JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON ADVANCED NANO CARRIERS TO OVERCOME THE COLORECTAL CANCER

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Abstract: Colorectal cancer (CRC) is one of the most lethal diseases in the world, due to the lack of effective early detection techniques and drug delivery technologies. To target and deliver chemotherapeutic and chemo preventive drugs directly to the colon and rectum, targeted oral drug delivery systems based on polysaccharides are being researched. The amount of the drug at the target location is increased by site-specific drug delivery to the colon, resulting in a lower dosage and fewer adverse effects. Surgery, chemotherapy, radiation therapy, and targeted therapies are currently available treatments for CRC. Nanoparticle-based formulations may facilitate early tumor detection and help conventional treatments to overcome their drawbacks, such as poor water solubility, non- specific biodistribution, and low bioavailability. We discussed numerous kinds of nanoparticles utilized in CRC diagnosis and medication administration in this study. We will also look at how these nanoparticles might enhance the precision of tumor-targeted medication delivery with less cytotoxicity against healthy colon tissue and enhanced efficacy. The unique properties of nanoparticles, such as their small size, high surface-to-volume ratio, and capacity to achieve multiple ligand interactions at the surface, provide significant advantages for the use of nanomedicines to treat many types of cancer. There are screening techniques that can lower the incidence by removing adenomas and can lower cancer-related fatalities by detecting the disease at an earlier stage. The combination of immunotherapy and vaccinations now is producing greater success against CRC. Enhancing cellular absorption, pharmacokinetics, and anti-cancer treatment efficacy are the recent goals of breakthroughs in nanotechnology-based drug delivery systems. This information might serve as a springboard for the future creation of multifunctional nano-constructions for the successful early diagnosis and treatment of colorectal cancer.

Key words: Colorectal cancer, Nanotechnology, Tumor targeting, Immunotherapy

I.INTRODUCTION

Colorectal cancer (CRC), commonly referred to as colon / bowel cancer, the third most frequent type of cancer worldwide, behind lung and breast cancers. It has been discussed how prevalent cancer is worldwide, and 13.2 million deaths from cancer are anticipated in 2030. In 2020, there were 935,000 fatal cases and around 1.9 million new cases of CRC worldwide. At the time of diagnosis, 21% of CRC patients had metastatic disease. Elderly people are most frequently affected by CRC, with a median age of diagnosis of 71. The majority of malignancies in the globe, or almost 9%, are colorectal cancers (CRC), which have a high death rate due to late-stage diagnosis and high recurrence rates. Research have highlighted the presence of cancer stem cells (CSCs), a minuscule subpopulation of cancer cells that are able to self-renew, differentiate, sustain tumor growth, as the cause of recurrence and metastasis. At-risk persons can be screened to help find CRC early on, which dramatically improves prognosis and lowers CRC mortality. In fact, after therapy, the five-year survival rate is over 90% if malignant polyps are discovered early. Regrettably, the majority of people with colon cancer receive their diagnosis at a time when their chances of survival are substantially lower. Most benign adenomatous polyps are the cause of colon and rectal cancer. Usually asymptomatic, the adenoma is only identified through standard screening. The primary premalignant lesion that causes colon cancer is this one. Because of the accumulation of acquired genetic and epigenetic alterations, invasive adenocarcinoma develops in a multistep process. About 25% of colorectal cancer cases among those with a family history of the disease include genetic syndromes such Familial Adenomatous Polyposis (FAP) or hereditary nonpolyposis colorectal cancer, which account for 5% of cases (HNPCC). Much progress has been achieved in the treatment of CRC during the past few years, and the survival rate has increased by nearly 200%.

