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Colon cancer and their targeting approaches through nanocarriers: A review

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ABSTRACT

Colon cancer is the fifth most common type of cancer in the world. Colon cancer develops when healthy cells in the lining of the colon or rectum alter and grow uncontrollably to form a mass known as a tumor. Despite major medical improvements, colon cancer is still one of the leading causes of cancer-related mortality globally. One of the main issues of chemotherapy is toxicity related to conventional medicines. The targeted delivery systems are considered the safest and most effective by increasing the concentration of a therapeutic substance at the tumor site while decreasing it at other organs. Therefore, these delivery systems required lower doses for high therapeutic value with minimum side effects. The current review focuses on targeting therapeutic substances at the desired site using nanocarriers. Additionally, the diagnostic applications of nanocarriers in colorectal cancer are also discussed.

KEYWORDS: Colon cancer; Targeting approaches; Chemotherapies; Nanocarriers; Gold nanoparticles; Liposomes

1. Introduction

Colorectal cancer (CRC) ranks third in prevalence worldwide after breast and lung cancer. As per the literature, new cases of CRC reached upto 1 880 725 where colon and rectum cancer contributed 1 148 515 and 732 210, respectively[1,2]. Several risk factors, such as a sedentary lifestyle, the environment, obesity, old age, a diet high in meat and associated products, a lack of physical exercise, tobacco, alcohol drinking, and congestion can contribute to the development of CRC. In addition to these factors, a few novel studies also suggested the role of mitochondria biogenesis and clearance in the development of CRC. It is known that NO and H_2O_2 diffusion, mitochondrial oxidative damage, and mitochondrial dysfunction all contribute to the development of CRC[3,4]. Symptoms of CRC include fat loss, blood in the feces, soreness, abdomen pain, changes in gut habits, abdominal weakness and increasing bloating, nausea, and vomiting[5].

Nanocarriers have a size range of less than 1 000 nm acting as drug-delivery carriers for many therapeutic substances. The unique benefits of nanocarriers, such as biocompatibility, decreased toxicity, good stability, improved permeability, retention impact, and accurate targeting, make them suitable for the treatment of colon cancer. Currently, nanocarriers are considered a means of early detection and successful therapy for CRC. As the distribution of drug systems is for medicinal and diagnostic reasons, several nanocarriers have been produced and investigated to date. To treat patients selectively and minimize toxicity, such nanocarriers are connected to targeting moieties. Active targeting frequently includes the ligation of targeting moieties that are recognized through colon cancer

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tissues, such as folate, monoclonal antibodies, vascular endothelial growth factor, aptamers, and membrane penetrating peptides, whereas extravasation and increased permeability are considerable factors in passive targeting. Moreover, delivery systems based on nanotechnology have gradually started to use smart carriers in CRC by ensuring the maximum availability of anticancer drugs at cancer sites[6].

The applications of several nanocarriers in the treatment of CRC are summarized in the current review article. Several nanocarrier-based targeting approaches that have been extensively used in CRC are compiled here, including the passive and active targeting approaches. Several ligation moieties have been discovered so far which are overexpressed under CRC-associated pathophysiological conditions. The article highlights those ligands that could be used effectively in the case of active targeting.

2. Colon cancer

There are many reasons for colon cancer, including a sedentary lifestyle, food habits, and obesity. The probability of getting colon cancer is increased in obese people compared to those who are considered to be of normal weight because of the environment and obesity. Weight loss, red blood cells in the feces, pain, abdominal discomfort, stool pattern changes, appetite loss, worsening congestion, nausea, and vomiting are signs of CRC. Anemia or genital hemorrhage is a serious concern in older people (over 50 years of age)[5]. Cancer is a condition, where a subset of the cells in the body repeatedly divides especially invading nearby tissues. Standard cancer stem cells are caused by adenomatous polyposis coli gene mutations, and they proceed in increments to CRC[7]. The three main etiological and genetic instability pathways for CRC are the CpG island methylator phenotype, microsatellite instability, and chromosomal instability (CIN). The occurrence of CRC is mostly caused by the CIN route and is distinguished by frequent aneuploidy (abnormal chromosomal numbers) and a lack of heterozygosity. Figure 1 demonstrates the pathophysiology of CRC at various stages of development and its many risk factors.

