CRITICAL REVIEW IN PHARMACEUTICAL SCIENCES

eISSN 2319-1082

Review Article

NOVEL STRATEGIES FOR THE TREATMENT OF COLON-CANCER WITH NANOPARTICULATE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Colon cancer is a neoplastic disorder of the large intestine,which probably derived from inherited or somatic genetic alterations and develop over the course of a lifetime. Colorectal carcinoma is hence regarded as the most common cause of cancer related death next to lung cancer as per the survey reports in USA, where many patients are presented with surgical resection stage but half of the presented cases are unable to survive from the disease. Colorectal cancer originates from the epithelial lining, most often as a consequence of mutations in the Wnt signaling pathway. Colon specific drug delivery had gained increased importance just for the delivery of drugs for the treatment of local diseases associated with the colon. With the emergence of nanotechnology that is being applied to cancer in two broad areas: the development of nanovectors, such as nanoparticles, which can be loaded with drugs or imaging agents and then targeted to tumors, and high throughput nanosensor devices for detecting the biological signatures of cancer. Nanoparticles exploit biological pathway to achieve payload delivery to cellular and intracellular targets. The nanoparticles also increase the half-life of the drug, and help in concentrating anticancer molecules to the tumor mass, providing optimal drug delivery, and minimizing drug toxicity. The nanoparticles are in the size range of 1 to 100nm in diameter, which makes them unique in being delivered to the cancerous tissues quickly than the bulk materials. As nanotechnology promises to be a new strategy for improving the prognosis of colon cancer patients, it would be very useful to analyze recent progress in this field of research. Polymeric nanocarriers with anticancer drugs conjugated or encapsulated, form a variety of different architectures including polymer-drug conjugates, micelles, nanospheres, nanogels, vesicles, and dendrimers Nanomedicine has the potential to increase the specific treatment of cancer cells while leaving healthy cells intact through the use of novel nanoparticles to seek and treat cancer in the human body.
Keywords: Colon Cancer, Nano-technology, Colorectal Carcinoma.

INTRODUCTION

About Cancer:

Cancer is a potentially fatal disease caused mainly by environmental factors that mutate genes encoding critical cell-regulatory proteins. The resultant aberrant cell behavior leads to expansive masses of abnormal cells that destroy surrounding normal tissue and can spread to vital organs resulting in disseminated disease, commonly a harbinger of imminent patient death. Cancer is a complex genetic disease that is caused primarily by environmental factors. The cancer-causing agents (carcinogens) can be present in food and water, in the air and in chemicals and sunlight that people are exposed to. Since epithelial cells cover the skin, line the respiratory and

alimentary tracts, and metabolize ingested carcinogens, it is not surprising that over 90% of cancers occur in epithelia. The causes of serious ill-health in the world are changing. Infection as a major cause is giving way to non communicable diseases such as cardiovascular disease and cancer. In 1996 there were 10 million new cancer cases worldwide and six million deaths attributed to cancer. In 2020 there are predicted to be 20 million new cases and 12 million deaths. Part of the reason for this is that life expectancy is steadily rising and most cancers are more common in an ageing population. More significantly, a globalization of unhealthy lifestyles, particularly cigarette smoking and the adoption of many features of the modern Western diet (high fat, low fiber content) will increase cancer incidence. Tobacco use and diet each account for about 30% of new cancer cases, with infection associated with a further 15%; thus, much of cancer is preventable. No individual can guarantee not to contract the disease, but it is so strongly linked to diet and lifestyle that there are plenty of positive steps that can be taken to reduce the chances: eat more fruit and vegetables, reduce the intake of red meat and definitely do not smoke. Carcinogens interact with the individual's constitution, both inherited and acquired, determining vulnerability to cancer induction. This vulnerability is based on how an individual deals with the carcinogens, ideally eliminating them in a harmless form before they do any genetic damage or being able to repair that damage. **[1]**

Classification

In terms of behaviour, tumours are either 'benign' or 'malignant'. Benign tumours are generally slow-growing expansive masses that compress rather than invade surrounding tissue. As such they generally pose little threat, except when growing in a confined space like the skull, and can usually be readily excised. However, many so-called benign tumours have malignant potential, notably those occurring in the large intestine, and these should be removed before malignancy develops. Malignant tumours are usually rapidly growing, invading surrounding tissue and, most significantly, colonizing distant organs. The ability of tumour cells to detach from the original mass (the primary tumour) and set up a metastasis (secondary tumour) discontinuous with the primary is unequivocal proof of malignancy. Tumours are also classified according to their tissue of origin; recognition of the parent tissue in a lymph node metastasis could establish the location of a hitherto undiagnosed primary tumours. **[1]**

Pathophysiology of Cancer

The commonly accepted basis of the pathogenesis of cancer is the damage to the genetic apparatus of cells (mutation, disturbance of gene expression, activation of tumor promoter gene, inactivation of tumor suppressor genes, etc.) . Based on this, the only pathogenic cancer therapy is the application of methods of cancer gene therapy (RNA approaches, drug resistance, hematopoietic progenitor cell gene transfer, cancer stem cells, homologous recombination, ribosome technology, antisense technology, tumor suppressors, gene delivery systems viral and non-viral, anti-gene therapy antisense, siRNA & ribosome; apoptosis, DNA synthesis and repair), aimed to eliminating the genetic damage and control over cancer cells. However, the methods of cancer gene therapy are only being developed and their use in clinical practice is the matter of the future. **[2]**

Causes of General Cancer

It is accepted to distinguish three etiological causes of cancer and respectively, three types of carcinogenesis: chemical carcinogenesis (chemical carcinogens benzpyrene, asbestos and over 800 chemicals) physical carcinogenesis (physical carcinogens ionizing radiation, ultraviolet radiation, etc.), biological carcinogenesis (biological carcinogens viruses, bacteria, fungi).

However, in clinical practice it is practically impossible to determine the etiological cause of cancer, and to prescribe the appropriate etiotropic cancer therapy in each case, so the causal cancer treatment does not exist. **[2]**

Anatomy and Physiology of Cancer

The first and longest part of large intestine is colon, a muscular tube about 5 feet long. Water and minerals nutrients are absorbed form the food matter in the colon. The colon had 4 sections:-

1. The first section is called as the 'Ascending Colon'. It starts where the small intestine attaches to the colon and extends upwards on the right side of the abdomen.
2. The second section is called as the 'Transverse Colon'. Since it crosses the body from the right to the left side in the upper abdomen.
3. The third section is the 'Descending Colon'. It continues downwards on left colon.
4. The fourth and last section is known as 'Sigmoid Colon' because of its "S" or sigmoid shape

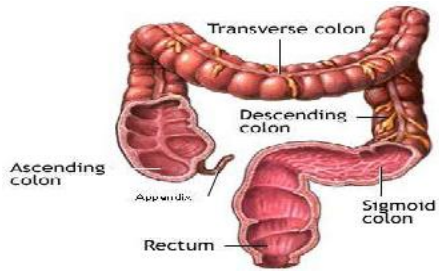

Figure: 1 Anatomy of a Human Colon **[8]**

The physiological factors governing the colon drug delivery are gastrointestinal transit, small intestine transit, colonic transit, Gastric emptying, Stomach and intestinal pH, Colonic Micro flora and Enzymes, Colonic absorption. It is must to go through the above considerations for the design of colon target drug delivery. **[3]**

Disorders of Colon.

Ulcerative colitis: Ulcerative colitis is a form of inflammatory bowel disease (IBD). It causes swelling ulcerating loss of function of large intestine. **[4]**

Crohn's disease: Crohn's disease is an incurable chronic disease of the intestinal tract, and its sister disorder collectively known as Inflammatory bowel disease.

Amoebiasis: An infection or disease caused by amoebas, especially of the species Entamoeba histolytica characterized by dysentery.

Diverticulosis: Small weak areas in the colon's muscular wall allow the colon's lining to protrude through ,formin tiny pouches called diverticuli**.**

Inflammatory bowel disease: A name for either's crohn's disease or ulcerative colitis.

Diarrhoea: stools that are frequent, loose or watery commonly called diarrhea.

Colon polyps: polyps are small growths. Some of these develop into cancer, but it takes a long time.

Colon cancer: cancer of the colon affecting more than 100,000 Americans. **[4]**

Inflammatory Bowel Disease

The idiopathic inflammatory bowel diseases comprise two types of chronic intestinal disorders: Crohn's disease and ulcerative colitis. Accumulating evidence suggests that inflammatory bowel disease results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host. Genetic studies highlight the importance of host–microbe

interactions in the pathogenesis of these diseases. Prominent among these genetic findings are genomic regions containing nucleotide oligomerization domain 2 (NOD2), autophagy genes and components of the interleukin-23–type 17 helper T-cell (Th17) pathway.2 The NOD2 protein is an intracellular sensor of bacterial peptidoglycan, and autophagy enables cells to regulate and degrade diverse intracellular components, including pathogens. The autophagy gene, *ATG16L1*, has been associated with Crohn's disease but not, thus far, with ulcerative colitis. The interleukin-23–Th17 pathway mediates microbial defense and intestinal inflammation. Multiple genes regulating this pathway have been associated with both Crohn's disease and ulcerative colitis. This review summarizes recent progress in studies of intestinal immunity and genetics in inflammatory bowel disease. **[5]**

Colon Cancer

Colon cancer is a neoplastic disease of the large intestine, which can be derived from both inherited or somatic genetic alterations that develop over the course of a lifetime. **[6]** .Colorectal cancer is the solid cancer which may arise from the colon or the rectum with many similar features and may be referred to as colon cancer or rectal cancer depending upon the site of origin. A million people around the globe develop colorectal carcinoma each year and half of these people usually die due to systemic disease within a span of five years from the time of diagnosis. Colorectal carcinoma is hence regarded as the most common cause of cancer related death next to lung cancer, where many patients are presented with surgical resection stage but half of the presented cases are unable to survive from the disease. The palliative therapy with radiation can be given in the patients. The chemotherapeutic therapy was not very promising in the past and resulted partial or infrequent shrinkage of tumor mass at high cost and less improvement in general status, whereas nowadays with the advancement of novel chemotherapeutic agents, the survival benefit and improvements in quality of life has been attained. The pathological aspects of colorectal carcinoma is variable in different population groups in the developed and underdeveloped countries.**[8]**

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the US. The American Cancer Society estimates that 136,830 people will be diagnosed with colorectal cancer and 50,310 people will die from the disease in 2014. The majority of these cancers and deaths could be prevented by applying existing knowledge about cancer prevention, increasing the use of recommended screening tests, and ensuring that all patients receive timely, standard treatment. In the past decade, there has been unprecedented progress in reducing colorectal cancer incidence and death rates in the US, largely due to the prevention and early detection of colorectal cancer through screening. However, in 2010 only 59% of people age 50 or older, for whom screening is recommended, reported having received colorectal cancer testing consistent with current guidelines. Screening has the potential to prevent colorectal cancer because it can detect precancerous growths, called polyps, in the colon and rectum. Although most polyps will not become cancerous, removing them can prevent cancer from occurring. Furthermore, regular screening increases the likelihood that colorectal cancers that do develop will be detected at an early stage, when they are more likely to be cured, treatment is less extensive, and recovery is faster. In addition to following recommended screening guidelines, people can reduce their risk of developing or dying from colorectal cancer by maintaining a healthy body weight; engaging in regular physical activity; eating a healthy, well-balanced diet; limiting alcohol consumption. **[7]**

eISSN 2319-1082

Epidemiology:

