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Review

Therapeutic Efficacy of Platinum Based Medicines Combined with Various Nanoparticles in the Treatment of Colorectal Cancer: A Comprehensive Review

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Abstract

Colorectal cancer continues to be a major cancer that affects patients in terms of morbidity and mortality. Chemotherapy using cisplatin, oxaliplatin among others based with platinum have remained the mainstay in the treatment of diverse cancer including the colorectal cancer. However, these treatments are not very effective because of drug resistance, systemic toxicity, and low selectivity. The advances in nanotechnology in the past years presented nanoparticles as potential drug delivery systems which provide sharp targeting, minimum toxicity and better therapeutic efficacy. This review aims at discussing how platinum-based drugs can complement nanoparticles, for example liposomes, dendrimers and gold nanoparticles for colorectal cancer treatment. This review, discussed how nanoparticles can improve the effectiveness of platinum drugs; present sample findings from preclinical and clinical research; and analyze the perspectives of such combinations for the current therapy shortcomings overcoming. Furthermore, authors have looked at the prospects and challenges of this relatively young branch of research and discuss the opportunities that can lie in personalized medicine concepts, as well as the further evolution of nanoparticles. The purpose of this review is to enhance the current knowledge of platinum-nanoparticle combinations and to outline its future directions for colorectal cancer treatment.

1. Introduction

Colorectal Cancer (CRC) has been one of the most famous cancers globally, where it stands as the third most common cancer and the second most common cause of cancer-related deaths among individuals [1]. According to Australian and international projections it is anticipated that more than 1.9 million new cases and 935,000 deaths, indicating that this disease has a high impact on patients and healthcare systems [2]. CRC is usually a consequence of the progression of adenomatous polyps located in the colon or rectum; it depends on genetic factors, risk factors causing changes in adenomatous polyps, and lifestyle factors [3]. However, the survival rate of patients with late-stage CRC still remains low even with the help of improved diagnosis and treatment activities, making the development of better therapeutic approaches a critical necessity [3]. Conventional treatment modalities like surgeries, radiotherapy, and chemotherapy have poor efficacy in metastatic disease, and therefore, researchers have sought to understand new and better therapeutic regimens [4].

Platinum-based chemotherapy remains a cardinal modality in oncology, with colorectal cancer among the affected diseases [5]. Cisplatin, carboplatin and oxaliplatin belong to this category and their mechanism of action involves the formation of DNA adducts that hinder the replication and transcription of cancerous cells, thereby causing cell death [6]. Nevertheless, despite its efficacy, platinum-based drugs have some drawbacks i.e severe toxic effects like nephrotoxicity, neurotoxicity, and hematological toxicity and the development of drug-resistant tumours gradually [7]. These side effects are usually due to this element, as it limits the amount of the drug that can be given and the overall effectiveness thereby lowering the therapeutic value [6,7]. Consequently, there is a rising demand for effective approaches for improving the efficacy of platinum-based agents without increasing toxic side effects [6].

The advancement of conventional chemotherapy is a recent development acknowledged to have some drawbacks and has led to the discovery of nanotechnology as an effective treatment of cancer through platinum-based drugs [4]. Nanoparticles (Np), which are particles with a size ranging from 1 to 100 nanometers, can be designed to transport drugs straight to the tumour site; this means that the concentration of the therapeutic agent is much higher at the targeted region and thus minimizes the effect on other tissues in the body [8]. Such a targeted delivery can lead to lowering the overall toxicity of the chemotherapeutic agents and enhance the therapeutic index [9]. Liposomes, dendrimers, polymeric nanoparticles, and inorganic NPs, including gold and silver particles, are some of the nanoparticles that have been used to investigate their ability to improve the efficiency of platinum drugs in cancer therapy [10]. These nanoparticles can be stimuli-responsive, meaning they can be programmed to respond to certain signals within the tumour microenvironment including pH or enzymes; this would ensure that the drug

release is controlled and sustained, thus enhancing the disease-combating value of the drug [11].

The integration of platinum-based drugs and nanoparticles in the treatment of colorectal cancer is another area of interest that has not been fully explored but holds a lot of potential [12]). Through the utilization of the properties of nanoparticles for instance, increased drug solubility, stability and bioavailability, researchers have come up with formulations which not only facilitate the delivery of platinum drugs but also help in reducing the toxic side effects of the same [4,5]. For instance, it has been observed that cisplatin encapsulated in liposomes, displayed less nephrotoxic effects in preclinical research when compared to its free form while retaining the corresponding anticancer effect [6]. Similarly, the literature reviews established that gold nanoparticles can enhance the radiosensitization effect and drug delivery utility, which in combination with platinum-based chemotherapeutic agents, increases the antitumor potential in cancer cells [8]. The developments are creating new opportunities for improved and safer cancer interventions, especially for patients with metastatic colorectal cancer [7].

The following paper presents a comprehensive literature review to investigate the therapeutic outcome of using platinum-based drugs with different nanocarriers in colorectal cancer [13]. It will present a detailed review of how nanoparticles improve the uptake and efficacy of platinum drugs, present the contemporary advances in the preclinical and clinical research in this field, and outline the potential difficulties and the prospects of the new drug combinations [13]. The review will also explain how nanoparticles can help to overcome drug resistance and reduce toxicity, which are two key determinants of the applicability of platinum-based treatments [14]. Thus, as this review aims to integrate the key findings of the recent literature on the effectiveness of the combined therapies, the author expects to provide relevant insights into the effect of these interventions for individuals diagnosed with colorectal cancer that may inform the advancement of personalized and precision medicine in oncology practice [15].

Nanoparticles specifically affected the performance of platinum-based drugs, it's important to explain the mechanisms through which nanoparticles enhance drug delivery, reduce toxicity, and improve therapeutic outcomes. Below is an enhanced explanation of how nanoparticles impact platinum-based drug performance [Table 1 and Figure 1].

Table 1. Summary of studies on platinum-based medicines combined with nanoparticles

Nanoparticles Used	Platinum Drugs	Key Findings	References
Various nanoparticles (liposomes, dendrimers, gold)	Cisplatin, carboplatin, oxaliplatin	Nanoparticles enhance drug delivery, reduce toxicity, and overcome resistance.	Buyana et al. (2022)[1]
Solid lipid nanoparticles, liposomes, polysaccharides, proteins, silica nanoparticles, metal nanoparticles, synthetic polymers	Oxaliplatin	Different carriers improve efficacy and reduce side effects of oxaliplatin.	Mahaki et al. (2023)[2]
Platinum (II) prodrug nanoparticles	Cisplatin hydrate	Synergistic effect with platinum prodrug improves breast cancer treatment.	Yang et al. (2020)[6]
Gold nanoparticles	Gold(I) derivatives as an alternative to platinum	Gold nanoparticles show potential as an alternative due to reduced side effects.	Shi L et al (2016) [9]
Polymeric nanoparticles	Platinum drugs combined with other therapeutic agents	Nanoparticles improve pharmacokinetics and tumour targeting, enhancing efficacy.	Deng et al. (2020)[3]
Matrix metalloproteinase-2 (MMP-2) responsive nanoparticles	Camptothecin and sorafenib	MMP-2 responsive nanoparticles show higher efficacy than single agents.	Shi et al. (2016)[9]
PEG-PLGA based nanoparticles	Sorafenib and PEDF	Combination nanoparticles enhance anti-tumor effects with low toxicity.	Chen et al. (2019)[10]
N, O-carboxymethyl chitosan nanoparticles	Oxaliplatin and resveratrol	Combined nanoparticles exhibit stronger anti-cancer activity than free drugs.	Wang et al. (2021)[11]
Mesoporous platinum nanoparticles	Doxorubicin and platinum drugs	Mesoporous nanoparticles integrate chemo and photothermal therapy for enhanced effect.	Fu et al. (2020)[12]
PEGylated lipid nanoparticles	Oxaliplatin and folinic acid	Combination nanoparticles achieve synergistic chemo-immunotherapy in colorectal cancer.	Guo et al. (2020)[5]

1. Improved Solubility and Stability: Platinum-based drugs, like cisplatin, often suffer from poor solubility, which limits their bioavailability. Nanoparticles can encapsulate these drugs, improving their solubility and stability in the bloodstream, ensuring they remain active for longer periods.

