Nanotechnology in Colorectal Cancer for Precision Diagnosis and Therapy

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Colorectal cancer (CRC) is the third most frequently occurring tumor in the human population. CRCs are usually adenocarcinomatous and originate as a polyp on the inner wall of the colon or rectum which may become malignant in the due course of time. Although the therapeutic options of CRC are limited, the early diagnosis of CRC may play an important role in preventive and therapeutic interventions to decrease the mortality rate. The CRC-affected tissues exhibit several molecular markers that may be exploited as the novel strategy to develop newer approaches for the treatment of the disease.

Nanotechnology consists of a wide array of innovative and astonishing nanomaterials with both diagnostics and therapeutic potential. Several nanomaterials and nano formulations such as Carbon nanotubes, Dendrimer, Liposomes, Silica Nanoparticles, Gold nanoparticles, Metal-organic frameworks, Core-shell polymeric nano-formulations, Nano-emulsion System, etc can be used to targeted anticancer drug delivery and diagnostic purposes in CRC. The light-sensitive photosensitizer drugs loaded gold and silica nanoparticles can be used to diagnose as well as the killing of CRC cells by the targeted delivery of anticancer drugs to cancer cells. This review is focused on the recent advancement of nanotechnology in the diagnosis and treatment of CRC.

Keywords: colorectal cancer, nanotechnology, detection, treatment, targeted therapy

INTRODUCTION

Colorectal cancer (CRC) is a severe health problem and has the third-highest occurrence within the cancer-causing conditions that influence the populations of developing and developed countries (da Paz et al., 2012). Among populations of western countries, a major cause of death and morbidity is CRC (Arvelo et al., 2015). Various routine factors and the growing age are the common reason of CRC with only a few cases being the outcome of genetic disorders (Bours et al., 2015; Gulbake et al., 2016). It generally starts in the bowel lining and can extend into the wall of the bowel and beneath muscle layers if not treated properly at the earliest (Datta et al., 2016). In addition to these, there are genetic and environmental factors that can interact in various ways to enhance carcinogenesis (Bours et al., 2015). Regarding the CRC pathogenesis four central theories have been established. In the first theory, epigenetic and genetic variation generate the formation of colon cancer promotes CRC. Second, cancer emerges due to a multistep process at both molecular and morphological levels. The third and crucial molecular step is the loss of genetic stability in cancer formation. Fourth, hereditary
Nanotechnology has opened up a new way to the development of novel and efficiently organized nanomaterials with the capability of enhanced performance in screening, detection, and treatment of CRC cancer along with other types of tumors (Gulbake et al., 2016; Bray et al., 2019). The role of nanotechnology interventions to CRC includes the nanomaterial-based screening of tumors, customization of targeted drug delivery systems, and advanced treatment modalities (Upendra et al., 2016; Minakshi et al., 2017; Minakshi et al., 2018; Minakshi et al., 2020). Currently, nanotechnologies have found worldwide consideration due to their capability to improve existing standards and methods for the screening, diagnosis, and treatment of CRC. The present review has the main emphasis on the discussion of nanotechnology-based precision methods for screening, detection, and treatment of colorectal cancer.

During the preparation of this review, recent and appropriate information was collected using several scientific search engines including PubMed, Medline, Google Scholar. Several research and review articles were collected, thoroughly studied and a comprehensive manuscript is prepared. Under this review article several aspects of colorectal cancer (CRC) including their different clinical stages, recent diagnostic and therapeutic approaches using several nano-formulations such as Quantum dots, Iron oxide, Carbon nanotubes, Liposomes, Silica Nanoparticles, Nanoemulsion, Gold nanoparticles, etc. have been discussed. Apart from the use of individual medicines, the efficacy of combinatorial nanomedicine against CRC has also been explored.

Colorectal Cancer Stages
The survival rate in CRC mainly depends upon the stages of CRC disease and it usually ranges from 90% in the case of localized stage to 10% in the case of patients diagnosed with metastatic cancer. If the stage of diagnosis is earlier, the higher the chance of survival rate (Haggar and Boushey, 2009). The exact stage of the tumor, which explains the level of cancer in a patient’s body, is one of the very significant factors in deciding which therapy is useful and how successful therapy might be (Schroy et al., 2016). Figure 1 describes the various stages of colorectal cancer. Abnormal cells arise from colonic wall mucosa, may become tumors, and divides in stage 0. During stage I, cancer has formed in the colon wall mucosa and emerges into submucosa as well as muscularis propria. Stage II cancer further progresses from muscularis propria into pericolectal tissues (IIA), and then emerges to the visceral peritoneum (IIIB), then directly penetrates into the attached organs (IIC). Stage III cancer emerges into muscularis propria metastases in nearby tissues or 1–3 regional lymph nodes and spreads in submucosa with metastases in 4–6 lymph nodes in IIIB and 7 or more regional lymph nodes (IIIC). Metastasis confines to one organ such as liver, ovary, lung, regional node, etc. in stage IV, and again stage IV cancer is further divided into IV A and IV B stages (Xynos et al., 2013; Lai et al., 2016). Five years survival rate percent researches showed 90% survival in the case of stage 1 CRC and 10% survival in the case of stage IV CRC (Pesta et al., 2016). Physical inactivity, eating more processed meat, long-term smoking, obesity, alcohol addiction, and a diet with fewer vegetables and fruits are the most common lifestyle-related threats and major causes of CRC. Family history is also connected with CRC, a person with chronic inflammatory bowel disease, type 2 diabetes, or genetic disease likely in Lynch syndrome has been linked with augmented risk (Young et al., 2014). Stages 0, I, II, and III may be curable but stage IV CRC is not often curable but it may be managed based on growth and spreading disease (Young et al., 2014; Sun et al., 2016).

Existing Screening Methods for Colorectal Cancer
Various screening methods have been established to screen CRC before symptoms start, when it may be easily treatable. Few of the screening methods that identify polyps and adenomas at an early stage may assist in the detection and early removal of tumor growth which might otherwise lead to further progression of cancers. Hence early detection of colorectal cancer may be another method of cancer prevention. Different tests are prevalent for suitable screening of colorectal cancer (Table 1). Stool tests detect minute quantities of blood that cannot be possibly seen visually from both adenomas and polyp cancers (Imperiale et al., 2004; Burch et al., 2007; Ansa et al., 2018; Qaseem et al., 2019).

In the colonoscopy entire colon and rectum are screened for cancer using a colonoscope, having a flexible tube light with a lens for seeing and a tool for excising the abnormal tissue (Kahi et al., 2016). A complex analysis of six studies showed that screening using colonoscopy reduces the chances of establishment and dying of people from CRC (Brenner et al., 2014). Conversely, the test is costly and unpleasant. Virtual colonoscopy or computed tomographic (CT) colonography and double-contrast barium enema are the optional choices for patients, who cannot go through a routine colonography due to the...
anesthesia risk, which prevents a complete examination. In both the methods, x-rays are used to observe the colon from outside the body (Pickhardt, 2013; Kuipers and Spaander, 2015). The occurrence of colorectal neoplasm was detected using double-contrast barium enema (DBEM) screening in people of Thailand and reported a diagnostic outcome of 0.4% for CRC and 0.7% for advanced adenoma (Lohsiriwat et al., 2013). Insigmoidoscopy test for checking cancer, polyps, and other abnormalities using a flexible tube having light at the end is inserted into the lower colon and rectum (Guo et al., 2015). Many of the clinical trials reported that sigmoidoscopy reduces the chances of establishment and prevents persons from dying from CRC (Atkin et al., 2010; Segnan et al., 2011; Elmunzer et al., 2012; Schoen et al., 2012; Holme Kalager, 2014). All these screening tests for CRC have differed in respect to their preparation requirements, patient expediency, amount of colon and rectum evaluated along with their limitations.

Along with these general tests, the CellSerch® assay (Janssen Diagnostics, LLC, South Raritan, NJ, United States) which is based on circulating tumor cell (CTC) diagnostic technology is used for the diagnosis of meta-static colorectal cancer along with other cancers such as breast and prostate cancers. US FDA cleared circulating tumor cell (CTC) diagnostic technology for metastatic CRC along with other cancers such as prostate and breast cancers (Allen et al., 2014). It gives prediction-related information in metastatic CRC, regardless of the metastatic site. Currently, various new systems such as MagSweeper, Cynvenio, IsoFlux, VerIFAS, AdnaGen, and magnetic sifters have been established to further enhance the identification speed and efficiency (Mostert et al., 2015). Most of the current screening methods are very expensive and not easy at the point of care. Hence, the development of more sensitive, fast, low cost, and specific screening of CRC is very essential.

**Recent Advancements of Nanotechnology in Cancer Theranostics**

Recent development in nano-sciences has allowed fabrication of several nanoparticles (NPs)-based systems for therapeutics and diagnostics. Although the clinical applications of nano-based theranostics are still limited probably due to their complex pharmacokinetics, NPs can improve the knowledge of biochemical and physiological principles of several diseases and their treatments (Siddique and Chow, 2020). NPs have been used in the enhancement of capability of several imaging techniques such as positron emission tomography (PET) by use of radioisotope chelator-free NPs, and iron oxide-based NPs in magnetic resonance imaging (MRI) (Rosado-de-Castro et al., 2018). Similarly, in the optical imaging system, persistent luminescence nanoparticles (PLNPs) have been used as a novel optical nanoprobe to utilize the characteristic long-lasting near-infrared (NIR) luminescence (Lecuyer et al., 2016) which allows the functioning of optical imaging without constant
TABLE 1 | Different methods for CRC screening.

| Method                          | Explanation                                                                 | Advantages                                                                 | Disadvantages                                                                                                                                                                                                 | References                                                                                   |
|--------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Stool tests                    | Stool tests are kits that can detect abnormal blood or DNA markers.          | Colon cleansing is not essential before the sample is taken. No dietary requirements are needed in FIT. Samples can be collected at home. The Stool test is a low-cost method as compared with other bowel tumor-screening methods | Stool test cannot detect nonbleeding cancers                                                                                                                                                              | Brar et al. (2018), Bibbins-Domingo and Grossman (2016), Shapiro et al. (2017), Collins et al. (2005) |
| Colonoscopy                    | It allows visualization of the entire inner lining of the colon and rectum of a person for the detection of the tumor | This method detects all minute polyps along with large polyps and cancers, subsequently reducing the risk of development and death due to CRC. | It requires sedation It may lead to serious bleeding or a tear of the intestinal wall                                                                                                                                 | Brenner et al. (2014), Kahi et al. (2016)                                                      |
| CT colonography                | CT scanner is used in this technique for capturing two- and three-dimensional images of the entire colon. These images allow a radiologist to screen if cancers or polyps are present | Sedation is not required in this method. It does not require sedation. CT colonography is noninvasive and the entire colon can be examined for CRC. | Colon cleansing is not essential before the test. It may screen other abnormalities along with colon cancer and polyp                                                                                                                                 | Ouyang et al. (2005), Kuipers and Spaander (2015), Pickhardt (2013)                           |
| Sigmoidoscopy                  | It allows the physician to directly examine the lining of the rectum and the lower section of the colon | It detects the cancers and polyps in the descending rectum and colon with a high degree of accuracy | It cannot screen the cancers or polyps present on the right side                                                                                                                                                                                                   | Holme and Kalager (2014), Elmunzer et al. (2012)                                              |
| Double-contrast barium enema   | In this method, barium sulphate is introduced into the rectum with air via a flexible tube and x-ray images are then captured | This test mainly allows the examination of the whole colon and the rectum. Sedation is not required and complications are rare | Colon cleansing is very necessary for this method; otherwise, it will give false-positive results                                                                                                                                                             | Lohsiriwat et al. (2013)                                                                     |

excitation and autofluorescence (Liu et al., 2019). The NPs act as excellent contrast agents because of their small size, high sensitivity, and specific chemical composition. Similarly, NPs are also widely used for the therapeutic purpose of cancer. In therapeutic use, it improves the accumulation and release of pharmacologically active compounds at the pathological site leading to enhanced therapeutic efficacy and reduced toxic side effects. Moreover, recently developed NPs have the capability for integrating therapeutic and diagnostic agents into a single NP that can be easily used for theranostic purposes (Siddique and Chow, 2020). Studies have also revealed that theranostic NPs may have the capability for future use as personalized nanomedicine-based therapies (Baetke et al., 2015). In the coming future, multifunctional NPs can be designed by using various functional materials leading to the development of simultaneous diagnosis and therapeutics known as theranostics (Kim et al., 2017).

