Precisive Colon Cancer Treatment: Exploring Novel Avenues Of Cancer Treatment Through Multistage Nanocarriers

Suhaib Ahmed SYED[1] [ID]**, Vivek Reddy MURTHANNAGARI[1]** [ID]**, Senthil VENKATACHALAM[1]*** [ID]**, Praharsh Kumar MANDADHI RAJENDRA[1]** [ID]**, Janani SK[1]** [ID]**, Jawahar NATARAJAN[1,2]** [ID]

[1]   Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India.
[2]   Centre of Excellence in Nanoscience & Technology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India
  *Corresponding author: senthil.v@jssuni.edu.in (S. Venkatachalam)

ABSTRACT: Promising therapy is requisite for the treatment of colon cancer to overcome the current treatment regimen and limitations associated with its adverse effects. Conventional chemotherapeutic drugs administered in the treatment constitute low solubility of anticancer drugs and lack of specificity, leading to serious side effects due to the nonspecific uptake of drugs by normal healthy cells. Additionally, surgery and radiotherapy involved in the treatment have not shown remarkable progress due to their cost effect and laborious process. Nanocarriers are being designed to overcome the limitations of drugs administered by the conventional route. They do not degrade in the gastrointestinal tract before reaching the colonic site and enhance their Enhanced permeation and retention (EPR) effect. This review emphasizes various nanoparticles and their surface-modified ligands help in the pathogenesis of colon cancer, how nanoparticles-mediated drug delivery system differentiate from conventional treatment and their various advantages in the prevention, diagnosis, and treatment of colon cancer. By utilizing various nano-formulation using various strategies employed in nanoparticles mediated drug delivery systems and enlists the mechanistic outcomes of nano-formulated drugs, targeting of the drug through active and passive mechanisms and their preclinical and in vivo experimental works and overcoming conventional treatments. We have made a wide review of various nanoparticle designs and aim to reveal possible mechanisms by targeting specific ligands such that cellular uptake, improved bioavailability, and pharmacokinetics could be enhanced. This information will be helpful in the expansion of these nanocarriers and aid in drug delivery treatment of colon cancer.

**KEYWORDS**: Chemotherapy drugs; Colon cancer; Nanocarriers; Drug delivery; Multidrug resistance; EPR effect.

1. INTRODUCTION

Cancer is depicted as the worst noxious disease with the highest cause of death worldwide, characterized by Proliferation with intense speed, growth suppressor evasion, and immune system obstruction. Cancer is one of the most deadly diseases and the top cause of death in the world, killing millions each year [1]. Colorectal cancer (CRC) is the world's third most common cancer and one of the major causes of death worldwide. Patients with colon cancer already have 60% of metastasis at diagnosis. Globally, cancer incidence and mortality are increasing at an alarming rate. As per GLOBOCAN 2020 estimates of cancer incidence and mortality generated by the International Agency for Research on Cancer worldwide, there were an estimated 19.3 million new cancer cases and almost 10 million cancer deaths [2]. In developed nations such as the United States and Canada, 50–60 percent of five-year net survival is there. In contrast, it exceeds 60% in America, Oceania, Europe, and a few other countries in Central and South America and Asia. However, 70% of deaths from cancer occur in middle- and low-income countries[3,4]. Cancer is a disease marked by uncontrolled cell proliferation due to the accumulation of numerous genetic and somatic alterations in genes that regulate cell proliferation and apoptosis [5].

Colon cancer is one of the cancers that develop due to a slew of genetic and epigenetic aberrations, which could be a major factor in the disease's progression. CRC inception is connected to inherited predictors, including aging, gender-related risk (higher in men), and genetic factors. Surgery, chemotherapy, radiation therapy, and targeted therapy are all methods for treating colon cancer [6,7]. In sum, the Food and Drug Administration (FDA) has approved 16 drugs for the diagnosis and treatment of colon cancer, from which twelve drugs are administered via intravenous (I.V) route, i.e., 5-fluorouracil(5-FU), irinotecan HCl, oxaliplatin, aflibercept, cetuximab, bevacizumab, ipilimumab, leucovorin calcium, nivolumab, pembrolizumab, panitumumab, ramucirumab (except 5-FU which can also be given as iv bolus injection) and four drugs [Lonsurf (combination of trifluridine and tipiracil), capecitabine and Regorafenib] are administered orally. Amongst these sixteen approved drugs nivolumab, cetuximab, panitumumab, bevacizumab, pembrolizumab, ramucirumab and ipilimumab belongs to the category of biological drugs [8]. Combinational chemotherapeutic drugs include CAPOX (capecitabine and oxaliplatin), FOLFOX(leucovorin calcium, 5-fluorouracil, and oxaliplatin), FOLFIRI (leucovorin calcium, 5-fluorouracil, and irinotecan HCl), XELIRI (Irinotecan and Capecitabine), XELOX (Oxaliplatin and capecitabine) [9]. Diagnosis can be screened through techniques like colonoscopy, sigmoidoscopy, computer tomograph scan, X-ray tomography, and faecal occult blood test. The current conventional therapies to treat CRC include chemotherapy, surgery, radiotherapy, and laparoscopy, but these therapies don't intend to cure the disease for a longer period. Early detection of the disease is very helpful in treating colon cancer.

The main drawbacks of conventional therapy include poor solubility, inadequate membrane transport properties, decreased permeability, minimal biodistribution, dose toxicity, and nonspecific targeting on normal cells [10]. The physiology of colon pH presents numerous challenges when releasing a drug to the colonic site, as the active pharmaceutical ingredient (API) must be better protected from the gastric pH of the stomach and intestines . The broad variability of pH at different sites of the gastrointestinal region (stomach pH 1.5-3.5, small intestine pH 6–7.4, large intestine pH 6.8-7.8, and rectum pH 7.8–8) makes it a strenuous cause to deliver drugs at the colon region while counteracting to environmental conditions. As a predictive tool, a new nano-drug delivery system has emerged to address the issues with conventional therapy. Nano drug delivery systems like controlled, targeted, sustained release in the gastrointestinal tract (GIT), buccal cavity, and rectal region deliver the drug more effectively than conventional dosage. Nanotechnology has made significant advances in cancer therapy [11]. Nano-based combinational drug delivery to tumor cells offers improved pharmacokinetic, and good bioavailability to the tumor region by enhanced permeability and retention (EPR) mechanism. Adding it helps to overcome systemic toxicity regarding normal tissues and various harmful effects from conventional cancer therapy [12]. In light of view, we will briefly elucidate different approaches and mechanisms in the treatment of colon cancer. This review discusses smart nanocarriers such as organic and inorganic nanocarriers. Organic nanoparticles constitute lipid substances (solid lipid nanoparticles, nanostructured lipid carriers, Liposomes), polymeric material (dendrimers, micelles, polymeric nanomaterials, polymerosomes), and carbon nanotubes. Inorganic nanoparticles constitute metallic, ceramic, and quantum dot nanoparticles. These nanoparticle-mediated drug delivery can be either a passive or active process. We discuss the current challenges and obstacles of nanocarriers in treating cancer. The following illustration shows the development of colon cancer in figure 1.
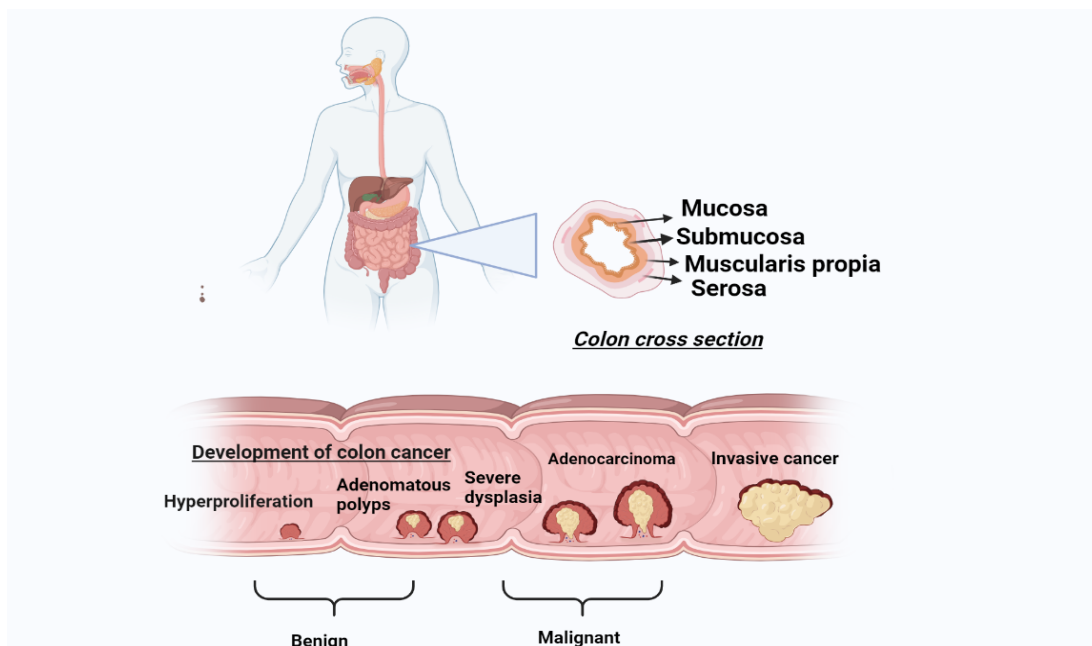
Figure 1. Schematic representation of the development of colon cancer Epidemiology

