Nanoparticles containing oxaliplatin and the treatment of colorectal cancer

Hanie Mahaki, Mona Mansourian, Zahra Meshkat, Amir Avan, Mohammad Gosseinshafiee, Reihaneh Alsadat Mahmoudian, Elnaz Ghorbani, Gordon Ferns, Hamed Manoochehri, Shaho Menbari, Mohsen Sheykhhasan, Hamid Tanzadehpanah

Publication date
07-12-2023

Document Version
Accepted version

Published in
Current Pharmaceutical Design

Link to external publisher version
https://doi.org/10.2174/0113816128274742231103063738

Nanoparticles Containing Oxaliplatin and the Treatment of Colorectal Cancer

Hanie Mahaki [1], Mona Mansourian [2], Zahra Meshkat [3], Amir Avan [4, 5, 6], Mohammad Hossein Shafiee [2], Reihaneh Alsadat Mahmoudian [4, 7], Elnaz Ghorbani [4], Gordon A Ferns [8], Hamed Manoochehri [9], Shaho Menbari [3, 10, 11], Mohsen Sheykhhasan [12] & Hamid Tanzadehpanah [3, 4, 7] *

[1] *Endovascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[2] *Mashhad University of Medical Sciences, Mashhad, Iran.*

[3] *Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[4] *Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[5] *College of Medicine, University of Warith Al-Anbiyaa, Karbala, Iraq,*

[6] *Faculty of Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, Australia.*

[7] *Basic Sciences Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran*

[8] *Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK.*

[9] *The Persian Gulf Marine Biotechnology Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran*

[10] *Department of Medical Laboratory Sciences, Faculty of Paramedical, Kurdistan University of Medical Sciences, Sanandaj, Iran.*

[11] *Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*

[12] *Department of Mesenchymal Stem Cells, Academic Center for Education, Culture and Research, Qom*

* Correspondence author:
Hamid Tanzadehpanah,
Email: h.tanzadehpanah@gmail.com
ORCID: 0000-0002-1711-5619
Tel: +989156548710

Running title: Nanoparticles of Oxaliplatin and Colorectal Cancer

Abstract

Background: Colorectal cancer (CRC) is a highly widespread malignancy and ranks as the second most common cause of cancer-related mortality. **Objective:** Cancer patients, including those with CRC, who undergo chemotherapy, are often treated with platinum-based anticancer drugs such as oxaliplatin (OXA). Nevertheless, the administration of OXA is associated with a range of gastrointestinal problems, neuropathy, and respiratory tract infections. Hence, it is necessary to devise a potential strategy that can effectively tackle these aforementioned challenges. The use of nanocarriers has shown great potential in cancer treatment due to their ability to minimize side effects, target drugs directly to cancer cells, and improve drug efficacy. Furthermore, numerous studies have been published regarding the therapeutic efficacy of nanoparticles in the management of colorectal cancer. **Methods:** In this review, we present the most relevant nanostructures used for OXA encapsulation in recent years, such as solid lipid nanoparticles, liposomes, polysaccharides, proteins, silica nanoparticles, metal nanoparticles, and synthetic polymer-carriers. Additionally, the paper provides a summary of the disadvantages and limits associated with nanoparticles. **Results:** The use of different carriers for the delivery of oxaliplatin increased the efficiency and reduced the side effects of the drug. It has been observed that the majority of research investigations have focused on liposomes and polysaccharides. **Conclusion:** This potentially auspicious method has the potential to enhance results and enhance the quality of life for cancer patients undergoing chemotherapy. However, additional investigation is required to ascertain the most suitable medium for the transportation of oxaliplatin and to assess its efficacy through clinical trials.

Keywords: Oxaliplatin; Nanotechnology; Nanocarriers; Colorectal cancer; Neoplasm

1. Introduction

1.1. Colorectal cancer

A neoplasm refers to an anomalous proliferation of tissue, which can manifest as either a benign or malignant condition. Benign neoplasms typically exhibit a sluggish growth pattern and lack the ability to metastasize. Nevertheless, malignant neoplasms typically exhibit accelerated growth and infiltrate adjacent anatomical regions [1]. In developed nations, cancer is an important contributor to mortality, while in developing nations; it ranks as the second leading cause of death. According to a projection, the United States is expected to witness a total of 1,958,310 individuals diagnosed with cancer by the year 2023, out of whom 609,820 fatalities are anticipated [2]. The prevalence of cancer is anticipated to rise, with an estimated 1.1 million cases worldwide by 2030 [3]. The third most frequently diagnosed cancer overall and the third greatest cause of cancer death for both men and women in the United States is colorectal cancer (CRC). In the year 2020, the incidence of colorectal cancer surpassed 1.9 million new cases. According to data from the World Cancer Research Fund, the countries exhibiting the highest rates of colorectal cancer are Hungary, Slovakia, Norway, Netherlands, Denmark, Slovenia, Portugal, Japan, Latvia, and Croatia. In the year 2020, these countries reported 9793, 4821, 4976, 17015, 5769, 2018, 10501, 148505, 1745, and 3706 new cases of colorectal cancer, respectively (World Cancer Research Fund, 2020). A projected 153,020 new instances of CRC, comprising 106,970 colon tumors and 46,050 rectum tumors, will be diagnosed in the United States in 2023. This will result in 52,550 CRC fatalities, including 3,750 deaths (7%) in people under the age of 50 [4](Fig. 1).

1.2. CRC pathogenesis

In addition to environmental, nutritional, genetic, and epigenetic risk factors, CRC pathogenesis is also influenced by various other risk variables, such as sporadic (85%), familial (25%), and hereditary (5–10%) factors [5]. The onset of neoplastic transformation of

healthy epithelium, which subsequently proceeds towards malignant phases, is influenced by genetic and epigenetic modifications [6, 7]. The genomic instability of colorectal cancer (CRC) and its pathogenesis may be attributed to three primary routes: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) pathways [8, 9]. Colorectal intraepithelial neoplasia (CIN) is observed in approximately 85% of adenocarcinoma transitions. This condition is distinguished by several key features, including the inactivation of the tumor suppressor gene APC, the activation of the oncogene KRAS, a loss of heterozygosity for the long arm of chromosome 18 (18q LOH) involving SMAD4, and the inactivation of TP53. These molecular alterations collectively contribute to the promotion of colorectal cancer (CRC) tumorigenesis [6, 8, 10, 11]. MSI accounts for just 15-20% of all colorectal cancer (CRC) cases. (MSI) is a distinctive characteristic of Hereditary Nonpolyposis Colorectal Cancer (HNPCC), often known as Lynch syndrome, and is observed in more than 95% of HNPCC patients. [12]. The most frequently mutated loci are TGF-βR2 and Bax. Moreover, it is common for individuals diagnosed with Lynch syndrome to exhibit microsatellite instability colorectal cancers (MSI CRCs) as a result of inherited mutations in any of the four mismatch repair (MMR) genes, namely MLH1, MSH2, MSH6, and PMS2 [13-15]. The presence of epigenetic instability in colorectal cancer (CRC) is evidenced by the occurrence of hypermethylation at specific loci that encompass CpG islands, sometimes accompanied by a concurrent reduction in overall DNA methylation levels. Changes in DNA methylation patterns have the potential to impact a wide range of signaling pathways, including as TP53, TGFβ/SMAD, Wnt, NOTCH, and receptor tyrosine kinases. These pathways are involved in several cellular processes, including cell cycle regulation, transcription regulation, DNA stability, apoptosis, cell-cell adhesion, angiogenesis, cell invasion, and metastasis [16-18]. Numerous genes have been recognized as being subject to methylation and subsequent silencing in colorectal cancer

(CRC). Notable examples of frequently methylated genes in this context are APC, MLH1, MGMT, SFRP1, SFRP2, CDKN2A, TIMP3, VIM, SEPT, CDH1, and HLTF [19].

1.3. Stages of CRC

Colorectal cancer is characterized by a progression through five distinct stages, denoted by numerical values ranging from zero to four. During the first stage of colorectal cancer (CRC), the development of polyps occurs within the epithelial lining of the colon's mucous membrane. Subsequently, during stage I, the polyps undergo a process of deterioration, transforming into tumors and initiating migration into the mucosa. The therapeutic efficacy of local tumor excision with surgical intervention throughout the aforementioned times can be achieved without the need for supplementary therapy. Various surgical techniques can be employed to address different conditions inside the gastrointestinal tract. These techniques include the removal of polyps from the intestinal wall, excision of tumor-affected portions of the intestine, standardized excision procedures, and subsequent reconnection of intestinal segments to establish ileostomy or colostomy. During the second stage of cancer, the potential for metastasis exists beyond the confines of the colon; nevertheless, lymph node metastasis does not occur at this particular time. During the third stage of cancer progression, the malignant cells disseminate to the colon wall and adjacent lymph nodes, while abstaining from invading neighboring organs. During these time intervals, it is imperative to administer a combination of radiotherapy and chemotherapy to the patients. Fluoropyrimidine, either as a standalone treatment or in combination with other chemotherapeutic agents, is commonly employed in the management of colorectal cancer (CRC). Furthermore, the determination of patients' survival time with localized malignancies may be facilitated by assessing their microsatellite instability status. Notably, individuals exhibiting significant microsatellite instability are expected to experience a prolonged survival period. Nevertheless, the administration of fluorouracil-based chemotherapy is deemed unsuitable for this particular

group of individuals and may potentially elicit detrimental consequences. During the fourth stage of cancer, there is a notable increase in the rate at which the disease disseminates to other organs inside the body. Currently, it is imperative to employ surgical intervention for tumor removal, in addition to implementing systemic chemotherapy or a combination of chemotherapy and targeted biological treatment to eradicate tumor cells. The application of biological targeted therapy in the treatment of colorectal cancer (CRC) involves the utilization of specific drugs such as bevacizumab, cetuximab, and panitumumab. Bevacizumab functions by inhibiting tumor angiogenesis through its ability to bind to the vascular endothelial growth factor produced by CRC cells. Cetuximab and panitumumab, on the other hand, target the overexpression of the epidermal growth factor receptor (EGFR) in CRC, thereby impeding the proliferation of tumor cells [20-23].

1.4. Oxaliplatin (OXA) and CRC

Chemotherapy is a treatment modality that may be employed throughout all stages of cancer, ranging from stage IA/IB to stage IV. Chemotherapeutic drugs or medicines have played a significant role in medical practice in recent decades and have consistently been the preferred treatment option for advanced-stage malignancies in cases where surgery or radiation therapy is contraindicated for particular reasons. Around half of cancer patients who undergo chemotherapy are administered platinum-based anticancer medications **(Scheme 1)** [24]. At present, there exist six platinum-based medications that have obtained marketing authorisation in different locations around the globe. These drugs include cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, and heptaplatin. Cisplatin, carboplatin, and oxaliplatin are widely recognized and extensively studied platinum-based chemotherapeutic agents. The US Food and Drug Administration granted approval for the use of cisplatin in the 1970s. Carboplatin was formulated as a less cytotoxic variant of cisplatin and has been employed for the treatment of similar malignancies as cisplatin (licensed in the late 1980s).

However, carboplatin has emerged as the preferred platinum-based therapeutic agent for the management of ovarian carcinomas. Oxaliplatin (OXA), a representative of the third generation of platinum-based antineoplastic agents, received regulatory clearance in Europe during the 1990s and in the United States over the last decade. Presently, its authorized indications are limited to the management of colorectal malignancies [25]. This pharmaceutical compound has distinct benefits in comparison to alternative platinum-based medications. OXA is commonly given as an anticancer medication owing to its extensive spectrum of anticancer effects and comparatively lower toxicities in comparison to cisplatin and carboplatin [26]. The in vitro system demonstrates that the cytotoxic activity of OXA is considerably more effective than that of carboplatin. As the duration of exposure rises, the action of the substance becomes more similar to that of cisplatin [27]. The diaminocyclohexane platinum coordination complex known as OXA is the initial instance of such a compound that has been made accessible for therapeutic use. The medicine exhibits non-cross-resistance with cisplatin or carboplatin, rendering it one of the limited number of efficacious drugs for the treatment of human colorectal cancer [28]. Furthermore, it has comparable anti-cancer efficacy to cisplatin when utilized for the management of esophageal and gastric malignancies. This compound is classified as an alkylating agent and a cytostatic medication, commonly employed in the chemotherapeutic treatment of malignant tumors, particularly those affecting the colorectal region. Additionally, it has efficacy against a wide range of cancers, including certain cell lines that have demonstrated resistance to cisplatin and carboplatin [29]. The pharmacokinetics of OXA are elucidated by the utilization of a 3-compartment model. Due to its lipophilic nature, this pharmaceutical agent exhibits rapid transmembrane permeability. The platinum-based medication hinders the mechanism of DNA replication. The literature has documented the presence of platinum compounds in several copper transporters, including the uptake transporter hCtr1 and the multispecific organic

cation transporter hOCT1. The efflux transporters ATP7A and ATP7B are responsible for the extrusion of Pt compounds, thereby suggesting their involvement in modulating cellular resistance or sensitivity. Nevertheless, the most often described mechanism of resistance is the reduction in platinum buildup [30]. Similar to other chemotherapeutic agents, OXA elicits numerous adverse effects in individuals undergoing treatment. Some of these adverse effects include anemia, chest discomfort, a persistent cough, abdominal pain, shortness of breath, back pain, anorexia, dizziness, constipation, fever, indigestion, headache, lethargy, nausea, sleeplessness, chills, and infections of the respiratory system [24]. However, peripheral neurotoxicity, myelosuppression, and gastrointestinal responses (diarrhea) are the most common adverse effects of OXA [31].

1.5. Nanotechnology

In the present day, systems rooted in nanotechnology have several diagnostic and therapeutic potentials. One potential approach to decreasing the negative effects of OXA toxicity is through the utilization of nanostructures as an encapsulation strategy [32]. The field of nanotechnology has had consistent growth in its application to cancer chemotherapy, radiation, diagnostics, and imaging. These advancements have shown promising potential in enhancing these areas and improving patient care [33]. Nanotechnology-based methodologies have demonstrated superior efficacy in delivering drugs to specific tissues compared to unbound formulations. Over time, various systems and technological approaches have been investigated for the purpose of encapsulating OXA, as encapsulating OXA induces drug accumulation in the tumor environment through passive targeting based upon the enhanced permeation and retention (EPR] effect [34]. It can be said about EPR; tumors often have leaky vasculature compared to healthy vasculature in normal tissues. Nano-drugs, when administered intravenously, can have prolonged circulation if they are not small enough (less than 50 nm) to be excreted by the kidney or large enough (more than 800 nm) to be rapidly

recognized and trapped by the reticuloendothelial system (RES), leak into the tumor tissue through leaky tumor vasculature, accumulates there, and then releases their therapeutic cargo [35]. The RES, which stands for reticuloendothelial system, is sometimes referred to as the mononuclear phagocyte system. The system is comprised of both cellular and noncellular components. The reticuloendothelial system [RES] plays a crucial role in the elimination of nanoparticles from the biological system, resulting in the achievement of subtherapeutic levels of therapeutic agents at the specific tissue site. Macrophages are a prominent constituent inside the reticuloendothelial system (RES) [36]. A number of chemotherapeutic nanomedicines, including Doxil/Caelyx, DaunoXome, Myocet, Abraxane, Lipusu, Nanoxel, Oncaspar, DepoCyt, Genexol-PM, Mepact, NanoTherm, Marqibo, ONIVYDE, DHP107, Vyxeos, Apealea, and Hensify, have been granted FDA approval and are presently available on the market for the treatment of diverse types of cancer. Consequently, a majority of nanomedicines utilized in the field of cancer treatment are formulated using liposomes [33]. In the case of OXA, Cheng, and Liu reported that only three nano-OXA Aroplatin, Lipoxal, and MBP-426 entered the clinical sector, but they were stopped in phases 2, 1, and 2, respectively [32]. Therefore, researchers aim to prepare a suitable nano-OXA, and have used different carriers and evaluated their efficiency.

2. Nanoparticles Containing Oxaliplatin

In this study, we review the nano-OXA delivery systems that were introduced in colorectal cancer treatment. These drug delivery systems were categorized into seven sections including; solid lipid nanoparticles, liposomes, polysaccharides, proteins, silica nanoparticles, metal nanoparticles, and synthetic polymer carriers.