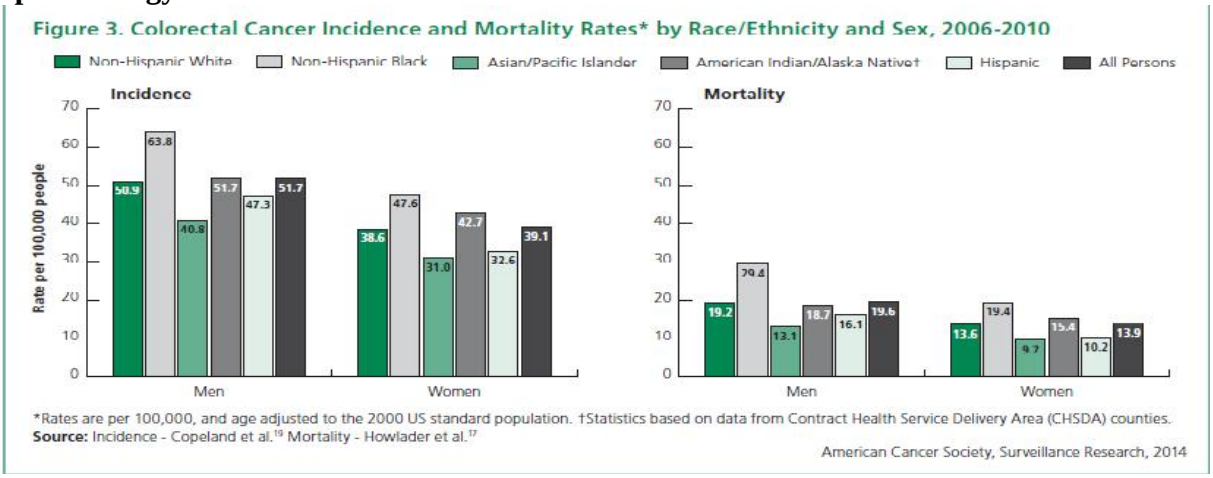

Figure: 2 Colorectal Cancer Incidence and Mortality rates **[7]**

Types of colon Cancer.

The diagnostic report of resected CRC specimen specifies the anatomical site of origin, histological type, parameters definite of local tumors and evidence of metastases. It can very much predict the chances of survival or susceptibility of the disease to chemotherapy. Clinico-pathological evaluation and quality control e.g the actual tumor size vs. the size assessment by imaging may be attained. The standardization and interpretative value of these diagnostic features are however variable. To attain specific and consistent pathological report of CRC, the globally accepted standard histological classification is by WHO, which classifies CRC into

a) Adenocarcinoma

b) Medullary Carcinoma (non gland forming carcinoma of uniform polygonal cancer cells infiltrated with lymphocytes and nested, organoid, trabecular pattern, referred to as undifferentiated carcinoma in the past-prognostically favourable)

c) Mucinous (colloid) adenocarcinoma (50% mucinous) (serves as an adverse prognostic factor when located at rectosigmoid)

d) Signet-ring cell carcinoma (50% signet-ring cells) (prognostically significant)

e) Squamous cell (epidermoid) carcinoma

f) Adenosquamous carcinoma

g) Small-cell (oat cell) carcinoma (prognostically unfavourable)

h) Undifferentiated carcinoma

i) Other (*e.g.*, papillary carcinoma) **[8]**

Stages of Colon Cancer

The clinical and pathologic stages may be different in some cases. The stages describe the extent of cancer in the body. The various stages of a cancer are one of the most important factors in determining prognosis and treatment. Staging is the process of finding out how far a cancer has spread.

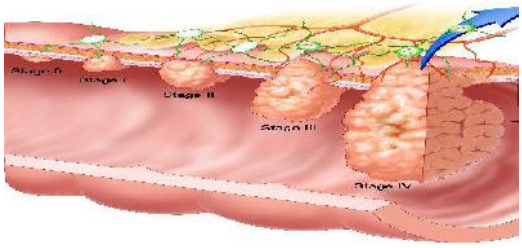

Figure 3: Various stages of colon cancer

Stage 0: Cancer has not grown beyond the inner lining of the colon
Stage 1: Cancer has grown through several layers of colon
Stage 2: Cancer has grown into the wall of the colon and may have extended into nearly tissue
Stage 3: Cancer has spread to nearby lymph nodes but not to other parts of body.
Stage 4: Cancer has spread to distant organs and tissues [**3]**

Grades of Colon Cancer

The tumors in CRC are graded by different methods but the common grading are as follows
Grade 1 (Well differentiated),
Grade 2 (Moderately differentiated),
Grade 3 (Poorly differentiated),
Grade 4 (Undifferentiated) or
Low Grade (Well differentiated and moderately differentiated)
High Grade (Poorly differentiated and undifferentiated) **[8]**

Pathophysiology of Colon Cancer

Colorectal cancer originates from the epithelial lining, most often as a consequence of mutations in the Wnt signaling pathway. These mutations can be either acquired or inherited. They mostly occur in the intestinal gland stem cells.

Tumor Suppressor Genes

In all colorectal cancer, *APC* is the most commonly mutated gene. It produces the APC protein, which prevents the accumulation of the β-catenin protein by binding to and degrading it. In the absence of APC protein, β-catenin highly accumulates in the cytoplasm, translocates to the nucleus, and binds to DNA, thus activating the transcription of several genes. These genes are responsible for stem cell renewal and differentiation. However, when improperly expressed at elevated levels they cause cancer. Some colorectal cancers have high β-catenin levels due to mutations

in its gene *CTNNB1*, and not in the *APC* gene. These mutations block the degradation of β-catenin. Other colorectal cancers have mutations in other APC analogues, such as NKD1, TCF7L2, AXIN1, or AXIN2. Another tumor suppressor, PTEN, normally inhibits the over expressed precise. T stands for the depth of the tumor, and to which level did it penetrate the colon wall. N refers to the involvement of lymph nodes. M stands for the degree of metastases that took place or whether the tumor has spread or not. **[9]**

Symptoms of Colon Cancer

1) Bleeding from the rectum
2) Blood in the stool or in the toilet after having a bowel movement
3) Dark or black stools
4) A change in the shape of the stool (e.g., more narrow than usual)
5) Cramping or discomfort in the lower abdomen

6) An urge to have a bowel movement when the bowel is empty
7) Constipation or diarrhea that lasts for more than a few days
8) Decreased appetite
9) Unintentional weight loss

In some cases, blood loss from the cancer leads to anemia (low number of red blood cells), causing symptoms such as weakness and excessive fatigue. Timely evaluation of symptoms consistent with colorectal cancer is essential, even for adults younger than age 50, colorectal cancer incidence is rare but increasing and for whom screening is not recommended. **[7]**

Colon cancer may cause one or more of the symptoms below:

1. A change in bowel habits, such as diarrhea, constipation or narrowing of the stool, which lasts for more than few days.
2. Rectal bleeding, dark stools or blood in the stool.
3. Cramping or abdominal (belly) pain
4. Weakness and fatigue
5. Unintended weight loss **[8]**

Table Number1: Risk Factors of colon cancer

Sr no.	Factors that increase risk of colorectal cancer	relative risk
1.	**Heredity and family history**	
	Family history	
	First degree relative	**2.2**
	More than 1 relative	**4.0**
	Inflammatory bowel disease	
	Crohn disease (colon)	**2.6**
	Ulcerative colitis(colon)	**2.8**
	Diabetes	**1.2**
2.	**Behavioral factors:**	
	Alcohol consumption	**1.6**
	obesity	**1.2**
	red meat consumption	**1.2**
	Processed meat consumption	**1.2**
	Smoking	**1.2**
3.	**Factors that decrease risk:**	
	Physical activity colon	**0.7**
	Fruit consumption	**0.9**
	Total dietary fibre	**0.9**

Test that can find both colon polyps and cancer

Flexible sigmoidoscopy: During this test, a sigmoidoscope a flexible, lighted tube about thickness of a finger with a small video camera on the end is inserted through the rectum and into the lower part of the colon to look at the part of the colon. Images from the scope are viewed abnormalities on a display monitor.

Colonoscopy*:* Colonoscope, which is basically a longer version of a sigmoidoscope is inserted through the rectum into the colon to look at the entire length of the colon. The colonoscope has video camera on the end that is connected to a display monitor.

Double – contrast barium enema*:* The double contrast barium enema (DCBE) is also called as air-contrast barium enema or a barium enema with air contrast. It may also be referred to as a lower GI series. It is basically a type of X-ray test. Barium sulfate, which is a chalky liquid and air are used to outline the inner part of the colon to look for abnormal areas on X-rays.

CT Colonography (Virtual colonoscopy): This test is an advanced type of computed tomography (CT or CAT) scan of the colon. A CT scan is an X-ray test that produces detailed cross-sectional images of the body. CT colongraphy has a special computer program which creates both 2-dimensional x-ray pictures and a 3-dimensional "fly-through" view of the inside of the colon, which allows looking for polyps or cancer The fecal occult blood test (FOBT) is used to find occult blood (blood that can't be seen with naked eye) in feces. The FOBT detects blood in the stool through a chemical reaction. If this test is positive, a colonscopy is needed to find the cause of bleeding.

Fecal immunochemical Test: The fecal immunochemical test (FIT) also called an immunochemical fecal occult blood test (iFOBT) is a newer kind of test that also detects occult (hidden) blood in the stool. This test reacts to part of the human hemoglobin protein, which is found in red blood cells.

Stool DNA Test: Instead of looking for blood in the stool, these tests look for certain abnormal section of DNA (genetic materials) from cancer or polyp cells. Cells from colon cancer or polyps with these mutations are often shed in the stool, where test may be able to detect them.

If symptoms or the results of the physical exam of the blood test suggest that colon cancer might be present. The following test must be done:

1. Biopsy
2. Imaging Tests.

a. Computer Tomography (CT/CAT) Scan
b. Ultrasound
c. Magnetic Resonance imaging (MRI) Scan
d. Positron Emission Tomography (PET) Scan
e. Angiography **[8]**

Different Treatment Methods for Colon Cancer

a) Surgery
b) Chemotherapy
c) Targeted therapy

a) Surgical Treatment

Surgical treatment is indicated in nearly all patients with newly diagnosed CRC unless survival is unlikely or life expectancy is very short due to advanced cancer or other diseases. Even in the presence of metastases, palliative surgical resection of the primary tumour may be advisable to

prevent further bleeding and impending obstruction. Radical surgery is the main treatment of CRC and offers the only possibility of permanent cure.

1. Open surgery

The standard approach to CRC is resection of the tumour-bearing segment of the bowel together with systematic removal of the draining lymphatics en bloc. Distal and proximal margins are recommended to be 5-10 cm. The remaining parts of the colon are anastomosed together to create a functioning colon. When anastomosis is not possible, which sometimes happens with emergency operations, a stoma is created. As for colonic cancers, depending on the location of the tumour the surgeon may select to do a right hemicolectomy, transverse colectomy, a left hemicolectomy or sigmoid resection. These operations are shown in Figure 4.

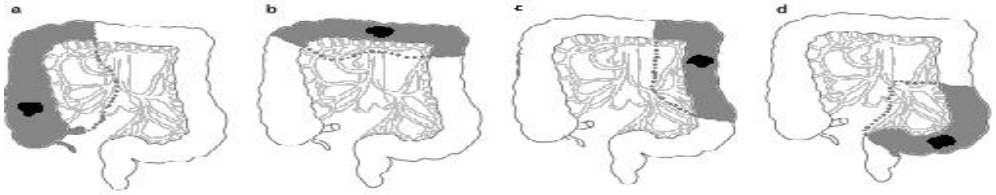

FIG.4: The surgical treatment of CRC depending on the location of the tumour a) right hemicolectomy b) transverse colectomy c) left hemicolectomy d) sigmoid resection (the resection line is marked with dashed line).

