Colorectal Cancer Treatment Based on Nanomaterials

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Colorectal cancer (CRC) is a global health problem responsible for 10% of all cancer incidences and 9.4% of all cancer deaths worldwide. The number of new cases increases per annum, whereas the lack of effective therapies highlights the need for novel therapeutic approaches. Conventional treatment methods, such as surgery, chemotherapy and radiotherapy, are widely applied in oncology practice. Their therapeutic success is little, and therefore, the search for novel technologies is ongoing. Many efforts have focused recently on the development of safe and efficient cancer nanomedicines. Nanoparticles are among them. They are unique with their properties on a nanoscale and hold the potential to exploit intrinsic metabolic differences between cancer and healthy cells. This feature allows them to induce high levels of toxicity in cancer cells with little damage to the surrounding healthy tissues.

colorectal cancer nanoparticles drug carbon-based NPs targeted therapy antitumor effects graphene oxide

1. Nanomaterials

Nanomaterials have attracted worldwide attention due to their capability in improving existing methods for cancer treatment. Some of the most promising therapeutic approaches based on nanomaterials are drug and gene delivery systems, photothermal therapy (PTT), magnetic hyperthermia (MHT), and photodynamic therapy (PDT). The broader applications of nanomaterials in CRC treatment include the customisation of targeted drug delivery systems and advanced treatment modalities [1]. Nanomaterials have several benefits as drug carriers. They increase the water solubility of some hydrophobic drugs and protect drugs dissolved in the bloodstream, improving their pharmacokinetic and pharmacological properties (increasing drug half-lives), target the delivery of drugs in a tissue or cell-specific manner, thereby limiting drug accumulation in the kidneys, liver, spleen, and other non-targeted organs and enhancing their therapeutic efficacy; and deliver a combination of imaging and therapeutic agents for the real-time monitoring of therapeutic efficacy [2][3][4][5][6][7]. Additionally, they can release the drug in a controlled or sustained manner. Stimuli-responsive nanoparticles can also help to lower the toxicity and to control the biodistribution of the drugs [8].

Historically, the development of the nanoparticle design underwent three different stages [4]. In the first stage, the attention has been set on studying the basic surface chemistry of NPs and therefore, they were distinguished by low biocompatibility and high toxicity. The second stage has been focused on the optimisation of the surface

chemistry to improve the stability of NPs under biological conditions and to target specific cells. In the third stage, the efforts have been concentrated on the development of stimuli-responsible or the so-called “smart” nanoparticles that can respond to biological (pH, oxidant medium, etc.) or external stimuli (temperature, light, etc.), can target specific cells and improve the biological efficiency [4].

The first discovered nanoparticles used as carriers for drugs and proteins were the liposomes in the 1960s [9]. Since then, many nanomaterials have been developed for drug carriers. In 2016, the FDA approved 51 nanoparticles, while, to date, more than 77 are in clinical trials [10]. Among all the approved materials for nanoparticles, most of them are polymeric and liposomal materials (**Figure 1**). However, researchers also pay attention to other nanomaterials, such as micelle, metallic, and protein-based materials as drug carriers (**Figure 1**). Each category of nanomaterials has unique strengths and limitations [8].

