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Functionalized liposomes for colorectal cancer therapy

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ABSTRACT

Colorectal cancer (CRC) is one of the most common cancers. Many patients do not live for several years following their diagnosis, highlighting the urgent need for new treatment options, including new drug delivery methods. An effective strategy to increase the effectiveness of the treatment of this cancer is the use of a liposomal delivery system, which provides the possibility of providing hydrophobic and hydrophilic compounds with better biocompatibility and reduction of side effects by using several advantages, thus causing anti-cancer activity. Better tumor, drug accumulation is longer and they do not show any cytotoxic effect on normal cells. In this review, we will present nanoliposomes containing various compounds and ligands studied in CRC treatment. We will discuss on the benefits of liposomal administration in various forms, along with their effectiveness, specificity, and drug accumulation. Nanoliposome carriers have enormous potential to overcome the present constraints of cancer treatment, and the creation of this technology gives new possibilities in CRC treatment.

Keywords: Colorectal cancer, Liposomal delivery system, Cancer treatment

INTRODUCTION

One of the worldwide major health challenges is cancer, which causes high mortality in all ages. Cancer is a complex process caused by the uncontrolled growth of cells and the survival of mutated and deformed cells [1]. Colorectal cancer (CRC) is the third most frequent malignancy, with a significant global spread and fatality rate.

The survival rate in people whose disease is diagnosed in the early stages is more than 90%, while the same survival rate in people who are diagnosed after pathological diagnosis is less than 10% [2]. So, diagnosing the disease in different stages plays a significant role in the treatment and prevention process. Approximately 60% of patients with CRC needs surgery and chemotherapy as standard treatment, when the disease is diagnosed [3]. Lack of in time treatment, metastasis and progression of the disease largely lead to the death of patients with CRC [4].

One approach to treating colorectal cancer (CRC) is chemotherapy. However, its use is often limited by systemic side effects and a lack of tumor specificity. To address these challenges, alternative treatment strategies have been developed. These include integrating conventional chemotherapy with targeted molecular therapies and leveraging nanotechnology for enhanced therapeutic efficacy [5]. The design of drug carriers using nanotechnology has created a great change in the treatment of various diseases, especially cancer treatment [6]. This type of new drug delivery system has shown more effectiveness compared to conventional treatment methods [7]. Among the advantages that nano-based drug carriers have, the following can be mentioned: longer circulation time [8], increasing the half-life of drugs and sensitive proteins [9], increasing the effect of drugs [10], increasing the solubility of drugs, hydrophobic [11], facilitating controlled and targeted drug release in the desired areas and also reducing side effects [12].

Liposome is one of these nanocarriers, which is widely used to deliver drugs to the intended location [13]. Among the advantages of treatment methods based on liposome carriers, low toxicity, high biodegradability, controllable bio circulation, easy change in lipid composition and physical characteristics, accurate target identification, and very few side effects can be mentioned [14]. It is also possible to trap hydrophobic and hydrophilic drugs in the liposome, which has a hydrophilic center and a hydrophobic double layer membrane [15], in addition, the liposome has the ability to continuously release the substance that inside it [16].

So far, many results of the use of liposomes in the clinical phase have been published [17] and some of them have also obtained the necessary licenses [18]. Currently, in the United States, major clinical phase studies are being conducted to treat cancer, fungal infections, and Kaposi's sarcoma linked with acquired immunodeficiency syndrome [19].

Liposomal bupivacaine (Exparel®, developed by Pacira Pharmaceuticals, San Diego, CA) received approval from the U.S. FDA in 2011 for use as a local surgical site injection to manage postoperative pain following hemorrhoidectomy and bunionectomy [20]. Liposomes are utilized in cancer treatment

