

Review

The Potential Role of Nanoparticles as an Anticancer Therapy in the Treatment of Rectal Cancer

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Abstract: Nanotechnology is a rapidly developing science and is applied in a variety of diagnostic and treatment technologies. Colorectal cancer is one of the deadliest human diseases, and hence, wide research is underway regarding its preventative measures. This review demonstrated that “nano” drug delivery systems have successfully transferred pharmaceutical drug particles at the nanoscale as compared to larger particles. Research has shown a higher rate of disease progression among patients who receive conventional drugs compared to those who were given nanoscale drugs. However, the behavior of the cellular components differs from the performance of larger cellular components of the same type; these differences are due to the physical interactions between the nanoparticles (NPs). The review aimed to discuss several recent research studies focused on delivering NPs for the treatment of colorectal cancer (CRC). The reviewed experiments have primarily compared the use of NPs alone or with the addition of an anticancer drug or nanocarriers. These three research methods may help solve past problems and propose new future approaches for colorectal cancer by utilizing the available nanotechnologies. Furthermore, the review illustrated the underlying idea behind NP carriers and stem cell delivery that can be used to create a rapid delivery system for stem cells.

Keywords: nano-drugs; colorectal cancer; nanocarriers; nanoparticles; anti-cancer agents



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1. Introduction

Colorectal cancer is the second leading cause of death from cancer. Microsatellite instability has been demonstrated to be effective in individuals who have not responded to standard treatment. CRC usually starts in the rectum and extends to the colon. Surgery, radiation, chemotherapy, and targeted medications are used to treat lymphoma. Radiation treatment destroys cancerous cells within the field of vision, most often by using photonic radiation to target the primary cancer spot. Gamma and X-ray imaging are very useful for cancer identification and therapy. There is a chance of rectal bleeding, pain, or lacerations. Cancer has been treated with interventional radiology. It has been shown that a combination of drugs may be utilized to postpone the onset of illness. Chemotherapy is preferred by some people over surgery. Patients may become exhausted, and many drugs may have negative side-effects. Finally, immunotherapy is a very successful cancer treatment.

The current techniques for treating colorectal cancer are problematic because they create significant challenges and have a negative impact on patients' quality of life. Conventional medications influence both normal and cancerous cells. To avoid unintended consequences, medications must be administered solely to malignant cells and not to healthy tissue. Recent advancements in nanomaterials and the discovery of new components with distinct properties have paved the way for the development of innovative

cancer therapeutics. They dissolve fully in the rectal cavity and may be an excellent alternative for targeted pharmaceutical delivery [1]. Several investigations into the effects of increasing NP administration and 5-FU therapy have been undertaken [2]. The effects of CNC (cellulose nanocrystal) and PAA (polyacrylic acid) nanogel mucoadhesives, as well as their complex cisplatin (CDDP), were investigated. Numerous CNC-PAA-CDDP simulations (Dynamic Light Scattering). Only 80% of the CDDP releases happened within 24 h, whereas around 35% of the CNC/PAA releases were complicated [3].

According to a recent study, frequently used drugs may be capable of treating colorectal metastatic hepatic cancer and improving liver metastatic colorectal cancer nanoformulation [4].

In CRC cells, NDAT has been studied for its influence on gefitinib's anticancer activities [5]. The effects of cisplatin-containing nanocubosomes on metformin survival and accumulation in colorectal cancer cells have been investigated [6]. Folnox, folinic acid, 5-fluoruracil, oxaliplatin, and FOLFOX are all considered standard colorectal cancer treatments. In orthotopic CRC mouse models, nanoflox has shown potential. A better chemo-immunotherapeutic response was seen in non-toxic combinations of nano-folox and 5-FU than with FOLFOX alone [7]. Surface engineering strategies for colonic cancer nanoparticles have been well studied [8].

Increased bioavailability, prolonged pharmaceutical release, tumor delivery, and lower toxicity are all advantages of incorporating FA/Nano-Cur into micelles [9]. Dendrimers are nano-sized, radially symmetric molecules having a well-defined, homogenous, and monodisperse structure. Their three macromolecular architectural classes produce poly-disperse products with various molecular weights. It is a polyvalency, self-assembling dendrimer with minimal cytotoxicity and solubility. Due to their unique properties, dendrimers are used in a wide range of medicinal applications [10]. The PEGylated Hyaluronic Acid-cleavable Nano Drug Delivery System targets the pH-responsive imine connections in the tumor microenvironment. HA-mPEG2 k-DOX particles (HA-mPEG2 k-DOX NPs). Cleaved PEGylated HA-mPEG2 k-DOX NPs selectively target CD44+ tumor cells. When the PEGylated HA-mPEG2 k-DOX NPs are cleaved, the anticancer effect is most potent, which reduces dose toxicity [11]. Telomerase is a universal therapeutic target in cancer cells due to its role in carcinogenesis. Because of their fewer side-effects than other medications, curcumin and chrysin have been proposed as possible molecular targeted therapies. SW480 colorectal cancer cells were used to test them. When PLGA-PEG NPs are used, curcumin and chrysin become more bioavailable and solubilized [12].

After the CRC specimen was created, magnetic SLNs were selected using a magnetometer. Serial slices, magnets, and immunohistochemically dyed blue SLNs were all utilized [13]. Aspirin promotes the formation of nitric oxide-hydrogen sulfide, a substance used to treat rectal cancer (NOSH). It is the preferred cell cancer agent with a pleiotropic mechanism of action, as well as the first NOSH-aspirin active medication used in rectal sickness at nanomolar concentrations [14]. Because of the severity of colorectal cancer, this review will solely include contemporary pharmacotherapy. It is a relatively new pharmaceutical discovery that has grown in popularity dramatically during the last five years. Nuclear drug carriers, NPs, and anticancer medicinal compounds are examples of NP technology. This review grouped previous research studies in this area and then categorized, evaluated, and compared them. This approach aims to promote the knowledge of these methodologies for scientists in this field and provide a simple overview of modern methods using NPs for the treatment of rectal cancer.

2. Colorectal Cancer Nanocarriers

Nanocarriers are nanoparticles that may be employed in medications. Polymers, as well as carbon-based compounds such as liposomes, are commonly employed as nanocarriers. Colorectal cancer therapy with irinotecan was tried using beta-lactoglobulin (-LG) as a nanocarrier. The NPs were made via physical inclusion. The size, drug packing, encapsulation effectiveness, and drug release were studied at various pH levels. The Irinotecan

complex docking simulation revealed two unique binding sites for the nanocarrier. Figure 1 depicts the different nanocarriers for anti-inflammatory drug delivery (AIAs).