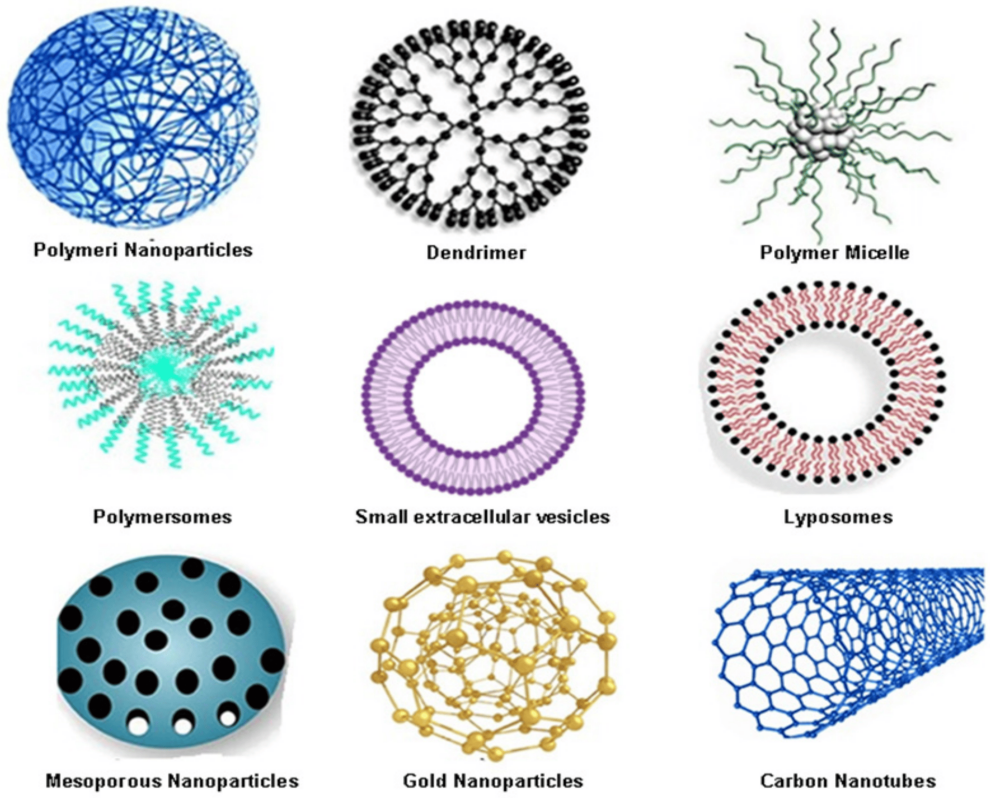

Figure 1. Types of nanomaterials in laboratory, preclinical, and clinical oncology practice. Images are adapted from [3].

Table 1 summarises the advantages and disadvantages of nanoparticles as drug delivery systems. Based on their chemical compositions, nanoparticles and nanostructured materials can be categorised into four types: organic nanomaterials (e.g., micelles, dendrimers, polymersomes, hydrogels, and nanoconjugates); inorganic (e.g., metals, metal oxide, and ceramic nanomaterials); carbon-based (fullerenes, carbon nanofibers, diamonds carbon nanotubes and graphene); and composite nanostructures. This classification further allows nanoparticle platforms to be broadly categorised as organic, inorganic, and hybrid.

Table 1. Advantages and disadvantages of nanoparticles as cancer-drug delivery systems.

Nanoparticles Type	Advantages	Disadvantages
Organic nanoparticles		
Polymeric nanoparticles	Biocompatible and biodegradable; ability to entrap both hydrophilic and hydrophobic drugs; easy to modify; controlled drug release; protect the drug from metabolic degradation; prolonged residence time—bio-adhesive properties; good tissue penetration; easy manipulation; stability of drug; delivery of a higher concentration of drug to the desired location; easy merged into other activities associated to a drug delivery	Burst effect; limited drug loading capacity; high cost; low cell affinity; toxicity of degradation products; non-degradable polymers tend to accumulate in tissue; promote allergic reaction; in vivo metabolism and elimination is not elucidated; rapid clearance out of the abdominal cavity; toxic, reactive residues, unreacted monomers increase the risk of chemical reactions and the formation of unwanted oligomers
Dendrimers	Lower polydispersity index; the outer surface of dendrimer has multiple functional groups; they can be designed and synthesised for a specific application	High cost of synthesis process; non-specific toxicity; low loading capacity
Polymeric micelles	Prolonged retention time; easily synthesis; can be coupled with targeting ligands to increase accessibility to tumour sites, reduce the side effects; ability to control drug dissemination over a long period	Increased systemic toxicity
Polymersomes	Chemical versatility; an ability for controlled release and improved cellular uptake of anti-cancer molecules; low toxicity	Toxicity risk of polymers or metabolites; Polymer aggregation; hydration may be a challenge
Small extracellular vesicles	Biocompatible; safe degradation products; non-toxic; non-immunogenic; possibility for cell targeting	Low water solubility
Liposomes	Increase the efficacy and therapeutic index of drugs; biocompatible and completely biodegradable; low toxicity; flexible; improved pharmacokinetics of cargo; able to entrap both hydrophilic and hydrophobic drugs; controlled release protects the drug from metabolic degradation prolonged residence time—precorneal and vitreous; decreased the exposure of sensitive tissue to toxic drugs	Poor stability; could crystallise after prolonged storage conditions; difficult to prepare and sterilise; high cost; poor or moderate drug loading capacity; immunogenicity; low solubility; short half-time; leakage and fusion of encapsulated drug/molecules
Inorganic nanoparticles		
Mesoporous silica	High drug and genes loading capacity; tunable pore size; large surface area;	Expensive; not enough information about cytotoxicity, biodistribution, biocompatibility’