Currently available treatment options for colon and rectal cancer include surgery, radiation therapy, chemotherapy, and, more recently, immunotherapy (molecularly targeted therapies). Chemotherapy remains the most widely used treatment for colon cancer patients. However, current chemotherapy methods are unable to distinguish between diseased and healthy cells, which means that while tumors receive minimal therapeutic benefit, healthy cells suffer grave adverse effects. Therefore, a technique that could maintain (or even improve) a medication's therapeutic efficacy while reducing its toxicity would be a major breakthrough in advanced colon cancer chemotherapy. Depending on the stage of the cancer, two or more of these treatments may be administered simultaneously or sequentially. It has long been known that intestinal inflammation caused by ulcerative colitis and Crohn's disease increases the risk of dysplasia and colorectal cancer (CRC). Therefore, drugs for inflammatory bowel disease may lower the risk of colorectal cancer. For instance, 5-aminosalicylic acid (5-ASA), an anti-inflammatory drug, has long been used to treat inflammatory bowel disease. 5-ASA has been studied for its ability to prevent cancer growth in addition to its anti-inflammatory properties because it appears to reduce the incidence of colorectal cancer. Conventional dosage schedules for CRC treatment or prevention deliver the drug to both desired and

undesired sites of action, which can have a number of unfavorable side effects. Neutropenia, anemia, hand-foot syndrome, diarrhea, gastrointestinal toxicity, mucositis, nausea, vomiting, exhaustion, hematologic abnormalities, and liver toxicity are a few of the side effects that are commonly associated with CRC medication therapy. In order to administer chemotherapeutic and chemo preventive medicines directly to the colon and rectum, targeted drug delivery devices are being researched. A lower dose is needed and the likelihood of adverse effects is decreased because to the site-specific delivery of a medicine to the colon, which improves drug concentration at the target location. Direct rectum delivery or oral administration of the drug can target the colon. Each choice has some advantages and some usage restrictions. Due to their constrained spread, suppositories have only been demonstrated to be locally efficacious in the rectum when used for rectal administration, whereas enema solutions have mainly been found to be effective in the sigmoid and descending colon. The large variability in the dispersion of both suppositories and enemas have been blamed for this lack of effectiveness. Hence, direct rectal administration is not a desirable strategy for a targeted medication delivery in the treatment and prevention of CRC since it is ineffective in delivering a dose to the entire area of the colon. The oral route has traditionally been used to give medications. Before the medication reaches the colon, the stomach and small intestine either absorb or eliminate the majority of the dosage form's pharmacological load, which is the fundamental barrier to the effective development of oral medication delivery methods that target the colon.

Nanotechnology-based drug delivery methods have showed considerable potential for enhancing cancer treatment. Over 150 anticancer treatments based on nanotechnology are currently in various phases of development, some of which are widely utilised in clinics.

II. STAGES OF CRC:

Histopathological characteristics may serve as the primary criterion for classification by the CRC. The diverse character of CRC has been significantly appreciated because to molecular research. There are four distinct stages of the CRC.

Stage-0: It is a relatively early stage of CRC in which colon mucosal lining polyps occur. Polypectomy is used during colonoscopy to completely remove all polyps and stop the development of CRC.

Stage-1: At this stage, the polyp turns into a tumor and infiltrates the mucosal inner lining. When a CRC reaches this stage, surgery is typically the only treatment option available since it allows the malignant and non-cancerous tissues to be separated. If CRC is discovered at this point, the life expectancy exceeds 90%.

Stage -2: If the cancer has metastasized outside of the colon but hasn't reached the lymph nodes, it is a defining characteristic. Depending on whether the cancer has gone to the muscle layer, the outermost layer of the colon, or beyond the colon, this stage is further divided into Stages IIA, IIB, and IIC. The sole treatment option at this time is resection surgery, and more than 80% of patients still survive.

Stage-3: The likelihood of surviving colon cancer at this stage is between 30% and 60%, where the disease has already spread to the colon's whole wall and its nearby lymph nodes. Depending on whether the cancer has spread to the inner, middle, or outside layer of the colon, as well as any nearby lymph nodes, this stage of cancer is divided into stage IIIa, b, and c. Chemotherapy and other forms of medical treatment are necessary in addition to surgery to treat this malignancy.