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to enhance the delivery of chemotherapeutic agents, improve drug bioavailability, target tumor cells specifically, and minimize systemic toxicity, thereby increasing therapeutic efficacy [21].
Aroplatin- containing liposome, which treats metastatic colorectal cancer, passed the second phase of clinical trials [22], or Depocyt is a cytarabine-containing liposome with the ability to be injected into the spinal cord, which is FDA (Food and Drug Administration) is used to treat lymphomatous meningitis [23].
One of the characteristics of drug-carrying liposomes is that they can be targeted based on specific goals, so that they go to the desired location and release the drug in that area [24]. Various factors are used for target the liposome, for example, for targeting specific tumors, ligands for the desired cancer can be placed on the surface of the liposome [25]. These ligands must have a number of characteristics, including the ability to appear and exposure, affinity and specificity for the tumor in question [26]. Also, the liposomes improve tumor treatment by accumulating the drug at the target site, and prevent the toxic effect of the drug on normal tissues [27].
For these reasons, liposomes are used as a drug delivery system that increases the shelf life of the drug in vivo and in vitro [28]. Multi-drug treatment regimens are also used as a good strategy to reduce side effects and increase the therapeutic effect of drugs because they target several different pathways at the same time [29]. In this article, a review of the advances in drug delivery of targeted liposomes, which that used as carriers of multiple drugs to treat colon cancer, discussed. Furthermore, the primary challenges associated with the targeted release approach for colon cancer are delineated, and recommendations for the future are emphasized.

Targeted nanoliposomes for colorectal cancer treatment

The use of intelligent or targeted drug transport methods have provided good results in reducing adverse drug reactions by delivering the right amount of drug to a specific region.

Accurate targeting of liposomal drug delivery systems reduces side effects in healthy tissues and has the potential to treat metastatic and recurrent cancer cells. Correct targeting of these systems offers several advantages, including; but not limited to: (i) selective internalization of therapeutic drugs by cancer cells, resulting in a lower risk of multidrug resistance (MDR) and fewer side effects in healthy tissues; (ii) the ability to pass the blood-brain barrier; and (iii) the ability to recognize, scan, and treat colon cancer cells that are metastatic, recurring, or linked to them [30].
Several clinical and preclinical studies have reported that the use of targeted nano-medicines to treat solid tumors is increasing [31]. Although targeted cancer therapy may seem simple, in fact, there is a significant challenge in this field due to the inherent complexities in the process of active targeting. For effective targeting, specific moieties must be placed on liposomes to achieve optimal affinity. Different reactive groups are used to modify the surface of liposomes depending on the intended purpose. In general, there are six methods for chemical functionalization: (a) cross-linking of imines with glutaraldehyde, (b and c) amide cross-linking of primary and free amine or carboxylic acid activated with p-nitrophenyl carbonyl, (d) using thiol and pyridyl dithiol groups with cross disulfide, (e) thiol maleimide click chemistry processes, and (f) hydrazone crosslinking of aldehyde and hydrazine groups [32].
The majority of research on medication targeting has relied on the use of certain ligands, including small molecules, peptides, monoclonal antibodies (mAbs), and aptamers. These ligands can directly bind to their receptors on or inside colon cancer or related cells. In addition, nanoliposomes can be directed to the vicinity of the tumor via a magnetic field or the acidic pH correlated with the tumor microenvironment or (TME) (Figure 1) [33].