Nanoparticles Type	Advantages	Disadvantages
nanoparticles	biocompatible and biodegradable; controlled porosity; versatility; non-toxic; easy endocytosis, and resistance to heat and pH	low stability formation of aggregates, haemolysis
Metallic and magnetic nanomaterials	Easy preparation and functionalisation; large surface area; multimodal application; high surface area; multiple forms (spherical, nanorod, triangles); biocompatibility; tuneable size; easy functionalisation excellent biodegradability in vivo; no leakage of encapsulated drugs	Low stability and storage; not enough information about uptake, biocompatibility, and low cytotoxicity *in vivo*
Carbon-based nanomaterials		
Carbon nanotubes	Water-soluble; multifunctional; less toxic; biocompatibility; biodegradability; able to entrap both hydrophilic and hydrophobic drugs; high loading capacity; a high number of possibilities for surface modification; high surface area, needle-like structure, heat conductivity, and chemical stability	Expensive to produce; low degradation; not enough *in vivo* studies

very

PNPs are solid, nanosized colloidal particles from biodegradable polymers. Depending on their structure, PNPs can be categorised as nanospheres (matrix type) or nanocapsules (reservoir type). Nanospheres are constructed by a polymeric network, and the bioactive material is dispersed/entrapped into the polymer matrix. Nanocapsules have membrane wall structures with an aqueous or oily core acting as a reservoir to contain the bioactive material. In both cases, the drug can be absorbed on the surface of the sphere or capsule [11][12]. For the preparation of PNPs, natural or synthetic polymers are used. Among the synthetic polymers, the most commonly used are polyethene glycol (PEG), polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, polyaspartic acid (PAA), and polyglutamic acid. Among the natural polymers, the most frequently used are chitosan, collagen, dextran, gelatine, albumin, alginate, and heparin [12][13]. All polymers are biodegradable, and in the body, these polymers degrade into monomers, which are removed through normal metabolic pathways. The advantages of PNPs to other nanocarriers used in cancer therapy are their better storage stability, higher drug loading capacity and more controlled drug release than polymeric micelles (PMs) and liposomes, better and controllable physicochemical properties, more homogeneous particle size distribution, and higher drug blood circulation time. All of these characteristics are highly desirable in the context of cancer treatment [12][13][14].

Recently, poly lactic-co-glycolic acid (PLGA) NPs have attracted huge interest because of their well-defined properties in safeguarding drugs' effective releases. These nanocarriers are developed as transporters for biomolecules (proteins, peptides, and nucleotides), vaccines and small drugs [1][15] and are expansively studied for potential applications in tumour therapy, especially for CRC. Some authors showed that curcumin-loaded PGLA NPs (C-PNPs) demonstrated an advanced cellular uptake in colorectal cancer HT-29 cells compared to pure curcumin, attributable to their sustained release and greater colloidal stability in gastrointestinal fluids and reduced size [16]. These results demonstrated the potential of C-PNPs in the development of an oral targeted drug system in

the colon after additional functionalisation with a specific targeting ligand [1][16]. Chitosan, as polymeric NPs, for example, have also been developed as a promising carrier for active pharmaceutical components in CRCs [1][17]. Recent data showed that, when the drug SN-38 was encapsulated in poly(D, L-lactide-co-glycolide) NPs and applied to human colorectal adenocarcinoma cell line205 (COLO-205), the detected cellular uptake and cytotoxicity were both approved [18]. For this reason, SN-38-loaded NPs are being investigated as essential drug delivery systems for the treatment of CRC [1][18] (**Table 1**).

The above-discussed results highlight the polymeric nanoparticles (PNPs) as one of the most widely used organic nanocarriers in cancer therapy. Furthermore, their applications are being broadened constantly, thus promising the effective treatment of different cancers, especially CRC.