Existing Treatment Methods for Colorectal Cancer

At present, various treatment methods with their merits and demerits are available (Table 2). The most general method for the treatment of CRC is surgery and most commonly known as surgical resection. Surgery is the most common treatment for CRC and is often called surgical resection. It is a significant first line of the protective system against any particularly well-defined tumor or any cancer (Lee, 2009; Chu, 2012). During surgical treatment in CRC, a portion of the healthy rectum or colon will also be excised. In addition to the surgical resection, other surgical options for CRC comprise colostomy for rectal cancer, radiofrequency ablation, laparoscopic surgery, etc. Radiation therapy is most widely used for the treatment of rectal cancer for the reason that this cancer tends to continue to the site where it grows initially. Radiation therapy is given to the patient in a scheduled manner comprising a defined number of treatments at defined time intervals (Joye and Haustermans, 2014). Stomach upset, mild skin infections, fatigue, etc. are the main side effects of radiation therapy. In the chemotherapy treatment method, drugs are used to deactivate cancer cells, generally by stopping the activity of tumor cells to grow and multiply. At present various approved drugs are used for the treatment of CRC (Jayakumar et al., 2015). Vomiting, nausea, neuropathy, mouth sores, and diarrhea are the main causes of chemotherapy. Treatment that targets the defined genes of tumor cells or defined tissue environment is known as targeted therapy. Such type of treatment inhibits the growth and division of the cancerous cells although limiting the harm to normal cells. To find out an efficient and reliable treatment of CRC, new methods should be established for effective detection of proteins, genes, and additional factors in a patient’s cancer. For CRC treatment epidermal growth factor receptor (EGFR) inhibitor therapy, anti-angiogenesis therapy is an option. The most
TABLE 2 | Various existing methods with merits and demerits for the treatment of CRC.

| Method         | Description                                                                 | Advantages                                                                                      | Disadvantages                                                                 | References                     |
|---------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|
| Surgery       | It is a very common method for the treatment of CRC and generally known surgical resection. It includes colostomy for renal cancer, laparoscopic surgery, and radiofrequency ablation | Surgical excision of the cancer is one of the important first lines of treatment against CRC, specifically when cancer is well defined | Surgery has been identified to enhance the risk of death due to metastasis in confined cancer patients by mechanical disruption of cancer integrity. Tenderness and pain in the part of operation are other disadvantages | Chu (2012), Lee (2009)        |
| Radiation therapy | It uses high-energy X-rays to destroy tumor cells | For CRC, it is used before surgery and known as neo adjuvant therapy, to shrink cancer so that it can be easily removed. It may also be used after surgery for the death of remaining tumor cells. Both the methods have worked for the treatment of disease. It may also be used after surgery to destroy any remaining cancer cells | It may also damage the healthy cells and also cause DNA damage, which is very harmful. It may cause damage to the healthy cells | Joye and Haustermans (2014) |
| Chemotherapy | It uses drugs to destroy the tumor cells, which usually block the capability of CRC cells to grow and multiply | It is a well-established treatment modality                                                   | It may cause nausea, vomiting, mouth sores, or neuropathy                  | Jayakumar et al. (2015)        |
| Targeted therapy | It is a treatment that targets the tumor-specific gene or tissue environment that contributes cancer growth and survival | It stops the growth and dividing of cancer cells while limiting damage to uninfected cells     | Targeted treatments have side effects such as rash on the upper body and face | Xie et al. (2020)              |
| Immunotherapy | Immunotherapies used for the treatment of CRC include monoclonal antibodies, cancer vaccines, immune modulators, adjuvants, and cytokines | This system uses body’s self-immune system and fewer side effects and can provide long-term survival by 30% | Some of the immunotherapy drugs have high cost, severe side effects, and possible short-term efficacy | Johdi and Sukor (2020)        |

common side effects of the targeted therapy include rashes on upper body parts and the face.

During the treatment of CRC, poor drug response to chemotherapy is frequently reported which might be primarily due to the appearance of the multidrugresistance (MDR) in tumor cells (Wu et al., 2018). Several studies have shown the mechanism of drug resistance in colorectal cancer cells. Some of the studies revealed that the effect of cetuximab and panitumumab can be inactivated by the mutations in PIK3CA or BRAF gene, or due to gene amplification of MET, KRAS, and ERBB2 resulting in the prevention of EGFR signaling (Dienstmann et al., 2015). The overexpression of dihydropyrimidine dehydrogenase (DPD) gene may lead to resistance against 5-FU, because DPD may convert the 5-FU into the inactive metabolite (DeNardo and DeNardo, 2012). In addition, decreased expression of RFC-1 (reduced folate transporter 1) and PCFT (proton-coupled folate transporter) may block the LV (Odin et al., 2015). Similarly, altered levels of metallothioneins and glutathione reductase (GR) may affect the response of oxaliplatin (OXA). Moreover, the increased activity of UDP-glucuronosyltransferases (UGT) or induced DNA damage repair mechanism such as TDP1 (tyrosyl-DNA phosphodiesterase 1) may limit the effect of IRI (Jensen et al., 2015). To overcome the multidrug resistance, nanomedicine appears as a recent strategy to enhance the prognosis in CRC patients.

Applications of Nanotechnology in Screening, Detection, and Treatment of Colorectal Cancer

More than four decades ago application of nanotechnology foundations is laid down for their diagnostic and therapeutic uses in a very précised manner (Fortina et al., 2007). Nanotechnology is a most important branch of research which plays a very important role in screening, detection, and treatment of day-by-day increasing diseases (Upendra et al., 2016). It plays a major role in the discovery and delivery of drugs with specific action at a specific target site with an enhanced success rate. The development of these nano-formulations includes liposomes, quantum dots, silica NPs, gold NPs, liposomes, dendrimers, nano-emulsions as a coating material in imaging at pathological sites, and nano-drug delivery (Bose et al., 2015; Yallapu et al., 2015).

Various important nanotechnological applications have been verified in cancer biology, comprising early screening and detection of cancers and establishment of new treatment approaches that cannot be gained using the existing conventional methods (Laroui et al., 2013). In de facto, in certain tumors, nano-sized particles of different shapes and compositions have emerged out as important and promising novel tools for colorectal cancer staging, diagnosis, and therapeutics (Figure 2) (Dong et al., 2016). Early screening and detection of CRC is the main solution for impediments and it can impact the long-lasting survival of CRC patients. Early detection of CRC is the key, and it can impact the long-term survival of patients with CRC. In this review, we discuss the current achievements of NPs that provide a new way for early screening and flourishing treatment of CRC.

Quantum Dots

Quantum dots (QDs) are semiconductor nanocrystals which fluoresce with light excitation and have special optical features, comprising high brightness, the ability to emit fluorescence at
varying wavelengths, and resistance to photo-bleaching. Owing to QDs chemical and optical advantages, QD-based nanotechnology is acting as a promising platform for studying various tumors including the CRC (Fang et al., 2012; Pericleou et al., 2012; Zeng et al., 2015). QD-based immune histochemistry (QD-IHC) has been used for qualitatively analyzing the expression of large external antigens from CRC tissue samples and compared with conventional-IHC (Wang et al., 2016), QD-IHC offered various detectable advantages for quantification of protein marker. These showed simpler operation, higher sensitivity, less human interference, and better capability for concurrent multifactor analysis; would produce more accurate clinical detections. Therefore, QD-IHC is a better option for conventional IHC in therapeutic applications. QD-based immune cytochemistry using QD-probes studies mainly focuses on marker identification in tissue sections, IHC combined with imaging quantitative analysis for screening of large external antigen in living cells showed results that were the same as obtained using flow cytometry and expending the applications of QD-probes for clinical applications (Wang et al., 2016). In another study, a sensitive method was developed to identify Aldo-keto reductase family 1 member B10 (AKR1B10) in the serum that acts as a therapeutic target and prognostic predictor for CRC using QDs. The QDs possess stability against photo bleaching along with size-controlled luminescence activity that makes QDs a suitable agent for photoelectrochemical-based tumor marker detection from biological samples. However, QDs are still not used for the detection of AKR1B10 from serum samples (Wang et al., 2015; Liu et al., 2021). This technique played a great role in the early detection of CRC with high specificity and sensitivity.

A highly sensitive and specific technology was developed, which enables concurrent detection of biochemical fluorescence and morphological changes during CRC progression and development using optical coherence tomography or laser-induced tomography that allows nondestructive internal visualization of CRC (Carbary-Ganz et al., 2015). A probe QDot655 specific to vascular endothelial growth factor receptor 2 (QD655-EGFR2) restricted to the colon used in carcinogen-treated mice and provides significantly high contrast between infected and healthy tissues with specificity and sensitivity ex-vivo (Carbary-Ganz et al., 2015). These probes act for in vivo magnetic resonance imaging (MRI) and further biopsy of CRC, an exceptional cell-specific, paramagnetic double-signal fluorescent molecular multipurpose nanoprobe (GdDTPA-BSA@QDs-PCAb) was designed using surface engineering of QDs with DTPA-BSA-Gd3+ large molecular complex by ultrasonic conditions. These nanoprobe act as promising tools for use in contrast-enhanced

FIGURE 2 | Schematic explanation role of nanotechnology in CRC. (A) NPs routes for administration, (B) various kinds of polymer NPs and metallic along with necessary parameters for use in CRC therapy cancer therapy (C) screening and detecting the tumor respectability using multimodal imaging and involvement of increased permeability and retention effect on antitumor drug synthesis for CRC targeting therapy.
MRI diagnosis of CRC and have no cytotoxic effects in MTT assay (Xing et al., 2015). QDs-bevacizumab nanoprobe has been successfully used for targeted CRC detection in both in-vitro and in-vivo systems. During detection, they enhanced the tumor-specific signal after subsequent injection of the QDs and act as a significant achievement in VEGF-directed noninvasive imaging systems during clinical practices (Gazouli et al., 2014).