Colorectal cancer (CRC) has ranked third among all cancers and the second most common cause of cancer-related deaths globally . The prevalence varies geographically, with the highest incidence in New Zealand and Australia, whereas Western Africa has the lowest incidence[13]. In India, an increasingly alarming rate of CRC cases is being reported. This could be due to adaptations of a sedentary lifestyle and dietary intake.

Colon cancer usually develops slowly over 10 to 15 years. Most cases of colorectal cancer are initiated in the inner lining of the colon or rectum. They develop polyps and further grow as cancerous tissue. Adenomatous polyps are certain polyps that grow to form cancerous despite only 10% of adenomas advancing to cancer [14]. If the cancer forms in a polyp, it can assimilate into the colon or rectum walls. Once it preaches through the walls of the colon region, it can spread to distant parts of the body via blood and lymph nodes(metastasis). Some of the factors which show the growth of cancer are loss of weight, dark-coloured stools, diarrhoea, blood in stool, and feeling of discomfort in bowel movement.

In this article, we have elucidated various mechanisms, roles and strategies of nanoparticles in the treatment of colon cancer. Their pre-clinical, clinical and marketed formulations have been described below.

1.1 Mechanism of CRC:

Nearly about 5% of cases of CRC are hereditary and closely related to lynch syndrome (hereditary nonpolyposis CRC), and the majority of the cases are sporadic [15]. Through genetic and epigenetic variations, they activate oncogenes and suppress tumor-inhibiting genes. In most of the neoplastic lesions (aberrant crypt foci, adenoma, and serrated polyps) in colon cancer, loss of genomic and epigenetic alterations has been discovered. This provokes the transformation and expansion of colon carcinoma cells to aggressive and malignant forms. The main activation is through the stem cells present at the basal region of the colon .

CRC may be classified into four different consensus molecular subtypes (CMS), namely hypermutable microsatellite unstable (Hyp-MSI), microsatellite stable (MSS) or chromosome unstable (CIN), hypermutable-microsatellite stable (Hyp-MSS), and CIMP cancer [16].The most alterations in CRC include in APC, catenin-beta1, BRAF, KRAS, SMAD4, transforming-growth factor-beta receptor 2*(TGFBR2), TP53*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-alpha *(PIK3CA),* which promote tumorigenesis by invading key signalling pathways like mitogen-activated protein kinase (MAPK), epidermal growth factor (EGF), phosphatidylinositol 3-kinase (PI3K) and Wnt–β-catenin or they affect genes that regulate control of cells such as DNA repair and proliferation [17]. The progression and

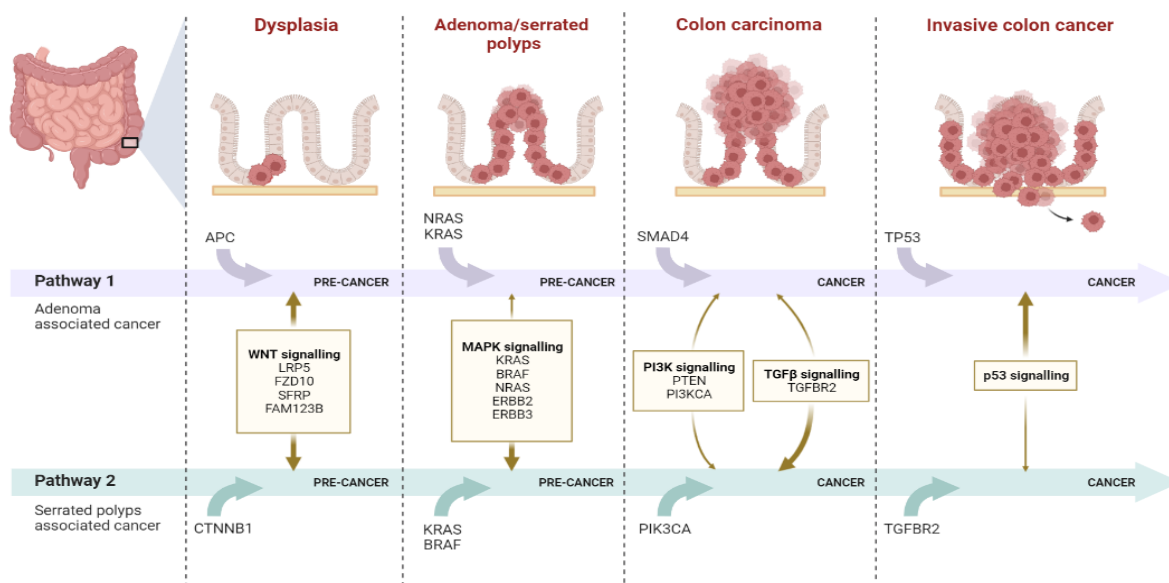mechanism acting on colon cancer are illustrated in figure 2.

Figure 2. Progression of colon cancer and their molecular mechanistic pathways

1.2. Staging of CRC

Colon cancer is classified according to the classification of tumor, node and metastases (TNM). It helps in the endosonographic staging of colon cancer. There are five stages: stage 0 (zero) and stages I to IV. It provides a common way of elaboration on cancer. An in-depth analysis of each part of the TNM classification is illustrated below [18,19].

TNM staging system

Tumor (T)
Using this TNM, T plus any number or letter describes how deeply the tumor has grown in the bowel lining. This stage is further divided into smaller sections to study each specification.

Node (N):
The N in the TNM denotes lymph nodes. They are short, bean-shaped, located throughout the body, and help combat infections. Lymph nodes present near the colon and rectum are called regional lymph nodes.

Metastasis (M)
M in the TNM indicates metastasis, which describes the spread of cancer to other body parts such as the lungs and liver. A brief classification is mentioned below in Table 1.

