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Nanoparticles: Attractive tools to treat colorectal cancer

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ABSTRACT

Colorectal Cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. Despite the notable advances achieved over the last few decades, CRC remains a hard-to-treat deadly disease in many patients. This is attributed mainly to chemo- and immuno-resistance, which frequently emerge soon after treatment with conventional therapeutics. Systemic treatments are also constrained by their many undesired and serious side effects. More recently, nanomedicine has emerged as an attractive modality that can overcome issues of therapeutic resistance, improper delivery, or suboptimal targeting of tumor cells. Many nanomaterials, having already been examined in pre-clinical and clinical studies, are now considered biocompatible and relatively safe. Indeed, around 50 nano-formulations have so far been approved as diagnostic and therapeutic agents in humans. Here, in this review, we describe a set of imperative nanoparticles (NPs) involved in diagnosing and treating CRC. In particular, we discuss the theragnostic roles of quantum dots, iron oxide NPs, Polylactide-co-glycolic acid (PLGA) NPs, dendrimer NPs, carbon nanotubes, liposomes, and gold NPs. We dissect the molecular and clinical evidence supporting the use of these NPs in CRC. We also highlight their implications in targeted drug delivery as well as their anti-tumorigenic properties and effects on the cardinal hallmarks of CRC. We conclude by highlighting the notion that nanomedicine is emerging as an attractive approach to address the unmet needs in managing several diseases, including CRC.

1. Introduction

Colorectal cancer (CRC) remains a highly morbid disease affecting a significant proportion of the global population. According to the world health organization (WHO), CRC is the third most common cancer worldwide after breast and lung cancers [1]. It affects both genders and is the third most common cause of cancer-related deaths [1].

CRC is instigated by several environmental and genetic factors and is often rarely encountered in non-genetically predisposed individuals before the age of 50 years [2,3]. Obesity, alcohol misuse, smoking, low physical activity, increased red and processed meat consumption, and low dietary intake of fruits and vegetables represent the top significant modifiable factors associated with an increased CRC incidence [3] (Fig. 1). On the other hand, among the non-modifiable risk factors which include age, male gender and a positive family history of CRC, age remains the pivotal factor. Early-onset CRC, accounting for up to 10% of all cases, is often encountered in patients with genetic disorders mainly hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome) and familial adenomatous polyposis (FAP) [3]. Moreover, compared to the general population, inflammatory bowel disease patients and those with a history of abdominal radiation are at a significantly higher risk [3–7].

CRC often originates from a neoplastic polyp arising from cancerous stem cells which harbor accumulating mutations in tumor suppressor genes or oncogenes [3,8,9]. These cells are the inciters of tumor development and the fuel of disease maintenance and progression. Their enhanced rate of proliferation makes them a target for most available therapies. At the molecular level, CRC emanates from multiple pathways that may occur simultaneously or disjointly [10,11]. Chromosomal instability is the main pathway leading to CRC development. This

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pathway predisposes to loss-of-function tumor suppressor gene mutations and/or gain-of-function oncogene mutations that occur in around 70% of all cases [10,11]. The rest of the cases are caused mainly by two other pathways: (1) the microsatellite instability pathway affecting DNA mismatch repair genes, and (2) the CpG island methylation pathway characterized by genetic hypermethylation and the subsequent silencing of tumor-related genes [10,11]. A cascade of tumorigenic events ensues because of these genetic mutations, especially in the presence of a contributory tumor microenvironment,. These events, denoted by tumor survival, growth, vascularization, invasion and metastasis, are the main target of any CRC treatment [10,11].

CRC detection is prompted either by development of symptoms or incidental discovery on routine screening with colonoscopy. Depending on the size (small/large), onset (early/late), and location (right colon/left colon/rectum) of the lesions as well as on the grade (low/high or poorly/well differentiated) and the stage (local/ metastatic) of the disease, patients may display different sets of symptoms ranging from no symptoms to rectal bleeding, fatigue, weight loss, anemia, constipation/diarrhea, and/or bowel abstraction [12–16]. The overall prognosis and survival are also based on the anatomic and histopathologic characteristics of the tumor [12–16].

Parameters that influence symptom development or severity are themselves the key determinants of treatment selection. Non-metastatic CRC is often managed surgically, and the need for adjuvant systemic chemotherapy or radiotherapy is later assessed based on pathology findings [3]. However, both resectable and non-resectable metastatic CRC often require treatment with systemic chemotherapy [3]. Selection of the proper treatment regimen is driven by a multitude of parameters and is often personalized based on the molecular subtype of the disease and its responsiveness to specific therapies.

The main chemotherapeutics used in managing metastatic CRC are capecitabine, fluorouracil, irinotecan, and oxaliplatin (Fig. 2) [3,17–19]. They are often used together and in combination with biologics and immunotherapeutics like anti-VEGF, anti-EGFR, anti-PD-1, BRAF inhibitors, and MEK inhibitors [3,20,21]. However, the acquirement of resistance to conventional therapeutics and the development of serious side effects, such as bone marrow suppression, infections, infertility and neuropathy remain the caveats to treatment success and quality of life improvement in the majority of patients [3,22–24]. These limitations can be circumvented using novel, biocompatible, and amenable drug delivery systems that allow tunable and targeted local release of the delivered therapeutics at the tumor site [22,25–27]. In this context, nanomedicine has emerged as an attractive approach to address the unmet needs of cancer treatment [22,25–27].

Over the past decades, nanomedicine applications have attracted increased attention in the fields of cardiology, microbiology, and oncology, among others [28–33]. However, its emergence and first successful application was in cancer patients. Doxil, a nano-preparation of doxorubicin, was the first U.S. Food and drug administration (FDA)-approved nanomedicine [29,34–36]. Its efficacy, tolerability, and pharmacodynamics were assessed initially in murine studies and then in a clinical trial of sixteen patients with ovarian cancer in 1991 [36,37]. In these studies, as compared to free doxorubicin, Doxil had a longer half-life and a slower clearance rate, and was associated with higher doxorubicin concentrations at the tumor site and its interstitial space. On the contrary, free doxorubicin induced a significantly less efficient tumor localization and was associated with more systemic side effects [36,37]. After this first clinical trial, Doxil was investigated in larger human studies and is now approved for patients with Kaposi's sarcoma, multiple myeloma, ovarian cancer, and metastatic breast cancer [29,36–38]. Its use has dramatically diminished the cardiac side effects associated with the original drug, doxorubicin, while offering an equivalent therapeutic efficacy [36].