2.1. Solid Lipid nanoparticles

Lipid-based nanoplatforms have emerged as very promising drug delivery systems (DDSs) with potential for successful translation into clinical trials for the treatment of colorectal

cancer (CRC). The liposome-based carrier is considered to be one of the safest drug delivery systems (DDSs) due to its exceptional biocompatibility and biodegradability. In fact, it was among the first nanoplatforms to get approval for clinical usage by the US Food and Drug Administration (FDA) [37]. They have a lipid matrix that can be easily modified for controlled drug release. Their highly hydrophobic core enables drugs to efficiently incorporate into the core, resulting in excellent colloidal stability in the body. Surface modification with polyethylene glycol (PEG) can increase their blood circulation properties. Additionally, SLNs can be designed to target specific tissues or cells, which can improve the efficacy of the drug and reduce side effects [38]. SLNs are composed of solid lipids, surfactants, and water. The selection of solid lipids can have an impact on the characteristics of solid lipid nanoparticles [SLNs). For instance, several solid lipids exhibit varying degrees of hydrophobicity, hence influencing the drug's solubility. These particles can be formulated using various methods, including ultrasonication, microemulsion, and high-pressure homogenization. Nevertheless, it is crucial to acknowledge that the approach employed in the development of the SLNs might also exert an influence on their characteristics. One potential effect of ultrasonication is the reduction in size of solid lipid nanoparticles (SLNs), but high-pressure homogenization has the potential to increase their size [39].

Triglycerides, beeswax, cetyl alcohol, carnauba wax, cholesterol, emulsifying wax, and cholesterol butyrate are a few typical solid lipids used to create SLNs [40]. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) were developed as highly secure colloidal carriers for the transportation of pharmaceuticals with low solubility. SLN/NLC possess the distinctive characteristic of being comprised of excipients that have already obtained approval for usage in pharmaceuticals intended for human consumption. This confers a significant advantage over other nanoparticulate systems that are produced using unique materials [41]. Nevertheless, certain solid lipid nanoparticles (SLNs) have the

potential to induce hepatotoxicity or nephrotoxicity. In order to evaluate the *in vivo* toxicity of solid lipid nanoparticles (SLN), it is necessary to conduct a comprehensive assessment. In their study, Weyhers et al. (2006) examined the effects of two different doses, specifically 200 µl and 400 µl, of solid lipid nanoparticle (SLN) dispersion on mice. The outcomes seen *in vivo* were contingent upon both the lipid matrix employed and the dosage delivered. No deleterious findings were seen in the case of cetyl palmitate-containing solid lipid nanoparticles (SLN). However, formulations including large doses of Compritol resulted in the buildup of the lipid in the liver and spleen, later leading to pathological changes [42]. About solid lipid nanoparticles, an in vitro drug release study of OXA loaded SLNs (OPSLNs) and OPSLNs and coupled folic acid (OPSLNFs) formulation revealed sustained drug release pattern for up to 6 days the highest anticancer potency activity and sensitivity of HT-29 cells to the drug entrapped, was OPSLNFs in comparison with OPSLNs and OXA solution. In contrast, OPSLNFs had considerably higher cytotoxicity than OPSLNs and free OXA solution [43]. In order to increase the uptake and efficacy of OXA chemotherapy in colon cancer cells (HCT116 and HT-29), Sundaramoorthy et al., (2016) prepared pro-apoptotic nanoparticles (NPs) with self-micellar anticancer lipid (SMAL). They demonstrated that, in contrast to free OXA that enters cells by passive diffusion across the cell membrane, the cytotoxic effects of SMAL-NPs and SMAL-OL are mostly attributable to enhanced caveolae-mediated endocytosis uptake, which results in high intracellular accumulation and increased cell death. The study suggests that the inhibitory effect of SMAL-OL on cyclin A and cyclin B, which are crucial regulatory proteins, may be a determining factor in the anti-apoptotic activity of these nanoformulations [44]. Rajpoot and Jain (2020) prepared unconjugated and folic acid conjugated SLNs (SLN-OXA and FA-SLN-OXA, respectively) for their potential against CRC. Outcomes for FA-SLN-OXA revealed more cytotoxicity against COLO-205 cells than free OXA and SLN-OXA. In-vivo investigation using Gamma

scintigraphy showed that the level of drug in the colonic tumor by ^{99m}Tc-EuB-FA-SLN-OP was significantly (p<0.0001) higher than that of ^{99m}Tc-EuB-SLN-OP [45]. In another study OXA loaded D-α-tocopherol polyethylene glycol 1000 succinate (TPGS)-based lipid nanoparticles (OXA/TLNP) were prepared by Wang et al., (2018) to enhance the anticancer effect in HT-29 colon cancer cells. TPGS has the potential to function as an emulsifying agent and a solubility enhancer in lipid nanoparticles. Additionally, it has been observed to exhibit inhibitory effects on P-glycoprotein (p-gp) efflux pumps, thereby circumventing the resistance to multidrug use in cancer cells, one crucial determinant associated with the lack of success in treatment outcomes [46]. The utilization of lipid nanoparticles based on TPGS and loaded with OXL has been shown to result in a noteworthy uptake of said nanoparticles. The IC50 value of free OXA was 4.25 μg/ml whereas the IC50 value of OXA/TLNP was 1.12 μg/ml (about 3-fold lower). Additionally, OXL/TLNP remarkably enhanced the apoptosis of cancer cells. About 52% of the cells were in the early stages of apoptosis, while 13% were in the late stages. In this case, early and late apoptosis phases for free OXA were 19.2 and 3.4%, respectively, indicating the potent anticancer effect of the lipid nanoparticles [38]. In a study conducted by Duan et al. (2019), it was demonstrated that the encapsulation of dihydroartemisinin (DHA) and OXA prodrugs effectively mitigates their disintegration and degradation. The researchers conducted a study with OXA/DHA core-shell particles that were coated with a lipid bilayer containing a cholesterol-DHA conjugate (chol-DHA). This coating allowed for precise control over the release of drugs in tumors, while also minimizing the exposure of drugs to the systemic circulation [47] (Table 1).

2.2. Liposomes

In the area of nanomedicine, liposomes have become potentially useful tools for drug and gene delivery. They have proven to lessen the toxicity of medications while increasing their efficacy. We recently demonstrated that the severity of neuropathy induced by oxaliplatin

encapsulated in PEGylated nanoliposomes was less than that of the free drug group [48]. Liposomes, consisting of bilayered phospholipids, serve as a partition between the intracellular and extracellular environments [49]. The amphipathic nature of phospholipids results in the formation of a stable structure where the hydrophilic heads orient towards the aqueous environment and the hydrophobic tails aggregate together. These carriers can encapsulate both hydrophilic and hydrophobic medications, making it possible to distribute a greater variety of medications this way [50, 51]. The initial generation of liposomes, known as conventional liposomes, is comprised of a phospholipid bilayer including anionic, cationic, or neutral phospholipids and cholesterol. These liposomes enclose a space filled with aqueous solution. The initial iteration of liposomes has a limited duration of existence while undergoing intravenous circulation, mostly as a result of their absorption by the reticuloendothelial system (RES]. The initial advancement in liposome technology (referred to as second-generation) was the attachment of polyethylene glycol (PEG) to a lipid anchor. This change resulted in the development of long-circulating liposomes that exhibited enhanced stability in the plasma, prolonged circulation duration, and reduced toxicity. Nevertheless, it is crucial to acknowledge that the dimensions of PEG-liposomes might potentially exert an influence on their stability and duration of circulation. As an illustration, it may be observed that cells have a higher propensity to internalize smaller PEG-liposomes, but bigger PEG-liposomes tend to undergo clearance by the immune system within the body [52]. The initial long-circulating liposomes that were thoroughly studied were liposomal doxorubicin that had been modified with polyethylene glycol (dox/PEG-L). The dox/PEG-L vesicles, with a diameter ranging from 80 to 90 nm, exhibited an extended blood circulation half-life of 2-3 days, surpassing that of the free drug by several hundred-fold. Additionally, the concentration of the administered medication in the tumor tissue was about six times greater compared to the unencapsulated drug [53]. In the present era, the field of

nanotechnology has made significant progress, leading to the emergence of the third generation of liposomes. This advancement involves the surface modification of liposomes through the incorporation of suitable ligands, including small molecules, vitamins, carbohydrates, polysaccharides, peptides, aptamers, antibodies, and enzymes [54]. The selection of phospholipids can exert an influence on the characteristics of liposomes. The inclusion of cholesterol in liposomes is essential due to its capacity to regulate membrane permeability, alter fluidity, and enhance the stability of bilayer membranes when exposed to biological fluids like blood and plasma [54]. The incorporation of dipalmitoylphosphatidylcholine (DPPC) and distearoylphosphatidylcholine (DSPC) into formulations gives rise to liposomes that exhibit temperature-dependent behavior. Liposomes possessing a transition temperature exceeding that of the average body temperature (42–44 °C) are very suitable for hyperthermia applications. DOPE is frequently utilized as a fundamental constituent in pH-sensitive liposomes. In an acidic environment, the liposomes containing DOPE along with weakly acidic amphiphiles such as phosphatidylserine (Ps), cholesteryl hemisuccinate (CHEMS), and phosphatidylglycerol (PG) undergo destabilization. This leads to the release of their cargo through an intensified process of liposomal fusion with the endosomal membrane [55]. Because OXA is a hydrophilic medicine and liposomes have a hydrophilic core that may enclose hydrophilic pharmaceuticals, they can be thought of as effective delivery systems for OXA. Prior research findings suggest that the use of liposomal encapsulation of OXA exhibits greater antitumor activity compared to the free drug because it is crucial to consider the mitigation of drug toxicity towards healthy tissues [56]. The thin film approach, reverse phase evaporation method, and modified heating method are the most used techniques for creating liposomes. According to the study, making stable and effective liposomes for OXA *in vivo* is easier with the thin film approach [57]. In contrast to PEG-liposomes, bare liposomes, and free OXA, Suzuki et al. (2008) discovered that intravenously

delivered OXA contained within transferrin-conjugated polyethylene glycol liposomes significantly inhibited tumor growth. [58]. Empty PEG-liposomes, free OXA, or PEG-liposomal OXA were all employed by Yang et al. (2011) to treat SW480 human colorectal cancer cells. They found that PEG-liposomal OXA induced a higher apoptotic response than free OXA or empty PEG-liposomes. Additionally, Cyclin D1 expression was increased whereas Cyclin A expression was decreased by PEG-liposomal OXA treatment. The results presented here demonstrate that entrapping OXA in PEG-liposomes boosts the anticancer activity of the chemotherapeutic drug. PEG-liposomal OXA may control the production of Cyclin A or Cyclin D1, as well as pro- and anti-apoptotic proteins, which affects apoptosis in SW480 human colorectal cancer cells [50]. Accordingly, it can be said that increased apoptosis caused by OXA is another aspect of the cellular response to PEG-liposomal OXA treatment, which manifests as a synergistic growth inhibitory effect in colorectal cancer cells [51]. In another study, the liposomes were co-loaded with OXA and irinotecan hydrochloride, one of the standard combination regimens for the treatment of colorectal cancer in clinics. According to an in vitro cytotoxicity analysis Co-loaded liposomes were found to be more harmful to CT-26 and HCT-116 cells than a combination of single loaded liposomes. Additionally, in CT-26 carrying BALB/c mice, co-loaded liposomes also demonstrated superior anti-tumor activity. Liposomes displayed lower toxicities than their free forms, based on *in vivo* safety evaluation [59]. Regarding the inadequate therapeutic concentration of free OXA *in vivo*, a profitable delivery system is needed, which can transfer OXA directly to tumor cells to take advantage of its anti-tumor effect. Therefore, transferrin (TF)–PEG-liposomes encapsulating OXA was able to perform well in satisfying these requirements. Since tumor cells have a far higher concentration of TF receptors than normal cells do, TF-PEG-liposomes would integrate into mouse Colon 26 tumors by TF receptor-mediated endocytosis and transport OXA into the cytoplasm. The literature examined the anti-tumor

activities of TF–PEG-liposomes encapsulating OXA by comparing and contrasting OXA encapsulated within Bare-, PEG-, and TF–PEG liposomes. A sort of tumor growth suppression by free OXA in and encapsulated within Bare- or PEG-liposomes, but the highest suppression was seen in OXA encapsulated within TF–PEG-liposomes. Additionally, in the animal model, liposomal OXA did not significantly affect liver, heart, or kidney function, and serum albumin, total protein, GOT, GPT, and BUN levels did not significantly differ from those of the non-treated and saline-injected animal models [58] (Table 2).

2.3. Polysaccharides

Polysaccharides are macromolecules made up of multiple monosaccharide repeats linked by glycosidic links. Based on their monosaccharide units, they can be categorized into homopolymers like glycogen, and starch, or heteropolymers such as chondroitin sulfate, chitosan [60], hyaluronic acid, and pectin. They have a large number of multi-functional groups that give them the ability to be a vesicle of different pharmaceutical agents. Due to the advantages of polysaccharides including abundance in nature, biocompatibility, water solubility, biodegradability, non-toxicity, low-cost processing, and bioactivity, they are a promising biomaterials in nanomedicine [61]. Chondroitin sulfate (CS), a cross-linked and readily water-soluble polysaccharide, is presented as a developing colon targeting carrier system for delivery of OXA to treat colorectal cancer. In this way, a cross-linked chondroitin sulfate-co-poly(methacrylic acid) (CSMA) hydrogels for colon targeting of OXA to treat colorectal cancer was prepared by Barkat et al., (2017). To assess the toxicity of the drug-carrier system to the biological system, a rabbit toxicity assessment of the produced formulations was also carried out. They reported that the formulations were nontoxic to the biological system [62]. The cellular affinity of hyaluronic acid (HA) is improved when it is treated with methacrylic acid. According to the study conducted by Magalhaes et al. (2014), it was shown that chondrocytes exhibit adhesion and display a spherical shape when included

into HA hydrogels that have undergone methacrylic acid alteration. Furthermore, with the modification of hydrogel using methacrylic acid, alterations to the molecular weight of HA enable the formation of a dense network with high cross-linking density in precursor solutions, facilitated by macaronomers such as polyethylene glycolic (PEGDM). Animal models are employed to sustain cellular viability and facilitate the generation of fresh cartilage tissue [63].

In another study, chemical cross-linking using various doses of CS and acrylic acid (AA) was used to create oral hydrogels. The manufactured hydrogels consequently displayed pH-sensitive swelling dynamics and drug release that was greater at pH "7.4". Additionally, no indications of lesions, disruptions, deformations, or any other pathological changes were seen in the vital organs [64]. Hydrogels, first identified in 1968, represent a category of network polymers characterized by their hydrophilic properties, enabling them to exhibit significant water absorption capabilities. These materials possess distinctive characteristics that provide moderate to high levels of physical, chemical, and mechanical stability when they are in their swelled form, depending on the individual application [65].

By physically incorporating OXA and tannic acid (TA) polymeric nanoparticles (OXA/TA NPs) into a thermosensitive hydrogel, OXA/TA NPs-hydrogel (OXA/TA NPs-H), Ren et al. (2019) created an injectable drug delivery method. The formulation utilizing the hydrogel limited the growth of CT26 peritoneal colon cancer *in vivo*, enhanced survival time, and improved quality of life in model mice. As a result, they hypothesized that OXA/TA NPs-H would be useful in the treatment of colorectal cancer. [66]. Hyaluronic acid (HA) is presented for designing a drug delivery system bearing OXA for colon tumor targeting. Although chitosan nanoparticles (CTNPs) are an effective delivery system for anticancer drugs by oral administration, compared with HA-coupled chitosan nanoparticles (HACTNPs), HACTNPs are reported to be more specific for delivery of drugs to colon tumors and more effective.