2.2. Dendrimers as Other Promising Colorectal Cancer Drug Nano-Delivery Systems

Dendrimers are nanosized three-dimensional hyperbranched macromolecules with tree-like arms or branches originating from the central core [12]. The arms have a high number of anionic, neutral, or cationic end groups. Each level of added branches to the core throughout the synthesis process is called a generation. Dendritic macromolecules tend to linearly increase in diameter and adopt a more globular shape with the increasing dendrimer generation [19]. The specific physicochemical properties, along with biodegradable backbones, facilitate the applications of dendrimers as delivery systems for drugs and genes [19][20][21][22]. The drugs and targeting ligands can be loaded onto the cavities in the dendrimer cores through hydrogen bonds, chemical linkages, or hydrophobic interactions. Several dendrimers have been developed for cancer therapeutics: polyamidoamine (PAMAM), PPI (polypropylene imine), PEG (poly(ethylene glycol)), Bis-MPA (2,2-bis(hydroxymethyl) propionic acid), 5-ALA (5-aminolevulinic acid) and TEA (triethanolamine) [20]. Dendrimers have been shown to successfully enhance the efficiency of doxorubicin, a drug commonly used to treat colon cancers [12][23]. Another anticancer drug, cisplatin, in conjugation with a dendrimer, was reported to have enhanced In vitro and *in vivo* activity as compared to free cisplatin after intraperitoneal or intravenous administration into a melanoma mice model having B16F10 tumour cells [12][24]. Zhuo et al. prepared 5-FU–dendrimer conjugates of different generations (0.5–5.5) and showed improved controlled release characteristics for the 5-FU anticancer drug [12][25]. Furthermore, PEGylated dendrimers in conjugation with doxorubicin had improved blood circulation time, reduced toxicity, and resulted in less drug accumulation. Additionally, their subcutaneous administration in a mouse model bearing the highly invasive colorectal cancer C26 cells led to the abolishment of the well-knownDOXunresponsiveness (Doxorubicin) of these tumour cells [12][26]. In another study, PEGylated polyamidoamine (PAMAM) dendrimers conjugated with 5-FU demonstrated a sustained release of the drugs both In vitro and *in vivo* in albino rats [12][27]. Huang W. et al. designed a delivery system for gambogic acid (GA) and other natural anticancer compounds for the treatment of an HT-29 human colon cancer xenograft model based on telodendrimers composed of linear polyethylene glycol (PEG)-blocking dendritic oligomers of cholic acid (CA) and Vitamin E (VE) [1][21]. These nanocarriers showed similar In vitro cytotoxic activity as the free drug against HT-29 human colon cancer cells [1][21] (**Table 1**). Furthermore, dendrimers can be used as an innovative way of effectively preventing metastatic initiation by the binding and cytotoxic killing of circulating tumour cell CTCs [1][27]. With these promising properties, dendrimers are

also called “therapeutic dendrimers” and deserve attention and profound investigation in cancer-targeted therapy [27].

2.3. Polymeric Micelles (PMs) as Favourable Organic Nanocarriers in Colon Cancer Therapy

PMs are formed by the spontaneous arrangement of amphiphilic block copolymers in aqueous solutions. They have a hydrophobic core–hydrophilic shell structure that is suitable for loading hydrophobic drugs into the core, thus improving drug solubility [28]. PM-based carriers are easily prepared and unforced for optimisation. Moreover, PMs can be coupled with targeting ligands to increase accessibility to tumour sites, decrease side effects, and allow controlled drug dissemination over a long period [29][30]. Recently, the development of a pH-responsive copolymer to optimise the delivery of the anticancer drug capecitabine (CAP) using nano-PMs and cyclodextrin (CD) for the treatment of colon cancer was reported. The authors proved that the micelles with their pH sensitivity perfectly target colon cancer, thus delivering the drugs under control to colon tissues with a release above 80% [31]. Therefore, they are considered “smart” nanocarriers for the delivery of anticancer drugs and imaging agents for various therapeutic and diagnostic applications. Noteworthy, several drug-loaded PM formulations have been approved for clinical trials for cancer treatments [32]. Genexol®-PM is a paclitaxel (PTX)-loaded PM formulation that is under a phase IV clinical trial for breast cancer treatment (reference number NCT00912639) [32]. Other clinical trials aim to validate it further as a promising chemotherapeutic drug for treating ovarian, breast, lung, cervical and pancreatic cancers.

A large number of preclinical studies on multifunctional PMs are also underway, showing that PM-based drug delivery systems are promising nanomedical platforms for drug delivery and cancer therapy and deserve a lot of attention and further investigation.