The standard chemotherapeutic first-line medicines are 5-fluorouracil, irinotecan, oxaliplatin, and leucovorin. This has improved the survival rate by 30%. Furthermore, Vemurafenib, an oral BRAFV600 inhibitor, is currently being tested in phase II preclinical trials for patients with BRAF (BamHI A right body) mutant metastatic colon cancers [20]. The FDA recently approved nivolumab, a monoclonal anti-PD1(programmed cell death protein 1), for treating metastatic colon cancers under the trademark Opdivo[21]. Various marketed formulated drugs are mentioned in Table 2.

Table 1. TNM classification of Colon cancer

Tumor category	Tumor characteristics
Tumor	
TX	Primary tumor which cannot be assessed.
T0	No evidence of primary tumors.
Tis	It refers to cancer in situ. Cancer cells are found in the epithelial layer, which are top layers lining inside the colon or rectum.
T1	Tumor invading submucosa, layer present below mucosa.
T2	Tumor penetrates muscularis propria, a deeper and thick layer of muscle contracts to force along the intestine.
T3	Tumor invades through muscularis propria into subserosa or grows into non-peritonealised tissues surrounding colon and rectum.
T4a	Tumor penetrating surface of visceral peritoneum, grow into all walls of colon cancer.
T4b	Tumor develops and attaches to other organs and structures.
Regional node metastasis	
NX	Regional lymph nodes could not be estimated.
N0	It does not spread to regional lymph nodes.
N1a	Tumor metastases to one regional lymph node.
N1b	Tumor metastases to two to three regional lymph nodes.
N1c	Nodules made of tumor cells near the colon that don't appear to be lymph nodes.
N2a	Tumor metastases in four to six regional lymph nodes.
Metastasis	
M0	Disease has not spread to distant body parts.
M1a	Cancer has spread to one body part beyond the colon.
M1b	Cancer has spread to more than one body part beyond the colon.
M1c	Cancer has spread to more body parts.

1.3. Criteria for selection of drugs for colonic site

The best choice for the selection of drugs for the colon region is the drugs have poor absorption from the stomach and intestines. The physicochemical nature of the drug and other factors such as chemical nature, stability and partition coefficient and absorption enhancers influence drug selection.

1.4. Role of various nanoparticles in treating colon cancer

Nanotechnology plays a significant role in treating colon cancer compared with conventional chemotherapy formulation. Most chemotherapeutic drugs in the treatment of CRC are administered by the I.V. route as they bypass first-pass metabolism. Still, it has some prerequisite requirements to be administered under medical supervision and may cause drug distribution through the circulatory system. The oral route might be the most convenient way to administer the drugs, but it has some drawbacks.

The main drawback in administering chemotherapeutic medications is they degrade in upper GIT and tend to develop multidrug resistance (MDR). Therefore, nanotechnology is an appropriate and effective treatment for colon cancer [22]. Recently nanotechnology has paved interesting new ways to explore novel treatment therapies for colon cancer as there are different types of nanoparticles, and a single classification is impractical. Various nano-formulated deliveries are being studied to deliver anticancer drugs, enhance the drug's half-life in systemic circulation, increase pharmacokinetic properties with a targeted approach, and bind to specific cell surface receptors to target the cell. Nanoparticles which have entered pre-clinical and clinical trials are represented in Tables 3 and 4 .

Table 2. Marketed formulations in the treatment of Colon cancer

Drugs acting via different mechanisms					
Drug	**Mechanism**	**Brand**	**Route**	**Adverse effects**	**Ref**
Irinotecan Hydrochloride	prevents religation of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death	colotecan	I.V	Diarrhoea, loss of appetite, constipation	[22]
Oxaliplatin	crosslinking of platinum and a specific base in the DNA sequence, it generates platinum-DNA adducts.	Eloxatin	I.V	Peripheral neuropathy, nose bleeding, hair loss, hepatotoxicity	[23]
Leucovorin	It is an active metabolite of folic acid and an essential coenzyme for nucleic acid synthesis	Leuget	I.V	Nausea, vomiting, hives	[24]
Capecitabine	It inhibits DNA synthesis by reducing normal thymidine production	Xeloda	Oral	Anemia, chest pain, anorexia, coughing up blood	[25]
5-fluorouracil	Inhibition of thymidylate synthase which leads to DNA damage	Axiflu	I.V	Bruising and bleeding, hand foot syndrome, loss of appetite, Diarrhoea	[26]
Nivolumab[a]	It binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2 with receptor	Opdivo	I.V	Severe itching, upper respiratory tract infections, low sodium level	[21]
Ipilimumab[a]	It binds to CTLA-4, blocking the inhibitory signal, which allows the CTLs to destroy the cancer cells	Yervoy	I.V	Feeling tired, rashes, vomiting	[27]
Vascular endothelial growth factor targeting drugs					
Ramucirumab[a]	It inhibits tumor angiogenesis	Cyramza	I.V	Couphing up blood, decreased urine output, irregular heartbeat	[28]
Bevacizumab[a]	It acts by selectively circulating binding VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors and inhibit blood vessels and vasculature	Avastin	I.V	Laboured breathing, burning, pain in hands, thrombosis	[29]
Epidermal growth factor receptor targeting drugs					
Cetuximab[a]	It binds to EGFR on cancer cells and prevents EGF from interacting to this receptor.	Erbitux	I.V	Redness, crusting around hair follicle, maculopapular rash, necrosis in severe condition	[30]
Panitumumab[a]	It works by blocking EGFR activation by binding to its extracellular domain.	Vectibix	I.V	Drowsiness, difficulty with swallowing, convulsions	[31]

a biological drug that FDA approves in the treatment of colon cancer

Advantages of nano-based drug delivery system

1) Improves bioavailability and efficacy.
2) The potential use of smart nanoparticles to enhance drug medicament release at the targeted region by exploiting both internal and external stimuli is the main benefit of their use [32].
3) Circumvents drawbacks of drug solubility and stability of the chemotherapeutic drug and prevents the medication from degradation by proteolytic enzymes and ameliorates the drug's half-life in the systemic circulation and enhances biodistribution, targeting and reducing toxic effects can be minimized [33,34].
4) They increase resistance time in the body (increase half-life and target specificity)

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5) A concomitant reduction in the quantity of drugs and reduced toxicity promotes safer delivery of chemotherapeutic drugs and protection from non-targeted cells and tissues from adverse effects.

It should be noted that factors such as size and shape influence the administration of an anticancer drug. Because of their small size and unique properties, nanoparticles play an important role in drug delivery. When nanoparticles are given intravenously, they can be taken up by the reticuloendothelial system (RES) or macrophage system through opsonization [35] and can efficiently pass-through tumor vessels as there are more leaky vasculatures opened in the epithelial walls of tumor tissue. The enhanced permeability and retention (EPR) is due to the presence of large pores(100-600nm) and lymphatic drainage in the tumor, which help to retain the chemotherapeutic drug and retain it for a longer period, as normal blood vessels typically open at 10 nm, whereas tumor vessels may open at a larger size [36].

Nanoparticles alone will not be sufficient to eradicate cancer cells effectively. Instead, if it is linked with the targeted delivery system, it can play a vital role in eradicating cancer cells and overcoming the toxicity caused to normal cells. The effective delivery of nanocarriers to the target site can be delivered by two delivery systems: passive targeting and active targeting.