Stage-4: At this point, the cancer has quickly spread to other body parts and organs such the liver, ovaries, testicles, and intestines. Only 3% of people survive. At this stage of colon cancer, treatment options include surgical resection, chemotherapy, radiation therapy, and surgical removal of the affected region of other body parts. Colonoscopy is advised for everyone who is 50 years of age or older during routine checkups.

III. SYMPTOMS OF CRC

Symptoms of colon cancer can include:

- A change in bowel habits, such as increased diarrhoea or constipation.
- Faeces with blood in them or rectal haemorrhage.
- Persistent abdominal pain, gas, or discomfort like cramps.
- A bowel movement that doesn't feel like it completely empties the bowel.
- Tiredness or weakness.
- Weight loss without exerting effort.
- Unexplained iron deficiency anaemia, or low red blood cell count.

IV. RISK FACTORS ASSOCIATED WITH CRC

1. MEDICAL HISTORY OF THE FAMILY AND PERSON:

- Family background and genetics
- Irritable bowel syndrome
- Polyps in the colorectal cavity
- Diabetes mellitus
- Cholocystectomy

2. LIFESTYLE:

- Nutritional habits
- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Alcohol consumption

3. OTHERS:

- Age
- Gut microbiota
- Gender and race
- Socioeconomic factors

V. PATHOGENISIS

Environmental factors or dietary choices may contribute to colorectal carcinogenesis by inflaming the colon mucosa. It is not surprising that the etiology of colitis-associated dysplasia and colorectal cancer, in which these diseases are developing, is largely dependent on host immune and inflammatory responses. It is thought that changes in epithelial cell motility, survival, and proliferation are caused by chronic inflammation, and that this is how colorectal cancer is caused. Unlike sporadic colorectal cancer, which is assumed to originate from one or two foci of dysplasia, colitis-associated colorectal cancer is thought to develop from multifaceted dysplasia, in which the inflamed colonic mucosa encounters a broad change of molecular changes linked to cancer before any histological signs of dysplasia. Microsatellite instability (MSI) and chromosomal instability (CIN) are two somatic genetic disorders that are most commonly associated with colorectal cancer. Although certain modifications in the colitis-associated dysplasia-carcinoma sequence occur with the same frequency in colitis-related colorectal cancer as in random colorectal cancer, there are differences in the timing and frequency of these modifications. According to the analyses, colorectal tumors associated with colitis have a distinct profile and are rich in mutations pertaining to cell adhesion, cell-to-cell signaling, and cell communication. These mutations may be linked to the dysregulated cytokines and inflammatory mediators associated with IBD. In spite of this, understanding that colitis-associated colorectal cancer might have a distinct genetic profile could present brand-new options for chemoprevention and the creation of biomarkers for colitis surveillance. Our knowledge of the pathogenesis of colitis-associated colorectal cancer and the possibilities for surveillance, intervention, and prevention may be greatly improved by expanding the genetic profiling work to include precancerous dysplasia and expanding to include additional assessments like DNA methylation and mucosal microbiome profiles.

VI. DIAGNOSIS

The ideal screening research would be extremely sensitive and specific, efficient, secure, easily accessible, useful, and practical, as well as economical. Currently, there are two different types of CRC screening methods: invasive and non-invasive.

1. Non-invasive tests

It includes stool-based tests and radiologic tests.

i) Stool-based tests:

The two stool-based diagnostics currently available are the guaiac-based fecal occult blood test (gFOBT) and the more contemporary fecal DNA testing (Multitarget stool DNA, MT-sDNA, Cologuard®). These tests are based on the hypothesis that malignancies, vascularized polyps, and adenomas can extravasate blood or shredded cell debris.

a) Guaiac-based fecal occult blood test:

The guaiac smear test is the most popular test for detecting fecal occult blood. Since the guaiac test reacts to the peroxidase activity of heme, it is vulnerable to reactivity with other peroxidases in the feces, such as those from particular fruits, vegetables, and red meat. Therefore, dietary limitations are required to prevent falsely positive results.