3. Targeting approaches

There has been an increasing interest in the development of effective therapy techniques based on nanocarriers for CRC in the last forty years. The majority of anticancer medications have low efficacy and related adverse effects because they are unable to discriminate between healthy cells and malignant cells. Targeted drug delivery based on nanocarriers may be an option in this situation for increased efficacy and decreased negative effects *via* passive or active methods. For therapeutic and diagnostic purposes, a variety of nanocarriers, including polymeric micelles, liposomes, nanoparticles, quantum dots, and dendrimers, have been utilized[8]. Targeting through nanocarriers is possible in the following ways:

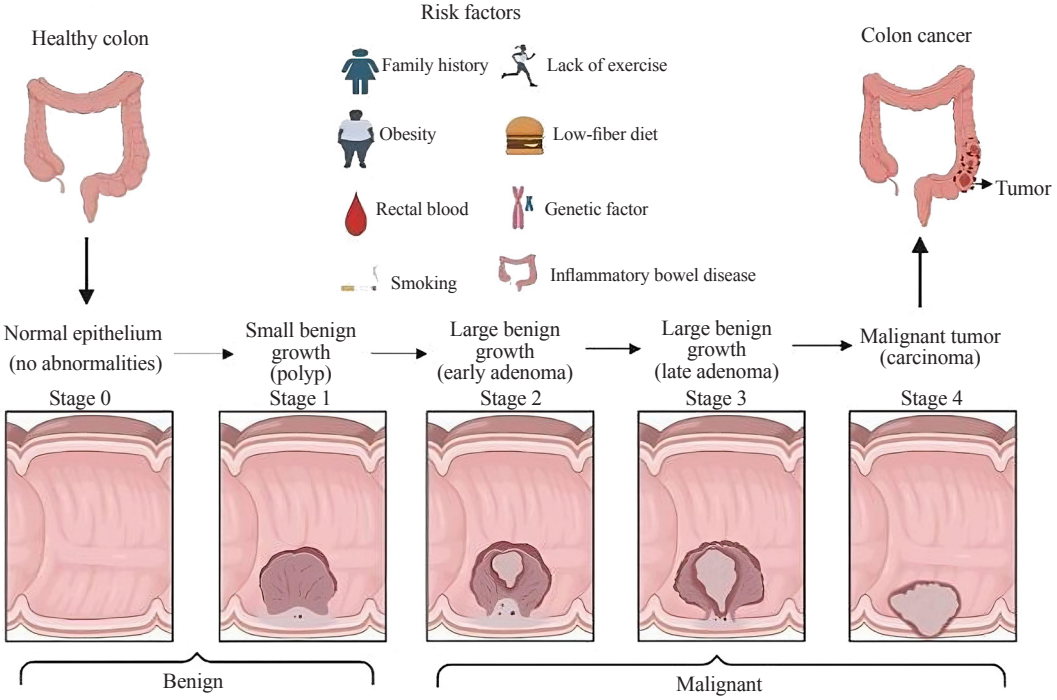

Figure 1. A diagram of the pathophysiology of colorectal cancer at various stages of development and its many risk factors.

3.1. Passive targeting

Utilizing tumor-related pathophysiological alterations can enable the passive targeting of loaded therapeutic material to CRC cells. Due to the flawed design of tumor vasculature, enhanced permeability and additional retention of nanoparticles in cancer cells are feasible. In contrast to the conventional technique, the endothelial voids between blood arteries that are connected to cancerous tumors are said to be greater (100 nm to 2 m) than normal, allowing for improved permeability of size-specific drug-loaded nanocarriers to the cancer cells. The fact that cancer tissues may have a compromised lymphatic system, which causes higher interstitial pressure at the centers of cancer cells than at their peripheries, is a reason for the passive targeting of nanocarriers. As a result, drug-loaded nanocarriers are kept in the interstitial region for a longer period and show better therapeutic value for the treatment of cancers[9].

Unlike traditional delivery techniques, nanocarriers have longer systemic circulation due to their avoidance of the reticular endothelial system, which further enhances the therapeutic effectiveness of the loaded anticancer drug. Because loaded nanocarriers are available for such a long time, certain cancer cells eventually pick them up. By coating or ligating nanocarriers with some hydrophilic chemicals, such as polyethylene glycol, opsonization (a technique for making stealth nanocarriers) can ensure the lengthy circulation of nanocarriers[10].

3.2. Active targeting

Active targeting of nanocarriers requires cancer cells to be recognized by the nanocarriers through molecular ligation. Therapeutic agents solely deposit at the cancer site by molecular recognition. Targeting molecules are often ligated on the surface of the nanocarrier for active targeting. The following formulations have been studied for the active targeting of the therapeutic substance in CRC[11].