Table 3. Preclinical *In-vivo* experiments utilizing nanoformulations for CRC therapy

Nanoformulation	Transporting drug	Animal model	Active targeting molecule	Ref
Polymerosomes	Doxorubicin	Balb/C mice subcutaneous tumor bearing nude mice	Tfr binding peptide	[37]
Polymeric NPs hydrogel	Oxaliplatin, Tannic acid	CT26 peritoneal carcinomatosis induced BALB/c mice		[38]
PEG-pH sensitive peptide modified liposome	Irinotecan and miR-200	CT26 subcutaneous tumor bearing BALB/c mice	Cell-penetrating peptide, the ligand to blood vessel and targeting peptide	[39]
PLGA NPs	Paclitaxel	LS174T subcutaneous tumor bearing BALB/c mice	Tumor penetrating peptide iRGD co-administration	[40]
PEGylated polytyrosine NPs	Doxorubicin	HCT 116 subcutaneous tumor bearing BALB/c mice	cRGD	[41]
Layer by layer assembly	Raltitrexed	CT26 subcutaneous tumor bearing BALB/c mice	Hyaluronic acid	[42]
PEGylated mesoporous ruthenium NPs	RBT (fluorescent probe)	CT26-CEA subcutaneous tumor bearing BALB/c mice	Antibodies for CD16 and CEA	[43]

Table 4. Clinical trials in CRC using nanoformulations

Drug	Formulation type	Clinical trial stage	Application	Ref
Doxil	liposomal Dox preparation	Phase II	Metastatic CRC	[44]
PEP02	Liposomal Irinotecan HCl + LV and 5-FU	Phase II	Metastatic CRC	[45]
Aroplatin	Liposomal Aroplatin	Phase II	CRC	[46]
Polymeric NPs + cetuximab + somatostatin	Combination of NPs cetuximab and decorated with somatostatin analogue	Phase I	Metastatic CRC	[47]

2. VARIOUS METHODS FOR TARGETED DRUG DELIVERY

2.1 Passive targeted drug delivery

In passive targeting nanoparticles, due to the presence of leaky tumor vasculature, they mostly accumulate in the pericytic tumor due to the enhanced permeability and retention (EPR) effect. The gap between normal epithelial cells and tumor vasculature ranges from 200-2000 nm depending on tumor size, type, and localization. The process of multiplication is uncontrollable in cancer cells, they continue to proliferate and divide to surrounding blood vessels and form more leaky blood vessels around the tumor cells by the process of neoangiogenesis. These leaky blood vessels are formed due to irregularities in the epithelial membrane and depletion of pericytes which lines endothelial cells [48]. Hence, molecules infiltrate through these vessels and to interstitium rapidly surrounding tumor cells. These drugs will reach the tumor site with the help of nanoparticles, and they penetrate the tumor cells by the process of passive diffusion. The EPR effects allow efficient nanoparticle delivery to the tumor site, hence internalizing the nanoparticles within tumor cells, resulting in an increased therapeutic effect [49,50].

Wong et al. have developed a multi-nanoparticular system that alters in size as it approaches different locations on tumor sites. They created gelatin particles that are 100 nm in diameter that shrinks to 10 nm when extravasated into tumour tissue due to breakdown by tumour-associated matrix metalloproteinases [51]. Consequently, studies on the EPR effect of tumor in humans are deficient. Indeed, most of the existing studies have focused on subcutaneous tumour models that multiply rapidly and have considerable EPR effects. As a result, experiments utilizing these models may indicate that passive targeted nanoparticles are inefficient [52] (may damage normal cells as well, thus there is a necessity to go for active targeting) and there is an urgent need to highlight a paucity of patient-based experimental data on the EPR effect. Such in-depth understanding will aid in the rational engineering of nanomaterials, which can be used in personalized medicine using nanoparticles to achieve even greater therapeutic effects [53].

2.2 Active targeting

Paul Ehrlich coined the term "Magic bullet" and put forth the concept of drug Targeting and therapeutic action. Active targeting also called "ligand-mediated receptor targeting" comprises affinity-based recognition, drug retention, and enhanced uptake by the tumor-targeted cells [54]. In active targeting, nanocarriers are functionalized with a specific ligand that preferentially interacts with cell surface receptors that are overexpressed on tumor cells, eliciting the internalization of the drug in tumor cells. Proteins (antibodies), nucleic acids (aptamers), receptors such as G-protein-coupled receptors (GPCRs), integrin receptors, folate receptors, epidermal growth factor receptors (EGFR), transferrin receptors, and other ligands (vitamins, peptides, and carbohydrates) are examples of ligands used for targeting [54-56]. They bind to a specific receptor which are overexpressed by carcinoma cells.

The active targeting concept improves drug delivery efficacy by maximizing nanoparticle internalization by target cells. Active drug targeting has manoeuvred to increase nanoparticle internalization by targeting the cells and enhancing their bioavailability of drugs. In one study, Technetium-99 marked eudragit beads surface coated folic acid coupled Irinotecan hydrochloride loaded solid lipid nanoparticles (Tc-EuBIRSLNF3) has shown the higher distribution of drug and greater cytotoxicity in the intestinal region when compared with irinotecan conjugated folic acid solid lipid nanoparticles (EuBIRSLN3) . Targeted therapy using eudragit beads and folic acid receptor irinotecan nanoparticles remarkably inhibited the development of colorectal tumors and showed potentiality for improved therapeutic activity. Colorectal tumors were significantly inhibited by targeted therapy using eudragit beads and folic acid receptor irinotecan nanoparticles, indicating the possibility of improved therapeutic outcomes [57]. Two important factors are necessary to maximize the efficacy and long-term survival of nanocarrier-based active targeting method in *in-vivo* development: specific targeting of drug and payload drug release. Active targeting must be designed for prolonged blood circulation and biocompatibility to prevent the nonspecific binding of nanoparticles to other cells. Tumor site macrophages, poor blood flow in tumor vessels, and an extracellular matrix environment pose a significant challenge in nanotherapy. Therefore, a clear concept needs to be studied in targeting nanoparticles by these processes. The following illustration shows a scheme representation of active and passive targeting in Figure 2.
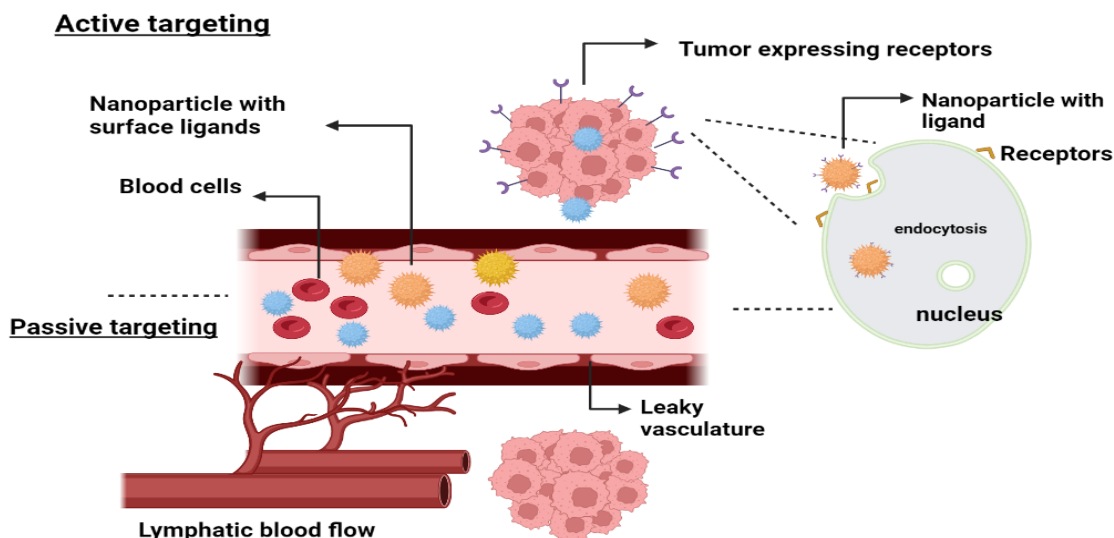
Figure 2. Nanoparticle-mediated drug delivery through the active and passive targeted mechanism

3. VARIOUS STRATEGIES OF NANOPARTICLES-MEDIATED DRUG DELIVERY SYSTEMS IN TREATING OF COLORECTAL CANCER (CRC)

Nanotechnology has made massive progress in recent years in the development of nanomedicine. The formulation of a drug into nanomedicine improves the bioavailability, pharmacokinetics, and sustained release, and reduces toxic effects. In the drug formulation, many drugs are hydrophobic and can't release their medications at the proper site, limiting their applications. When the drug is formulated through nanotechnology, biodistribution, solubility, and pharmacokinetic properties reduce toxicity and improve efficacy. Additionally, by incorporating ligands onto the surface, chemical conjugation and attachment of monoclonal antibodies (mAbs) improve specific site targeting and drug degradation. Nanosystems are of two types: open control systems and closed control systems. In an open control system, they are governed by external factors such as magnetic, and the electric field controls the drug release, whereas, in the closed control system, they are governed by internal factors such as pH, temp, redox potential, and enzyme degradation. Few strategies have been enlisted below [58,59].