2.4. Polymeric-Based Nanocarriers as an Emerging Opportunity for Successful Drugs and Nucleic Acids Delivery in Colorectal Cancer

Polymersomes are spherical nanostructures made up of amphiphilic block copolymers, in which a hydrophobic bilayer encloses an aqueous core opposite to the polymeric micelles [20]. Moreover, they represent hollow shell nanoparticles with unique properties to deliver distinct drugs. Polymersome surfaces can be modified with target-specific ligands to bind receptors overexpressed on the surfaces of tumour cells, thus improving the cellular uptake of anticancer molecules [33][34][35][36][37]. Polymersomes have low toxicity, even at high concentrations, because cancer cells internalise them much higher than healthy ones [33][38]. The integration of stimuli-sensitive molecules can also control the drugs released from polymersomes [33][39]. All these benefits make polymersomes widely explored in numerous biomedical applications, including drugs, nucleic acid delivery [33][39][40], gene transfer [41] and diagnostics [42] (**Table 1**).

Recent results highlighted the properties of two polymersomes: poly(ethylene oxide)-b-poly(γ-methyl-ε-caprolactone) (PEO-PMCL) and vinyl sulfone PEO-PMCL, as harmless bioresorbable polymersomes with high

potential for drug delivery. Their binding and release properties were tested in DLD-1 human colon cancer cells, where cisplatin has been encapsulated in them. The unique property of these nanocarriers was the presence of PR_b, which is an α5β1-specific targeting peptide that is specifically expressed in the treated cells. This led to the precise and targeted delivery effectiveness of cisplatin to the colon cancer cells and, in turn, reduced their viability. Interestingly, when these polymersomes with cisplatin were delivered to CACO-2 human epithelial cells, known to express low levels of α5β1 integrin, the cytotoxicity was lowered. This was solid proof that their specificity for drug-targeted delivery was indeed high [43]. These and other results demonstrate that PR-b-functionalised bioresorbable polymersomes serve as a smart approach for minimising the side effects of standard cisplatin chemotherapy for colorectal cancer and deserve a lot of interest and further investigation [44].

2.5. Small Extracellular Vesicles (sEVs)—The Trojan Horse for Many Cancers

Small extracellular vesicles (sEVs) have an important role in intercellular communications. sEVs released from different cells exert huge effects on CRC cell proliferation and metastasis. They also serve as biomarkers for CRC diagnosis and prognosis and are potent drug delivery systems in treating CRC patients [45]. EVs are vesicles secreted by the cells into the extracellular space and encapsulate lipids, nucleic acids and proteins. Due to their similarity to natural cell contents, EVs are not recognised by the immune system as foreign substances and, consequently, evade removal by immune cells and reach the target of interest. These unique properties make EVs relevant for drug delivery, expecting to overcome the inefficiency, cytotoxicity, and/or immunogenicity associated with synthetic delivery systems properties. EVs are categorised into three distinct types: microvesicles, exosomes, and apoptotic bodies. Among these three types of EVs, the most used as nanocarriers in cancer treatment are the exosomes [46]. There are studies demonstrating the potential of exosomes to be loaded with anticancer drugs such asDOX and cisplatin and to be delivered to the tumour site. There are signalling-related membrane proteins on the surfaces of exosomes, some of which possess strong immunogenicity and exert antitumour effects by activating immune cells [46][47]. For example, exosomes from dendritic cells (DCs) carry MHC-I, which binds to tumour-derived peptides, and this complex can activate immune cells to exert antitumour effects [46][47][48]. Specific proteins also can be anchored to exosomes through glycosyl-phosphatidyl-inositol (GPI), which further proves that GPI-anchored EGFR nanobodies on the exosomes can bind EGFR-expressing tumour cells. Data show that this binding efficiency was higher than using nanoantibodies directly [46][47][48][49][50].

2.6. Liposomes as Colorectal Therapeutics

Liposomes are lipid-based spherical vesicles with an aqueous core enclosed by lipid bilayers [1]. They have single or multiple bilayer membrane assemblies formed from natural or synthetic lipids. Depending on the number of bilayer membranes, liposomes can be unilamellar or multilamellar vesicles and, depending on the size, small or large. Liposomes also vary concerning composition, surface charge, and method of preparation [12]. Due to their smaller size, the ability to incorporate various substances, and phospholipid bilayer in nature, they are considered the most effective drug delivery systems in cells [1][51]. The liposomes are the first nanoparticles used in clinical medicine for drug delivery [1][52] and are still one of the most widely used drug delivery systems for peptides, nucleic acids, and proteins [1][53]. In the mid-1990s, the FDA approved for clinical practice liposome formulations