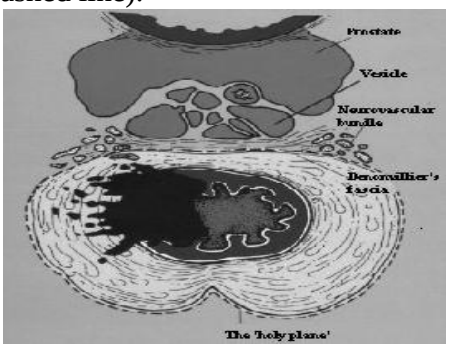

FIG.5: Total mesorectal excision. The resection line is marked with a dashed line.

2. Laparoscopic surgery

Laparoscopic surgical techniques are widely used as a standard procedure for surgery for colon cancer and at some institutions for rectal cancer. Several clinical trials have shown that in the short-time outcome laparoscopic approach for CRC is associated with a shorter hospital stay, less postoperative pain, shorter duration of postoperative ileus, decreased morbidity and improvements in the quality of life (QoL). In the long-term, there has been no difference in morbidity, the rates of recurrence or cancer-related mortality between laparoscopic and open surgery. The technique of laparoscopic colorectal surgery is demanding but in experienced hands, laparoscopic colorectal resection can be performed safely for all, also for ‘‘high-risk” surgical patients and the elderly.

3. Local surgery

In general, local treatment of CRC, including endoscopic removal of colonic polyps and trans anal resection of the rectal tumour, has become widely accepted. Trans anal local excision is useful with curative intent for T1, well differentiated rectal cancers that are under 3 cm in diameter and occupy under 40 % of the circumference of the rectal wall. The depth of mural penetration is correlated with the risk of nodal metastases. For T1 tumours the risk of associated

nodal metastases is 6-11% and for T2 tumours 10-20% . Local excision should be reserved for low-risk cancers in patients who accept an increased risk of tumour recurrence, prolonged surveillance, and possible need for aggressive radical surgery in the follow-up or for patients with very poor general condition as a palliative procedure.

4. Surgical palliation

Traditional surgical palliation of obstruction hampers the prompt start of oncological treatment. Bowel obstruction is the first symptom in 7-29 % of CRC patients. Acute malignant colorectal obstruction is thus a frequently encountered surgical emergency. Emergency operations involving the unprepared and obstructed bowel result in increased mortality and high postoperative morbidity rates and poorer cancer-specific survival. Since its introduction in 1991, self expanding metallic stents (SEMS) have provided an alternative to palliative surgery in preventing or relieving colorectal obstructi. Over the last decade, the use of SEMS has markedly increased and it seems to be an effective alternative in the palliative treatment of patients with malignant colorectal obstruction particularly in the left-sided colon . SEMS has also been effective as a bridge to surgery to enable a single - stage surgical procedure and avoid temporary or permanent stoma. This temporary procedure gives the opportunity to perform accurate tumour staging, leading to avoidance of surgery in patients with disseminated disease or unacceptable surgical risk. [9]

b) Chemotherapy for Colon Cancer

Table Number 2: conventional drugs used in the treatment of colon cancer **[12]**

S.n.	Drug name.	Mode of Action	Side effects	Dose.
1	Fluorouracil	a fluorinated pyrimidine, which is thought to act primarily by inhibiting thymidy-late synthase, the ratelimiting enzyme in pyrimidine nucleotide synthesis. Additional mechanisms of action include direct incorpo-ration into RNA to interfere with RNA transcription and, to a lesser extent, direct incorporation into DNA	neutropenia and stomatitis are the most common toxic effects less hematologic and gastroin-testinal toxicity, but palmar–plantar erythrodysesthesia (“hand–foot syndrome”) is more common.	
2	Capcitabine	It is an oral 5-FU pro-drug with no anti tumour activity itself. 26 It is metabolised in the body via three sequential enzyme steps to produce 5-FU within tumours. Capecitabine is preferentially activated in tumour tissue.		The reco. dose is 1250 mg/m2 administered twice daily. equivalent to 2500 mg/m2 total daily dose) for 14 days followed by a 7-day rest period.

eISSN 2319-1082

3	Irinotecan	Topoisomerase I. enzyme is involved in the uncoiling of DNA for replication and transcription, and it causes single stranded DNA breaks. Such breaks are normally transient and repaired; however, camptothecin stabilizes these breaks, leading to DNA fragmentation and cell death through interaction with the replication fork	The toxic effects of irinotecan include diarrhea, bone marrow suppression, nausea, vomiting, and alopecia. Polymorphisms of UGT1A1 appear to correlate with the severity of the gastrointestinal effects and bone marrow suppression	20 mg/ml Injection
4	Oxaliplatin	Oxaliplatin (Eloxatin) is a third-generation platinum derivative that forms bulky DNA adducts and induces cellular apoptosis	Renal dysfunction, alopecia, and ototoxic effects are uncommon but neuropathy is more frequent	100 mg and 50 mg Injection
5	Ralitrexed	Raltitrexed is a folate-based direct and specific thymidylate synthase inhibitor.	Raltitrexed was believed to have a more favourable toxicity profile, with less stomatitis and leucopenia, but reports of elevations in liver enzymes and increased morbidity and mortality secondary to severe diarrhoea and neutropenia have prompted recommendations for more judicious monitoring with this agent	

Table Number 3: marketed formulation of colon cancer **[12]**

S.n.	Drug/Combined Drug	GENERIC NAME	BRAND NAME
1	5-FU/LV	5-FU=Fluorouracil LV=leucovorin	_ _
2	Capecitabine alone	Capecitabine	Xeloda®
3	CapeOX	Cape=capecitabine OX=oxaliplatin	Xeloda® Eloxatin®
4	FOLFOX	FOL=leucovorin F=fluorouracil OX=Oxaliplatin	Eloxatin®
5	FOLFOXIRI	FOL=leucovorin F=fluorouracil OX=Oxaliplatin IRI=irinotecan	Eloxatin® Camptosar®
6	Irinotican	Irinotecan	Camptosar®
7	Trifluridine+tipiracil	Trifluridine+tipiracil	Lonsurf®

eISSN 2319-1082

3) Targeted therapy for colon cancer

Table Number 4: Targeted drug therapy for colon cancer **[12]**

S.n.	Drug	Mode of Action	Dose	Side effects
1	Bevacizumab	It attaches to VEGF before it attaches to receptor as a result no VEGF attaches to receptors no growth signals are found	25g/ml injection	High blood pressure, diarrohea, feeling tired and weak, nosebleeds, stroke, heart attack, kidney damage, holes in the intestine, bleeding within the body
2	Ramicirumab	It Attaches to VEGF receptors on the outside of the endothelial cells,blocks VEGF from attaching		Common: High blood pressure, diarrohea. Serious: Bleeding, blood clots, holes in thengut, slow wound healing
3	Panitumumab	It attaches to ends of EGRF that are out side of the cell thus EGFis blocked from attaching and trigring growth signals.		Common: Acne like rash, infection, mouth sours, nausea, diarrhea, lower blood magnesium level Serious: Heart, lung, eye damage
4	Cetizumab	It attaches to ends of EGRF that are outside of the cell thus EGFis blocked from attaching and trigring growth signals.	2 mg/ml Injection	Common: Acne like rash, infection, mouth sours, nausea, diarrhea, lower blood magnesium level Serious: Heart, lung, eye damage
5	Regorafenib	It attaches to VEGF before it attaches to receptor as a result no VEGF attaches to receptors no growth signals are found		High blood pressure, diarrohea, feeling tired and weak, nosebleeds, stroke, heart attack, kidney damage, holes in the intestine, bleeding in the body
6	Zivaflibercept	It attaches to VEGF before it attaches to receptor as a result no VEGF attaches to receptors no growth signals are found		

Table Number 5: marketed formulations for colon cancer **[12]**

S.N.	BrandName	DRUG NAME	DISEASE
1	Avastin®	Bevacizumab	Colon cancer
2	Erbitux®	Cetixumab	Colon cancer
3	Vectibix®	Pantizumab	Colon cancer
4	Cyramza®	Ramucirumab	Colon cancer
5	Stivarga®	Regorafenib	Colon cancer
6	Ziv-aflibercept	Zaltrap®	Colon cancer

NANOPARTICLES

Nanoparticles can be defined as objects ranging in size from 1-100 nm that due to their size may differ from the bulk material. Presently, different metallic nanomaterials are being produced using copper, zinc, titanium, magnesium, gold, alginate and silver. Nanoparticles are being used for diverse purposes, from medical treatments, using in various branches of industry production such as solar and oxide fuel batteries for energy storage, to wide incorporation into diverse materials of everyday use such as cosmetics or clothes. **[10]**

TYPES OF NANO-PARTICLES

Silver: Silver nanoparticles have proved to be most effective because of its good antimicrobial efficacy against bacteria, viruses and other eukaryotic micro-organisms.They are undoubtedly the most widely used nanomaterials among all, thereby being used as antimicrobial agents, in textile industries, for water treatment, sunscreen lotions etc. Studies have already reported the successful biosynthesis of silver nanoparticles by plants such as *Azadirachta indica*, *Capsicum annuum* and *Carica papaya*.

Gold: Gold nanoparticles (AuNPs) are used in immunochemical studies for identification of protein interactions. They are used as lab tracer in DNA fingerprinting to detect presence of DNA in a sample. They are also used for detection of aminoglycoside antibiotics like streptomycin, gentamycin and neomycin. Gold nanorods are being used to detect cancer stem cells, beneficial for cancer diagnosis and for identification of different classes of bacteria.

Alloy: Alloy nanoparticles exhibit structural properties that are different from their bulk samples. Since Ag has the highest electrical conductivity among metal fillers and, unlike many other metals, their oxides have relatively better conductivity, Ag flakes are most widely used. Bimetallic alloy nanoparticles properties are influenced by both metals and show more advantages over ordinary metallic NPs27.

Magnetic: Magnetic nanoparticles like Fe3O4 (magnetite) and Fe2O3 (magnetite) are known to be bio compatible. They have been actively investigated for targeted cancer treatment (magnetic hyperthermia), stem cell sorting and manipulation, guided drug delivery, gene therapy, DNA analysis, and magnetic resonance imaging (MRI) **[10]**

DISADVANTAGES OF NANOPARTICLES

1. Extensive use of polyvinyl alcohol as a detergent –issues with toxicity.
2. Limited targeting abilities.
3. Discontinuation of therapy is not possible.
4. Cytotoxicity.
5. Pulmonary inflammation and pulmonary carcinogenicity.
6. Alveolar inflammation.
7. The disturbance of autonomic imbalance by nanoparticles having direct effect on heart and vascular function. **[11]**

NANOPARTICLES IN COLON CANCER

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles such as carriers have shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs. The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have large surfaces. Since the adhesion is of non- specific nature, bioadhesion can be induced by binding nanoparticles with

biological surfaces. For the covalent attachment, the nanoparticle surfaces has to show free functional groups such as carboxylic or amino residues [**13]**

OBJECTIVE OF THE STUDY:

The main objective of the present work is given as follows:

1. The main objective is to gain all the background information about the Colon-Cancer, their causes, signs and symptoms, mortality rate trends etc.
2. To know the newer techniques and advancements in the field of drug delivery system.
3. To know the side effects of the drugs used in the treatment.
4. To check the combination therapy of drugs (if any available) for the best possible results.
5. To know the role of various nanoparticles in colon cancer.
6. To know the therapeutic effect of drug loaded nanoparticles in colon cancer.