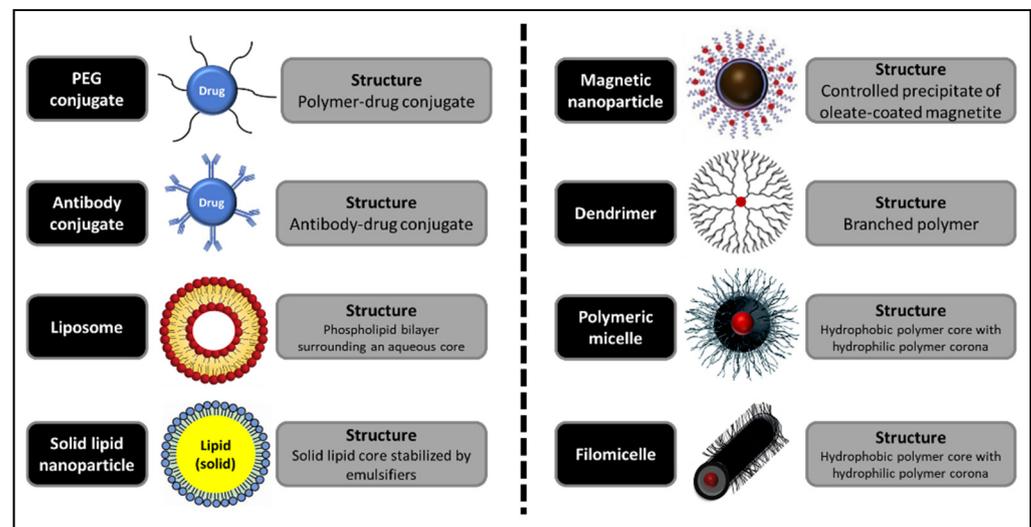


Figure 1. Schematics of the common classes of NCs.

Modified cyclodextrin and oxaliplatin self-assemble to generate a redox supramolecular nanocarrier. If the nanocarrier grows in over-expressing HCT-116 cells and releases medicine, the anticancer therapy is optimized [15]. The ability of dendrimers (PAMAM) to boost the therapeutic index of capecitabine was examined in azoxymethane rectal adenocarcinoma models. NPs were also investigated. The capecitabine/dendrimer complex's concentration (dLC) and encapsulation effectiveness (EE) were assessed [16]. To treat colorectal cancer, lipid-polymer hybrid nanocarriers with ligand-modified, irinotecan-loaded genes were produced. Solvent evaporation was used to make hyaluronic acid, irinotecan, and co-loaded LPNs. Every medicine and gene have an average loading capacity.

Colorectal cancer cells and a colorectal animal model were transfected with this nanosystem in vitro and in vivo [17]. Biocarriers have developed a controlled load nanocarrier. The emulsification–diffusion method produced PHBV carriers charged with 5-FU, and their particle shape and dimensions (SEM, DLS) were studied. Making a two-drug liposomal formulation required a modified thin-film hydration method that interfered with both medicines. The best molar ratio was utilized to treat colorectal cancer with this medication combination. Two human rectal cancer cell lines had much greater cytotoxicities with dual-drug liposomes than with solo, free-combinatorial medications. Angiogenesis inhibition, cell proliferation, and apoptosis potential are improved in dual-medicinal liposomes [18].

Molecular survival (SurMB) and nanosheet graphene oxide (GO) are attached via super molecular interactions. SurMB-binding GO's strength was greatly increased by Joe and Dabcy's hydrogen bonding with the GD carriers. Moreover, SurMB-Joe-loaded nanocarriers were internalized by malignant SW480 cells [19]. The nanocarriers carrying 5-FU and the gene were employed at 145 nm. In vivo, roughly 60% of gene-positive cells were obtained [20]. Metformin (MF) repurposed as a CRC adjuvant proved effective. Several research attempts were made to increase MF's effectiveness. Another study urged the creation of novel semi-interpenetrating networks (Semi-IPN) based on chitosan (CS) to increase trapping and MF for efficient CRC therapy [21].

Another study generated a stable liposome nanocarrier with increased the chemical effects. Apigenin's increased pharmacological activity altered membrane characteristics, resulting in a stable, solid, non-smooth, and optimally released nano-kinetic carrier. After extensive testing, the medication and its liposomal counterparts were found to be compatible with normal fibroblast cells [22]. DACHPt is a platinum-focused chemotherapeutic

drug. Gold nano-shells offer good photothermal effects and can be used in synergistic combinations for chemotherapy [23].

2.1. Effect of Nano-carriers on Epithelial Cell Morphology HT-29

HT-29 and HCT-116 adenocarcinoma cells with epithelial characteristics. The HT-29 cell line has been employed as an in vitro tumor model for xenobiotic transport [24]. The cytotoxicity of 5-FU-charged polymer nanocarriers was studied in human adenocarcinoma cells (HT-29 cell line). The nanocarriers reduced cell viability when loaded with 5-FU. The polymer itself was not cytotoxic; however, the pharmaceutical carrier killed the human adenocarcinoma cells [25]. We obtained and analyzed xylans with substitution levels ranging from 0.034 to 1.11. PX was utilized to encapsulate silica NPs.

The nano-objects were described and tested for therapy of colorectal cell lines. Free TPPOH was 40-fold more potent against HCT-116 and HT-29 cells than PX Mossad [26]. It contributed to cell cycle arrest in HT-29 CRC cells. It also increased apoptotic cell death by activating PARP-1 and p53. RS-PP-050 inhibited catenin transcription in cells via reducing T-cell factor/lymphocyte improvement (TCF/LEF) production, which upregulated the target gene. The apoptotic function of human colorectal cancer HT-29 (SGK206 and SGK242) proliferation has been examined. Etodolac inhibited apoptosis more than SGK 206 and SGK 242 [27].

2.2. Nanocarriers for LCS-1 Delivery

Because it targets tumor cells, selective toxicity looks to be a scientific technique. This study's goal is to kill cancer cells while sparing the redox-regulated SOD1 (RI) synthetic cell (CRCs). LCS-1 (lung screen-1) is a liquifier with low lepidocarpon hydrochloride solubility. Using a bespoke LCS-1-loaded nanocarrier (LCS-1-NC) cell, a deadly link between superoxide 1 inhibition and the bloom syndrome defect (BLM) was explored [28]. A cancer therapeutic synthesis technique uses somatic mutations to directly destroy cancer cells. LCS-1 (SOD1 inhibitor) CRC cells are targeted by utilizing the identified synthetic lethal interaction between SOD1 and BLM. One research created an LCS-1 nanocarrier [29].