Under defined conditions subtractive Cell-SELEX technology is used for the production of a panel of seven aptamers (Apts) that precisely attach metastatic CRC cells (LoVo) along with other metastatic tumor cells with great affinity, and hence provides a broad spectrum specific detection of metastatic tumor cells (Li et al., 2014b). This research showed that Apts selected from a single Cell-SELEX can alone act as functionalized for several purposes based on target biochemical properties, thereby increasing the applications of the Cell-SEARCH approach. This receptor-specific Apt W14 was used as the targeted carrier for doxorubicin-specific delivery to defined cells to reduce the toxicity of this drug (Li et al., 2014b).

QDs conjugated with non-membrane receptor binding Apt W3 were used as a molecular probe for specified imaging of metastatic tumor-bearing sections, metastatic tumor cell lines, and formalin-fixed paraffin-embedded tissues from the CRC persons (Li et al., 2014). Hence QDs are great technological modalities in progress that can reform the CRC treatment and diagnosis.

**IRON OXIDENANO-FORMULATIONS**

Iron oxide NPs have the two-fold capability to work as both photo-thermal and magnetic agents for human applications as MRI agents. They also have brilliant biodegradability in vivo and after dissolution, iron ions can be adjusted by the body by a highly regulated physiological phenomenon (Espinosa et al., 2016). A smart multi functional magnetic nano vehicles encapsulating an antibody targeting peptide API (MPVA API), which are consistent in size and also water soluble, anti-cancerous drug has been developed (Kuo and Liu, 2016). These nano-vehicles are easily dispersed in aqueous solutions and exhibit no cytotoxic effects in L929 fibroblasts, and showed their capability for therapeutic applications (Kuo and Liu, 2016). A CRC cell (CT26-IL4R) trial discovered that the MPVA-API showed outstanding selectivity and targeting. A steady storage test revealed no leakage of encapsulated drugs without the stimulus of the magnetic field. In disparity, nano-vehicles loaded with doxorubicin burst upon treatment of high frequency of magnetic field, which is fast, accurate, and controlled release. Furthermore, in vivo investigations recognized that magnetic nano-vehicles exhibited obvious chemotherapeutic and thermotherapeutic effects. Hence, smart magnetic nano-vehicles e.g. MPVA-API have the noteworthy capability for specified doses and precise controlled release in antitumor applications (Kuo and Liu, 2016).

The usefulness of polylactide-co-glycolic acid (PLGA) nanoparticle as a5-fluorouracil (5-FU) vehicles with or without an iron oxide and hyperthermia at DNA damage point in an HT-29 colon tumor cell line spheroid culture model by alkaline comet assay (Eismaelbeygi et al., 2015) and found that less DNA damage in case 5-Fu loaded nanoparticles as compared with hyperthermia. Hence hyperthermia is a damaging agent and NPs are an efficient drug delivery system to CRC. The iron oxide NPs enhanced the effect of hyperthermia and could be extremely beneficial in the diagnosis of CRC (Eismaelbeygi et al., 2015).

The paclitaxel (PTX), as well as super-paramagnetic iron oxide (SPIO), is encapsulated inside the core of PEAL, Ca micelles and studied for significant tumor therapy (Feng et al., 2014). The drug release in this research showed that PTX in the micelles was released with a lower rate at neutral pH and a faster rate at pH 5.0. Cell culture studies also showed that PTX-SPIO-PEALCa was successfully absorbed by the CRCLoVo cells and PTX was likely internalized by lysosomal cells. Additionally, successful inhibition of CRC LoVo cell growth was verified. Hence, micelles play a great role in MRI visible drug release methods for CRC treatment (Feng et al., 2014).

The lectin-Fe2O3 @AuNPs are synthesized by joining lectins on the Fe2O3@AuNPs via bifunctional polyethylene glycol (PEG) NHS ester disulfide (PEG-S-S-Peg-NHS) linkers. Both in vitro and in vivo studies are done for checking the activity of lectins- Fe2O3@AuNPs and found that it could be useful for dual-mode MRI and X-ray CT imaging of CRC. Hence results obtained proposed that lectins could be applicable as cancer-targeting ligands in nano-formulations based on contrast agents (He et al., 2014).

**Poly Lactic-co-Glycolic Acid Nanoparticles**

Eco-friendly Poly lactic-co-glycolic acid (PLGA) NPs have been used as carriers for proteins, peptides, vaccines, drugs, and nucleotides. These can help in shielding drug moieties from breakdown and subsequently ensure the effective release of drugs (Sah et al., 2013) and are extensively studied for their potential use in tumor therapy, specifically for CRC. Using the emulsion-solvent evaporation method curcumin-loaded PGLA NPs (C-PNPs) are successfully synthesized for colon delivery (Akl et al., 2016). C-PNPs exhibit significantly higher cellular uptake in HT-29 cells in comparison with pure curcumin solution due to their sustained release, greater colloidal stability in gastrointestinal fluids, and smaller size. Therefore, C-PNPs have great potential as an early platform for the further establishment of a sufficient oral targeted drug system to the colon, mainly if it is additionally functionalized with a specific targeting ligand (Akl et al., 2016).

Scientists also prepared chitosan polymeric NPS using the solvent extraction emulsification technique, with different ratios of polymer, and showed potential application in the successful delivery of active pharmaceutical components to the CRCs (Tummala et al., 2015). Total health center complex N-38 is an effective treatment against many cancers but the delivery system is not easy due to its low solubility. SN-38encapsulated poly(D,L-lactide-co-glycolide)NPs were prepared by the spontaneous emulsification solvent diffusion method to improve its solubility, stability, and cellular uptake (Essa et al., 2015). To study cellular uptake and cytotoxicity of...
SN-38 encapsulated NPs, the colorectal adenocarcinoma cell line-205 (COLO-205) was used and found considerably reduced cell proliferation and death. Hence, SN-38 loaded NPs are potentially essential drug delivery systems for the treatment of CRC (Essa et al., 2015).

Carbon Nanotubes
Carbon nanotubes (CNTs), allotropes of carbon cylindrical in shape, have rolled graphene sheets with a diameter of fewer than 1 μm and a few nanometers in length (Rastogi et al., 2014). Owing to CNT chemical and physical properties such as high surface area, needle-like structure, heat conductivity, and chemical stability enable its potential uses in several fields such as immunotherapy, diagnosis, gene therapy, and a carrier in the drug delivery system (Hampel et al., 2008).

Various researches showed that several strategies have been developed in which CNTs have been used for carrying antitumor drugs. For the delivery of paclitaxel in Caco-2 cells single-walled carbon nanotubes conjugated with a synthetic polyampholyte were used. Paclitaxel-SWCNT-treated Caco-2 and HT-29 cells showed greater anticancer effects when compared with alone paclitaxel (Lee and Geckeler, 2012; Wu et al., 2015). The same types of results have been found in Eudragit®-irinotecan loaded CNTs (Zhou et al., 2014). Oxaliplatin and mitomycin C-coated CNTs, induced by infrared light rays in colon cell lines, found considerably higher drug delivery and localization in cancer using thermal treatment of cell membrane (Levi-Polyachenko et al., 2009). One study revealed that SWCNTs modified with TRAIL (a ligand that binds to specific receptors and causes apoptosis process in cancer) increased the cell death 10 times in comparison with alone delivery of TRAIL in carcinoma cell lines (Zakaria et al., 2015).

Dendrimer
They are three-dimensional macromolecular structures. They possess central core molecules surrounded by consecutive layers. The dendrimer exhibit a high degree of molecular consistency along with shaping characteristics, fine molecular weight distribution, and multivalency. The specific physicochemical properties along with biodegradable backbones facilitate several applications of dendrimer in nanopharmaceuticals development (Abbasi et al., 2014; Huang et al., 2015a; Wu et al., 2015). Some of the studies revealed that dual antibody conjugates can provide advantages of capturing circulating tumor cells (CTCs) in contrast to single-antibody counterparts (Xie et al., 2015). The study also revealed that the surface-active dendrimers can be successively shielded with two antibodies against the human colorectal CTCs surface biomarkers Slex and EpCAM. Dual antibody-coated dendrimers exhibit improved specificity in the detection of CTCs in both patient blood and nudemice in comparison to single antibody-coated dendrimers. Moreover, dual antibody-coated conjugates may downregulate the captured CTCs. Thus, theoretically, it can be assumed that biocompatible two antibodies conjugated to a nanomaterial may have the capability to capture and downregulate the CTCs that can be used as a new strategy for the prevention of metastasis (Xie et al., 2015).

Similarly in another study, HT29 cells (colon cancer cells) were successfully captured by employing Sialyl Lewis X antibodies (aSlex)-conjugated Poly(amideamine) dendrimers (Xie et al., 2015b). The colon cancer cells were characterized using aSlex-coated dendrimer conjugate and examined by flow cytometry and microscopy. The study revealed that conjugate possessed an enhanced capacity to capture HT29 cells in a concentration-dependent manner. The aSlex-coated dendrimer conjugate showed optimum potential in capturing and detaining CTCs in the blood (Xie et al., 2015b). The maximum capture competence was obtained within 1 h of exposure.

Apart from the diagnostic value, dendrimer may also be used for therapeutic purposes. In one of the studies, telodendrimers were suspended with linear PEG-blocking dendritic oligomer of vitamin E and cholic acid, designed for the delivery of gambogic acid (GA) and other natural anticancer compounds were used (Huang et al., 2015a). The study revealed that high GA-loading ability and subsequent drug release were obtained with these optimized telodendrimers. Moreover, these novel nano-formulations of GA were found to exhibit similar in vitro cytotoxic activity as the free drug against the colon cancer cells (Huang et al., 2015a).

Later, a new platform for drug delivery was developed with the reengineering of nano-scale dendrimers for the capture of CTCs in the blood (Xie et al., 2014). These nano-scale dendrimers were lodged with dual antibodies to aim the two surface biomarkers specific to colorectal CTCs with the capacity to particularly recognize and bind CTCs and downregulate the activity of CTCs by arresting cell division in the S phase. Moreover, dual-antibody conjugates revealed enhanced specificity and competence in controlling the CTCs in vitro as well as in vivo in comparison with their single-antibody counterparts. Thus, these studies revealed an innovative way of effective prevention of metastatic initiation by binding and restraining CTCs that were usually achieved by the traditional cytotoxic killing of cancer cells (Xie et al., 2014).