3.1 Redox potential drug release

Redox potential is a distinctive internal signal that allows redox-responsive nanoparticles to disintegrate in tumor tissue. In redox potential drug release, a redox nanocarrier reacts when in contact with a functional group, reducing or oxidizing (Glutathione, peroxide) the surrounding environment in and out of the cells. Chemical alterations can also cause changes in the polymer's hydrophobicity, resonance shift of electrons and chemical bond cleavage, and change in hydrophobicity of polymer and the integrity of nanoparticles which results in drug payload release [60]. The main advantage of redox-responsible nanoparticles is their stability in normal tissue, which can reduce toxicity and side effects, and shows high reactivity to high glutathione (GSH) concentration in cancer cells and release of drug in the cytoplasm [61,62]. For example, Han utilized redox-responsive disulfide bonds to attach transferrin (Tf) to the surface of MSNs as both a capping agent and a targeting group, effectively encapsulating the chemotherapy drug doxorubicin (DOX). In the presence of GSH, DOX can burst and leak out. It is biocompatible, accumulates in tumor cells, and dramatically increases the targeting moiety [63].

3.2 pH-mediated drug release

The effects of varying pH on drug delivery to specific organs have been studied, and intracellular compartments (such as lysosomes or endosomes) associated with pathological situations, such as cancer or inflammation, can trigger the release of the medication. The extracellular pH of tumor cells is generally acidic and secretes acidic metabolites like lactic acid produced by anaerobic glycolysis in hypoxia. During

tumor development, there is a drop in pH from 7.4 to 6.5. Acid pH activates lysosomal enzymes and expresses genes involved in metastatic elements. Thus, the acid microenvironment is approximately related to tumor development. According to the Warburg effect, the tumor favours developing lactate by using an anaerobic glycolysis pathway to produce energy [64]. High lactate levels reflect metastasis, tumor occurrence and development in some patients. Lactate export from T lymphocytes is inhibited by high lactate release by tumor cells, thereby altering metabolic functions. The change in the pH study between normal cells and pathological cells triumphs for the controlled release of the drug [65]. The mechanism of various stimuli of different nanocarriers is mentioned in table 4. In an acidic medium, Pre-treatment of the tumor cells promotes the generation of proteinases (cathepsins and MMPs) and proangiogenic factors (IL-8 and VEGF-A) and instigates the spread of experimental metastasis to the lung after administering to nude mice tail vein. Additionally, acidic pH in soft tissue sarcomas can be predicted using P-31 magnetic resonance spectroscopy to evaluate cancer spreads to metastasis [66].

3.3 Stimuli-based targeting

Thermoresponsive medication delivery is one of the most explored stimuli-responsive techniques, with thorough research done in oncology. Polymeric micelles, Liposomes and nanoparticles (poly(N-isopropyl acrylamide), PNIPAM), which have a lower threshold solution temperature are examples of thermoresponsive systems. Even though PNIPAM is the preferred polymer building block for thermosensitive polymeric drug nanocarriers. For example, other polymers such as poly(γ-2-(2-(2-methoxyethoxy)-ethoxy)ethoxy-ε-caprolactone)-b-poly(γ-octyloxy-ε-caprolactone) can be used to make thermosensitive polymeric drug nanocarriers. It has a high phase transition temperature, making it easier to deliver drugs at low temperatures (40 °C) [67].

3.3.1 Multistimuli-responsive drug delivery

More than one stimulus is used to optimize drug delivery and sensitivity. Because an oxidative environment and a pH gradient coexist in some clinical circumstances, redox responsiveness and pH can be employed in together cases. For instance, Antisense-bcl2 oligonucleotides and doxorubicin were appended to a four-arm PEG with acid-cleaving and redox-reducible linkers so that tumorigenesis could be inhibited [68]. Ionically self-assembled nanoparticles and liposomes that responded to pH and temperature were more effective at releasing drugs [69].

Table 5. Stimuli response drug release

Stimuli	Drug	Nanocarrier	Target	Reference
Temperature	Doxorubicin	Liposomes	Unresectable hepatocellular carcinoma	[70]
pH	Doxorubicin	Hybrid micelles	Breast cancer	[71]
	Tamoxifen	Chitosan Nps	Breast cancer	[72]
Magnetic field	Homocamptothecin	Iron oxide nanoparticles	Squamous cell carcinoma	[73]
Light	Artemisinin	TiO_2–iron oxide nanoparticles	Breast cancer	[74]

4. PHYSICOCHEMICAL ALTERATION PROPERTIES OF NANOCARRIERS IN COLON CANCER TREATMENT

Nanocarriers are precisely engineered to transport several therapeutic medications to various types of cancers. Nanocarrier behaviour varies dramatically because of the nature of nanoconjugates and their diverse interactions with the biological environment, such as protein corona formation, cellular uptake endocytotic processes, and clearance pathways. A summary of the physicochemical properties of nanocarriers and internalization effects is described below.

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4.1 Size of NPs

The primary step in designing the nanoparticles (NPs) passes through the cell membrane's integrity and size, which usually ranges in nanometers(nm). The link between nanoparticle size and the endocytotic rate is still unknown. The impact of nanoparticle size on cellular internalization has attracted considerable attention. Gold nanoparticles and silica nanoparticles, specifically, have been extensively investigated. According to Liu et al., PEGylated gold nanoshells on silica nanorattles (pGSNs) have various particle size effects on cellular absorption. Using a Transmission electron microscope (TEM), nanoparticles of different sizes (GSNs-112 nm, GSNs-142 nm, and GSNs-315 nm) have a normal spherical morphology and are highly dispersed. The findings suggested that smaller pGSNs could maximize cellular uptake and blood circulation time in MCF-7 cells [75]. HeLa cells intracellular uptake of 14, 30,50, and 74-nm GNPs indicated that 50-nm-sized N.P.s had the highest cellular uptake. The internationalization mechanism is clearly unknown, but endocytosis has been identified as a possible candidate [76].

4.2 Shape of NPs

Nanoparticles exist in various shapes like spherical. Cubed, rod-like, oval. It's evident that morphology plays a vital role in blood circulation, distribution, cellular uptake and targeted delivery. NPs with a more significant aspect ratio have a higher affinity to enter cells via   passive or active transport. Da Silva et al. reported that Carbon nanotubes (CNTs), having a cylindrical shape and a high surface-to-volume ratio, can effortlessly penetrate the cell membrane. In contrast, rod-shaped NPs have more versatile binding sites [77].