Chitosan, being a prominent polysaccharide in the field of drug administration, has limited solubility in water while demonstrating solubility in aqueous solutions with an acidic pH. Furthermore, as a result of the existence of active amino groups, chitosan has the potential to undergo chemical modifications in order to enhance its physical characteristics. Chitosan and its modified derivative-based nanoparticles has the ability to selectively accumulate at specific cancer locations through both active and passive processes [67]. Jain et al., (2010) reported that the entrapment efficiency of HACTNPs was less and they also had a decrease in drug release that could be due to the structural integrity of HA coupling [68]. In another study, HA-coated AL nanogels functionalized with folic acid (F/HA/AL nanogels), were designed for targeted drug delivery of OXA. The advantages of using nanogels for drug delivery systems are their ability to control delivery and improve the stability of drugs According to the results; F/HA/AL/OXA nanogels could penetrate HT29 cells and inhibit cancer cell proliferation compared to free OXA. They were also able to regulate the expression of the apoptosis-related gene in HT29 cells [69]. Farmanbar et al., (2022) designed superparamagnetic (Fe3O4) nanoparticles using the water extract of chia seeds. The nanoparticles were subsequently covered in chitosan (CS), Fe3O4@CS core-shell, and used to transport the drugs irinotecan (IRI) and OXA, which were designated as Fe3O4-OXA@CS core-shell and Fe3O4-IRI@CS core-shell, respectively. The IC50 values of nano-drugs against colorectal cancer cells CT-26 showed that the lowest amounts were related to nano drugs containing OXA (79.6 ppm) and IRI (61.1 ppm) compared with Fe3O4@CS (246.6 ppm) [70]. The study conducted by Alavi et al. (2023) aimed to assess the efficacy of core-shell ZnO nanoparticles (ZnO-NPs@polymer shell) loaded with OXA by polymerization. This evaluation was carried out using in vitro experiments and *in vivo* mice models specifically designed for colorectal cancer. The biological findings revealed that the ZnO-Gd-OXA compound effectively suppressed tumor development through the stimulation of

reactive oxygen species and the inhibition of fibrosis. These results highlight the potential of ZnO-Gd-OXA as a promising therapeutic agent for the treatment of colorectal cancer, emphasizing the need for more investigations in this area [71]. In a separate investigation, ion crosslinking and emulsification crosslinking techniques were employed to fabricate nanoparticles of N,O-carboxymethyl chitosan OXA (CMCS-OXE NPs) and N,O-carboxymethyl chitosan resveratrol (CMCS-Res NPs), respectively. The results of *in vivo* investigations conducted on BALB/c mice shown that the combined administration of both types of nanoparticles has considerably more efficacy in suppressing colon cancer compared to the use of free medication or a single type of nanoparticle. The combination treatment including both types of nanoparticles has a more pronounced anti-colon cancer effect compared to the administration of free medicines or the use of either type of nanoparticle in isolation [72].

According to the findings of Kaur et al. (2021), the incorporation of OXA and vanillic into polysaccharide-based functionalized polymeric micelles (FPMs) has the potential to enable targeted delivery specifically to the colon. This targeted approach may result in improved therapeutic effectiveness, since lower medication dosages might be administered. Furthermore, the incorporation of vanillic acid alongside oxaliplatin in functionalized polymer micelles (FPMs) may confer colon-targeting capabilities, hence enhancing efficacy and safety. This approach has the potential to target numerous pathways, beyond the limitations of existing adjuvant chemotherapies now available in the market for colon cancer therapy [26].

OXA was encapsulated into chitosan-graft-poly-N-isopropylacrylamide (CS-g-PNIPAAm) co-polymeric nanoparticles in order to create a tumor-targeting drug delivery system. The MTT assay and fluorescence microscopy examination revealed that the tumor microenvironment dramatically increased drug release and cell uptake. The authors claim that

the OXA tumor-targeted medication delivery using the generated nanoparticles showed remarkable promise [73].

For the purpose of colonic distribution of OXA, cross-linked pectin-based LA-co-MAA hydrogels were synthesised in one study using the free radical polymerization approach. A dose-dependent effect was seen against Vero, MCF-7, and HCT-116 cell lines when free OXA and OXA-loaded hydrogels were tested using the MTT assay. The blank hydrogels were shown to be cytocompatible. The oral tolerance study performed on rabbits confirmed that the hydrogel dispersion was well-tolerable up to 3650 mg/kg of body weight without inducing any histopathological or haematological abnormalities as compared with the group that served as the control [74]. Dutta and Sahu (2012) encapsulated superparamagnetic iron oxide nanoparticles (SPIONs) and OXA within pectin cross-linked with $Ca2^{+}$ to produce magnetically functionalized pectin nanocarriers. The nanocarriers demonstrated a protracted discharge of OHP in a phosphate buffer solution that was upheld at pH 5.5 and 7.4. The profile of drug release complied with a mechanism that was controlled by both swelling and diffusion [75]. Using a hot-melt extrusion technique and an FDM printer, Mirdamadian et al. (2022) sensitized eudragit L100-55 filament with OXA loaded alginate nanoparticles (OXA-NPs) to create 3D printed tablets with good drug homogeneity and selective OXA release in the colonic environment. Compressed tablets did not exhibit any significant antitumor effect, most likely due to non-selective drug release in the stomach and upper intestine environments; whereas 3D printed tablets containing OXA-NPs demonstrated an impressive antitumor effect that was comparable with intravenous OXA solution (p 0.05) with a better safety profile [76]. Another polysaccharide is cyclodextrins (CDs), which are notable for their capacity to combine with a variety of guest molecules to generate inclusion compounds in aqueous solutions. Three water-soluble OXA complexes were created in one work by inclusion complexation with b-cyclodextrin (b-CD), c-cyclodextrin (c-CD), and HP-b-

cyclodextrin [77]. It was discovered that the complex with CDs in 1:1 stoichiometry inclusion modes enhanced the water solubility of OXA. Against HCT116 and MCF-7 cells, the inclusion complexes showed about two times as much cytotoxicity as free oxaliplatin. The oxaliplatin/CD complexes' acceptable water solubility and enhanced cytotoxic activity may be helpful for their usage in anti-tumor therapy [77]. Bentonite/cellulose nanocomposite as another polysaccharide was synthesized for capsulation of OXA. The composite shows continuous and slow release of the drug, with 94.3% cell viability for the normal cells (CCD-18Co), and 23% for the colorectal cancer cells (HCT116) [78]. These authors in another work (2020) functionalized cellulosic fibers with kaolinite (EXK/CF) to prepare a carrier for OXA against HCT116. With maximum release percentages of 86.4 and 95.2% for about 100 hours, the EXK/CF composite demonstrated a promising loading capacity. Compared to free OXA, the nano-composite showed a better safety impact on CCD-18Co cells and a larger harmful impact on HCT116 cells [79] (Table 3).

2.4. Proteins

One of the other nanoparticles for delivering drugs are protein nanoparticles [80]. Cisplatin, carboplatin, and OXA's in vitro protein binding rates (PBR) were found to be 98%, 25-50%, and 98%, respectively, whereas the three medications' *in vivo* plasma protein binding rate concentrations were 96%, 15%, and 80%, respectively. According to research by Kato et al. (2019), cisplatin and OXA bind to human serum albumin (HSA) irreversibly and may also interact with tissue protein and/or DNA irreversibly. Their therapeutic drug monitoring is hindered by the challenges associated with forecasting the tissue concentrations of cisplatin and OXA from their plasma concentration [81]. The most important blood serum protein, HSA, has the ability to transport a significant number of molecules containing ions, medications, and other ligands to the target area [82-84]. In the study by Ziaaddini et al.,

(2020), bovine serum albumin (BSA) was used as biocompatible nanocarrier (BSANPs) to synthesize a nanoparticles formulation.

The BSANPs were loaded with OXA, and FTIR, AFM, and FESEM methods were used to verify the loading. When compared to OXA alone, the MTT assay for the OXA@BSANPs showed an increase in normal cell viability and an increase in cancer cell mortality [85]. Maleimide-modified, mono-functionalized platinum (IV) and OXA complexes enable preferential binding to HSA in the circulation. By preventing quick renal clearance, this not only prolongs the plasma half-life but also increases the drug's preferred accumulation in tumor tissue due to the EPR effect. Pichler et al. in 2013 reported the first maleimide-functionalized OXA (IV) prodrug KP2156, which was able to bind to Cys34 of albumin and enables to release OXA in a highly tumor-specific manner [86]. They demonstrated in their subsequent work (2021) that KP2156 creates extremely stable albumin adducts in the blood that have a superior pharmacological profile, including noticeably delayed terminal excretion half-life and increased effective platinum dose (measured by ICP-MS) [87]. The albumin-bound medication builds up in the cancerous tissue, where it is activated by reduction to release OXA after entering the cancer cells by clathrin and caveolin-dependent endocytosis. In contrast to free OXA and a non-albumin-binding succinimide analogue, KP2156 exhibits substantial, sustained anticancer action against CT26 colon cancer tumors *in vivo* based on cell cycle arrest and apoptotic cell death [88]. In the study by Mayr et al. (2017), *in vivo* anticancer tests using mice bearing the CT26 gene revealed that, in contrast to cisplatin derivatives, the OXA-based complexes had outstanding greater activity than the free drug, leading to the cure of the majority of treated mice [88]. In addition to HSA, β-lactoglobulin can also be a suitable protein for the preparation of pharmaceutical and nutritional nanoparticles, due to their high-water solubility, stability at an acidic pH, and stability against gastric pepsin, abundance, and gel-forming ability [89]. In addition, nanoparticles utilized in

oral medication delivery systems designed for targeting the colon must effectively address challenges related to pH sensitivity and transit duration inside the gastric environment. In the context of oral delivery, it is imperative to safeguard the formulation to mitigate the risks of degradation, untimely drug release, and early absorption prior to reaching the colon. The aforementioned challenges can be effectively addressed with the implementation of enteric coating on the nanoparticle delivery method. The enteric coating serves as a protective barrier that shields the encapsulated medicine from the acidic conditions of the stomach, while also regulating its release in order to target specific locations within the lower gastrointestinal tract [90]. Therefore, these features enable them to bind to OXA for the treatment of colorectal cancer [89, 91, 92]. Monti et al. (2022) conducted a study examining the possible application of the OXA/β-lactoglobulin complex as drugs with anticancer properties. Significantly, the cytotoxicity findings indicate that the complex resulting from the interaction between the anticancer agent and the protein exhibits more cytotoxicity compared to the unbound medicines, since it elicits the same cellular death mechanism. The authors propose that the reversible binding of Pt to the Met side chain indicates the potential use of β-lactoglobulin as a medication delivery mechanism for Pt-based compounds [91]. Reduced nanographene oxide (rNGO) and -lactoglobulin protein were employed in 2023 by Almajidi et al. for better and more efficient encapsulation, loading, and release of OXA medicine (rNGO/-Lg@OXP) in colon carcinoma cells. According to the predicted charge transfer value for rNGO/-Lg@OXP ($\Delta N_{max} = 0.16$), electrons from the drug were transferred to the nanocomposite, resulting in stereo electronic resonance, hardening, and stabilizing their geometric structure. Due to of the drug's electrical stereo resonance with the nanocomposite, rNGO/-Lg@OXP is more toxic to colon cancer cells than free OXA but less hazardous to healthy tissues [93]. In a different study, β-lactoglobulin nanocapsules containing OXA were created in three different pHs (3, 4.5, and 7) and tested for their efficacy in treating colon

cancer both with and without low methoxyl pectin. According to research, OXA complexed β-LG nanocapsules with low methoxyl pectin can be a highly attractive choice for use in oral medication administration for the treatment of colon cancer [94] (Table 4).

2.5. Silica Nanoparticles

Mesoporous silica nanoparticles (MSN), have gained much attention as a delivery system due to their outstanding properties including: non toxicity, physicochemical stability, easy modification, high loading capacity, tunable pore structures, and size, and high specific surface area. Their high surface areas and straight narrow channels give them the ability to facilitate adsorption of drugs into their structures and being decorated with some molecules that help them with the delivery process [95-97]. In order to mitigate the systemic harmful impact, mesoporous silica nanoparticles (MSNs) can be modified with cell-targeting ligands, enabling the localization of nanocarriers to specific cells or tissues through their affinity for cell-specific receptors. The TAT-peptide, which encompasses the YGRKKRRQRRR sequence, exhibits the ability to interact with importin α and β receptors present on cancer cells. As a result, it may effectively target the nuclear pore complexes of these cells, facilitating their entry into the nucleus [98]. By immobilizing the AS141-aptamer onto the surface of core@shell AuNP@MSNs that are functionalized with DNA and capped with AgNPs, the resulting nanocarriers exhibit cancer cell targeting capabilities, as well as redox and light responsiveness [99]. Additionally, it has been shown that folic acid (FA) may directly functionalize the surface of mesoporous silica nanoparticles (MSNs) or act as capping agents. This functionalization enhances the process of FA receptor-mediated endocytosis in cancer cells, hence facilitating targeted administration of chemotherapeutic agents. Consequently, this approach helps reduce systemic damage to healthy cells [100, 101]. According to Moghadam et al. [2023), the utilization of a secure and biocompatible silica substrate, specifically mesoporous silica nanoparticles, for stabilizing Pt-drugs has the

potential to yield several benefits. These advantages include the reduction of dosage and associated side effects, improved drug solubility and stability, and enhanced control over drug release during the chemotherapy process [102]. In this way, an article designed MSN–OXA conjugates for the first time as a drug delivery system and resulted in improved cytotoxicity against cancer cells in comparison with free OXA. Thus, it can be regarded as a possible application in cancer therapy with decreased side effects and enhanced therapeutic efficacy [96]. OXA and miRNA-204-5p loaded polyethyleneimine-hyaluronic acid (PEI-HA) assembled mesoporous silica nanoparticles (OXmi-HSMN) were designed in another formulation for the administration of OXA to increase the therapeutic efficacy of the loaded therapies. The HA-conjugated NP system will increase selectivity with better delivery efficiency to colorectal cancer cells compared to non-targeted nanoparticles. It also exhibited a noticeable inhibition of tumor growth which was higher than both free OXA and OXA-MSN [97]. The utilization of nanostructured carriers for the encapsulation of miRNAs enables the precise targeting of cancer cells, while minimizing any potential harm to healthy tissues. The utilization of nanoparticles (NPs) in cancer treatment shows promise due to their tiny size and the favorable surface-to-size ratio, which allows for the encapsulation, protection, and controlled release of miRNAs [103]. OXA/HCE6-MSNs, demonstrated also a greater inhibitory effect on cancer cells in comparison with free OXA. Additionally, it can boost the apoptosis of cancer cells along with the inhibition of their growth [104]. To introduce targeting receptors against colon cancer cells HCT-116, through co-precipitation and the sol-gel technique, Tabasi et al. (2021) created OXA superparamagnetic Fe3O4/Mesoporous Silica Nanoparticles (MSNs). It was then functionalized using NH2-bonding. According to MTT assay data, NH2 was able to express a higher OXA intracellular uptake and more CD44-binding than free OXA, which resulted in a drop in the IC50 of free OXA and NCs-drug loaded, from 7.5 g/mL to 3.2 g/mL [105]. In a different (2015) work,

mesoporous silica nanoparticles (MSNs) encapsulating OXA were decorated with the cancer-targeting ligand Arg-Gly-Asp peptide (RGD). Polyethylene glycol (PEG) and polyethyleneimine (PEI) were used to modify the nanoparticles. They considerably increased OXA's anticancer effectiveness, which was far more than chitosan's (CTS) [106] (Table 5).

2.6. Metallic Nanoparticles

Metal nanoparticles have attracted significant attention, especially in the field of cancer therapy [107]. They for drug delivery can offer several advantages over traditional drug delivery methods. These nanoparticles can also be designed to specifically target certain cells or tissues by some ligands (Aptamer, peptides, antibody and more) increasing the effectiveness of the drug and reducing side effects. Additionally, they can improve the bioavailability and stability of the drug. The production of metal nanoparticles may be categorized into two distinct methods: the physical process and the chemical process. The physical process, also known as the top-down process, involves the division of nanoparticles from their equivalent bulk material. The chemical process, also known as the bottom-up process, involves the controlled aggregation of atoms to produce them. The chemical process may be further classified into two distinct groups, namely the dry process and the wet process. The dry procedure encompasses both vapor deposition and sputtering techniques. Chemical operations often start with the reduction of metal ions or the thermal disintegration of metal complexes, resulting in the formation of 0-valent metal atoms. Subsequently, these atoms undergo controlled aggregation in a carefully regulated manner. Chemical reduction is predominantly employed as a preparatory technique for the synthesis of metal nanoparticles. The aforementioned methodology is regarded as a very promising preparative method for the creation of nanoparticles. It is well recognized for its reproducibility, ease of implementation, and cost-effectiveness. The process of alcohol reduction has been identified as an effective method for the synthesis of metal nanoparticles, with a particular emphasis on the production

of polymer-stabilized nanoparticles belonging to the platinum group metals. In addition, the sputtering process is classified as a dry process and is widely recognized as a distinctive preparative technique for producing metal nanoparticles. Magnetron sputtering devices are cost-effective tools often employed for the fabrication of inorganic thin films [108].