2. Targeted Delivery: One of the primary advantages of nanoparticles is their ability to be functionalized with targeting ligands or antibodies, which guide the drug directly to cancer cells, minimizing the impact on healthy tissues..

3. Controlled Release: Nanoparticles can be engineered to release the encapsulated platinum-based drugs in a controlled manner. This sustained release ensures that therapeutic drug concentrations are maintained at the tumor site over an extended period, enhancing efficacy and reducing the need for frequent dosing. This also helps mitigate the peak-dose toxicity often seen with traditional chemotherapy.

4. Overcoming Drug Resistance: Cancer cells can develop resistance to platinum-based drugs like cisplatin. Nanoparticles help bypass some of these resistance mechanisms like enhanced drug efflux or DNA repair in cancer cells. By improving drug penetration and ensuring consistent drug levels at the tumor site, nanoparticles can help maintain the effectiveness of platinum drugs even in resistant tumors.

By incorporating these specific mechanisms, it becomes clearer how nanoparticles are actively enhancing the performance of platinum-based drugs.

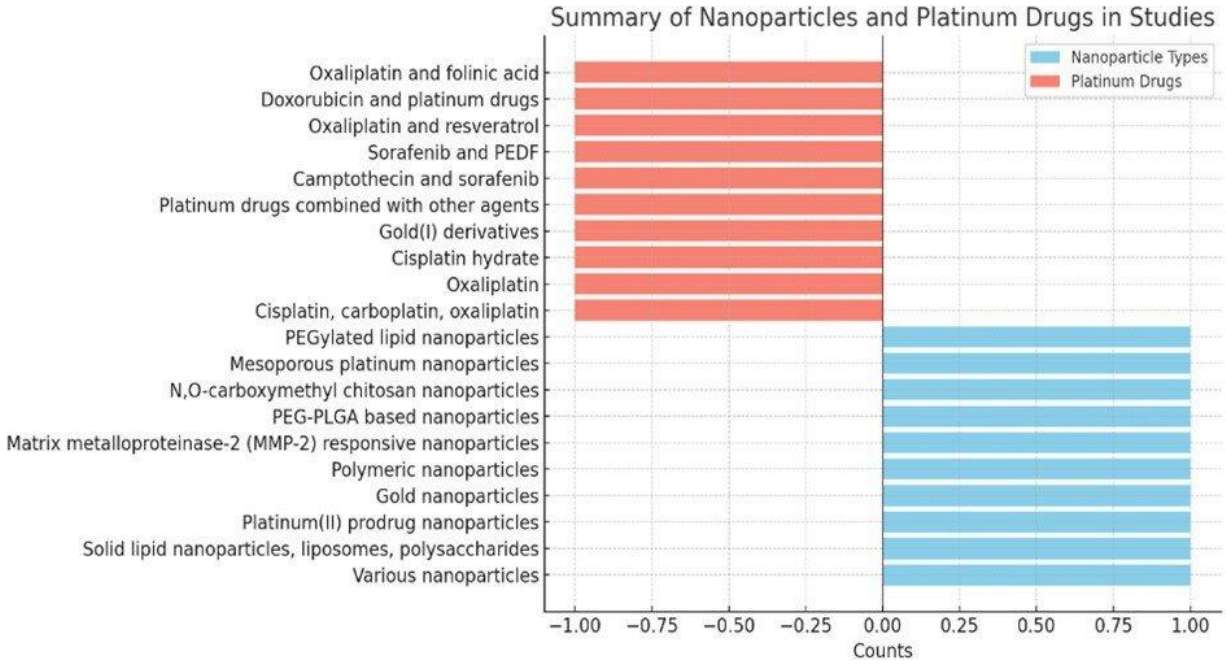

Figure 1. Summary of nanoparticles and platinum drugs in studies presented in Table 1.

2. Lysosomal Sequestration of Chemotherapeutic Drugs

A significant challenge in cancer chemotherapy, particularly with platinum-based drugs, is the ability of cancer cells to evade drug-induced cell death. One mechanism through which this resistance is mediated is lysosomal sequestration, where cancer cells trap chemotherapeutic agents within their lysosomes, preventing them from reaching their target sites, of nucleus or mitochondria. Lysosomes are acidic organelles responsible for degrading and recycling cellular components, but in cancer cells, their role is expanded to contribute to drug resistance [3]. Platinum-based chemotherapeutic agents like cisplatin, carboplatin, and oxaliplatin are commonly used to treat colorectal cancer and other solid tumors. These drugs typically function by forming DNA adducts that interfere with DNA replication and transcription, leading to cell cycle arrest and apoptosis. However, in many cancer cells, these drugs are sequestered in the lysosomes, particularly because they are hydrophobic or weakly basic. Lysosomal sequestration occurs due to the acidic pH of the organelle, which traps basic drugs, preventing them from accessing their primary targets-the nucleus and the DNA within it. This process leads to reduced therapeutic efficacy, allowing cancer cells to evade the cytotoxic effects of chemotherapy [6].

Mechanistically, lysosomal sequestration involves several factors. The acidic environment of the lysosome facilitates the ion trapping of weakly basic drugs. Additionally, cancer cells may overexpress lysosomal-associated membrane proteins (LAMPs), which can further assist in the uptake and sequestration of drugs into lysosomes [8]. This process is compounded by alterations in lysosomal pH and the presence of drug efflux transporters that pump the drug into the lysosome or out of the cytoplasm entirely. Once sequestered, the drugs are effectively isolated from their intended molecular targets, allowing the cancer cells to survive despite high intracellular concentrations of the chemotherapeutic agents. Lysosomal sequestration also

plays a significant role in multidrug resistance (MDR), a condition where cancer cells become resistant to a broad range of chemotherapeutic agents. The sequestration of drugs like cisplatin inside lysosomes not only reduces their cytotoxic potential but also limits the amount of drug available to kill the cancer cells, leading to relapse and treatment failure. This mechanism is one of the many ways cancer cells adapt to survive under chemotherapeutic pressure, contributing to the overall challenge of treating aggressive cancers like colorectal cancer [13-15].

To counteract the effect of lysosomal sequestration, recent research has focused on the use of nanoparticle-based drug delivery systems. Nanoparticles can be engineered to bypass lysosomal uptake or release their drug cargo before the drugs enter the lysosomal compartments. For example, nanoparticles can release platinum drugs directly into the cytoplasm or near the target organelles, avoiding entrapment in lysosomes. Additionally, nanoparticles can be designed with pH-responsive coatings that trigger drug release only when they reach the tumor microenvironment, further enhancing their therapeutic efficacy. The lysosomal sequestration of platinum-based drugs represents a major hurdle in cancer chemotherapy, contributing to drug resistance and reduced treatment outcomes. However, advances in nanotechnology offer promising solutions to overcome this barrier, improving the efficacy of chemotherapeutic agents and offering new hope for the treatment of colorectal cancer and other solid tumors.