2.3. Effects of Nanocarriers with CXCR4 Chemokine Receptor Protein

KIR (Killer Ig-like Receptors) inhibits macrophage movement. It interacts with G-protein receptors and promotes chemotaxis (migration) (a cell migration retardant that increases the motility of the leukocytes). The CXCR4 chemokine receptor is a G-protein receptor. Metastatic colorectal and subcutaneous tumors were compared to non-C4 target ligand-protein carrier-GFP uptake. However, primary cancer cells C22-GFP and H6-GFP showed no substantial C4 uptake. Targeted pharmacokinetics with pharmacodynamics enhances tumor absorption and cytotoxicity by enhancing cytoadherence. While it reduces the large aggregate concentrations of molecules in cells, they are kept within bounds. The ligand promotes normal tumor metabolism with little damage. They had accurate choices of related sites on the CXCR4-binding enzymes, which led to the formation of a multi-crucial viral peptide sequence [30].

T22-GFP-H6 tumor absorption, a CXCR4-target ligand-protein carrier, and a non-ligand GFP-H6 carrier were compared in subcutaneous and metastatic colorectal cancer co-administration. A targeted ligand has the pharmacokinetic advantage of increased tumor absorption and the pharmacodynamic benefit of reduced tumor cell cytosol aggregation [31]. In both human and animal models, the high-specificity (or wide) binding forms of the T22-GFP-based HA2 subfraction (expansion) accumulate in the main tumor. This behavior was confirmed in animals or CXCR4-T receptor-transfected individuals when a CXCR4-receptor antagonist was administered in vivo. Human colorectal tumor models have revealed that the peptide-caged proteins (cell-penetrating peptides) boost protein NPs (dissemination) for better patient targeting abilities in the right location to improve accuracy in medication administration.

3. Colorectal Cancer NPs

A particle of matter with a dimension of 1 to 100 nanometers (nm) is known as an NP or UFO particle. This word may refer to bigger particles up to 500 nm or fibers and tubes up to 100 nm. Figure 2 shows the polymer NPs used to treat colorectal cancer. The microenvironment at the IBD inflammatory site was evaluated for pathophysiological traits that might indicate targeted delivery. Multiple NP targeting techniques in the IBD are depicted in the image, including size, load, ligand, degradation, and microbiome-mediated approaches. It also discusses current developments in NP IBD treatment [32]. Another study used a 1,2-dimethylhydrazine (DMH) in vivo model to investigate the anti-rectal cancer activity of 1-(1H-benzo [d] imidazol-2-yl)-6-phenyl pyrimidine-2-amine-charged chitosan NPs (BZI 3 nano).

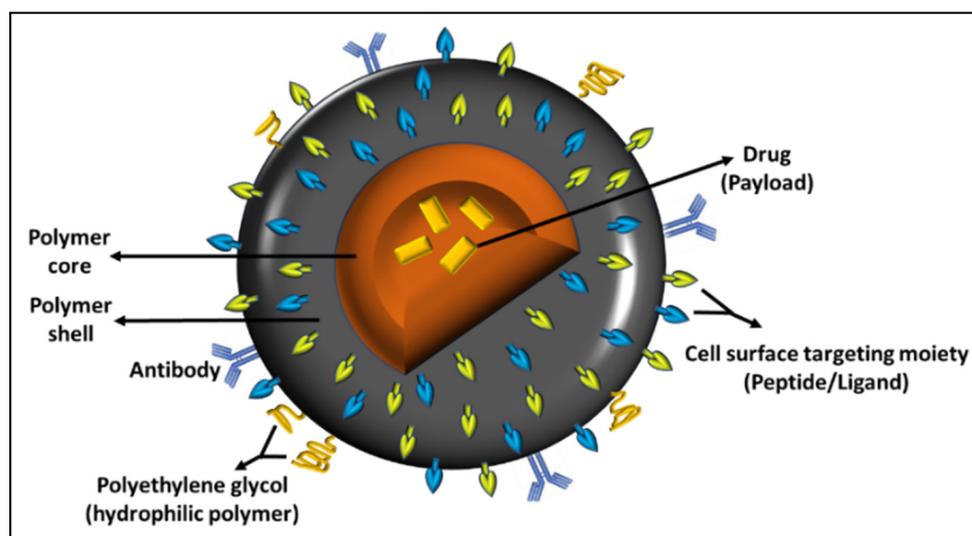


Figure 2. Rectal cancer treatment polymer nanoparticles.

The impact of the new BZI 3 nano on the production of ACF in the DMH rat model was also studied [33]. The anticancer activity of core-shell NPs made of silica core and xylan shell was studied. TPPOH was covalently bonded to xylan for drug-controlled circulation. The photothermal effect of Au-Ag@PDA was studied in HCT-116 colonic cells and xenograft nude mice. The Au-Ag@PDA NPs reduced cell growth and promoted apoptosis in cancer cells. In vivo dosages of 50–100 g of Au-Ag@PDA NP phototherapy slowed tumor growth. Toxic Au-Ag@PDA NPs killed colorectal cancer cells by several routes, including caspase-dependent and caspase-independent autophagy [34].

A first-line irinotecan drug model (IRT) was constructed using chitosan-based polyelectrolyte complexes with superparamagnetic NP orientation. Colloidal PECs were simply made using chitosan and PGA, using an all-in-water process that avoided hazardous chemicals. Iso-dispersed NPs (10 nm) were placed in IRT-charged nano-PECs. Optimized nano-PECs outperformed free medicines in terms of anti-rectal cell efficacy [35]. To make PNP-Ce6, an emulsion/solvent evaporation technique was used, and tLyp-1 peptides were added. tPNP-Ce6 may help treat drug-resistant colorectal cancer. tLyp-1 peptides were added to dual-response NPs (PNP-Ce6) via emulsion/solvent evaporation. This tPNP-Ce6 development should enhance colorectal cancer therapy [36].

The synergistic impact of NPs and irradiation was studied in HCT-116 colorectal cancer cells overexpressing PROM1. The PROM1-NP was 17.2 nm in size and had a surface charge of 13.5 mV. The intracellular absorption was greater than with NP or Irinotecan alone. HCT-116 cell growth was reduced by PROM1-NP treatment. In vitro radiosensitization showed PROM1-NP to be more effective than NP or irinotecan alone. PROM1-NP with irradiation treatment slowed HCT-116 growth considerably. In vivo, PROM1-NP outperformed irinotecan and non-in vivo NP as a radiosensitizer [37]. Coating chitosan-based

nanocarriers with nutraceuticals reduces opsonization and promotes passive targeting. The WHO standardization was the first step. Qualitative LC-HRMS/MS analysis explored the active components, notably the cytotoxic ones. HPLC selected cinnamaldehyde and rosmarinic acid. It was then encapsulated in solid lipid NPs (core) and chitosan (shell) to take advantage of both materials' characteristics [38]. Rectal cancer patients may benefit from combining RTX, a thymidylate synthase inhibitor, with radiation. To improve delivery and treatment effectiveness, HA-coated NPs encapsulating RTX (HARPs) were layer-by-layer assembled. They had a diameter of 0.115 nm, a polydispersity index of 0.112, and a zeta potential of -22 mV.