3.2.1. Nanoparticles

Many nanoparticle combinations loaded with anticancer medicines have been taken into account during the past 50 years for the efficient therapy of CRC. The main goal of first-generation nanoparticles was to use physiological changes (enhanced penetration and retention effects supplied by the vascular and lymphatic drainage of CRC) occurring during the disease to combat the condition passively. Later, consideration was given to next-generation receptor-based active targeting with targeted delivery of drug-loaded nanoparticles into cancer cells alone. The numerous interactions (monoclonal antibodies, enzymes, and dendrimers) linked to the nanoparticle occurs for cancer cell activity identification and served as a guide for the movement of the nanoparticles. The study conducted by Fay *et al*. demonstrates that the conatumumab (AMG 655)-coated nanoparticles are more absorbed by the colorectal HCT116 cancer cell. They show that camptothecin, an encapsulated therapeutic substance, was delivered specifically to HCT116 cancer cells to induce apoptosis[12]. Hydrogel-based chitosan/alginate nanoparticles were prepared in a similar work by Abdelghany *et al*., for the encapsulation of meso-tetra (*N*-methyl-4-pyridyl) porphine tetra tosylate. The prepared nanoparticles were coated with antibodies that target death receptor 5 for selective uptake by the HCT116 cells during the 16 h incubation[13].

3.2.2. Liposomes

The liposomes consist of phospholipids derived from either plant or animal sources and can be unilamellar or multilamellar tiny artificial spherical vesicles[14]. The size of the liposomes varies from 20 nm to 1 000 nm, and they have a spherical hydrophobic phospholipid bilayer structure around an aqueous core domain[15]. As a non-toxic molecule that can encapsulate both hydrophilic and hydrophobic therapeutic substances, liposomes provide better protection to the encapsulated therapeutic substance from environmental degradation throughout the systemic circulation[16,17]. In drug delivery systems, liposomes are frequently utilized as a carrier for a variety of anticancer substances[18]. However, liposomes are limited with numerous drawbacks, such as poor encapsulation efficiency, poor solubility, brief half-life, and rapid burst drug release[19–21].

To enhance the drug's effectiveness and safety, a research was performed to prepare 5-fluorouracil-loaded liposomes and they were actively targeted to CRC by the ligation with folic acid. The cytotoxicity of formulations on the HT-29, Caco-2, CT26, HeLa, and MCF cell lines was evaluated using the MTT assay after 48 h. When compared to the free medication and control groups, an *in–vivo* investigation found that folate-ligated liposomes effectively inhibited tumor growth[22]. To encapsulate 5-fluorouracil, Mansoori *et al*., developed hyaluronic acid-modified liposomes and tested them against a colorectal cell line (HT29) that expresses CD44 and a hepatoma cell line that does not express CD44. Hyaluronic acid-decorated liposomes were found to be 114.77 nm in size on average. Based on the expression of CD44, the MTT experiment indicated time-dependent specific cancer cell death. The results demonstrated that produced liposomes have improved anticancer activity by active targeting[23].

3.2.3. Dendrimers

Organic and hyperbranched macromolecules, known as dendrimers with a size of 1 to over 10 nm, have a shape like a tree[16,17]. With a high drug encapsulation rate, dendrimers are different drug delivery technology. Because of their special characteristics including consistent size and dispersion, extensive branching, a known molar mass, and chemical makeup, dendrimers are an appealing carrier for drug delivery applications[24–26]. The monomers that make up the dendrimer's core have two or more extra groups that can connect to other moieties[27]. Dendrimers are often created using one of two

methods: Convergent strategies versus divergent methods[28].

Dendrimers are widely used in cancer medication delivery and cancer cell detection due to their precise size and branching patterns. In a recent study, Myc *et al*., used polyamidoamine dendrimers with methotrexate by the ligation of folic acid as a targeting agent[29]. The outcomes of tests on both cytotoxicity and specificity indicated that dendrimer conjugates significantly improved anticancer activity. In a related study, Alibolandi *et al*. developed a polyamidoamine dendrimer for site-specific targeting of HT29 and C26 CRC cells that were loaded with camptothecin and connected with S1411 anti-nucleolin aptamers. Additionally, the system was tested on mice with C26 tumors, and the outcomes of the investigation showed improved therapeutic efficacy[30]. More recently, Sun *et al*., reported a generic method for creating nano assemblies from phospholipids and hydrophilic and hydrophobic dendrimers[31].