Among other metallic nanoparticles as drug delivery systems, gold nanoparticles (AuNPs) have many advantages including higher uptake by cells, hydrophilicity, and non-immunogenicity [109]. Also, they proved to be biocompatible and less toxic due to a core containing gold which is encircled by a protecting outer layer of organic ligands [109, 110]. Although AuNPs are non-toxic, their functionalization with substances that are linked to cancer, such as folate, aptamers, peptides, or antibodies, may make them toxic [110]. AuNPs penetrated cells via different ways like passive uptake, phagocytosis, pinocytosis, non-specific receptor-independent endocytosis, or receptor-mediated endocytosis [110]. They are a useful drug delivery system because they are suitable for conjugating various drugs, peptides, proteins, and antibodies [111]. By improving drug delivery, platinum-based chemotherapy can greatly reduce the side effects of OXA which occur from nonspecific attacks on rapidly dividing cells [112]. Based on the high surface areas of AuNPs, they can attach to a large number of available platinum drug molecules potentially, make a good delivery system for other nonplatinum-based drugs and a platinum (IV) complex by considering the ability of platinum drugs to be actively targeted to both solid tumors and leukemias [112]. An article demonstrated that OXA was successfully encapsulated inside AuNPs with significant particle size, drug-loading, and entrapment efficiency. The results suggested that the synergy and site-specific approach of immuno- AuNPs, decreased the side effects on healthy cells, which is the reason for the improved anti-cancer activity of the nanoparticles. The safety of the nanoparticles was also confirmed by performing different serum and blood tests. Comparing Oxaliplatin conjugated gold nanoparticles (Co-Ox-AuNPs)

by antibody DR5 with unconjugated nanoparticles, a similar uptake, and internalization as in the case of HCT-116 cells were observed. Nevertheless, Co-Ox-AuNPs showed a synergistic activity of antibodies that resulted in a reduction in xenograft tumor models [111]. For better medication distribution, Brown et al. (2010] prepared OXA within to a gold nanoparticle. Thiolated poly(ethylene glycol) (PEG) monolayers containing carboxylate groups were used to functionalize bare gold nanoparticles [Pt(1R,2R-diaminocyclohexane)(H2O)2]. In order to create a supramolecular combination with 280 ± 20 drug molecules per nanoparticle, 2NO3 was added to the PEG surface. In the colon cancer cell lines HCT116, HCT15, HT29, and RKO as well as the A549 lung epithelial cancer cell line, the platinum-tethered nanoparticles were tested for cytotoxicity, drug uptake, and localisation. The cytotoxicity of the platinum-tethered nanoparticles was comparable to or superior to free OXA all cell lines [112]. Copper sulfide (CuS] nanoparticles were created in one work by Gholami et al. (2022) to improve the anticancer effects of OXA against the colorectal cancer cell line CT26. The internal surface area in UiO-66-NH2 was the cause of the OXA. The MTT findings showed that UiO-66-NH2 did not significantly cause any cytotoxicity. Compared to OXA-UiO-66-NH2, which has an IC50 of 37.58 ppm, OXA-CuS@UiO-66-NH2 has a reported IC50 of 7.97 ppm. Additionally, OXA-CuS@UiO-66-NH2 can promote the apoptosis process in cells, indicating that the presence of CuS increased the proportion of apoptosis and cellular death [113]. Investigated in human colorectal cancer (HT-29) cells are the synthesis and production of OXA-loaded iodine nanoparticles (INPs), their characterisation, cell toxicity, radiosensitivity, cell apoptosis, and cell cycle test. INPs by themselves had no effect on cell cycle progression or apoptosis, but OXA-loaded INPs combined with radiation doses of 2 and 6 MV increased apoptosis. INPs' ability to increase radiation dose absorption makes them potential radio-sensitization nanoprobe agents for the treatment of HT-29 cells [114]. A metal–organic framework by UiO-66-NH2 (U) and its magnetic UiO-66-NH2 form (MU)

were used to enhance OXA efficacy. In 2- and 3-dimensional models of colorectal cancer, it was demonstrated that the developed medicines had increased anticancer activity and efficacy when compared to OXA by evaluating cell viability, proliferation and migration, and morphology. In terms of drug release, the IC50 values for OXA, MU(OXA), and U(OXA) were determined to be 6.10, 18.47, and 47.02 ppm, respectively. U(OXA) and MU(OXA) were therefore more effective than OXA [115]. Gogineni et al. (2020) created hybrid liposome-magnetic nanoparticles that were loaded with Cy5.5 dye and oxaliplatin, referred to as L-NIR-Fe3O4/OX. The findings of the study indicate that the application of an alternating magnetic field effectively induces site-specific delivery of oxaliplatin at elevated concentrations. This intervention demonstrates enhanced survival outcomes in rats with colorectal liver metastatic tumors [116]. The use of Fe3O4 in magnetically decorated nanocarriers in the delivery of anticancer OXA was satisfactorily investigated, as they can have many advantages of a nanodrug along with the fact that they show low to no toxicity in humans. A few studies have already reported on magnetic nanoparticles created for OXA delivery. Jabalera et al., investigated a biomimetic magnetic nanoparticles (BMNPs) mediated by MamC connected to OXA in 2019. In order to support the development of targeted chemotherapy against CRC in the future, the potential of OXA-BMNP nanocomposites for local drug delivery was presented. Because tumor cells quickly internalize the nanoassembly by endocytosis, these authors showed that combining the OXA with the BMNPs increases its toxicity to much greater levels than the free medication [117]. The biological activities of OXA-BMNPs nano-assemblies that were encapsulated in phosphatidylcholine unilamellar liposomes [both pegylated and non-pegylated) were examined in the following study (2020). Their findings show that the OXA-BMNPs nanoassemblies' biocompatibility and cellular absorption are enhanced by the addition of a lipid cover and further pegylation, without appreciably lowering their cytotoxic effect against

colon cancer cells [118] (Table 6). The HDAPPs (Hybrid Donor-Acceptor Polymer Particles) utilize photothermal nanoparticles that consist of electrically conductive donor-acceptor polymers. These nanoparticles are designed to function as theranostic agents, enabling both fluorescence imaging and thermal ablation of cancer. Additionally, the nanoparticles are coated with the amphiphilic surfactant DSPE-PEG-OH to enhance their stability and biocompatibility. The formulation was developed with the objective of advancing next-generation thermal treatments, with a specific focus on the utilization of photothermal nanoparticles. The study showcased the efficacy of hyperthermia in enhancing the effects of oxaliplatin by the utilization of photothermal nanoparticles, which exhibited a positive correlation with the cellular thermal dosage [119].

2.7. Synthetic polymeric carriers

Synthetic polymeric carriers have shown great potential in the field of cancer drug delivery due to their ability to target specific cells and tissues. These advanced drug delivery systems have the potential to improve the efficacy and safety of cancer treatments, while reducing side effects for patients [120]. Two major synthetic polymers that can be used as drug carriers are poly lactic-co-glycolic acid (PLGA) and dendrimers. PLGA is a biodegradable polymer that can be used to encapsulate drugs and target cancer cells [121]. Dendrimers are highly branched, nanoscale polymers that can be designed to specifically target cancer cells [122]. Both of these carriers have demonstrated promise for enhancing drug delivery and lowering toxicity in the treatment of cancer. Polyamidoamine dendrimers (PAMAM), the first dendritic platform that has been systematically studied among a variety of dendritic platforms including poly (propylene imine), poly-L-lysine, melamine, poly (etherhydroxyamine), poly (esteramine), and polyglycerol. It demonstrated great ability in drug and gene transfection [123, 124]. Nazlı and Gedik (2021) created several formulations of OXA using dendrimers, specifically PAMAM G3.5 and PAMAM G4.5. The researchers demonstrated that the

solubility of oxaliplatin exhibited a mostly linear rise in response to varying concentrations of dendrimers. PAMAM G4.5 dendrimers have the capability to form complexes with a higher loading capacity of oxaliplatin compared to PAMAM G3.5 dendrimers, ranging from 2 to 5 times greater. Additionally, the IC50 value of the PAMAM G3.5 conjugate was determined to be 0.72 μM, whereas the IC50 value for unmodified oxaliplatin was measured to be 14.03 μM. The researchers successfully built a dendrimer-based medication delivery system that had promising potential for further enhancement [125].

The pegylated PAMAM G3.5 (which is equivalent to generation 4.0.) can be used to protect dendrimer from immunological detection. Despite emphasizing the 75.69% drug loading efficiency (DLE), Oxaliplatin encapsulated in pegylated PAMAM G3.5 dendrimer (G3.5-PEG@OXA) would also be more beneficial in comparison with free OXA. First, G3.5-PEG@OXA could kill cancer cells effectively but with a reduced toxicity on normal cells in transportation within the human body. Second, G3.5-PEG@OXA can prevent the release of OXA into the blood stream and without a burst within first few hours [124]. In the following, the studies that have so far increased the efficiency of OXA in the treatment of CRC have been discussed. In one study, OXA was added to three polymeric matrices, including PLGA, polyethylene glycol (PEG), and a copolymer of PLGA conjugated with PEG (PLGA-PEG), to investigate how this medicine interacts with these materials and how well it diffuses into the environment. It was discovered that PEG did not control the release of OXA. In turn, the drug release characteristics of PLGA and PLGA-PEG are relatively comparable. Through a relaxing mechanism, the medication was fully released from PLGA and PLGA-PEG in 5 hours. Additionally, as PEG enhances biocompatibility and biomasking, acquired results demonstrate the development of a drug release mechanism, enabling full utilization of the drug to improve the treatment of cancer and even the welfare of the patients [125-126]. Electrospun polylactide (PLA) nanofibers loaded with 5-fluorouracil (5-Flu) and OXA were

created to test their anticancer effects on HCT8 cells both in vitro and *in vivo*. Drug-loaded fiber mats had in vitro cytotoxicity that was comparable to the combination of free 5-Flu and OXA, but they outperformed intravenous injection of free drugs *in vivo* anticancer activity, showing decreased tumor growth rate and prolonged mouse life [127]. For pH-responsive colon target delivery of OXA, Barkat et al. (2016) developed chemically cross-linked polyethylene glycol-co-poly(methacrylic acid) oral hydrogels (PEGMA 4000). The created hydrogels were verified to be non-toxic and biocompatible for biological systems by a toxicology research on rabbits. They stated that hydrogels could be a great option for colon-targeting OXA therapy for colorectal cancer with no side effects [128].

As prospective delivery systems for the anticancer drug OXA, nanoparticles based on biocompatible methoxy poly(ethylene glycol)-b-poly(D,L-lactide) (mPEG113-b-P(D,L)LAn) copolymers were created and the highest loading content of the drug (76%) in the carrier was showed [129]. In a work published in 2022 by Zumaya et al. produced and assessed anti-CD133 monoclonal antibody (Ab)-conjugated PLGA nanocarriers for the targeted delivery of OXA and superparamagnetic nanoparticles (IOOA) to colorectal cancer cells [130]. They reported that in contrast to the PLGA_IO-OA_OXA, which released the drug more gradually and steadily, the concentration of the released OXA from the PEGylated PLGA_IO-OA_OXA grew very quickly, reaching 100% release after just 2 hours. In that study, a viability assay was used to investigate the affinity of Ab-coated nanoparticles for CD133-positive cells in CaCo-2 cells using fluorescence microscopy [130]. In hyaluronic acid (HA) and carboxymethyl cellulose sodium (CMCNa)-based cross-linked (HC) hydrogels, OXA-loaded PLGA microparticles were added. These hydrogels demonstrated enhanced bioavailability and mean residence duration in rats following intraperitoneal treatment [131]. In one study, PLGA-OXA microspheres dramatically inhibited tumor growth in the tumor-bearing mice, which was associated with lower expression of proliferating cell nuclear

antigen and higher expression of terminal deoxynucleotidyl transferase dUTP nick end labeling in tumor cells [132]. A biodegradable nanoparticle was developed to encapsulation of 5-fluorouracil (5-FU) and OXA using PHBV/PLGA, and by HPLC determined the values of both drugs in the nanoparticle [133]. Another study used cholesterol-coated PLGA nanoparticles to effectively encapsulate and transport retinoic acid and OXA for anticancer efficacy in colorectal cancer. In vitro cell viability and proliferation of tumor cell lines (CT-26 and SW-480) were reduced after nanoparticle therapy as compared to controls. Furthermore, pro-apoptotic protein expression was increased whereas anti-apoptotic protein expression was decreased in vitro and *in vivo* [134] (Table 7).

3. Tumor targeting strategies:

The utilization of nanoparticles has been shown to effectively mitigate the systemic toxicity associated with therapeutic administration by facilitating drug accumulation specifically at tumor sites [135]. Solid tumors have a heightened density of blood vessels in order to fulfill the nutritional and oxygen demands necessary for the proliferation of tumor cells. Moreover, it is worth noting that the tumor exhibits a deficiency of operational lymphatic arteries, and there exists a considerable distance between the endothelial cells of the tumor. This structural characteristic allows for the potential extravasation or retention of macromolecular medications [136]. The process responsible for the accumulation of nanoparticles into tumor cells is commonly referred to as the increased permeability and retention (EPR) effect [136]. Nevertheless, previous studies have demonstrated that the level of vascularization in colorectal cancer (CRC) is very limited. There exist debates about the Enhanced Permeability and Retention (EPR) effect in colorectal cancer (CRC). In recent years, researchers have increasingly recognized the heterogeneity of tumor-targeting facilitated by the enhanced permeability and retention (EPR) effect [137]. Therefore, it is imperative to augment the

targeting efficacy of nanoparticles relying on enhanced permeability and retention (EPR) effect by integrating them with additional targeting mechanisms [138, 139](Fig. 2).

Ligand-functionalized nanoparticles have the ability to selectively aggregate within the tumor site via a ligand-receptor interaction, hence facilitating the targeted delivery of therapeutic agents. The nanoparticles in question are referred to as active targeting nanoparticles [140]. Hence, the utilization of nanoparticle systems including active targeting mechanisms has promise in facilitating the targeted delivery of medications to tumor sites, hence contributing to a reduction in systemic drug toxicity [141]. In recent years, there has been a prevalent utilization of the receptor-ligand binding strategy in the active targeting design of nano-drug targeted delivery systems for colorectal cancer (CRC). This approach involves the utilization of various receptors that are highly expressed in CRC, including but not limited to the folate receptor, epidermal growth factor receptor (EGFR), CD44, epithelial cell adhesion molecule (EpCAM), CD133, αvβ3 integrin receptor, carcinoembryonic antigen, nucleolin, mannose receptor, hyaluronic acid receptor, N-acetyl-d-glucosamine, transferrin receptor, checkpoint kinase 2, CXCR4+, lipoprotein receptor-related protein-1, MUC1, neuropilin-1 (NRP-1), P-selectin, sigma-2 receptors, somatostatin receptors (SSTRs), and glucocorticoid receptor. A greater emphasis was placed on the investigation of nanoparticles that specifically target EpCAM, folate receptor, epidermal growth factor, and CD44 [20].

In conjunction with the ligand-receptor binding approach, nanoparticles can also employ bionic technology to actively target tumors. This technology primarily involves the utilization of biofilms for nanoparticle coating. This approach not only hinders the recognition of nanoparticles by the immune system but also leverages membrane proteins, glycoproteins, and homologous adhesion to facilitate targeted accumulation of nanoparticles within the tumor. The nanoparticles under investigation primarily employ erythrocyte membrane as the predominant material for their bionic cell membranes [142], cancer cell membrane [143],

leukocyte membrane [144], and so on. In addition, in order to enhance the characteristics of nanoparticles, it is advantageous to employ a strategy of camouflaging the nanoparticles using hybrid cell membranes [20].

