-3, p53, and Bax, accelerating tumor suppression (Zhan et al., 2022). It appears that when modification of GNPs is performed, their selectivity towards tumor cells is enhanced, which is beneficial for the purposes of PTT and chemotherapy. The CD44-targeted GNPs have been prepared for the delivery of doxorubicin in breast cancer therapy and provide PTT with a particle size of 71.34 nm. The process of loading doxorubicin in GNPs was performed via electrostatic interaction with an entrapment efficiency of 75%, and after exposure to 808 nm irradiation, it caused PTT that exerted synergistic impact with chemotherapy in ROS production, apoptosis induction, and providing tumor ablation (Kalyane et al., 2022). Surprisingly, the findings are not limited to in vitro experiments; in vivo studies have revealed that using GNPs for combination photo- and chemotherapy is important in cancer therapy (Yang et al., 2022).

However, the use of nanoparticles is more than the simple delivery of chemotherapy agents in cancer therapy, and nanostructures can be used for suppressing the progression of drug-resistant tumor cells (Choe et al., 2021). Yolk-shell-structured nanoparticles possess a unique yolk-void-shell configuration and display important characteristics such as low density, a large surface area, good loading ability, and hollow outer shells (Purbia and Paria, 2015). In a recent effort,

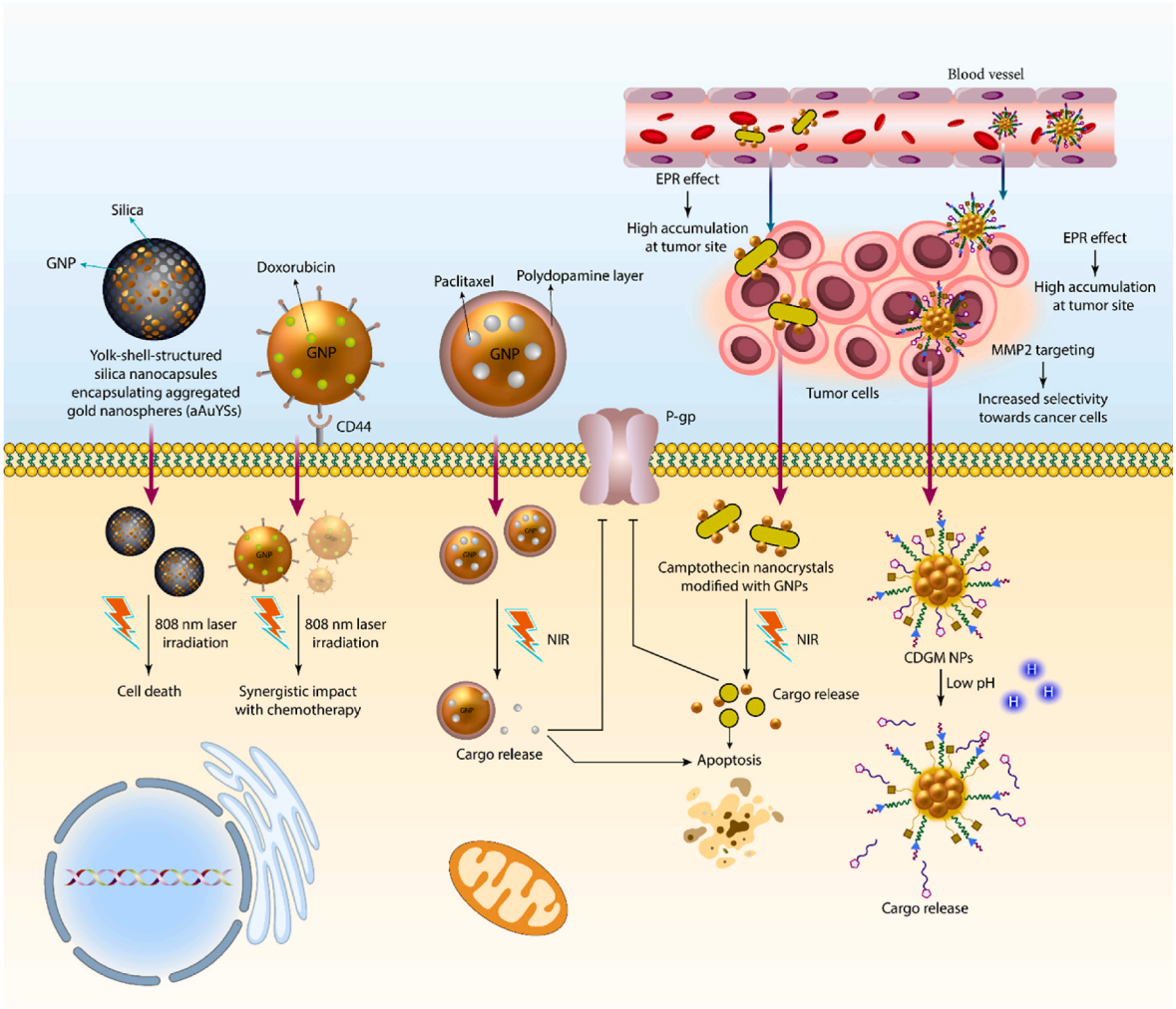

Fig. 8. The use of GNPs for purpose of PDT and PTT in cancer therapy. Phototherapy has emerged as a new kind of therapy for cancer, and due to the potential of GNPs in absorbing light, they can induce PTT and PDT to promote the potential of chemotherapy in tumor suppression.

yolk-shell-structured silica nanocapsules encapsulating aggregated gold nanospheres (aAuYSs) have been utilized in suppressing the progression of drug-resistant ovarian tumor cells. In the silica interior of aAuYSs, GNPs were loaded, and then they showed absorbance of 808 nm laser irradiation for PTT. The induced cell death in doxorubicin-resistant ovarian tumor cells, as well as further investigation, revealed that these nanostructures, in combination with doxorubicin, can have a synergistic effect in PTT and chemotherapy of ovarian tumors (Choe et al., 2021).