Fecal occult blood as a colorectal cancer screening test has a number of drawbacks. One-time tests have a sensitivity of just 50%–60%, and while rehydration can increase sensitivity, this will produce reaction variability, making the approach worthless as a screening procedure. Low sensitivity increases the likelihood of acquiring a false sense of security and the amount of false negative outcomes. Fecal occult blood typically identifies false positive instances, which are then exposed to unneeded further testing, typically a colonoscopy. The low compliance rates of screening programmers are another issue.

Fecal immunochemical assays (FITs), which use sensitive methods to detect hemoglobin, are currently replacing fecal occult blood testing using the guaiac smear in several countries. The usability of the tests varies; some are more approachable and have great specificity.

b) Stool DNA testing:

In August 2014, Cologuard®, a multi-target stool DNA product, received FDA approval for regular CRC screening. A stool DNA test looks for abnormal DNA in the stool, including NDRG4 promoter regions, mutant KRA, actin, FIT, and abnormally methylation BMP3 and FIT. A potential method for the early detection of colorectal cancer has been proposed: the detection of aberrant DNA in stool samples. The best combination of molecular markers has yet to be identified.

ii. Radiologic Tests:

Double contrast barium enema and computed tomographic colonography (CTC) are two radiologic tests. Their main duty is the radiographic visualization and diagnosis of advanced colonic polyps or cancer, as well as the potential for the detection of extra-colonic abnormalities (through CTC).

Using a qualitative polymerase chain reaction (PCR) in vitro diagnostic approach, the recently created blood test (Epi procolon®) detects mutant methylation septin9 DNA in EDTA plasma drawn from patient whole blood specimens. CRC has been linked to the presence of methylated SEPT9.

a) Computed tomographic colonography (CTC):

The term "virtual colonoscopy" (VC) / CTC refers to the use of magnetic resonance imaging (MRI) or CT scanning to create two- and three-dimensional images of the colon (large intestine), from the lowest part, the rectum, to the lower end of the small intestine, and to display the images on an electronic display device. It has the ability to detect disorders or diseases outside the colon.

b) Double-contrast barium enema:

Even though double-contrast barium enema (DCBE) allows for the examination of the entire colon, colonoscopy and computed tomographic colonography (CTC) have higher diagnostic sensitivity and specificity. In spite of massive polyps and malignancies, the sensitivity of DCBE (48%) is much lower than that of colonoscopy, and it is more prone to produce in false positives (artefacts misdiagnosed as polyps) than colonoscopy. Patients with atypical barium enema should get a colonoscopy after that. However, DCBE is a frequently used therapy and its ability to find up to 50% of big polyps would encourage its adoption in the lack of other resources.

2. Invasive tests:

It includes colonoscopy and flexible sigmoidoscopy (FS), which have the advantage of obtaining a pathology specimen while providing direct sight and identification of a colonic polyp or advanced neoplasia.

a) Colonoscopy:

Through colonoscopy, polyps in the colon can be found, removed, and sampled for malignancy. Colonoscopy has a high specificity and sensitivity for the detection of polyps and cancer. Based on studies of consecutive colonoscopies, the miss rate for polyps is 15-25 % for adenomas smaller than five millimeters in diameter and 0%–6% for lesions of 10 mm or more. Colonoscopy plus polypectomy has been shown in cohort studies to decrease the expected incidence of CRC by 76–90%. Colonoscopy offers neoplasm visibility that is at least as good as sigmoidoscopy and direct evidence suggests that screening sigmoidoscopy reduces colorectal cancer mortality. There were no deaths or perforations associated with the surgery in the two large screening colonoscopy investigations (a total of 4500 average-risk patients were examined), and morbidity was minimal (0.1-0.3%). However, compared to other screening procedures, a colonoscopy is more expensive (requires a professional examiner, takes time), inconvenient for the patient (requires total bowel cleansing), and not all examinations can see the entire colon.

b) Sigmoidoscopy:

Up to around 60 cm from the anal edge, flexible sigmoidoscopy enables direct inspection of the inner surface of the large bowel. This method can be used to remove polyps or collect tissue samples for histological analysis as well as to detect colorectal polyps and malignancies. In contrast to a colonoscopy, the technique takes less time, requires less time to prepare the bowel, has little morbidity, and does not require anesthesia for exams that do not require polypectomy. Flexible sigmoidoscopy has these advantages over colonoscopy. However, it has the obvious drawback of missing lesions on the right side when only the left colon is examined. Due to the significant number of right-sided adenomas that develop without distal tumors and are therefore missed by flexible sigmoidoscopy, sensitivity for the entire colon is low and ranges from 35 to 70%, even though the specificity of the findings by the endoscopic procedure is very high (98-100%, few false positives). In order to test for early cancer detection and prevention in asymptomatic persons, sigmoidoscopy is employed. Case-control studies have unequivocally demonstrated that screening sigmoidoscopy reduces colon cancer mortality in the studied area by 60–70% and cuts the incidence of CRC in half.

VII. STRATEGIES TO IMPROVE CRC CHEMOTHERAPY

Utilizing a nanodrug delivery system to minimize unintentional drug dispersion within strong tissues and deliver anti-cancer drugs to colorectal cancer cells has been studied. Unlike typical drug delivery methods, nanoparticles (NPs) have the potential to protect cancer drugs from enzymatic degradation and first-pass metabolism in the stomach and small intestine. This could increase the amount of medication available for targeted distribution within the colon. Most of the drug-rich NPs available today are designed to be injected intravenously (IV), where they accumulate in blood vessels before killing cancerous cells. Therapeutic nanoparticle delivery to the colon may be able to remove barriers to successful CRC treatment. The administration of 5-FU nanodrugs for the treatment of colorectal cancer is described below.

❖ **Solid lipid nanoparticles:**

Solid lipid nanoparticles (SLNs) grown in significance as a substitute colloidal carrier system. This mode of distribution offers a number of distinct benefits, including affordability, viability, simplicity of scaling up, high water dispersibility, increased entrapment for hydrophobic medicines, and extended-release characteristics. In their study, Alaa Eldeen and their colleagues created SLNs utilizing a straightforward double-emulsion technique that provides greater flexibility and lessens the stress of the encapsulated medication throughout the preparation process. The uptake of anticancer medications inside colon cancers could be significantly enhanced by the SLNs system.

❖ **Chitosan-based nanoparticles:**

These nanoparticles have drawn more interest because of their many therapeutic applications, including the delivery of proteins, genes, and cancer-fighting agents via oral, nasal, intravenous, and ophthalmic routes. To target the colon with medication delivery and lessen the toxicity of these potent treatments on healthy cells, researchers Shashank Tummala and colleagues 5-FU nanoparticles loaded with chitosan were created in 2015. They came to the conclusion that the formed chitosan nanoparticles enhanced the drug's localization at

the colon region and that this localization was followed by a protracted release mechanism that lasted for 24 hours. As more of the medicine is concentrated in the colorectal cancer, this may result in less drug-induced toxicity to healthy cells. The patient also gains from these modifications because it is possible to lower dosage frequency and drug. In a different study, Tan et al. made chitosan nanoparticles with 5-FU loaded on them to improve medicine targeting and localization to tumor cells. Their in vitro release assays showed a continuous, regulated release of 5-FU from chitosan nanoparticles after a 48-hour incubation period; the release amount varied from 29 to 60% depending on the pH environment. The scientists ended by recommending that 5-FU-encapsulated chitosan nanoparticles be used in studies examining pH-responsive smart medication delivery for the treatment of cancer.

❖ **PLGA nanoparticles:**

Poly (lactic-co-glycolic acid) PLGA, a polymer with desirable properties like biodegradability and biocompatibility, a polymer that is among the most advanced for creating polymeric nanoparticles. In order to treat CRC with a target delivery method, Sutar et al. produced the 5-FU nanoparticles utilizing PLGA and Eudragit S-100.They used PLGA and pH-sensitive polymer to create the nanoparticles using the emulsion droplet coalescence technique. Using the MTT assay method, the in-vitro anticancer effectiveness of synthesized 5-FU nanoparticles was examined on HT-29 cell lines. The findings showed that the target colon cancer cells were mostly affected by the nano formulation, with a cell lysis rate of roughly 80%. They came to the conclusion that 5-FU-loaded nanoparticles could be a feasible delivery strategy for tackling colorectal cancer based on the findings.