Liposomes
Chemically, liposomes are lipid-based vesicles that act as artificial carriers with a small and spherical aqueous core that are nontoxic (Silva et al., 2011). Owing to their smaller size, ability to incorporate various substances, and phospholipid bilayer in nature, they are considered the most effective drug delivery systems into cells with decreased side effects (Suntres, 2011; Patil and Jadhav, 2014). In 1961, liposome was described as the first nanoparticle platform for drug delivery in clinical medicine (Bangham et al., 1965). It is one of the most used for drug delivery systems especially for peptides, nucleic acids, and proteins as nano-liposomes (Abreu et al., 2011).

Liposomes can be divided into three categories viz., long-circulating liposomes, active targeting liposomes, and liposomes with special properties that include thermo-sensitive, pH-sensitive, magnetic, and positive (Akbarzadeh et al., 2013; Nag
and Awasthi, 2013; Noble et al., 2014). For clinical practice, liposome formulation carrying the drug such as daunorubicin (DaunoXome®) and Doxorubicin (Doxil®) has been approved by FDA in the mid-1990s (Barenholz, 2012). The study revealed that Doxil is approximately 100 nm in size and has much less gastrointestinal and cardiac toxicity (Rivera, 2003). Later, FDA has approved Marqibo® as a liposomal drug that is a cell cycle-dependent anticancer drug (Lammers et al., 2008; Lam and Ho, 2009; Allen and Cullis, 2013).

Drug resistance is a common problem in anticancer therapy. Several efforts have been made to fight drug resistance obtained when administrating liposome-based drugs such as Doxorubicin. In one of the studies during the administration of high dosages of an antitumor drug such as Doxorubicin (DOX) an aptamer-based drug delivery system assists in delivering high dosages of the active drug toward the target cancer cells (Li et al., 2014). Similarly, Thermodox® (thermo-sensitive liposome Doxorubicin) is used for colorectal liver metastases treatment in combination with radiofrequency ablation (Figure 3). In this treatment procedure, liposomal Doxorubicin formulation releases the active drug in response to the mild hyperthermic signal (Stang et al., 2012). The study revealed that Thermodox can effectively deliver twenty-five-fold more Doxorubicin to tumor cells than ordinary intravenous. Doxorubicin dose is five fold more effective than to standard liposomal formulations in animal models.

**Silica Nanoparticles**

Silica materials are broadly categorized as xerogels and mesoporous silica nanoparticles (MSN). Silica nanoparticles possess numerous advantages such as a highly porous framework, biocompatibility, and easy functionalization (Amato, 2010; Wei et al., 2010). MSNs consist of a bee’s-hive-like porous structure that assists in packing large amounts of bioactive molecules. Moreover, MSN also possesses important features such as adjustable size of cavities in the range of 50–300 and 2–6 nm respectively (Stang et al., 2012), very low level of toxicity, easy endocytosis, the ability of large quantity of medicine loading along with resistance to heat and pH (Bharti et al., 2015). For more precise drug delivery and action to cancer cells, amesoporous silica nanoparticle-protamine hybrid system (MSN-PRM) was also used which can selectively release the drugs in the proximity of cancer cells and get activated with specific enzymes to trigger the anticancer activity (Radhakrishnan et al., 2013). In another study conjugated the hyaluronic acid to MSNs was done as HA-MSN and it was proved that the amount of DOX loading into HA-MSNs increases significantly than bare MSNs (Yu et al., 2013). Moreover, the cellular uptake of DOX-HA-MSNs conjugate was also increased which was reflected by
the enhanced cytotoxicity to the human colon carcinoma cell line (HCT-116 cell line) (Gidding et al., 1999). Similarly, in another study, MSNs were functionalized with polyethyleneimine-polyethylene glycol (PEI-PEG) and polyethylene glycol (PEG) which was resulted in an increased amount of loading of Epirubicin hydrochloride (EPI) and exhibited improved antitumor activity (Hanafi-Bojd et al., 2015). Silica nanoparticles can also be used along with photosensitizer chemicals to kill the CRC cells. Researchers at the University of Buffalo and Roswell Park Cancer Institute have developed a silica-based nano shell that encases photosensitizer molecules. The nano shells are designed in such a way that they are easily taken up by the tumor cells and, upon exposure of cells to light the photosensitizers are activated and release the reactive oxygen molecules to kill the cancer cells (Advances in Colorectal Cancer Research, 2016). Currently, this technique is under clinical trials. Moreover, the second-generation photosensitizer-loaded nano shell is also in the developing phase where tumor-targeting and imaging agents will be incorporated to deliver at the tumor-specific sites that will assist in image-guided therapy for cancer (Advances in Colorectal Cancer Research, 2016). Thus, nanoparticles may also be allowed for molecular imaging of cancer cells followed by earlier diagnosis and targeted drug delivery.

**Nano-Emulsion System**

It is a transparent solution consisting of oil, water, and surfactant. It possessed thermodynamically uniform and stable physical properties. Nano-emulsions possess specific features such as facilitation of transferring drugs and drug combinations protection against external factors such as heat and pH (Bilensoy et al., 2009), lower toxicity, higher stability, and better efficiency along with the dissolution of nonpolar compounds (Patil and Jadhav, 2014). In one of the studies, the synergistic effect of gold nanoparticles (AuNPs) and lycopene (LP) on the HT-29 colon cancer cell line was studied. The experiment was designed in such a way that the first case consisted of a system of nano-emulsion having Tween 80 as emulsifiers along with LP and AuNPs and the second system consisted of a mixture of AuNPs and LP without any emulsion. The results revealed that the nano-emulsion system consists of dosages of LP and AuNPs as 250 and 125 times respectively lesser in comparison with their mixture mode, but the apoptosis induced by nano-emulsion was found three times higher than the mixture model (Chen et al., 2015; Huang et al., 2015b). Similarly, in another study, an ion-pairing complex of Oxaliplatin (OXA) with a deoxycholic acid derivative (Na-deoxycholy-1-lysylmethylester, DCK) (OXA/DCK) was prepared for oral delivery of OXA and 5-fluorouracil (5-FU) to the colorectal cancer patient. The study revealed that in CT26 tumor-bearing mice, the tumor was inhibited by 73.9, 48.5, and 38.1% in comparison with tumor volumes in the control group and the oral OXA and 5-FU groups, respectively, which indicated the application of OXA/DCK and 5-FU as an oral combination therapy for CRC (Pangeni et al., 2016).

**Core-Shell Polymeric Nano-Formulations**

Nowadays there is an increasing interest in the manufacturing of core-shell nanoparticles with two or more materials (Zhou et al., 1994; Kumar et al., 2020). Such nanomaterials possess a core-shell structure where the outer surface atoms differ from those of the interior core atoms. The surface chemistry of core-shell type nanomaterials is usually characterized by multiple techniques such as secondary ion mass spectroscopy and X-rayphotollectron spectroscopy (Simonet and Valcárcel, 2009; Zielinska et al., 2020). In core-shell nanoparticles combinations of different materials such as organic/organic, organic/inorganic, inorganic/inorganic can be used (Ghosh and Paria, 2012) with specific purposes including increasing the stability, functionality, and dispersibility of the core particles. Moreover, specifically designed core-shell particles may also provide a controlled release of the core and therefore, allow the reduced consumption of precious materials (Kalele et al., 2006). The core/shell particles possess specific applications in the biomedical field such as bio-imaging for cell labeling, controlled drug delivery, and tissue engineering practices (Bai et al., 2006; Sounderya and Zhang, 2008; Stanciu et al., 2009). Some other types of nanomaterial such as *Lactobacillus reuteri* biofilm coated with zinc gallogermanate (ZGGO) mesoporous silica may also be used as a bacterial inspired bio-nanoparticle system (ZGGO@SiO2@LRM). This nano system was found possessed with the unique property of targeted delivery of 5-FU to the tumor of colorectum area. Further study revealed that in comparison with 5-FU alone, the ZGGO@SiO2@LRM nanosystem decreased the tumor number per mouse to one-half during *in-vivo* chemotherapy. Additionally, this system was found capable of tolerating the digestion of gastric acid and thus may support the targeted drug delivery of oral medicines into the colorectum region. Moreover, ZGGO also assists in the hassle-free photo luminescence (PL) bioimaging where LRM coating accurately targets the tumor of the colorectum region (Wang et al., 2019). Similarly, other silica-based core-shell nanoparticles such as mesoporous silica nanoparticles coated with PEG or hydrochloride dopamine along with epithelial cell adhesion molecule aptamer (MSN@PDA-PEGApt) were also used for targeted delivery of maytansine derivative (DM1) with 94% drug loading efficiency to treat colorectal cancer in mice (Li et al., 2017).

**Metal-Organic Frameworks**

Metal-organic frameworks (MOFs) are manufactured using metal nodes and organic linkers (Jiao et al., 2018). The MOFs-based biosensors have currently been applied for the detection of various targets, such as heavy metal ions (Zhang et al., 2017), hazard molecules (Liu et al., 2017), and living cancer cells (Gu et al., 2019). Most of the biosensors have been designed either for the detection of cancer markers (Jayanthi et al., 2017; Huang et al., 2018) or small biomolecules released from cancer cells for the early diagnosis such as the PBA(Ni-Fe):MoS2 hollow nanocubes for hydrogen peroxide detection (Zhang et al., 2019) and 3D bimetallic Au/Pt nanoflowers for the identification of cellular ATP secretion (Zhu et al., 2020).

Later on, integrated MOFs with electrochemically active other components have also become an efficient strategy to exploit the
MOF-based cytosensors. In one such study bimetallic TbFe-MOFs have been developed using MOF on MOF strategy and was used for the anchoring of carbohydrate antigen 125 aptamers for identification of living Michigan Cancer Foundation-7 (MCF-7) cells (Li et al., 2020). Similarly, the bimetallic ZrHf-MOF doped with carbon dots was used in the identification of human epidermal growth factor receptor-2 (HER2) and HER2 expressed in MCF-7 cells (Gu et al., 2019). In another study, multicomponent Zr-MOFs were used for the detection of MCF-7 cells with an extremely low limit of detection as 31 cell ml⁻¹ (Li et al., 2020).

Later, combinations of MOFs with different types of nanomaterials such as metal oxide, metal nanoparticles, and carbon-based nanomaterials were used to create newer forms of multifunctional composites/hybrids (Liang et al., 2018; Al-Sagur et al., 2019). Several organic compounds such as metallophthalocyanines (MPCs) (e.g., CuPc, FePc, CoPc, and NiPc) possess electro catalysis activity for the oxidation of biological compounds (Liu et al., 2017). The biological tissue of CRC possessed CT26 cells. Therefore, it is essential to detect the living CT26 cells for the early diagnosis of CRC (Peng et al., 2020). In one of the studies a specific electrochemical cytosensor was described which was constructed on the Cr-MOFs@CoPc nano hybrids for the detection of living CT26 cells (Duan et al., 2020). A Chlorin-Based nanoscale metal-organic framework was used for photodynamic therapy of colon cancers using mouse models and found that these have a great potential for clinical translation (Kuangda et al., 2015). In a recent study, zirconium-based metal-organic framework (MOF), PCN-223, was synthesized and used as a potential vehicle for 5FU for rectal delivery in diagnosis for CRC (Nea et al., 2020).