It is certain that nanomaterials will be acknowledged and engulfed by the immune system subsequent to intravenous administration, hence resulting in unfavorable side effects and diminished effectiveness. Furthermore, the inadequate vascularization of colorectal cancer (CRC) results in a diminished quantity of nanoparticles delivered by intravenous injection to the affected site, thus restricting the effectiveness of these nanoparticles [145]. Consequently, an increasing number of scientists are dedicated to the development of orally delivered nano formulations that retain the ability to target colorectal cancer (CRC). In addition, the utilization of oral administration has the potential to enhance patient adherence to prescribed treatment regimens [20]. In order to accomplish this objective, it is imperative for colon-targeted drug delivery systems to effectively inhibit gastrointestinal degradation of the medication prior to its arrival in the colon. This mechanism ultimately leads to an elevation in drug concentration inside the tumor. In many reports about colon-targeted therapy, pH [146], time [147], or enzyme-responsive [148] nanoplatforms are designed for CRC.

4. Disadvantages and limitations of nanoparticles

So far, the effects and capabilities of nanoparticles have been discussed. But it should be mentioned that although the studied nanoparticles have good capabilities in the treatment of cancer, some limitations and possible side effects have made their use more attentive and cautious [149-155]. Solid lipid nanoparticles (SLNs) are subject to several constraints in drug administration, mostly stemming from their restricted loading capacity and stability concerns. These limits have the potential to diminish the efficacy of treatments and compromise the shelf life of the products. Notwithstanding these challenges, drug delivery systems of this

nature continue to exhibit promise, offering significant potential for continued advancement and enhancement [149].

The instability and destruction of liposomes can have a detrimental impact on the effectiveness of drugs, while the production process of liposomes is both expensive and time-consuming, which presents obstacles for achieving commercial scalability [150].

Although polysaccharides have demonstrated promise in the field of drug administration, they are accompanied by several drawbacks such as inadequate stability, restricted bioavailability, and challenges in regulating release rates [151].

The use of protein nanoparticles for medication administration is confronted with several challenges, including production expenses, possible immunological reactions in certain individuals, and concerns regarding stability during the processes of storage and transportation [152]. Silica nanoparticles provide health hazards as a consequence of their possible toxicity, inflammatory properties, and challenges associated with precise control and localization, hence leading to undesired adverse outcomes [153]. Metal nanoparticles have the potential to present health hazards and can accumulate in many organs and tissues. Consequently, the process of synthesizing and purifying these nanoparticles becomes both expensive and time-consuming, thereby reducing their accessibility for medication delivery purposes [154]. The utilization of synthetic polymer carriers in drug administration has been associated with several adverse effects, including toxicity, immunological responses, and environmental harm. These negative outcomes can be attributed to the non-biodegradable properties of these carriers, which can lead to their buildup in the environment. Hence, it is important to exercise careful consideration before employing them [155]. Furthermore, the distinct characteristics that come from the diminutive dimensions of nanoparticles have significant prospects for medical applications. However, it is imperative to acknowledge the concurrent emergence of safety issues due to the physicochemical attributes of nanoparticles, which may induce

modifications in pharmacokinetics and enable their traversal beyond biological barriers. Furthermore, the intrinsic toxicity of certain minerals, such as heavy metals, and their capacity to collect and last inside the human body have posed a significant obstacle in their application and implementation. The achievement of effective clinical use of these nanoparticles is heavily contingent upon their stability, duration of circulation within the body, capacity to reach disease locations, availability for interaction, and safety characteristics. Hence, it is imperative to employ rational design strategies in order to tailor these structures for particular applications, enhance their pharmacokinetic properties, and mitigate off-target toxicity, hence facilitating their successful translation to clinical settings [156]. For instance, some nanoparticles have been found to exert detrimental effects on several organs, including the reproductive system [157]. The potential consequences of being exposed to Superparamagnetic iron oxide nanoparticles (SPION) include various toxic side effects. These include the leakage of lactate dehydrogenase from cellular membranes, impaired function of mitochondria, inflammation, the formation of apoptotic bodies, chromosome condensation, the generation of reactive oxygen species (ROS), and DNA damage [157, 158]. Table 8 is prepared in this case.

5. Perspective

This review of various articles identified that most of the synthesized OXA nanomedicines were prepared based on the EPR effect, which is not enough, and it seems necessary to use specific ligands that have the ability to target cancer. Certain ligands have a higher degree of specificity in targeting cancer cells compared to others; nonetheless, it is important to note that the total eradication of systemic toxicity cannot be guaranteed. The reason for this phenomenon is because nanoparticles have the potential to be internalized by non-malignant cells, despite their intended targeting towards cancerous cells. The mitigation of systemic toxicity can be achieved by the utilization of nanoparticles of sufficiently tiny dimensions,

facilitating their rapid clearance from the body. However, it is important to acknowledge that this approach may not always be feasible. However, the literature has observed that the application of surface decoration on nanoparticles using specific ligands, such as proteins (including antibodies, antibody fragments, growth factors, and transferrin), peptides (such as cyclic RGD, octreotide, AP peptide, and tLyp-1 peptide), aptamers (such as A10 and AS1411) [159-160], and polysaccharides (such as hyaluronic acid), as well as small biomolecules (including folic acid, galactose, bisphosphonates, and biotin), can result in enhanced retention and accumulation of nanoparticles within tumour tissues. These ligands boost the selectivity and efficiency of nanoparticles, in addition to improving their stability. As a result, the future of nanomedicine is extremely bright with regards to the development of technologies. However, it is abundantly obvious that early detection procedures are one of the most important components in improving the prognosis for cancer patients. Early-stage malignancies are often lot simpler to treat, and early identification greatly increases 5-year survival rates while also lowering patient expenses.

6. Conclusion

Chemotherapy is a frequently employed therapeutic approach for cancer management, which encompasses the utilization of platinum-derived medications such as oxaliplatin, cisplatin, and carboplatin. Oxaliplatin, a third-generation platinum-derived antineoplastic agent, has demonstrated efficacy in the treatment of colorectal cancer. Individuals diagnosed with colon cancer necessitate extended periods of therapy and are obligated to adhere to a regimen of frequent medication administration spanning many months, and in some cases, even years. Due to this circumstance, it is imperative that the pharmaceutical substance is supplied using nanocarriers that facilitate a sustained release of the therapeutic agent. The drug delivery methods were categorized into seven groups, including solid lipid nanoparticles, liposomes, polysaccharides, proteins, silica nanoparticles, metal nanoparticles, and synthetic polymer

carriers. Multiple studies have demonstrated that the utilization of different carriers for the administration of oxaliplatin can enhance its efficacy and mitigate adverse effects. However, more investigation is required to ascertain the most suitable carrier and assess its effectiveness in clinical trials. Consequently, the utilization of nanocarrier systems in the administration of oxaliplatin for the management of colon cancer holds the potential to enhance therapeutic efficacy and enhance the overall well-being of patients.

Consent for publication

Not applicable.

Availability of data and materials

This study is a review article that was prepared after collecting the data available in the published articles.

Funding

This work was supported by the Basic Sciences Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran. [Grant Number: 991375].

Conflict of interest

The authors declare no conflict of interest financial or otherwise.

Acknowledgements

The authors would like to acknowledge Vascular and Endovascular Surgery Research Center, and also Basic Sciences Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran.

References

1. Boutry J, Tissot S, Ujvari B, Capp J-P, Giraudeau M, Nedelcu AM, et al. The evolution and ecology of benign tumors. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2022;1877(1):188643.

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 2023;73(1):17-48.

3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

4. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 2023;73(3):233-54.

5. Bogaert J, Prenen H. Molecular genetics of colorectal cancer. Annals of Gastroenterology. 2014;27(1):9.

6. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa A-E. Molecular mechanisms of colon cancer progression and metastasis: recent insights and advancements. International Journal of Molecular Sciences. 2020;22(1):130.

7. Manoochehri H, Asadi S, Tanzadehpanah H, Sheykhhasan M, Ghorbani M. CDC25A is strongly associated with colorectal cancer stem cells and poor clinical outcome of patients. Gene Reports. 2021;25:101415.

8. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010;138(6):2059-72.

9. Sheykhhasan M, Ahmadyousefi Y, Seyedebrahimi R, Tanzadehpanah H, Manoochehri H, Dama P, et al. DLX6-AS1: a putative lncRNA candidate in multiple human cancers. Expert Reviews in Molecular Medicine. 2021;23:e17.

10. Markowitz SD, Bertagnolli MM. Molecular Basis of Colorectal CancerMolecular Origins of Cancer. The New England Journal of Medicine. 2009;361(25):2449.

11. Tsang AH-F, Cheng K-H, Wong AS-P, Ng SS-M, Ma BB-Y, Chan CM-L, et al. Current and future molecular diagnostics in colorectal cancer and colorectal adenoma. World Journal of Gastroenterology: WJG. 2014;20(14):3847.

12. Geiersbach KB, Samowitz WS. Microsatellite instability and colorectal cancer. Archives of Pathology & Laboratory Medicine. 2011;135(10):1269-77.

13. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control. 2009;16(1):14-22.

14. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6):2073-87. e3.

15. Abkenar BR, Mohammadi A, Amoli HA, Soleimani AA, Korani M, Mahmoodi H, et al. Non-coding RNAs are correlated to TGF-β receptor type 2 in patients with colorectal cancer. The Journal of Gene Medicine. 2023;25(3):e3472.

16. Cohen Y, Merhavi-Shoham E, Avraham RB, Frenkel S, Pe'er J, Goldenberg-Cohen N. Hypermethylation of CpG island loci of multiple tumor suppressor genes in retinoblastoma. Experimental Eye Research. 2008;86(2):201-6.

17. Hesson LB, Wilson R, Morton D, Adams C, Walker M, Maher ER, et al. CpG island promoter hypermethylation of a novel Ras-effector gene RASSF2A is an early event in colon carcinogenesis and correlates inversely with K-ras mutations. Oncogene. 2005;24(24):3987-94.

18. Bastian PJ, Ellinger J, Heukamp LC, Kahl P, Müller SC, von Rücker A. Prognostic value of CpG island hypermethylation at PTGS2, RAR-beta, EDNRB, and other gene loci in patients undergoing radical prostatectomy. European Urology. 2007;51(3):665-74.

19. Puccini A, Berger MD, Naseem M, Tokunaga R, Battaglin F, Cao S, et al. Colorectal cancer: epigenetic alterations and their clinical implications. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2017;1868(2):439-48.

20. Wang K, Shen R, Meng T, Hu F, Yuan H. Nano-drug delivery systems based on different targeting mechanisms in the targeted therapy of colorectal cancer. Molecules. 2022;27(9):2981.

21. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. International Journal of Clinical Oncology. 2020;25:1-42.

22. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based

adjuvant chemotherapy for colon cancer. New England Journal of Medicine. 2003;349(3):247-57.

23. Sandouk F, Al Jerf F, Al-Halabi M. Precancerous lesions in colorectal cancer. Gastroenterology Research and Practice. 2013;2013.

24. Lila ASA, Kiwada H, Ishida T. Selective delivery of oxaliplatin to tumor tissue by nanocarrier system enhances overall therapeutic efficacy of the encapsulated oxaliplatin. Biological and Pharmaceutical Bulletin. 2014;37(2):206-11.

25. Oun R, Wheate NJ. Platinum Anticancer Drugs. In: Kretsinger RH, Uversky VN, Permyakov EA, editors. Encyclopedia of Metalloproteins. New York, NY: Springer New York; 2013. p. 1710-4.

26. Kaur J, Gulati M, Gowthamarajan K, Vishwas S, Chellappan DK, Gupta G, et al. Combination therapy of vanillic acid and oxaliplatin co-loaded in polysaccharide based functionalized polymeric micelles could offer effective treatment for colon cancer: A hypothesis. Medical Hypotheses. 2021;156:110679.

27. Mohammed MQ, Retsas S. Oxaliplatin is active in vitro against human melanoma cell lines: comparison with cisplatin and carboplatin. Anti-cancer Drugs. 2000;11(10):859-63.

28. Lévi F, Metzger G, Massari C, Milano G. Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clinical Pharmacokinetics. 2000;38:1-21.

29. Szefler B, Czeleń P. Will the Interactions of Some Platinum (II)-Based Drugs with B-Vitamins Reduce Their Therapeutic Effect in Cancer Patients? Comparison of Chemotherapeutic Agents such as Cisplatin, Carboplatin and Oxaliplatin—A Review. International Journal of Molecular Sciences. 2023;24(2):1548.

30. Tippayamontri T, Kotb R, Paquette B, Sanche L. Cellular uptake and cytoplasm/DNA distribution of cisplatin and oxaliplatin and their liposomal formulation in human colorectal cancer cell HCT116. Investigational New Drugs. 2011;29:1321-7.

31. Kang L, Tian Y, Xu S, Chen H. Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. Journal of Neurology. 2021;268:3269-82.

32. Cheng Q, Liu Y. Multifunctional platinum-based nanoparticles for biomedical applications. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2017;9(2):e1410.

33. Kemp JA, Kwon YJ. Cancer nanotechnology: Current status and perspectives. Nano Convergence. 2021;8(1):34.

34. Kasi PB, Mallela VR, Ambrozkiewicz F, Trailin A, Liška V, Hemminki K. Theranostics Nanomedicine Applications for Colorectal Cancer and Metastasis: Recent Advances. International Journal of Molecular Sciences. 2023;24(9):7922.

35. Kobayashi H, Watanabe R, Choyke PL. Improving conventional enhanced permeability and retention (EPR) effects; what is the appropriate target? Theranostics. 2014;4(1):81.

36. Friedman H. The Reticuloendothelial System: A Comprehensive Treatise Volume 5 Cancer. 2012.

37. Yang C, Merlin D. Lipid-based drug delivery nanoplatforms for colorectal cancer therapy. Nanomaterials. 2020;10(7):1424.

38. Wang Y, Zhang X, Zhang W, Dong H, Zhang W, Mao J, et al. Combination of oxaliplatin and Vit. E-TPGS in lipid nanosystem for enhanced therapeutic efficacy in colon cancers. Pharmaceutical Research. 2018;35(2):1-9.

39. Khairnar SV, Pagare P, Thakre A, Nambiar AR, Junnuthula V, Abraham MC, et al. Review on the scale-up methods for the preparation of solid lipid nanoparticles. Pharmaceutics. 2022;14(9):1886.

40. Gad S, Yousry A, Hassan T, Aidy S. Nanocarriers as pulmonary drug delivery systems. Records of Pharmaceutical and Biomedical Sciences. 2022;6(3):113-9.

41. Doktorovová S, Kovačević AB, Garcia ML, Souto EB. Preclinical safety of solid lipid nanoparticles and nanostructured lipid carriers: Current evidence from in vitro and *in vivo* evaluation. European Journal of Pharmaceutics and Biopharmaceutics. 2016;108:235-52.

42. Weyhers H, Ehlers S, Hahn H, Souto E, Müller R. Solid lipid nanoparticles (SLN)–effects of lipid composition on in vitro degradation and *in vivo* toxicity. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2006;61(6):539-44.

43. Rajpoot K, Jain SK. Colorectal cancer-targeted delivery of oxaliplatin via folic acid-grafted solid lipid nanoparticles: preparation, optimization, and in vitro evaluation. Artificial Cells, Nanomedicine, and Biotechnology. 2018;46(6):1236-47.

44. Sundaramoorthy P, Ramasamy T, Mishra SK, Jeong K-Y, Yong CS, Kim JO, et al. Engineering of caveolae-specific self-micellizing anticancer lipid nanoparticles to enhance the chemotherapeutic efficacy of oxaliplatin in colorectal cancer cells. Acta Biomaterialia. 2016;42:220-31.

45. Rajpoot K, Jain SK. 99mTc-labelled and pH-awakened microbeads entrapping surface-modified lipid nanoparticles for the augmented effect of oxaliplatin in the therapy of colorectal cancer. Journal of Microencapsulation. 2020;37(8):609-23.

46. Muhammad P, Hanif S, Li J, Guller A, Rehman FU, Ismail M, et al. Carbon dots supported single Fe atom nanozyme for drug-resistant glioblastoma therapy by activating autophagy-lysosome pathway. Nano Today. 2022;45:101530.

47. Duan X, Chan C, Han W, Guo N, Weichselbaum RR, Lin W. Immunostimulatory nanomedicines synergize with checkpoint blockade immunotherapy to eradicate colorectal tumors. Nature Communications. 2019;10(1):1899.

