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Novel Approaches for Treatment of Colorectal Cancer- An Overview

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Abstract

Colorectal cancer (CRC) is considered as the third most common cancer and the fourth foremost cause of death worldwide. Various attempts have been made to diagnose and treat CRC. However, the incidence and mortality rates are still high. For CRC, currently available chemotherapy delivers the drugs usually to both cancerous as well as normal cells, hence resulting in various undesirable side effects. Therefore, nowadays more emphasis is been given on targeted drug delivery systems as it directly reaches to site of action with minimal unwanted side effects. This review focuses on novel approaches for the treatment of CRC. Plant-derived drugs shows promising anticancer activity and have various advantages over chemotherapeutics agents have also been explored. The current paper also elaborates on synthetic drugs, plant-derived drugs and drugs targeting to overexpressed proteins in CRC including recent clinical trials in combinations with other chemotherapeutics for the treatment of CRC.

Keywords: Colorectal cancer; Overexpressed protein in CRC; Targeted drug delivery; Plant derived drugs

Introduction

Colorectal cancer (CRC) is the third most common cancer leading to death worldwide . The global burden of colorectal cancer is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030. The CRC starts from the lining of the bowel and if not treated, could grow into the muscle layers underneath and the bowel wall . The age, family history, personal history, ethnic backgrounds and racial are the major risk factors. Common symptoms for CRC include rectal bleeding, abdominal pain, unintended weight loss, being overweight, and diet including mostly red meat. Treatments become effective when cancerous cells are detected in the early stages. Commonly available treatments for CRC are based on radiation therapy, chemotherapy and surgery . Most commonly used chemotherapeutical agents are platinum derivatives (oxaliplatin), antimetabolites (Capecitabin, 5-fluorouracil), topoisomerase inhibitors (irinotecan) and Tegafur/uracil (UFT). However, chemotherapeutics due to its non-specificity do not only affect the cancerous cells but also affects the normal cells . To treat CRC targeted drug delivery is one of the vital approaches. Targeted cancer therapy can discriminate the small differences between normal cell and cancer cells. The site-specific delivery of chemotherapeutics would increase the effectiveness with reducing side effects. Early detection of CRC with the help of advanced screening techniques will reduce the risk of CRC. Due to advancements in the screening techniques and targeted drug treatments, the death toll rate for CRC can be minimized.

Major constraints associated with CRC are poor availability of drugs at the distal part of colon and rectum, presence of efflux pump on tumor cells, high possibility of exposure of normal cells to antineoplastic agents. Large intra- and inter-individual variability in physiological conditions of GIT leads to either premature release of drug in the small intestine or no drug release in the colonic region, thus affecting targetability and availability of drugs at the tumor site. Cell uptake and cell cytotoxicity study reports of CDDS are not available in majority of published articles. Due to this, chemotherapeutics are not able to reach at colon site, which forms the major setback to consider. This review article summarizes novel approaches and novel formulations to treat CRC in last decade.

Global burden of colorectal cancer

Cancer incidences and mortality rates due to cancers are growing rapidly worldwide. Over 1.8 million new Colon cancer cases and 881,000 deaths due to this were estimated to occur in year 2018 [1].The highest incidences of colon cancer were found in parts of Europe (eg. In Slovenia, Hungary, Slovakia, Norway and the Netherlands), Northern America, Eastern Asia (Japan and the Republic of Korea, Singapore [in females]), Australia/New Zealand. Among all, Hungary and Norway ranking first in colon cancers in males and females, respectively. Rectal cancer incidence rates have a similar regional distribution, while the highest rates are seen in Macedonia among females and in the Republic of Korea among males. Rates of both colon and rectal cancer occurrence tend to be low in most regions of Southern Asia and Africa. CRC is more common compared to other types [2]. Colorectal cancer represents 10.5 % of all new cancer cells (Figure 1)(Figure 2).

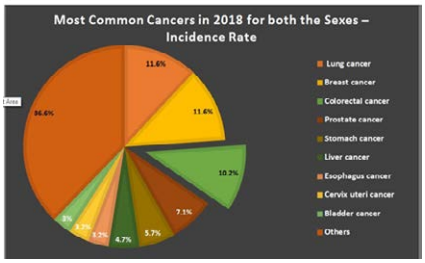

Figure 1: Incidence rate of most common cancers for both the sexes in 2018.

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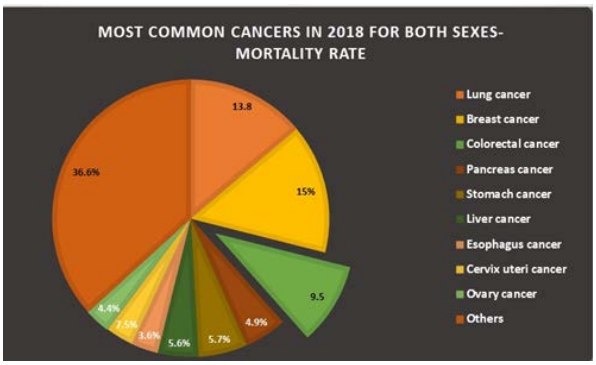

Figure 2: Mortality rate of most common cancers for both the sexes in 2018.

Gastrointestinal system consists of colon and rectum, which are parts of the digestive system. It plays an important role in absorption of water, electrolytes, absorption of short-chain fatty acids and transport and storage of feces. When humans ingest the food, it travels through various parts of gastrointestinal tract. There are four different parts of the colon based upon how food matter is travelling in gastrointestinal system, first ascending colon, second descending colon, third transverse colon and fourth sigmoidal colon. First part, ascending colon it begins with a pouch named the cecum, where undigested food is received from the small intestine and extends upward on the right side of the abdomen [3]. The second section is named the transverse colon as it travels across the body from the right to the left side. The third section is named the descending colon as it descends (travels down) on the left side. The fourth section is named the sigmoid colon as it is of "S" shape; the sigmoid colon connects the rectum, which further gets joined to the anus.