❖ **Folic acid and PLGA conjugates:**

Folic acid (FA) is frequently used as a targeted moiety for many anticancer medications. It has the ability to precisely bind to folate receptors, which are present in the majority of cancer cells. Furthermore, it appears that when cancer progresses, the density of folate receptors also rises. FA can therefore be utilized as a targeted drug to treat metastatic tumors, especially those that are advanced in stage. Based on this supposition, FA has been coupled with a variety of anticancer substances to enable precise targeting of cancer cells. By using a modified W/O/W multiple emulsion and solvent evaporation process, PLGA nanoparticles with 5-FU were developed. The cytotoxicity of nanoparticles is greatly influenced by the high FA conjugation ratio. The MTT assay was used to examine the drug-loaded nanoparticles' in vitro cell viability, and the produced nanoparticles demonstrated improved anticancer activity. In comparison to pure 5-FU, treatment with PLGA and FA conjugates resulted in the lowest cell vitality, according to an in vitro investigation on cell viability.

❖ **Eudragit S100 coated citrus pectin nanoparticles:**

In the treatment of colorectal cancer and other colonic illnesses, pectin, a natural polymer, can carry drugs specifically to the colon. A targeted delivery system for colon cancer was created using 5-FU citrus pectin nanoparticles (CPNs) coated with Eudragit S100 (E-CPNs). A 1.5-fold increased cytotoxicity capability of nanoparticles was seen in the test against the cancerous HT-29 cells when compared to a 5-FU solution in an in vitro cytotoxicity assay. In vivo data showed unequivocally that Eudragit S100 successfully shielded nanoparticles, allowing them to reach the intestinal region. The drug release from the nanoparticles there lasted for a long time after they had been absorbed.

❖ **Quantum dots:**

Quantum dots are semiconductor nanocrystal particles with a size range of 2 to 10 nm, and their fluorescence emission is influenced by their size. Due to their excellent photostability, prolonged excitation wavelengths, high quantum efficiency, and narrow emission band, Quantum dots are semiconductor nanocrystal particles with a size range of 2 to 10 nm, and their fluorescence emission is influenced by their size. Due to their excellent photostability, prolonged excitation wavelengths, high quantum efficiency, and narrow emission band, quantum dots are favored for biological imaging. Numerous in vitro and in vivo studies have used quantum dots as fluorescent markers for cancer, with nontargeted or xenograft labeling as their only in vivo use. The expression of the VEGFR2 receptor, which is increased in CRCs, has been demonstrated using the VEGFR2-targeted QDot655 (QD655-VEGFR2) to be able to identify tumors that express the receptor in vivo.

❖ **Iron oxide nanocrystals:**

Oncologists frequently employ iron oxide as a diagnostic and treatment technique. Iron oxide nanoparticles' superparamagnetic characteristics have drawn interest for their potential biomedical uses because of their biocompatibility and lack of toxicity. With an iron oxide nanocrystal-filled magnetic core and a variety of medicinal substances coated in its polymer outside, the diameter spans from 1 to 100 nm. Due to their tiny size, slow rate of deposition, effective surface area, and ease of cellular transport, these NPs exhibit a range of biological properties. When used with magnetic hyperthermia, iron oxide NPs coated with 5-FU successfully slow the growth of tumors in mice with heterotopic human colon cancer.

❖ **Dendrimer nanoparticles in CRC:**

Dendrimers are spherical, extremely branching molecules having three-dimensional chemical structures. Because of their biodegradable backbones, dendrimers are incredibly valuable in nano pharmaceuticals. It is generally known that dendrimers can be used in a variety of theranostic and drug delivery systems for the treatment of cancer. Anticancer conjugated dendrimers are capable of delivering the medication intracellularly, obviating the need for an efflux transporter and increasing the bioavailability of the loaded molecular cargo. They are also employed for the delivery of diagnostic chemicals for imaging with tumor targets.