Roughly 10 years after the advent of Doxil, Abraxane was introduced as an effective nano-formulation of paclitaxel, and was then granted FDA approval for use in patients with metastatic breast cancer [29]. According to two recent meta-analyses, Abraxane has been examined by various clinical studies as a mono- or combined-therapy [39,40]. Its

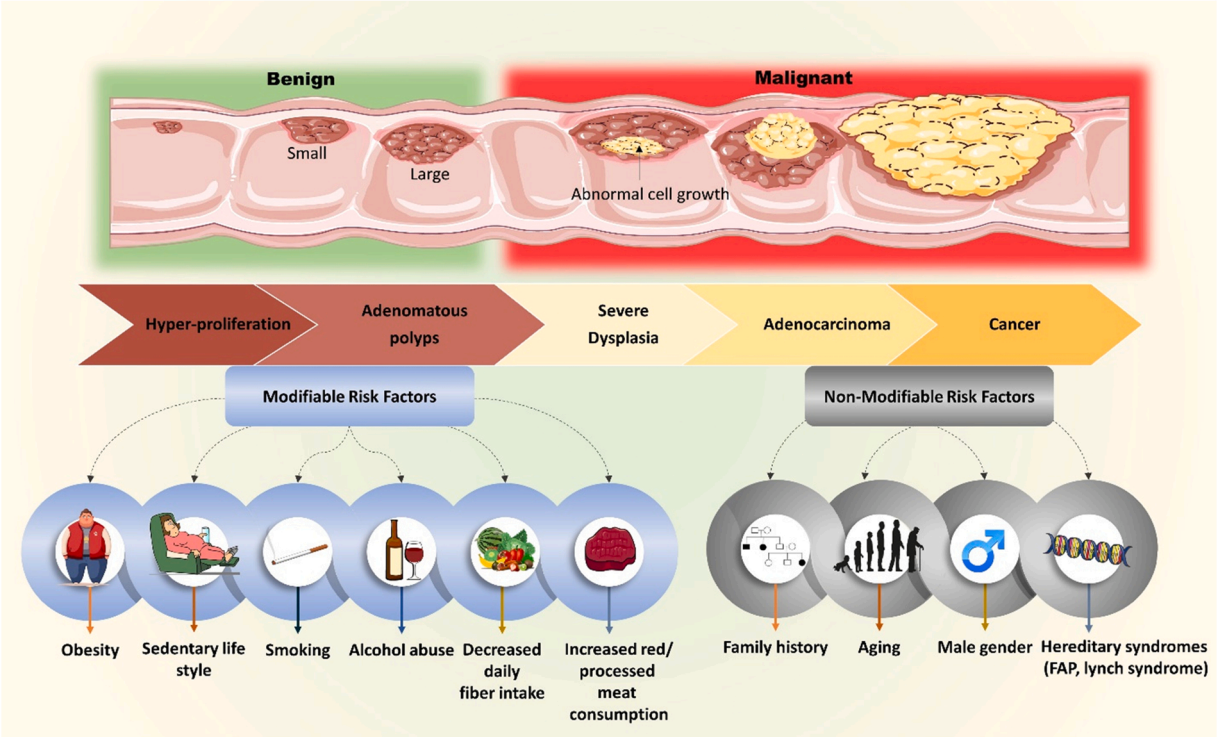

Fig. 1. CRC is mediated by a set of environmental and genetic factors that include modifiable and non-modifiable. CRC lesions frequently originates from benign polyps and transform into malignant tumors after the accumulation of mutations at the level of oncogenes and tumor suppressor genes. It then progresses from confined local lesions to metastatic ones.

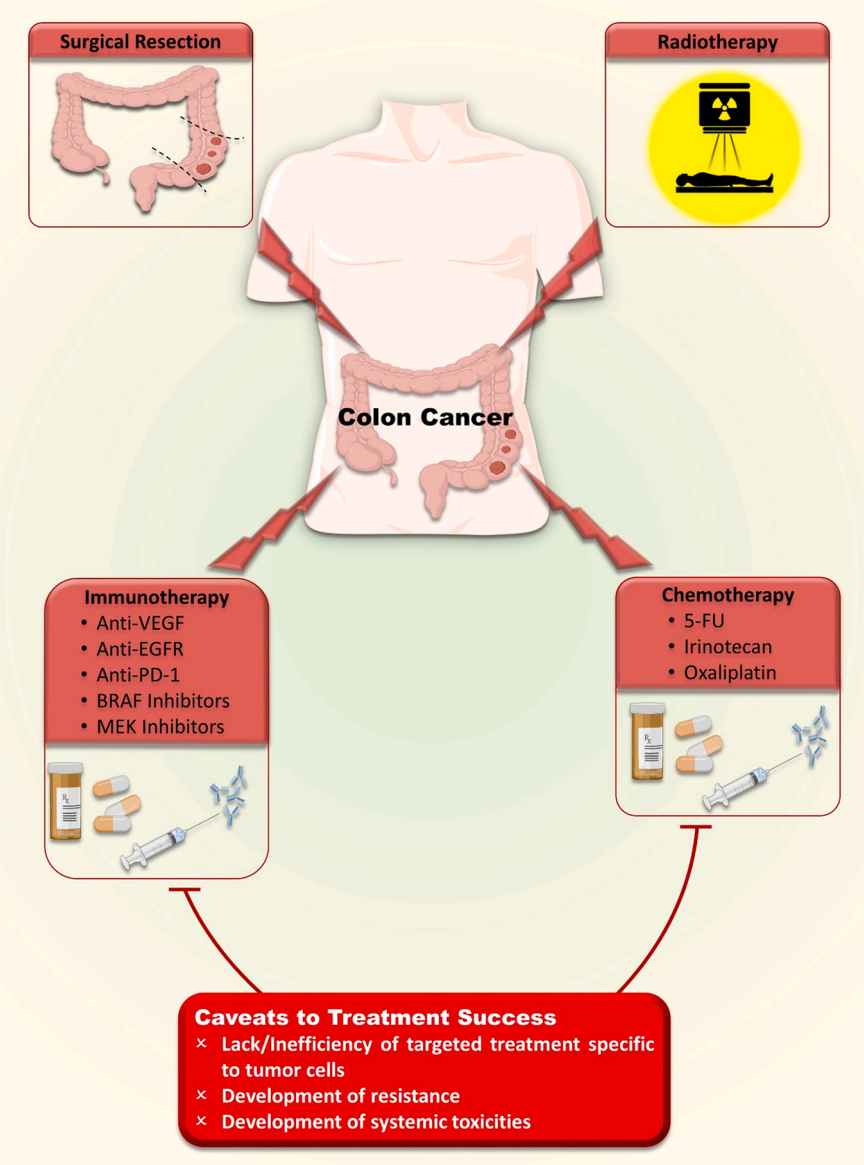

Fig. 2. CRC treatment involves surgical resection and/or radiotherapy and/or chemo- / immuno-therapy. The selection of the treatment is based on both the stage and the grade of the tumor. The main limitations to treatment success include (1) the lack of efficient targeted therapies, (2) the development of drug resistance, and (3) the associated systemic toxicities that follow the administration of most systemic treatments.

efficacy and safety have been compared to conventional paclitaxel in a multitude of randomized controlled clinical trials [40]. Abraxane was found as efficacious as conventional paclitaxel in most studies, and was superior to the original formulation in east Asian patients and in those pre-treated with other regimens [40]. Evidence regarding Abraxane toxicity is controversial with some studies reporting a favorable toxicity profile [39,40]; and others reporting an increased incidence of peripheral neuropathy among patients treated with Abraxane instead of soluble paclitaxel [40]. In sum, both Abraxane and Doxil are approved by FDA and the European medicines Agency (EMA) and are currently used in clinic.