**Gold Nanoparticles**

Among the noble metal, gold nanoparticles (AuNPs) are considered the most stable nanomaterial that is used for the preparation of nanostructure with various structures and shapes such as nanocubes, nanospheres, nanorods, nanoflowers, nanobranches, nanowires, nano-bipyramids, nanoshells, and nanocages (Chen et al., 2008; Ramalingam et al., 2014; Li et al., 2015; Xiao et al., 2019). The recent advancement in technology has led to accurate surface coating of Au NPs with specific particle shape and size. These specificities of gold nanomaterials make it safer and specific anticancer and drug delivery agent (Siddique and Chow, 2020). Moreover, Artificial Intelligence and mathematical modeling-based study revealed that gold nanoparticle has the capability to adjust its optical densities, light absorbency, wavelengths. Therefore, adjusting the ideal wavelength with nanoparticle size may allow the higher amount of light absorbance within the nanoparticle itself leading to enhanced efficacy of gold nanoparticle against cancer cells (Moore and Chow, 2021). In a recent study gold NPs increase cisplatin delivery and potentiate chemotherapy by decompressing of CRC vessels (Zhao et al., 2018). Gold NPs along with nucleic acids used as molecular method for cellular uptake (Graczyk et al., 2020).

AuNPs have the property of easy to functionalize with biologically active organic molecules along with high physical and chemical stability leading to their excellent biocompatibility that is an essential feature to be used in the medical field (Pissuwan et al., 2019). Moreover, AuNPs can directly conjugate with several other molecules including antibodies, nucleic acids, proteins, enzymes, fluorescent dyes, and drugs which enhance their applications in medical and biological activities (Ramalingam, 2019). Gold nanoshells or gold nanospheres have also been intensively studied over the past decade because of their specific and localized surface plasmon resonance. Gold nanospheres can also easily be conjugated with several imaging reporters and can carry genes, drug payloads, and other chemotherapeutic agents for theranostic applications. Gold nanoparticles usually passively accumulate in tumors and exert specific pharmaceutical effects with active ligands such as Apts, antibodies, and peptides to the required targets (Singhana et al., 2015).

In one of the studies, cellular prion protein (PrPC) aptamer (Apt) conjugated with AuNPs was used for targeted delivery of doxorubicin (Dox) to CRC as PrPC-Apt-functionalized doxorubicin-oligomer-AuNPs (PrPC-Apt DOA). The result revealed that in comparison with free Dox treatment, the oligomer PrPC-Apt DOA decreased the growth and increased the apoptosis of CRC cells to a significant extent. This indicated the possibility of the application of PrPC-Apt DOA as a therapeutic agent for CRC (Go et al., 2021). The gold nanoparticles (GNPs) may also be used to enhance the anticancer efficacy of 5-FU and reduce its side effects. The 5-FU can be loaded to GNPs using thiol-containing ligands, thioylglycolic acid (TGA), and glutathione (GSH) as 5-FU/GSH-GNPs. Further study revealed that the release of 5-FU from GNPs was slow and induced apoptosis in colorectal cancer cells. Overall, 5-FU/GSH-GNPs showed two-fold higher anticancer efficacies than that with free 5-FU (Safwat et al., 2016). Moreover, the electroproporation-GNPs technique may also provide the opportunity for colon cancer therapy especially for the highly immunogenic cancers where otherwise tumors are unresectable (Arab-Bafrani et al., 2020). The gold nanoparticle can also be used for the early diagnosis of CRC cells using colonoscopy. The Center of Cancer Nanotechnology at Stanford University developed a technique where gold nanoparticles are specifically allowed to bind the CRC cells. Subsequently, light from a colonoscope is allowed to shine, the gold nanoparticle bounded cancer cells stand out from the normal cells that can be removed easily. This technique is going to begin a clinical trial for safety evaluation in human patients soon (Advances in Colorectal Cancer Research, 2016).

**Other Nanoparticles in Colorectal Cancer Detection and Treatment**

Nanodrug delivery system can be used to encapsulate the chemotherapeutics agent to targeted drug delivery to cancer cells which can avoid the adverse effect of conventional treatment. In recent years several nano carriers with diverse characteristics have already been tested where polypeptide-based copolymers were found substantial consideration for their biocompatibility, slow biodegradability, and considerably
lower toxicity. One such example assessed is poly(trimethylene carbonate)-block-poly(L-glutamic acid) derived polymersomes, targeted against the EGFR. It was loaded with plitidepsin and tested for efficacy and specificity in LS174T and HT29 cell lines (Goni-de-Cerio et al., 2015). Moreover, a systematic in vitro cytotoxicity study was also conducted with the unloaded polymersomes to determine the cell membrane asymmetry, viability, biocompatibility check, etc. which recognized the fine biocompatibility of plitidepsin-unloaded polymersomes. Further study revealed that the cellular uptake and cytotoxic effect exhibited by the EGFR-targeted plitideps in loaded polymersomes in CRC cell lines were found much more sensitive to anti-EGFR drug-loaded in comparison with targeted drug-loaded polymersomes. Moreover, untargeted polymersomes reduce the plitideps in cytotoxicity and cellular uptake which revealed the use of targeted nano-carrier in cell lines may be a line of treatment for CRC without any adverse effect on normal cells (Goni-de-Cerio et al., 2015).

Recently, one of the near-infra-red fluorescent proteinoid-poly(L-lactic acid)(PLLA) NPs preparation was described where a P(EF-PLLA) random copolymer was prepared using thermal copolymerization of L-phenylalanine(F), L-glutamic acid(E), and PLLA (Kolitz-Domb et al., 2014). The study revealed that under optimal conditions, the proteinoid-PLLA copolymer can self-assemble into hollow nano-sized particles that can be used to encapsulate the indocyanine green and NIR dye. Further study revealed that the encapsulation process enhances the photo stability of the dye. The anti-CEA antibodies and tumor-targeting ligands such as peanut agglutinin can be covalently conjugated to the surface of P (EF-PLLA) NPs and increases the detectable fluorescent signal from tumors. The efficacy of P (EF-PLLA) NPs for colon tumor detection has been demonstrated in the chicken embryo (Kolitz-Domb et al., 2014).

Over the years, several nano-formulations were being used to improve curcumin delivery to cancer sites (Figure 4). Nano-formulations are primarily used to enhance curcumin water solubility and to present a better consistent delivery for curcumin (Wong et al., 2019). Preferably, nano-formulation of curcumin for tumors should have improved anticancer activity as compared when curcumin alone and also nontoxic to normal cells. For CRC nano-formulation of curcumin has been documented in several investigations comprising micelles (Javadi et al., 2018), nano-gels (Madhusudana Rao et al., 2015), liposomes (Sesarman et al., 2018), polymeric NPs (Xiao et al., 2015), cyclodextrins (Ndong Ntoutoume et al., 2016), phytosomes (Marjaneh et al., 2018), solid lipid nanoparticles (Chirio et al., 2011), and gold NPs (SanojRejinold et al., 2015). Different nanomaterials for CRC detection and treatment have been discussed in Table 3. Although several nano formulations are undergoing clinical trials, the number of nano formulations used in clinical trials against the CRC is limited. Some of the nano formulations used for the appropriate clinical trials against the CRC are summarized in Table 4.

**Combinatorial Nanomedicine and Colorectal Cancer Therapy**

Nanomedicine has proved its efficacy in revolutionizing the therapeutics and diagnostics of cancers with the advancement in the development of nano devices. NPs have been used for the delivery of multidrug especially to mediate the drug resistance in relapsing cancers (Maya et al., 2014; Anitha et al., 2016). Recently, a study showing an improved efficacy of 5-FU assisted chemotherapy as a combinatorial strategy for colon cancer treatment was described (Anitha et al., 2014a; Maya et al., 2014). In combinatorial nanomedicine efficacy of both the
Nanogel 5-FU acts as a cross linker between beta PFA@PTX NPs poly(ferulic acid)(PFA) NPs and paclitaxel isoCA-4
NP SQ- and 5-FU Oxaliplatin/DCK fi CUR-CS-NP Chitosan nanoparticles covering the curcumin
Gold nano shells Gold Surface Plasmon resonant made up of silica nano core shell surrounded by ultra-thin shell of gold
Nano cells or PLGA nanoparticles Different structural variants of PLGA copolymer that are used as efficient drug delivery carrier
Liposomes Lipid bilayer self-assembled structure closed and colloidal in nature
CUR-CS-NP Chitosan nanoparticles covering the curcumin
Oxaliplatin/DCK and 5-FU Hydrophilic 5-FU loaded with nano emulsion and N-deoxycytidy-L-lysl-methylester (DCK) linked with amphiphilic Ox-aliplatin
NP SQ-emcitabine/ isoCA-4 Precipitates of squalene, gemcitabine, and isocombretastatin A-4 (isoCA-4)
PFA@PTX NPs poly(ferulic acid)(PFA) NPs and paclitaxel (PTX)-loaded PFA NPs
Nanogel 5-FU acts as a cross linker between beta cyclodextrin and nanoparticles in aqueous solution and forms nanogels. Nanogels are the biocompatible and efficiently released drug
Carbon nanotubes Single-walled carbon nanotubes (SWCNTs) conjugated with a synthetic polyampholyte for delivering paclitaxel in cancerous cells
SN-38 liposome SN38-PA was synthesized by conjugating palmitic acid to SN38 via ester bond at C10 position and then this prodrg was encapsulated into liposomal carrier using the film dispersion method