REVIEW OF LITERATURE:

M Manikandan *et al.* reported that targeting of drugs to specific sites of action provides several advantages over non-targeted drugs. Colon specific drug delivery had gained increased importance just for the delivery of drugs for the treatment of local diseases associated with the colon. For the successful targeting of drugs to the colon, the drug needs to be protected from degradation, release and or absorption in the upper portion of GI tract and then to ensure the abrupt or controlled release in the proximal colon. General approaches for colon targeting drug delivery includes use of prodrugs, pH dependent system, time dependent systems and colonic microflora activated systems. Multifunctional nanoparticles play a significant role in cancer drug delivery. Nanoparticles exploit biological pathway to achieve payload delivery to cellular and intracellular targets. The targeting schemes explored for many of the reported nanoparticles systems suggest the great potential of targeted delivery to revolutionize cancer treatment. **[14]**

Danda Sreelatha *et al.* reported that oral administration of different dosage forms is the most common form of administration due to greater patient compliance and flexibility. Targeted drug delivery system is the system in which the dosage form is modified to deliver the drug at the target region or at the disease region. In colon targeted drug delivery system the drug is targeted to the colon. The colon targeted drug delivery system is used for the treatment of various diseases related to colon like inflammatory bowel disease, crohn's disease, colon cancer, etc. This targeting of drug to the disease site lowers the requirement of higher doses of drug thus reducing the dosage frequency and cost of the drugs. Colon targeted drug delivery system will also lower the systemic side effects. This review article compares the different approaches to colon targeted drug delivery like pH and time dependent, prodrug, microbial triggered drug delivery, azo hydrogels, pressure controlled drug delivery, pulsatile drug delivery system, osmotic controlled drug delivery system, etc. The microbial triggered drug delivery system is based on the enzymes released by different microflora in the colon. Of the different approaches the new approaches like pressure controlled, osmotic controlled drug delivery systems are highly effective. **[15]**

S. GILL *et al.* reported that colorectal cancer is a leading cause of cancer death world-wide. There have been important advances in the chemotherapeutic management of colorectal cancer as a result of a deliberate collaborative process of well designed clinical trials. From the earlier standard of 5-fluorouracil-based therapy alone, the recent availability of newer agents, including

capecitabine, irinotecan and oxaliplatin, has significantly expanded the options available for the management of patients with advanced colorectal cancer, with consequent improvements in survival. For patients with resected, high-risk, localized disease, adjuvant systemic chemotherapy improves survival. The identification of new chemotherapy regimens, the use of predictive testing and the integration of novel targeted therapies with cytotoxic chemotherapies are areas of active clinical investigation. **[16]**

Mariana Varna *et al.* reported that ongoing progress in nanotechnologies has led to their implementation for *in vivo* diagnostic and therapy. Thus, the main applications of inorganic nanoparticles are imaging for diagnosis and cell tracking, photothermal and drug-delivery therapies. Following nanoparticles *in vivo* administration, the systemic circulation can distribute them to every body organ and tissue. Precise characterization of nanoparticles distribution and accumulation in the different body parts in preclinical models is required before any application in humans. The biodistribution of inorganic nanoparticles has been analysed in different preclinical models, particularly mouse, rat and rabbit. This review covers the *in vivo* biodistribution of different inorganic nanoparticles in preclinical models: gold nanoparticles, silica nanoparticles, iron oxide magnetic nanoparticles, quantum dots and carbon nanotubes. **[17]**

Suzanne Hagan *et al.* reported that in developed countries, colorectal cancer (CRC) is the third most common malignancy, but it is the second most frequent cause of cancer-related death. Clinicians are still faced with numerous challenges in the treatment of this disease, and future approaches which target the molecular features of the disorder will be critical for success in this disease setting. Genetic analyses of many solid tumours have shown that up to 100 protein-encoding genes are mutated. Within CRC, numerous genetic alterations have been identified in a number of pathways. Therefore, understanding the molecular pathology of CRC may present information on potential routes for treatment and may also provide valuable prognostic information. This will be particularly pertinent for molecularly targeted treatments, such as anti-vascular endothelial growth factor therapies and anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapy. KRAS and BRAF mutations have been shown to predict response to anti-EGFR therapy. As EGFR can also signal via the phosphatidylinositol 3-kinase (PI3K) kinase pathway, there is considerable interest in the potential roles of members of this pathway (such as PI3K and PTEN) in predicting treatment response. Therefore, a combined approach of new techniques that allow identification of these biomarkers alongside interdisciplinary approaches to the treatment of advanced CRC will aid in the treatment decision-making process and may also serve to guide future therapeutic approaches. **[18]**

Madalina Palaghia *et al.* reported that colorectal cancer (CRC) is currently considered the third most common neoplasm in the world according to the World Cancer Research Fund International with 1.4 million cases diagnosed in 2012, and the second malignity as cause of death. Approximately 1/5 of patients present directly with metastatic disease (mCRC), and 30 to 50% develop metastasis after surgical treatment for initially localized disease. The aims of the current study are to review the diagnostic particularities, treatment options and clinical evolution of mCRC. Metastatic process in CRC is long and complex, involving several mechanisms, molecular pathways and cellular types. Advances in medical imaging now allow an early and accurate diagnosis of metastatic lesions no matter their location. The progress of fundamental research in CRC led to understanding the molecular basis of the metastatic process that was further translated into novel chemotherapic and biological agents, thus increasing overall survival and and progression-free survival rates. Resection of liver, lung and brain metastases is

crucial for survival when achievable and is more effective when completed by an oncological treatment and rigorous follow-up. All patients with mCRC should be discussed by a multidisciplinary team (surgeon, oncologist, radiologist, and gastroenterologist) in order to identify the most appropriate therapeutic management. **[19]**

Singh Amritpal *et al.* reported that the colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.**[20]**

Ahmad Gholamhoseinian Najar *et al.* reported that epidermal growth factor receptor (EGFR) is over-expressed in several human cancers. This would suggest that inhibition of EGFR is a reasonable approach for cancer treatment. In this study we investigated EGFR blocking and its effects on the mediated signaling such as MAPK and STATb in HT29 cells. For this aim we used FITC-labeled EGFR antisense oligonucleotides encapsulated with PAMAM nanoparticles to inhibit EGFR expression. Cellular uptake of antisense was investigated by fluorescence microscopy and flow cytometry analysis. The effect of EGFR antisense on the expression of EGFR in HT29 cells was examined by real time PCR and Western blots, which showed that antisense encapsulated with PAMAM decreased the level of EGFR mRNA and protein. In addition, real time PCR results confirmed that EGFR inhibition had an effective role in the reduction of EGFR dependent downstream genes. In conclusion, EGFR antisense encapsulated with PAMAM nanoparticles down regulated EGFR and EGFR-mediated genes**. [21]**

Jayakumar Jerobin *et al*. reported that colorectal Cancer (CRC) is a major worldwide health problem owing to its high prevalence and mortality rates. In the USA, CRC is the third most commonly diagnosed cancer and third leading cause of cancer death in both men and women. Approximately 95 percent of colorectal cancers are adenocarcinomas. Other types of cancer that can occur include mucinous carcinomas and adenosquamous carcinomas. Traditional chemotherapeutic drugs remain the major treatment for advanced colorectal cancer. However, due to the lack of tumor specificity these drugs also destroy healthy tissue and organs, which has been the main reason for treatment failure and mortality. To improve the efficacy of drug delivery, active targeted nanotechnology-based drug delivery systems are gaining considerable attention as they have the potential to reduce side effects, minimize toxicity, and improve efficacy of anticancer treatment. The transport of classical drugs by nanoparticles has shown great promise in terms of improving drug distribution and bioavailability.The nanoparticles also increase the half-life of the drug, and help in concentrating anticancer molecules to the tumor mass, providing optimal drug delivery, and minimizing drug toxicity. The nanoparticles are in the size range of 1 to 100nm in diameter, which makes them unique in being delivered to the cancerous tissues quickly than the bulk materials. As nanotechnology promises to be a new strategy for improving the prognosis of colon cancer patients, it would be very useful to analyze recent progress in this field of research. This review discusses the current status of nanoparticle-mediated cancer drug delivery, the challenges restricting its application, and the potential implications of its use in colon cancer therapy. **[22]**

Nusrat bano *et al*. reported that colorectal cancer is the solid cancer which may arise from the colon or the rectum with many similar features and may be referred to as colon cancer or rectal cancer depending upon the anatomical site of origin. It is one of the most common cancers and the leading cause of cancer related deaths in many countries. A significant rise in the incidence rate of the disease has been reported worldwide, especially in the countries of South Asia where the disease had a low incidence rate in the past. The clinical presentation of the colorectal cancer patient from this region is inclusive of young age and advanced disease stage. The awareness regarding the disease features and screening of the disease is scarce. This review provides a concise update on the pathological aspects of colorectal carcinoma and an insight on the clinical picture of the disease in the diverse population of Pakistan. **[23]**

Barish *et al.* reported that the formulation 5-Fluorouracil loaded sustained release nanoparticles with the size of around 250 nm and to increase the encapsulation efficiency of the drug. The nanoparticles were prepared by simple ionic gelation method using various concentrations of chitosan and TPP. The prepared nanoparticles were evaluated for particle size, shape, charge, encapsulation efficiency, *in vitro* drug release and *in vitro* cytotoxicity. The optimized 5FU loaded nanoparticle showed size of 232±4 nm with PDI of 0.30±0.07, Zeta potential of +5 ±1mv, encapsulation efficiency of 69.2% and the drug release is 97.4% at 24 hrs. These results demonstrate that the possibility of delivering 5 Fluorouracil to colorectum with enhanced encapsulation efficiency. **[24]**

Yiming Ma *et al*. reported that colorectal cancer (CRC) is a serious health problem worldwide and current interventions combining surgery and chemotherapy are frequently ineffective at preventing cancer recurrence and progression in patients. This is largely due to conventional routes of administration of anti-cancer drugs, through which drugs that are administered intravenously often cannot reach target sites (especially tumours in the colorectal region) at therapeutic concentrations. Colon-specific delivery systems through oral administration are a promising means for improving treatment of CRC by increasing the local drug concentration in the colon. This approach can be further improved by encapsulating drug-loaded nanoparticles in oral formulations that offer opportunities for targeted delivery and enhanced drug uptake specifically by cancer cells, thus minimising side effects on surrounding healthy cells in the colon. This thesis describes the development of a colon-specific delivery system capable of releasing individual drug-loaded nanoparticles in the colorectal region to improve chemotherapy for CRC. Eudragit® RS nanoparticles were used as a model scaffold for formulation development of colon-specific delivery systems. Alginate-based carriers, hypromellose capsules and chitosan-hypromellose microcapsules and chitosan-hypromellose microcapsules incorporating drug-loaded nanoparticles were investigated as vehicles for delivering nanoparticles or model drugs to the colon. **[25]**

Sutar PS *et.al.* reported that development of novel PLGA based nanoparticle delivery system of 5-Fluorouracil to treat colorectal cancer. pH sensitive polymer, Eudragit S-100 and PLGA were used to design the dosage form to target colonic region. Emulsion droplet coalescence method was employed to formulate nanoparticles. These nanoparticles were further characterized for their size, morphology, zeta potential, drug entrapment, Particle Size analysis, cytotoxicity study, in vitro release study and kinetic analysis. Formulation F2 proved to be better and showed 72.89 ± 1.41 drug entrapment with ideal particle size of 132.57nm ± 12.62. In vitro release of F2 formulation showed a lag phase for 4 hrs (pH 1.2 and pH 6.8). Initially, there was a burst release of 17.22% at 7th hr and further there was a controlled release up to 78.23% for 24 hrs. In vitro

kinetic study indicated that the formulations followed first order release pattern and anomalous transport kinetics, i.e. a combined mechanism of pure diffusion and Case II transport. For biological evaluation, HT29 (Human colorectal Adenocarcinoma) cell lines were selected and anti-tumoral efficacy was analyzed using MTT (3- [4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide) assay. Results showed that 80% of cell lysis took place. Formulation F2 was a promising formulation to target colon cancer cells. **[26]**