48. Alaei M, Moetamani-Ahmadi M, Mahaki H, Fiuji H, Maftooh M, Hassanian SM, et al. Nanoliposomal oxaliplatin ameliorates chemotherapy-induced neuropathy. Neuroscience Letters. 2023:137367.

49. Tanzadehpanah H, Mahaki H, Manoochehri H, Soleimani M, Najafi R. AS1411 aptamer improves therapeutic efficacy of PEGylated nanoliposomes loaded with gefitinib in the mice bearing CT26 colon carcinoma. Journal of Nanoparticle Research. 2022;24(12):252.

50. Yang C, Liu H-Z, Fu Z-X. Effects of PEG-liposomal oxaliplatin on apoptosis, and expression of Cyclin A and Cyclin D1 in colorectal cancer cells. Oncology Reports. 2012;28(3):1006-12.

51. Yang C, Liu H-Z, Lu W-D, Fu Z-X. PEG-liposomal oxaliplatin potentialization of antitumor efficiency in a nude mouse tumor-xenograft model of colorectal carcinoma. Oncology Reports. 2011;25(6):1621-8.

52. Yang C, Fu ZX. Liposomal delivery and polyethylene glycol‐liposomal oxaliplatin for the treatment of colorectal cancer. Biomedical Reports. 2014;2(3):335-9.

53. Gabizon AA, Patil Y, La-Beck NM. New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy. Drug Resistance Updates. 2016;29:90-106.

54. Khan AA, Allemailem KS, Almatroodi SA, Almatroudi A, Rahmani AH. Recent strategies towards the surface modification of liposomes: an innovative approach for different clinical applications. 3 Biotech. 2020;10:1-15.

55. Aghdam MA, Bagheri R, Mosafer J, Baradaran B, Hashemzaei M, Baghbanzadeh A, et al. Recent advances on thermosensitive and pH-sensitive liposomes employed in controlled release. Journal of Controlled Release. 2019;315:1-22.

56. Zalba S, Contreras AM, Haeri A, Ten Hagen TL, Navarro I, Koning G, et al. Cetuximab-oxaliplatin-liposomes for epidermal growth factor receptor targeted chemotherapy of colorectal cancer. Journal of Controlled Release. 2015;210:26-38.

57. Zalba S, Navarro I, Trocóniz IF, de Ilarduya CT, Garrido MJ. Application of different methods to formulate PEG-liposomes of oxaliplatin: evaluation in vitro and *in vivo*. European Journal of Pharmaceutics and Biopharmaceutics. 2012;81(2):273-80.

58. Suzuki R, Takizawa T, Kuwata Y, Mutoh M, Ishiguro N, Utoguchi N, et al. Effective anti-tumor activity of oxaliplatin encapsulated in transferrin–PEG-liposome. International Journal of Pharmaceutics. 2008;346(1-2):143-50.

59. Zhang B, Wang T, Yang S, Xiao Y, Song Y, Zhang N, et al. Development and evaluation of oxaliplatin and irinotecan co-loaded liposomes for enhanced colorectal cancer therapy. Journal of Controlled Release. 2016;238:10-21.

60. Moghadam NH, Salehzadeh S, Rakhtshah J, Tanzadehpanah H, Moghadam AH, Hajibabaei F, et al. Improving antiproliferative effect of the nevirapine on Hela cells by loading onto chitosan coated magnetic nanoparticles as a fully biocompatible nano drug carrier. International Journal of Biological Macromolecules. 2018;118:1220-8.

61. Debele TA, Mekuria SL, Tsai H-C. Polysaccharide based nanogels in the drug delivery system: Application as the carrier of pharmaceutical agents. Materials Science and Engineering: C. 2016;68:964-81.

62. Barkat K, Ahmad M, Minhas MU, Khalid I. Oxaliplatin-loaded crosslinked polymeric network of chondroitin sulfate-co-poly (methacrylic acid) for colorectal cancer: its toxicological evaluation. Journal of Applied Polymer Science. 2017;134(38):45312.

63. Magalhães J, Crawford A, Hatton PV, Blanco FJ, Roman JS. Poly (2-ethyl-(2-pyrrolidone) methacrylate) and hyaluronic acid–based hydrogels for the engineering of a

cartilage-like tissue using bovine articular chondrocytes. Journal of Bioactive and Compatible Polymers. 2014;29(6):545-59.

64. Barkat K, Ahmad M, Minhas MU, Khalid I, Malik NS. Chondroitin sulfate-based smart hydrogels for targeted delivery of oxaliplatin in colorectal cancer: Preparation, characterization and toxicity evaluation. Polymer Bulletin. 2020;77:6271-97.

65. Maspes A, Pizzetti F, Rossetti A, Makvandi P, Sitia G, Rossi F. Advances in bio-based polymers for colorectal cancer treatment: Hydrogels and nanoplatforms. Gels. 2021;7(1):6.

66. Ren Y, Li X, Han B, Zhao N, Mu M, Wang C, et al. Improved anti-colorectal carcinomatosis effect of tannic acid co-loaded with oxaliplatin in nanoparticles encapsulated in thermosensitive hydrogel. European Journal of Pharmaceutical Sciences. 2019;128:279-89.

67. Virmani T, Kumar G, Sharma A, Pathak K, Akhtar MS, Afzal O, et al. Amelioration of Cancer Employing Chitosan, Its Derivatives, and Chitosan-Based Nanoparticles: Recent Updates. Polymers. 2023;15(13):2928.

68. Jain A, Jain SK, Ganesh N, Barve J, Beg AM. Design and development of ligand-appended polysaccharidic nanoparticles for the delivery of oxaliplatin in colorectal cancer. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;6(1):179-90.

69. Shad PM, Karizi SZ, Javan RS, Mirzaie A, Noorbazargan H, Akbarzadeh I, et al. Folate conjugated hyaluronic acid coated alginate nanogels encapsulated oxaliplatin enhance antitumor and apoptosis efficacy on colorectal cancer cells (HT29 cell line). Toxicology in Vitro. 2020;65:104756.

70. Farmanbar N, Mohseni S, Darroudi M. Green synthesis of chitosan-coated magnetic nanoparticles for drug delivery of oxaliplatin and irinotecan against colorectal cancer cells. Polymer Bulletin. 2022;79(12):10595-613.

71. Alavi N, Maghami P, Fani Pakdel A, Rezaei M, Avan A. The advance anticancer role of polymeric core-shell ZnO nanoparticles containing oxaliplatin in colorectal cancer. Journal of Biochemical and Molecular Toxicology. 2023;37(5):e23325.

72. Wang Y, Ma J, Qiu T, Tang M, Zhang X, Dong W. In vitro and *in vivo* combinatorial anticancer effects of oxaliplatin-and resveratrol-loaded N, O-carboxymethyl chitosan

nanoparticles against colorectal cancer. European Journal of Pharmaceutical Sciences. 2021;163:105864.

73. Patil AS, Gadad AP, Hiremath RD, Joshi SD. Biocompatible tumor micro-environment responsive CS-g-PNIPAAm co-polymeric nanoparticles for targeted Oxaliplatin delivery. Journal of Polymer Research. 2018;25(3):77.

74. Ullah K, Sohail M, Buabeid MA, Murtaza G, Ullah A, Rashid H, et al. Pectin-based (LA-co-MAA) semi-IPNS as a potential biomaterial for colonic delivery of oxaliplatin. International Journal of Pharmaceutics. 2019;569:118557.

75. Dutta RK, Sahu S. Development of oxaliplatin encapsulated in magnetic nanocarriers of pectin as a potential targeted drug delivery for cancer therapy. Results in Pharma Sciences. 2012;2:38-45.

76. Mirdamadian SZ, Varshosaz J, Minaiyan M, Taheri A. 3D printed tablets containing oxaliplatin loaded alginate nanoparticles for colon cancer targeted delivery. An in vitro/*in vivo* study. International Journal of Biological Macromolecules. 2022;205:90-109.

77. Zhang D, Zhang J, Jiang K, Li K, Cong Y, Pu S, et al. Preparation, characterisation and antitumour activity of β-, γ-and HP-β-cyclodextrin inclusion complexes of oxaliplatin. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2016;152:501-8.

78. Abukhadra MR, Mohamed AS, El-Sherbeeny AM, Nadeem A, Ahmad SF. Synthesis of exfoliate bentonite/cellulose nanocomposite as a delivery system for Oxaliplatin drug with enhanced loading and release properties; cytotoxicity and pharmacokinetic studies. Chemical Physics Letters. 2020;755:137818.

79. Tian L, Abukhadra MR, Mohamed AS, Nadeem A, Ahmad SF, Ibrahim KE. Insight into the loading and release properties of an exfoliated kaolinite/cellulose fiber (EXK/CF) composite as a carrier for oxaliplatin drug: Cytotoxicity and release kinetics. ACS Omega. 2020;5(30):19165-73.

80. Moghadam NH, Salehzadeh S, Rakhtshah J, Moghadam AH, Tanzadehpanah H, Saidijam M. Preparation of a highly stable drug carrier by efficient immobilization of human serum albumin (HSA) on drug-loaded magnetic iron oxide nanoparticles. International Journal of Biological Macromolecules. 2019;125:931-40.

81. Kato R, Sato T, Iwamoto A, Yamazaki T, Nakashiro S, Yoshikai S, et al. Interaction of platinum agents, cisplatin, carboplatin and oxaliplatin against albumin *in vivo* rats and in vitro study using inductively coupled plasma-mass spectrometory. Biopharmaceutics & Drug Disposition. 2019;40(7):242-9.

82. Molaei P, Mahaki H, Manoochehri H, Tanzadehpanah H. Binding sites of anticancer drugs on human serum albumin (HSA): a review. Protein and Peptide Letters. 2022;29(8):651-75.

83. Tanzadehpanah H, Mahaki H, Moradi M, Afshar S, Moghadam NH, Salehzadeh S, et al. The use of molecular docking and spectroscopic methods for investigation of the interaction between regorafenib with Human Serum Albumin (HSA) and calf thymus DNA (Ct-DNA) In the presence of different site markers. Protein and Peptide Letters. 2021;28(3):290-303.

84. Tanzadehpanah H, Mahaki H, Samadi P, Karimi J, Moghadam NH, Salehzadeh S, et al. Anticancer activity, calf thymus DNA and human serum albumin binding properties of Farnesiferol C from Ferula pseudalliacea. Journal of Biomolecular Structure and Dynamics. 2019;37(11):2789-800.

85. Ziaaddini V, Saeidifar M, Eslami-Moghadam M, Saberi M, Mozafari M. Improvement of efficacy and decrement cytotoxicity of oxaliplatin anticancer drug using bovine serum albumin nanoparticles: synthesis, characterisation and release behaviour. IET Nanobiotechnology. 2020;14(1):105-11.

86. Pichler V, Mayr J, Heffeter P, Dömötör O, Enyedy ÉA, Hermann G, et al. Maleimide-functionalised platinum (IV) complexes as a synthetic platform for targeted drug delivery. Chemical Communications. 2013;49(22):2249-51.

87. Schueffl H, Theiner S, Hermann G, Mayr J, Fronik P, Groza D, et al. Albumin-targeting of an oxaliplatin-releasing platinum (iv) prodrug results in pronounced anticancer activity due to endocytotic drug uptake *in vivo*. Chemical Science. 2021;12(38):12587-99.

88. Mayr J, Heffeter P, Groza D, Galvez L, Koellensperger G, Roller A, et al. An albumin-based tumor-targeted oxaliplatin prodrug with distinctly improved anticancer activity *in vivo*. Chemical Science. 2017;8(3):2241-50.

89. Tanzadehpanah H, Bahmani A, Hosseinpour Moghadam N, Gholami H, Mahaki H, Farmany A, et al. Synthesis, anticancer activity, and β-lactoglobulin binding interactions of multitargeted kinase inhibitor sorafenib tosylate (SORt) using spectroscopic and molecular modelling approaches. Luminescence. 2021;36(1):117-28.

90. Wathoni N, Nguyen AN, Rusdin A, Umar AK, Mohammed AFA, Motoyama K, et al. Enteric-coated strategies in colorectal cancer nanoparticle drug delivery system. Drug Design, Development and Therapy. 2020:4387-405.

91. Monti DM, Loreto D, Iacobucci I, Ferraro G, Pratesi A, D'Elia L, et al. Protein-based delivery systems for anticancer metallodrugs: Structure and biological activity of the oxaliplatin/β-lactoglobulin adduct. Pharmaceuticals. 2022;15(4):425.

92. Ghalandari B, Divsalar A, Eslami-Moghadam M, Saboury AA, Haertlé T, Amanlou M, et al. Probing of the interaction between β-lactoglobulin and the anticancer drug oxaliplatin. Applied Biochemistry and Biotechnology. 2015;175:974-87.

93. Almajidi YQ, Althomali RH, Maashi MS, Ahmad I, Saleh EAM, Kareem A, et al. Nanocomposite of reduced nanographene oxide with β-lactoglobulin protein (rNGO/β-Lg) as a carrier of the anticancer drug oxaliplatin (Eloxatin). Diamond and Related Materials. 2023:110015.

94. Ghalandari B, Divsalar A, Saboury AA, Parivar K. The new insight into oral drug delivery system based on metal drugs in colon cancer therapy through β-lactoglobulin/oxali-palladium nanocapsules. Journal of Photochemistry and Photobiology B: Biology. 2014;140:255-65.

95. He H, Xiao H, Kuang H, Xie Z, Chen X, Jing X, et al. Synthesis of mesoporous silica nanoparticle–oxaliplatin conjugates for improved anticancer drug delivery. Colloids and Surfaces B: Biointerfaces. 2014;117:75-81.

96. Marcelo GA, Montpeyo D, Novio F, Ruiz-Molina D, Lorenzo J, Oliveira E. Luminescent silicon-based nanocarrier for drug delivery in colorectal cancer cells. Dyes and Pigments. 2020;181:108393.

97. Yang H, Liu Y, Qiu Y, Ding M, Zhang Y. MiRNA-204-5p and oxaliplatin-loaded silica nanoparticles for enhanced tumor suppression effect in CD44-overexpressed colon adenocarcinoma. International Journal of Pharmaceutics. 2019;566:585-93.

98. Pan L, He Q, Liu J, Chen Y, Ma M, Zhang L, et al. Nuclear-targeted drug delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles. Journal of the American Chemical Society. 2012;134(13):5722-5.

99. Tang Y, Hu H, Zhang MG, Song J, Nie L, Wang S, et al. An aptamer-targeting photoresponsive drug delivery system using "off–on" graphene oxide wrapped mesoporous silica nanoparticles. Nanoscale. 2015;7(14):6304-10.

100. Zhang Q, Liu F, Nguyen KT, Ma X, Wang X, Xing B, et al. Multifunctional mesoporous silica nanoparticles for cancer-targeted and controlled drug delivery. Advanced Functional Materials. 2012;22(24):5144-56.

101. Hoang Thi TT, Cao VD, Nguyen TNQ, Hoang DT, Ngo VC, Nguyen DH. Functionalized mesoporous silica nanoparticles and biomedical applications. Materials Science and Engineering: C. 2019;99:631-56.

102. Moghadam ME, Sadeghi M, Mansouri-Torshizi H, Saidifar M. High cancer selectivity and improving drug release from mesoporous silica nanoparticles in the presence of human serum albumin in cisplatin, carboplatin, oxaliplatin, and oxalipalladium treatment. European Journal of Pharmaceutical Sciences. 2023;187:106477.

103. Martino E, D'Onofrio N, Anastasio C, Abate M, Zappavigna S, Caraglia M, et al. MicroRNA-nanoparticles against cancer: Opportunities and challenges for personalized medicine. Molecular Therapy Nucleic Acids. 2023;32:371.

104. Zhang P-J, Liu M-D, Fan F-Y, Liu K-X. A Study on Mesoporous Silica Loaded With Novel Photosensitizers HCE6 and Oxaliplatin for the Treatment of Cholangiocarcinoma. Frontiers in Oncology. 2021;11:665182.

105. Tabasi H, Hamed Mosavian MT, Sabouri Z, Khazaei M, Darroudi M. pH-responsive and CD44-targeting by Fe3O4/MSNs-NH2 nanocarriers for Oxaliplatin loading and colon cancer treatment. Inorganic Chemistry Communications. 2021;125:108430.