These nano-inventions, among others, have revolutionized the field of cancer management and encouraged the innovation of novel nano-carriers and nano-formulations. Here, in this review, we aspire to examine the role of nanomedicine in improving CRC treatment, in general, and in boosting the delivery of the available chemotherapeutics to the lesional and metastatic sites, in particular. We first provide a synopsis of the available biocompatible nanoparticles (NPs) that can be employed in achieving this. We also highlight their use either as therapeutic or as carriers of available chemotherapeutics.

2. Nanoparticles for CRC management

NPs' use in cancer diagnostics and therapeutics has been heavily explored during the past four decades [41–43]. Their diversity and ease of manipulation have granted them different structural and biological properties, making them suitable for various application in CRC management that include diagnosis, staging, and treatment [44] (Fig. 3).

NPs can enhance a drug's solubility and biostability while enabling its targeted and controlled release (Fig. 4). Taken together, these attributes allow for higher efficacy, reduced toxicity and improved safety profile of utilized drugs complexed within NPs. In addition, NPs can reverse acquired drug resistance by delivering their cargo directly to their intracellular targets, inside the cytoplasm or nucleus [45,46].

Here, we focus on seven different NPs that exhibit validated and potent efficacy against CRC. These particles comprise three classes namely organic, metal-based, or polymerized NPs. Each class has unique properties inferring a different set of advantages and uses.

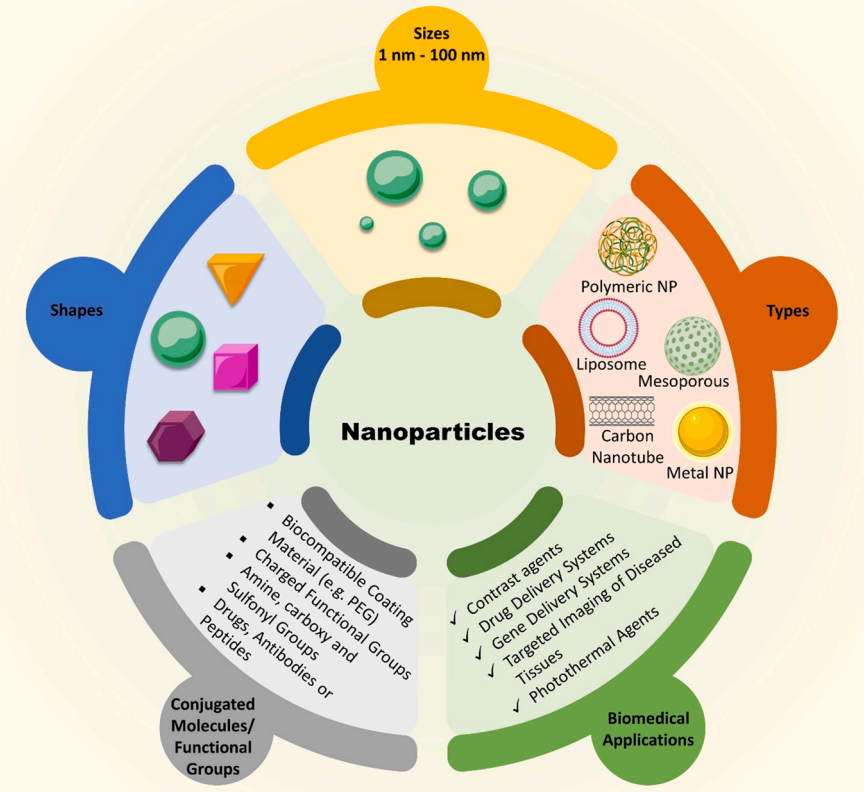

Fig. 3. Various NPs have so far been utilized in cancer medicine. They consist of organic or inorganic materials, and are subdivided according to their size and shape. The biocompatibility, biostability, and function of these NPs can be modified via the incorporation of biocompatible molecules and the manipulation of the NP chemistry.

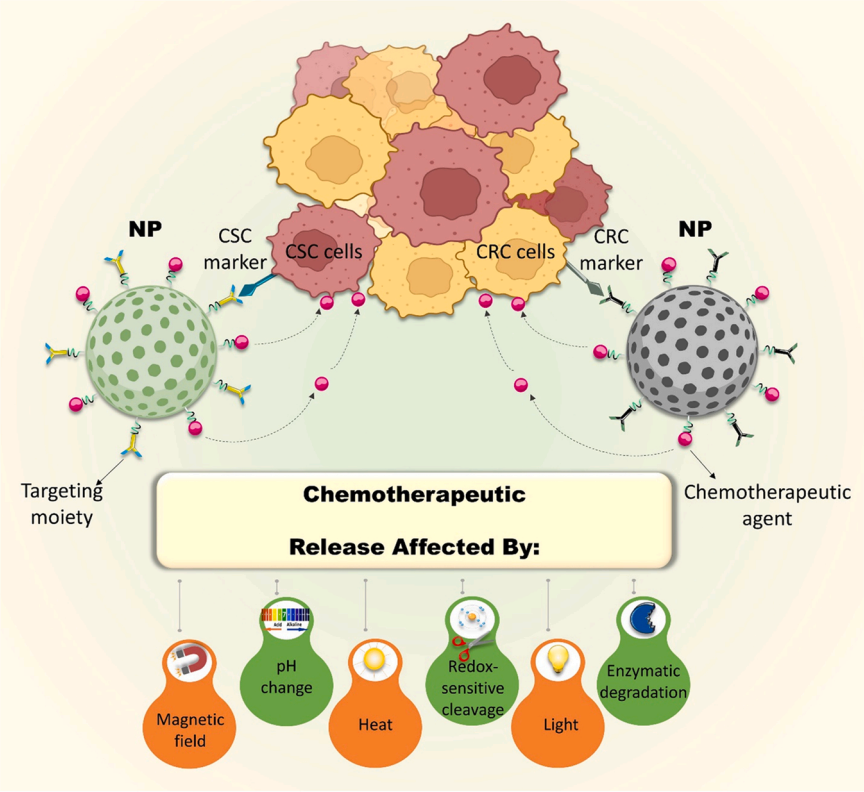

Fig. 4. NPs offer unique means for targeting specifically CRC cells and even cancer stem cells (CSC). This is achievable because these molecules can be easily modified and tagged with anti-CRC markers and anti-CSC targets.

2.1. Quantum dots

Quantum dots (QDs) are semiconductor nanocrystals that fluoresce upon excitation by ultraviolet energy. They emit light at different wavelengths particularly in the near-infrared (NIR) region (700–900 nm) and are resistant to photo-bleaching [47,48]. QDs' ability to emit NIR light makes them ideal fluorescent labels for biomedical imaging where NIR light is needed to ensure adequate tissue penetration [49]. Owing to these optical properties, QDs have been perceived as promising tools in the diagnosis of CRC [50].

