OPEN ACCESS

Review Article

"Unravelling Colorectal Cancer: From Origin to Treatment"

Kake Ramya[1], Anbu Jayaraman[2*], Harshitha Gond[1], Vaishnavi Patel[1]

[1]Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, Karnataka, India- 560054.
[2]Head of the Department, Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, Karnataka, India- 560054.

Abstract: The colon and rectum are the primary organs affected by colorectal cancer (CRC), which is the primary cause of cancer-related morbidity and mortality. Inflammation, particularly in disorders like inflammatory bowel diseases, increases the risk of colorectal cancer, with environmental factors playing a crucial role. The majority of adenocarcinomas typically develop from the epithelial cells that line the colon and rectum as a result of a complex series of genetic and epigenetic modifications. Benign precursor lesions such as adenomatous polyps trigger the slow progression of CRC over a period of ten years or longer. Its etiology is influenced by sporadic, familial, and hereditary forms; prominent hereditary syndromes include Lynch syndrome and familial adenomatous polyposis. Chromosome instability and microsatellite instability are the two main tumorigenic pathways that underpin the pathophysiology of CRC, exhibiting regional differences in the global epidemiology. *Approaches*: TNM classification is the basis for diagnosis, and various treatment modalities, such as surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and gene therapy, are employed during treatment. Surgical treatments, from minimally invasive procedures to colectomy, are essential and highlight the importance of total excision of the mesocolic region. The standard therapeutic approach consists of chemotherapy and targeted agents; however, newer like gene therapy and immunotherapy show promise. In order to improve outcomes and lessen the burden of the disease, combating CRC requires comprehensive strategies that include early detection, prevention, and innovative therapeutic interventions.

Keywords: Colorectal Cancer, Inflammatory Bowel Diseases, Adenomatous Polyps, Immunotherapy, Lynch Syndrome.

INTRODUCTION

The large intestine is the portion of the digestive tract where water is absorbed from indigestible contents. The large intestine includes the cecum, appendix, entire colon, rectum, and anal canal. It begins at the terminal ileum with the cecum. The ascending colon runs superiorly on the right side of the abdomen from the right iliac fossa to the right lobe of the liver. At this point, it makes a left turn at the right colic flexure (hepatic flexure). Ascending colon is a retroperitoneal organ and has paracolic gutters on either side. The transverse colon is the third, most mobile, and longest part of the large intestine. (Dumont F *et al.*, 2017) It is found between the right and left colic flexures. The left colic flexure is less mobile than the right and is attached to the diaphragm through the phrenocolic ligament. The transverse colon

is attached to a mesentery, the transverse mesocolon, which has its root along the inferior border of the pancreas. The transverse colon continues as the descending colon (Smereczyński A et al., 2018).

The two are demarcated at the splenic flexure. The descending colon is a retroperitoneal organ and related to paracolic gutters on either side. It terminates into the sigmoid colon, which is the fifth part of the large intestine. The sigmoid colon links the descending colon to the rectum. The sigmoid colon is an S-shaped loop of varying length and becomes the rectum at the level of S3 (P Kahai, *et al.*, 2017)

The key functions of the colon include water and nutrient absorption, Vitamin absorption, Feces

*Corresponding Author: Dr. Anbu Jayaraman
Head of the Department, Department of Pharmacology, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, Karnataka, India- 560054.M S Ramaiah University of Applied Sciences