4.3 Corona NPs

When a nanoparticle directly interacts with biological fluid, it changes surface structure, nature and cell interactions. Biological molecules in body fluid can adsorb on the surface of NPs, forming a corona around them. Biological molecules in body fluid can bind to the surface of NPs, yielding a corona around them. The uptake of NPs by particular cells can differ in the presence and absence of corona in their composition [78]. Some biological molecules in this region form irreversible contact with the nanoparticle's surface, inducing de facto the subsequent behaviour. Corona formation affects stability, distribution, macrophage sequestration, and specificity of targeting molecules by attaching specific ligands to nanocarrier. It has been proven that the rate of internalization of silica NPs in a serum-free biological environment is higher than the rate of uptake in a serum-containing biological environment. There are two types of corona structures: hard and soft corona. A hard corona is formed when biological molecules are irreversibly bound to NP Surface, and a soft corona reversibly binds to the hard corona [79]. The span of the hard corona is upto several hours, as it mainly defines NP Surface properties. Because of the restricted number of spaces, small molecules cover the surface first, followed by larger molecules to form a corona. The major challenge faced in the targeted delivery of NPs is cellular uptake by phagocytosis. In the biological fluid environment, NPs are surrounded by various biomolecules such as extracellular matrix, albumin, lipoproteins, and immunoglobulins that form a corona. The receptors on the phagocytic cell membrane adhere to the proteins and internalize surface NPs [80]. Although phagocytosis doesn't uptake these NPs, the corona layer covers the ligand, and these NPs are not recognized by the target site and hence lose their specificity. An effective treatment method is to coat with a barrier like a layer comprising polyethylene glycol (PEG), termed PEGylation, as it creates steric hindrance and inhibits protein absorption.

4.4 Surface charge

The surface charge of NPs is vital for directing interaction at the biological interface. The entry of nanocarriers is determined primarily by surface charge. The charge present on the cell membrane is negative, positively charged NPs are more attracted toward the cell membrane and internalized by endocytosis. Nanoparticle *in-vivo* biodistribution reveals that negatively charged particles are more efficient at accumulating in tumor locations [81]. Micellar nanoparticles have been studied for their in vivo fate and cellular uptake. It was found that tumor cells readily ingested negatively charged nanoparticles, then studied using multiple endocytotic paths to determine the process [82]. In addition, anions such as phosphatidylserine migrate toward the tumor surface, facilitating charge interactions and ligand-receptor

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interaction, which aids in augmenting site-specific targeting to the colonic region. Since chitosan nanoparticles are positively charged, they assist in site-specific targeting of the colon the cell membrane of colon cancer. Precise results were obtained when the cationic liposomes were favoured to target tumor cells [83]. From the above colloquy, it's clear that the surface charge of nanoparticles regulates cellular uptake reliant on cell type and endocytosis process. The surface charge of these nanocarriers governs their distribution within the cell, which must be functionalized to avoid unwanted uptake by healthy cells and achieve target selectivity.

4.5 Surface chemistry of nanoparticles

In developing nanocarriers in biomedical applications, the design of surface chemistry is crucial. Besides, functionalizing with surface corona and engineered nanomaterials reduces toxicity and enhances stability. PLGA nanoparticles are stabilized with a polyethylene glycol (PEG) hydrogel layer on the surface to minimize opsonization by the phagocytic sector and improve blood circulation. These NPs were functionally surface-modified with chitosan to assess their tumor-targeting efficiency, which may specifically target rapidly proliferating tumor endothelial cells. Chitosan-modified PLGA nanoparticles accumulated 2.4 times faster than unmodified PLGA nanoparticles [84]. Additionally, ligands are targeted using antibodies, peptides, proteins, aptamers, nucleic acid-based ligands, and oligosaccharides [85]. Thus, surface functionalization must investigate carefully study to reduce toxic effects and increase tumor specificity.

5. NANOCARRIERS FOR DRUG DELIVERY TO COLON CANCER

A wide category of nanoformulations comprising organic and inorganic nanomaterials have been developed for single or combinational drugs to detect and treat cancer. A brief review of various types of nanoparticles has been discussed below.

5.1. Inorganic nanocarriers for cancer therapy

Inorganic NPs are metal oxide or metallic particles having an inorganic core and an organic shell that helps stabilize particles in the biological and provide functional sites for targeted drug delivery [86]. This classification is further grouped into metallic, ceramic nanoparticles, and quantum dots for colon cancer treatment. These ceramic nanocarriers have properties that lie between metals and non-metals. Metallic NPs have a vast surface area and porosity, encapsulating higher drug dosages [87]. Silver and gold are mainly used among various metals due to their biomedical importance. They also possess anti-microbial properties and help in the treatment of cancer.

5.1.1. Silver (Ag) nanoparticles

Silver NPs (AgNPs) have been widely used in medicine. Due to silver's antibacterial characteristics, it is employed in consumables. AgNPs have been used with chemotherapeutic drugs to elevate therapeutic efficacy, when conjugated with plant-based pharmaceuticals, they exhibit non-toxic delivery vehicles. According to Gurunathan et al., medications like flavonoids or anticancer drugs can be coupled with AgNPs to act as capping agents and stabilize the method. An aqueous solution of naringenin (50 M) and silver nitrate has been used to make the AgNPs (2 mM). The particle size after coating with chitosan was found to be 50 nm. AgNPs had a particle size of 6 ±1 nm. The therapeutic efficiency of silver nanoparticles was enhanced by capping them with polymers such as starch, chitosan, and polyvinyl pyrrolidine (PVP) [88].

5.1.2. Gold (Au) nanoparticles

Gold nanoparticles (AuNPs) are unique because of their surface morphology, biochemical behaviour, electron affinity density, and optical absorption. AuNPs are inorganic nanoparticles with an inorganic core and an organic polymer or metal shell. Organic polymers or metals protect the core material from the biological microenvironment. Covalent or non-covalent interactions can be used to load therapeutic drugs onto AuNPs. Indeed, AuNPs may be easily modified on the surface, they are perfect for drug delivery and precision targeting. In a study, Meena et al. synthesized AuNPs to co-deliver doxorubicin and kaempferol in colon cancer treatment. It was chemically treated using PEG and then

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loaded with the drug. PEG was utilized to modify the surface and was attached via electrostatic interaction. In the absence of a targeted ligand, AuNPs accumulate in tumor vasculature via the EPR effect due to their small particle size. Due to the presence of PEG, AuNPs persist in circulating in the body for an extended period, evading phagocytosis. Dox and Kaempferol had 68.42 and 73.33 percent entrapment efficiencies, with drug loadings of 2.79 and 3.70 percent [89].

5.1.3. Magnetic and super magnetic nanocarriers

Magnetic and superparamagnetic iron oxide nanoparticles (SPIONs) were used to identify nanomaterials targeting specific types of disease. SPIONs have unique features that allow them to accumulate in a particular tissue when exposed to an external magnetic field. Magnetic resonance imaging and magnetic hyperthermia are produced when subjected to an alternating magnetic field (AMF). As a result, these nanocarriers are highly effective in chemotherapy. Concurrently, in a recent study, prostate cancer has been treated with iron oxide nanoparticles (FeO) that target two receptors simultaneously. These nanoparticles are loaded with paclitaxel drug delivery systems. The research shows that iron oxide nanoparticles can be taken up by the human prostate cancer cell line PC-3 very well. Compared to normal prostate epithelial cells, in vitro magnetic resonance imaging reported significant binding and accumulation of iron oxide nanoparticles in PC-3 cells [90]. Active targeting could be accomplished by placing tumor-specific antigens on the surface of SPIONs, rather than antigens associated with tumors that may also be found on healthy cells [91].