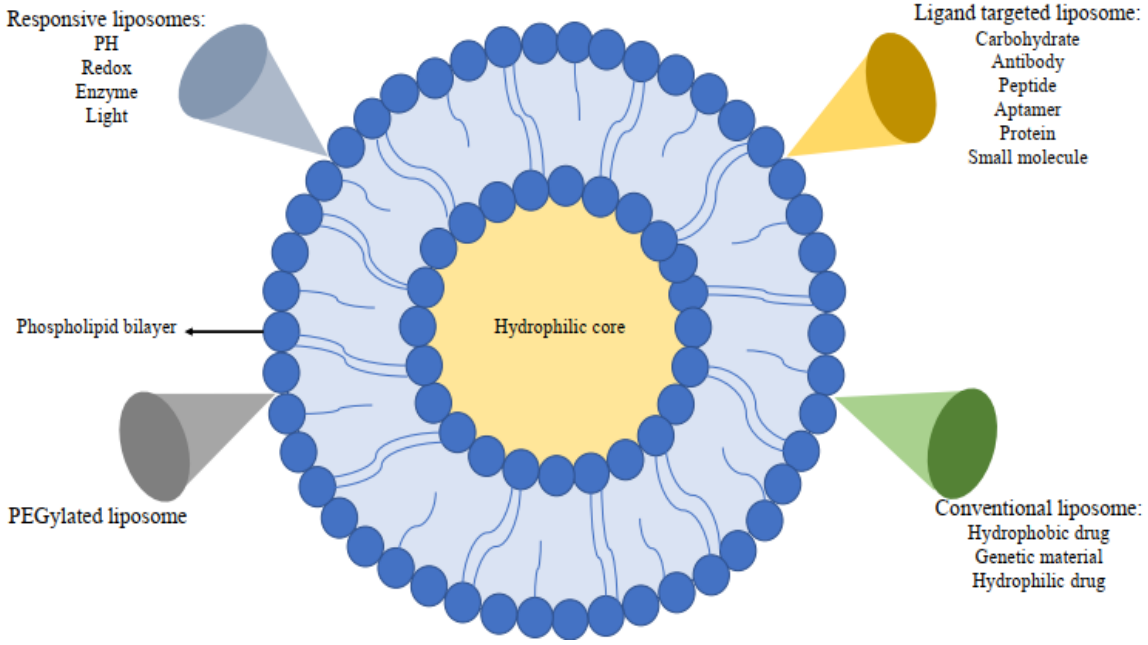

Fig. 1. Functionalized liposome delivery mechanisms for solid tumor therapy [33].

Types of drug-loaded nanoliposomes

According to recent studies, most of the new generation drugs that are used to treat diseases have the ability to provide accurate and targeted delivery systems [34]. According to the results published in Nature Nanotechnology, the use of drugs based on nanotechnology is increasing, of course, liposomes are the most common type of nanomaterials used as drug carriers due to their characteristics and advantages [35].

Sometimes, due to a series of limitations that some drugs may have individually in treatment, including neutralizing responses, overlapping pathways, cross-talk, etc., their combination with other drugs is used [36].

Nanoliposomes loaded with chemical drugs

Apigenin is a natural flavone that is being considered as a possible chemotherapeutic drug for the treatment of colon cancer [37]. For the effectiveness of this hydrophobic drug, a liposome carrier is used, which facilitates drug delivery [38]. The therapeutic effect of liposome containing apigenin is such that it stops the cell cycle in the G2/M phase [37]. 5-Fluorouracil (5-FU) is also a chemical that is used as an antitumor in the treatment of colon cancer [39]. The combination of 5-FU and apigenin via liposome carrier significantly increases the cytotoxic effect on CRC. Thus, it increases inhibition of angiogenesis, better reduction of cell proliferation and potential increase of apoptosis.

In general, it has been shown that the increase in the potential in vivo properties of this drug combination is due to the passive targeting activity of this carrier, and this drug can also be used in clinical cases [13].

In order to make 5-FU more effective and reduce its toxic effect, 5-FU is encapsulated in long-circulating liposomes (LCL-5-FU) and combined with liposomal prednisolone phosphate (LCL-PLP), which is a known anti-angiogenic compound against C26 colon cancer cells were investigated. Combined liposomal drug treatment in this case almost completely inhibits tumor growth, which is mostly related to the anti-inflammatory and anti-angiogenic effects of these compounds [40].

Considering the important role of folic acid in the body and the high expression of the folate receptor in some cancers, it is possible to use the high affinity of this receptor for folic acid in the colon tumor to direct anticancer drugs to the desired location [41]. Oxaliplatin is widely used to treat colon cancer. The anti-tumor effect of this substance is due to the inhibition of DNA replication and synthesis [42]. In a study the effect of liposomes conjugated with folic acid and containing Oxaliplatin enclosed with alginate beads and Eudragit-S-100, which is specifically degraded in the colon, was shown that this compound has the potential to target colon tumors [1].