3. Mechanism of Action of Platinum-Based Medicines

The platinum-based chemotherapeutic agents, cisplatin, carboplatin, and oxaliplatin, are commonly used in cancer treatments involving CRC. These agents have been found to play a significant role in cancer therapy since they are capable of halting cell division and translation of genetic information, thereby leading to the death of cancer cells. Fluorescence studies of normal and tumour cells indicate that the main effects of these drugs are mediated through the formation of platinum-DNA adducts that interfere with a variety of cellular processes. However, in CRC treatment, the effectiveness of platinum-based drugs is muted due to issues of drug resistance and toxicity which has fueled the search of synergistic therapies especially drug delivery systems [16].

Cisplatin, the first platinum drug, has been shown to interact with cellular DNA to form both intra and interstrand crosslinks that interfere with DNA replication and transcription [15]. They induce several cellular events like activation of DNA repair activity, cell cycle arrest, and apoptosis. However, the cisplatin effectiveness is often compromised by its toxicities, which include nephrotoxicity, neurotoxicity, and ototoxicity and emergence of acquired resistance. Mechanisms of resistance include the following: enhanced DNA repair, decreased drug accumulation and uptake resulting from altered cell membranes and proteins named P-glycoprotein, and inactivation by thiol-containing molecules [17].

The second generation of platinum drugs, carboplatin, was designed to have less toxicity than cisplatin while still being effective in treating tumours [18]. While possessing a comparable mechanism of action with cisplatin, it has a different pharmacokinetics and toxicity, because of the bidentate dicarboxylate ligand, leading to slower DNA binding. However similar to cisplatin, carboplatin also deals with resistance mechanisms and increased drug efflux and improved DNA repair-related activities in cancer cells.

Oxaliplatin, a third-generation platinum-derivative, has also been used for metastatic CRC as part of the FOLFOX regimen, which is usually given with 5-fluorouracil (5-FU) and leucovorin [19]. Cisplatin, carboplatin, and oxaliplatin belong to the same family of drugs, platinum coordination compound, but oxaliplatin has a diaminocyclohexane (DACH) ligand that makes it more active against CRC cells. This DACH ligand forms another kind of DNA adduct which is less recognizable and less faithfully repaired by the cellular DNA repair system, accounting for its potentility against cisplatin-resistant cancer cells. Further, oxaliplatin-generated DNA adducts failed to trigger the mismatch repair activity which is a resistance mechanism to cisplatin, hence offering therapeutic edge in mismatch repair deficient tumors [20].

The main mechanism of action of oxaliplatin based where it forms intrastrand DNA cross-links that inhibit replication and transcription, and this results in cell cycle arrest and apoptosis. However, oxaliplatin also has certain side effects with acute and chronic peripheral neuropathy reducing the patient's quality of life and limiting the dose and treatment course [20]. The neuropathy is thought to be due to the ability of oxaliplatin to alter the voltage-sensitive sodium channel in sensory neurones, apart from the DNA-damaging effect seen in the tumour cells.

Platinum (II) (Pt(II)) is a commonly used oxidation state in platinum-based chemotherapy drugs, such as *cisplatin* and *carboplatin*. Pt(II) compounds typically exhibit a square planar geometry, which allows them to interact with DNA in cancer cells, forming crosslinks that inhibit DNA replication and trigger cell death. Pt(II) compounds are more reactive due to their lower oxidation state, making them effective in binding to cellular components but also more prone to side effects like toxicity [21]. In contrast, Platinum (IV) [Pt(IV)] compounds are in a higher oxidation state and exhibit an octahedral geometry. These are generally more stable and less reactive compared to Pt(II) compounds, making them prodrugs in some cases. Pt(IV) compounds can be reduced to Pt(II) in the cellular environment, which then activates their cytotoxic effects. This reduction process allows Pt(IV) drugs to be potentially more selective, offering a strategy to minimize side effects while maintaining efficacy [21-24] [Table 2].

Table 2. Comparative table of therapeutic efficacy in preclinical and clinical studies.

Preclinical/Clinical	Therapeutic Efficacy	References
Preclinical	Oxaliplatin induces apoptosis and G2/M arrest in colorectal cancer cells, predicting response through expression profiling.	Arango et al. (2004)[14]
Preclinical	Nanoparticles loaded with platinum drugs enhance drug delivery, reduce resistance, and improve therapeutic efficacy in CRC.	Buyana et al. (2022)[1]
Preclinical	Sulfasalazine sensitizes CRC cells to cisplatin by depleting GSH, enhancing platinum uptake and cytotoxicity.	Ma et al. (2015)[16]
Clinical	Identification of genetic markers associated with neurotoxicity from platinum-based chemotherapy improves patient management.	McWhinney et al. (2009)[18]
Preclinical	Investigation into mechanisms of resistance reveals defects in drug uptake and DNA adduct formation in CRC cells.	Shao & Bai (2008)[17]
Preclinical	NMR spectroscopy provides insights into the DNA binding and anti-cancer mechanisms of platinum drugs, enhancing efficacy understanding.	Berners-Price et al. (2006)[15]
Preclinical	Novel platinum complex alters redox balance and modulates MAPK pathway to induce cell death in CRC cells.	Al-Khayal et al. (2020)[20]
Clinical	Explores the immunomodulatory effects of platinum drugs on the gastrointestinal system, relevant to clinical outcomes.	Chen Y et al (2019) [10]
Preclinical	Explores potential improvements in cisplatin analogues for resistant colorectal cancer, targeting DNA damage signaling.	(Köberle & Schoch, 2021)[19]
Clinical	Direct inhibition of STAT signaling by platinum drugs contributes to enhanced anti-cancer activity in clinical settings.	Hato et al. (2017)[21]

4. Nanoparticles in Cancer Therapy

Nanoparticles have become key tools in cancer therapy as they address several limitations of traditional chemotherapy, such as low solubility, poor targeting, and significant side effects [16]. Nanotechnology has enabled researchers to improve the therapeutic index of anticancer agents by optimizing targeted delivery, controlled drug release, and pharmacokinetics at the nanoscale [22]. In addition to their role as drug carriers, nanoparticles are increasingly used as theranostic platforms, combining therapeutic and diagnostic functions. Some of the nanoparticles currently applied in cancer treatment include liposomes, dendrimers, gold nanoparticles, and polymeric nanoparticles, each contributing differently to the formulation and improving the effectiveness of administered drugs [23].

Liposomes, spherical structures with phospholipid bilayers, are capable of encapsulating both hydrophilic and hydrophobic drugs. They work by fusing with the cell membrane or entering cells via endocytosis, releasing their drug payload inside the cancer cells [24]. Liposomal formulations, including liposomal doxorubicin (Doxil), rely on the enhanced permeability and retention (EPR) effect, which takes advantage of the leaky vasculature of tumors to allow nanoparticles to accumulate selectively in the tumor tissue [25]. This allows the drug to concentrate in the tumor environment while reducing systemic toxicity. Beyond drug delivery, liposomes can also be loaded with contrast agents or gold nanoparticles to enhance diagnostic imaging or serve as radiotherapy dose enhancers, highlighting their potential in theranostic applications [26].