More investigation has revealed that when drug nanocrystals are decorated with GNPs, they can mediate PTT, which is important for overcoming chemoresistance (Wang et al., 2022b). The field of combination therapy has been improved by drug nanocrystals, which have a high surface area that is beneficial for improving the bioavailability of drugs. Moreover, drug nanocrystals are able to trigger the EPR effect, providing passive targeting to cancer sites (Zhou et al., 2016; Zhan et al., 2017). Drug nanocrystals are also beneficial in reversing P-gp-mediated chemoresistance and preventing the efflux of drugs (Da Silva et al., 2017; Wang et al., 2011). In a recent effort, the surface of drug nanocrystals has been modified with GNPs, and in addition to the delivery of camptothecin, they stimulated apoptosis and reduced P-gp expression that is due to the combination of PTT and chemotherapy (Wang et al., 2022b).

According to these studies, it is recommended to use GNPs for the purpose of photo- or chemotherapy to impair the progression of tumor cells and sensitize them to anticancer drugs (Faid et al., 2022; C et al., 2021; He et al., 2022; Huang et al., 2021; Mapanao et al., 2021; Liu et al., 2020; Hou et al., 2019; Yang et al., 2017; Zhu et al., 2018a). Since GNPs possess good PTT efficacy and previous discussions revealed that they are capable of providing targeted delivery of anticancer drugs, future studies may focus on the co-delivery of drugs and genes as well as PTT in cancer therapy, which is known as "photo-/chemo-/gene-therapy of cancer." Moreover, major emphasis is on the role of GNPs in mediating PTT, but there are a few studies showing the role of GNPs in providing PDT in cancer suppression. In an experiment, novel kinds of gold nanoclusters have been developed based on tumor-targeted Ce6-doxorubicin-GNCs-MMP2 polypeptide nanoparticles (CDGM NPs) for providing chemo- and phototherapy. The click chemistry was used for the synthesis of nanostructures, and both Ce6 and doxorubicin were loaded for purposes of PDT and chemotherapy, respectively. Due to the EPR effect, nanostructures demonstrate high accumulation at the tumor site, and modification with polypeptides has also increased their selectivity towards cancer cells. The nanostructures have also been modified with PEG to increase their biocompatibility and blood circulation time. The nanoparticles were pH-sensitive, and exposure to low pH levels can result in cargo release due to the presence of acid-sensitive attachment between doxorubicin and the cis-aconitic anhydride (CA) that is the cis-acontityl linkage. In order to reduce tumorigenesis, these nanoclusters induce both chemotherapy and PDT (Xia et al., 2018). More importantly, GNPs can be used for the purposes of PTT, PDT, and chemotherapy in cancer suppression (Xu et al., 2018). When irradiation with a wavelength of 630 nm occurs, it leads to ROS generation that can suppress tumorigenesis and promote the potential of chemotherapy in cancer therapy (Bhattacharya et al., 2022).