CRC begins with the projection of tissue called as "polyp". These polyps can be cancerous or it can be noncancerous too. In general, there are two main types of polyps i.e. Adenomatous polyp (adenomas) and Hyperplastic polyps [4]. Adenomatous polyps are precancerous which can change into cancer like conditions whereas, Hyperplastic polyps are the most common type of polyp but in general, they are not precancerous. The normal colon consists of 4 layers starting from mucosa, sub mucosa, muscle layer and serosa. Figure 3 shows the various layers of colon.(Figure 3)

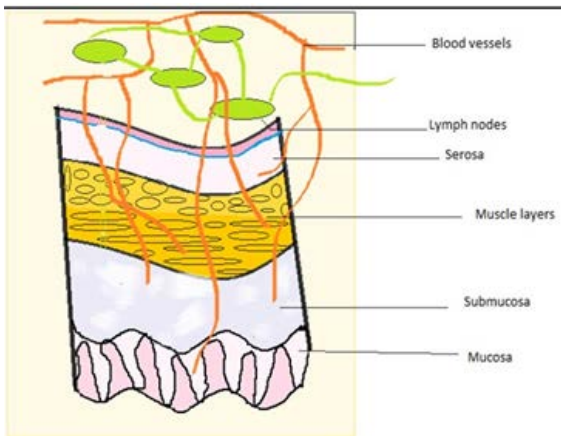

Figure 3: Normal human colon tissue layers.

Colorectal cancer based on Histopathological conditions are classified into four stages i.e. Stage 0, Stage I, Stage II, Stage III and Stage IV.In stage 0 of CRC, tumour growth starts from inner lining of mucosa and patients are diagnosed easily. In stage I, CRC has spread to the upper layer i.e. sub mucosa and surgery is the best option to treat at this stage with 90% of survival rate. In stage II, CRC spreads to the third layer i.e. muscular layer and sometimes to lymph node as well as beyond colon [5]. Resection surgery is the best option to treat this type of cancer with 80% of survival rate. In stage III, CRC spreads to the serosa as well as lymph nodes and surgery to eradicate the section of the colon with cancer together with nearby lymph nodes, followed by adjuvant chemotherapy is the standard treatment for this stage with 30% -60% of survival rate. In stage IV (advanced stage), cancer spreads to the other vital organs like liver, lungs etc. In most Stage IV cases of CRC, surgery is unlikely to cure along with chemotherapy as only 3% of overall survival rate increases after the surgery. Figure 4 is the pictorial depiction of tumour growth . (Figure4)

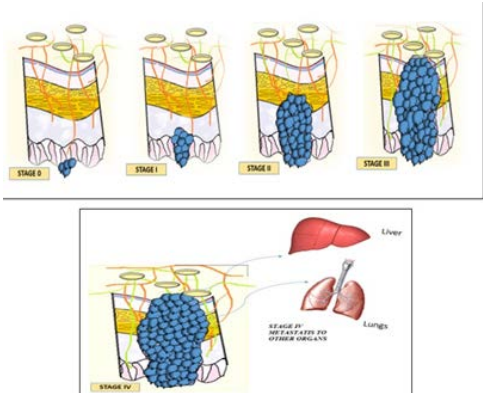

Figure 4: Different stages of CRC. Stage 0: Tumour growth starts from inner lining of mucosa; Stage 1: CRC has spread to the upper layer i.e. submucosa; Stage 2: CRC spreads to the third layer i.e. muscular layer; Stage 3: CRC spreads to the serosa as well as lymph nodes; Stage 4: CRC has spread to the other vital organs like liver, lungs etc.

Treatment for colorectal cancer and need of novel approaches

Due to advancements in treatment, CRC is now being categorized from deadly disease to an illness, which can easily be cured. Survivorship is a distinct phase of CRC . CRC can be treated by several ways depending upon its stage. Local therapies are useful in earlier stages of CRC, which involve surgery, radiation and ablation therapy. Local therapy treats the tumour without affecting the rest of the body. Whereas, systemic treatments involved chemotherapeutics, targeted therapy and immunotherapy. Different colon-specific drug delivery system approaches for colorectal cancer are pH-dependent system, bacteria-dependent system, time-dependent system and pressure-dependent system [6]. General mechanism by which anticancer drugs commonly show its action are DNA alkylation by direct alkylating agents, interference with synthesis of vital co-factors, interferences with DNA/RNA protein precursors and interferences with cellular structures and processes. To achieve 100% bioavailability, it is necessary to target the tumour site in the colon which is the most difficult and challenging task and research are still going on to formulate novel and specific drug delivery systems to target the cancer site in the colon [7]. Novel treatment helps in achieving the targeted drug delivery at the site. For treatment of early stages of CRC, surgery/removal of polyp is the best option without further medications. Studies have shown that adjuvant therapy increases the percent of survival

rate of stage II and stage III CRC patients [8]. Novel approaches viz. immunotherapy, formulations-based therapy approach, gene therapy and natural therapy have shown a considerable increase in the overall survival rate of CRC patients.

Immunotherapy

Immunotherapy is the most modern method that has shown clinical benefits in past few years. It is also called as biological therapy. Immunotherapy treatments are designed to boost the body's natural defence to fight against the cancer. Adjuvant therapy using Cytokines, monoclonal antibodies, tumour assisted antigens and vaccines are used as immunotherapeutic agents [9]. These agents have the potential to activate or suppress the immune response of the body. Immunotherapy becomes the most suitable option in case of chemotherapeutic and radiation resistant tumors . Strategies for using cancer immunotherapy primarily focuses on the activation of MHC (major histocompatibility complex)-restricted T cells, γδT cells and αbT cells which share certain effector functions such as cytokine production and potent cytotoxic activity. Systemic high-dose interleukin-2 (IL-2) was approved by FDA in 1992 for metastatic melanoma and kidney cancer [10]. IL-2 was one of the first immunotherapeutic agents approved for cancer therapy. Recently, on 10th July 2018, FDA approved the combination drug Ipilimumab and Nivolumab for the treatment of metastasis CRC cancer. An ongoing challenge to treat CRC, is to design strategies to deliver immune-modulating drugs to suitable immune cells at target tissue sites (e.g., tumours and tumour-draining lymph nodes) whereas, minimizing non-specific systemic circulation. Immunotherapy can be local or systemic [11]. Improvements in animal models play an important role for the future success of immunotherapy in the efficient treatment of CRC .

Multiparticulate drug delivery

Traditional methods of chemotherapeutics for the treatment of CRC are distributed in desired as well as undesired site [12]. This can be prevented by site-specific delivery of chemotherapeutics to the cancerous region in colon.