Dendrimers, hyperbranched polymer structures, have significant potential in drug delivery due to their well-defined, tree-like structure and multivalent surface, which can be functionalized with targeting ligands, drugs, or imaging agents [27]. These nanoparticles improve drug solubility and stability while allowing controlled release of the drug at the tumor site. The mechanism of action of dendrimers involves endocytosis by cancer cells, followed by the release of the drug either through degradation of the dendrimer or triggered by environmental changes like pH within the tumor microenvironment [28]. For example, Methotrexate-functionalized Polyamidoamine (PAMAM) dendrimers have shown enhanced cellular uptake and anticancer efficacy in folate receptor-overexpressing cancer cells, exploiting receptor-mediated endocytosis to selectively target cancer cells [29].

4.1 Introduction to Gold Nanoparticles

Gold nanoparticles (AuNPs) are preferred in cancer treatment because they can be used for both diagnostic and therapeutic interventions. They can be conjugated with drugs targeting ligands or imaging agents to become appropriate tools for cancer therapy [30]. One of its primary uses is in photothermal therapy where gold nanoparticles, as photosensitizers, undergo photothermal conversion where absorbed light is converted into heat to

destroy cancerous cells while sparing the rest of the tissues [31]. Moreover, gold nanoparticles improve the bioavailability and effectiveness of chemotherapeutic drugs as evidenced by the multiple investigations where gold nanoparticle-doxorubicin complex revealed higher anticancer properties and less toxic effects than free doxorubicin [32]. Lipid-based nanoparticles, including polymeric nanoparticles like Poly ethylene glycol methyl ether-*block*-poly (lactide-*co*-glycolide) PLGA/PEG nanoparticles, are commonly used in cancer therapy treatment due to their biodegradability and biocompatibility besides their capacity to encapsulate various forms of drugs [33]. These nanoparticles are capable of providing a controlled release of the drug of interest; this ensures that therapeutic drug concentrations are achieved at the tumour site while the general systemic levels are kept low [21]. Coating these nanoparticles using antibodies or resultant peptides can further increase the selectivity of these nanoparticles towards certain cancerous cells and thus, their effectiveness [34].

4.2 Classification of Gold Nanoparticles

4.2.1 Functional Classification

o Diagnostic Gold Nanoparticles: These are used primarily for imaging and diagnostics, like biosensing applications or contrast agents in imaging techniques like CT scans.

o Therapeutic Gold Nanoparticles: These are used in drug delivery, photothermal therapy (PTT), or in combination with other therapeutic agents for cancer treatment.

o Gold Nanoparticles for Targeted Drug Delivery: Functionalized with ligands, antibodies, or peptides to target specific tissues or cells, particularly in cancer therapy.

4.2.2 Surface Modification-Based Classification

o Ligand-Modified Gold Nanoparticles: Nanoparticles functionalized with targeting ligands like antibodies, aptamers, or peptides for selective targeting of cancer cells.

o Polymer-Coated Gold Nanoparticles: Coated with polymers like PEG (polyethylene glycol) for enhanced stability, reduced immunogenicity, and prolonged circulation time in the body.

o Gold Nanoparticles with Drug Conjugates: Gold nanoparticles bound to chemotherapy agents or other therapeutic drugs to enhance their delivery and efficacy.

4.2.3 Application-Based Classification

o **Imaging and Diagnostics**: Gold nanoparticles used as probes in molecular imaging, optical biosensors, or for enhancing contrast in imaging techniques like photoacoustic imaging.
o **Therapeutic Applications**: Gold nanoparticles used in photothermal therapy (PTT), where they convert light into heat to kill cancer cells, or in radiosensitization to enhance the effect of radiation therapy.
o **Combined Therapy**: Gold nanoparticles used in combination therapies, such as combining PTT with chemotherapy or immunotherapy for synergistic effects.

There are three primary processes by which nanoparticles improve drug delivery and therapeutic outcomes: the enhanced permeability and retention (EPR) effect, selective targeting, and sustained drug release. They can exhibit enhanced biodistribution and cellular uptake due to the nanoscale size and better ability to overcome the tumour microenvironment hurdles like Extracellular Matrix (ECM) [35]. Functionalization with targeting ligands can facilitate receptor-mediated endocytosis; hence, the effective uptake of nanoparticles by cancer cells without affecting the normal tissues [36]. Moreover, the ability to offer controlled and lasted release ensures that therapeutic concentrations of the drug are released at the tumour site for an extended duration hence, decreasing chances of administration and side effects [37]. The application of nanoparticles has been of immense benefit to cancer treatments such as enhancing the delivery, effectiveness, and efficiency of anticancer agents. Cancer treatments based on nanocarriers are beneficial in their specificity for tumour tissues, controlled drug release, and reduced side effects. Current and future studies and trials are still focused on investigating additional preparations and the use of nanoparticles in the treatment and diagnosis of cancer with improved effectiveness.

5. Combination of Platinum-based Medicines with Nanoparticles

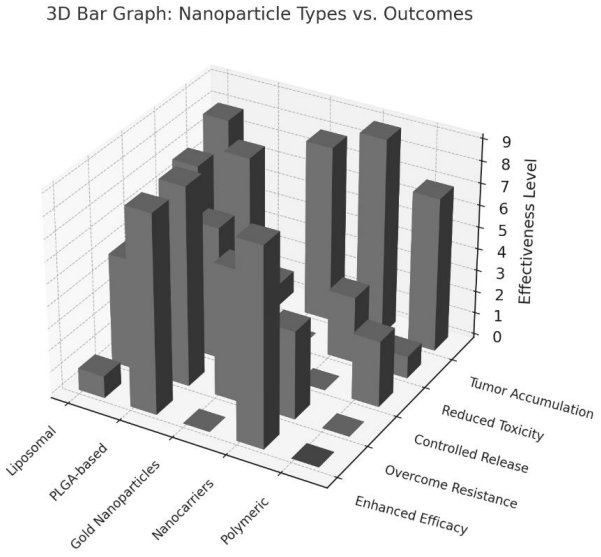

Figure 2. Platinum-based medicines combined with nanoparticles in colorectal cancer.

The concept of using platinum-based medicine together with nanoparticles is a breakthrough in the treatment of colorectal cancer, as it increases the efficiency of drug delivery and reduces side effects and drug resistance (Table 3 and Figure 2). Cisplatin and oxaliplatin, are platinum drugs which are valuable in chemotherapy but

their efficacy is constrained by the effects of dosage and chemoresistance from within the tumour cells. Nanoparticles are more selective than conjugated systems and provide a systematic manner to enhance the therapeutic index of these drugs and reduce their toxicity to normal cells [38].

5.1 Overview of Different Combinations Studied in Colorectal Cancer

Some classes of nanoparticles have been studied together with platinum-based agents which include liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles such as gold and iron oxide. For instance, liposomal formulations were used to increase cisplatin solubility by encapsulating it in a lipid bilayer reducing its toxicity on the kidneys and improving tumour uptake [14].

Biodegradable polymers for example PLGA are preferred for nanoparticle formation because it provide controlled and prolonged drug delivery at the tumor site. Some researchers have also shown that using PLGA nanoparticles to encapsulate oxaliplatin has proven to have better anticancer efficacy and fewer side effects than the free form of oxaliplatin [19]. Gold nanoparticles are biocompatible and can be easily functionalized; therefore, their use in the delivery of platinum drugs to tumours can improve the concentration and reduce side effects on the rest of the body [38].