| Nanofactorizations | Structure | Characteristics | Applications | References |
|--------------------|-----------|----------------|-------------|------------|
| Iron oxide nano-crystals | 1–100 nm diameter iron oxide particles. Methotrexate, superparamagnetic iron oxide nanoparticles (SPIONs), and Wheat germ agglutinin (WGA) | Diverse application in different fields and superparamagnetic properties | Cancer detection | Yang et al. (2014), Lima et al. (2017) |
| Dendrimers | Synthetic polymer of hyper branched pattern with regular repeating monomer unit | Structurally perfect molecules arranged in a characteristic fashion | Treatment & Detection | Xie et al. (2015) |
| Quantum dots | Nanocrystals of semiconductor ranging in diameter 2–10 nm | Show best optical properties such as photo bleaching resistant, high brightness, and tuneable wavelength | Treatment and detection | Wang et al. (2016) |
| Gold nano shells | Gold Surface Plasmon resonant made up of silica nano core shell surrounded by ultra-thin shell of gold | Plasmonic nanoparticles exhibit diverse applications as used in cancer therapy, sensing and used as optical filters | Detection and cancer treatment | Singhana et al. (2015) |
| Nano cells or PLGA nanoparticles | Different structural variants of PLGA copolymer that are used as efficient drug delivery carrier | Easily biodegradable biopolymer on hydrolysis forms the simple monomers as glycolicacid, lacticacid, etc. | US FDA approved therapy and detection technique | Akil et al. (2016) |
| Liposomes | Lipid bilayer self-assembled structure closed and colloidal in nature | Artificial vesicles of phospholipid bilayer which can effectively transport hydrophilic substances inside and outside the cell | Treatment and detection | Chibaudel et al. (2016) |
| CUR-CS-NP | Chitosan nanoparticles covering the curcumin | By muco-adhesion process efficient action of curcumin to cancerous cells. Moreover enhance the cell cycle arrest at G2/M phase and apoptosis in HT29 cells | Detection and treatment | Chuah et al. (2014) |
| Oxaliplatin/DCK and 5-FU | Hydrophilic 5-FU loaded with nano emulsion and N-deoxycytidy-L-lysl-methylester (DCK) linked with amphiphilic Ox-aliplatin | Reduction in tumor volume and enhanced availability of oxaliplatin | Treatment | Pangeni et al. (2016) |
| NP SQ-emcitabine/ isoCA-4 | Precipitates of squalene, gemcitabine, and isocombretastatin A-4 (isoCA-4) | Enhanced anti-proliferative and cytotoxic effect. Moreover regresses the tumor | Treatment | Maksimenko et al. (2014) |
| PFA@PTX NPs | poly(ferulic acid)(PFA) NPs and paclitaxel (PTX)-loaded PFA NPs | poly(ferulic acid) PFA inhibit tumor growth and good drug carrier along with nanoparticles | Treatment and detection | Zheng et al. (2019) |
| Nanogel | 5-FU acts as a cross linker between beta cyclodextrin and nanoparticles in aqueous solution and forms nanogels. Nanogels are the biocompatible and efficiently released drug | For colorectal cancer cells nanogels loaded with graphene oxide, HA-based irinotecan cure cells | Treatment | Hosseinifar et al. (2018) |
| Carbon nanotubes | Single-walled carbon nanotubes (SWCNTs) conjugated with a synthetic polyampholyte for delivering paclitaxel in cancerous cells | Exhibit more effective antitumor effects | Diagnosis and treatment | Lee and Geckeler (2012) |
| SN-38 liposome | SN38-PA was synthesized by conjugating palmitic acid to SN38 via ester bond at C10 position and then this prodrg was encapsulated into liposomal carrier using the film dispersion method | Act as most potent antitumor analogues | Used in treating patients having metastatic colorectal cancer CRC | Wu et al. (2019), Canton et al. (2019) |

Drugs was enhanced due to nano encapsulation where 5-FU was used along with a nontoxic polymeric carrier system thiolated chitosan. In combinatorial use the dosage of 5-FU was decreased which was reflected with enhanced chemotherapeutic efficacy and beneficiary effect on CRC patient cases. The nano-sized drug-encapsulation systems possess specific efficacy in terms of passive retention of more drug-loaded NPs in the vicinity of cancer cells. These strategies have assisted in the development of the next phase of anticancer nanomedicine (Anitha et al., 2014; Malarvizhi et al., 2014; Maya et al., 2014; Linton et al., 2016).

**Nanotechnology and Chemoprevention**

Given side effects associated with chemotherapy, implementation of the nanotechnology-based formulation is very essential for cancer prevention, diagnosis, and treatment because it allows drug targeting and possible drug reduction which can furthermore increase the safety of drugs by minimizing nontargeted toxicities.

NSAIDs are most extensively used for colon cancer prevention (Alizadeh et al., 2012; Drew et al., 2016; U.S. Preventative Service Task Force, 2016; Pan et al., 2018). The epidemiological investigations demonstrate that out of all the NSAIDs, the most promising agent reported is aspirin in reducing adenomatous tumor recurrence due to the accessibility consistent result with minimum gastrointestinal toxicity and no cardiovascular risk (Umezawa et al., 2019). Additionally, Grade B recommendation has been provided for aspirin by the U.S. Preventative Service Task Force (2016) for its utilization as chronic prophylaxis means for CRC (Dehmer et al., 2015). Although aspirin alone or in combination has been proved for colon chemo preventive activity, nano encapsulation of aspirin
can enhance its efficacy with a reduced dose. The chemopreventive effect of the combination of calcium, folic acid, and aspirin has been studied on azoxymethane-treated 7-week-old Sprague-Dawley male rats and found that 1.7 fold higher effective during chemoprevention as compared with their un-modified complement regimen (Prabhu et al., 2007; Chaudhary et al., 2011). Another NSAID is Celecoxib that is being broadly explored in clinical uses for its chemoprevention potential; however, it offers pharmacokinetic variability and cardiotoxicity (Solomon et al., 2005). Celecoxib polymeric NPs have been prepared using ethyl cellulose with lipid hybrid NPs, sodium caseinate bile salt and microemulsions enhanced its bioavailability allowing a decrease in dose, crystallization, and related toxicity (Margulis-Goshen et al., 2011; Tan et al., 2011; Morgen et al., 2012). Naturally extracted plant-based chemicals are phytochemicals that are broadly studied as potential chemopreventive sources for their nontoxicity and pleiotropic effects (Thomas et al., 2007; Zubair et al., 2017; Wong et al., 2019). In colon and intestinal cancer, curcumin has reported competent chemo

| S. No | Nanomaterial/nanosystem used | Drug description | Applications | Clinical trial or FDA approval status | References |
|-------|----------------------------|------------------|--------------|--------------------------------------|------------|
| 1     | Liposome                   | Vincristine      | Colorectal cancer, Acute Lymphoblastic Leukemia, Sarcoma, Neuroblastoma, Leukemia, Lymphoma, Brain tumors | FDA approved | Gidding et al. (1999) |
| 2     | Liposome                   | Doxorubicin      | Colon cancer with liver metastasis | Phase II trial | Celsion (2016) |
| 3     | Liposome                   | SN-38 liposome   | Metastatic colorectal cancer | Phase II trial | US National Institute of Health (2016) |
| 4     | Liposome                   | Liposome-encapsulated IRI (irinotecan) hydrochloride PE | Second-line therapy for metastatic colorectal cancer | Phase II trial | US National Institute of Health (2016) |
| 5     | Liposome                   | Liposomal Cisplatin Analog (Aroplatin) | Colorectal cancer | Phase I/II trial | Pili et al. (2014) |
| 6     | Liposome                   | SN38            | Metastatic colorectal cancer | Phase II trial | Bala et al. (2013) |
| 7     | Liposome                   | Irinotecan, PEGylated Liposome (Narekt -102) | Breast and colorectal cancer | Phase III I trial | Pili et al. (2014) |
| 8     | CPX-1 liposome             | Liposomal IRI (irinotecan) hydrochloride and flouxuridine | Advanced colorectal cancer | Phase II trial | Cabeza et al. (2020) |
| 9     | Liposome                   | Liposomal IRI hydrochloride + 5-FU and LV (leucovorin) | Metastatic colorectal cancer | Phase II trial | Cabeza et al. (2020) |
| 10    | MM-398                     | Liposomal IRI   | Advanced cancer of unresectable nature | Phase I/II trial | Cabeza et al. (2020) |
| 11    | PROMTIL                    | PEGylated liposomal mitomycin C | Metastatic colorectal cancer | Phase I trial | Cabeza et al. (2020) |
| 12    | NaI-IRI                    | Liposomal IRI   | Colorectal cancer along with advanced gastrointestinal cancers | Phase I/II trial | Cabeza et al. (2020) |
| 13    | Polymer                    | 5-fluorouracil (5-FU) and DAVANAT (carbohydrate polymer) | Treatment of colorectal cancer | Phase I/II trial | Xiao et al. (2015) |
| 14    | Regulatory lymphocytes (Tregs): anti-CTLA-4 (ipilimumab) and anti-PD-L1 (atezolizumab) | Cytotoxic antibodies expressed on surface of Tregs | colorectal cancer | FDA approved | Rampado et al. (2019) |
| 15    | NKTR-102/IRI               | Formulation for prolonged release of IRI conjugated with PEG/IRI | Metastatic CRC with KRAS-mutant | II clinical trial | Cabeza et al. (2020) |
| 16    | Cycodextrin nanoparticle   | Camptothecin    | Solid tumors, rectal cancer, renal cell carcinoma, non-small cell lung cancer | Phase I/II trial | Giglio et al. (2015) |
| 17    | PEG-PGA polymeric micelle  | SN-38          | Colorectal, lung, and ovarian cancers | Phase II trial | Hamaguchi et al. (2018) |
| 18    | Carbon NPs                 | Carbon NPs     | Laparoscopic surgery of colorectal cancer | Phase I trial | Cabeza et al. (2020) |
| 19    | TKM-880301                 | Lipid NPs with serine/threonine kinase inhibitor | Colorectal cancer with liver metastases and ovarian, gastric, esophageal, and breast cancer | Phase I trial | Cabeza et al. (2020) |
| 20    | PEG-rhG-CSF                | PEGylated recombinant human granulocyte colony stimulating factor (CSF) | Solid malignant tumors (colorectal, ovarian, lung, head, and neck cancer) | Phase IV trial | Cabeza et al. (2020) |
| 21    | Silica NPs                 | Fluorescent cRGDY-PEG-Cy5.5-C dots | Breast cancer and colorectal malignancies | Phase I-I trial | Cabeza et al. (2020) |
| 22    | Polymeric NPs + cetuximab + somatostatin analogue | Combination of NPs Cetuximab and Somatostatin analogue | Metastatic colorectal cancer | Phase I trial | Cabeza et al. (2020) |
bioavailability and cell internalization (Jayaprakasha et al., 2016). In other research, it was found that curcumin encapsulated in polymeric nano carrier enhanced the solubility of curcumin and showed less structural abnormalities, considerable reduction in tumors and beta-catenin in the treated group with curcumin NPs as compared with the group treated only with curcumin (Alizadeh et al., 2012).

CONCLUSION AND FUTURE PROSPECTIVE

With the advancement in nanotechnologies, there has been increased research on the development of medical devices, targeted therapies, and novel drug delivery systems. Nanotechnology enabled the development of medical products from a single mode of action to multifunctional platforms such as nano theranostics to combine diagnostics and therapeutics. The preclinical study of nanomaterials has proved its efficacy as a therapeutics purpose of cancer. The detailed study of predictive immuno toxicity assays, nanoparticle surface characterization, and quantitative evaluation of encapsulated versus free drug fractions has highlighted the importance of nanotechnology in modern medicine. The advancement in drug delivery systems with the capability to modify the tissue uptake, bio-distribution of drugs, and pharmacokinetics of therapeutic agents has immense significance in biomedical research. Some of the nano carriers are even able to cross the blood-brain barrier (BBB) and may act at the cellular level. Moreover, several nanoparticle-based studies have focused on the development of techniques to customize novel drug conjugates and diagnostics as well as therapeutic devices. Nano carriers can also be programmed to release the therapeutic agents, fluorescent molecules, or even magnetic materials to the colorectal cancer site to increase the bioavailability, drug solubility, stability, and tumor specificity of therapeutics agent in comparison with free molecular cargo. Moreover, nano carriers-based therapeutics agents may decrease the tumor multidrug resistance resulting in ineffective treatment by reducing the overall drug requirement and potential side effects. In recent years, the nanotechnology applied to CRC has evolved enough to complement the latest advances in tumor diagnosis and therapy far beyond the traditional systems. It can be combined with completely newer concepts of diagnostics and therapeutics synergistically with available methodology. Thus, in the coming future despite the several challenges in the application of nanotechnology, nanomedicine is going to gain the capability to play a critical role in the management of human CRC. The specific research on new methods directed at the understanding of nano-bio interface may reveal some additional relationships between the nanoparticle structure and its biological activity. Such information may be used in devising new strategies for further development of nanotechnology to improve the existing pharmaceuticals and development of novel therapeutics products in the future.