Prados J *et al*. reported that the number of patients with colorectal cancer, the third most frequently diagnosed malignancy in the world, has increased markedly over the past 20 years and will continue to increase in the future. Despite recent advances in chemotherapy, currently used anticancer molecules are unable to improve the prognosis of advanced or recurrent colorectal cancer, which remains incurable. The transport of classical drugs by nanoparticles has shown great promise in terms of improving drug distribution and bioavailability, increasing tissue half-life and concentrating anticancer molecules in the tumor mass, providing optimal drug delivery to tumor tissue, and minimizing drug toxicity, including those effects associated with pharmaceutical excipients. In addition, colon cancer targeting may be improved by incorporating ligands for tumor-specific surface receptors. Similarly, nanoparticles may interact with key drug-resistance molecules to prevent a reduction in intracellular drug levels drug. Recently published data have provided convincing pre-clinical evidence regarding the potential of active-targeted nanotherapeutics in colon cancer therapy, although, unfortunately, only a few of these therapies have been translated into early-phase clinical trials. As nanotechnology promises to be a new strategy for improving the prognosis of colon cancer patients, it would be very useful to analyze recent progress in this field of research. This review discusses the current status of nanoparticle-mediated cancer-drug delivery, the challenges restricting its application, and the potential implications of its use in colon cancer therapy**. [27]**

Justin La Rocque *et al.* reported that nanotechnology is a field which has been at the forefront of research over the past two decades. The full potential of nanotechnology has yet to be fully realized. One subset of nanotechnology that has emerged is nanomedicine, which has been able to exploit the unique properties of nano-sized particles for therapeutics. Nanomedicine has the potential to increase the specific treatment of cancer cells while leaving healthy cells intact through the use of novel nanoparticles to seek and treat cancer in the human body. However, there are undoubtedly toxicities, which have not yet been fully elucidated. Various nano-carriers such as nanoshells, nanocrystals, nanopolymers, quantum dots, and dendrimers, and their role in early cancer detection and treatment have been discussed in this article. **[28]**

Deep Kwatra *et al*. reported that Acquired radiation resistance is one of the major causes of radio therapy failure and subsequent tumor relapse. Multiple approaches have been utilized to limit the radiation resistance while simultaneously enhancing the efficacy and safety of radiation therapy. The three major approaches for the improvement of radiation therapy have involved (I) ehancing radiosensitization of tumor tissue; (II) rversing of radiation resistance in tumor tissue; and (III) ehancing radioresistance of the healthy tissue. Nanoparticles have played a key role in the enhancement of the radiation therapy by acting both as a therapeutic as well as a carrier for other therapeutics. In this review we summarize the research being carried out using different species of nanoparticles for enhanced radiosensitization in cancer. **[29]**

Li *et al*. reported that the investigation aimed at developing doxorubicin (DOX)-loaded Eudragit coated chitosan nanoparticles to treat colorectal cancers. The main objective was to limit the side effects of DOX and to increase its chemotherapeutic efficiency when loaded in nanoparticulate

systems. The drug-loaded delivery system was characterized for its pH sensitive release pattern. The pH targeting approach is considered as one of the most successful strategy in colon cancer targeting. Our results show that Eudragit coating prevented the drug release at the upper gastrointestinal tract (pH 1.2 and pH 6.8). This enables the colon cancer targeting potential for E-CH-DOX. The nanoparticle showed an enhanced cellular uptake in HCT-116 cancer cells and showed significant anticancer effect in a time- and dose-dependent manner. The apoptosis assay further confirmed the superior cytotoxic effect of E-CH-DOX. The cells treated with nanoparticle formulations showed the maximum presence in early and late apoptosis stages. The *in vivo*animal study further confirmed the tumor regression ability of E-CH-DOX with lowest tumor volume. These results clearly suggest the role of E-CH-DOX in the potential treatment of colorectal cancers**. [30]**

Armin Imanparast *et al*. reported that colorectal cancer (CRC) is the third major cause of cancer death globally, with about 694,000 deaths each year. Recent studies have shown that cancer stem cells (CSCs) play an important role in cancer relapse and metastasis. Inhibition of COX-2, Wnt / beta-catenin, HIF-1 alpha, K-Ras, NF-kβ, P53 signaling pathways and activation of TGF-β are amongst proposed strategies against colorectal cancer. Specific markers of CSCs including CD133, CD24, CD29, CD44 and Lgr5 are also of importance in diagnosis and monitoring of the disease. Therefore, the use of nanoparticles can be discussed in two different fields: 1. using nanoparticles in diagnosis and targeting CSCs, 2. targeting the cancer cells directly, where nanoparticles can affect the cell signaling pathways and expression patterns to prevent extension of tumor cells. In addition, nanoparticles can be used as the carriers for anti-cancer drugs and drug delivery, which in turn may enhance effectiveness of treatment. This review covers the novel signaling pathways in colorectal cancer and also gives a brief explanation about the role of some nanostructures that enhance treatment efficiency. **[31]**

Chintan H. Kapadia *et al.* reported that although surgery, radiation therapy, and chemotherapy have significantly improved as treatments for cancer, they can rarely control metastatic disease and cures remain scarce. Promising recent developments suggest that cancer immunotherapy may become a powerful new therapy that clinicians can offer cancer patients. The opportunity to orchestrate the body's own immune system to target, fight, and eradicate cancer cells without destroying healthy cells makes this an extremely attractive treatment modality. Our increased knowledge in anti-tumor immunity and the immunosuppressive tumor microenvironment (TME) has provided many therapeutic strategies to battle cancer. That combined with advancements in the field of particulate delivery systems provide a mechanism to deliver these immunotherapeutics to their specific targeted cells and the TME. In focus on the current status of immunotherapy and the potential advantages of utilizing nanocarriers within the field. **[32]**

Melissa S Wason *et al*. reported that the diverse abilities of cerium oxide nanoparticles (CONPs) have encouraged researchers to pursue CONPs as a therapeutic agent to treat a number of diseases, including cancer. *In vitro* and *in vivo* studies have shown CONPs to be toxic to cancer cells, inhibit invasion, and sensitize cancer cells to radiation therapy. However, CONPs display minimal toxicity to normal tissues and provide protection from various forms of reactive oxygen species (ROS) generation. The antioxidant capabilities of CONPs, which enable radiation protection, have also resulted in the exploration of these particles as a potential treatment for other disorders characterized by ROS accumulation, such as diabetes and macular degeneration. While critical information regarding the uptake, retention, and clearance of these particles is incomplete and conflicting reports exist about *in vitro* toxicity, most research into the

various applications of CONPs has yielded promising data. This review highlights the current research into cerium oxide nanoparticles as a novel therapeutic for the treatment of cancer and other diseases. **[33]**

Jasvir Kaur *et al.* reported that colorectal cancer develops from the polyps (outgrowths) formed into the distal part of digestive system. These polyps are known as adenomas and are precursors to cancer. Once the development of colorectal cancer starts, it can further spread to other body parts via lining and wall of colon and rectum. Depending on the stage of colorectal cancer, it can be treated either by chemotherapy, surgery, radiation therapy or by immunotherapy. Following chemotherapy various approaches have been employed by researchers for targeting drugs successfully to the colonic region by circumventing the upper part of gastrointestinal tract. These approaches include pH-dependent, time-dependent and microflora-activated systems. As colon is rich in aerobic and anaerobic microflora, thus microflora activated systems can be used efficiently to deliver drug molecule to the target site. Various drug molecules have been reported to treat and prevent colorectal cancer, provided an efficient carrier system is developed that can deliver drug molecule to the colonic region only. This review will mainly focus on some possible approaches which can be successful to achieve drug targeting to colon to treat colorectal cancer. **[34]**

Sophie Laurent *et al*. reported that during the last decade, significant scientific research efforts have led to a significant growth in understanding of cancer at the genetic, molecular, and cellular levels providing great opportunities for diagnosis and treatment of cancer diseases. The hopes for fast cancer diagnosis and treatment were significantly increased by the entrance of nanoparticles to the medical sciences. Nanoparticles are attractive due to their unique opportunities together with negligible side effects not only in cancer therapy but also in the treatment of other ailments. Among all types of nanoparticles, surface-engineered super paramagnetic iron oxide nanoparticles (SPIONs) have been attracted a great attention for cancer therapy applications. This review covers the recent advances in the development of SPIONs together with their opportunities and challenges, as theranosis agents, in cancer treatment. **[35]**

Congcong Lin *et al*. reported that colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer death in the world. Currently available chemotherapy of CRC usually delivers the drug to both normal as well as cancerous tissues, thus leading to numerous undesirable effects. Much emphasis is being laid on the development of effective drug delivery systems for achieving selective delivery of the active moiety at the anticipated site of action with minimized unwanted side effects. Researchers have employed various techniques (dependent on pH, time, pressure and/or bacteria) for targeting drugs directly to the colonic region. On the other hand, systemic drug delivery strategies to specific molecular targets (such as FGFR, EGFR, CD44, EpCAM, CA IX, PPAR and COX-2) overexpressed by cancerous cells have also been shown to be effective. This review aims to put forth an overview of drug delivery technologies that have been, and may be developed, for the treatment of CRC. **[36]**

Leila Hamzehzadeh *et al*. reported that nanoparticles have been at the center of research focus as a new promising material for the treatment of cancer in recent years. Although many chemotherapy drugs for cancer treatment are available, their potential toxicity is the main point of concern. On the other hand, the conventional chemotherapeutic approach has not been found to be very efficient in colorectal cancer (CRC) as the drug molecule does not reach the target site with an effective concentration. A major challenge in cancer therapy is to destroy tumor cells without harming the normal tissue. To overcome this problem scientists are trying to use

nanoparticles to directly target cancer cells for a more effective treatment and reduced toxicity. Different nanoparticles such as: liposomes, polymeric nanoparticles, dendrimers, and silica have been developed to carry a variety of anticancer agents including: cytotoxic drugs, chemo modulators, siRNA and antiangiogenic agents. **[37]**

Nehal M El-Deeb *et al.* reported that recently, the biosynthesis of nanoparticles has been well explored which draws attention to its possible biomedical applications especially in cancer therapy. In the current study, the novelty in the biosynthesis of silver nanoparticles (AgNPs) using honey bee extract has been explained. This study was also aiming at investigating the anti-colon cancer activities of the biogenic AgNPs along with its capping biomolecules *in vitro*. The obtained biogenic AgNPs were well characterized by X-ray diffraction (XRD), energy dispersive X-ray (EDX), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). It was found that the formed AgNPs have spherical shape with size range from 12 to 18 nm embedded in honey bee biomolecules. The cytotoxicity results of AgNPs on peripheral blood mononuclear cells (PBMC) indicated that the obtained AgNPs could be used safely with concentrations upto 39 µg/ml. On the other hand, the potentialities of the biogenic AgNPs against colon cancer proliferation recorded 60% inhibition using its nontoxic dose with a down regulation of the expression of Bcl2 and survivin gene. By the extraction of AgNPs capping biomolecules to explain the exact fraction that is responsible for the anticancer properties, it was found that both AgNPs and its capping biomolecules have anti-proliferative effects with a priority to the naked AgNPs. **[38]**

Manoj Kumar Sarangi *et al*. reported that the colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for instance, allow topical treatment of inflammatory bowel disease. Treatment could be made more efficient if it was possible for drugs to be targeted like a shot to the colon. Systemic side effects could also be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally inactivated in the upper portions of the gastrointestinal tract. Primary approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent systems and microbial triggered drug delivery system achieved limited success and accepting limitations. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODESTM and osmotic controlled drug delivery are unparalleled in terms of achieving *in vivo* site specificity and feasibility of fabrication operation **.[39]**