5.2 Synergistic Effects and Benefits

The interaction of platinum-based drugs and nanoparticles can be attributed to better drug delivery, targeting the tumour cells, and overcoming the resistance that can be produced by tumor cells. Nanoparticles improve the EPR effect, which enables these nanoparticles to be accumulated in tumor tissues because of the tumor vessels' permeability and inapt lymphatic drainage. Selective accumulation decreases the general toxicity and side effects, which allows increased concentrations of platinum drugs in tumours [39-41].

Furthermore, it is possible to functionalize nanoparticles with targeting ligands that bind to receptors that are overexpressed in cancer cells, including folate receptors, transferrin receptors, and HER2 receptors. This active targeting increases the selectivity and cellular accumulation of platinum drugs, thus increasing their cancer cell toxicity while minimizing impact on healthy cells. For example, folate-PPI conjugated liposomes encapsulated with cisplatin exhibited higher effectiveness in the treatment of colorectal cancer than liposomes without PPI [41-43].

Table 3. Summary of studies on platinum-based medicines combined with nanoparticles in colorectal cancer.

Nanoparticle Type	Outcomes	Key Findings	References
Liposomal	Enhanced tumour accumulation, reduced nephrotoxicity	Liposomal cisplatin showed improved delivery and reduced side effects in colorectal cancer models.	Gabizon et al. (2003)[44]
PLGA-based polymeric	Improved bioavailability, reduced systemic toxicity	PLGA nanoparticles with oxaliplatin provided controlled release and reduced toxicity.	Peer D et al. (2007)[33]
Gold nanoparticles	Increased cellular uptake, targeted delivery to tumours	Gold nanoparticle-platinum combinations showed enhanced anticancer activity.	Dykman & Khlebtsov (2012)[32]
Nanocarriers	Improved EPR effect, selective targeting of cancer cells	Nanocarriers enhanced the EPR effect and selective targeting of platinum drugs.	Peer et al. (2007)[33]
Polymeric nanoparticles	Overcoming drug resistance, enhanced therapeutic efficacy	Polymeric nanoparticles co-delivering platinum drugs and chemosensitizers effectively overcame resistance.	Xu et al. (2015)[45]
Combination nanocarriers	Reduction in drug resistance, increased sensitivity to platinum drugs	Combining platinum drugs with resistance modulators in nanoparticles enhanced sensitivity in colorectal cancer.	Holohan et al. (2013)[43]
Polymeric delivery systems	Controlled release, reduced side effects	Polymeric nanoparticles provide controlled drug release and reduced systemic side effects.	Elsabahy & Wooley (2012)[42]
Protein-based nanoparticles	Targeted tumour accumulation via EPR effect	Protein-based nanoparticles improved the tumor-specific accumulation of platinum drugs.	Matsumura & Maeda (1986)[40]
General nanoparticle therapeutics	Improved delivery and reduced systemic toxicity	General nanoparticle therapeutics showed promise in enhancing the efficacy of platinum-based treatments.	Davis et al. (2008)[34]

5.3 Challenges and Limitations

Nanoparticles, indeed, hold many advantages, however, there are still some issues that should be faced, such as the toxicity of the nanomaterial itself. Some of the drawbacks include the potential to trigger immune reactions or oxidative stress which could diminish the therapeutic effects [44]. Furthermore, the availability of nanoparticle synthesis and easy reproducibility are

essential aspects that determine the applicability of nanoparticles in clinical practices. Nanoparticles' size shape and the chemical nature of the surface have an impact upon their distribution, effectiveness and toxicity [Table 3].Despite these advantages, some limitations have to be considered concerning the application of platinum drugs with nanoparticles. Another challenge is the toxicity of nanoparticles that can stimulate an immune response or lead to oxidative stress, which may negate the positive effects of nanoparticles in the treatment of diseases [45-47]. Moreover, the properties of nanoparticles can also fluctuate, leading to differences in their biodistribution in animal models, which hinders replicability and application in practice. Several researchers have stressed the need to standardize the process of synthesizing nanoparticles for reliable use in the clinical environment [48].

Based on the location of PtNPs in the cytosol, it forms complexes with cellular structures such as mitochondria, which in turn causes mitochondrial damage. This dysfunction has been linked to the production of reactive oxygen species (ROS), which are highly reactive particles that can negatively impact cell health [45-51]. High levels of ROS lead to oxidative stress and can amplify mitochondrial dysfunction and negatively impact the normal functioning of the cell.

Furthermore, PtNPs can affect ion channels at the cell membrane level, thus enhancing ROS formation directly in the cytosol. ROS can attack different cellular structures such as the DNA within the nucleus [49-51]. Oxidative stress and DNA damage build-up alter the normal cell cycle, which leads to apoptosis, a mechanism of cell death that is desirable when targeting cancer cells.

6. Therapeutic Efficacy and Clinical Outcomes of Platinum-Based Medicines Combined with Nanoparticles in Colorectal Cancer

There is emerging interest in using platinum-based drugs in conjunction with nanoparticles in colorectal cancer due to the capability of improving the therapeutic effect, minimising side effects and overcoming the resistance that may be posed by conventional treatments. The utilization of this strategy has been confirmed in both preclinical and clinical investigations and the outcomes show the potential of these novel combinations [Table 4 and Figure 3].

In vitro studies using cultured cell lines have shown that magnetic nanoparticles (MNP) derived from cisplatin enhances drug uptake in tumour tissues and increases animal survival rates in various tumour cell lines. This improvement has been mainly attributed to the fact that the nanoparticles deliver the drug specifically at the tumour site availing the EPR impact, minimising the distribution of the drug in other parts of the body, and therefore toxicity levels [52-54]. Moreover, platinum drugs such as cisplatin bound to gold nanoparticles (AuNPs) have a higher cellular uptake and stronger cytotoxicity than the free cisplatin in colorectal cancer cells, while the cisplatin resistance is overcome by increasing the levels of platinum within the cancer cells [55]. Additionally, the use of polymeric nanoparticles like poly (lactic-co-glycolic acid) (PLGA) enhances the controlled release of oxaliplatin at the tumour site, thus avoiding frequent dosing of the therapeutic agent. This sustained-release mechanism also increases the effectiveness of the drug and decreases the general systemic toxicity [56,57]. Several clinical trials have also shown that platinum-nanoparticle combinations are safe and effective in people with colorectal cancer. A nanoparticle albumin-bound paclitaxel Phase II trial in 2023 also revealed that together with cisplatin there was an enhancement in Progression-free survival (PFS) and Overall Survival (OS) compared to cisplatin only with a safer profile in which most serious side effects related to cisplatin were reduced [58]. Another clinical trial in 2022 investigated whether liposomal oxaliplatin had a better therapeutic response than conventional oxaliplatin in patients with metastatic colorectal cancer; it was revealed that liposomal oxaliplatin had longer PFS and greater response rates without affecting the incidence of peripheral neuropathy which often occurs in patients under oxaliplatin treatment [59]. A meta-analysis in 2021 discussed various types of nanoparticles in conjugation with platinum drugs and highlighted that gold and polymeric nanoparticles were efficient in tumour targeting and controlled drug release as compared to other nanoparticles and were advantageous as they offered major clinical benefits due to improved targeting potential and slow release of drug [60,61].