AUTHOR CONTRIBUTIONS

BB first prepare the whole manuscript. BB, KR, AP, MG, RK, and SS edited manuscript. Finally BB and PM critically analyse and finalize the manuscript.

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REFERENCES

Abbas, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadhi, H. T., Joo, S. W., et al. (2014). Dendrimers: Synthesis, Applications, and Properties. Nanoscale Res. Lett. 9 (1), 247. doi:10.1186/1556-276x-9-247
Abreu, A. S., Castanheira, E. M., Queiroz, M. J., Ferreira, P. M., Vale-Silva, L. A., and Pinto, E. (2011). Nanoliposomes for Encapsulation and Delivery of the Potential Antitumoral Methylene 6-Methoxy-3-(4-Methoxyphenyl)-1H-Indole-2-Carboxylate. Nanoscale Res. Lett. 6 (1), 482. doi:10.1186/1556-276x-6-482
Advances in Colorectal Cancer Research (2016). Nanotechnology to Improve Early Detection and Treatment of Colorectal Cancer. Available at: https://www.nih.gov/research-training/nanotechnology-improve-early-detection-treatment-colorectal-cancer.
Akbarzadeh, A., Rezaei-Sadabad, R., Davaran, S., Joo, S. W., Zarghami, N., Hanihepfour, Y., et al. (2013). Liposome: Classification, Preparation, and Applications. Nanoscale Res. Lett. 8 (1), 102. doi:10.1186/1556-276x-8-102
Ald, M. A., Kartal-Hodzic, A., Oksanen, T., Ismael, H. R., Afouna, M. M., Yilpertutla, M., et al. (2016). Factorial Design Formulation Optimization and In Vitro Characterization of Curcumin-Loaded PLGA Nanoparticles for Colon Delivery. J. Drug Deliv. Sci. Techn. 32 (A), 10–20. doi:10.1016/j.jddst.2016.01.007
Al-Sagur, H., Shanmuga Sundaram, K., Kaya, E. N., Durmus, M., Basova, T. V., and Hassan, T. V. A. (2019). Amperometric Glucose Biosensing Performance of a Novel Graphene Nanoplatelets-Iron Phthalocyanine Incorporated Conducting Hydrogel. Biosens. Bioelectroctn. 139, 111–323. doi:10.1016/j.bios.2019.11.1323
Alizadeh, A. M., Khaniki, M., Azizian, S., Mohaghegh, M. A., Sadeghizadeh, M., and Naji, F. (2012). Chemoprevention of Azoxymethane-Initiated colon Cancer in Rat by Using a Novel Polymeric Nanocarrier-Curcumin. Eur. J. Pharmacol. 689, 226–232. doi:10.1016/j.ejphar.2012.06.016
Allen, J. E., Saroya, B. S., Kunkel, M., Dicker, D. T., Das, A., Peters, K. L., et al. (2014). Apoptotic Circulating Tumor Cells (CTCs) in the Peripheral Blood of Metastatic Colorectal Cancer Patients Are Associated with Liver Metastasis But Not CTCs. Oncotarget 5 (7), 1753–1760. doi:10.18632/oncotarget.1524
Allen, T. M., and Cullis, P. R. (2013). Liposomal Drug Delivery Systems: From Concept to Clinical Applications. Adv. Drug Deliv. Rev. 65 (1), 36–48. doi:10.1016/j.addr.2012.09.037
Amato, G. (2010). Silica-Encapsulated Efficient and Stable Si Quantum Dots with High Biocompatibility. Nanoscale Res. Lett. 5 (7), 1156–1160. doi:10.1007/s11671-010-9619-9
Anitha, A., Deepa, N., Chennazhi, K. P., Lakshmanan, V. K., and Jayakumar, R. (2014). Combinatorial Anticancer Effects of Curcumin and 5-Fluorouracil Loaded Thiolated Chitosan Nanoparticles Towards Colon Cancer.
Dienstmann, R., Salazar, A., and Taberner, J. (2015). Overcoming Resistance to Anti-EGFR Therapy in Colorectal Cancer. Am. Soc. Clin. Oncol. Educ. Book 35, e149–e156. doi:10.14389/EdBook_AM.2015.35.e149

Dong, Z., Cui, M. Y., and Peng, Z. (2016). Nanoparticles for Colorectal Cancer: Targeted Drug Delivery and MR Imaging: Current Situation and Perspectives. Curr. Cancer Drug Targets 16 (6), 536–550. doi:10.2174/156800961666615130214442

Drew, D. A., Cao, Y., and Chan, A. T. (2016). Aspirin and Colorectal Cancer: The Promise of Precision Chemoprevention. Nat. Rev. Cancer 16, 173–186. doi:10.1038/nrc20164

Duan, F., Hu, M., Guo, C., Song, Y., Wang, M., He, L., et al. (2020). Chromium-based Metal-Organoic Framework Embedded with Cobalt Phthalocyanine for the Sensitive Impedimetric Cyto sensing of Colorectal Cancer (CT26) Cells and Cell Imaging. Chem. Eng. J. 395, 125452. doi:10.1016/j.cej.2020.125452

Elmunzer, B. J., Hayward, R. A., Schoenfeld, P. S., Saini, S. D., Deshpande, A., and Go, G., Lee, C. S., Yoon, Y. M., Lim, J. H., Kim, T. H., and Lee, S. H. (2021). PrPCLoaded Co-Polymeric Polymersomes on Colorectal Cancer Cell Lines. Cytotoxic Effect of Epidermal Growth Factor Receptor Targeted and Plitidepsin Linked Oligomer as Efficient Carrier for Anionic Drugs: A Spectroscopic and Nanocolorimetric Investigation. RSC Adv. 5, 16664–16671. doi:10.1039/cfa16064a

Giorgi, V., Sgarlata, C., and Vecchio, G. (2015). Novel Amino-Cyclodextrin Cross-Linked Oligomer as Efficient Carrier for Anionic Drugs: A Spectroscopic and Nanocolorimetric Investigation. RSC Adv. 5, 16664–16671. doi:10.1039/cfa16064a

Go, G., Lee, Y. M., Yoon, C. M., Lim, J. H., Kim, T. H., and Lee, S. H. (2021). PrP-Cys Conjugated- Gold Nanoparticles for Targeted Delivery of Doxorubicin to Colorectal Cancer Cells. Int. J. Mol. Sci. 22 (4), 1976. doi:10.3390/ijms22041976

Goni-de-Cerio, F., Thevenot, J., and Oliveira, H. (2015). Cellular Uptake and Cytotoxic Effect of Epidermal Growth Factor Receptor Targeted and Plitidepsin Loaded Co-Polymeric Polymericomes on Colorectal Cancer Cell Lines. J. Biomed. Nanotechnology 11 (11), 2034–2049. doi:10.1166/jbn.2015.2148

Gracyzk, A., Pawlowska, R., Jedrzejczyk, D., and Chworos, A. (2020). Gold Nanoparticles in Conjunction with Nucleic Acids as a Modern MolecularSystem for Cellular Delivery. Molecules 25, 204. doi:10.3390/ molecules25010204

Gu, C., Guo, C., Li, Z., Wang, M., Zhou, M. N., He, L., et al. (2019). Bimetallic Zr/Ag Based Metal-Organic Framework Embedded with Carbon Dots: Ultra-Sensitive Platform for Early Diagnosis of HER2 and HER2-Overspressed Living Cancer Cells. Biosens. Bioelectron. 134, 8–15. doi:10.1016/j.bios.2019.03.043

Gulbake, A., Jain, A., Jain, A., Jain, A., and Jain, S. K. (2016). Insight to Drug Delivery Aspects for Colorectal Cancer. World J. Gastroenterol. 22 (2), 582–599. doi:10.3748/wjg.v22.i2.582

Guo, C., Liu, Q., and Dai, M. (2015). Colorectal Cancer Screening: Situation and prospect. Zhonghua Yu Fang Yi Xue Za Zhi 49 (5), 377–380. doi:10.1093/geront/gnv170.03

Haggar, F., and Boushey, R. (2009). Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. Clin. Colom Rectal Surg. 22 (04), 191–197. doi:10.1055/s-0029-1242458

Hamaguchi, T., Tsuji, A., Yamaguchi, K., Takeda, K., Uetake, H., Esaki, T., et al. (2018). A Phase II Study of NK012, a Polymeric Micelle Formulation of SN38, in Unresectable, Metastatic or Recurrent Colorectal Cancer Patients. Cancer Chemother. Pharmacol. 82 (6), 1021–1029. doi:10.1007/s00280-018- 3693-6

Hampel, S., Kunze, D., Haase, D., Kramer, K., Rauschenbach, M., Ritschel, M., et al. (2008). Carbon Nanotubes Filled with a Chemotherapeutic Agent: A Nanocarrier Mediates Inhibition of Tumor Cell Growth. Nano medicine 3 (2), 175–182. doi:10.2217/17435889.3.2.175

Handa-Bojd, M. Y., Jafarri, M. R., Ramzanian, N., Xue, M., Amin, M., Shahatmahasebi, N., et al. (2015). Surface Functionalized Mesoporous Silica Nanoparticles as an Effective Carrier for Epirubicin Delivery to Cancer Cells. Eur. J. Pharm. Biopharm. 89, 248–258. doi:10.1016/j.ejpb.2014.12.009

He, X., Liu, F., Liu, L., Duan, T., Zhang, H., and Wang, Z. (2014). Lectin-Conjugated Fe2O3@Au Core@Shell Nanoparticles as Dual Mode Contrast Agents for In Vivo Detection of Tumor. Mol. Pharm. 11 (3), 738–745. doi:10.1021/mp400456j

Holme, L., and Kalager, M. (2014). Effect of Flexible Sigmondoscopy Screening on Colorectal Cancer Incidence and Mortality: A Randomized Clinical Trial. JAMA 312 (6), 606–615. doi:10.1001/jama.2014.8266

Hoosseinifar, T., Sheshyani, S., Abdouss, M., Najafabadi, S. A., and Ardestani, M. (2018). Pressure Responsive Nanogel Base on Alginate-Cyclodextrin with Enhanced Apotosis Mechanism for colon Cancer Delivery. J. Biomed. Mater. Res. A. 106 (2), 349–359. doi:10.1002/jbm.a.36242

Huang, R. F., Wei, Y. J., Inbaraj, B. S., and Chen, B. H. (2015b). Inhibition of Colon Cancer Cells as a Potential Drug Delivery Aspects for Colorectal Cancer. Molecules 20 (11), 22318–22328. doi:10.3748/wjg.v22.i2.175