High expression of indoleamine 2,3-dioxygenase 1 (IDO1) in tumor cells causes suppression of the immune system, which is also associated with poor prognosis in human colorectal cancer [43]. Therefore, the liposome containing Oxaliplatin (Oxa (IV)) and conjugated with alkylated phospholipid NLG-919 (aNLG) was used as an IDO1 inhibitor in the treatment of colon cancer. The aNLG/Oxa (IV)-Lip can cause the release of cytotoxic oxaliplatin into the cytosol and cause immunogenic cell death of cancer cells. The aNLG/Oxa (IV)-Lip in vivo showed that it has a longer circulation time and a strong antitumor effect, and also has a greater permeability in tumor CD8+ T cells [44].

Irinotecan hydrochloride (CPT-11) is a water-soluble drug that acts as an inhibitor of DNA topoisomerase I [45]. The combination of Oxaliplatin and CPT-11, with different functional mechanisms, causes the development of antitumor activity [46,47]. In addition, due to the presence of a hydrophilic core that can cause the encapsulation of hydrophilic drugs, liposome is used for the simultaneous transport of CPT-11 drug combination [48]. For this reason, in a study, Zhang et al put the combination of these two drugs into liposome and evaluated their effects in vitro and in vivo. The results of this study showed that liposome causes the accumulation of combined drugs in the tumor site compared to free drugs and has a greater anticancer effect [47].

One of the treatment methods and prevention of angiogenesis process (one of the basic processes of tumor growth and development) at the tumor site is the use of signaling pathway inhibitors, especially vascular endothelial growth factor 2 (VEGFR-2) [49–51].

Apatinib mesylate acts as a selective and strong inhibitor against VEGFR-2, which is also known as a strong antitumor by having anti-angiogenic activity, but due to its low bioavailability, poor solubility in water and low oral absorption, the use of this drug is limited [52]. Docetaxel (Taxotere®) is also used in the treatment of solid tumors due to its role in cell cycle disruption and apoptosis-like activity [53]. The combination of Apatinib and Docetaxel can act as a strong antitumor synergistic agent [54]. The simultaneous use of these two compounds in vitro inhibits cell proliferation and induces apoptosis of CT-26 cells, which indicates the anti-tumor and anti-angiogenesis activity of this medicinal compound [5].

By encapsulating doxorubicin in combination with fibrin gel and Apatinib in a self-synthesized Apatinib liposome (lipo-Apatinib), cellular uptake of doxorubicin increases in vitro. The combination of DOX-FG and Lipo-Apatinib significantly improves the antitumor effect in CRC. This drug combination successfully inhibits tumor proliferation and induces apoptosis [55].

PEG liposome containing Doxorubicin and curcumin enhances the antitumor effect on CT26 tumor cells. This anti-tumor effect depends on the inhibitory effect of this compound on most of the pre-tumor processes such as angiogenesis, inflammation, oxidative stress, invasion, resistance to apoptosis and downregulation of Th1/Th2 cells [56].

Nanoliposomes loaded with plant extracts

Although chemotherapy has been effective in improving the survival rate of patients with colorectal cancer, the continuous use of chemotherapy faces obstacles due to its resistance and adverse effects. So safe and natural alternative treatment methods are needed to reduce these long-term negativity consequences is necessary. Medicinal plants, which have inherent bioactive compounds, have shown significant apoptogenic and cytotoxic activity against a wide range of cancer types and thus are a useful alternative to conventional

chemotherapy. According to studies, among these compounds, polyphenols such as curcumin, ellagic acid and gallic acid [57,58] have a preventive role against colon cancer.

Considering that the first anti-cancer drug was extracted from natural sources such as plant alkaloids, therefore, extensive attention was also paid to investigated the cytotoxicity of herbal drugs [57]. Favorable medicinal properties and extensive therapeutic indicators make the use of herbal medicines as anti-cancer agents [58]. Plants have various anticancer mechanisms, for example, they can suppress cancer proliferation, inhibit tumor cell growth, induce apoptosis, and inhibit angiogenesis. This variety of action mechanisms causes the treatment of different types of cancers such as breast, head and neck, etc. [59,60].