The uptake of untargeted and HA-coated particles was 5-fold higher in CT26 cells as assessed by flow cytometry [39]. AAG (17-allylamino-17-demethoxygeldanamycin) and gold NP (GNP) therapies have anticancer effects in a human CRC line (HCT-116) by targeting the related pathways. We tested the cytotoxicity of 17-AAG, GNP, Ir, and mixed HCT-116 cells with water-soluble tetrazolium salt-1. The cells were examined for DNA fragmentation and apoptosis. Caspase-3 is a key apoptosis protein [40]. TPPOH is a cancer and tumor targeting agent. We found that TPPOH-X coated 80 nm silica NPs (SNPs) had phototoxic effects, mediated by post-PDT ROS production, and enhanced cell uptake in human CRC lines compared to free TPPOH. Apoptotic cell death was caused by TPPOH-X SNPs-PDT and autophagy suppression [41]. Synthesized silver/Lactobacillus rhamnosus GG nanoparticles (Ag-LNPs) were investigated for anticancer activities.

GG cell lysate, 1 mg/mL, was combined with 1 mM silver nitrate and incubated for 72 h to make silver/Lactobacillus rhamnosus NPs. A variety of gradations were employed. PNPs that trap chemotherapeutic drugs may be used to treat lung metastasized CRC. FDA-assembled PNPs accumulated biocompatible copolymer blocks in the lung tissue but not in the liver, spleen, or kidneys. They were confirmed by fluorescent NP imaging and PI3 K inhibition. PNPs with PI3 K inhibitors (wortmannin and PX866) reduced CRC lung metastasis, but PNPs with SN-38 completely abolished it [42]. ANP targets an overexpressed colorectal cell surface biomarker (EpCAM). The aptamer conjugated NPs were characterized by SEM, TEM, and AFM. Their antiproliferative effect against carcinoma cells was studied in vitro and in vivo [43].

RGD Peptide with Nanoparticles in Colorectal Cancer Treatment

By inserting a lipid on the surface of RBCm-NPs, an anti-EGFR-iRGD recombinant protein was created. In high-EGFR colorectal cancer models, active tumor-targeting ability was found compared to RBCm-PLGA NPs. iE-RBCm-GA/PLGA NPs were demonstrated to be anti-tumor-efficient. The impact of GA in improving biocompatibility of iE-RBCm-GA/PLGA NPs was studied in colorectal cancer models [44]. To improve colorectal cancer cell targeting, plasmonic nanostructures incorporating a cyclic RGD peptide were designed. To obtain effective targeting action, the RGD peptide requires a lengthy PEG chain and a short oligomycin spacer. In direct PEG nanostructure binding, the cyclic RGD peptide loses its targeting capability [45]. The PLGA-PTX was co-administered with iRGD to assess its tumor-targeting and anticancer efficacy in colorectal cancer therapy. It sustained cytotoxicity against colon cancer cells and conserved healthy cells compared to free PTX. The PLGA-PTX treatment caused G2/M cell cycle arrest and death, inhibiting cancer cell migration and invasion. In vitro, PLGA-PTX and iRGD increased cytotoxicity. Integrin and neuropilin-1 were shown to be overexpressed in numerous mouse tumor vasculatures. When combined with iRGD, this allowed for the targeted distribution of NPs in vivo tumor tissues [46].

Rectal cancer patients may take RGD-ATST/TAGE NPs together with Tangeretin NPs (TAGE) and Atorvastatin NPs (Dingleberry). Using a PEG-bonding machine (e.g., PEG-cRGDfK and nPEG (polyethylene glycol)) for cyclical arginine-glycine-aspartic acid (RGD) sequences (cRGDfK-PEG-TOSD). RGD-ATST/TAGE nano-systems were created using nano-tech crystals. The researchers used a combination-effects experiment to assess the two medications' deadly effects on rectal cancer cells using a mouse cancer model.

and ATF (acidic triterpene fraction). The lucidum was alkaline extracted, acidified, and impregnated with 90% ethanol. On the UV spectrophotometer, the total NTF and ATF contents were determined. Human rectal cancer has been shown to be cytotoxic to SW480, SW620, SW1116, and NIH3T3 cells. The anticancer NTF *in vivo* was tested on SW620 cells in athymic nude mice. The active NTF components were separated by column and HPLC using an activity-led separation and purification approach. Western blotting confirmed 1H, 13C, and MS structures.

NTF treats rectal cancer. Additionally, ganoderic alcohols are implicated in mitochondrial pathway alterations and antifungal action [52]. The vitality of antimicrobial cells has been assessed using 27 cyanopyridines. We evaluated 2-amino-3-cyanopyridine 3n's anticancer activity in HCT-116, RKO, and DLD-1 cells. Tests to detect cell migration and proliferation included scratch and colony building. STAT3, MCL-1, and survivin were analyzed. The micromolar IC₅₀ activity of 2-amino-3-cyanopyridine 3n demonstrated considerable suppression of colony formation and migration [53]. The Wnt/-catenin signaling pathway is one of the main targets of CRC chemotherapy. The Wnt/catenin pathway activity was calculated using 19-O-triphenylmethyl andrographolide (RS-PP-050). However, it also works independently of GSK-3 [54], a Wnt-negative regulator.

Synthetic combretastatin A4 (CA-4) from South African cafferum was recently developed to increase natural product medication efficiency and stability. The antiproliferative properties of the CA-4 analogs were tested on the SW48 cancer cell line. Ten 3-amino-2-azetidinone derivatives were chosen among 10 3-amino-2-azetidinones. By forming amide connections at position 3, these compounds could synthesize various derivatives that might modify hydrolysis-resistant behavior. In moderate reaction conditions for the 3-aminoazetidinone ring, a cycling cycle with a heavy diastereo scillant effect outperformed a synthesis. The IC₅₀ values for both techniques ranged from 14.0 to 564.2 nM. The most active chemical inhibited the polymerization of tubular tubules [55].

There are nine tables 3,4,5-methoxyphenyl-containing asymmetric diarylpentanoid derivatives. Their anticancer efficacy was examined against T84, LoVo, and SW620, HT29, RKO, and NCI-H508 BRAF-mutated colorectal cancer cell lines. The methoxy and neighboring diarylpentanoid groups were shown to be more cytotoxic than the other groups. One of the lead compounds (compound 8) had a cumulative cytotoxicity index of 9.9 in SW620 and RKO cells [56]. *In vitro*, a blue LED radiation cocktail was investigated with two multi-target anticancer medicines, AT 406 and Rocaglamide. Male cells were marginal and suppressed. The HCT116 cells were 95% apoptotic while the HT29 cells were 95% apoptotic. Typical MRC-5 cells showed little or no cell inhibition following treatment. It induced ROS [57] production and colorectal cell apoptosis. Disulfiram (DSF), an alcohol antagonist, induces apoptosis when copper is present (Cu). The combination of DSF and Cu on colorectal carcinogenic cell apoptosis altered the two ICD markers, CRC (calreticulin) and HSP 70.