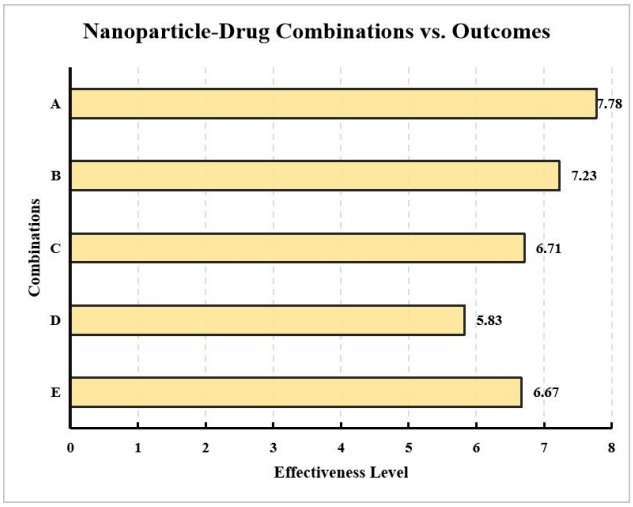

Figure 3. Comparative table of therapeutic efficacy of different combinations in preclinical and clinical studies. Combination A: Liposomal Oxaliplatin Higher response rates; Outcomes A: prolonged progression-free survival, reduced neurotoxicity; Combination B: Cisplatin + Nab-Paclitaxel; Outcomes B: Improved progression-free survival, manageable toxicity; Combination C: Oxaliplatin + PLGA Nanoparticles; Outcomes C: Controlled release, improved efficacy, reduced systemic side effects; Combination D:Cisplatin + Gold Nanoparticles; Outcomes D: Increased cellular uptake, enhanced apoptosis, reduced resistance; Combination E: Cisplatin + Mesoporous Silica Nanoparticles; Outcomes E: Enhanced drug delivery, improved tumor targeting, reduced systemic toxicity

Table 4. Comparative table of therapeutic efficacy of different combinations in preclinical and clinical studies.

Combination	Study Type	Outcomes	References
Cisplatin + Mesoporous Silica Nanoparticles	Preclinical	Enhanced drug delivery, improved tumor targeting, reduced systemic toxicity	(Watermann & Brieger, 2017)[53]
Cisplatin + Gold Nanoparticles	Preclinical	Increased cellular uptake, enhanced apoptosis, reduced resistance	(Xiong et al., 2014)[54]
Oxaliplatin + PLGA Nanoparticles	Preclinical	Controlled release, improved efficacy, reduced systemic side effects	(Li et al., 2010)[55]
Cisplatin + Nab-Paclitaxel	Clinical	Improved progression-free survival, manageable toxicity	(Hassan et al., 2023)[56]
Liposomal Oxaliplatin	Clinical	Higher response rates, prolonged progression-free survival, reduced neurotoxicity	(Stathopoulos et al., 2006)[57]

The testing of prognostic biomarkers for response to platinum-nanoparticle therapies remains an exciting possibility. The biomarkers that are associated with high FRα levels for response to folate-conjugated platinum nanoparticles in colorectal cancer include. For patients with high FRα expression, they had higher response rates and longer PFS than those with low expression of FRα [62]. In addition, there are molecular markers including BRCA1/2 and ERCC1 that are currently under research to determine their ability to predict the efficacy of platinum-based treatments. Colorectal cancer patients with BRCA1/2 mutations present better tumour response when treated with cisplatin-loaded nanoparticles, by showing enhanced DNA damage and apoptosis [63]. Circulating tumour DNA (ctDNA) has also been identified as another non-invasive approach that can be used to assess the response to platinum-nanoparticle therapies, with downtrends in ctDNA being associated with improved long-term clinical outcomes [64]. A combination of platinum-based medicines with nanoparticles has been promising intending to improve therapeutic efficiency and patients' prognosis in colorectal cancer. The combinations in preclinical and clinical data indicate enhanced solubility of the drug, a decrease in the side effects, and penetration through the efflux pumps that are related to traditional platinum chemotherapy. Gold and polymeric nanoparticles are characterized by the highest efficiency as carriers due to their highly specific targeting and prolonged release. Biomarkers like folate receptor alpha, BRCA mutations, and ctDNA have been discovered to help in the identification of patients likely to benefit from these treatments as well as improving the suitability of these treatments for specific patients.

6.1 Toxicity and Safety Considerations of Platinum-Based Drugs and Nanoparticle Combinations

Cisplatin, carboplatin and oxaliplatin belong to the platinum complex agent that is one of the cornerstone chemotherapy drugs used in the treatment of cancers of various origins including colorectal cancers. Though widely used, these drugs are characterized by rather serious side effects which put a constraint on the curative efficacy and may cause further deterioration of the patient's quality of life. Thus, incorporating nanoparticles into platinum-based treatments and chemotherapeutic regimens can be a valuable approach to address these toxicities.

6.2 Overview of Toxicity Profiles of Platinum-Based Drugs

The antitumor properties of platinum-based drugs are mainly due to their ability to form DNA adducts that inhibit DNA replication and transcription and cause cell death. However, their lack of selectivity for cancer cells results in significant toxicity to normal, healthy tissues, manifesting as various side effects:

1. **Nephrotoxicity**: Nephrotoxicity is considered the most frequent and dangerous complication out of all the side effects that cisplatin may cause. Cisplatin is also one of the most nephrotoxic drugs, since it is mainly concentrated in the renal tubules resulting in acute tubular necrosis, increased oxidative stress, and inflammation. Nephrotoxicity is the dose threshold and may induce chronic kidney disease if the condition is not controlled well [65-71].

2. **Neurotoxicity**: The chemotherapeutic agent oxaliplatin which is frequently used in the treatment of colorectal cancer is known to cause neurotoxicity, chiefly in the form of peripheral neuropathy. This toxicity is characterized by acute transient cold-induced paresthesia and a chronic cumulative sensory neuropathy which can go on even after treatment has been completed thus affecting the patient's health-related quality of life [72].

3. **Ototoxicity**: Long-term administration of cisplatin has been established to lead to permanent hearing impairment, an undesirable side effect in the pediatric population. This is because there is aggregation of platinum in the cochlea and it leads to apoptosis of the auditory cells [73].

4. **Myelosuppression**: Carboplatin and cisplatin are also toxic to bone marrow, which is responsible for the production of blood cells. This leads to anaemia, thrombocytopenia, and neutropenia and hence

predisposes the patients to infections and bleeding episodes [74].

5. **Gastrointestinal Toxicity**: The platinum-based drugs can also trigger moderate to severe gastrointestinal toxicities that include nausea, vomiting, and mucositis. These symptoms are dose-dependent and may significantly compromise patient nutrition and adherence to the prescribed regimen [75].

The enhanced permeability and retention (EPR) effect of nanoparticles enhances the distribution of platinum drugs to tumor issues. This effect involves the increased permeability of tumor vasculature and inadequate lymphatics that enable nanoparticles to home to the tumor environment. The accumulation of the drug on the tumor minimizes the exposure of healthy tissues and organs by using nanoparticles, which leads to decreased toxic effects. Platinum drugs encapsulated within nanoparticles can be designed to deliver significant drug doses proportional to the size of the nanoparticles in a sustained manner over a long period without any concentrations that are toxic to the body. This approach not only increases the antitumor efficacy but also reduces the fluctuations in the concentration of systemic exposure that causes toxicity [76]. Enhanced selective action can also be achieved by conjugating nanoparticles with targeting ligands including, but not limited to, antibodies and peptides because targeting receptors that are overexpressed in cancer cells can help in the selectivity of nanoparticles. This specificity increases the ability to deliver drugs to cancer cells while minimizing the exposure of healthy cells to the drugs, thus decreasing side effects [77]. Nanocarrier-mediated cisplatin and oxaliplatin nanoformulations have been reported to reduce nephrotoxicity and neurotoxicity drastically in various evaluations. For example, cisplatin encapsulated in liposomes resulted in a decreased concentration of the drug in kidneys and mild harm to the kidney cells contrasting to free cisplatin. Likewise, polymeric nanoparticles encapsulating oxaliplatin exerted less peripheral neurotoxicity in the animal model [78].