with two drugs: daunorubicin (DaunoXome®) and Doxorubicin (Doxil®) [1][54]. Later, the FDA approved Marqibo® as a liposomal drug that is a cell cycle-dependent anticancer drug [1][55][56] (**Table 1**). To overcome drug resistance resulting from liposome-based drugs, they are used as an aptamer to target cancer cells [1][57]. The liposomal delivery system appears to be one of the most promising nanocarriers for CRC treatment. In the last three years, this delivery system has entered extensive preclinical research for CRC therapy [1][58]. Liposome-based nanoproducts, presently under clinical investigations for CRC treatment, are CPX-1, LE-SN38 and Thermodox. CPX-1 (Irinotecan HCl: Floxuridine) successfully ended its phase II clinical trials [59] and recent data show that patients diagnosed with CRC are already getting chemotherapy with oxaliplatin Andirinotecan [59]. The application of the liposome formulation LE-SN38 in HT-29 tumour-bearing mice, on the other hand, was investigated. The results showed that the tumour growth was repressed by 51, 79, and 90% after 10 days of treatment at doses of 10, 20, and 40 mg/kg, correspondingly [60]. Nonetheless, LE-SN38, which was in phase II, was applied at a dose of 35 mg/m^2 every 21 days for a minimum of two cycles, in patients with metastatic CRC, but did not exert anticancer activity [61]. Thermodox is another liposomal drug candidate in CRC clinical trials. It involves thermally sensitive liposomal doxorubicin as an adjuvant therapy combined with radiofrequency thermal ablation in the treatment of recurrent or refractory colorectal liver metastases [62][63]. And even though the study comparing Thermodox to radiofrequency thermal ablation monotherapy has been terminated, the results are not yet presented [63].

At present, several agents under preclinical investigation have shown auspicious In vitro results with possible applications for CRC, including oxaliplatin-loaded long-circulating liposomes (PEG-liposomal L-oHP) [64], liposomal curcumin [65] and doxorubicin-encapsulated liposomes [66].

These data highlight the potential of liposomes as drug carriers in colorectal carcinoma cells and further deliver promises for decreasing the adverse effects of standard chemotherapy.

3. Colorectal Cancer Drug Delivery Based on Inorganic Nanocarriers

3.1. Mesoporous Silica Nanoparticles (MSNs) as Carriers of Large Amounts of Biomolecules

MSNs belong to silica (SiO_2) class materials that have gained huge interest for drug delivery due to their beehive-like porous structure that allows the packing of large amounts of bioactive molecules. Other important features of MSNs are the adjustable sizes of cavities in the range of 50–300 and 2–6 nm, respectively, the low level of toxicity, easy endocytosis, and resistance to heat and variable pH [1][67][68]. The MSN–protamine hybrid system (MSN-PRM) has been designed for a more selective release of the drugs to cancer cells and was activated with specific enzymes to trigger anticancer activity [1][69]. The conjugation of MSNs with hyaluronic acid has been shown to significantly increase the amount of DOX loading into HA-MSNs compared to bare MSNs [1][70] and to increase the cellular uptake of DOX-HA-MSN conjugate, which was reflected by the enhanced cytotoxicity of the human colon carcinoma cell line (HCT-116 cell line) [1][71]. In another study, MSNs were functionalised with polyethyleneimine-

polyethene glycol (PEI-PEG) and polyethylene glycol (PEG), which also increased the amount of loading of epirubicin hydrochloride (EPI) and exhibited improved antitumour activity [1][72] (**Table 1**).

In CRC treatment approaches, silica nanoparticles were used together with a photosensitizer to destroy the CRC cells [73]. These silica-based nanoshells have been designed to enclose photosensitizer molecules in such a way to be easily taken up by the CRC tumour cells. Upon exposure of these cells to light, the photosensitizers are activated thus releasing reactive oxygen molecules to kill the cancer cells [1][74]. Currently, this technique is adopted in cancer treatment in numerous clinical trials. Thus, nanoparticles may also be applied for the molecular imaging of cancer cells, followed by earlier diagnosis and targeted drug delivery.