Plants usually contain secondary metabolites that have a wide range of different biological and medicinal activities, including antimicrobial, anti-inflammatory, antioxidant, cardioprotective, hypoglycemic, and anticancer properties [61–63].

Gallic acid (3,4,5-trihydroxybenzoic acid) (GA) and Quercetin (Qu) are phenolic compounds that have antioxidant, anti-inflammatory, analgesic, neuroprotective, anticancer and antidiabetic properties [64]. The possible antitumor effect of these two compounds seems to be inhibition of cell proliferation, induction of apoptosis, and protection of human cells against oxidative damage without negative effects on normal cells [65]. Nanoliposomes containing GA, Qu and the mixture of these two compounds together against breast, colorectal and lung cancer cells have shown that in vitro. The mixture of the two compounds as well as Qu does not cause any increase in cytotoxicity after loading into nanoliposomes, while which is a minor effect caused by GA after loading. Based on these observations, it can be concluded that nanoliposomes can increase or decrease the cytotoxic activity of bioactive agents, which depends on the physical and chemical properties of the loaded drug and the type of targeted cancer cells [66].

The extract of *Hypericum perforatum L.* (HP) as well as curcumin (CUR), which is obtained from the rhizome of turmeric (*Curcuma longa L.*), have several properties, including anti-inflammatory properties, antioxidant activities, anticancer, antiproliferative, cytotoxic, and they induce apoptosis, and for this reason, they are widely used in traditional medicine and even in food consumption [67,68]. HP and CUR have anticancer properties by activating apoptosis signal pathways, including caspase activation and cell cycle arrest, inhibition of metastasis and angiogenesis, suppression of proliferation, and modulation of cell signaling pathways [69,70]. In addition, based on the results of various studies, CUR may have a positive effect as an inhibitory agent against gastrointestinal cancers, including CRC [71]. In vitro, nanoliposomes containing both CUR/HP compounds have shown significant cytotoxic and pro-apoptotic activity against SW1116 and SW48 colon cancer cell lines. Based on this, the HP/CUR-Lip complex can be used as an effective method to achieve the synergistic effect of HP and CUR, and further induce apoptosis in the treatment of colorectal cancer [72].

Crocin is an unusual water-soluble carotenoid responsible for the crimson color of saffron. In a study of the effect of nanoliposome containing crocin on C26 colon carcinoma cells, considering the required dose (100 mg/kg), it showed that this nanoliposome composition has a high index and therapeutic effect for the treatment of colon cancer [73]. Crocin is an active medicinal compound that has the potential to inhibit tumorigenesis in all types of malignant cells in laboratory conditions [74]. For example, according to previous research, it has been determined that saffron is an inducer of tumor cell apoptosis and inhibits the proliferation of hepatocellular (HepG2) and cervical (HeLa) cancer cells [75].

Ginger contains many active compounds that cause its anti-inflammatory, antioxidant and anti-cancer effects [76]. The anticancer effect of ginger is caused by the induction of cancer cell death, stopping the cell cycle, inhibiting metastasis, and preventing angiogenesis [77]. The anti-tumor activity of ginger on gastrointestinal cancers occurs through the modulation of signaling molecules, inflammatory cytokines, caspase molecules and proteins involved in the regulation of cell growth [76]. It has been shown that pegylated nanoliposomes containing ginger at a dose of 100 mg/kg increase the expression of genes involved in the immune system, such as Bax and IFN-γ, in mouse models with colon cancer compared to ginger extract, also, the number of tumor-infiltrating lymphocytes (TILs) and CTLs (cytotoxic T cell lymphocyte) cell count in tumor tissue have been shown increases in this case. So, in this way, this compound can be used as an anti-colon cancer drug [78].

Nasturtium officinale, a perennial aquatic weed containing various bioactive components including phenolics and flavonoids, is considered as an important medicinal plant [79]. Flavonoid compounds increase the expression of p53, Bax and caspase-3 genes and cause anti-cancer effects [80]. Phenol-rich fractions (PRF) containing nanoliposomes from Nasturtium officinale at a concentration of 100 mg TPC/kg BW/day cause further improvement of gene expression in mouse models. The higher health promoting activity of nanoliposome-encapsulated PRF could be due to its increased intestinal absorption, bioavailability, bioavailability and bioactivity. In conclusion, nanoliposome-encapsulated PRF can be used as a promising anticancer agent against colorectal cancer [81].