Multiple studies have established QDs' role in CRC diagnosis. QD-based immunohistochemistry (QH-IHC) offers several advantages over conventional IHC in detecting CRC antigens in tissue biopsies. Indeed, as compared to conventional IHC, QD-IHC is a simple operation that provides higher sensitivity, less human interference, and more accurate detection of CRC markers [51]. Moreover, targeting tumor-specific markers with biocompatible amenable molecules like NPs can help in diagnosing CRC and predicting its prognosis. For instance, QDs-bevacizumab nanoprobes were able to target CRC specific markers in vitro and in vivo, thereby improving detection of tumor cells on imaging [52]. QDs have also been used to identify Aldo-keto reductase family 1 member B10 (AKR1B10) in the serum, which improved early detection of colorectal cancer [53]. Others have utilized dual-emission radiometric fluorescent QD nanohybrid to visually differentiate CRC cells [54]. Rather impressively, these QD nanoprobes were also capable of distinguishing cells in the G2 phase from ones in other cell cycle stages [54].

Other studies have employed QDs to detect surface proteins like glucose transporter 1 (Glut1) on CRC cells. Glut1 is highly expressed by tumor cells because of their high metabolic rate [55], and an increased Glut1 expression is linked with high-grade CRC and distant metastasis [55,56]. Interestingly, QD-based nanoprobes composed of a fluorescent QD core and a gadolinium-based surface have been tagged with anti-Glut1 antibodies [56]. Using MRI, these QD-based nanoprobes facilitated the localization of diseased tissues through the tracking of in vivo Glut1 expression [56]. They showed excellent colloidal stability in both acidic and basic media and were not only stable in vivo but also in vitro. They were also used to optimize tissue biopsy since they can serve as fluorescent probes in IHC [56]. Additionally, in another preclinical study, QDs were utilized to target vascular endothelial growth factor receptor 2 (VEGFR2), which is considered an adequate predictor of prognosis upregulated in advanced CRC [57]. Moreover, QDs bioconjugated with anti-VEGF2 antibodies have been used as contrast agent in fluorescence-based imaging [58], which allowed significant differentiation between malignant and normal colon cells. Together, these studies support the use of these NPs in CRC diagnosis.

Besides being adequate tools for bioimaging, QDs can also act as carrier for chemotherapies and may potentiate the anti-cancer activity of these medications. Fine porous zinc oxide (ZnO) QD NPs (ZnO QD NPs) appear to exhibit a promising potential in the fight against cancer. Indeed, ZnO QD NPs have been shown to suppress viability and promote apoptosis in cultured CRC cells [59]. They were also used to deliver a new anticancer class named unsymmetrical bisacridine derivatives (UAs) [60]. Interestingly, QDs were shown to increase cellular uptake of UAs, arrest cell cycle, and induce apoptosis in CRC cells [61]. Similarly, QDs appear to potentiate the antiproliferative effect of certain drugs in CRC but not in normal cells [62].

Radiotherapy in mice bearing human CRC cells has been shown to be boosted by a novel silver nanocomposite constituting of combined PEGylated graphene QDs and silver nanoprisms [63]. These composites appear to radiosensitize CRC cells and inhibit the growth of tumor cells more efficaciously than radiation alone. Indeed, it is this coating of silver NPs with pegylated QDs that imparts the superior outcomes, largely because QDs preserve the shape of silver NPs and enhance their efficacy [63]. Taken together, these applications and others provide compelling evidence for the usefulness of these NPs as improved, sensitive, and accurate cancer diagnostic tools. Further pre-clinical animal and clinical human studies are needed to elucidate the exact role of QDs in CRC management as well as their potential toxicities.

2.2. Iron oxide NPs

Because of their magnetic and photothermal properties, iron oxide NPs have been approved by the FDA as MRI contrast agents and cancer hyperthermia therapy [28,64–68]. They are also approved for iron deficiency anemia since they can serve as a potent iron source after being degraded by the reticuloendothelial system (Table 1) [69]. Furthermore, they can be safely applied in humans and are known to have a well-tolerated cytotoxic profile [28], in addition to being easily processed and cleared by the human body [28]. Their magnetic properties are utilized for drug delivery rendering them employable for selective targeting. Indeed, by helping in selective delivery of anti-tumorigenic medications, the contents of these NPs can be released exclusively at the target site following the application of a magnetic field that triggers their burst [70]. Consistent with this, superparamagnetic iron oxide-based NPs have been recently shown to be effective for multimodal cancer therapy [71].

The magnetism of iron oxide NPs also plays a role in CRC diagnosis, as the example of Lectin-Fe_2O_3 AuNPs shows [97]. These nanocomplexes are produced by joining lectins with iron oxide (Fe_2O_3) and gold NPs (AuNPs) via bifunctional polyethylene glycol (PEG) NHS (an amino derivative of PEG) ester disulfide linkers. It was subsequently shown that these agents play a role in CRC imaging by targeting tumor cells where they can be detected by dual-mode MRI, X-ray, or CT [97]. Furthermore, for aggressive cancers with a high stroma content, diagnostic imaging utilizing contrast agents conjugated with a peptide having a high affinity to extracellular matrix (ECM) proteins is thought to be very promising and vital. Importantly, superparamagnetic iron-oxide NPs have been utilized for selective targeting, and thus imaging, of specific extracellular proteins in the tumor environment [98].

As for their therapeutic potential, iron oxide NPs appear to be viable drug vehicles adequate for preventing the undesired degradation of drugs during transport, all while enabling selective targeting of diseased tissues. This then enhances the efficacy of the drug and minimizes the associated side effects. In this context, cell penetrability and cytotoxicity of iron-oxide NPs with doxorubicin conjugates (Dox-NPs) are significantly higher than those of free doxorubicin (Dox) in human CRC cells (HT-29) [99]. Hence, a particular dose of free Dox can be potentially substituted by a lower dose of Dox-NPs while ensuring equivalent efficacy. Dox-NPs application in vivo is also feasible and can be ensured via the application of a magnetic field. Similarly, paclitaxel-loaded superparamagnetic iron oxide NPs were applied to murine CRC models [100]. To optimize selective targeting of the tumor, an external magnet was placed adjacent to the tumor site. Importantly, tumor growth was significantly lower in animals treated with paclitaxel-loaded iron oxide NPs compared to free docetaxel [100]. The iron oxide NPs-based magnetic carrier of paclitaxel served also as a contrast agent for the MRI visualization of tumors (Fig. 5) [100]. In line with these reports, the distinctive theragnostic properties of iron oxide NPs have also been highlighted by other animal studies, further supporting their use [67,101].

By virtue of their photothermal properties, an additional anticancer effect of iron oxide NPs has also been reported. For instance, iron oxide core NPs have been shown to potentiate the anti-tumor effect of 5-fluorouracil loaded polylactide-co-glycolic acid NPs (PLGA) [102]. The effect was accomplished by increasing the negative influence of hyperthermia on HT-29 CRC cell lines, thus establishing a role for iron oxide NPs in CRC treatment [102]. More recently, iron oxide NPs were also shown to be able to sensitize Apo2L/TRAIL (Tumor necrosis factor-related apoptosis-inducing ligand)-resistant CRC cells by targeting the tumor cells and generating ROS. This subsequently triggered c-Jun N-terminal kinase activation which caused autophagy-assisted

Table 1
Table discussing the advantages and disadvantages of each NPs type and highlighting the availability of FDA approved formulations.