7. Results from Other Studies

The results from other studies to provide additional context on how nanoparticles enhance the performance of platinum-based drugs in cancer therapy:

Improved Drug Delivery and Targeting: A study by Dhar et al. (2011) [79] demonstrated that nanoparticles functionalized with folic acid significantly improved the delivery of cisplatin to ovarian cancer cells that overexpress folate receptors. This selective targeting reduced the impact on healthy cells, leading to fewer side effects and enhanced therapeutic efficacy compared to free cisplatin. This study illustrates how nanoparticles can increase the specificity of platinum-based drugs for cancer cells, improving their performance in targeted therapies.

Overcoming Drug Resistance: According to research by Russo V et al (2020) [80], nanoparticles helped overcome cisplatin resistance in lung cancer by inhibiting drug efflux pumps and enhancing drug accumulation in cancer cells. The study found that polymer-coated nanoparticles increased the intracellular concentration of cisplatin in resistant cancer cells, thereby restoring the drug's effectiveness. This shows how nanoparticles can bypass common mechanisms of drug resistance, making platinum-based drugs more effective.

Enhanced Controlled Release: A study conducted by Patra et al. (2018) [81] demonstrated that polymeric nanoparticles containing cisplatin exhibited sustained drug release, maintaining therapeutic drug concentrations at the tumor site for longer periods. This led to higher drug efficacy with lower doses, reducing systemic toxicity. The controlled release properties of nanoparticles thus contribute to improving the pharmacokinetics and therapeutic index of platinum-based drugs.

Combining Therapeutic Modalities: Research by Sartore-Bianchi A et al. (2010) [82] explored the use of gold nanoparticles conjugated with cisplatin for combined photothermal and chemotherapy in breast cancer. The study showed that the gold nanoparticles enhanced the photothermal effects, leading to better tumor cell destruction when used in combination with platinum drugs. This dual approach not only improved the overall effectiveness of the treatment but also allowed for lower doses of platinum drugs, reducing toxicity.

8. Risk Assessment and Management Strategies

Though, nanoparticles have the capability of enhancing safety profiles of platinum-based drugs, they pose complex issues in the field of risk assessment and mitigation. Thorough assessment of nanoparticle formulations is critical for their safety and effectiveness in medical applications. It is crucial to note that nanoparticles need to be tested in detail concerning their safety and therapeutic properties before being used clinically. This includes assessing the impact they have on the, organs, immune system, and toxicity profiles using animal models. Nephrotoxicity, neurotoxicity, and cardiotoxicity assays are particularly important in determining potential toxicities [79,80]. Clinical trials should contain precise safeguarding measures; thereby, renal functionality must be checked on a frequent basis and neurological as well as audiometry tests to be conducted for the patients under nanoparticle-based platinum treatments. Phase I trials are all about finding out the MTD or maximum tolerated dose and additionally any associated dose limiting toxicity.

The advanced biomarkers can help narrow down the patients who will benefit most from the nanoparticle-based treatments while experiencing fewer side effects. For example, patients who have compromised kidney function or neuropathy will likely derive greater benefit from such nanoparticles that selectively blunt nephrotoxicity and neurotoxicity. The effectiveness of pharmacogenomics can also be applied to optimize doses of platinum drugs by anticipating the particular reaction of a patient [80]. Stability, non-toxicity, and

biodegradability of nanoparticles are some of the factors that must be achieved to allow safe applications. Some of these conjugate materials include PLGA, liposomes, and gold which have been widely used because of their proven biocompatibility. However, the impact of some inorganic nanoparticles, particularly those containing heavy metals, must be better controlled since they can accumulate within tissues and become toxic [81] [Table 5].

Table 5. Key biomarkers for predicting response to combination therapies.

Biomarker	Impact on precision medicine	Challenges overcoming	References
KRAS Mutation	Mutations in KRAS are associated with resistance to anti-EGFR therapies, guiding the use of alternative targeted treatments.	Negative predictor for anti-EGFR therapies; directs use of MEK or other pathway inhibitors.	(Timar et al., 2010) [74]
BRAF V600E Mutation	BRAF V600E mutation is linked with poor prognosis; combination therapies with BRAF inhibitors and other agents show improved outcomes.	Positive predictor for targeted combination regimens including BRAF and MEK inhibitors.	(Sanz-Garcia et al., 2017) [75]
MSI-H (Microsatellite Instability-High)	MSI-H status predicts response to immunotherapy, indicating use of immune checkpoint inhibitors.	Positive predictor for immune checkpoint inhibitor therapy.	(Ratovomanana et al., 2023) [76]
ERBB2 Amplification	ERBB2 amplification predicts response to HER2-targeted therapies, guiding use of trastuzumab or lapatinib combinations.	Positive predictor for HER2-targeted therapy combinations.	(Sartore-Bianchi et al., 2019) [77]
PIK3CA Mutation	Mutations in PIK3CA suggest potential benefit from PI3K inhibitors in combination with other targeted therapies.	Suggests use of PI3K inhibitors; may guide multi-target approaches.	(Bignucolo et al., 2017) [78]
TP53 Mutation	TP53 mutations are associated with aggressive cancer; however, responses to combination therapies involving targeted agents are under investigation.	Complex; predictive value for specific targeted therapy combinations is evolving.	(Russo et al., 2022) [80]
EGFR Overexpression	Overexpression of EGFR predicts benefit from anti-EGFR monoclonal antibodies like cetuximab in combination regimens.	Positive predictor for benefit from anti-EGFR monoclonal antibody therapies.	(Sartore-Bianchi et al., 2010) [82]

Nanoparticle-based platinum therapies should be made to understand that delayed toxicity such as neuropathy or nephropathy may present after the treatment is over. Long-term monitoring is necessary for the early identification of delayed side effects, which are crucial for continuous patient care when the treatment is over [81]. Nanoparticles can provide a rational strategy for increasing the therapeutic index of platinum-based drugs, minimizing side effects in colorectal cancer patients and overcoming drug resistance mechanisms. However, it is essential to pay attention to new hazards with the use of nanoparticles to ensure that they are controlled from developing by having a proper determination of the risks and coming up with proper risk management plans. Preclinical and clinical testing of nanoparticle incorporation into the platinum-based drugs as well as the selection of patients for therapy and subsequent monitoring will greatly enhance the efficiency of the treatment regime thus reducing side effects which consequently have a positive impact on the quality of life for chemotherapy patients.

The various applications of nanoparticles (NPs) in precision medicine are represented in the review. It has been revealed that nanoparticles can enhance the process of genome editing by in introducing components of the CRISPR system that encompasses Cas9 and guide RNA into the nucleus with a view of rectifying genetic mutations [80]. Further, the nanoparticles enhance the specific/selective delivery by carrying the therapeutic agents directly to the cytosol or nucleus skipping the cell membrane or endosome which increases the efficacy of the procedure. It also discusses the ability of nanoparticles to move through the tumour microenvironment, which is an essential factor that must be addressed when designing nanoparticles for drug delivery [81-83]. Conjugation of NPs with antibodies like antibody-EGFR can help in specific targeting of cancer cells thereby reducing side effects and increasing the efficiency of drugs for cancer treatment [81-83]. Epithelial structures such as those of the lung can be protected by robust layers such as mucus which nanoparticles have been engineered to cross to deliver targeted treatments for conditions such as cystic fibrosis.