The effectiveness of GC1118 (anti-EGFR IgG1 antibody) alone or in combination with PI3K/mTOR/AKT inhibitors for KRAS-mutant metastatic CRC has been proven [58]. *Chlorella vulgaris* exopolysaccharide was studied for its physicochemical, antioxidant, and anticancer activities. An average molecular weight of 1.88×10^4 Da exopolysaccharide content was 364.3 mg/L. Exopolysaccharides include 10–11 sugars and derivatives. It also scavenged DPPH and hydroxyl radicals with a 59.6–71.5 percent efficiency. Its anticancer efficacy was also tested on the human rectal cancer line HCT8, with significant cell viability inhibition [59].

Twelve antimicrobial CRC targets were docked from 40 glycyrrhetic acid derivatives. GL and oxide derivatives; GL; 3-amine derivatives; five HCR derivatives combined; and six HCR derivatives combined. Five by-products were filtered. Four of the 12 CRC targets proposed were EGFR, FAK, LDHA, and TS [60]. Treatments for cancer often reduce toxicity and resistance. Dietary compounds such as OPC and curcumin were investigated for their function in carcinogenic cell pathways. *In vitro*, they outperformed individual drugs against various colorectal cell lines. Six main colorectal cancer cell lines showed cooperative

control of DNA gene expression profiling and cell cycle pathways. OPC and curcumin together were more effective in modulating protein export, porphyrin metabolism, and glutathione metabolism [61].

4.1. Role of Epidermal Growth Factor Receptor (EGFR) in Colorectal Cancer Treatment

EGFR is significantly glycosylated in the outer root and floral apical epidermal cells, increasing oocyte seeding and fertilization. In this way, the kinases may phosphorylate additional substrates. This causes autophosphorylation of the original kinase and promotes its production and autophosphorylation. Therefore, autophosphorylation happens in a conformation-dependent manner. The EGFR tyrosine kinase activity is necessary for the signal molecule activation. The kinase treats EGFR-positive lung cancer by inhibiting EGFR phosphorylation. ST6Gal1 catalyzes EGFR sialylation linked with gefitinib. In gefitinib-resistant CRC cells, NDAT increased anti-proliferation via inhibiting ST6GAL1 and PI3K. The nude additively supportive mouse model of HCT116 colorectal cell xenograft activity was improved by NDAT.

HCT116 cells produce cisplatin and metformin nanocubosomes. A Cas9 protein nanoliposomal (NL) part and a single guide RNA (SgRNA) complex (Cas9-RNP) were produced for KRAS mutant editing. The NL particle contained the Cas9-RNP in biocompatible lipid molecules. The antibody-modified NL particles accurately describe EGFR-expressing CRC cells and successfully deliver gene editing complexes [62]. On uses monoclonal antibodies (cetuximab and panitumumab) to treat metastatic CRC (mCRC). KRAS mutations have more powerful EGFR ligands than wild-type KRAS. These results were based on three KRAS-mutant CRC PDX (patient-derived xenografts) and three wildtype KRAS PDX variations. PI3K/AKT activity was detected in the presence of GC1118 (an EGFR antibody). The dual PI3K/mTOR inhibitor NVP-BEZ-235 significantly inhibited colorectal cancer cell proliferation in CRC PDX cells with KRAS and inherently high AKT activity.

4.2. Combining Nanocarriers with Compounds in Colorectal Cancer Treatment

The nanocarriers might transport anticancer medications. Drug efflux pumps, tumor system cells, and DNA damage repair pathways and have all made treating specific types of brain cancer difficult. The advantages of combining medicine with a treatment program have grown. Concurrently, synergistic drug-carrier combinations have improved [63]. The significance of micro- and nanomotors in biology. In addition, JNPs may be customized to specific medicinal delivery needs. An enzyme in the nucleus, Topoisomerase I (Topo I), cleaves and re-cleanses one of the two double-helix strands of DNA, adjusting its topological shape. Inhibition causes DNA strand breaks, cell death, and apoptosis. Solid tumors have more Topo I than healthy tissues. As a consequence, Topo I has great promise as a tumor target [64]. Opening the lactone ring reduces cytotoxic action and has negative physiological implications (pH 7.4, 37 °C). Aside from CPT, no licensed medications use CPT or its variants. Other organic compounds have been studied. Indenoisoquinoline and dibenzonaphthyridines were used in clinical trials. Similar to CPTs, indenoisoquinolines and dibenzonaphthyridines are chemically stable, can overcome cell resistance, and can stabilize enzyme-DNA breaking complexes [65]. Camptothecin is used to treat cancers such as rectal cancer. Its chemotherapeutic potential is hampered by its insoluble nature. Encapsulated in CEF (cyclodextrine-EDTA- Fe_3O_4) (cyclodextrin-EDTA- Fe_3O_4), CPT is free of these limitations. This formulation makes cancer cells soluble and CPT accessible. Mag-Responsive Anticancer Drugs are highly beneficial. The chemistry of CPT-CEF has been studied. Its ability to induce apoptosis in HT29 rectal cancer and A549 lung cancer cells was studied. The quadruplex binds to the G-quartet and the groove. Quinoline was crucial. The most active cytotoxic molecule was found to be (4,4'-(1,3-phenylene) bis(1,2,3-triazole-4,1-diyl) (compound 1d). The HT-29 rectal cancer cell line is enriched in cancer stem-like cells [66].

5. Validation Studies

Tests on MTT viability were performed on HCT116, SW620, and HCT8 DSF/Cu cells. The impact of a CRC xenograft DSF/Cu model on ICD tumor molecules was investigated. DSF/Cu has anti-colorectal cancer actions, resulting in molecular ICD expression [67]. The MTT test assessed CPT-cytotoxicity. CEF's Propidium iodide and Annexin V staining, mitochondrial membrane depolarization (JC-1 dye), and caspase-3 were assessed in CPT-CEF-treated cancer cells. As seen by G1 phase arrest, the nanocarrier may potentially have synergistic effects on the cell cycle. CPT-CEF decreased the viability of HT29 and A549 cells and activated caspase-3 in rectal cancer cells. This data shows that CEF may be employed successfully to treat rectal cancer as a significant nanocarrier for CPT [68]. By preventing tumor growth, the illness's remission was sustained.