Conventional drug delivery systems exhibit more side effects and are not able to reach the targeted site in effective concentration. In contrary, targeted drug delivery systems due to its specificity, overcome the obstacles of being nonspecific bio-distribution, drug resistance and unwanted adverse effects of conventional drug delivery systems [13]. Nanotechnology has several advantages for the advancement of targeted drug delivery. The efficacy of a multiparticulate drug delivery system is directly related to its particle size. Smaller the particle size larger is the surface area. Due to this property, it has gain a lot of advantages like increase in solubility, increase in bioavailability and it can easily cross the blood-brain barrier [14]. Nanoparticles are particles with a diameter of less than 1 μm, consisting of various biodegradable material such as natural and synthetic polymers, lipids, polymers, phospholipids and metals. They include nanotube, nano pores, quantum pores, nano shells, dendrimers, liposomes, nano rods, nano spheres, nanowires, nano belts, nano rings and nano capsule. The advantages of nanoparticles are that it can change the pharmacokinetics of drug, reduce the toxicity and enhance the therapeutic markers hence, it causes development of multifunctional nanoparticles.

Gene therapy

Recent studies have recognized that ineffective therapies are attributed to a lack of understanding of specific molecular mechanisms involved in carcinogenesis [15]. Gene therapy is a potential novel treatment for treating the CRC by targeting a particular gene, which is present in/on CRC cell.For cancer treatment, gene transfer technology is a significant approach for increasing the effectiveness of the current chemotherapeutical regimen .In CRC, it was found that, a variety of miRNAs (microRNAs) (such as miR-30d, miR-145, miR-455 and miR-600) are differen¬tially expressed during CRC progression. Hence, this could be another approach in drug development to target the miRNA . It has been observed that in CRC development and progression, the KRAS (Kirsten rat sarcoma viral oncogene homolog) gene is mutated in 30-50% cases of CRC tumours. Furthermore, mutations of other genes including SMAD4, TP53 and PIK3CA are identified to trigger the tumour malignancy and provoke metastasis [16]. The most logical approach to gene therapy is the rectification of a single gene defect, which produces the disease phenotype as a series of genetic mutation occurs during tumour progression. Therefore, by rectifying only one vital defect in a malignant cell, growth arrest or apoptosis could be induced. A key limiting-factor in gene therapy is the low efficiency of gene transfer with the currently available vectors. Developments in tumour-specific targeting, combination treatments and vector technology can translate into clinically significant advantages [17]. Additionally, combining gene therapy approaches together or in conjunction with conventional treatments can provide important synergistic benefits in the management of CRC .

Natural supplement therapy

The search for anti-cancer agents from plant sources started early in 1950s. Health experts assessed that about 70% of CRC could be prevented by diet and nutrition. Vitamin D, Calcium, quercetin and curcumin are some naturally occurring agents, which have shown anticancer activities [18]. Over 60% of currently used anticancer drugs are from natural origin . Some natural phenolic compounds like phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans quinones etc. obtained from medicinal herbs plays an important role in cancer treatment. They contribute to apoptosis by arresting cell cycle, proliferation, cell adhesion and migration. Inhibiting DNA binding also regulates carcinogen metabolism, some may also block the signaling pathways. Many naturally occurring agents entered into clinical study, but the study gets terminated due to a lack of efficacy or unacceptable toxicity. It is important to emphasis on preclinical and clinical studies along with a precise understanding of pharmacology of new compounds that may give selective anticancer drug.

Common chemotherapeutics used for the treatment of colorectal cancer

Chemotherapy is an effective approach for the treatment of CRC. Chemotherapy drug attacks the cell, which undergoes divisions very quickly leading to apoptosis. Chemotherapy could be used at different times during the treatment of CRC. Adjuvant chemotherapy is given after surgery with an approach to kill any cancerous cells that could have been left behind during surgery as that might have escaped from the main tumour and settled in other parts of the body but are too small to see on imaging tests. This will reduce the chances of reoccurrence of cancer. Neo-adjuvant chemotherapy is given before surgery to shrink the cancerous cell, which makes it easier to remove it during surgery [19]. This approach is often used for the treatment of rectal cancer. For advanced cancers that are spread to other organs like liver, chemotherapy can be used to shrink tumours and helps in relieving the symptoms they're causing. Table 1 shows a list of commonly used synthetic drugs with their mechanism of action for the

treatment of CRC. (Table 1)

Sr. No	Drug	Mechanism of action (MOA)
1	5-Flurouracil	5-Flurouracil acts in several ways, principally as a thymidylate synthase (TS) inhibitor. Inhibition of this enzyme results in blockage of synthesis of pyrimidine thymidine which is a nucleoside required for DNA replication.
2	Oxaliplatin	Platinum based drug results in the formation of platinum-DNA adducts, which appear to be more effective at blocking DNA replication.
3	Capecitabine	Act as a prodrug, gets converted to 5-FU after metabolism which shows antineoplastic and antimetabolite activity.
4	Irinotecan HCL (semisynthetic derivative)	It is a semisynthetic derivative obtained from natural source camptothecin, which is Act as DNA topoisomerase I (Topo I, inhibitor. The formation of a cleavable complex of drug–Topo I–DNA results in lethal double-strand DNA breakage and cell death
5	Regorafenib	Regorafenib contains an oral multikinase inhibitor that targets a range of angiogenic vascular endothelial growth factor (VEGF) receptor tyrosine kinases which involved in the growth of new tumour blood vessels.

Table 1: Synthetic Drugs for the treatment of colorectal cancer.

5-Fluorouracil

5-Flurouracil is used as first-line chemotherapeutic treatment for CRC, commonly known as fluoropyrimidine discovered by Heidelberger and colleagues in 1957. It is a pyrimidine analogue having antineoplastic and antimetabolite activity. 5-FU is an analogue of uracil, in which fluorine is substituted at the C-5 position of uracil in place of hydrogen . 5-Flurouracil and its several metabolites possess different mechanisms, which work against various types of cancers. It acts as a cytotoxic agent by interfering with DNA synthesis through inhibition of thymidylate synthase. 5-FU also interferes with nucleoside metabolism as it can easily get incorporated in RNA and DNA helix and causes cytotoxicity leading to apoptosis . It has been used for more than 40 years in the treatment of CRC . 5-FU absorption through oral route is poor, hence it is majorly given by parenteral route. It is often given in combination with other chemotherapeutics in case of metastatic cancer.