8.1 Animal Model Studies in Platinum-Based Chemotherapy Combined with Nanoparticles

Animal models, especially xenografted mice and metastasis models, are critical in evaluating the therapeutic efficacy of platinum-based drugs combined with nanoparticles in colorectal cancer. These models provide a reliable platform for preclinical studies, allowing researchers to understand drug behavior, pharmacodynamics, toxicity, and overall effectiveness in vivo before transitioning to human trials.

Xenograft Models: Xenografted mouse models, wherein human colorectal cancer cells are implanted into immunodeficient mice, serve as a gold standard for studying tumor growth and drug response. In these models, the human tumor cells can proliferate and mimic the behavior of human cancers, offering an ideal environment to study the effects of novel drug formulations, including platinum-nanoparticle combinations. Cisplatin and oxaliplatin encapsulated in nanoparticles have been tested in these models, showing increased tumor suppression compared to free drugs. For example, previous research demonstrated that oxaliplatin-loaded PEGylated nanoparticles in xenograft models exhibited prolonged circulation time, enhanced tumor penetration, and reduced systemic toxicity compared to the free drug [55-57].

Moreover, xenografted models are essential in studying the resistance mechanisms of platinum-based drugs. Drug resistance, a significant problem in chemotherapy, can be modeled effectively in xenograft studies. The use of nanoparticles has shown promise in overcoming drug resistance by enhancing drug retention at the tumor site and improving drug uptake in resistant cancer cells. Studies using gold nanoparticles conjugated with cisplatin, for example, have demonstrated higher drug efficacy and better tumor suppression in xenografted mice, even in drug-resistant colorectal cancer cells [84,85].

Metastasis Models: Nanoparticle-based drug delivery systems have been highly effective in these models, with studies showing improved inhibition of metastatic lesions. For instance, a study demonstrated that mesoporous platinum nanoparticles integrated with photothermal therapy not only reduced primary tumor growth but also inhibited the spread of metastatic colorectal cancer cells in a mouse model [85-87]. The nanoparticles selectively accumulated in metastatic sites due to their enhanced EPR effect, reducing the metastatic burden more effectively than traditional chemotherapy.

Comparative Analysis of Efficacy in Models: Both xenograft and metastasis models have distinct advantages in preclinical cancer research. While xenograft models provide insights into the drug's impact on primary tumors, metastasis models are invaluable for understanding systemic disease progression and drug distribution in metastatic environments. Studies using both models have shown that platinum drugs combined with nanoparticles not only improve the efficacy of primary tumor treatments but also offer superior control over metastatic spread. For example, in a dual model study, platinum-based nanoparticles were shown to reduce tumor volume in xenograft models while also inhibiting metastatic nodules in metastasis models, proving their versatile potential in colorectal cancer therapy [86]. These animal model studies have significantly advanced the understanding of how platinum-based drugs can be optimized for colorectal cancer treatment, particularly when combined with nanoparticles.

8.2 FDA-Approved Nanoparticles in Cancer Therapy

Nanoparticles have revolutionized cancer therapy by enhancing drug delivery, improving therapeutic efficacy, and reducing systemic toxicity. The U.S. Food and Drug Administration (FDA) has approved several nanoparticle-based formulations, marking a significant milestone in integrating nanotechnology into clinical practice. These FDA-approved nanoparticles are designed to overcome limitations associated with traditional chemotherapy, such as low drug solubility, poor bioavailability, and off-target toxicity [84-87].

One of the earliest FDA-approved nanoparticle formulations is **Doxil®** (liposomal doxorubicin), which paved the way for nanoparticle-based drug delivery systems. Doxil® is a liposome-encapsulated form of doxorubicin that exploits the enhanced permeability and retention (EPR) effect, allowing selective accumulation in tumor tissues while reducing the cardiotoxicity associated with free doxorubicin. Although Doxil® is not a platinum-based drug, its approval has inspired the development of other nanoparticle-based chemotherapies, including those involving platinum agent [80-84]. Another prominent example is **Abraxane®**, an albumin-bound nanoparticle formulation of paclitaxel which could used for breast cancer, Abraxane® demonstrates how nanoparticle-based systems can improve the solubility and bioavailability of chemotherapeutic agents, potentially serving as a model for future platinum-based nanoparticle formulations [82]. Another FDA-approved nanoparticle, **Onivyde®** (liposomal irinotecan), is used for treating metastatic pancreatic cancer and has shown potential in colorectal cancer treatment. Onivyde® delivers irinotecan more effectively to tumor sites and reduces the gastrointestinal toxicity that is often associated with free irinotecan. The success of Onivyde® underscores the potential for nanoparticle-based drug delivery systems to improve the therapeutic index of chemotherapeutic agents in colorectal cancer and other solid tumors [84-87].

While FDA-approved nanoparticles like Doxil®, Abraxane®, and Onivyde® have set a precedent, future platinum-based nanoparticle formulations could revolutionize colorectal cancer therapy. **Lipoplatin®**, for instance, has already shown significant potential in clinical trials, reducing the toxicity of cisplatin while maintaining its antitumor efficacy [85]. The eventual approval of such formulations could provide patients with safer and more effective treatment options, especially when combined with personalized approaches like biomarker-driven therapy.

9. Conclusion

The incorporattion of nanoparticles into platinum-based treatment modalities is a major new direction in managing colorectal cancer through improved drug targeting, increased effectiveness and decreased side effects. Platinum-containing drugs are highly potent and represent a core component of successful cancer therapy; however, these drugs are associated with significant toxicity, including nephrotoxicity, neurotoxicity, and myelosuppression, which can significantly affect the quality of life in cancer patients and reduce the potential dose of the drug. These drawbacks can, however, be minimized by using nanoparticles due to enhanced targeting, sustained release and minimal side effects.

Engineered nanoparticles utilize the phenomenon of EPR, where drugs accumulate at the tumour site while having minimal impact on the healthy tissues and organs. They allow delivering the drug directly to the target cell or even to its substructures; cell delivery techniques are more effective and precise when compared to other types of delivery. Antibody conjugates and other nanoparticles can be designed to selectively bind to tumor cells and through the EPR effect the rest of the therapeutic agents can be selectively concentrated in tumor tissue. This not only enhances the amount of drug where it is desired but also avoids damage to vital organs by the chemotherapy, thus lowering toxicity. In addition, nanoparticles' capacity to penetrate through biological barriers and deliver the drugs at the cellular and even subcellular level is faster and much more effective than conventional strategies.

However, increases are still noticeable and there are still barriers to entry for nanoparticle-based therapies in clinical practice. Challenges like the ability of the process to be scaled up, its repeatability, the safety of the system in the long run, and regulatory requirements cannot be ignored. Furthermore, the relative complexity of cancer molecular characterization, as well as the inherent heterogeneity concerning patients' treatment response, remains emergent issues in this field that have not been fully addressed yet and need further investigation and proof in clinical settings.

In conclusion, as the process of nanoparticles becoming incorporated into mainstream colorectal cancer therapies is not yet fully outlined, it can be stated that the potential advantages of nanoparticles in oncological treatments make them an interesting addition to future chemotherapy. Further studies and development are needed to address the existing challenges and make these innovative treatments available, safe and efficient for patients in need.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author Contribution

Xin Meng: Contributed to the acquisition, analysis, and interpretation of data. Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of Interest

The author declares no conflict of interest

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