Kothawade P. D *et al.* reported that lot of research is undergoing in colon specific drug delivery as this drug delivery route is not only useful for targeting the drugs required in the treatment of diseases associated with colon, but also as a potential site for the local and systemic delivery of peptide and proteins and other therapeutic drugs. Precise colon drug delivery requires the triggering mechanism in the delivery system that can respond only to the physiological conditions specific to the colon. The primary conventional approaches used to obtain colon-specific delivery were based on prodrugs, pH and timedependent systems or microflora activated systems and achieved limited success. However, recently continuous efforts have been taken on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. The focus of this review is to provide detailed insight into the conventional as well as recent approaches used to target the therapeutic agents specifically to the colon. **[40]**

Ning Zhao *et al.* reported that gold nanoparticles (AuNPs) exhibit superior optical and physical properties for more effective treatment of cancer through incorporating both diagnostic and

therapeutic functions into one single platform. The ability to passively accumulate on tumor cells provides AuNPs the opportunity to become an attractive contrast agent for X-ray based computed tomography (CT) imaging in vivo. Because of facile surface modification, various size and shape of AuNPs have been extensively functionalized and applied as active nano probes and drug carriers for cancer targeted theranostics. Moreover, their capabilities on producing photoacoustic (PA) signals and photothermal effects have been used to image and treat tumor progression, respectively. **[41]**

Nour Karr *et al.* reported that cancer therapy often requires frequent and high drug dosing. Yet, despite the significant progress in cancer research and the wide versatility of potent available drugs, treatment efficacy is still hurdled and often failed by the lack of pharmaco-selectivity to diseased cells, indiscriminate drug toxicities and poor patient compliance. Thus, innovative pharmaceutical solutions are needed to effectively deliver the cytotoxic drugs specifically to the tumor site while minimizing systemic exposure to frequent and high drug doses. Polymeric nanocarriers, particularly nanoparticles, have been extensively studied for improved oncological use. Such nanocarriers hold great potential in cancer treatment as they can be biocompatible, adapted to specific needs, tolerated and deliver high drug payloads while targeting tumors. Active targeting, as opposed to passive targeting, should add value to selective and site specific treatment. Active targeting of nanosized drug delivery systems is firmly rooted in the Magic Bullet Concept as was envisioned by Paul Ehrlich over 100 years ago. This targeting strategy is based on the molecular recognition of tumor biomarkers which are over-expressed on cancer cells, via specific vector molecules conjugated to the surface of the drug carrier. These vector molecules dictate the carrier's biodistribution and its biological affinity to the desired site of action. **[42]**

Anbarasan B *et.al* reported that that study was to investigate the synthesis of Fe3O4 nanoparticles by chemical precipitation method. The Fe3O4 nanoparticles were coated with the polymers PLGA PEG and loaded with the drug capecitabine for the targeting of colon cancer which will be distributed in the large intestine by applying, the external magnetic field. It gets localized in the area of colon cancer cells. After the applied external magnetic field, the iron oxides (Fe3O4 nanoparticles) get heated to 37ºC - 40ºC and the tumour cell gets destroyed. The Fe3O4 nanoparticles were also called as super paramagnetic Iron oxide nanoparticles. They were very smart materials and mostly used for the applications in medicine like targeted drug delivery system, diagnostic cancer imaging and their therapeutic applications. **[43]**

Ling Zhang *et.al* reported that gene therapy provides a novel method for the prevention and treatment of cancer, but the clinical application of gene therapy is restricted, mainly because of the absence of an efficient and safe gene delivery system. Recently, we developed a novel nonviral gene carrier, ie, heparin-polyethyleneimine (HPEI) nanoparticles for this purpose. HPEI nanoparticles were used to deliver plasmid-expressing mouse survivin-T34A (ms-T34A) to treat C-26 carcinoma in vitro and in vivo. According to the in vitro studies, HPEI nanoparticles could efficiently transfect the pGFP report gene into C-26 cells, with a transfection efficiency of 30.5% ± 2%. Moreover, HPEI nanoparticle-mediated ms-T34A could efficiently inhibit the proliferation of C-26 cells by induction of apoptosis in vitro. Based on the in vivo studies, HPEI nanoparticles could transfect the Lac-Z report gene into C-26 cells in vivo. Intratumoral injection of HPEI nanoparticle-mediated ms-T34A significantly inhibited growth of subcutaneous C-26 carcinoma in vivo by induction of apoptosis and inhibition of angiogenesis. The research suggests that

HPEI nanoparticle-mediated ms-T34A may have a promising role in C-26 colon carcinoma therapy. **[44]**

Alicia A. Taylor *et.al* reported that nanoparticles (NPs) are becoming prevalent in consumer goods, including foods and cosmetics. Understanding the interactions between NPs and bacteria in an engineered model colon can indicate potential impacts of NP exposure on the gut, and therefore overall human health. Human microbiome health has important implications to overall individual health. This work aims at quantifying the phenotypic response to NP ingestion of a model microbial community within a model colon. Three NPs at environmentally relevant concentrations (0.01 lg/L ZnO, 0.01 lg/L CeO2, and 3mg/L TiO2) were individually introduced into a model colon to identify the subsequent impact on the gut microbial community. Results indicate that NPs cause the microbial community's phenotype to partition into three distinct phases: initial conditions, a transition period, and a homeostatic phase, with the NP-exposed community displaying significant differences ($p < 0.05$) from the unexposed community in multiple phenotypic traits. Notably, phenotypes, including short-chain fatty acid (SCFA) production, hydrophobicity, sugar content of the extracellular polymeric substance, and electrophoretic mobility, which indicate changes in the community's stability, were affected by the NPs. TiO2 NPs led to extended phenotypic transformations for hydrophobicity when compared with the other NPs, likely due to its lack of dissociation and greater stability. Overall, the NPs caused nonlethal, significant changes to the microbial community's phenotype, which may be related to overall health effects**. [45]**

Deeksha tripathi *et.al.* reported that cancer is a major health concern in the world. Chemotherapy is widely used to treat cancer either alone or in combination with other therapy. Chemotherapy is associated with several problems such as lack of specificity, poor aqueous solubility and multidrug resistance. Nanotechnology has emerged as promising approach to treat cancer effectively. Nanotechnology based nanoparticles have shown great potential in overcoming limitations of conventional chemotherapy. Nanoparticles have several properties such as tunable size and required surface characteristics which make them ideal candidate for drug targeting. Several types of nanoparticles are engineered to target tumor sites without causing any harm to normal cells. Major advantage of drug loaded nanoparticles is, they reach to tumor sites with minimal loss and affect only defected cell without any harm to normal cells. Nanoparticles accumulate specifically to desired cell either by passive or ligand based target mechanism. Some nanoformulations have approved and some are under clinical trials.**[46]**

Che-Ming Jack Hu *et.al* reported that the combination chemotherapy and nanoparticle drug delivery are two areas that have shown significant promise in cancer treatment. Combined therapy of two or more drugs promotes synergism among the different drugs against cancer cells and suppresses drug resistance through distinct mechanisms of action. Nanoparticle drug delivery, on the other hand, enhances therapeutic effectiveness and reduces side effects of the drug payloads by improving thei rpharmacokinetics. These two active research fields have been recently merged to further improve the efficacy of cancer therapeutics. This review article summarizes the recent efforts in developing nanoparticle platforms to concurrently deliver multiple types of drugs for combination chemotherapy. We also highlight the challenges and design specifications that need to be considered in optimizing nanoparticle-based combination chemotherapy. **[47]**

Vineet Mathur *et.al* reported that the use of solid lipid nanoparticles in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under

investigation for drug delivery and more specifically for cancer therapy technology is the latest trend in the cancer therapy. It helps the pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. Cancer is a class of disorders characterized by abnormal growth of cells that proliferate in an uncontrolled way and a major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue, which causes severe side effects and results in low cure rates. Thus, it is very hard to target the abnormal cells by the conventional method of the drug delivery system. In harmony with these approaches, this review's basic approach is that the defining features of solid lipid nanoparticles are embedded in their breakthrough potential for patient care. This review article describes the possible way to exploit solid lipid nanoparticle technology to targeted drug therapy in cancer. We looked at the usefulness of solid lipid nanoparticles as a tool for cancer therapy. **[48]**

Saroj Kumar Pradhan *et.al* reported that in order to achieve a successful colon targeted drug delivery system, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the gastrointestinal tract (GIT) and then ensure abrupt or controlled release in the proximal colon. Such a system can be formulated by utilizing microbial triggering degradation of polymer coating/ gastro intestinal (GI) transit time (time dependent)/ pH dependent approach etc. But unfortunately it has been found that colonic microflora, GI transit time and pH varies considerably inside a human system by several factors, in addition to this the native biodegradable polysaccharides which are used widely for the microbial triggering colonic drug delivery system (CDDS), are having high aqueous solubility on account of which a single unit colon targeted drug delivery systems may suffer from dose dumping due to overall catastrophic failure of the film around a monolith, which would then release the whole drug, that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. **[49]**

Rong Tong *et.al* reported that the polymers play important roles in the design of delivery nanocarriers for cancer therapies. Polymeric nanocarriers with anticancer drugs conjugated or encapsulated, also known as polymeric nanomedicines, form a variety of different architectures including polymer-drug conjugates, micelles, nanospheres, nanogels, vesicles, and dendrimers. **[50]**

Veli Cengiz Ozalp *et.al* discussed that aptamers are functional nucleic acid sequences which can bind specific targets. An artificial combinatorial methodology can identify aptamer sequences for any target molecule, from ions to whole cells. Drug delivery systems seek to increase efficacy and reduce side-effects by concentrating the therapeutic agents at specific disease sites in the body. This is generally achieved by specific targeting of inactivated drug molecules. Aptamers which can bind to various cancer cell types selectively and with high affinity have been exploited in a variety of drug delivery systems for therapeutic purposes. Recent progress in selection of cell-specific aptamers has provided new opportunities in targeted drug delivery. Especially functionalization of nanoparticles with such aptamers has drawn major attention in the biosensor and biomedical areas. Moreover, nucleic acids are recognized as an attractive building materials in nanomachines because of their unique molecular recognition properties and structural features. An active controlled delivery of drugs once targeted to a disease site is a major research challenge. Stimuli-responsive gating is one way of achieving controlled release of nanoparticle cargoes. Recent reports incorporate the structural properties of aptamers in controlled release systems of drug delivering nanoparticles. **[51]**

Ishita Aggarwal *et.al* reported that the colorectal cancer (CRC), commonly called colon cancer, is a cancer of the colon or rectum. Although colon cancer is highly treatable, the National Cancer Institute of Canada (NCIC) acknowledges it as the third most common cancer and the second most common cause of cancer-related deaths among Canadians. Scientific studies have shown that colon cancer is caused, in part, by the overproduction of a molecule called Interleukin-8 (IL-8), which is released from the surface of tumor cells. Once generated, IL-8 binds to specialized proteins, called CXCR2 receptors, on the surface of nearby cancer cells. Binding of IL-8 to CXCR2 produces signals within tumor cells that activate molecules called transcription factors. The activation of various transcription factors, including NF- B and AP-1, via the Akt and MAPK signaling pathways, ultimately causes the growth and survival of colon cancer cells. Hence, reducing the expression of IL-8 by cancer cells may have therapeutic implications for patients suffering from colon cancer. Although various treatment methods have been developed to inhibit the production of IL-8, most techniques pose a safety risk to patients because they may interact with the human immune system in unpredictable ways. This review suggests that the safest treatment method to target IL-8 is the use of nano-particles, specifically quantum dots (QDs), to transport small interfering RNA (siRNA**)** into colon cancer cells. Once delivered, siRNA can silence IL-8 expression, reducing the risk of cancerous growth. **[52]**