Tummala et al., have formulated 5-FU loaded enteric-coated nanoparticles which shows localization of drug at colon site and large bowel. Results illustrated that the developed 5-FU enteric-coated nanoparticles showed less toxic side effects, prevented drug degradation at gastric pH and sustained release over a prolong period of time (24 hrs). In another study, PLGA nanoparticles of 5-FU have been prepared by Tawfik et al using the nano-precipitation technique. They concluded that 5-FU shows time-dependent as well as prolonged effect due to PLGA. Othman et al. prepared a 5-FU microsponges (MS) for the treatment of CRC. Micro sponges were prepared by using oil in oil emulsion solvent diffusion technique to target and modify the release of active ingredients from the formulation showed enhanced stability and decreased side effects. The results also showed that 5-FU loaded microsponges were more effective than pure 5-FU in cell viability assay. Ganguly et al., worked on 5-FU loaded enteric-coated PEG-cross-linked chitosan microspheres prepared by emulsion cross-linking method followed by solvent evaporation. Result showed that Minimum inhibitory concentration (IC50) values for both standard plain 5-FU and 5-FU-loaded microspheres were 5.00 ± 0.004 µg/mL and 16.5 ± 1.9 µg/Ml; respectively indicating improved safety profile of the microsphere formulation. Wang et al., prepared an in situ thermosensitive gel-mediated 5-FU microemulsion for the treatment of CRC. 5-FU water-in-oil microemulsion was prepared using liquid soyabean oil, span oil, Tween 80, and propylene glycol. Prepared microemulsion formulation was then mixed with thermosensitive gel under mechanical stirring. Result showed that the microemulsion facilitated 5-FU transportation into the target tissue and thermosensitive gel increased the stability of the 5-FU microemulsion as well as the retention time in rectal membrane.

Capecitabine

Capecitabine is used as an adjuvant therapy which was approved by US FDA in 2005 for the treatment of CRC. It can be used either alone or in combination with other chemotherapeutic agents. Capecitabin was established as an alternative option for the combination of 5-FU and leucovorin. Bolus administration of 5-FU gets rapidly disappears because it has a half-life of 8-14 min. Oral administration of capecitabin which acts as a prodrug of 5- FU, easily passes through the intestinal barriers and after metabolism majorly gets activated to 5-FU through an enzymatic reaction. There are 3 steps in metabolism of capecitabine. Firstly, once the drug reaches the intestine there is a conversion of capecitabin to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxyesterase. Further, it gets converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase and lastly, it gets converted to 5-FU by thymidine phosphorylase.Preclinical and clinical studies have proven that capecitabine is highly effective and shows more than 50% tumour inhibition in comparison to other chemotherapeutics like 5-FU and leucovorin. Capecitabin has improved safety profile. Response rate of oral capecitabin is equivalent to IV administration of FU/LV. The oral dose of capecitabine is 1250 mg/m2 twice daily, which is therapeutically similar to a monthly dose of 5-FU and leucovorin.

Various researchers have developed a different novel formulation of capecitabine to target CRC. Capecitabin loaded microspheres effective at a low dose and showed minimum side effects, increased bioavailability and sustained drug release up to 24 hrs, formulated capecitabine tablet with an aim to develop colon-specific, fast disintegrating core tablet using croscarmellose sodium (CCS) as a super disintegrating agent with direct compression method. Further, coating is done by dip coating method using ES100 and CAP (cellulose acetate phthalate). Results showed improvement in bioavailability. Capecitabin loaded chitosan microspheres prepared by Jena et al., for CRC targeting with an aim to enhance the bioavailability, reduce dose, minimize side effect and shows sustain drug release for 24 hrs. The optimized microspheres showed colon-specific controlled release properties and thus could be effective for CRC treatment formulated a capecitabine loaded pH-sensitive nanoparticle for the treatment of CRC. The results showed an increase in percent cytotoxicity activity

in HT-29 human colon cancer cell lines at a concentration of 50µg/ml - 500µg/ml in comparison to pure drug, formulated a capecitabine loaded alginate-pectinate-chitosan beads by an ionotropic gelation method for colon targeting. An in vitro wash off test shows a 70% mucoadhesion of the developed beads. Results revealed that the developed beads loaded into enteric-coated capsules showed a negligible release in gastric pH as well as intestinal pH, subsequently showing a 49.23 % release in colonic pH in 4 hours. This study concluded that the developed beads showed a colon-specific controlled release properties and hence can be effective for the CRC treatment .

Oxaliplatin

Oxaliplatin is a first diamino-cyclohexane-containing platinum-based drug approved by USFDA in august 2002 for the treatment of CRC. Oxaliplatin inhibits DNA replication and transcription through the formation of intra and inter strand DNA adduct. Oxaliplatin are bulkier groups and hydrophobic in nature compared to cisplatin or carboplatin. This property aids in enhancing the DNA inhibition activity. It is more potent than other platinum-based compound like cisplatin. It was first developed as combination therapy, mostly given with 5-FU and leucovorin . Due to absence of hematologic toxicity, it becomes an attractive approach to combine oxaliplatin with other anticancer drugs. It is most commonly used in metastatic type of CRC. When oxaliplatin is administered in combination with 5-FU it shows a response rate of 40-50% with median survival of 18 months. Hence, it is used as a first line therapy for treatment of CRC. Currently, many clinical trials of oxaliplatin in combination with other chemotherapeutics are ongoing (NCT03451370,NCT03748680, NCT01196260). Urbanska et al., have prepared mucoadhesive chitosan coated alginate microspheres of oxaliplatin with an aim to release the drug in intestinal tract after passing via acidic gastric environment. Results illustrated a significant reduction in tumour burden in an orthotopic mouse model and also reduces a mortality rate. Hassanzadeganroudsari et al., developed a Oxaliplatin loaded nanoparticles by reverse phase evaporation method and coated with hydrophilic polymer polyethylene glycol 3350. Results illustrated that Oxaliplatin entrapped in nanoparticles was found to be more stable and thus the plasma half-life is prolonged and adverse effects are reduced to minimum, formulated a hyaluronic acid (HA) and carboxymethyl cellulose sodium-based novel cross-linked hydrogels (HC hydrogels) loaded with oxaliplatin with an aim to prevent intra-abdominal adhesion following CRC therapy. In vitro diffusion study demonstrated a sustained drug release from hydrogels as compared to solutions. In in vivo Sprague Dawley rat model low adhesion scores was observed for oxaliplatin loaded HC hydrogels demonstrating intra-peritoneal adhesion inhibition. Thus, study concluded that HC hydrogels was effective as an intra-abdominal anti-adhesion barrier and allow for the delivery of intra-peritoneal oxaliplatin for the treatment of CRC. Yang et al., have formulated oxaliplatin long-circulating liposomes (PEG-liposomal L-oHP) with an aim to enhance therapeutic index of CRC. The study concluded that developed PEG-liposomal L-oHP shows a better tendency to target tumour tissue and demonstrated a significantly greater impact on apoptosis compared to free oxaliplatin.