3.2.4. Gold nanoparticles

Due to their distinct optical, physical, and electrical features, gold nanoparticles (AuNPs) are most frequently employed as a preferred material in various disciplines[16,17,32]. Based on their size, shape, and physical characteristics, the AuNPs may be divided into Au nanospheres, Au nanorods, Au nanocages, and Au nanoshells, with diameters ranging from 2 to 100 nm[33,34]. The special properties of AuNPs for drug delivery techniques include inertness, biocompatibility, large surface area, excellent stability, and low toxicity[35]. AuNPs' enormous potential in diagnostics for the detection of biomarkers and imaging in existing cancer treatments is one of their primary developing applications[36,37]. Due to the ease with which gold can bind functionalizing or targeting ligands, localized surface plasmon resonance of AuNPs has been extensively explored in a variety of applications ranging from biomolecular sensing to therapeutic interventions[38].

It has emerged as an attractive drug delivery system for the treatment of a variety of diseases due to its advantages in facile synthesis, vast surface area, flexible surface chemistry, and easy functionalization. It is possible to make a useful delivery system that releases its payload in response to an external signal[39]. Xie *et al*. conducted a study to describe an efficient method for using multiple Sialyl Lewis X antibodies-conjugated polyamidoamine dendrimers for specific binding with colon cancer (HT29) cells. The findings demonstrated that the compound increased HT29 cell capture in a concentration-dependent manner, with a maximum capture efficiency of 77.88%[40].

3.2.5. Quantum dots

Semiconductor particles having optical and electrical properties that are nanometer-sized, when excited, become luminous at wavelengths ranging from visible to infrared. This characteristic makes these particles particularly useful for imaging and diagnostic purposes in a range of diseases, including CRC. Numerous studies have been conducted on quantum dots, which are steered by ligands absorbed by CRC cells, and which suggest their potential utility as CRC diagnostic tools. Quantum dots designed to attach to vascular endothelial growth factor receptor 2 have been created by Carbary-Ganz *et al*. According to the outcomes of immunofluorescence and immunohistochemistry, the generated quantum dots were

Table 1. The use of several nanocarriers targeting methods in colorectal cancer.

Formulation	Ligand for active targeting	Therapeutics	Outcomes	Ref
Nanoparticles	Conatumumab (AMG 655)	Camptothecin	Improve cytotoxicity activity in HCT116	[12]
Nanoparticles	Nucleolin-targeted aptamers (AS1411)	Docetaxel	Improve antitumor efficacy	[44]
Poly (lactide-co-glycolide) nanoparticles	CD95/Apo-1 receptor antibody	Camptothecin	Enhanced cytotoxic activity in HCT116	[45]
Chitosan nanoparticles	Hyaluronic acid	Oxaliplatin	Increased medication absorption at the cancer location	[46]
Chitosan nanoparticles	Hyaluronic acid	5- Fluorouracil	HT-29 colon cancer cells take in more nanoparticles	[47]
Guar gum nanoparticles	Folic acid	Methotrexate	Enhanced Caco 2 cell suppression	[48]
Liposomes	Folic acid	5- Fluorouracil	Higher antitumor efficacy	[22]
Liposomes	Hyaluronic acid	5- Fluorouracil	Enhance better anticancer activity	[23]
Polyamidoamine dendrimers	Folic acid	Methotrexate	Improve cytotoxicity and specificity of anticancer activity	[29]
Polyamidoamine dendrimers	AS1411 anti-nucleolin aptamers	Camptothecin	Improve therapeutic efficacy	[30]
Gold nanoparticles	Thioglycolic acid and glutathione	5-Fluorouracil	Enhance anticancer activity	[49]
Gold nanoparticles	Anti-PD-L1	Doxorubicin	Localized colorectal cancer may be treated with PD-L1-AuNP-DOX in conjunction with synergistic targeted chemo-photothermal therapy	[50]
Quantum dots	Vascular endothelial growth factor	-	Directed specifically at colon cancer in mice	[41]
Quantum dots	Bevacizumab	-	Detection of overexpressed vascular endothelial growth factor receptors in colorectal cancer cells without physical contact	[42]
Quantum dots	Endothelial growth factor receptor	Cetuximab	Better inhibitory action	[51]

preferentially deposited on colon cancer in mice[41]. Quantum dots conjugated with bevacizumab were created by Gazouli *et al*. for molecular imaging in CRC. The findings of this study also demonstrated a straightforward, practical, and non-invasive method for detecting excessive vascular endothelial growth factor receptor expression in CRC cells[42]. In addition to their use in diagnostics, quantum dots have demonstrated their ability as therapeutic drug carriers in CRC. In a recently completed study, Eudragit RS 100 was used to create curcumin-loaded quantum dots. Researchers discovered that the produced formulation exhibits higher bacterial and CRC cell inhibition. Despite the paucity of research in this field, it has been concluded that ligation-based targeting of drug-loaded quantum dots may provide a useful alternative to diagnostic application in the management of CRC[43]. Targeted nanoparticles can be encapsulated with various anticancer medications, as shown in Table 1.