S. Pradeep Kumar *et al* reported that the review focus on the potential opportunities and challenges available in new area of colon targeted drug delivery system. The colon is a site where both local and systemic delivery of drugs can take place. Colon was considered as "BLACK BOX" as, most of drugs are absorbed from upper part of GIT tract. Lack of digestive enzymes and long transit time, has been provided to design colon specific drug delivery system. Present topic into the utilization of the metabolic activity and the colonic environment in the lower gastrointestinal tract has attained immense value in the design of novel colon targeted drug delivery systems by the utilization of natural biodegradable polymers. It is more effective to treat colonic diseases such as ulcerative colitis, colorectal cancer, and Crohn's disease with direct delivery of drugs to the affected area. Newly developed colon specific drug delivery system (CDDS), which includes pressure controlled colonic delivery capsules (PCDCS), CODES and osmotic controlled drug delivery are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process.**[53]**

Bodaiah Bonigala *et.al.* reported that the **c**ancer is a lethal disease or a destructive phenomenon arises in human beings because of genetic factors or exposure to toxic chemicals or viral infections etc. Radio therapy is very promising in the treatment of cancer compared to other treatments. However normal cells are also destroyed along with tumor cells in this treatment. Application of nanomedicine in the treatment of cancer is a novel approach. From research findings it can be known that MTT assay is generally used and widely accepted method in screening invitro anticancer activity of metal naoparticles. In addition biosynthesized silver nano particles(AgNPs) have exhibited remarkable activity against cancer cell lines in MTT assay. Green synthesized silver nanoparticles inhibit the proliferation of cancer cells by activating the apoptosis process or changing the cellular chemistry. Biosynthesized AgNPs may also block the tumor growth by damaging the function of mitochondria or generaration of ROS. Plants are the natural treasures of secondary metabolites. In the green synthesis these phytochemicals acts as reducing and stabilizing agents of silver nanoparticles. The plant mediated AgNPs have shown dose and time dependant antitumor activity on cancer cells. The present study deals with the nature of different plants used in the synthesis of silver nanoparticles. **[54]**

S.Bhunchu *et.al.* reported that the nanoparticulate drug delivery systems enhance cancer treatment by direct entry of nanometer particles into the fenestration in the vasculature of cancer cells. Nanoparticles for encapsulation of anticancer drugs are preferably prepared using natural polymers as carriers, with polysaccharides being particularly favorable. Alginate and chitosan polysaccharides have been widely used in nanoparticulate drug delivery systems because of their biodegradable, biocompatible, non-toxic and bioadhesive properties. **[55]**

Gandhali A Deshpande *et.al.* reported that the nanotechnology is prominent in medicine for various applications. Nanotechnology is a multidisciplinary field, which covers diverse arrays of devices made using principles of engineering, biology, physics, and chemistry. The increasing number of nanomedicines is approved clinically, used safely, which highlights the important role of nanotechnology in the field of cancer research. The successful application of nanotechnology to the targeted smart drug therapy ISA rapidly growing component of armamentarium against cancer. Nanotechnology is being applied to cancer in two broad areas: the development of nanovectors, such as nanoparticles, which can be loaded with drugs or imaging agents and then targeted to tumors, and high throughput nanosensor devices for detecting the biological signatures of cancer. This advanced technology provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy, and medicine**. [56]**

Maria Pilar Vinardell *et.al*. reported that nanoparticles have received much attention recently due to their use in cancer therapy. Studies have shown that different metal oxide nanoparticles induce cytotoxicity in cancer cells, but not in normal cells. In some cases, such anticancer activity has been demonstrated to hold for the nanoparticle alone or in combination with different therapies, such as photocatalytic therapy or some anticancer drugs. Zinc oxide nanoparticles have been shown to have this activity alone or when loaded with an anticancer drug, such as doxorubicin. Other nanoparticles that show cytotoxic effects on cancer cells include cobalt oxide, iron oxide and copper oxide. The antitumor mechanism could work through the generation of reactive oxygen species or apoptosis and necrosis, among other possibilities. **[57]**

Pratibha Muntha *et.al.* reported that drug delivery is the administration of a therapeutically active substance into the body of the patient using a route of administration which will give maximum therapeutic effect. Targeted drug delivery designs the drug delivery systems in such a way that the dosage form releases the active ingredients in the targeted area which will result in reduced side effects and helps in achieving maximum therapeutic benefit Nanoparticles as drug delivery systems are now playing a major role in the area of targeted drug delivery systems especially in the treatment of cancer. Nanoparticles indicate nanostructures with intermediate size between microscopic and molecular structure. Nanoparticles can exist in different shapes of spherical, filamentous, tubular, and irregular. They even have applications in various other fields related to cosmetics, cancer therapy, food addictives etc. **[58]**

Mayur M Patel *et.al.* reported that colorectal cancer (CRC) is the third most common cancer in the world and the second most common cause of cancer related deaths. Conventional treatment of CRC is comprised of drug (chemotherapeutic agents) administration by parenteral route, which delivers the drug to both normal as well as cancerous tissues, thus leading to numerous undesirable effects. Enormous research is going on worldwide for designing an alternative route of administration, among which oral colon-targeted drug delivery systems have gained immense attention amongst scientific community. Direct delivery of drugs at the site of action leads to an increase in the availability of drugs at the targeted region. This causes a reduction in the amount

of drug required to exert same therapeutic effect, thus reducing the incidents of adverse effects. Various maneuvers (pH-dependent, time-dependent and microflora-activated systems) have been attempted by researchers for targeting drugs successfully to the colonic region by circumventing the upper part of gastrointestinal tract**. [59]**

Yang *et.al.* reported that colorectal cancer is the most common form of gastroenteric cancer worldwide. Photodynamic therapy is emerging as an attractive method to treat cancers. Candidate targets of photodynamic therapy include epidermal growth factor receptors, cholesterol and low-density lipoprotein, estrogen receptors, the nucleus and DNA, folic acid receptors, cholecystokinin A receptors, lectin saccharide receptors, and tumor-specific antibodies. Specifically, in colorectal tumors, anti-DR5 antibody and cancer-specific antibody moieties are involved. Cancer cells incorporate greater quantities of sugars, and glycoconjugated photosensitizer has remarkable internalization and cytotoxicity in colon/colorectal cancer cells. Simultaneously, to circumvent the bio-distribution limitation, other molecules, including lectins, Hyaluronic acid, and peptides, have also been considered for colorectal cancer. Other novel strategies indirectly targeting colorectal cancer include pH-responsive PS, enzymatically activated photosensitization, and cancer-suppressing immune cells, mainly macrophages. Recently, nanoparticles have gained attention as a versatile platform for multi-functional photodynamic therapy**. [60]**

DISCUSSION:

The importance of colon target drug delivery is that the drug released from the system must be sensitively active in the colon. Drug targeting to the diseased colon are advantageous in reducing the systemic side effects, lowering dose of the drug and supplying the drug only when it is required and maintaining the drug as possible for colon targeted drug delivery. There is a need to develop a novel approach which is specific for colon targeting. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. The challenge remains to develop and validate a dissolution method that incorporates the physiological features of the colon. In future, various multifunctional novel nanoparticles based drug delivery may be designed and developed for the treating the colon cancer. Due to their incredible properties, nanoparticles have become significant in many fields in recent years such as energy, health care, environment, agriculture etc. Nanoparticle technologies have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable substances. Nanoparticles represents promising drug carrier for various drug delivery systems Nanotechnology is breakthrough technology pervading all fields newer applications of this field are being explored worldwide. Nanoparticles represents a technology to overcome solubilities and bioavailability problems of drugs which can be generally applied to all poorly soluble drugs. Any drug can be transformed to drug nanoparticles leading to increasing saturation solubility, dissolution rate and providing in general feature of an increased adhesiveness to surfaces. Nanoparticulate drug delivery system is increasingly viewed as an advantageous solution for biological drugs. In addition, nanoparticles provide efficient treatment by enabling targeted and controlled release thus in feature nanoparticulate drug-delivery system seem to be a viable and promising strategy for the biopharmaceutical industry. The development of drug delivery systems that are able to modify the biodistribution, tissue uptake and pharmacokinetics of therapeutic agents is considered to be of great importance in biomedical research. Controlled release in drug delivery can significantly enhance the therapeutic effect of a drug. The attractive properties of nanomedicines include their ability to

controlled release of drugs, the targeting of specific tissues and the biocompatibility. Because of their size, nanoparticles can be taken up very efficiently by cells forming a stable nanocomplex thereby protecting it from nuclease degradation and allowing effective delivery to the tumor site. Despite the challenges restricting its application, it is possible that nanomedicine in future would play a crucial role in the treatment of human CRC, and also in the enhancement of normal human physiology. The *in vivo* biodistribution pattern of inorganic nanoparticles depends on particle size and surface engineering. Surface PEGylation reduces the uptake rate by macro- phages and prolongs the circulation half-life. Similarly, nanoparticle accumulation in tumors is also dependent on the size and surface engineering of inorganic nanoparticles. Some of them are devoid of toxicity and could be further developed in clinics for imaging and/or therapeutic purposes. The study demonstrates the ionic gelation method can be used to load hydrophilic drugs and produce the size of less than 200 nm. The concentration of CS, TPP and sonication time strongly effect the particle size formation of the CS-NP. The CS-NP composed of 0.6% CS and 0.2% TPP was selected as the optimized formulation which produced smaller particle with better encapsulation. *In vitro* cytotoxicity study suggested the safety of the prepared 5 Fluorouracil loaded chitosan nanoparticles conjugated with hyaluronic acid which can be potential carrier to deliver hydrophilic drugs to target colorectum. Furthe *In vivo* will confirm the targeting efficiency of Fluorouracil loaded chitosan nanoparticles conjugated with hyaluronic acid to treat colorectal cancer. In cancer therapies, the ideal drug delivery system is the one that places the drug only at the target tumour cell. Although there are many exciting new avenues in drug targeting both in colonic and systemic treatment for CRC, the ideal scenario is still beyond our grasp. In reality, to effectively target drugs to the tumour cell, the prepared drug delivery system has to fulfill four vital requirements: retain, evade, target and release. The heterogeneity of cancer cells also complicates the issue. Thus, all of these factors, and many others that remain unknown, should be taken into consideration for developing better drug delivery for CRC. Unfortunately, current chemotherapeutic treatment for CRC uses high doses of cytotoxic medicaments, specifically adjuvant combinations of 5-FU and Irinotecan, which result in adverse effects to the affected patient. It is necessary to develop new nanomedicines with multifunctional characters that bring together different chemotherapeutic agents; ideally this would allow double or triple therapies with lower systemic doses, and significantly reduce undesirable side-effects.

CONCLUSION

Cancer is a complex genetic disease that is caused primarily by environmental factors. Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the US. The importance of colon target drug delivery is that the drug released from the system must be sensitively active in the colon. Drug targeting to the diseased colon by nanoparticulate system are advantageous in reducing the systemic side effects, lowering dose of the drug and supplying the drug only when it is required and maintaining the drug as possible for colon targeted drug delivery.

ACKNOWLEDGEMENT:

The authors are highly thankful to all staff members of Dept. of Pharmaceutics (P.G.Studies) Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab, India and University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, India for their constant encouragement and support for preparing this article. Without which,it wouldn’t be possible to prepare this presented work.