Irinotecan

Irinotecan is a synthetic, water-soluble derivative obtained from the plant alkaloid Camptothecin. It acts as a second line therapy for the treatment of CRC. Based on a clinical trial study in 1970's, it was proven that it has an anti-tumor activity but due to unwanted side effects and unfavorable toxicity profile it has lost its clinical interest. Camptothecin acts on s-phase of DNA replication by stabilizing the complex formed between topoisomerase I and DNA, eventually resulting in lethal DNA breaks investigated the use of liposomal Irinotecan in combination with 5-FU. The exposure times on cytotoxicity was assessed in vitro against HT-29 or LS174T human colon carcinoma cells. Synergistic interactions were observed following prolonged exposure to IRI/5-FU combinations. The study concluded that the liposomal Irinotecan is more effective as compared to Irinotecan alone or in combination with 5-FU.

Regorafenib

Regorafenib is an oral small-molecule multiple kinase inhibitor approved by USFDA on October 25, 2012 for the treatment of metastatic colorectal cancer (mCRC). Regorafenib is the generic name for the trade name Stivarga. Regorafenib is a small molecule inhibitor of multiple protein kinases, comprising those involved in the pathological processes of oncogenesis (RET, KIT, BRAF, RAF-1, BRAFV600E), tumour angiogenesis (TIE2, VEGFR-1, -2 and -3) and maintenance of the tumour microenvironment (FGFR, PDGFR). It has a distinct profile targeting angiogenic, stromal and oncogenic receptor tyrosine kinases (RTKs). Regorafenib has been the only promising multi tyrosine kinase inhibitor that has been successfully tested in a Phase III clinical study (NCT03829462). Regorafenib is now added in the US National Comprehensive Cancer Network guidelines for colon or rectal cancer as an additional line of therapy for metastatic disease patients who are refractory to chemotherapy. The suggestions are to use regorafenib in the third-line setting in patients with mutant KRAS tumours and in the third- or fourth-line setting in those with wild type KRAS tumours. Correspondingly, regorafenib is also added in the European Society for Medical Oncology guidelines for CRC as a third or fourth-line option in advanced disease patients . Grothey A et al., conducted an international, multicentre, randomised, placebo-controlled phase III trial of regorafenib in previously treated mCRC patients. The patients were administered oral regorafenib at a dose of 160 mg or placebo once daily, for the first 3 weeks of each 4-week cycle. 1052 patients were screened, out of which 753 patients initiated treatment (regorafenib n=500; placebo n=253; population for safety analyses) and 760 patients was randomised to administered regorafenib (n=505) or placebo (n=255). Results showed that OS was achieved at a preplanned interim analysis and the median overall survival rate obtained was 6•4 months in the regorafenib group versus 5 months in the placebo group. Treatment-related adverseevents was observed in 154 (61%) patients assigned placebo and in 465 (93%) of those assigned regorafenib . Based on clinical trial reports Aljubran et al., assess the efficacy of regorafenib in 78 metastatic colorectal cancer patients. Reports concluded that regorafenib was found to have an equal efficacy as obtained from reported pivotal registration trial.

Targeted drug delivery

Targeted drug delivery system, sometimes called smart drug delivery, is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body compared to others. This can be achieved by developing clinically useful novel targeted formulations. Targeted therapies are generally better tolerated than traditional chemotherapy. The targeted receptors can be either tumour specific or tissue specific. Cell surface receptors and their cognate ligands provide unique opportunities for drug development [20].Basic targeting is achieved by a specific interaction between the drug and its receptor (Figure 5, Table 2).In CRC, many proteins get overexpressed during the tumour progression. Thus, by actively targeting these specific protein it will affects its function and minimizes the toxicity to normal tissue [3](Figure 5)(Table 2).

Proteins which are overexpressed	Targeting drug
EGFR (Epidermal growth factor receptor)	Cetuximab, Panitumab
EpCAM (Epithelial cell adhesion molecule)	Edrecolomab, Curcumin
FGFR (Fibroblast growth factor receptor)	Doxirubicin, Paclitaxel
CD 44 (Cluster of differentiation-44)	Doxirubicin hydrochloride
COX-2 (Cyclooxygenase -2)	Celcoxib
FT (Folate receptor targeting)	5- Flurouracil

Table 2: Proteins overexpressed in colorectal cancer and its targeting drug.

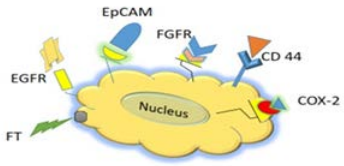

Figure 5: Overexpressed proteins in colorectal cancer.

Bevacizumab

Bevacizumab is a monoclonal antibody approved by USFDA in 2004 as first line agent for the treatment of metastatic colorectal cancer. It blocks all the isoform of vesicular endothelial growth factor. Bevacizumab causes the reduction in VEGF protein levels by binding to its receptors, thus neutralizing this ligand's function and decreasing neovascularization of tumours. The elimination of bevacizumab is independent of liver function; it mainly occurs through cellular internalization and further intracellular catabolism. In clinical trials, it was proven that it improves overall survival and response rate in metastatic colorectal cancer. Current researchers now focused on combination with other cytotoxic drugs, which will helps in improvement of overall survival, progression rate survival and response rate. Subsequently, Phase III studies (E3200, ML18147 and NO16966) confirmed that adding Bevacizumab to chemotherapy regimens improves progression-free survival (PFS) and overall survival (OS) in comparison to chemotherapy alone. Since, last few decades it is used for metastatic colorectal cancer in combination with 5-FU. Despite the benefits of bevacizumab in mCRC, access to treatment can be problematic. The specific barriers to accessing bevacizumab appear to vary according to the country, healthcare system and clinical scenario concerned. Access may be limited due to affordability, insurance coverage and treatment cost which creates barrier to use bevacizumab in many countries. Physicians frequently had to provide medical justification for bevacizumab use due to issue related to treatment costs. The imminent expiry of patents protecting bevacizumab provides other manufacture with the opportunity to produce highly similar version known as bio-similars. Most of the bevacizumab biosimilar currently in development are in clinical trials in patient with non-small cell lung cancer and further authorization for mCRC indication will be based on extrapolation [18]. Systemic administration of Bevacizumab comes with several side effects like arterial hypertension, proteinuria, thromboembolic events and bleeding. Hence, further investigation isneeded to be done for an alternative option.