According to the current view from the contemporary perspective, SPIONS are an enticing carrier in oncotherapy (tumor for prostate, brain breast) [92]. Jalalian et al. demonstrated SPIONs for epirubicin delivery in combination with aptamers as a molecular targeting agent in the treatment of colon cancer. Because 5TR1 is excellent for selective targeting of epithelial cancer cells that overexpress a Mucin-1 glycoform, they chose it in conjunction with the SPION-containing epirubicin. Epirubicin or the aptamer coupled with the SPION had 14.1 and 22.72 g/mg drug loadings, respectively. The selectivity of generated SPIONs against free drugs was determined via cellular internalization in C26 colon cancer cells. Between Target and non-target cells, SPIONs showed a statistically significant ($P < 0.05$) difference in fluorescence intensity. When employed on C26 cells, the MTT test revealed that the drug-loaded aptamer conjugated SPIONs outperformed blank SPIONs, blank Apt-SPIONs, and pure drugs. C26 cells had the lowest viability when exposed to the biconjugate generated, at 45.7 percent, demonstrating the formulation's efficacy [93]. In a different study, iron oxide nanoparticles were used to deliver the mice's OVA, an anti-cancer vaccine. OVA containing iron oxide nanoparticles significantly boosted immune cell activation and cytokine production, resulting in robust humoral and cellular immunological responses. The data showed that OVA-iron oxide nanoparticles halted the growth of tumors in mice and better tissue compatible with organs after they were injected into intra-tumoral injection [94].

5.2 Ceramic nanocarriers

Ceramic nanoparticles comprise inorganic compounds mesoporous silica, hydroxyapatite, zirconia, titania and alumina [95]. They are bio-inert and have porous structures. Ceramic nanoparticles have several advantages, making them a promising tool for controlling drug delivery. These include easy preparation, high load capacity, and easy incorporation to hydrophilic and hydrophobic systems. Below, various types of ceramic nanocarriers are enlisted in brief.

5.2.1 Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MsNPs) are drug delivery distinguished by their large surface area, low toxicity, and narrow size distribution [96]. MsNPs are preferred for drugs that target the colon by protecting against different pH levels due to the size and shape of the pore. For instance, Li et al. proposed novel nanocarrier systems for curcumin-specific targeting and controlled release. They delivered curcumin to breast cancer cell lines loaded with hyaluronan or polyethyleneimine-folic acid using surface-modifiable mesoporous silica nanomaterials and tested them in a mouse xenograft model. Folic acid-modified mesoporous silica nanomaterials outperformed hyaluronan-modified mesoporous silica nanomaterials in terms of uptake. Both nanoformulations were found to outperform non-targeted nanocarriers in terms of cellular uptake. These formulations were low in toxicity and biocompatibility, effectively inhibiting tumour growth. These MsNPs can release the drug in response to stimuli. In the presence of exogenous or

endogenous stimuli, these nanocarriers cause drug release to the target site [97].

5.3 Carbon based nanocarriers

Carbon-based nanomaterials (CBNs) have piqued researchers' interest in various fields due to their unique structural dimensions and physicochemical properties, including carbon nanotubes, fullerene, nanodiamonds, mesoporous Carbon and graphene.

5.3.1 Carbon based nanotubes for colon cancer

Carbon nanotubes (CNT) are hollow cylinders made of carbon atoms from graphite. They have good thermal, mechanical, and electrical properties and the surface area needed for size distribution and surface functionalization to achieve target specificity. Externally attachment or outer surface attachment is done by covalent or non-covalent bonding. Carboxylic groups aid chemical conjugation on the drug and amino groups on the surface of CNTs and coupling agents. Physical conjugation is done through π–π bonding and electrostatic adsorption [98]. CNTs are classified into two types. CNTs with single and multiple walls. Single-wall carbon nanotubes (SWCNTs) are a type of carbon material classified as one-dimensional. They are made of graphene sheets that have been rolled up to form hollow tubes with walls one atom thick. In contrast, multi-walled carbon nanotubes (MWCNTs) are hollow, cylindrically shaped carbon allotropes with a high aspect ratio, with walls formed by multiple one-atom-thick sheets of Carbon [99]. Their recognition by cancer cells is through the attachment of specific antibodies. Hence, they are internalized and transported into the nucleus. Heister et al. explored using SWCNTs containing doxorubicin (DOX) and a monoclonal antibody as a fluorescent marker within the carbon nanotube structure. DOX uptake via monoclonal antibody attachment in CNTs resulted in 100 % drug delivery efficacy *in vitro* cellular uptake studies using WiDr colon cancer cells [100]. Loading the drug into nano-formulation, in this view, serves no purpose in the formulation. To ensure efficacy, they should tend to release the medicine at the desired site of action and localize the nanoparticles.

5.4 Organic nanocarriers in treating colon cancer

Organic nanocarriers are nanoparticles made by combining polymers and lipids. Polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, nanogels, and dendrimers are examples of organic nanoparticles.

5.4.1 Polymeric nanoparticles for Colon cancer

Polymeric nanoparticles are biodegradable, biocompatible, and easily modified by chemical reactions. Subsequently, the FDA and European Medicine Agency have synthesized and approved different varieties of natural, synthetic, and semi-synthetic polymers. Because of their unique features, such as medication solubility, stability, and tumor site accumulation, they can be altered [101]. Polymeric NPs are a solid-matrix system in which a drug is dispersed or conjugated to the polymeric system. In an attempt to avoid their recognition and removal by a mononuclear phagocyte, they are generally coated with poly(ethylene oxide), poly(ethylene glycol), and poly(acrylic acid) [102]. Natural polymers such as albumin, chitosan, and heparin have been used in FDA drug delivery nano-formulation.

For prostate cancer treatment, a study developed resveratrol surface encapsulated PLGA [poly (lactic-co-glycolic acid)]. These NPs demonstrated significantly lower cell viability and higher cytotoxicity toward LNCaP cells than free resveratrol. In the cytotoxicity assay, resveratrol-coupled poly(lactic-co-glycolic acid) nanoparticles had two times lower IC_{50} and IC_{90} values than free resveratrol [103]. Besides, nanoparticles formed by silk fibroin (natural polymer) have attained stealth response in drug delivery due to the ability to deliver anti-neoplastic drugs, low cost, and manipulation, and enhance their potential activity. The following illustration depicts an overview of different nanoparticle mediated drug delivery in figure 3.
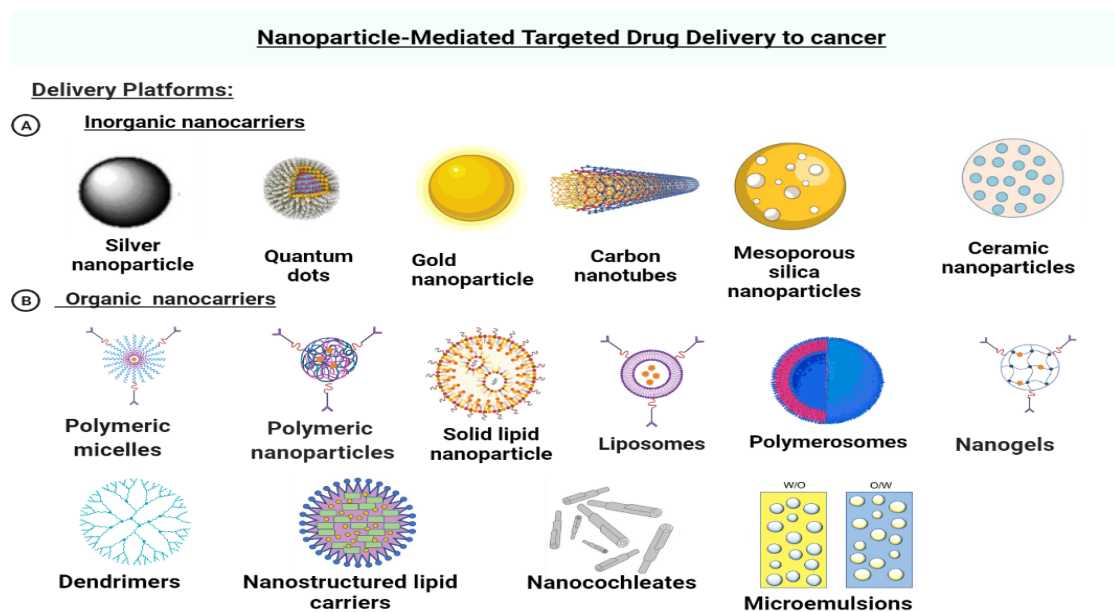
Figure 3. Various nanoparticle-mediated drug delivery to colon cancer