6.4. Stimuli-responsive devices

6.4.1. pH-responsive

The discussion in previous sections revealed that GNPs are promising candidates for cancer chemotherapy by mediating targeted delivery, providing a platform for co-delivery, and triggering PTT and PDT. The use of smart nanocarriers in tumor suppression is one of the most recent advances in cancer therapy. The smart nanostructures can be responsive to endogenous or exogenous stimuli, and one of them is pH. The tumor microenvironment has an acidic pH that is due to glycolysis and the high proliferation of cancer cells, while the pH in normal and healthy tissues is near 7.4. Therefore, if linkages and bonds in GNPs can be degraded at a pH level near the tumor microenvironment, they can release cargo in response to pH, thereby providing targeted cancer therapy. In an experiment, GNPs were fabricated that were able to selectively target angiogenic endothelial cells through the identification of αvβ3 and folate for increasing cellular uptake in tumor cells. The conjugation of doxorubicin on the surface of GNPs was conducted by a hydrazone bond that is pH-sensitive. In response to acidic pH, these GNPs release doxorubicin, and upon exposure to NIR irradiation, it causes PTT that is beneficial for apoptosis induction, angiogenesis inhibition, and proliferation suppression in melanoma (Wang et al., 2019). It appears that the ability of nanostructures to respond to specific features of tumor microenvironment is critical for achieving desirable drug delivery (Wang et al., 2017; Luo et al., 2017; Bigham et al., 2022). When nanostructures respond to pH-level of tumor microenvironment, the process of drug delivery can be improved (Prescott et al., 2000). There are a number of acid-responsive linkages, including hydrozone bond (Prabaharan et al., 2009; Yuan et al., 2010), benzoic imine bond (Deng et al., 2015; Zeng et al., 2017), and cis-acontityl linkage (Srinophakun and Boonmee, 2011; Zhu et al., 2010) that render the characteristic of pH-responsiveness to nanocarriers. It has been reported that conjugation of doxorubicin to surface of dendrimers can lead to pH-sensitive features due to the presence of cis-acontityl linkage (Kratz et al., 2002; Di Stefano et al., 2004). In an experiment, PAMAM dendrimers were functionalized with folic acid, and then doxorubicin was conjugated to the dendrimers via cis-acontityl bond. At the next step, the prepared doxorubicin dendrimers were entrapped by GNPs. The Au core size was 2.8 nm, and they showed high stability. Due to presence of cis-acontityl linkage, the nanostructures released doxorubicin in a pH-sensitive manner, which led to site-specific drug release and effective cancer therapy (Fig. 9) (Zhu et al., 2018b).

In the previous section, it was discussed that GNPs can be used for PTT and PDT. Now, there has been effort put into developing GNPs that demonstrate PTT impact and pH-responsive function. Doxorubicin has been conjugated to gold nanorods via a hydrazone bond that is pH-sensitive and can release the drug in the tumor microenvironment. The doxorubicin-loaded gold nanorods internalize in HepG2 cells via endocytosis, and after exposure to NIR irradiation (808 nm wavelength), they cause PTT along with chemotherapy in cancer suppression (Chen et al., 2018b). Metal-organic frameworks (MOFs) are considered porous materials that can be utilized for the encapsulation of drugs, fluorescent molecules, and nanostructures (Chalati et al., 2011; Della Rocca and Lin, 2010, 2010deKrafft et al., 2009; Eddaoudi et al., 2002; Govindaraju et al., 2018; Luo et al., 2018). In an experiment, doxorubicin-loaded, ZIF-8-encapsulated GNPs were prepared as pH-sensitive nanocarriers for cancer therapy. Due to loading into ZIF-8, doxorubicin and GNPs did not show release in neutral medium and prevented toxicity in normal cells. Importantly, exposure of ZIF-8 to low pH levels causes the release of GNPs and DOX that cause PDT and chemotherapy, respectively (Zhang et al., 2020c). Another critical aspect is the creation of hybrid nanocarriers with properties of two nanostructures. In a recent approach, a micelle-GNP hybrid nanosystem was developed for doxorubicin delivery with an encapsulation efficiency of 41–61% that caused drug release at acidic pH levels, and both in vitro and in vivo experiments highlighted the function of this hybrid nanosystem in cancer therapy (Lin et al., 2017). Therefore, pH-sensitive GNPs are highly recommended for drug delivery and cancer suppression.