REFERENCES:

1. Malcolm R Alison, "Cancer", encyclopedia of life sciences / & 2001 Nature Publishing Group, page no. 1-8.
2. Oleg V. Bukhtoyarov et al. "Pathogenesis of Cancer: Cancer Reparative Trap" Journal of Cancer Therapy, 2015, Published Online May 2015, page no.399-412
3. M Manikandan et.al, "Design of Nano particles for Colon Target Drug Delivery A Review", Research Journal of Pharmaceutical, Biological and Chemical Sciences, Oct-Dec 2011 Volume 2 Issue 4 Page No. 128
4. Cherkuri Sowmya et.al, "Colon Specific Drug Delivery System :A Review On Pharmaceutical Approaches With Current Trends" International Research Journal of Pharmacy 2012, vol 3 (7),page no.45-53
5. Clara Abraham, M.D et.al "Inflammatory Bowel Disease" N Engl. J Med 2009 http://www.nejm.org/doi/full/10.1056/NEJMra0804647.article
6. Timothy J Yeatman et al "Colon Cancer" Encyclopedia Of Life Sciences / & 2001 Macmillan Publishers Ltd, Nature Publishing Group page no. 1-6
7. Rick Alteri, et al "colorectal cancer facts & figure" 2014-2016 page no. 1-24
8. R Manavalan et al, "Design of Nanoparticles for Colon Target Drug Delivery – A Review",Research Journal of Pharmaceutical, Biological and Chemical Sciences ,October – December 2011 Volume 2 Issue 4 Page No. 128
9. Pirita Varpe, "surgical treatment of colorectal cancer- controversial issues" Turku, february 2010 ,page no11-52
10. Saba Hasan, "A Review on Nanoparticles: Their Synthesis and Types", Research Journal of Recent Sciences Vol. 4(ISC-2014), 1-3 (2015) page no.1
11. Nishikant C Shinde **"**Research Journal of Pharmaceutical, Biological and Chemical Sciences" January – March 2012 RJPBCS Volume 3 Issue 1 Page No. 922
12. National Comprehensive Cancer Network®, "NCCN Guidelines For Patient" NCCN.org/patients/Survey version1.2016,V 1.2016 page no.29-34.
13. Danda Sreelatha et.al."Colon targeted drug delivery-a review on primary and novel approaches" Journal of Global Trends in Pharmaceutical Sciences, Volume 4, Issue 3, July-September 2013, pp -1175.
14. M Manikandan et al, "Design of Nanoparticles for Colon Target Drug Delivery – A Review", Research Journal of Pharmaceutical, Biological and Chemical Sciences, October – December 2011 Volume 2 Issue 4 Page No. 136
15. Danda Sreelatha et.al."Colon targeted drug delivery-a review on primary and novel approaches" Journal of Global Trends in Pharmaceutical Sciences. Volume 4, Issue 3, July-September 2013, pp -1183
16. S. GILL et.al, "colorectal cancer chemotherapy" Aliment Pharmacol.Ther,2003;p.p 683-692.
17. Mariana Varna et al. "In Vivo Distribution of Inorganic Nanoparticles in Preclinical Models" Journal of Biomaterials and Nanobiotechnology, 2012, Published Online May 2012 Page no. 269-279.
18. Suzanne Hagan et.al,"Targeted therapies in colorectal cancer-an integrative view by PPPM" The EPMA Journal 2013; page no.1-16.
19. Madalina Palaghia et.al, "Metastatic Colorectal Cancer: Review of diagnosis and treatment options " Journal of Surgery; Volume 10 ; Published December 28, 2014; page no.1-8
20. Singh Amritpa et.al, "Novel approaches for colon targeted drug delivery system" International Journal of Research and Development in Pharmacy and Life Sciences Vol.; 3 February - March, 2014; p.p. 877-886
21. Ahmad Gholamhoseinian Najar et al. " EGFR Antisense Oligonucleotides Encapsulated with Nanoparticles Decrease EGFR, MAPK1 and STAT5 Expression in a Human Colon Cancer Cell Line" Asian Pacific Journal of Cancer Prevention, Vol 14**,** 2013 page no. 495-498.
22. Jayakumar Jerobin et al. " Recent Developments in Nano medicine Treatment Options for Colorectal Cancer" OMICS Group e.Books; July 2015; page no.1-15
23. Nusrat bano, "Review of colorectal carcinoma and specific disease features in the population of Pakistan" Asian Journal of Pharmaceutical and Clinical Research Vol 6, Suppl 1, 2013 page no. 1-5.
24. Barish et al "formulation and evaluation of 5 fluorouracil nanoparticles for the treatment of colorectal cancer" Asian Journal of Research in Biological and Pharmaceutical Sciences. vol(3), 2015, page no109 – 117.
25. Yiming Ma,"Controlled delivery of nanoparticles to the colon for tumour targeting" Australian Iinstitute for bioengineering and nanotechnology, page no. 1-3.
26. Sutar ps et.al., "Preparation and characterization of 5-fluorouracil loaded plga nanoparticles for colorectal cancer therapy" unique journal of pharmaceutical and biological sciences; sep-oct 2013 ; page no.52-58.
27. Prados J et.al, "Colon cancer therapy :recent developments in nanomedicine to improve the efficacy of chemotherapeutic agents" Anticancer agents Med chem. 2013;page no.1204-1216

28. Justin la Roque et.al, "Cancer Detection and Treatment of the role of Nanomedicines" Molecular Biotechnology;july2009;volume 42;issue 3,page no358-356
29. Deep Kwatra et.al, "Nanoparticles in radiation therapy:a summary of various approaches to enhance radiosensitization in cancer" Radiation cancer research,vol 2,august 2013,page no.4
30. Li Chang-Feng et.al, "Doxorubicin-Loaded Eudragit-Coated Chitosan Nanoparticles in the treatment of Colon cancers" Journal of Nanoscience and Nanotechnology,volume 16,7 july 2016 page no.6773-6708.
31. Armin Imanparast et.al "New Approaches to Colorectal Cancer Treatment; an Overview" Cancer Press, vol 2 no 2 page no.2016
32. Chintan H. Kapadia et.al, "Nanoparticulate immunotherapy for cancer" Journal of Controlled Release 2015; page no.1-14.
33. Melissa S Wason et.al, "Cerium oxide nanoparticles: potential applications for cancer and other diseases" Am J Transl Res 2013 page no.126-131
34. Jasvir Kaur et al, "Colon Targeted Drug Delivery System To Treat Colorectal Cancer: A Review World Journal Of Pharmacy And Pharmaceutical Sciences" Volume 5, Issue 01,page no, 407-420.
35. Sophie Laurent et al, "Superparamagnetic iron oxide nanoparticles: promises for diagnosis and treatment of cancer" Int J Mol Epidemiol Genet ,2011:2(4) page no.367-390.
36. Congcong Lin et al, "Exploring Different Strategies for Efficient Delivery of Colorectal Cancer Therapy" Int. J. Mol. Sci. 2015, page no.1626936–26952.
37. Leila Hamzehzadeh et al, "New Approaches to Use Nanoparticles for Treatment of Colorectal Cancer" A Brief Review" Nanomed Res J 1(2); Autumn 2016, page no.59-68
38. .Nehal M El-Deeb et al**, "**Novel Trend in Colon Cancer Therapy Using Silver Nanoparticles Synthesized by Honey Bee" J Nanomed Nanotechnol Volume 6; 2015, page no.1-6.
39. Manoj Kumar Sarangi et al, "Colon Targeted Drug Delivery System-An Approach for Treating Colonic Ailment" J Crit Rev, Vol 2, 2015,page no.1-17.
40. Kothawade P. D et al, "Conventional and Novel Approaches for Colon Specific Drug Delivery: A Review" e - Journal of Science & Technology (e-JST) 6,2011, P.p 33-56.
41. Ning Zhao Gold nanoparticles for cancer theranostics: A brief update Journal of Innovative Optical Health Sciences Vol. 9, No. 4 (2016),pp-10.
42. Nour Karra The Ligand Nanoparticle Conjugation Approach for Targeted Cancer Therapy Current Drug Metabolism, 2012, 13, 2012 Vol. 13, page no 1
43. Anbarasan Ba et al, "Development Of Formulation And In-Vitro Evaluation Of Capecitabine Loaded fe3o4 Nanoparticles Modified With Plga-Peg Polymer For Colon Cancer Treatment" Sri Ramachandra Journal Of Medicine, Jan- June 2015, Vol.8, Issue 1.
44. Ling Zhang et.al, "Gene therapy for C-26 colon cancer using heparin-polyethyleneimine nanoparticle-mediated survivin T34A" International Journal of Nanomedicine 2011 p.p 2419-27
45. Alicia A. Taylor et al, "Metal Oxide Nanoparticles Induce Minimal Phenotypic Changes in a Model Colon Gut Microbiota" Environmental Engineering Science Volume 00, Number 00, 2015 page no 1
46. Deeksha tripathi et al, "Nanoparticles: A Novel Avenue in Cancer Therapy" Int. J. Pharm. Sci February 2016 page no.90-98.
47. Che-Ming Jack Hu et al**, "**Nanoparticle-assisted combination therapies for effective cancer treatment Therapeutic Delivery (2010) 1(2), page no. 323–334.
48. Vineet Mathur et al, "Solid lipid nanoparticles in cancer therapy" International Journal of Drug Delivery 2 (2010) page no.192-199.
49. Saroj Kumar Pradhan et al. "Multiparticulate Combined Approaches for Colon Specific Drug Delivery" International Journal of Biomedical Research October,2011 page no. 476-485.
50. Rong Tong et al. "Anticancer Polymeric Nanomedicines Department of Materials Science And Engineering" University of Illinois at Urbana-Champaign, Urbana,USA,1 Page No. 345.
51. Veli Cengiz Ozalp et.al, "Aptamer-Gated Nanoparticles for Smart Drug Delivery" Pharmaceuticals august 2015 page no. 1137-1157.
52. Ishita Aggarwal et.al,"Targeting The Interleukin-8 Signaling Pathway In Colorectal Cancer: A Mini-Review" Journal Of Young Investigators August 2013,Vol.25 Page No. 108.
53. S.Pradeep Kumar et.al, "Novel Colon Specific Drug Delivery System: A Review" International Journal of Pharmacy and Pharmaceutical Science January, 2012 page no.24.

54. Bodaiah Bonigala et al, “Anticancer activity of plant mediated silver nanoparticles on selected cancer cell lines” Journal of Chemical and Pharmaceutical Research, 2016,page no.376-381.
55. S. Bhunchu et al, “Biopolymeric Alginate-Chitosan Nanoparticles As Drug Delivery Carriers For Cancer Therapy” Ph.D. Program In Nanoscience And Technology (International) 2014 page no. 563–570.
56. Gandhali A Deshpande et al “Cancer Nanotechnology: The Recent Developments in the Cancer Therapy” Glob J Nano Volume 1 ,May 2016 page no.1.
57. Maria Pilar Vinardell et.al, “Antitumor Activities of Metal Oxide Nanoparticles” Nanomaterials 2015, 5 page no.1004-1021.
58. Pratibha Muntha et.al**, “**Nanoparticles as Targeted Drug Delivery Systems-A Novel Approach in Cancer Therapy” Research & Reviews in Pharmacy and Pharmaceutical Sciences published december,27/2013 page no.2320-2322.
59. Mayur M Patel et.al, “Getting into the colon: approaches to target colorectal cancer” Expert Opinion on Drug Delivery Published on 05 Jun 2014 page no. 1343-1350.
60. Yang et.al, “Nanoscale Photodynamic Agents for Colorectal Cancer Treatment: A Review” Journal of Biomedical Nanotechnology, Volume 12, July 2016, pp. 1348-1373.