3.2.6. Carbon nanotubes

Carbon nanotubes are gaining the attention of researchers for the last two decades. They are considered a good choice for the delivery of an anticancer therapeutic substance to the site of action because of their strong hydrophobicity. Additionally, several targeting moieties can be coupled with the delivery system for the effective identification of tumor cells. Depending on the number of layers, these nanostructures can be single-walled, double-walled, or multi-walled when produced from rolled-up graphite sheets. Important characteristics of carbon nanotubes include their light weight, tiny size, superior strength, and great conductivity[52,53].

Wang *et al*. demonstrated that a greater aspect ratio of thin multi-walled nanotubes is the comparatively better choice because they accumulate more near the cancer cells. They compared narrow multiwalled nanotubes (9.2 nm average diameter) and broader multiwalled carbon nanotubes (39.5 nm average diameter) and concluded that narrow multiwalled nanotubes showed better therapeutic value with selective targeting[54]. In another study, Arora *et al*. demonstrated the enhanced anticancer properties of docetaxel when conjugated with multi-walled carbon nanotubes[55].

4. Nanocarrier toxicity and future perspectives

Nanocarriers are extensively being used in the diagnosis, treatment, and prevention of cancer. However, because of their small size and their distinctive properties, it confers safety-related issues. Many studies revealed that the accumulation of nanocarriers in different cells and tissues may lead to major health hazards. Ma-Hock *et al*, demonstrated that inhalation of a liquid aerosol of CdS/$Cd(OH)_2$ core-shell quantum dots causes respiratory toxicity in male Wistar rats[56]. Another study conducted by Kim *et al*. confirmed that the silver nanoparticles altered the level of cholesterol and alkaline phosphatase which may be due to liver toxicity. They hypothesized that the release and accumulation of metal ions from silver nanoparticles may be responsible for these harmful consequences. Additionally, they demonstrated that NPs given intravenously or intraperitoneally tend to cause mild liver toxicity[57]. Size-specific clearance from the kidney has been followed by the nanocarriers. Large particles may be retained in the kidney for a longer time and may cause nephrotoxicity. Coccini *et al*. demonstrated that cadmium-containing silica nanoparticles caused nephrotoxicity and fibrosis in rats with increased expression of interleukin 6 and transforming growth factor beta 1. It was concluded that nephrotoxicity was developed due to the retention of nanoparticles in the kidney[58]. The studies also demonstrated the easy passes of nanocarriers to the brain by passive diffusion or by receptor-mediated endocytosis which may further increase nanocarrier-related brain toxicity. With the alignment of this hypothesis, researchers demonstrated hemorrhage and changes in the level of neurotransmitters in the brains of mice after intranasal administration of titanium dioxide nanoparticles[59].

Despite the enhanced therapeutic values, nanocarriers may also cause several cellular and organ toxicity. Therefore, a potential toxicity concern by using clinical approaches should be undertaken while preparing the nanocarriers for a certain disease or disorder. The clinical toxicological effects of nanocarriers should be fully understood. The exposure kinetics and clearance study should be well planned during the scale-up manufacturing and even the packaging of nanocarriers carrying the chemotherapeutic substances. Further, the retention and possible impact on particular cells and tissues should be studied clinically. These controlled sets of data may be useful to minimize the occurrence of nanotoxicity with improved anticancer activity.

5. Conclusion

For customized oncology that encompasses cancer detection, diagnosis, and treatment, nanotechnology has emerged as a key tool. Nanocarriers play a crucial role in cancer treatment by reducing the drawbacks of traditional chemotherapy. A new technique of targeting chemotherapeutic substances at the cancer site is possible by nanocarriers. Decorated nanocarriers may be an effective tool for the selective targeting of therapeutics and herbal anticancer substances in the treatment of CRC. In the near future, extensive clinical testing and mass manufacture of nanoformulations will be necessary for clinical application.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Authors' contributions

NS conceived the idea and guided the content of the article. RK and RKW collected and compiled the data. NS and KK gave the final edits to the manuscript. NS and RK equally participated in all activities before the approval of the final manuscript.

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