Because only a very small percentage of the medicine reaches the tumor target site at an appropriate concentration, the chemotherapeutic strategy to treating CRC has not been shown to be effective. The primary cause of tumor metastasis is the migration of cancer cells, or CTCs (Circulating tumor cells are defined as tumor cells that are lost from primary tumors or metastatic locations in early-stage cancer patients and enter the bloodstream). Numerous techniques (such as size-based filtration, microfluidics-based, etc.) were employed to separate and capture CTCs from enormous populations of interfering cells because of the importance of CTCs as a predictor of poor prognosis, but these efforts were not entirely effective. Dendrimers that have been coupled with antibodies have been

used in a number of ways to identify colorectal CTC, including PAMAM dendrimers that were used to trap colon carcinoma HT29 cells.

Dendrimers have also been mentioned for application in *invitro* anticancer therapy in addition to diagnostic use.

- Capecitabine-conjugated G4 PAMAM dendrimers showed reduced tumor growth and capecitabine side effects.
- In C26 and HT29 colorectal cells, gold nanoparticles enclosed in a PAMAM dendrimer coupled with curcumin displayed greater cellular uptake, internalization, and cytotoxicity.
- Employing L-lysine dendrimers with polyoxazoline conjugated with SN-38 (the active metabolite of irinotecan) and camptothecin-loaded PEGylated PAMAM dendrimers functionalized with AS1411 (anti-nucleolin aptamers) to target CRC cells site-specifically decreased adverse effects while boosting efficacy.

VIII. FUTURE DIRECTIONS

i. Entrectinib:

An innovative, orally absorbable, selective tyrosine kinase inhibitor called entrectinib targets tumors that have mutations in NTRK1/2/3 (encoding TrkA/TrkB/TrkC), ROS1 or ALK that activate protein. The best Trk inhibitor available for clinical use, entrectinib, has no unfavorable off-target action. The second of the "Studies of Tumor Alterations Responsive to Targeting Receptor Kinases" is termed STARTRK-2, and it is a Phase 2 clinical trial that is testing this product candidate. The Phase 2 clinical trial of entrectinib, conducted across multiple centers, is an open-label study, that may enable registration and uses a basket design to screen patient tumour samples for the pertinent targets. Preliminary clinical results have shown entrectinib to be active against a wide range of molecular targets and tumor types, and such a basket design makes the most of this activity.

ii. SPECTAcolor platform:

Cancer patients' therapies are progressively being modified to account for the specific biological features of the patient and disease. Therefore, in order for a patient to enroll in the proper clinical trial for their specific cancer kind, molecularly In order to check for CRC biomarker mutations in adult patients with advanced-stage CRC, the European Organization for Research and Treatment of Cancer (EORTC) has developed a collaborative molecular screening platform called Screening Patients for Efficient Clinical Trial Access in Advanced CRC's (SPECTAcolor). This platform provides the necessary infrastructure. Spectacolor successfully enrolled more than 500 patients in its first launch, demonstrating its potential to support next-generation cancer clinical studies across 19 clinical locations. As a result, in 2016 the coordinator of SPECTAcolor, Dr. Gunnar Folprecht, presented results at the ESMO convention. Characterization of the patient's tumor is now a requirement.

IX. RECENT DEVELOPMENTS IN THE DIAGNOSIS AND STAGING OF CRC

a) Utilization of Biomarkers in CRC:

A biomarker is a biological element that can be employed to evaluate the presence, progression, or effects of a certain disease. Biomarkers need to possess a number of essential qualities, including high sensitivity, specificity, and safety, in addition to being simple to test, useful for determining an accurate diagnosis, and assisting in the choice of treatment.