6.4.2. Redox-responsive

Overall, nanobiotechnology is a growing field that aims at improving drug delivery, gene therapy, and tumor imaging (Liu et al., 2007; Dizaj et al., 2014). When nanoparticles are applied for the purpose of drug delivery, they are beneficial in protecting the entrapped drug and can result in prolonged drug release with low adverse impacts (Kumaraswamy et al., 2014; Kissling et al., 2016; Nosrati et al., 2022b). Recently, precision medicine has been a hot topic, and it aims to develop

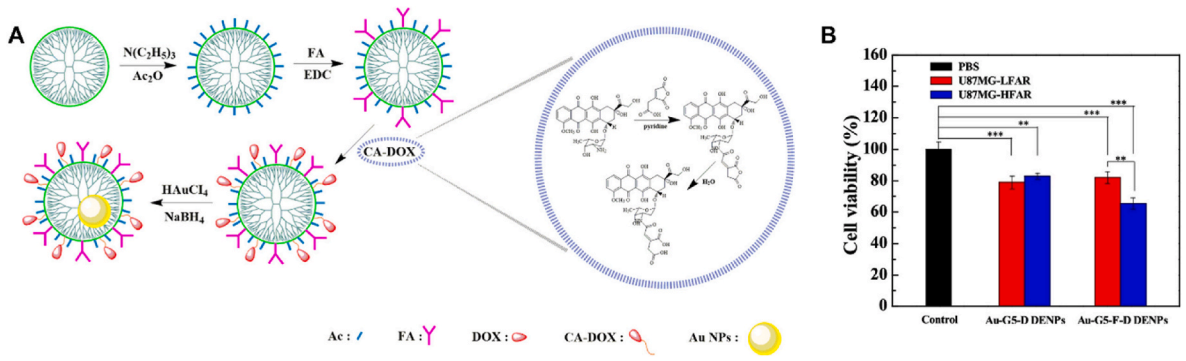

Fig. 9. A-C) The synthesis mechanism of nanoparticles and their mechanism of action in response to light for purpose of cancer therapy. Reprinted with permission from ACS (Zhu et al., 2018b).

nanobiomaterials for therapeutic and diagnostic purposes (Lu et al., 2018). Therefore, exploitation of unique tumor microenvironment features can help in providing effective stimulus-responsive nanocarriers. In addition to pH, the redox imbalance present in tumor microenvironment can be utilized for the development of stimulus-responsive nanocarriers, and it has been reported that DM1-doped porous gold nanoshells can be used for redox-sensitive delivery of antitumor drugs in breast cancer therapy. The resulting nanostructures had a particle size of 78.6 nm, and they showed good colloidal stability with pH-sensitive drug release. The decoration of gold nanoshells was performed with