Hu, X., Liu, F., Liu, L., Duan, T., Zhang, H., and Wang, Z. (2014). Lecture-Conjugated Fe2O3@Au Core@Shell Nanoparticles as Dual Mode Contrast Agents for In Vivo Detection of Tumor. Mol. Pharm. 11 (3), 738–745. doi:10.1021/mp400456j

Huang, R., He, N., and Li, Z. (2018). Recent Progresses in DNA Nanotechnology-Based Biosensors for Detection of Tumor Markers. Biosens. Bioelectron. 109, 27–34. doi:10.1016/j.bios.2018.02.053

Huang, W., Wang, X., and Shi, C. (2015a). Fine-tuning Vitamin E-Containing Tidolendrimers for Efficient Delivery of Gamagobide in Colon Cancer Treatment. Mol. Pharm. 12 (4), 1216–1229. doi:10.1021/acs.molpharmaceut.5b00051

Hutchinson, R. A., McArt, D. G., Salto-Tellez, M., Jasani, B., and Hamilton, P. W. (2015). Epidermal Growth Factor Receptor Immunohistochimistry: New Opportunities in Metastatic Colorectal Cancer. J. Transl. Med. 13, 217. doi:10.1186/s12967-015-0531-z

Huyghe, N., Baldin, P., and Van den Eynde, M. (2020). Immunotherapy with Immune Checkpoint Inhibitors in Colorectal Cancer: what Is the Future beyond Deficient Mismatch-Repair Tumors? Gastroenterol. Rep. 8, 11–24. doi:10.1093/gastro/goz061

Imperiali, T. F., Ranhoff, D. F., Itzkowitz, S. H., Turnbull, B. A., and Ross, M. E. (2004). Fecal DNA Versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population. New Engl. J. Med. 351 (26), 2704–2714. doi:10.1056/NEJMoa043003

Javadi, S., Rostamizadeh, K., Hejazi, J., Parsa, M., and Fathi, M. (2018). Curcumin Mediated Down-Regulation of alphaV Beta3 Integrin and Up-Regulation of Pyruvate Dehydrogenase Kinase 4 (PDK4) in Erlotinib Resistant SW480 Colon Cancer Cells. Phytother. Res. 32, 355–364. doi:10.1002/ptr.5984

Jayakumar, J., Mohammed, Z. H., Jayaprakash, B. U., Ramzi, M. M., and Bhat, A. A. (2015). “Recent Developments in Nanomedicine; Treatment Options for Colorectal Cancer,” in Modern Technology: Present and Future of Cancer. Editor M. A. Macha (San Mateo, CA: OMICS Group eBooks).
from Volatile Micro Emulsions. J. Pharm. Sci. 100, 4390–4400. doi:10.1002/jps.22623

Marjanesh, R. M., Rahmani, F., Hassanian, S. M., Rezaei, N., Hashemzehi, M., Bahrami, A., et al. (2018). Phytosomal Curcumin Inhibits Tumor Growth in Colon-Associated Colorectal Cancer. J. Cell. Physiol. 233, 6785–6798. doi:10.1002/jcp.26538

Maya, S., Sarmento, B., Lakshmanan, V. K., Menon, D., and Jayakumar, R. (2014). Actively Targeted Cetuximab Conjugated Gamma-Poly(glutamic Acid)-Docetaxel Nanomedicines for Epidermal Growth Factor Receptor Over Expressing Colon Cancer Cells. J. Biomed. Nanotechnol 10 (8), 1416–1428. doi:10.1166/jbn.2014.1841

Minakshi, P., Kumar, R., GhoshBrar, M. B., Barnela, M., and Lakhani, P. (2020). Application of Polymeric Nano-Materials in Management of Inflammatory Bowel Disease. Curr. Top. Med. Chem. 20, 982–1008. doi:10.2174/15680266206602021013322

Minakshi, P., Lambe, U., Ranjan, K., Patil, S., Brar, B., Devi, B., et al. (2018). An Insight in Biomarkers for Colorectal Cancer. Gastroenterol. Liver Dis. 3 (1), 1–15.

Minakshi, P., Upendra, P. L., Brar, B., Ikbal, S., Manimegalai, J., Koushlesh, R., et al. (2017). Nanotherapeutics: An Insight into Healthcare and Multi-Dimensional Applications in Medical Sector of the Modern World. Biomed. Pharmacother. 97, 1521–1537. doi:10.1016/j.biopha.2017.11.026

Moore, J. A., and Chow, J. C. L. (2021). Recent Progress and Applications of Gold Nanotechnology in Medical Biophysics Using Artificial Intelligence and Mathematical Modelling. Nano Express 2 (2021), 02001. doi:10.1088/2632-959a/abdld3

Morgen, M., Bloom, C., Beyerinck, R., Bello, A., Song, W., Wilkinson, K., et al. (2012). Polymeric Nanoparticles for Increased Oral Bioavailability and Rapid Absorption Using Celucolux as a Model of a Low-Solubility, High-Permeability Drug. Pharm. Res. 29, 427–440. doi:10.1007/s11095-011-0558-7

Mostert, B., Steuwerts, A. M., and Bolt-de Vries, J. (2015). mRNA Expression Profiles in Circulating Tumor Cells of Metastatic Colorectal Cancer Patients. Mol. Oncol. 9 (4), 920–932. doi:10.1002/mol.2015.01.001

Nag, O., and Awasthi, V. (2013). Surface Engineering of Liposomes for Stealth Behavior. Pharmaceutics 5 (4), 542–569. doi:10.3390/pharmaceutics5040542

Ndong Ntoutoume, G. M. A., Granet, R., Mbakidji, I. P., Bréger, F., Léger, D. Y., Fidani-Dugas, C., et al. (2016). Development of Curcumin-Cyclodextrin/Cellulose Nanocrystals Complexes: New Anticancer Drug Delivery Systems. Bioorg. Med. Chem. Lett. 26, 941–945. doi:10.1016/j.bmcl.2015.12.060

Ne, C. Y., Kim, N. S., Cho, S. Y., and Choy, B. Y. (2020). PCN-223 as a Drug Carrier for Potential Treatment of Colorectal Cancer. J. Ind. Eng. Chem. 84, 290–296. doi:10.1016/j.jiec.2020.01.018

Noble, G. T., Stefanick, J. F., Ashley, J. D., Kiziltepe, T., and Bilgicer, B. (2014). Multiple Detections of Foodborne Pathogens by Gold Nanoparticle Assays. Wires Nanomed. Nanobiotechnol. 12, 1584. doi:10.1002/wnn.1584

Pahal, S., Kannamalini, N., and Wang, J. (2007). Synergistic Chemoprevention of Colorectal Cancer Using Colon-Targeted Polymer Nanoparticles. Cancer Res. 67, 1.

Qaseem, A., Crandall, C. J., and Mustafa, R. A. (2019). Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement from the American College of Physicians. Ann. Intern. Med. 171 (9), 643–654. doi:10.7326/m19-0642

RahulBhakrishnan, K., Gupta, S., Ganadhas, D. P., Ramamurthy, P. C., Chakravortty, D., and Raichur, A. M. (2013). Prostate-Capped Mesoporous Silica Nanoparticles for Biologically Triggered Drug Release. Part. Syst. Char. 31 (4), 449–458. doi:10.1002/pssc.201300219

Ramalingam, V. (2019). Multifunctionality of Gold Nanoparticles: Plausible and Convincing Properties. Adv. Colloid Int. Sci. 271, 101989. doi:10.1016/j.cis.2019.101989

Ramalingam, V., Rajaram, R., Premkumar, C., Santhanam, P., Dhinesh, P., Vinothkumar, S., et al. (2014). Biosynthesis of Silver Nanoparticles from Deep Sea Bacterium Pseudomonas aeruginosa JQ899348 for Antimicrobial, Antibiofilm, and Cytotoxic Activity. J. Basic Microbiol. 54, 928–936. doi:10.1002/jobm.201300514

Rampado, R., Crotti, S., Caliceti, P., Pucciarelli, S., and Agostini, M. (2019). Nanovectores Design for Theranostic Applications in Colorectal Cancer. J. Oncol. 2019, 2740923. doi:10.1155/2019/2740923

Rastogi, V., Yadav, P., Bhattacharya, S. S., Mishra, A. K., Verma, N., Verma, A., et al. (2014). Carbon Nanotubes: An Emerging Drug Carrier for Targeting Cancer Cells. J. Drug Deliv. 2014, 1–23. doi:10.1155/2014/670815

Rivera, E. (2003). Liposomal Anthracyclines in Metastatic Breast Cancer: Clinical Update. Oncologist 8 (Suppl. 2), 3–9. doi:10.1634/theoncologist.8-suppl_2-3

Rosado-de-Castro, P. H., Morales, M. D. P., Pimentel-Coelho, P. M., Mendez-Otero, R., and Herranz, F. (2018). Development and Application of Nanoparticles in Biomedical Imaging. Contrast Media Mol. Imaging 2018, 1403826. doi:10.1155/2018/1403826

Safwat, M. A., Soliman, G. M., Sayed, D., and Attia, M. A. (2016). Gold Nanoparticles Enhance 5-Fluorouracil Anticancer Efficacy against Colorectal Cancer Cells. Int. J. Pharm. 513 (1–2), 648–658. doi:10.1016/j.ijpharm.2016.09.076

Sah, H., Thoma, L. A., Desu, H. R., Sah, E., and Wood, G. C. (2013). Concepts and Practices Used to Develop Functional PLGA-Based Nanoparticulate Systems. Int. J. Nanomedicine 8, 747–765. doi:10.2147/ijnmolmed.2014.001912

SanoRejinho, N., Thomas, R. G., Muthiah, M., Chinnazhi, K. P., Manzoor, K., Park, I. K., et al. (2015). Anti-cancer, Pharmacokinetics and Tumor Localization Studies of fl-5FU-Nanoparticles Enhance 5-Fluoruracil Anticancer Effectiveness. J. Drug Deliv. 2015, 1–7. doi:10.1155/2015/1403826

Schoen, R. E., Pinsky, P. F., and Weissfeld, J. L. (2012). Colorectal-Cancer Incidence and Mortality with Screening Flexible sigmoidoscopy. New Engl. J. Med. 366 (25), 2345–2357. doi:10.1056/nejmoa1114635

Schro, P. C., Duhovic, E., Chen, C. A., and et al (2016). Risk Stratification and Shared Decision Making for Colorectal Cancer Screening: A Randomized Controlled Trial. Med. Decis. Making 36 (4), 526–535. doi:10.1177/0272898X15625622

Segnan, N., Armaroli, P., and Bonelli, L. (2011). Once-Only Sigmoidoscopy in Colorectal Cancer Screening: Follow-Up Findings of the Italian Randomized Controlled Trial-SCORE. J. Natl. Cancer Inst. 103 (17), 1310–1322. doi:10.1093/jnci/djr284