NPs Type	FDA-approved in Human	Advantages	Disadvantages/Toxicities	Ref.
Quantum Dots	In 2011, C dots, a QD-based agent, was approved as a diagnostic probe added to PET scan in patients with metastatic melanoma to allow targeted imaging.	1. Biocompatible and photostable 2. Emit light at different wavelengths 3. Adequate for deep tissue imaging	1. Slowly metabolized 2. May accumulate in tissues 3. Have a Low aqueous solubility 4. Need to be coated/modified to improve solubility and biostability 5. Complex structure/chemistry 6. Not biodegradable	[72,73]
Iron oxide NPs	Multiple iron oxide NPs-based formulations were approved as iron deficiency anemia treatment, MRI contrast agents, and cancer hyperthermia therapy.	1. Biocompatible 2. Amenable to modification 3. Can be manipulated using an external magnetic field 4. Adequate for hyperthermal therapy 5. Can be cleared by the body 6. Can serve as a source of iron	1. Have a Low aqueous solubility 2. Need to be coated with organic polymers to improve solubility and biostability 3. May cause anaphylaxis or hypersensitivity 4. May cause oxidative damage	[74–80]
Polylactide-co-glycolic acid (PLGA) NPs	Currently, a multitude of PLGA NPs-conjugates are approved as drug delivery systems and/or diagnostic probes.	1. Biocompatible 2. Biodegradable 3. Have a low potential for toxicity and hypersensitivity 4. Can be easily modified and synthesized in different sizes/shapes 5. Offer a high drug loading capacity 6. Allow tunable release of loaded drugs	1. Negatively charged 2. Serve as contrast agents only if coated with inorganic metals	[74,77,78, 81,82–84]
Dendrimers	Up till now, only one dendrimer-based therapeutic is approved.	1. Biocompatible 2. Biodegradable 3. Amenable to modification 4. Offer a high drug loading capacity 5. Can easily penetrate tissues and biological barriers 6. Owns anti-microbial properties 7. Water-soluble	1. Serve as contrast agents only if coated with inorganic metals 2. Cytotoxic	[77,85]
Carbon Nanotubes	No therapeutic or diagnostic formulations are yet approved.	1. Have a large surface area 2. Chemically stable 3. Display adequate thermal conductivity	1. Not biodegradable 2. Insoluble in aqueous media 3. Need to be coated with organic polymers to improve solubility and biostability 4. May induce an inflammatory response and cause liver and lung toxicity	[86–88]
Liposomes	Many liposome-encapsulated anti-cancer medications have been approved with Doxil being the first one.	1. Biocompatible 2. Biodegradable 3. Amenable to modification 4. Allow a wide range of drug delivery (can transport hydrophobic and hydrophilic molecules). 5. Offer a high drug loading capacity 6. Allow tunable release of loaded drugs 7. Have a low potential for toxicity and hypersensitivity 8. Amenable to modification 9. Thermosensitive 10. Non-immunogenic	1. Early degradation and premature leakage of loaded drugs 2. Short half-life 3. High cost of production 4. Have a Low aqueous solubility	[74,77,78, 89,90,91]
AuNPs	A few AuNPs are currently approved as diagnostics/ therapeutics for human.	1. Biocompatible 2. Possess favorable optical properties 3. Amenable to modification 4. Can absorb near-infrared light 5. Adequate for deep tissue imaging	1. May cause oxidative damage 2. Not biodegradable 3. Need to be coated with organic polymers to improve solubility, biostability, and biodegradability	[74,77, 92–96]

DR5 upregulation [103]. More recently, iron oxide NPs have been used in synthesizing gold nano-cubes that, in combination with photothermal therapy, offer superior results, albeit in liver cancer cells [104]. Whether the same can be reproduced in CRC remains to be established.

It is important to mention that iron oxide NPs have been shown to overcome problems associated with nanoparticle-sensitized photoporation, a process that requires contact between NPs and cells. This contact indeed renders this process relatively difficult to translate into the clinical setting. However, light-sensitive iron oxide NPs embedded in biocompatible nanofibers have been shown to facilitate photothermally effected membrane permeabilization without needing these NPs to be in direct contact with cells [105]. These nanofibres did successfully deliver biomolecules to cancer cells, and more importantly, were able to cause in vivo tumor regression [105]. Similarly, activated iron oxide-hydroxide nanospindles have been shown to "light up" CRC cells, rendering them suitable for MRI-guided photothermal therapy [106]. Interestingly, these nanospindles appear to be highly biosafe in a murine model even after a 3-month duration of treatment [106]. Collectively, iron oxide NPs are important CRC theragnostic as they offer an opportunity to overcome issues of drug resistance and systemic toxicities, while allowing the use of lower drug doses and ensuring an efficacy equivalent to that of the free drug.

2.3. Polylactide-co-glycolic acid (PLGA) NPs

PLGA NPs are biodegradable carriers used to transport proteins, peptides, vaccines, and drugs in the human body. They offer several advantages that include controlled drug release and strong tissue

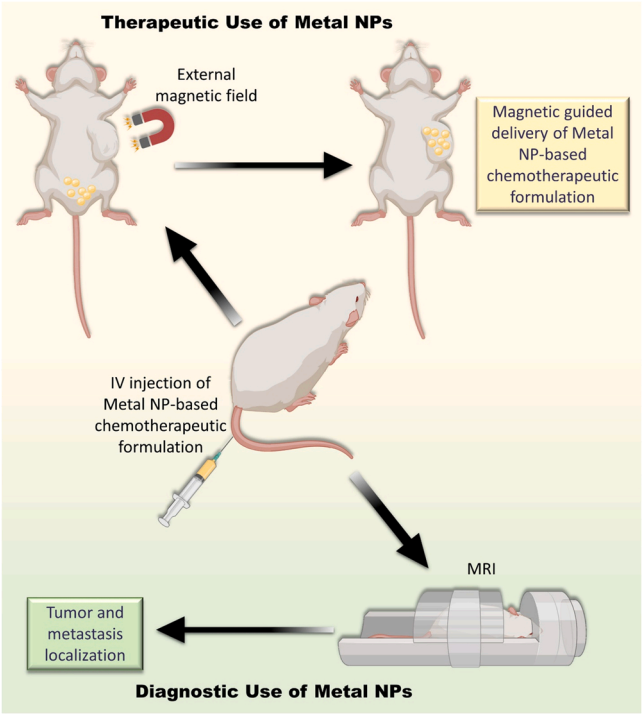

Fig. 5. Metal-based NPs, like iron oxide NPs and AuNPs, are outstanding theragnostic molecules known for their biocompatibility, photothermal and magnetic properties as well as their ease of synthesis, manipulation, and application. They offer simultaneous diagnostic and therapeutic benefits in the context of solid cancers like CRC. Their unique magnetic properties enable their magnetic-guided delivery to the tumor site. Location of these NPs and of the tumor site can be further detected using MRI, offering thus diagnostic applications.