Antibody-targeted nanoliposomes

Recently, as a result of the rising prevalence of colorectal cancer, targeted treatments are widely used to treat this disease [82]. Meanwhile, monoclonal antibodies such as cetuximab (CTX) and panitumumab target and deactivate specific signaling pathways that plays a key role in the development and progression of this cancer through Epidermal Growth Factor Receptor (EGFR) [83]. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of various types of cancer [84].

Celecoxib (CLX) can selectively inhibit cyclooxygenase-2 (COX-2) activity [85]. COX-2 enzyme has a very high expression in various tumors, including colon cancer [86]. COX-2 (or prostaglandin endoperoxidase synthase 2) is regulated in response to inflammatory factors, growth, and tumor stimuli [87]. EGFR has a very high expression in a wide range of solid tumors [88]. CTX is a chimeric monoclonal antibody that acts selectively against EGFR [89]. Targeting both EGFR and COX-2 can increase their synergistic

effect together. EGFR-targeted immunoliposomes loaded with CLX have a significant toxic effect on cancer cells, especially cells that overexpress EGFR [90].

Oxaliplatin (L-OH), a platinum derivative, is currently used in combination with CTX to treat CRC with high EGFR expression. By encapsulating L-OH in liposomes and improving its pharmacokinetic properties, selective accumulation and targeted delivery of the drug to the tumor site can be achieved [91]. The effect of L-OH liposomes containing complete fragments of CTX or CTX-Fab on the expression of different levels of EGFR in four CRC cell lines showed that the use of CTX-Fab provides targeted L-OH liposomes that provide greater drug delivery and efficacy. It has anti-tumor properties compared to liposomes containing CTX and non-targeted liposomes [92].

Integrinβ6 (ITGβ6) is a protein that is highly expressed in the epithelium of malignant colon cancer cells, but is not normally found in the epithelium of normal cells, so it is related to the progression, metastasis and chemotherapy resistance of colon cancer [93]. The effect of PEGylated immunoliposomes containing 5-FU and also targeted with monoclonal antibody E7P6 which recognizes the extracellular domain of ITGβ6 showed, that immunoliposomes targeted for ITGβ6 have high intracellular uptake, and the growth of HT-29 and SW480b6 cell lines (colon cancer cell lines) almost to more than 90%. Additionally, cell apoptosis was increased approximately 1.5-fold by targeted immunoliposomes loaded with 5-FU. Therefore, targeted immunoliposomes against ITGβ6 are very efficient for targeted drug delivery in colon cancer and can be considered as a new and promising strategy for clinical treatment [94].

Frizzled proteins (FZDs) are cell surface receptors that are highly expressed in CRC cells [95]. Several studies have proven that FZDs plays an important role in various functions of cancer cells, including increasing their proliferation, migration, invasion, angiogenesis, and chemical resistance [96–100]. Among these FZD proteins, FZD10 is used as one of the promising receptors for the development of targeted CRC therapy due to the fact that it is expressed only in cancer cells and not in adjacent normal cells [101]. Scavo et al evaluated the anticancer effect of immunoliposomes loaded with 5-FU, conjugated with an antibody against FZD10 (anti-FZD10/5-FU/LPs), on two different CRC cell lines. The results of their work showed that the cytotoxic activity of 5-FU in the case of anti-FZD10/5-FU/LPs increases even at its lowest concentration [102].

MCC-465 is an immunoliposome-encapsulated doxorubicin. Pegylated liposome of doxorubicin (PLD) and non-targeted MCC-465 have no significant antitumor activity against colon cancer cell lines, however, when conjugated with monoclonal antibody, GAH, show better antitumor effects against colon cancer cell lines [103].