A three-stage, low-cost approach for detecting synergism in numerous chemicals was presented. Using MTT and SRB assays with 14 compounds, dosage response curves were produced for MCF-7 and MDA-MB-231. These curves screened synergy [69]. A unique non-viral gene carrier, magnetic gold NP, was used to cure *in vivo* and *in vitro* cancer. The siRNA plasmid was effectively transfected into cells using gold NPs. In the MTT test, magnetic gold NPs had little cytotoxicity and reduced cell viability ($P < 0.05$) [70]. Annexin V/PI staining was performed to assess Ag-LNP toxicity and apoptotic cell counts. TEM revealed NPs of 233 nm in size. FTIR spectroscopy revealed Ag-LNPs with biomolecules; XRD revealed face-centred Ag-LNP crystals [71]. The HT-29 cell line was employed for the MTT test, and AGS evaluated this nanocarrier. In a cytotoxicity test, the pharmaceutical nanocarrier had a greater impact than the free medication.

6. Discussion

Several studies have indicated that nanoparticle-sized compounds are effective in treating cancer. These medications are based on nanostructured compounds, which include characteristics or components that contribute to their physical appearance and interaction with cells. Table 1 compares the different particle types employed in nanomedicines. It describes each particle's name, how the manufacturing and production process influences the particle radius, and how and when to identify each particle. Beta-lactoglobulin is a solvent for hydrophobic compounds. Low-density lipoprotein (LDL) employs two therapeutic compounds delivered as a single dose. Apigenin, a component of pink pepper, might be utilized to treat cancer using lipids. Some diatoms, such as *Panemuconas* and *Pleurotus*, can encapsulate drugs efficiently and at the right weight. In HCT116 cells, the redox-dependent polyamine transporter is overexpressed and accumulates.

T22 is a nanoconjugate that can deliver floxuridine (folinic acid) to tumor cells. The polyamino amino (PAMAM) chemical may be enhanced to be less harmful to healthy tissues. These molecules may also interact to produce a lipid-polymer NP hybrid that targets and engulfs cancer cells. This technique may be used to restrict tumor cell development locations and invasiveness. The drug loaded PHBV has minimal cytotoxicity. This carrier has also attracted interest for its ability to destroy HT-29 human adenocarcinoma cells. Professor G. Hamhuis' investigations into the ITGB3-SurMA-loaded and G-protein-loaded hexahistidine carriers showed that they improved gene retention, protein transfection, and DNA survival in the genome. For example, 5-FU and ganciclovir, for example, may act together to treat cancer, but research is continuing.

Table 1. A comparison between different types of molecules used in nanodrugs.

Classification	Nano-Drug Agent	Function and Merits	Average	References
			Diameter in nm	
Nanocarriers	Apigenin liposomes (AL)	establishing apigenin as a potential chemotherapeutic agent.	120	[15]
	A redox-responsive supramolecular (RRS)	preferentially accumulate in polyamine transporter over-expressing HCT116 cells.	240	[16]
	Nanoconjugate (NC) (T22-GFP-H6-FdU)	delivering Floxuridine to CXCR4+ cells.	14.6 ± 0.14	[17]
	Hyaluronic acid modified, irinotecan and gene co-loaded LPNs (HA-I/D-LPNs)	developing ligand-modified, irinotecan and gene co-loaded lipid-polymer hybrid nanocarriers for targeted colorectal cancer combination therapy.	182.3 ± 5.1	[18]
	Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)—PHBV	exhibiting low cytotoxicity and the drug-loaded carrier acts in an efficient manner to kill HT-29 human adenocarcinoma cells.	420 ± 10	[19]
	SurMB-Joe-loaded GO	enhancing the efficacy of gene retention, cell transfection and genomic material survivability.	-	[20]
	5-FU and gene co-loaded	treating cancer due to the synergistic effects	145	[21]
	LCS1	killing cancer cells using somatic mutations in cancer cells.	-	[22]
	poly[2-(N,N-dimethylamino)ethyl methacrylate]-poly(ϵ -caprolactone) (PDMA-PCL) micellar template-based gold nano-shell	Exhibiting a profound inhibition of tumor growth compared to chemotherapy or photothermal therapy alone.	-	[23]
	Beta-lactoglobulin (β -LG)	solubilizing and transport of hydrophobic molecules.	139.86 ± 13.75	[24]
	PAMAM-G4-NH ₂ , azoxymethane and capecitabine	investigating the potentiality of polyamidoamine (PAMAM) dendrimer to improve capecitabine therapeutic index and decrease its adverse side effects on healthy tissues.	-	[25]
	Liposomal drug loaded (LDL)	co-deliver two therapeutic entities for enhanced chemotherapeutic effect.	200	[28]
	Chitosan (CS)-based semi-interpenetrating network (semi-IPN)	enhancing entrapment and sustained release of MF for efficient treatment of CRC.	Ranging between 135 and 220 nm	[29]
Three polymeric shells, namely, aminocellulose (AC), branched poly(amidoamine), and paraben-PEG	encapsulating LCS-1. Encapsulation efficiency and drug loading.	-	[30]	

Table 1. Cont.

Classification	Nano-Drug Agent	Function and Merits	Average	References
			Diameter in nm	
Nanoparticle	BZI 3 nano	have the anticancer potential of the scaffold and selective, good target for drug discovery.	-	[33]
	Silica core and xylan containing 5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrin (TPPOH)	covalently linked to xylan.	78.43 ± 19.92	[34]
	Au-Ag@PDA	having strong near-infrared absorbance and no cytotoxicity but high photothermal conversion efficiency.	808	[35]
	nano-PECs	high potential for drug encapsulation and improved anti-rectalcell efficacy.	10	[36]
	T22-GFP-HA2-H6	Tumor tissue selectivity over unspecific cell penetration, upon systemic administration of the material.	30 and 45	[37]
	PROM1-NP	It is more effective as a radiosensitizer than irinotecan and non-in vivo NP.	17.2 ± 0.2	[38]
	HA	Determining optimal tumor growth delay and subsequent treatment efficacy.	115	[40]
	(17-AAG) and gold nanoparticle (GNP)	Inhibiting cell viability, and increased apoptosis occurrence by upregulating caspase-3 expression.	-	[41]
	Ag-LNPs	Synthesizing anticancer AgLNPs using probiotic bacteria which it can be more investigated through in vivo tests in order to be used for different biomedical applications.	233	[42]
	PNPs	Offering a new approach to reduce toxicity of cancer therapy and has the potential to improve outcomes for patients with lung metastasis.	100	[43]
	ie-rBcm-ga/Plga NPs	better antitumor efficacy than free GA in spite of the similar effects of cytotoxicity and apoptosis to GA in vitro.	153 ± 3.83	[44]
	PNP-Ce6	having great potential in enhancing the therapeutic efficacy of drug-resistant colorectal cancer.	98.32 ± 3.65	[45]
	SNPs	Apoptotic cell death induced by TPPOH-X SNPs-PDT and the interest of autophagy inhibition to increase anticancer efficacy.	80	[46]
	apt-ANP	Maximum retention of apt-ANP in the rectals compared to free drug and aptamer-free apigenin-loaded nanoparticle (ANP).	226	[48]
	LC-HRMS/MS	treating human rectalcarcinoma with a low dose leading to decreasing side effects and allowing uninterrupted therapy.	254.77	[66]
PLGA-PTX	Retaining preferential cytotoxicity toward various colorectal cancer cells while effectively sparing healthy cells.	147.5 ± 9.5	[67]	

Table 1. Cont.