3.2. Metallic and Magnetic Nanomaterials as Photosensitizers in Colorectal Cancer Treatment

Metallic and magnetic nanomaterials have some specific optical, magnetic, and photothermal properties that make these types of nanomaterials useful for different biomedical applications. Iron oxide is a prime example of a metallic nanomaterial that can be used in different ways. It has super-magnetic properties that allow it to be used both for imaging techniques and for the targeted delivery of drugs and molecules. Metallic nanoparticles can be conjugated with other types of nanomaterials and can be combined with other types of therapy, such as photothermal therapy (PTT). Iron oxide NPs have excellent biodegradability *in vivo* because after dissolution in the human body, the iron ions can be adjusted physiologically [1][75]. Recent reports have appeared that show that smart multifunctional magnetic nanovesicles encapsulating the antibody-targeting peptide AP1 (MPVA AP1) are a promising anticancer drug [1][76]. These nanoformulations did not exhibit a cytotoxic effect in L929 fibroblasts but demonstrated outstanding selectivity and targeting toward CRC cells (CT26-IL4R). No leakage of encapsulated drugs in the absence of magnetic field stimulation has been revealed. Moreover, nanovesicles loaded with doxorubicin burst upon treatment with a high-frequency magnetic field, which caused a fast, accurate, and controlled drug release. Therefore, smart magnetic nanovesicles like MPVA-AP1 have a notable capability for delivering specified doses and precisely controlled releases in antitumour applications [76]. Iron oxide NPs enhance the effect of hyperthermia and are extremely beneficial in the diagnosis of CRC [77]. For example, polylactide-co-glycolic acid (PLGA) nanoparticles loaded with 5-fluorouracil (5-FU) and iron oxide demonstrated greater DNA damage in an HT-29 colon tumour cell line as compared with hyperthermia [77]. Other studies have shown that paclitaxel (PTX) and the super-paramagnetic iron oxide (SPIO), encapsulated inside the core of PEAL Ca micelles [78], have been released from micelles slower at neutral pH and faster at a pH of 5.0. Cell culture studies have also shown that PTX-SPIO-PEALCa is successfully absorbed by CRCLoVo cells, while PTX is internalised by lysosomal cells. Additionally, the successful inhibition of CRC LoVo cell growth has been verified. Hence, micelles promise a great role in MRI visible drug release methods for CRC treatment [78] (**Table 1**).

3.3. Carbon-Based Nanomaterials

The family of carbon-based nanomaterials includes fullerenes, carbon nanotubes, graphene and its derivatives, nanodiamonds, and carbon-based quantum dots [79]. This diverse family of nanomaterials has unique physicochemical features like excellent mechanical, electrical, thermal, optical, and chemical properties. Therefore, they gather huge interest and are under research in diverse areas, including biomedical applications as carriers of

various types of therapeutic molecules for disease treatment and tissue repair and the imaging of cells and tissues. Moreover, their antibacterial and anti-inflammatory properties are also extensively studied [79].

Carbon nanotubes (CNTs) are broadly used types of carbon nanoparticles in biomedical research. They are cylindrical, with rolled graphene sheets, with a diameter of fewer than 1 μm and a few nanometres in length [1][80]. Their high surface areas, needle-like structures, heat conductivity, and chemical stability enable their use in immunotherapy, diagnosis, gene therapy, and a carrier in different drug delivery systems [1][81]. Several antitumour-drug-carriers strategies based on CNTs have been developed. In one of them, the single-walled carbon nanotubes (SWCNTs) conjugated with a synthetic polyampholyte for the delivery of paclitaxel demonstrated greater anticancer effects in Caco-2 and HT-29 cells compared to paclitaxel alone [1][82]. A similar effect was observed using Eudragit®–irinotecan-loaded CNTs [1][83]. Additionally, oxaliplatin and mitomycin C-coated CNTs, induced by infrared light rays, have shown a considerably higher drug delivery and localisation in cancer colon cell lines [1][84]. Some data show that SWCNTs modified with TRAIL (a ligand that binds to specific receptors and causes the apoptosis process in cancer) increase cell death ten times in comparison with the mono-delivery of TRAIL in carcinoma cells lines [1][85].

Recent progress in nanotechnology and biotechnology has contributed to the development of precisely targeted cancer therapies based on nanomaterials. Carbon nanomaterials and graphene play a pivotal role in this due to their high variability, chemical stability, and unique characteristics. However, to enable drug delivery platforms, the major emphasis should lie in the investigation of the molecular mechanisms of nanoparticle delivery to the cell. These pathways are crucial in allowing the effect of the nanoformulations on cellular compartments and cellular fate in general. Moreover, a detailed understanding of the pharmacologic and toxicological properties of these nanomaterials, and a well-adjusted and detailed assessment of their risks and benefits to human health, have been under broad investigation recently.