Microsatellite instability (MSI), chromosomal instability (CIN), and the CpG island methylator phenotype (CIMP) are the three main changes seen in CRC. These modifications result in changes to proteins, metabolites, DNA, RNA, or other molecules that can be detected in tumor samples, blood, or stools and utilized as biomarkers. Although more research is required for their validation, molecular tests are anticipated to be more precise, sensitive, and patient-friendly than the currently employed methods (colonoscopy, sigmoidoscopy, double contrast barium enema, computer tomographic colonoscopy, and fecal blood test, or FOBT).

Currently, MSI and KRAS mutations in tumor samples are the most frequently employed biomarkers in CRC for tumor classification, illness prognosis, and treatment management. Although there are additional indicators used for diagnosis, such as the measurement of FOBT and CEA, they often have a high specificity but a relatively low sensitivity. This is the fundamental justification for why scientists are looking for more effective chemicals for CRC early diagnosis. The application of kits to assess the CpG island methylator phenotype, miRNA, and gene microarrays that can be identified in feces or blood are among the most noteworthy findings in this arena. The majority of these kits are being tested in clinics and appear to have a bright future.

The current screening methods for CRC have drawbacks related to their invasiveness, low specificity and sensitivity, and high cost, making the discovery of new molecular biomarkers with predictive and/or prognostic significance in CRC a crucial issue to improve anti-cancer treatments and patient outcomes. Numerous molecular biomarkers have been investigated over the past 20 years, and the results are optimistic but there are a number of flaws that make the conclusions less reliable. First of all, because the majority of published research used small sample sizes or were retrospective analyses of a single marker, forecasts lack resolution and reproducibility. Second, data interpretation and analysis continue to be difficult tasks.

Despite all of the genuine drawbacks that they do have, the use of biomarkers has a promising future in the diagnosis and prognosis of CRC as well as in the creation of individualized and focused therapy.

b) Gene-Expression Profiling (GEP):

Research evaluates the gene expression in samples of normal and malignant tissue, as well as samples from different phases of the disease, using the Gene Expression Profiling (GEP) approach. These comparisons are thought to be a useful tool for finding out more about the prognosis of each patient's disease and the optimal course of therapy.

Even so, despite the fact that GEP tests have become more and more popular recently and have the ability to benefit patients (by reducing the side effects and undesirable consequences of adjuvant treatments) as well as society (by saving money on medical care for those who won't benefit from it). According to the National Comprehensive Cancer Network (NCCN, 2015), in terms of their

predictive value for the potential benefit of chemotherapy, there is presently. Furthermore, the NCCN has decided that there is insufficient evidence to use these assays as the basis for selecting an adjuvant therapy, therefore more research in this area is necessary to discuss the diagnostic and therapeutic validity.

X. CONCLUSION

Colorectal cancer (CRC) is a serious global public health concern due to its high incidence and fatality rates. In order to give researchers and physicians an updated perspective on the most important insights into this disease, we have evaluated the most recent findings in CRC research as well as the most recent findings in diagnostic and therapy approaches. With so many challenges to address throughout time, the strategic approaches for localized colon disease therapeutics continue to be a growing area of study, in this sense, nanomedicine, an emerging science, has transformed the medical sector and sheds light on the effective cancer therapy being observed globally. That guarantees a regulated drug delivery to the affected area, enhancing efficacy and lowering drug-related side effects. As a result, it might increase patient compliance and raise the quality of life for those who are affected. The current study on colorectal cancer places a lot of emphasis on cutting-edge medication delivery methods that have been shown helpful in the treatment of colon cancer. Recent advancements in screening, preventive, genetic and biomarker research, dietary supplement therapy, immunization, and chemotherapy have all greatly increased detection and significantly lowered mortality numbers. In order to solve the problem of localization and site-specific administration, new carrier-mediated formulations of anti-cancer medications are needed. These delivery methods effectively cause cancer cells to undergo apoptosis and can stop the spread of the disease. Concisely, the unique and highly sophisticated drug delivery technologies hold considerable potential for the efficient and effective treatment of colon cancer. More research is required in this era since the colon is a place that serves to expel metabolic waste and fewer products are being absorbed in this area.

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