Classification	Nano-Drug Agent	Function and Merits	Average	References
			Diameter in nm	
Anti-cancer agents	SN38	Folate-decorated functional micelles with disulfide bonds could be an effective chemotherapeutic agent for rectal cancer treatment.	150	[49]
	poloxamer-TPGS	Increasing drug encapsulation efficiency for exosomes, improved dissolution and strongly enhanced cytotoxicity of aspirin to cancer cells.	111	[50]
	liposomal venoms (LV)	Exhibiting better efficacy and act more vigorously as an anti-cancer agent on the colorectal cancer cell line.	235.8 ± 12.5	[51]

The immune-suppressed and latent cancer cells might attack the healthier cells when aroused and subjected to the body's hyperimmune reaction. Because LCS2 (one of several LCSs) may trigger mutations in cancer cells, it looks to be a good candidate for cancer therapy. The poly [2- (N, N-dimethylamino) ethyl methacrylate] More than chemotherapy alone, poly(caprolactone) [PDMAEMA] micellar template-based gold nano-shell NPs significantly inhibited tumor development. However, both erythropoietin/plasminogen activator complexes and free epoetin have anticancer properties. Stem cells are being explored to cure cancers and assist in surgery. The exposed core or silica is first covalently bonded to TPPOH (5-hydroxy-10-15-20-triphenylporphyrin). The Ag-Au@PDA system has a wide absorption spectrum. It is non-cytotoxic but more photothermolytic than Au@PDA. Targeted medications like Nano-PECs have shown great promise in treating rectal cancer in a targeted hermetic approach. PNP-CE6 is a new chemical that targets non-resistant cancer cells. T22-GFP-HA2-H6 is injected and may precisely infiltrate tumor cells while not infiltrating unspecific cells. PROM1-NP's benefits are merely the top of the iceberg. MIBE is a tumor-specific radiosensitizer. Magnetically treated NPs may be utilized to eliminate viruses, and certain single-stranded RNAs can be directed to the bag-1 virus.

Figure 4 illustrates that medication particle size decreases with micron size. The results show the maximum and lowest radii of the waste and aluminum percentages. Figure 5 displays the average size for each metal NP weight range. The scatter plot showed that the maximum Au-Ag NP occurred when NP-NP was partitioned. Figure 6 compares the average radius of the anticancer medicines. The Poloxamer-TPGS fractions have the largest LV fraction radius. Hormone therapy may slow the development of tiny tumors and minimize treatment duration. In this work, 8-Ti/GNPs/Li induced chemotherapy in a cell culture. The outer nuclear membrane and intracellular ribosomes were also lost. In cell cultures, it causes apoptosis (cell death). Apoptosis is triggered by the receptor tyrosine kinase FRS2. Pro-apoptotic factor Cell suicide requires Beclin-1 activity.

Loss of cell organelles may cause early mitochondrial breakdown, a recognized cause of cell death. These studies show that removing tumor-associated cancer cells selectively removes a greater population of cancer cells. An Ag-LNP enabled a pro-biotic bacterium to make anticancer Ag-LNPs. This method is useful in both in vitro and in vivo biological testing. This technology provides a fresh but unethical method. It employs toxicity in cancer therapy without utilizing real patient survival data. In this innovative procedure, the body's natural functions are blended with the medication to increase survival rates. The same goes for NPs used for rectal detox. They both act on rectal cells in this investigation. Functional synthetic micelle containing disulfide links that may be used to treat rectal cancer. Polymeric chemicals may improve exosome encapsulation efficiency, allowing for the effective encapsulation of anti-cancer toxins. A pharmacological exosome might better target cancer cells. Thus, poloxamers may enhance exosome function in cell membranes. Poloxamers may cause synergistic plasma membrane damage and/or enhanced apoptosis in tumor cells.

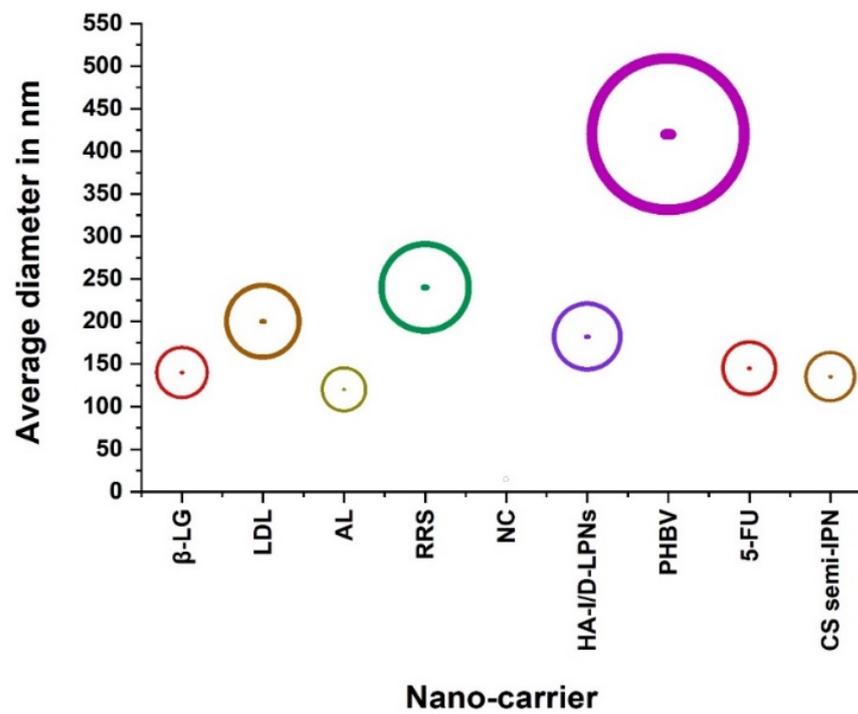


Figure 4. Average diameters of nano-carrier therapy.