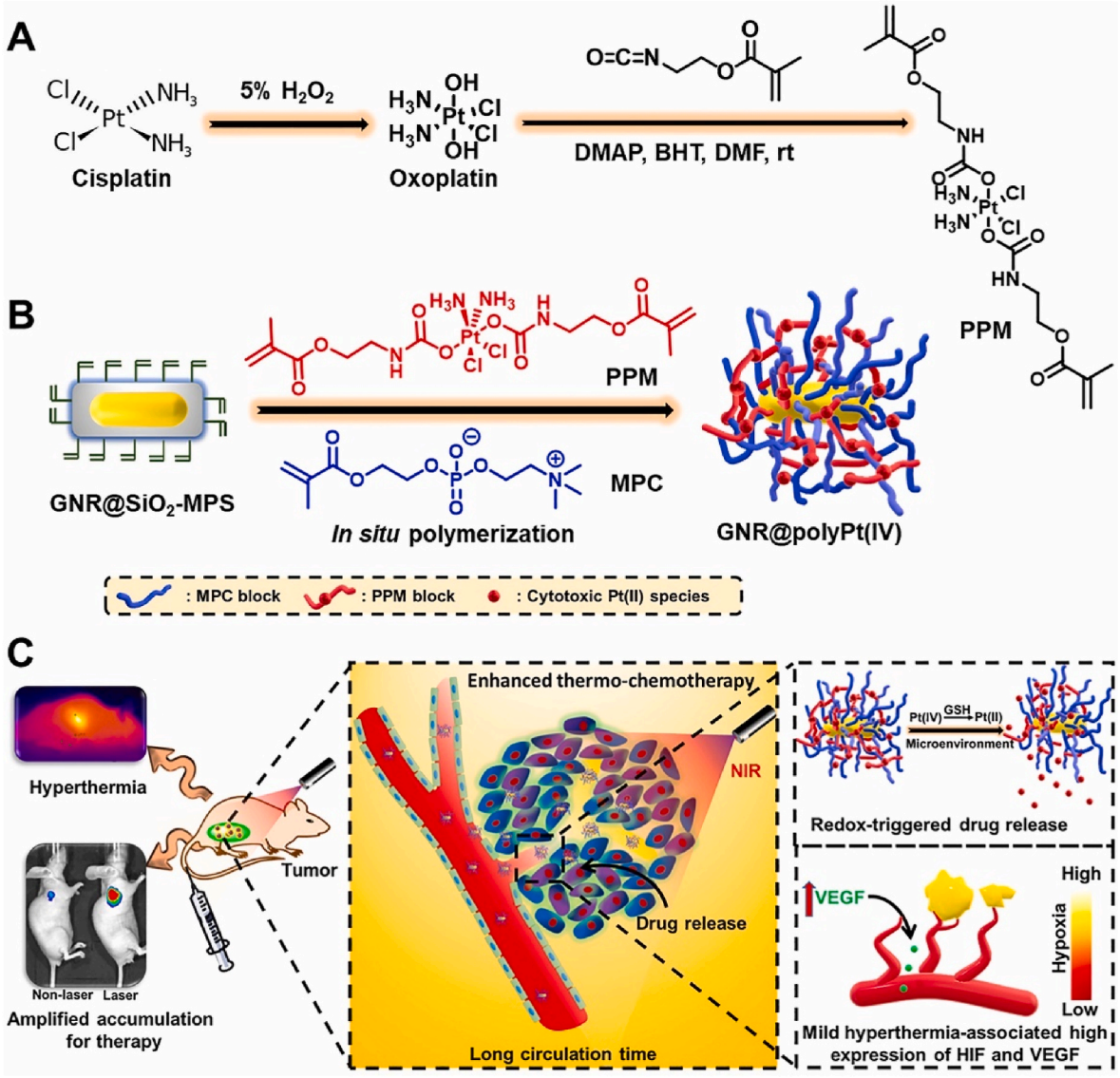

Fig. 10. A) Synthesis nanoparticles, B) the viability of cancer cells after exposure to nanostructures. Reprinted with permission from Elsevier (Guo et al., 2021).

mPEG and trastuzumab; the latter is for providing selective delivery by binding to the HER2 receptor. The nanocarriers were able to stimulate apoptotic cell death due to tubulin stimulation, caspase-3 activation, and HSP70 down-regulation. Moreover, nanostructures demonstrated inhibition of M2 macrophages and suppressed the metastasis of breast tumor cells (Xu et al., 2021b). In another effort, in-situ polymerized polyplatinum (IV)-coated gold nanorods have been designed that release cargo in response to redox state, and they demonstrated improved cancer site accumulation after systemic administration, leading to effective cancer chemotherapy and phototherapy (Fig. 10) (Guo et al., 2021).