Cetuximab

Cetuximab is a IgG1 monoclonal antibody, which was initially accepted by USFDA in 2004 as a third line single agent in patients who failed to improve health condition with common therapeutics like oxaliplatin and Irinotecan based chemotherapy. Cetuximab specifically targets the epidermal growth factor receptor (EGFR). The EGFR is commonly expressed as 170,000 K Da trans membrane glycoprotein. EGFR is involved in signalling pathway affecting cellular growth, differentiation and proliferation. Cetuximab binds to the extracellular domain of EGFR, which consist of ligand binding site. Mechanism of anti-EGFR antibody blockade lead to cell cycle arrest. Cetuximab is still not used as a first line therapy because a reliable data is not available in clinical trials, thus it is commonly used in combination therapies. Randomised studies of cetuximab carried out in combination with irinotecan, infusional fluorouracil, and leucovorin (FOLFIRI shows a high tumour response rate. The addition of cetuximab to a combined first-line chemotherapy regimen of (FOLFIRI) significantly reduces the risk of progression of mCRC compared with the chemotherapy alone [17].

Ederocolomab

Ederocolomab is a first murine IgG2a monoclonal antibody, which was approved in Germany in 1995 as an adjuvant therapy for the primary colorectal tumour and gets USFDA approval in year 2006. It specifically targets epithelial cell adhesion molecule (EpCAM) which are overexpressed in colorectal carcinoma.EpCAM is 39 kDa glycoprotein known to be present in epithelial cancer cells which enhances the proliferation of tumour, invasion rate and metastasis, ultimately leads to decrease in the overall survival rate . Monotherapy of Ederocolomab is more significant than combination therapy; it increases disease free survival and overall survival rate. Randomised study conducted by Riethmuller and colleagues on 189 patients with stage III CRC revealed that the mortality rate was decreased by 32%. Ederocolomab in combination therapy was well tolerated with other drug but did not increases the overall survival rate.

Nivolumab

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody, which was approved by USFDA in 2014 for the treatment MSI-H (High microsatellite instability) or dMMR (DNA mismatch repair) metastatic CRC. PD-1 is an inhibitory receptor expressed on the surface of B cells, T cells, macrophage and NK cells. Endogenous binding of PD-1 with one of its two ligands PD-L1 and PD-L2 led to production of an inhibitory signal resulting in decrease of T cell proliferation, cytokine production and cytotoxic activity.Nivolumab has a high affinity for PD-L1 receptor. Due to a manageable safety profile, it is well tolerated and suitable for use in most of the patients. A phase II study of nivolumab was conducted in 74 metastatic DNA mismatch repair deficient/microsatellite instability–high CRC patients. Most of the patients (54.1%) have received more than three prior therapies. The most common adverse events related to drug shown, were diarrhoea, fatigue, rash and pruritus. Grade 3 or 4 adverse events related to drug observed, were upregulation of lipase and amylase levels. Five patients discontinued the treatment due to colitis, increased alanine aminotransferase, acute kidney injury, stomatitis and duodenal ulcer. Twenty-three patients were died during the study; none of these deaths was related to treatment. Nivolumab has shown a durable response as well as long term survival in pre-treated patients with

dMMR/MSI-H mCRC and it was concluded that it could be a new option for treatment of these patients [19].

5-FU conjugated with folate

Folate receptor (FR) exists in various malignant tumors. Its expression is highly overexpressed in several human cancers and highly inhibited in normal tissues. Overexpression of FR was determined by an in vitro model for the examination of targeted delivery systems. Folic acid (FA), a water soluble vitamin is one of the ligands having a high affinity for FR. Hence, FA and folate conjugates have established a significantly improved delivery to FR-positive cancer cells. Folic acid or its conjugates binds with the folate receptor located at the surface of cancer cells and are internalized to intracellular compartments to form endosomes. FA can be easily incorporated into nanoparticles for the enhancement of targeting efficiency against cancer cells because of its high affinity, small size and lack of toxicity. The novel formulation developed for the folate receptor targeted drug delivery using folic acid are discussed below.

Handali Et al., formulated a 5-FU containing targeted liposomes with an aim to improve the safety and efficacy of drug. The FA was used as a targeting ligand. The entrapment efficiency of the optimized batch was found to be 39.71% with a particle size around 174 nm. Results illustrated that 5-FU targeted liposomes showed a higher cytotoxicity then liposomal 5-FU and pure 5-FU in CT26, HT-29, HeLa, MCF-7 and Caco-2 cell lines. The in vivo results of %-FU targeted liposomes showed a significant reduction in tumour volume as compared to 5-FU [75]. El-Hammadi Et al., developed a folic acid-decorated and PEGylated poly (D,L-lactide-co-glycolide) nanoparticles (FA-PEG-PLGA NPs) for the targeted delivery of 5-FU to colon and breast cancer cells. Nanoparticles of PLGA, PEG-PLGA, and FA-PEG-PLGA was prepared by nanoprecipitation method under optimum formulation conditions. The above developed nanoparticles exhibited a negligible cytotoxicity in human tumour (MCF-7 and HT-29) and normal (MCF-10A and CCD-18) cell lines. In vitro study revealed that 5-FU-loaded FA-PEG-PLGA NPs showed a 4-fold less half maximal inhibitory concentration (IC50) as compared to 5-FU-loaded PLGA NPs in folate-overexpressed MCF-7 breast cancer cells and HT-29 colon cancer cells [5].

Plant derived drugs

Medicinal plants are promising source of anticancer drugs used by more than 70% population for the treatment of cancers. Herbal medicines have advantages over chemotherapeutics as these have less side effects, cost effective and easy availability of the medications for the treatment. Majority of herbal extracts lead to inhibition of CRC growth via induction of autophagy or apoptosis, by triggering various signaling pathways and cell cycle arrest at different phases . Phenolic compounds seem to be the vital active molecules responsible to these anti-colorectal effects. Remarkably, herbal formulations could be used as a potential formulation for anti-colorectal cancer therapies due to their synergistic action. Additionally, studies should be conducted to isolate, identify and use various phytochemicals in the treatment of CRC or chemoprevention and improve patient's outcome. Genotoxic and toxicological evaluations of the several herbal products exhibiting promising anti-colorectal activities (purified compounds, herbal mixtures or crude extracts) should be carried out. Moreover, synthesis of analogues of bioactive compounds to enhance their solubility, bioavailability and effectiveness can be more advantageous to these products. Correspondingly, associating herbal products and synthetic drugs might be of great interest as a promising therapeutical approach against CRC.