penetrability, in addition to their low potentials for toxicity and hypersensitivity [107]. Importantly, these drug carriers can be limited by their stability and particle size, which can be modified by modulating the consistent polymer or altering the chemical structure and properties [107]. Besides, their biodegradability makes them ideal therapeutic candidates in the management of any cancer, including CRC [108]. For instance, despite the overwhelming anticancer effects of curcumin, its use has been limited by its poor bioavailability. Interestingly, curcumin-loaded PLGA NPs resulted in higher curcumin uptake by CRC cells compared to pure curcumin solution [109]. This improvement in curcumin delivery is attributed to the enhanced colloidal stability of PLGA NPs in gastrointestinal fluids, their smaller size, and their sustained release [109]. Similarly, the use of mangostin alone is limited by its poor stability, bioavailability, targeted accumulation in tumor cells, and its hydrophobic nature. However, when encapsulated with PLGA nanoparticles, these limitations were overcome, and noticeable improvement in therapeutic benefits and efficacy of mangostin were reported [110].

PLGA NPs have also been employed to improve efficacy of commonly used drugs like 5-fluouracil (5-FU). Indeed, 5-FU-loaded PLGA NPs induced CRC cell death and provided an improved well-tuned release of 5-FU compared to free 5-FU [111]. Contextually, 5-FU and an oxygen carrier (perfluorocarbon) were combined with PLGA NPs modified with epidermal growth factor (EGF) [112]. This combination allowed for selective targeting of tumor cells expressing high levels of EGF receptor (EGFR). Expectedly, this selective targeting improved efficacy, as it induced significantly higher rates of apoptosis and cytotoxicity, and lower rates of tumor expansion and growth. Additionally, the coupling of perfluorocarbon to this composite overcame the problem of tumor hypoxia associated with the development of 5-FU resistance [112]. Furthermore, reduced efficacies resulting from 5-FU resistance and short life span appear to be circumvented by virtue of the selective targeting and sustained release ensured by the nanocarrier.

These nanocarriers have also been used to increase cytotoxicity of irinotecan against human CRC cells [113]. Irinotecan is a drug that inhibits the S-phase by hyperstabilizing DNA topoisomerase I complex, a cellular enzyme overexpressed in many types of tumors including CRC. By doing so, it inhibits re-ligation of DNA strands, eventually leading to the formation of lethal DNA breaks [114]. The use of irinotecan in the clinic is limited by its systemic toxicities that include severe neutropenia and diarrhea [114]. Hence, it was hypothesized that the delivery of this drug using biodegradable, safe, and stable polymers like PLGA NPs can potentially overcome these toxicities while improving irinotecan efficacy. Delivering irinotecan with a PLGA nanocarrier can be modulated to target selectively the diseased tissues while sparing the healthy tissues from the systemic effects of irinotecan [113]. Additionally, a potential therapeutic effect can be achieved with a lower dose of irinotecan, which in turns imparts a favorable toxicity profile. Congruently, a PLGA-based nanomicelle was introduced as an excellent candidate for delivery of irinotecan to human cancer cells and was shown to induce higher cytotoxicity than free irinotecan [113]. Its in vivo use will prevent the uptake of irinotecan by the reticuloendothelial system and improve its delivery, while providing higher targeted toxicity against cancer cells [113]. Indeed, very recently, PEG-PLGA NPs have shown efficacy in boosting immunotherapy of colon cancer in mice [115]. Similarly, PLGA NPs entrapped to folic acid were proposed to selectively deliver a chemotherapeutic agent to targeted colon cancer cells [116]. These implications may be applicable to other drugs of similar profile unlocking many new avenues in drug delivery. Nonetheless, further human studies are needed to validate the efficacy of these carriers and to assess their safety.

Furthermore, cholesterol-coated PLGA NPs have also been used to co-carry retinoic acid and oxaliplatin [117]. Importantly, these NPs potentiated the in vitro and in vivo efficacies of these drugs, and induced a significant reduction in drug resistance and tumor metastasis [117]. Congruently, there is promise in treating and monitoring CRCs by producing carcinoembryonic antigen (CEA)-targeting PGLA NPs. These NPs can detect the level of soluble CEA and thus can monitor CRC remission and relapse when tagged with high affinity ligands suitable for binding soluble CEA. Rather impressive, when tagged with low affinity ligands, these molecules can bind preferentially to the tumor cells and serve as therapeutic carriers [118]. Not surprisingly, PLGA NPs are now FDA-approved drug carriers that can serve as tools for improving and revolutionizing CRC treatment.

2.4. Dendrimers

Dendrimers are polymeric NPs with unique structural properties. They have a three-dimensional structure consisting of a central core molecule surrounded by branched layers consecutively added to the core [119]. These dendrimers can acquire a variety of functional groups on their outer surface, making them excellent tools for drug delivery and monitoring of treatment success [119]. For instance, polyamidoamine dendrimer NPs (PAMAM) modified with cholesteryl chloroformate and alkyl-PEG were used to co-deliver doxorubicin and TRAIL plasmid to C26 CRC cells [120]. These NPs potentiated the effects of their cargo in both in vivo and in vitro experiments [120]. Interestingly, their ease of modification and manipulation has rendered them ideal candidates for encapsulating and delivering a wide array of drugs [121]. In addition to their ability to carry high dosages and deliver a combined regimen of drugs, they are well-tolerated biocompatible NPs that can be metabolized and eliminated by the renal system [121].

Due to its mechanism of action entailing DNA damage, capecitabine affects negatively multiple organs, particularly those having increased rates of cell division: hair, liver, blood, and bone marrow cells. Dendrimer-conjugated capecitabine exhibited higher efficacy than free capecitabine in murine CRC models [122]. Indeed, the

dendrimer-conjugated drug showed superiority in reducing tumor size and also in diminishing the toxic effects on blood and liver cells [122]. Another anti-cancer drug currently employed in the clinical setting and limited by its narrow therapeutic index is irinotecan [123]. The conjugation of the active metabolite of irinotecan with dendrimers was capable of increasing its selectivity to tumor cells while reducing its effect on healthy cells. This also resulted in a higher efficacy and reduced toxicity [123].