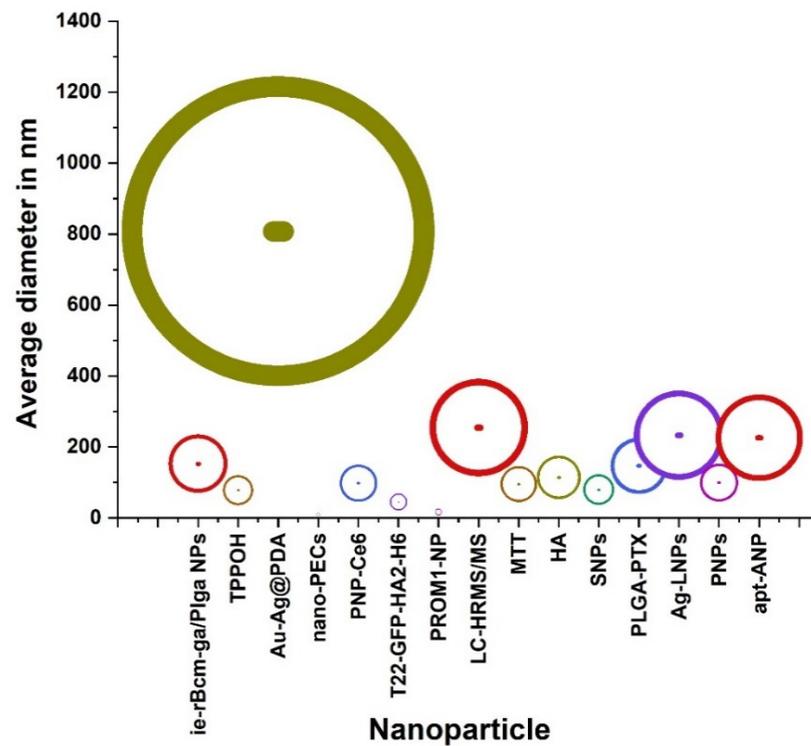


Figure 5. Average diameters of nanoparticles therapy.

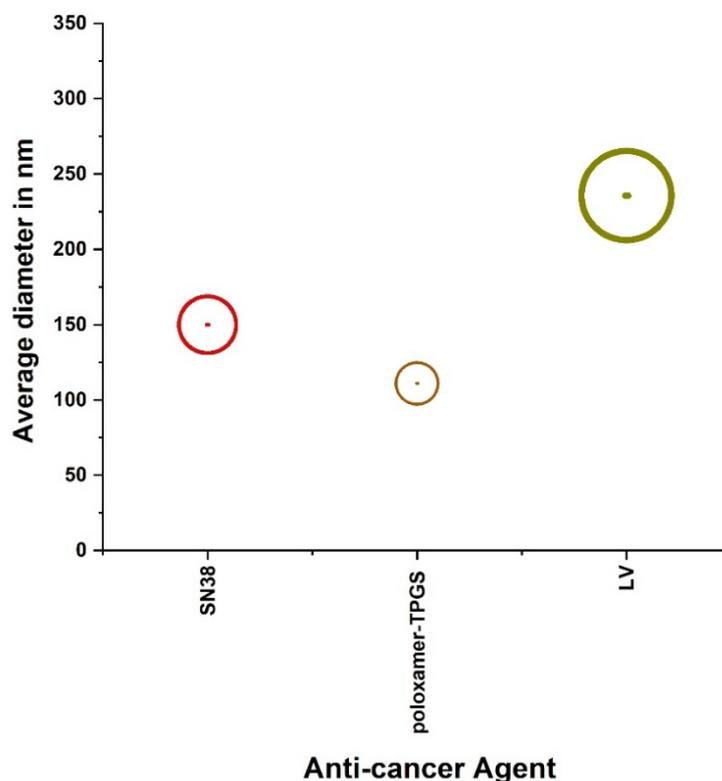


Figure 6. Average diameters of anti-cancer therapy.

Solutions and Future Perspectives

For example, nanoparticles (NPs) are increasingly being employed to deliver medications in the treatment of colorectal cancer. These substances have been demonstrated to help treat this condition. Several hurdles must be overcome before a good cancer treatment system can be developed. A perfect pharmaceutical system can overcome biological barriers, detect damaged tissues, and provide an instantaneous amount of a therapeutic chemical or combination. A very successful colorectal NP-based medication delivery system exists, but patients with colorectal cancer must be treated with regenerative drugs. Theoretically, medications sent to the gut target cancer. Despite technological breakthroughs, surgical procedures have limits. The specificity of the rectal drug site is minimal. The small intestine may be loosened or empty, or the colon may be empty. Nanotechnology may enhance the potency of drugs. The fact that these particles may create energy from motion, light, temperature, or blood sugar bodes well for the future. The emitted energy may be used to target certain cells. Nanocluster stability and surface reconstruction are major issues for this cutting-edge technology.

Thermal noise, Brownian motion, and temperature tolerance may impact NP movement [72]. Researchers believe they are losing NPs while treating cancer. The feed-through problem is also difficult. Handling nanoparticles is problematic due to the necessity for precise detection techniques. However, chemotherapy has poor side-effects and safety profiles. The issues include drug resistance, toxicity, inadequate biodistribution specificity, and cellular pharmacology. So only a tiny percentage of these drugs reach the tumor. A solid lipid nanoparticle drug delivery method might increase the efficacy and safety of traditional cancer chemotherapy. A well-constructed NP system may supply many NPs. So, in the realm of chemotherapeutic drug administration, benefits are developing to accomplish passive tumor targeting and reduce issues. Future nano-supply systems will target active chemicals more precisely to inflammatory areas.

Systemic absorption is undesirable in many oral treatments. The illness demands maximal exposure to tissues and systemic injections to avoid harmful consequences. Oral administration of novel drugs with poor physicochemical properties has been proven to

lower therapeutic dosage and systemic side-effects. Inflammatory bowel biodistribution and accumulation have been accomplished. Clinical translation within these transportation systems is still pending many challenges. To make large-scale production efficient and dependable, the notion of medication distribution must be simplified. It is vital to figure out how these formulas transfer from animals to people. Further research is required to establish safe and effective dosing formulations.

7. Conclusions

The use of nanotechnology delivery in rectal cancer treatment is a highly promising recent development for treating this disease. Due to the severity and the increased mortality rate of rectal cancer patients, recent research has analyzed this mechanism and its direct and indirect effects on rectal cancer cells. These studies varied in the methodology and advanced materials used. Compared to traditional medicines, they demonstrated a higher ability to kill these cancer cells. This review presented several recent studies that focused on this field and provided a benchmark comparison by classifying them into two categories: NPs and anticancer agents. This comparison revealed several advantages of these techniques and their ability to effectively deal with rectal cancer. This review aims to broaden further research into this field due to its presentation of nano-drug delivery technology in comprehensively targeting rectal cancer by presenting all the characteristics of these mechanisms in a simple manner.

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