106. You Y, Hu H, He L, Chen T. Differential Effects of Polymer-Surface Decoration on Drug Delivery, Cellular Retention, and Action Mechanisms of Functionalized Mesoporous Silica Nanoparticles. Chemistry–An Asian Journal. 2015;10(12):2744-54.

107. Yan J, Hanif S, Zhang D, Ismail M, Wang X, Li Q, et al. Arsenic prodrug-mediated tumor microenvironment modulation platform for synergetic glioblastoma therapy. ACS Applied Materials & Interfaces. 2022;14(32):36487-502.

108. Yonezawa T. Preparation of metal nanoparticles and their application for materials. Nanoparticle Technology Handbook: Elsevier; 2018. p. 829-37.

109. Yafout M, Ousaid A, Khayati Y, El Otmani IS. Gold nanoparticles as a drug delivery system for standard chemotherapeutics: A new lead for targeted pharmacological cancer treatments. Scientific African. 2021;11:e00685.

110. Mohd-Zahid MH, Mohamud R, Abdullah CAC, Lim J, Alem H, Hanaffi WNW, et al. Colorectal cancer stem cells: A review of targeted drug delivery by gold nanoparticles. RSC Advances. 2020;10(2):973-85.

111. Tummala S, Kumar MS, Pindiprolu SK. Improved anti-tumor activity of oxaliplatin by encapsulating in anti-DR5 targeted gold nanoparticles. Drug Delivery. 2016;23(9):3505-19.

112. Brown SD, Nativo P, Smith J-A, Stirling D, Edwards PR, Venugopal B, et al. Gold nanoparticles for the improved anticancer drug delivery of the active component of oxaliplatin. Journal of the American Chemical Society. 2010;132(13):4678-84.

113. Gholami M, Hekmat A, Khazaei M, Darroudi M. OXA-CuS@ UiO-66-NH2 as a drug delivery system for Oxaliplatin to colorectal cancer cells. Journal of Materials Science: Materials in Medicine. 2022;33(3):26.

114. Rasouli N, Shahbazi-Gahrouei D, Hematti S, Baradaran B, Salehi R, Varshosaz J, et al. Assessment of Oxaliplatin-Loaded Iodine Nanoparticles for Chemoradiotherapy of Human Colorectal Cancer (HT-29) Cells. Polymers. 2022;14(19):4131.

115. Hashemzadeh A, Amerizadeh F, Asgharzadeh F, Drummen GP, Hassanian SM, Landarani M, et al. Magnetic Amine-Functionalized UiO-66 for Oxaliplatin Delivery to Colon Cancer Cells: In Vitro Studies. Journal of Cluster Science. 2022;33(5):2345-61.

116. Gogineni VR, Maddirela DR, Park W, Jagtap JM, Parchur AK, Sharma G, et al. Localized and triggered release of oxaliplatin for the treatment of colorectal liver metastasis. Journal of Cancer. 2020;11(23):6982.

117. Jabalera Y, Garcia-Pinel B, Ortiz R, Iglesias G, Cabeza L, Prados J, et al. Oxaliplatin–biomimetic magnetic nanoparticle assemblies for colon cancer-targeted chemotherapy: An in vitro study. Pharmaceutics. 2019;11(8):395.

118. Garcia-Pinel B, Jabalera Y, Ortiz R, Cabeza L, Jimenez-Lopez C, Melguizo C, et al. Biomimetic magnetoliposomes as oxaliplatin nanocarriers: In vitro study for potential application in colon cancer. Pharmaceutics. 2020;12(6):589.

119. McCarthy B, Singh R, Levi-Polyachenko N. Oxaliplatin-resistant colorectal cancer models for nanoparticle hyperthermia. International Journal of Hyperthermia. 2021;38(1):152-64.

120. Hosseini S, Mohammadnejad J, Salamat S, Zadeh ZB, Tanhaei M, Ramakrishna S. Theranostic polymeric nanoparticles as a new approach in cancer therapy and diagnosis: a review. Materials Today Chemistry. 2023;29:101400.

121. Pardeshi SR, Nikam A, Chandak P, Mandale V, Naik JB, Giram PS. Recent advances in PLGA based nanocarriers for drug delivery system: a state of the art review. International Journal of Polymeric Materials and Polymeric Biomaterials. 2023;72(1):49-78.

122. Nikzamir M, Hanifehpour Y, Akbarzadeh A, Panahi Y. Applications of dendrimers in nanomedicine and drug delivery: a review. Journal of Inorganic and Organometallic Polymers and Materials. 2021;31:2246-61.

123. Nabavizadeh F, Fanaei H, Imani A, Vahedian J, Amoli FA, Ghorbi J, et al. Evaluation of nanocarrier targeted drug delivery of Capecitabine-PAMAM dendrimer complex in a mice colorectal cancer model. Acta Medica Iranica. 2016:485-93.

124. Nguyen DTD, Bach LG, Nguyen TH, Ho MH, Ho MN, Nguyen DH, et al. Preparation and characterization of oxaliplatin drug delivery vehicle based on PEGylated half-generation PAMAM dendrimer. Journal of Polymer Research. 2019;26:1-14.

125. Nazlı H, Gedik G. In-vitro evaluation of dendrimeric formulation of oxaliplatin. Pharmaceutical Development and Technology. 2021;26(7):750-64.

126. Pereira ED, Cerruti R, Fernandes E, Peña L, Saez V, Pinto JC, et al. Influence of PLGA and PLGA-PEG on the dissolution profile of oxaliplatin. Polímeros. 2016;26:137-43.

127. Zhang J, Wang X, Liu T, Liu S, Jing X. Antitumor activity of electrospun polylactide nanofibers loaded with 5-fluorouracil and oxaliplatin against colorectal cancer. Drug Delivery. 2016;23(3):784-90.

128. Barkat K, Ahmad M, Usman Minhas M, Khalid I, Nasir B. Development and characterization of pH-responsive polyethylene glycol-co-poly (methacrylic acid) polymeric network system for colon target delivery of oxaliplatin: its acute oral toxicity study. Advances in Polymer Technology. 2018;37(6):1806-22.

129. Kadina YA, Razuvaeva EV, Streltsov DR, Sedush NG, Shtykova EV, Kulebyakina AI, et al. Poly (Ethylene Glycol)-b-Poly (D, L-Lactide) nanoparticles as potential carriers for anticancer drug oxaliplatin. Molecules. 2021;26(3):602.

130. Zumaya ALV, Rimpelová S, Štějdířová M, Ulbrich P, Vilčáková J, Hassouna F. Antibody conjugated PLGA nanocarriers and superparmagnetic nanoparticles for targeted delivery of oxaliplatin to cells from colorectal carcinoma. International Journal of Molecular Sciences. 2022;23(3):1200.

131. Abuzar SM, Ahn J-H, Park KS, Park EJ, Baik SH, Hwang S-J. Pharmacokinetic Profile and Anti-Adhesive Effect of Oxaliplatin-PLGA Microparticle-Loaded Hydrogels in Rats for Colorectal Cancer Treatment. Pharmaceutics. 2019;11(8):392.

132. Li J-Q, Wang S-L, Xu F, Liu Z-Y, Li R. Therapeutic effectiveness of slow-release PLGA-oxaliplatin microsphere on human colorectal tumor-bearing mice. Anti-cancer Drugs. 2010;21(6):600-8.

133. Handali S, Ramezani Z, Moghimipour E, Rezaei M, Dorkoosh FA. A novel method for the simultaneous determination of 5-fluorouracil and oxaliplatin in new biodegradable PHBV/PLGA nanoparticles. Journal of the Iranian Chemical Society. 2019;16:609-15.

134. C. de SL Oliveira AL, Araújo Júnior RFd, Gomes de Carvalho T, B. Chan A, Schomann T, Tamburini F, et al. Effect of oxaliplatin-loaded poly (d, l-Lactide-co-Glycolic Acid)(PLGA) nanoparticles combined with retinoic acid and cholesterol on apoptosis, drug resistance, and metastasis factors of colorectal cancer. Pharmaceutics. 2020;12(2):193.

135. Park J, Choi Y, Chang H, Um W, Ryu JH, Kwon IC. Alliance with EPR effect: combined strategies to improve the EPR effect in the tumor microenvironment. Theranostics. 2019;9(26):8073.

136. Maeda H, Bharate G, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. European Journal of Pharmaceutics and Biopharmaceutics. 2009;71(3):409-19.

137. Anitha A, Maya S, Sivaram AJ, Mony U, Jayakumar R. Combinatorial nanomedicines for colon cancer therapy. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2016;8(1):151-9.

138. Golombek SK, May J-N, Theek B, Appold L, Drude N, Kiessling F, et al. Tumor targeting via EPR: Strategies to enhance patient responses. Advanced Drug Delivery Reviews. 2018;130:17-38.

139. Nichols JW, Bae YH. EPR: Evidence and fallacy. Journal of Controlled Release. 2014;190:451-64.

140. Hu Y, He Y, Ji J, Zheng S, Cheng Y. Tumor targeted curcumin delivery by folate-modified MPEG-PCL self-assembly micelles for colorectal cancer therapy. International Journal of Nanomedicine. 2020:1239-52.

141. Wang H, Yu J, Lu X, He X. Nanoparticle systems reduce systemic toxicity in cancer treatment. Nanomedicine. 2016;11(2):103-6.

142. Liu J-M, Zhang D-D, Fang G-Z, Wang S. Erythrocyte membrane bioinspired near-infrared persistent luminescence nanocarriers for *in vivo* long-circulating bioimaging and drug delivery. Biomaterials. 2018;165:39-47.

143. Wang Z-H, Liu J-M, Zhao N, Li C-Y, Lv S-W, Hu Y, et al. Cancer cell macrophage membrane camouflaged persistent luminescent nanoparticles for imaging-guided photothermal therapy of colorectal cancer. ACS Applied Nano Materials. 2020;3(7):7105-18.

144. Zhang Q, Dehaini D, Zhang Y, Zhou J, Chen X, Zhang L, et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. Nature Nanotechnology. 2018;13(12):1182-90.

145. Kumar B, Kulanthaivel S, Mondal A, Mishra S, Banerjee B, Bhaumik A, et al. Mesoporous silica nanoparticle based enzyme responsive system for colon specific drug delivery through guar gum capping. Colloids and Surfaces B: Biointerfaces. 2017;150:352-61.

146. Samprasit W, Opanasopit P, Chamsai B. Mucoadhesive chitosan and thiolated chitosan nanoparticles containing alpha mangostin for possible Colon-targeted delivery. Pharmaceutical Development and Technology. 2021;26(3):362-72.

147. Taymouri S, Ahmadi Z, Mirian M, Tavakoli N. Simvastatin nanosuspensions prepared using a combination of pH-sensitive and timed-release approaches for potential treatment of colorectal cancer. Pharmaceutical Development and Technology. 2021;26(3):335-48.

148. Abid M, Naveed M, Azeem I, Faisal A, Nazar MF, Yameen B. Colon specific enzyme responsive oligoester crosslinked dextran nanoparticles for controlled release of 5-fluorouracil. International Journal of Pharmaceutics. 2020;586:119605.

149. Pandey S, Shaikh F, Gupta A, Tripathi P, Yadav JS. A recent update: solid lipid nanoparticles for effective drug delivery. Advanced Pharmaceutical Bulletin. 2022;12(1):17.

150. Dymek M, Sikora E. Liposomes as biocompatible and smart delivery systems–The current state. Advances in Colloid and Interface Science. 2022;309:102757.

151. Chen J, Hu L. Nanoscale delivery system for nutraceuticals: Preparation, application, characterization, safety, and future trends. Food Engineering Reviews. 2020;12(1):14-31.

152. Kianfar E. Protein nanoparticles in drug delivery: animal protein, plant proteins and protein cages, albumin nanoparticles. Journal of Nanobiotechnology. 2021;19(1):159.

153. Pieła A, Żymańczyk-Duda E, Brzezińska-Rodak M, Duda M, Grzesiak J, Saeid A, et al. Biogenic synthesis of silica nanoparticles from corn cobs husks. Dependence of the productivity on the method of raw material processing. Bioorganic Chemistry. 2020;99:103773.

154. Jamkhande PG, Ghule NW, Bamer AH, Kalaskar MG. Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. Journal of Drug Delivery Science and Technology. 2019;53:101174.

155. Ghasemiyeh P, Mohammadi-Samani S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. Drug Design, Development and Therapy. 2020;14:3271-89.

156. Damasco JA, Ravi S, Perez JD, Hagaman DE, Melancon MP. Understanding nanoparticle toxicity to direct a safe-by-design approach in cancer nanomedicine. Nanomaterials. 2020;10(11):2186.

157. Ajdary M, Keyhanfar F, Moosavi MA, Shabani R, Mehdizadeh M, Varma RS. Potential toxicity of nanoparticles on the reproductive system animal models: A review. Journal of Reproductive Immunology. 2021;148:103384.

158. Singh N, Jenkins GJS, Asadi R, Doak SH. Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION). Nano Reviews. 2010;1(1):5358.

159. Manoochehri H, Jalali A, Tanzadehpanah H, Taherkhani A, Najafi R. Aptamer-conjugated nanoliposomes containing COL1A1 siRNA sensitize CRC cells to conventional chemotherapeutic drugs. Colloids and Surfaces B: Biointerfaces. 2022;218:112714.

160. Yang C, Liu HZ, Fu ZX, Lu WD. Oxaliplatin long-circulating liposomes improved therapeutic index of colorectal carcinoma. BMC Biotechnology. 2011;11:1-8.

Table 1. OXA loaded solid lipid nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizes Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Solid lipid OXA nanoparticles	Tristearin, DSPE, Lipoid S75, Tween 80	Folic acid Folate receptors expressing cells	146.2 ± 4.4 nm 158.8 ± 5.6 nm 0.211 ± 0.02 0.241 ± 0.03 -22.6 ± 1.1 mV -28.4 ± 1.6 mV Spherical shape and smooth surface	In cell culture (HT-29)	[43]
	SMAL (102/ 104/ 108), DPPC, DPPG	Not	110 ± 3.25 nm 96 ± 2.71 0.264 0.125 -20 mV -18.4 mV Irregularly arranged spherical	In cell culture (HCT116 and HT-29)	[44]
	Suppocire NB, Lipoïd s75, Soybean oil, Vitamin E TPGS, Myrj s40	Not	126 ± 2.35 nm 158 ± 3.15 nm Not -11.5 ± 2.3 mV Spherical shape	In cell culture (HT-29)	[38]
	Tristearin, DSPE, Eudragit S100	Folic acid Folate receptors expressing cells	146.9 ± 2.1 nm 158.2 ± 2.5 nm 0.209 ± 0.02 0.247 ± 0.03 -22.4 ± 1.3 mV -28.5 ± 1.9 mV Spherical shape	In cell culture (COLO-205) & Orally in Balb/c mice (n = 6) [1]	[45]

[1] Data were compared with Two-way ANOVA using GraphPad Prism version 7.03 software.

Table 2. OXA loaded liposome nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Liposome	Lecithin, cholesterol, DSPEPEG2000	PEG	151.56 ± 15.57 -23.68 ± 2.35 Not Not	In cell culture (SW480) & intravenously in Balb/c nude mice (n = 6) [1]	[160]
	Lecithin, cholesterol, DSPEPEG2000	PEG	Not Not Not Not	In cell culture (SW480)	[50]
	DSPC, Cholesterol, DSPEPEG(2000)	PEG, Transferrin (TF) Transferrin expressing cells	Not Not Not Not	In cell culture (Colon 26) & intravenously in BALB/c mice (n = 4) [2]	[58]
	Egg phosphatidylcholine, cholesterol	Not	184.83 ± 2.82 175.03 ± 36.13 0.090 ± 0.015 0.150 ± 0.097 -3.40 ± 0.51 -8.82 ± 2.84 Spherical shape	In cell culture (CT26 and HCT-116) & Subcutaneously In BALB/c mice (n = 5) [3]	[59]

[1] Data were compared using One-way analysis of variance (ANOVA) and student's t-test using spss 17.0.
[2] Data were compared using unpaired Student's *t*-test.
[3] Data were compared using t-Test (Excel 2007, Microsoft).