Curcumin

Traditionally, curcumin is used as an anti-inflammatory agent from ages and it is one of the main components of turmeric rhizome i.e. curcuma longa. It is also well known for its antioxidant and antimicrobial property. In last 30 years it was proven that curcumin can be used for the prevention and treatment of cancers. Curcumin induces apoptosis through various mechanism like transcription factors, targeting pathways, membrane receptors, kinase and cytokines [80]. In cell culture studies curcumin has shown significant efficacy where as in clinical studies it shows limited efficacy because of conventional oral administration. To circumvent these barriers, alternative drug delivery strategies and system should be explored [20].

M. Madhavi et al., formulated a sustained release curcumin microsphere using eudragit S100 polymer with the help of O/O emulsion solvent evaporation method to treat CRC. In vitro in vivo drug studies demonstrated that the above formulation achieved a site specific drug delivery with sustained release of the drug. Curcumin has shown an anticancer activity, but stability and bioavailability limit its use in formulations. Thus, to overcome these above issues Wang et al., developed a novel micellar formulation of curcumin in which curcumin nanoparticles are encapsulated in stearic acid-chitosan oligosaccharide (CSO-SA) polymeric micelles which showed more stability and better in vitro anti-tumour activity. Results revealed 6-fold increase in anti-tumour activity compared to pure curcumin. In another study, curcumin microspheres were prepared by Suresh Kumar et al., with high molecular weight hydroxypropyl methylcellulose (HPMC) and biodegradable pectin which prevents drug release from the upper GIT. Birgani et al., have prepared nanovesicles called Dendrosomes to reduce the toxicity of anticancer drug to normal cell. In which, they efficiently encapsulate a curcumin in spherical micellar formulation resulting in increased aqueous solubility and bioavailability of curcumin [85]. Vajpayee et al., prepared colon targeted curcumin microsphere by ionic cross-linking technique using calcium chloride with an aim to recognize suitable polymer-based microspheres showed promising mouth to colon in vitro release profile. Two polymers (sodium alginate: guar gum / sodium alginate: xanthan gum) were used in different concentration to make three formulations with each polymer. Results illustrated that xanthum gum microspheres had a more retarded release in colon than guar gum microspheres [13].

Naringenin (NAR)

Naringenin flavonoid (4,5,7-trihydroxyflavanone), isolated from the pollen of Typha angustata, commonly found in marshy land and flood plains. It was found in studies that it significantly inhibits the cell proliferation in a dose-dependent manner. In humans, it acts as an estrogenic substance whereas, in plants it acts as an endogenous regulator. Flavonoids depending on their degree of condensation and the position and number of substitutions their biological activities get varies. NAR contains three hydroxy groups, and O-substitutions can easily be carried out at the 4'- and 7-hydroxy groups positions. However, at the 5-hydroxy group position O-substitutions results in formation of hydrogen bond (H-bond) with the ketone at C-4, making it less accessible. From the cell based clonogenic assay, it was observed that NAR derivatives inhibits HCT116 cancer cells effectively. This study was in agreement with the study carried out by Song et al. where in vitro anti-cancer activities of NAR were performed in human colon cancer cell lines such as HCT116, SW480, LoVo and HT-29 were. Results showed that NAR inhibits the expressions of these cell lines

by activating ATF3 (Activating transcription factor 3) expression. In addition, ATF3 overexpression increased naringenin-mediated cleavage of PARP (Poly (ADP-ribose) polymerase) and ATF3 knockdown attenuated PARP cleavage by NAR. NAR can be combined with DNA acting drugs to potentiate its activity via pro-apoptotic signaling pathways and negative survival signaling thus, reducing its side effects. The preclinical studies are needed to be carried out in order to prove its further efficacy [14].

Oridonin

Oridonin is a tetracycline diterpenoid compound isolated from Rabdosia rubescens, a Chinese herb having potential anti-tumour activities. Gao et al. observed oridonin induced apoptosis and senescence in CRC cells by increasing histone hyperacetylation and regulation of p16, p21, p27 (cyclin-dependent kinase inhibitor) and c-myc (family of regulator genes and proto-oncogenes that code for transcription factors). Oridonin induces apoptosis in variety of cancer cells like prostate cancer, breast cancer, acute leukemia and non-small lung cancer. The basic mechanism of Oridonin is that it arrests the cell cycle progression of G2/M or G0/G1 phase and induces apoptosis. It also induces apoptosis through signals mediated by Fatty acid synthase (FAS) ligand and FAS receptor in human lymphoma cell. In HCT 116, HT 29, SW1116 cell lines, Oridonin showed inhibition of cell proliferation in dose and time dependent manner . FAS might be a therapeutic target in cancer treatment. Knockdown of the expression of FAS in CRC cells by siRNA leads to induction of apoptosis. Kwan et al., found a reduced viability of CRC cells SW620 and SW480 through knockdown of FAS. Zhuo Yao et al., determined the anticancer activity of Oridonin in both in- vitro and in-vivo CRC cells. They identified that glucose metabolism is a potential target for CRC treatment. Results illustrated that Oridonin causes metabolic imbalances through reduction of lactate export and inhibition of glucose uptake by significantly down regulating the protein levels ofMCT1 and GLUT1 in vitro and in vivo, respectively.

Betulinic acid

Betulinic acid (3β, hydroxy-lup-20(29)-en-28-oic acid) (BA) is a pentacyclic triterpenoid isolated from the bark of Betula alba (the common white birch). It shows several activities such as anti-retroviral, anti-inflammatory, anti-malarial properties, as well as, a more recently determined, as a potential anticancer agent by inhibiting topoisomerase. BA was one of the first natural products identified and isolated from plants in 1788. One characteristic feature of BA cytotoxicity is its ability to trigger the mitochondrial pathway of apoptosis in cancer cells. BA is a highly lipophilic molecule with low aqueous solubility and this results in reduction in in vivo uptake of this compound. Hence, development of specialized formulations/carriers like liposomes could help in enhancing the in vivo efficacy of BA as an anticancer agent. BA results in induction of apoptosis via production of reactive oxygen species, opening of mitochondrial permeability transition pores and induction of changes in mitochondrial membrane potential leading to activation of caspases, DNA fragmentation and release of mitochondrial apogenic factors. BA induced apoptosis in SW480 and RKO colon cancer cells and inhibited tumour growth in athymic nude mice bearing RKO cells as xenograft. BA also leads to downregulation of expression of Sp1, Sp3 and Sp4 transcription factors which are overexpressed in colon cancer cells and decreased levels of various Sp-regulated genes comprising vascular endothelial growth factor, survivin, epidermal growth factor receptor, p65 subunit of NFκB, pituitary tumour transforming gene-1 and cyclin D1.