6.4.3. *Multifunctional*

The light-responsive GNPs were discussed in the section on phototherapy (section 5.4). One of the advances in the development of smart nanostructures is the combination of some stimuli to increase the potential of cancer therapy. In one approach, two endogenous stimuli can be combined for the development of smart GNPs. Redox- and pH-sensitive GNPs have been developed as smart nanoplatforms for the delivery of doxorubicin, methotrexate, and 6-mercaptopurine with entrapment efficiencies of 37%, 12%, and 49%, respectively, and this loading was performed by ionic interaction. Furthermore, the cytotoxicity results demonstrated the high anticancer activity of these nanostructures (Ghorbani and Hamishehkar, 2017). In another approach, pH and light as internal and external stimuli, respectively, can be utilized for the purpose of cancer therapy. The pH and light sensitive GNPs were conjugated with thiolated poly (ethylene glycol)-biotin to increase sensitivity to tumor cells by upregulating the biotin receptor. Then, doxorubicin was conjugated to DNA decorated on the surface of GNPs; this bond is pH-sensitive (pH 5), and in response to irradiation at 808 nm, it can release cargo. The nanomaterials demonstrated high cellular uptake and prevented the efflux of drugs in drug-resistant tumor cells (Zhang et al., 2016). Fig. 11 shows stimuli-responsive GNPs in cancer therapy.

7. Conclusion and remarks

The current review focused on the role of GNPs in cancer chemotherapy. The reason for highlighting this aspect is because therapy failure has been a significant issue in the treatment of cancer patients, and physicians have advocated for the development of innovative strategies to overcome chemoresistance. The existence of MDT has led to the development of chemoresistance to several antitumor compounds; consequently, the introduction of new anticancer medications will not be of much assistance, since cancer cells can acquire resistance again. This paper focuses on the use of GNPs for the delivery of chemotherapy drugs in cancer therapy. One of the most significant advantages of GNPs is their ability to provide a platform for drug co-delivery as well as drug and gene co-delivery. At the first approach, two types of antitumor compounds with different modes of action are loaded into GNPs, and then these nanoparticles then facilitate their co-delivery to inhibit the growth of tumor cells. Next, a molecular pathway that is responsible for drug resistance development, such as STAT3, is selected, and then its suppression by gene delivery can increase sensitivity to chemotherapy. However, because GNPs have poor biocompatibility, there has been an effort to improve their safety by using nature-derived materials, and some agents, such as chitosan, have been used for this purpose, which not only increase biocompatibility but also enhance cytotoxicity towards tumor cells. Moreover, when GNPs are modified with compounds such as hyaluronic acid or folate, their selectivity towards tumor cells increases, hence enhancing the cytotoxicity of these nanostructures. Since GNPs are able to absorb the irradiation, they can be used for PTT and PDT; in PTT, they generate heat by increasing the drug sensitivity of tumor cells, and in PDT, they increase ROS generation by mediating cell death. Moreover, smart GNPs, including light-, redox-, pH-, and multi-responsive nanostructures, have been developed for the purpose of cancer therapy and targeted delivery of chemotherapy agents that improve accumulation at the tumor site. Since these discussions approve the functionality of GNPs in cancer therapy, future studies can focus on clinical translation and improving the survival rate of cancer patients.

The cancer therapy field requires combination of different disciplines to obtain an outcome that is satisfactory for cancer patients. The current