Aptamer functionalized nanoliposomes

Aptamers are single-stranded oligonucleotides that are identified through the systematic evolution of ligands by exponential enrichment (SELEX) process, and thus selectively bind to target molecules [104]. Preparation of aptamers is a very simple process [105]. They cause not immunogenicity in the human body and can be gradually decomposed and eliminated by nucleases, thus causing minimal toxicity [106].

Recently, among other methods of applying liposomes and targeted drug delivery systems, aptamers are widely used as effective targeting ligands [107].

Liposomes containing 5-FU and targeting with anti-nucleolin aptamer (AS1411) as ligand and coated with alginate/chitosan PEC have been investigated as a promising method for the treatment of colon cancer. Based on MTT cytotoxicity results on HT-29 cells, liposomes conjugated with aptamer significantly increased cell death compared to liposomes without aptamer and free drug. These nanoliposomal carriers are suitable for drug delivery to the target tissue and have a positive effect on the colon cancer treatment process [108].

Anti-nucleolin aptamer AS1411 (Apt-Lip-GEF) is widely used to target liposomes [109,110]. Nanoliposomes carrying gefitinib (GEF) targeted with anti-nucleolin aptamer AS1411 (Apt-Lip-) showed higher antiproliferative activity in CT26 tumor cells than HEK293 cells, and it was also observed in the colorectal tumor model that this compound was effectively compared to the form the release of GEF reduces the tumor cells growth [111].

Nanoparticles based on cationic liposome loaded with MiR-139-5P and surface modified with anti-epithelial cell adhesion molecule (EPCAM) aptamer are used for targeted treatment of CRC. These targeted nanoparticles inhibit the growth of HCT8 cells in vitro and suppress the colorectal tumor model. Therefore, this MANPs carrier can be used as an effective and suitable carrier to deliver the desired therapeutic miRNA to the CRC tumor site [112]. MiR-139-5P inhibits CRC invasion and migration by targeting Notch1 and being downregulated [113].

The results of investigating nanoliposome containing DOX and functionalized with anti-EpCAM aptamer on C26 colon cancer cell line have shown that the performance of this nanoliposome in cancer treatment is promising and also needs further investigation [114].

Magneto liposomes (MLPs)

Depending on the desired goals and specific conditions, researchers have developed new liposomes for smart therapy in the human body that respond to environmental stimuli such as temperature [115], pH [116], light [117], magnetic field [118,119], etc. they answer These specific environmental stimuli are used as the driving force for drug release based on the interaction between stimuli and liposomes [120]. Among these stimuli, magnetic stimulation has become one of the most potential strategies as release and targeting stimuli [121].

MLPs have many advantages in cancer treatment and diagnosis, including the delivery of antitumor drugs, hyperthermia therapy, diagnosis using imaging techniques, and even cell migration [122].

The MTT assay of magnetic liposomes loaded with DOX showed that these drug carriers have no cytotoxicity to L-929 cells, so this combination has excellent biocompatibility and causes a higher percentage of cell death on CT-26 and has a better effect compared to hyperthermia or chemotherapy alone. Therefore, the synergistic effects between chemotherapy and hyperthermia increase the ability to kill cancer cells [123].

Magnetic nanocarriers containing DOX and targeted with atherosclerotic plaque-specific peptide-1 (AP-1) efficiently bind to colon cancer cells (CT26-IL4Rα) and thereby induce tumor-targeted selection. This combination has great potential for use in the treatment of colon cancer [124].

Apart from the many advantages that MLPs have, biocompatibility and high performance after entering the cell are essential for their successful application [125]. By examining MLPs based on maghemite nanoparticles (γ-Fe2O3) on tumor and non-tumor colon cell lines, it was determined that these MLPs, based on their physical, chemical and biological properties, can be used effectively treat colon cancer [122]. Also, by examining the cytotoxicity of MLPs loaded with 5-FU in colon fibroblast cell lines CCD-18 and human colon cancer T-84, the absence of cytotoxicity was reported in these cells. If 5-FU is placed in the matrix of nanoparticles, more amounts of the drug can be loaded and its release will be more stable. Therefore, it was found that MLPs have important properties, including magnetically targeted delivery, hyperthermia inducibility, high 5-FU loading capacity, and hyperthermia-induced wide drug release, which indicate their potential for combination therapy against colon cancer [126].

pH-responsive liposomes

pH-sensitive liposomes are a type of liposomes that are stable at physiological pH (pH 7.4), but undergo changes in acidic conditions (such as tumor environment) and can release their contents [119]. According to the results obtained from the various reports, these are more efficient in delivering anticancer drugs than conventional or long-circulating liposomes due to their fusion properties [127].