Another important application of these NPs is the incorporation of antibody conjugates on the surface of dendrimers that capture circulating tumor cells (CTCs). For instance, surface-active dendrimers can be manipulated to target a CRC biomarker Slex (Sialyl Lewis X), an antigen incorporated in CRC cells extravasation and metastasis [124]. These dendrimers were superior in selectively detecting and downregulating colon CTCs, giving them both diagnostic and therapeutic roles. Moreover, PAMAM NPs conjugated with AuNPs and a peptide called circular heptapeptide GX1 were able to selectively home to the vascular endothelium of the tumor [125]. This nanoplatform was effective in detecting the CRC lesions and also in delivering the FAM172A gene, a gene involved in inducing the apoptosis and restraining the proliferation of the cancer cells, to the tumor cells [125,126]. The cytotoxicity of this platform was significant in the presence of photothermal therapy (PTT); a significant reduction in tumor size was noted in HCT-8 tumor-bearing mice after 14 days of treatment. This effect was particularly noticeable in the group receiving both the FAM172A gene via the nanoplatform in addition to PTT [125]. Collectively, these flexible biocompatible NPs provide important theragnostic CRC applications. However, further studies are needed to validate their safety since it was postulated that dendrimers can exhibit cytotoxic effects on their own (Table 1). That said, it is important to stress here that PAMAM dendrimers do not evoke a strong immune response, and are thus considered nonimmungenic. This makes them relatively safer than viral or nonviral vectors used in gene delivery for cancer treatment. Moreover, dendrimers have the ability to bind to charged DNA or siRNA, and the tertiary amine groups in their interior possesses a strong pH buffering ability that allows for easier escape from endosomal damage [127]. Altogether, these features make dendrimers effective and attractive alternatives to vector therapy of cancer [128].

2.5. Carbon nanotubes (CNTs)

CNTs are cylindrical allotropes of carbon with rolled graphene sheets fewer than 1 μm in diameter and a few nanometers in length [129]. Their high surface area, heat conductivity, chemical stability, and needle-like structure make them viable tools in antitumor drug delivery, amid other uses [130–132]. In fact, these NPs have been used in carrying a battery of drugs that include chemotherapeutics, immunomodulators, and gene therapies. They are also important sensitizers of PTT and photodynamic therapy (PDT) [132].

Single-walled carbon nanotubes (SWCNTs) conjugated with a synthetic polyampholyte were used to deliver paclitaxel to Caco-2, a colon cancer cell line, showing greater efficacy in comparison to paclitaxel alone [133]. Modified single-walled carbon nanotubes (SWCNT) fitted with TRAIL, which precipitates ligand-induced apoptosis, exhibited ten-fold higher efficacy than TRAIL alone [134]. Similarly, SWCNTs hybridized with type-II nanocrystalline cellulose potentiated the anticancer effects of capecitabine against a CRC cell line, though the hybrid itself elicited interesting anticancer effects and imaging benefits making it a potential theragnostic [135].

Recently, gemcitabine-loaded hyaluronic acid conjugated PEGylated multi-walled carbon nanotubes (MWCNTs) effectively targeted colon cancer cells. In addition, these MWCNTs released gemcitabine at higher rates in acidic conditions (pH 5.3) in comparison to physiological conditions, thus decreasing toxicity while effectively reducing tumor volume [136]. Recently, MWCNTs were used to encapsulate paclitaxel and thus to achieve a higher loading of this anticancer drug [137].

CNTs also play a role in PDT, where for instance hyaluronic acid and a photosensitizer, chlorin e6 (ce6), coated the walls of single-walled CNTs. This synthesized nano-biocomposite then resulted in increased efficacy of PDT on cancer cells as opposed to ce6 alone [138]. Moreover, CNTs can facilitate tumor localization and trace CRC metastasis to lymph nodes during surgery [139,140]. This was achieved after CNTs were infused into the surrounding of the tumor, absorbed exclusively by lymphatics, and tracked in surrounding lymph nodes. More recently, it was also shown that intratumoral CNT-CpG complex inhibits local and metastatic CRC tumors [141]. Taken together, accumulating evidence provides the basis for the proposition that CNTs are suitable for overcoming multidrug resistance in CRC, improving local tumor targeting, tracing CRC metastasis, and facilitating its surgical resection. Nonetheless, up till now, no CNT-based nanoformulation is approved by the FDA due to their potential hepatic and respiratory toxicities (Table 1). This indicates that further studies are needed to examine the safety and the theragnostic benefit of these NPs.

2.6. Liposomes

Liposomes are lipid-based vesicles with a small aqueous spherical core, and they act as artificial drug carriers. Their half-life is largely determined by vesicle size, which can vary from 0.025 μm to 2.5 μm. In addition, their membranes can be single or double-layered. Depending on the size and number of their layers, liposomes are either multilamellar or unilamellar vesicles [142]. Their small size, carrier properties, and phospholipid bilayer make them a very effective drug delivery system with minimal side effects [143]. Indeed, the notion that they are biodegradable, biocompatible, relatively non-toxic, and can carry both lipophilic and hydrophilic drugs makes them very attractive. The FDA had already approved a liposome formulation carrying doxorubicin in 1995, and later also approved Marqibo, a liposomal formulation of vincristine [144–146].

A bifunctional liposome with oxaliplatin-prodrug conjugated to phospholipid and alkylated NLG919 (an IDO1 inhibitor) was used to target cancer cells and to limit their immunosuppressive capabilities mediated by indoleamine 2,3-dioxygenase 1 (IDO1). These liposomes were found to have a long blood circulation time and were able to synergistically target cancer cells by the dual release of oxaliplatin and IDO1 inhibition [147].

Liposomes appear to limit CRC metastasis and angiogenesis, as shown by a study examining liposomes loaded with pigment epithelium-derived factor (PEDF). These PEDF-DNA-loaded liposomes inhibited invasion and migration of CRC cells and induced pro-apoptosis effects in vitro. When applied to a mouse model, they were found to reduce metastasis of tumor nodules and prolong survival time [148]. Others have used pH-sensitive liposomes to deliver multiple anticancer drugs some of which may impart photodynamic therapeutic effects as well [149]. In some instances, surface modification of liposomes may be required to improve selectivity, and thus potentially reduce toxic side effects [150]. It is important to mention here that recently, hybrid vesicular systems of liposomes and polymersomes, also known as lipopolymersomes, are being developed as they provide minimal disadvantages compared to either liposomes and polymersomes alone. These systems combine the advantages of both entities (liposomes and polymersomes) and provide the combined benefits of improved structural integrity of the bilayer and increased serum stability, while also preserving the soft nature of liposomes and the increased encapsulation efficiency of cargos in the bilayer partition [151]. Indeed, these platforms exhibit rather impressive efficiency in delivering camptothecin in CRC, both in vitro and in vivo [151]. In line with these results, a very recent paper showed that a unique multifunctional liposome (MFL) enhanced absorption and release of cytotoxic drugs into colon cancer cells, thereby inducing apoptosis and suppressing metastasis [152].

More recent evidence further cements the premise the liposomes can indeed improve drug delivery to colon cancer cells, and consequently

the management of CRC. For instance, lipid-encapsulation of irinotecan has significantly improved the ultimate response to this drug in colon cancer, while also limiting this drug's toxicity in in vivo systems [153,154]. Indeed, compared to the free drug, this liposomal preparation of irinotecan exhibited a higher antitumor effect as well as a longer duration of action against CRC, making it an attractive approach in the management of this disease [153]. Importantly, liposomes not only help in targeted delivery and reduced toxicity of certain drugs, but also in resolving solubility issues associated with certain therapeutic agents. For instance, a liposomal nanoformulation of zina (ZnL(AcO)) showed significant superiority over the free zinc complexes in suppressing tumor progression and reducing the tumor burden to a level similar to the standard drug used in CRC treatment, namely 5-FU [155]. More importantly, the tumor volume reduction achieved by these liposomal complexes was elicited at a lower dose, thereby indirectly reducing the potential adverse effects [155]. Together, the results obtained in this study strongly suggest that liposomes can solve solubility issues of some metal-based complexes [155]. In CRC, liposomes and liposome-based formulations have also been shown to play an important role in circumventing resistance, which remains a major hurdle in the fight against this disease [156–158]. Indeed, it was recently shown that aptamer-conjugated nanoliposomal formulations robustly sensitized colon cancer cells to chemotherapeutic agents, thereby aiding in overcoming chemoresistance [159]. Similarly, liposomes have been shown to be instrumental in sensitizing colon cancer cells to 5-FU [160]. Bifunctional liposomes appear to reduce the potential resistance to doxurubucin in CRC cells [161]. Taken together, these findings explains the increasing interest in liposomes as promising tools in the fight against chemotherapeutic resistance.