Table 3. OXA loaded polysaccharides nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line and animal model	Ref.
Polysaccharides	Chondroitin sulfate, Acrylic acid, ammonium peroxodisulfate, EGDMA	Not	Not Not Not Pores and rough surface	Oral in rabbit (n = 3)	[64]
	Tannic acid, PLAR, polyvinyl alcohol	Not	163.50 ± 6.98 nm 0.144 ± 0.027 Not Spherical	In cell culture (CT26) & Intraperitoneal in BALB/c mice (n = 6) [1]	[66]
	Chitosan, Hyaluronic acid, Sodium tripolyphosphate,	hyaluronic acid expressing cells	136 ± 6.0 nm 152 ± 5.2 nm 0.155 0.110 +40.3 ± 1.4 mV +10.0 ± 0.5 mV Spherical	In cell culture (HT-29) & C57 Balb/c mice (n = 18) [2]	[68]
	Alginate, Hyaluronic acid,	Folate Folate receptors expressing cells	186 nm 200 nm 0.217 0.112 -2.20 mV -22.0 mV Spherical	In cell culture (HT29)	[69]
	Water extract of chia seeds, Chitosan, Fe3O4@CS core–shell,	SPIONs	92.5 nm 0.24 − 16.72 mV spherical and uniformed shape	In cell culture (CT-26)	[70]
	Carboxymethyl chitosan, Tween-80, CaCl2,	Not	190.0 nm 0.23 ± 0.06 - 17.3 ± 0.5 Not	In cell culture (SW480 and CT26), & tail vein injection in BALB/c mice (n = 5) [3]	[72]
	Chitosan, N, N-methylenebisacrylamide, Nisopropylacrylamide	Not	162 ± 11 nm 0.028 54 ± 12 mV Less spherical geometry	In cell culture (HT29 and human fibroblast)	[73]
	Pectin, lactic acid, N,N′-methylenebisacrylamide	Not	Not Not Not circular pit	In cell culture (MCF-7, HCT-116, and Vero) & Orally in	[74]

				Rabbits (n = 4) [4]	
	Eudragit L100-55, alginate	Not	271.3 to 550 nm Not - 11.2 to - 25.6 Porosity	In cell culture (CT26) & Intravenous and oral in mice (n = 5) [5]	[76]
	β-cyclodextrin, γ-cyclodextrin, and 2-hydroxypropyl-β-cyclodextrin	Not	Not Not Not Irregularly shaped crystals	In cell culture (HCT116 and MCF-7)	[77]
	Cellulose fibers and Bentonite composed chemically of SiO2, Fe2O3, Al2O3, Na2O, MgO, TiO2, CaO, and LOI	Not	12.9 nm Not Not Tiny chunks	In cell culture (CCD-18Co and HCT116)	[78]
	Kaolinite, Cellulose Fiber	Not	Not Not Not Pseudohexagonal	In cell culture (CCD-18Co HCT116)	[79]

[1] Data were compared using one-way analysis of variance (ANOVA) using SPSS 20.0.
[2] Data were compared using an analysis of variance.
[3] Data were compared using Student's *t*-test.
[4] Data were compared using ANOVA.
[5] Data were compared using either one-way or two-way ANOVA with a Tukey post hoc test by the GraphPad Prism Software.

Table 4. OXA loaded protein nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Protein	Maleimide, albumin	Cys34 of albumin	Not Not Not Spherical	In cell culture (CT26) & intravenously in Balb/c mice (n = 4) [1]	[87]
	Human serum albumin	Cys34 of albumin	Not Not Not Not	In cell culture (CT26) & intravenously in Balb/c mice (n = 4) [2]	[88]
	β-lactoglobulin	Not	Not Not Not Not	In cell culture (HT29, Caco2, and A431)	[91]
	β-lactoglobulin, Nanographene oxide	Not	182 nm Not -22 mV -25 mV spherical	In cell culture (HT29)	[93]
	β-lactoglobulin, low methoxyl pectin	Not	164 nm 0.10 - 8.88 spherical	Not	[94]

[1] Data were compared using one-way ANOVA and Dunnett's multiple comparison tests.
[2] Data were compared using One-way ANOVA and Dunnett posttest

Table 5. OXA loaded silica nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Silica nanoparticles	Mesoporous silica nanoparticles, polyethyleneimine, hyaluronic acid	Polyethyleneimine CD44-overexpressed cells	76.2 ± 1.25 nm 138.4 ± 1.69 nm 0.165 -22.3 ± 1.86 mV -10.3 ± 1.42 mV Spherical	In cell culture (HT-29) & injection in Balb/c mice (n = 8) [1]	[97]
	FeCl2·4H2O, FeCl3·6H2O, Cetyl trimethylammonium bromide, and 3-Aminopropyltriethoxysilane	Not CD44-overexpressed cells	80 nm 0.065 19 mV Agglomerated	In cell culture (HCT-116)	[105]
	OXA@MSNs (Hexadecyl trimethyl ammonium chloride, tetraethyl orthosilicate, tetraethyl orthosilicate), Chitosan, Polyethyleneimine poly(ethylene glycol)	RGD peptide	136 nm, 137 nm, 117 nm Not 35 mV 22 mV - 22 mV Spherical	In cell culture (SW480)	[106]

[1] Data were compared using Student's t-test or one way analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons, using the software GraphPad Prism.

Table 6. OXA loaded metallic nanoparticles and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Metallic nanoparticles	NaAuCl4 2H2O, Sodium citrate	Anti-DR5 antibody DR5 expressing cells	17 ± 1.01 nm 0.13 -18 + 0.18 mV spherical	In cell culture (HCT 116 and MCF-7) & tail vein injection in Nude mice (n = 6) [1]	[111]
	NaAuCl4 · 2H2O, Sodium citrate, PEG linker	Thiolated poly(ethylene glycol)	176 ± 25 Not +14 ± 7.0 Not	In cell culture (A549 HCT116, HCT15, HT29, and RKO)	[112]
	UiO-66-NH2, CuS@UiO-66-NH2, and OXA-CuS@UiO-66-NH2	CuS	122.5 ± 48.94 nm Not Not N spherical	In cell culture (CT26)	[113]
	Iohexol, carbohydrazide, amino PEG, chitosan	Not	104 nm 123 nm 0.587 1 -14 mV -12 mV Circular	In cell culture (HT29)	[114]
	DMF, ZrCl4, 2-aminoterephthalic acid	NH2	160.3 ± 81.2 nm 312.0 ± 51.4 nm Not - 38 mV - 41.4 mV Spherical	In cell culture (CT26)	[115]

[1] Data was presented as mean ± S.D without Statistical analysis.

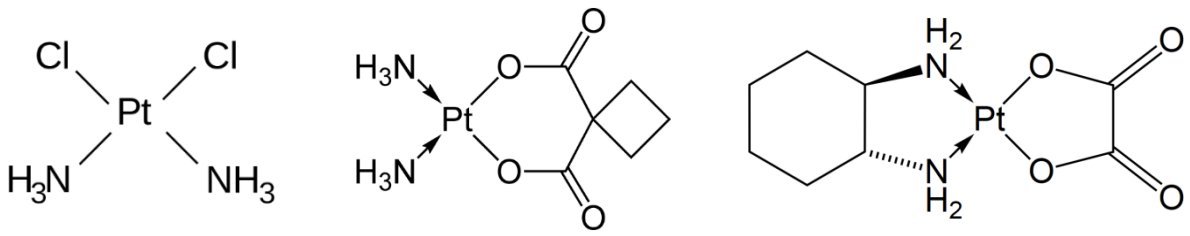
Table 7. OXA loaded synthetic polymeric carriers and colorectal cancer.

Carrier	Formulation	Functionalization and targeted cells	Characterizations Size (mean±SD) PDI (mean±SD) Zeta (mean±SD) Shape	Cell line/ animal model	Ref.
Synthetic polymeric	Poly(L-lactide)	Not	300 nm Not Not Rode	In cell culture (HCT8, CT26) & implanted into Balb/c mice (n = 8)	(127)
	PLGA and poly(lactide-co-glycolide)-poly(ethylene glycol)	Anti-CD133 monoclonal antibody	190 ± 59 nm 285 ± 74 nm 130 ± 51 nm 0.06 ± 0.003 0.191 ± 0.026 0.2 ± 0.009 -5 ± 6 mV -3 ± 4 mV 5 ± 4 mV Spherical	In cell culture (CaCo-2)	(130)
	Poly-(d,l-lactide-co-glycolide) (PLGA)	Not	1100.4 ± 257.7 nm Not Not Uniform size and spherical	Introduced intraperitoneal in rats (n = 5) [1]	[131]
	Poly-lactic-coglycolic acid	Not	< 100 mm Not Not spherical	In cell culture (HCT116) & intratumorally in Balb/c nude mice (n = 10) [2]	[132]
	Poly (d,l-lactic-co-glycolic acid)	Not	801.7 ± 165.4 nm 678.3 ± 118.5 nm 505.6 ± 64.30 nm 0.598 0.694 0.199 -21.4 ± 8.4 mV -25.8 ± 15.9 mV -27.6 ± 42.1 mV Spherical	In cell culture (CT-26 and SW-480) & Intratumorally in Balb/c mice (n = 8) [3]	[134]

[1] Data were compared using t-test or two-sided RM ANOVA and Bonferroni test.
[2] Data were compared using Student's t-test.
[3] Data were compared using one-way ANOVA followed by Bonferroni's post hoc test, Kruskal–Wallis test followed by a Dunn's multiple comparison tests.

Table 8. Disadvantages of nanoparticles in drug delivery.

Nanoparticles	Disadvantages	Ref.
Solid lipid	Limited drug loading capacity, low stability	[149]
Liposome	Instability and degradation, costly and time-intensive	[150]
Polysaccharide	Poor stability, limited bioavailability, and difficulty in controlling release rates	[151]
Protein	Expensive to produce and causing immune responses, stability during storage and transportation.	[152]
Silica	Toxicity and inflammation in the body, difficult to prepare nanoscale, and control their size.	[153]
Metal	Accumulate in organs and tissues, leading to potential toxicity and long-term health effects. synthesis and purification of metal nanoparticles can be expensive and time-consuming	[154]
Synthetic polymeric	Some toxic and immune reactions in the body; may also be non-biodegradable and accumulate in the environment and damage ecosystems.	[155]



Cisplatin **Carboplatin** **Oxaliplatin**

Scheme 1: Chemical structures of three clinically approved platinum drugs.

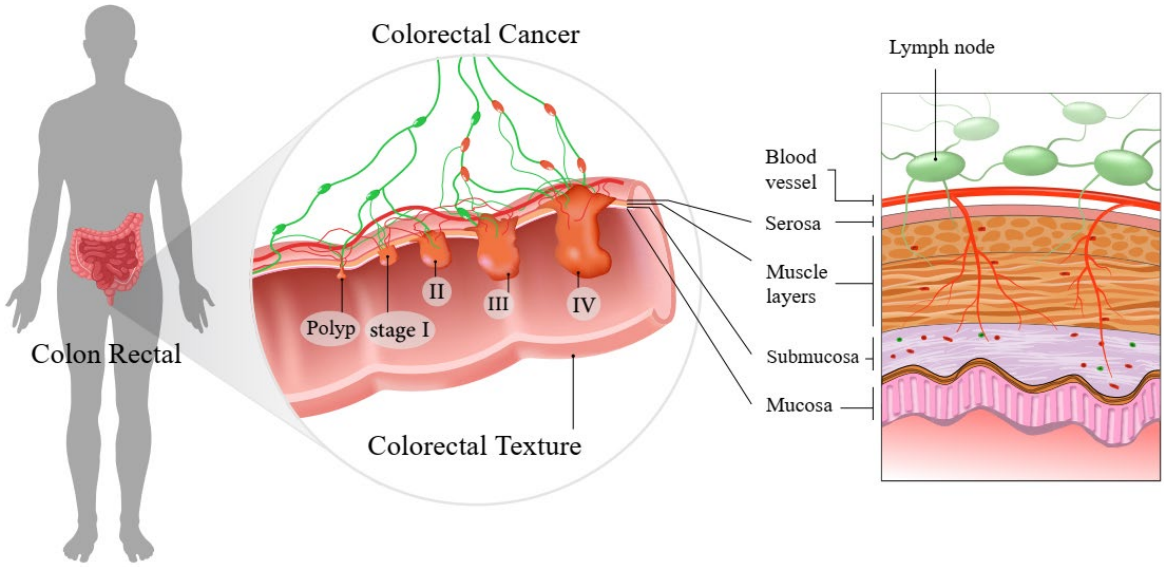


Figure 1. Colorectal cancer stages. Colorectal cancer progresses through a series of five major distinct stages, commencing at stage zero, often known as polyp, and advancing sequentially to stage four. In Stage 0 of colorectal cancer (CRC), the tumour is confined to the mucosal layer. In Stage I, the tumour has extended beyond the inner lining of the CRC but has not yet metastasized to the lymph nodes. Lymph nodes are diminutive organs that constitute an integral component of the immune system, functioning as filters. Stage II colorectal cancer (CRC) refers to a condition when the cancerous growth has penetrated the outer muscular layer of the colon or rectum, but has not metastasized to the nearby lymph nodes. Stage III colorectal cancer (CRC) is characterized by the presence of metastasis in one or several lymph nodes, indicating that the cancer has extended beyond the primary site of the colorectal tumour. Colorectal cancer at stage IV has metastasized to distant sites, including the liver or lungs, and is accompanied by lymph node involvement.

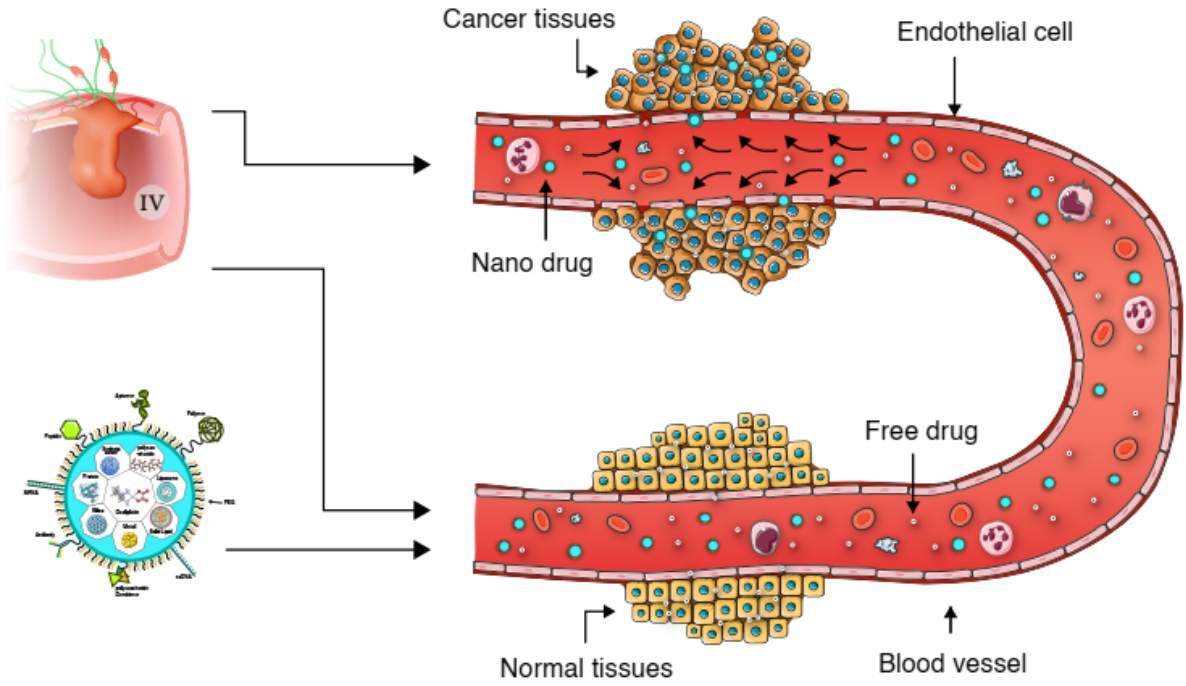


Figure 2. The enhanced permeability and retention (EPR) effect and its role in passive drug targeting to colorectal cancer.

Graphical abstract

Nanoparticles Containing Oxaliplatin