Irinotecan (IRN) is a synthetic derivative of camptothecin that acts as a topoisomerase I inhibitor. IRN is used to treat colon cancer, which also causes serious side effects, such as diarrhea and myelocyte suppression [128]. The results of the investigation of a pH-sensitive folate coating liposome containing IRN in the treatment of colon tumors in a mouse model, showed a pH-dependent method with a long-term and sustained release system, and a high capacity of intracellular drug delivery. Extensive necrosis occurred in the tumor tissue in the areas containing IRN, and better antitumor activity was shown. Thus, this type of colorectal cancer carrier can potentially be an effective alternative to conventional treatment [129].

Release results of liposomal nanoparticles containing pH-sensitive 5-FU (pHLNps-5-FU) showed that this compound has the highest release rate of 5-FU at pH 3.8, almost twice that of pH 7.4. As a result, pHLNp3-5-FU can be a potential candidate for the treatment of colorectal cancer [130].

One of the effective methods for colon tumor treatment is liposomes coated with pH-sensitive polymer and containing biologically active compounds. For example, liposomes loaded with Betulinic acid and coated with pH-sensitive polymer Eudragit S100 (pH-BA-LP) have been shown that significantly inhibit tumor proliferation and cell migration in colorectal cancer. pH-BA-LP increases NK cells and CD3+ cells in tumor tissues, and it was also found that it can exert an antitumor effect by enhancing autoimmunity [131].

The main obstacles related to the targeted release method for colon cancer

Active targeting techniques minimize off-target effects and enable the targeted delivery of therapeutic medicines to CRC cells [132].

Despite the new strategies based on the use of nanoliposomes in the targeted treatment of CRC at different clinical levels, there are still some challenges, such as improving the localization, biodistribution, biocompatibility and efficiency of these nanopharmaceutical systems in vivo, for the accurate diagnosis and treatment of cancer, as well. are left Among the new nanotechnology platforms, liposome-based therapies have emerged as one of the most promising nanotools for the treatment of various tumors, including colorectal cancer [133].

Another important challenge in targeted drug delivery is tumor heterogeneity in different stages of the disease, which can also limit the effectiveness of treatment results. This tumor heterogeneity causes variations in the molecular profile and uneven expression of target receptors in various parts of the colorectal tissue, including the proximal colon, distal colon, and rectum [134].

There are several challenges related to the design of nanocarriers. These challenges include the following two groups: 1) the laboratory procedure used to manufacture nanocarriers, which has a big impact on their physicochemical characteristics as size, shape, type of surface coating, and drug loading capability. 2) difficulties with nanocarriers' in vivo behavior, such as biodistribution, toxicity, anticancer agent release, targeted medication delivery from receptor binding sites, and the makeup of the tumor microenvironment [132].

Another problem is to adjust the surface charge of nanocarriers and their toxicity potential, so the toxicity of nanocarriers is a serious factor that should be given special attention before using them in drug delivery and clinical applications [135].

CONCLUSION

Functionalized liposomes represent a promising advancement in colorectal cancer therapy, offering enhanced drug delivery, tumor specificity, and reduced systemic toxicity. By leveraging surface modifications, targeted ligands, and encapsulation strategies, these nanocarriers improve therapeutic efficacy while minimizing adverse effects, paving the way for more effective and personalized treatment approaches. Further research and clinical validation are essential to optimize their application and realize their full potential in colorectal cancer management. In future studies, it is possible to further investigate the challenges and obstacles in the development of drug delivery based on nanoliposomes technology in the treatment of colon cancer.

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