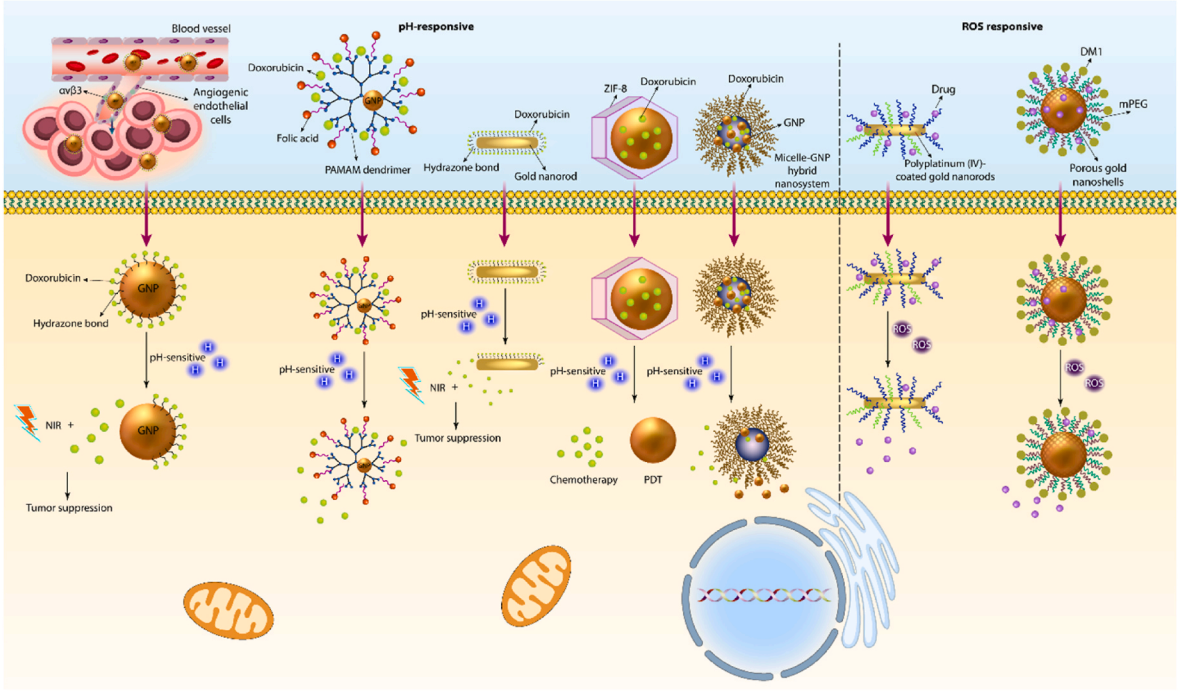

Fig. 11. Development of smart GNPs for cancer therapy. The multifunctional GNPs can be responsive to pH, redox and light to mediate site-specific delivery of drugs in cancer chemotherapy.

manuscript did not focus on a certain type of cancer, but it proposed some methods and strategies that can be used for all cancers, regardless of their kinds. One of the main reasons for choosing GNPs for cancer therapy is that such nanostructures have intrinsic cytotoxicity against tumor cells. Hence, when they are applied along with drugs in cancer therapy, it can lead to a synergistic impact. However, conventional GNPs are no longer a hot spot for cancer therapy since multifunctional, smart and targeted kinds of GNPs have been introduced and designed. Each cancer type may demonstrate upregulation of some of the specific receptors on its surface, such as folate receptor, CD44 and others. Therefore, conventional GNPs should be modified with ligands targeting such receptors in cancer therapy to enhance internalization. This approach is highly suggested during cancer chemotherapy, as chemotherapy drugs have side effects on normal cells and tissues, and when their targeted delivery is provided, their side effects reduce. However, the clinical application of GNPs still requires much investigation. This is due to some toxicological studies showing that GNPs may display toxicity on normal cells, and therefore, modification with natural and biopolymers to improve their biocompatibility is recommended.

After the introduction of combination cancer therapy, there was a hope that therapy failure in cancer patients would be solved. Although combination cancer therapy brought much hope to the treatment of patients, it was found that there is still a need for progress in this therapy and that its benefits for the treatment of cancer patients can be improved. The concept of nanomedicine is that it can improve the potential of both monotherapy and poly-chemotherapy in cancer suppression. Therefore, even if combination cancer therapy has promising results, its efficacy can be improved by loading it on nanoplatforms such as GNPs. In addition, GNPs can mediate the co-delivery of drugs or drug/gene combinations in cancer therapy. Another important aspect of GNPs is that, due to their ability to absorb light, they can mediate PDT and PTT in combination cancer therapy. All of these discussions are in line with the benefits of using GNPs in cancer therapy, and again, their clinical application still requires improving their biocompatibility.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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