5.4.2 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal drug carriers composed of a solid lipid phase and surfactants as stabilizers. For carrying hydrophilic and lipophilic drugs. Compared to polymeric and inorganic nanoparticles, SLNs are less toxic, tolerable, and biocompatible. At body temperature, these lipid particles remain solid. The hot homogenization method, microemulsion, high-pressure homogenizer, and spray drying are the method for synthesizing SLNs [104]. A study by Shen et al. developed doxorubicin (DOX) and supramagnetic iron oxide NPs loaded with SLNs, and surface functionalized with dextran and folic acid conjugates. Dextran prevents SLNs from absorption in GIT and degrades in the colon by dextranase, revealing folate receptors. Results showed that dextran-coated on the surface of SLNs promoted drug targets to NPs two-fold compared to uncoated SLNs. Hence surface conjugating with these receptors plays a vital role in drug delivery to specific sites [105].

5.4.3 Nanostructured lipid carriers

Given the success of solid lipid carriers, the second generation of lipid carriers was developed to address the shortcomings of SLNs, such as drug expulsion and low entrapment efficiency. Nanostructured lipid carriers (NLCs) comprise solid lipid and liquid lipid, as it helps in drug loading [106]. A study by Xiao-yan et al. developed nanostructured lipid carriers by surface conjugation with hyaluronic acid to deliver paclitaxel (PTX). The *in vitro* cytotoxicity of PTX NLC, HA-NLC, and Taxol was compared. When compared in three different cell lines, the IC$_{50}$ value of HA-NLC was much lower than that of Taxol, indicating that HA-NLC had higher cytotoxicity (0.25 ± 0.04). The cytotoxicity of PTX-NLC (0.41 ± 0.02) was higher than that of Taxol (3.73 ± 0.41), which may be due to the cytotoxicity of PTX drug and CTAB surfactant on the surface of NLC. Compared with Taxol and PTX-NLC, HA-NLC (0.25 ± 0.04) had the highest cytotoxicity against all cell lines. HA-NLC showed a potency of almost ten folds greater cytotoxicity than Taxol. It may be due to specific binding to CD44 receptors on the surface of cells, and active drug transportation, while Taxol and PTX-NLC were transported by passive diffusion. As a result, NLCs with surface conjugation plays a significant role in drug transport because they prolong drug circulation time by binding to specific CD44 receptors on the cell membrane [107].

6. NANOTECHNOLOGY IN THE THERANOSTIC TREATMENT OF COLON CANCER

As colorectal cancer (CRC) divides at an alarming rate, early diagnosis remains a significant challenge as most cases are often recognized as metastatic. Colonoscopy, positron emission tomography (PET), computer tomography (CT), magnetic resonance imaging (MRI), and transrectal ultrasonography

(TRU) are new methods for screening CRC that have gained popularity in the medical field for pre-treatment or post-treatment stage comparison and evaluation [108]. Nonetheless, every method has its limitations, such as difficulty determining wall tissue infiltration (T-stage) and identifying perirectal spicules. Although MRI was less accurate in identifying small polyps, it has been shown to detect hepatic metastases with high efficiency [109]. Transrectal sonography is effective at locating penetration levels and distinguishing between different intestinal wall layers, but it is less effective at identifying lymph nodes in CRC [110]. After radiotherapy, fluorodeoxyglucose positron emission tomography (FDG-PET) revealed false-positive clinical phase results in CRC patients with cysts and nonspecific inflammatory reactions. [111].

These current imaging techniques for CRC treatment lack some undesired side effects, low specificity, and targetability. Employing NPs not only for drug carriers but also for imaging and diagnostic applications offers tremendous benefits to CRC patients. One example is peanut agglutinin (PNA), which can be used as an imaging agent in florescence endoscopy to diagnose early-stage CRC tissue [112]. New diagnostic techniques, such as Raman scattering (RS) and fibre optic probes, can also examine hollow organs and treat CRC. RS is a novel technology that utilizes single-cell suspension, Raman cell screening, and diagnosis [113].

7. RECENT ADVANCES AND CHALLENGES IN NANO DRUG DELIVERY SYSTEM FOR TARGETING CRC

The administration of drugs to reach the colonic site remains a challenge due to the heterogeneity of cancer stem cells, multiple pathways involved in the formation of tumor, and chemotherapeutic drug administration in colon cancer which results in high-dosage drug administration, increased adverse effects, non-specificity which results in designing a suitable targeted drug delivery system enhancing anti-tumor activity, low dosage administration and reducing toxicity to normal healthy cells.

Nanoparticles provide unique opportunities for designing and modulating properties that are not available with other therapeutics. As more clinical data become available, the nanoparticle drug delivery approach should be enhanced further. As they are evolving as new, highly sophisticated multifunctional nanoparticles, their clinical results add fuelling zeal for therapeutic mode.

Engineering nanomaterials have achieved par-excellence results with surface modifications. Through this technique, drugs loaded with nanoparticles can permeate through leaky vasculature blood vessels, enhance the biodistribution in the circulatory system, and improve pharmacokinetics; tumor site accumulation is considered an important parameter in drug delivery. This nanotechnology can achieve further controlled release of drugs to attain desired therapeutic effects. Due to the presence of minute particle size (nm), Nanoparticles can easily permeate through blood vessels and form a stable complex in the body, ensuring target specificity to the tumor region. Nanotechnology is still advancing in cancer therapy, though there is a boom in this area.

Furthermore, upscaling this product to large batches is a formidable challenge. Despite entering phase I and II clinical trials, some colon cancer vaccines face various challenges, such as tumor-associated targets and antigens. As a result, extensive research is required to provide excellent drug delivery to treat tumor cells.

8. CONCLUSION

Many challenges must be overcome when designing a specific drug delivery to the colon region. However, treating methods for colon cancer remains a challenge. Nanotechnology is gaining as a multifaceted tool in treating colon cancer worldwide. This review discusses the latest progress of nanotechnology in drug delivery to colon cancer as it overcomes the drawbacks of current treatment methods. These nanoparticles receive an immense interest in oncology mainly due to biodegradable delivery systems (liposomes, solid lipid nanoparticles, polymeric nanoparticles). Both passive and active nanoparticle-mediated targeting for cancer chemotherapy has been studied and applied. Many of these studies have been submitted to clinical trials to improve bioavailability, reduce dosage forms, and reduce patients' extreme pain. Previously, formulation methods mainly concentrated on a single drug mechanism, such as avoidance of drug release in GIT and drug release in the colon region.

In conclusion, the triumph of using nanoparticles is high bioavailability, solubility, stability, and less toxicity. Hence these developed nanoparticles, regardless of being used as a carrier for drugs, therapeutic

agents, and imaging agents, need to be characterized physiochemically and pharmacologically before approving for human use. Before receiving FDA approval for clinical trials, long-term and short-term toxicity studies in cell culture and animal models must be carried out. Utilizing nanotechnology and diagnostic imaging tools to cure cancer and understand its mechanism at the molecular level will assist in early detection and prevention, thereby creating a new ray of hope in future medicine.

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