Combination therapy

New combination treatments can extend the survival of many patients. In combination therapy, individual drug dose can be reduced and hence, the side effects of chemotherapeutics. Anti-cancer agents are more effective when they are used in combination. Individual drug has their own mechanism, hence become more effective and decreases the chance of resistance that is produced by cancer cells for any drug when it is used in combination. On July 10, 2018 ipilimumab (Yervoy) was granted an accelerated approval in combination with nivolumab (Opdivo) for the treatment of MSI-H or DMMR Metastatic CRC. 5-FU and leucovorin are a standard adjuvant therapy used for CRC. In this combination addition of oxaliplatin improves the efficacy of the combined drugs. FOLFOX is a backbone for the treatment of CRC [97]. Combine metronomic chemotherapy with oxaliplatin, which is in the form of PEG coated liposomes. Results shows an excellent anti-tumour activity with less overlapping side effects. This is mainly due to liposomes of oxaliplatin have high permeability and prolong retention in the tumour. Hence, it can be used an alternative to FOLFOX first line chemotherapy with less side effects and acceptable tolerance. In EGFR-overexpressed cell lines, intracellular drug delivery through targeted liposomes leads to increment in receptor density reaching up to 3-fold higher levels than with non-targeted liposomes.A phase I study to determine the maximum tolerated dose and to assess its safety and efficacy was conducted of irinotecan, oxaliplatin, continuous infusion of 5-FU and leucovorin (FOLFOXIRI) in combination with cetuximab in nine Japanese patients with RAS wild-type mCRC. No patients have showed a dose limiting toxicity. Amongst nine patients, one patient showed a complete response (CR), 7 patients showed partial response and one patient showed a progressive disease, with an overall response rate of 89%. Thus FOLFOXIRI plus cetuximab combination has proven a significant anti-tumour activity and a favorable toxicity profile in RAS wild-type mCRC patients [100]. A phase III study of SOX [S-1(tegafur, gimeracil, and oteracil potassium) /oxaliplatin] vs COX (capecitabine/oxaliplatin) was conducted to evaluate whether SOX is noninferior to COX in terms of PFS in previously untreated with systemic therapy for mCRC patients. The overall response rate was 34.2% and 48.9 % with COX and SOX, respectively. The study concluded that SOX is non-inferior to COX in terms of efficacy in the first line treatment of mCRC. A phase II study of Z (ziv-aflibercept) in combination with FOLFIRI in was conducted to assess the safety and efficacy in 62 patients with mCRC. Patients were administered with a dose of 4mg/kg of Z with FOLFIRI [400mg/m2 bolus 5-FU, 2400 mg/m2 continuous infusion 5-FU, 200 mg/m2 levofolinate, 180 mg/m2 irinotecan]. The study showed the median OSwas 15.59 months and ORR (full form Objective response rate) of 8.3% .

Chen Jen ma et al., evaluated oncologic outcomes of regorafenib in combination with FOLFIRI with dose-escalated irinotecan in 41 previously heavily treated mCRC patients. Results shown that the overall disease control rate was found to be 58.5%, while the median PFS and OS was 6 and 12 months, respectively. This study concluded that the regorafenib combined with FOLFIRI with dosed escalated irinotecan appeared to have a potential activity with suitable oncological outcomes conducted a phase II trial of regorafenib followed by cetuximab (R-C) in comparison to cetuximab followed by regorafenib (C-R) in KRAS exon 2 wild-type mCRC patients. Results showed that median OS for C-R and R-C was 11.6 and 17.4 months, respectively, with a hazard ratio (HR) of 0.61 for OS. The HR observed for PFS1 (regorafenib in R-C versus cetuximab in C-R) was 0.97, and PFS2 (C in R-C versus R in C-R) was 0.29. This study concluded

that therapeutic sequence of R-C was found to have a longer OS than the current standard sequence. A phase I/II study of capecitabine in combination with TRAP (ziv-aflibercept) was conducted in mCRC patients to define a recommended phase II dose study and assessed the clinical activity, safety and tolerability. It was concluded that Capecitabine in combination with TRAP has showed an acceptable safety profile and a promising clinical activity at the recommended phase II dose. A non-inferiority phase III study of cetuximab vs panitumumab was conducted in chemotherapy refractory wild type KRAS exon 2 mCRC patients. Results showed that panitumumab was found to be non-inferior to cetuximab and has similar overall survival benefit . A randomized phase 3 study of combination (Bevacizumab + capecitabine) was carried out in 70 patients to prove the safety and efficacy of the combination in the comparison with capecitabine alone. Results demonstrated that the progression-free survival was significantly longer with combination than with capecitabine alone. A phase IV study was conducted to evaluate the safety and efficacy of Bevacizumab in combination XELOL for the treatment in mCRC or advanced CRC (aCRC) patients. The combination was found to be efficacious with acceptable toxicity in mCRC or aCRC in terms of progression free survival (PFS). Another phase I study of axitinib in combination with Bevacizumab and chemotherapy or chemotherapy alone in mCRC and other solid tumors in thirty patients were conducted. The pharmacokinetic parameters were also assessed during study. Five cohorts' groups were made. Patients were administered with axitinib with 5mg b.i.d in combination with Bevacizumab (1, 2, 5mg/kg) plus FOLFOX in 1-3 cohorts. FOLFIRI and FOLFOX were administered with axitinib to cohort 4 and 5, respectively. The results illustrated that axitinib was well tolerated in combination with FOLFOX plus bevacizumab (2mg/kg), FOLFOX or FOLFORI. There was no occurrence of PK interaction. Patel et al., performed the in vitro studies of curcumin in combination with FOLFOX on HT-29 and HCT-116 cell lines and concluded that the combination is more efficacious with 68% to 73% of growth inhibition.

Conclusion

CRC treatment requires various therapeutic approach. However, chemotherapy has shown certain limitations resulting in search of alternative sources. Plant-derived drugs have shown some promising antitumor effect. Further investigation on plant-derived drugs can be fruitful approach for the treatment of CRC. Targeted drug delivery by specific targeting of overexpressed proteins in CRC can be the best way for the design of the novel drugs. Although many drugs targeting the overexpressed proteins have been approved and are already in market. There is need to develop more efficacious treatment. Further, drug resistant occurrence causes difficulties in treatment. Therefore, various combination chemotherapy trials are ongoing to overcome the resistance and other side-effects of the alone treatment. In future, as there are improvements in understanding of the biology of the disease new treatment approaches have to be explored.

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Conflict of Interest

None.

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