2.7. Gold nanoparticles (AuNPs)

AuNPs are biocompatible nanocarriers employed in a variety of medical fields including cancer [162–164]. Their exceptional physiochemical and optical properties have made them suitable for both targeted (active) and non-targeted (passive) delivery. Their use as drug vehicles is also endorsed by their ease of synthesis and amenability to surface modification [162–164]. Indeed, these NPs are adequate carriers for a wide range of drugs including nucleic acids (e.g. 5-FU), antibodies (e.g. anti-EGFR), and proteins, among others.

Despite having an adequate biostability that renders them optimal for in vivo use, AuNPs' biostability can be further enhanced by selective coating with polymers like polyethylene glycol and dextran [162,165]. This can overcome the premature clearance of these molecules by the reticuloendothelial system and prevent their uptake by macrophages. Additionally, their size and shape are critical determinants of effective drug delivery, cellular uptake, and biostability [162–165]. These parameters are usually manipulated to optimize therapeutic efficacy of various agents.

In CRC, AuNPs have been heavily investigated in animal and human studies. Indeed, they enjoy the lion's share of nanotechnology research. They have been used to favorably modulate various CRC hallmarks including apoptosis, angiogenesis, proliferation, and metastasis. Their use in delivering various anti-CRC treatments, particularly cisplatin, 5-FU, and anti-EGFR, has been well-documented and supported [164,166,167]. Similarly, they were shown to be effective in improving tumor responsiveness to radiotherapy [168,169], and in localizing and staging CRC using imaging like MRI, CT scan, and photoacoustic imaging [170].

Because caspases are crucial mediators and executioners of apoptosis, drugs that activate them would be important in the fight against cancer. For instance, 17-allylamino-17-demethoxygeldanamycin (17-AAG), an inhibitor of heat shock protein 90, efficiently activates caspases and induces apoptosis in cancer cells [171,172]. In a pre-clinical trial, a combination of 17-AAG with irradiation (IR) and AuNPs resulted in higher cytotoxic effects on cancer cells compared to 17-AAG alone. Combining 17-AAG with AuNPs and IR increased Caspase-3 expression and activation, precipitated apoptosis and resulted in enhanced cytotoxicity [173]. Similarly, adding tiopronin-coated AuNPs (Tio-AuNPs) to X-ray radiations robustly suppresses CRC survival [174]. Moreover, AuNPs can be regarded as radiosensitizers as they contributed to higher cytotoxic effects on HT-29 CRC cells exposed to megavoltage x-rays energy [175]. The mechanism for their radio-sensitization properties could be due to their ability to evoke oxidation of the mitochondrial membrane and trigger its depolarization [176,177]. Together, these and other studies support the notion that supplementation and modification of other therapeutic agents with AuNPs increase their apoptotic effect.

Suppressing the proliferation of CRC cells is another important phenotype to target. Because they often overexpress EGFR, cancer cells become suitable targets for anti-proliferative drugs targeting EGFR [178]. When AuNP-coated anti-EGFR antibodies were added with the classic drug, 5-FU, a potentiated impairment in CRC cell proliferation was noted [179]. This cements the argument that NPs, particularly AuNPs, can potentiate the efficacy of anti-proliferative drugs and improve their selectivity to tumor cells.

AuNPs have been shown to be instrumental in drug delivery approaches that enhance targeted specificity and help reduce cancer cell resistance to essential drugs like doxorubicin (DOX) [180,181]. *Pedrosa* et al. combined cetuximab, an anti-EGFR antibody, with an anti-tumor Zinc-based nano-system composed of multifunctional AuNPs to target EGFR-overexpressing CRC cells and induce death of the DOX-resistant cancer cells [181]. Indeed, Zn(II) coordination compounds (Zn $(DION)_2Cl_2$) (ZnD) were delivered to DOX-resistant CRC cells with the help of multi-functional AuNPs, and cetuximab was used to specifically target resistant cells that overexpress EGFR. ZnD increased caspase 3/7 activity and consequently apoptosis ensued, while cetuximab exerted anti-proliferative and anti-angiogenic effects in addition to the successful targeting of the tumor cells [181]. This application of AuNPs potentiated targeting of DOX-resistant CRC cells through the delivery of ZnD using AuNPs and cetuximab [181]. These results emphasize the major role of AuNPs in addressing drug-resistant CRC.

Moreover, AuNPs can be also employed in CRC diagnosis. AuNPs loaded with specific tumor antibodies, such as the anti-plasma membrane heat shock protein 70 (Hsp70) antibody, have been shown to be contrast agents suitable for detecting the primary tumor along with its metastasis [170]. Interestingly, AuNPs have the potential to be easily modified and coupled with an array of CRC specific antibodies. This characteristic along with their unique physiochemical properties endorse their use in the field of cancer imaging. In addition, given their unique photo-thermal and photo-acoustic properties, AuNPs can act as a mean for combining photothermal therapy with immuno- or chemotherapy which can result in turn in superior therapeutic outcomes [182,183]. Together, AuNPs are outstanding theragnostic nanoelements adequate for improving both CRC treatment and diagnosis.

3. Concluding remarks

Nanotechnology is widening the horizon of therapeutic options for cancer, including CRC. Increasing evidence supports the notion that NPs not only improve efficient delivery of drugs into their target cancer cells, but also modulate the intrinsic tumorigenic properties of these cells [176,177]. Furthermore, nanomedicine is emerging as a promising tool against the overwhelming obstacles of CRC diagnosis and treatment. It offers a solution to the growing issue of CRC resistance to conventional chemo- and immuno-therapeutics, and facilitates the conquest of the unremitting hallmarks of CRC. Altogether, it is apparent that nanomedicine is becoming an attractive approach for allowing personalized management, and consequently for significantly improving CRC survival and prognosis. The implementation of this approach is evident by the existence of dozens of FDA-approved nanoformulations that can be modified and applied in various biomedical applications. Hence, we postulate that the incorporation of nanomedicine to CRC management is

an inevitable advent. Nonetheless, additional pre-clinical and clinical studies of higher quality are urgently needed to endorse the safety of this approach and generate safe and effective CRC targeted formulations.

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Conflict of interest

The authors declare there is no conflict of interest to be reported.

Data Availability

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

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