We provided a schematic illustration of some of the pathways for NP delivery to the cells and highlighted the implications on the cellular compartments and their fates in **Figure 2**. The well-studied mechanism of nanoparticle delivery to the cell involves the following steps: NPs get into cells in different ways, mainly through diffusion, endocytosis, and/or binding to receptors, and induce reactive oxygen species (ROS) generation, LDH and MDA increase, and cytokines release, which, in turn, can cause oxidative stress, loss in cell functionality, pro-inflammatory responses, and mitochondrial damage. The uptake of graphene into the nucleus may cause DNA-stranded breaks and the induction of gene expression via the activation of transcription factors, cell death, and genotoxicity.

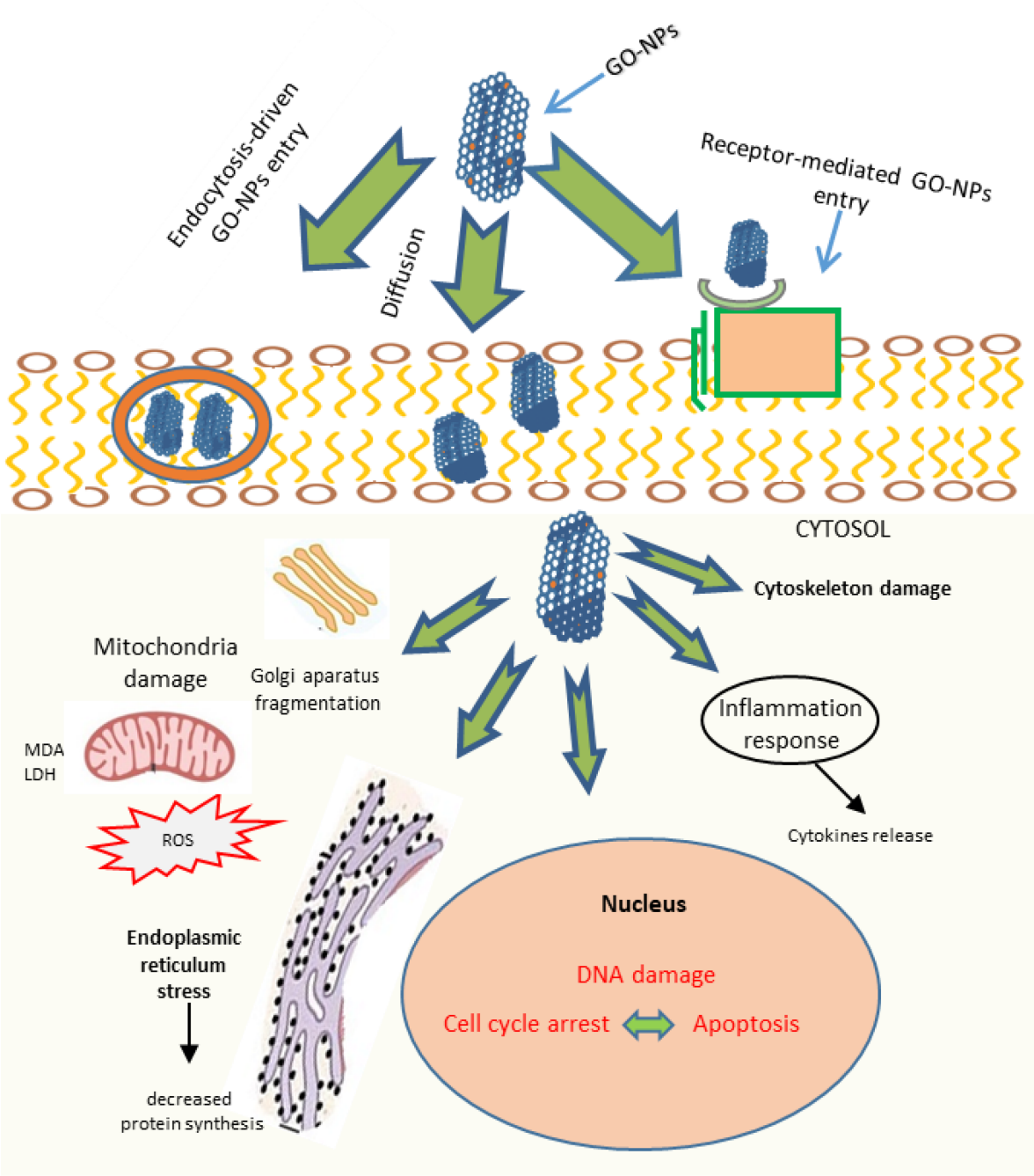

Figure 2. Schematic diagram of the molecular pathways for nanoparticle delivery to cancer cells and potential antitumor effects.

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