91

compaction, Potassium, and chloride secretion, moving waste material toward the rectum.
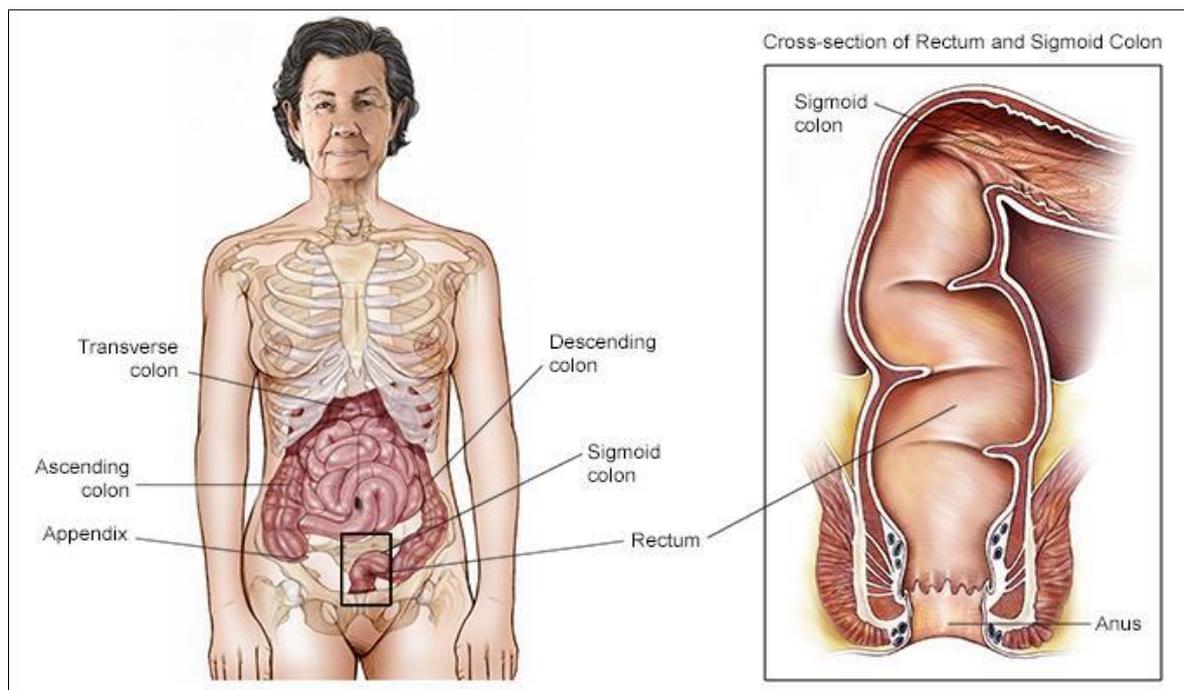

Fig. 1: Structural arrangement of colon; detailed exploration

Colon cancer, which ranks second in mortality and third in incidence among all cancers, is one of the most prevalent cancers (Wong *et al.*, 2019). The majority of human CRC cases are caused by environmental risk factors rather than heritable genetic changes, including chronic intestinal inflammation, food-borne mutagens, and specific intestinal commensals (Feagins *et al.*, 2009).

Colorectal cancer is characterized by the invasion of neoplastic epithelial cells below the muscularis mucosae of the colorectal wall (Kobaek *et al.*, 2000). The development of colon cancer is closely linked to chronic inflammation, and prior research has shown that people with inflammatory bowel disease (IBD) who also have colitis have a higher chance of getting colon cancer. Abdominal pain changed chronic bowel habits, irregular bowel movements, involuntary weight loss, nausea, vomiting, malaise, anorexia, and abdominal distension are among the symptoms that this condition manifests clinically. Distal cancers exhibit conspicuous rectal bleeding, in contrast to proximal cancers that may cause mixed blood in the stool. As a result, anaemia could appear as a side effect (Calva *et al.*, 2009).

Most colon and rectal cancers are caused by adenocarcinoma, a type of cancer that arises from the cells lining the inner tissue of the colon and rectum. This dominates the tumor population. Adenocarcinoma is the particular topic of this section. Other cancers can also start in the colon or rectum, though they are less common. These include lymphoma, small cell carcinoma, gastrointestinal stromal tumors (GIST), and neuroendocrine tumors of the gastrointestinal tract.

Chronic inflammation causes oxidative stress, DNA damage, and the inactivation of tumor suppressor genes. Clonal expansion occurs in somatic epithelial cells due to a cascade of events that result in epigenetic (e.g., methylation) and genetic (e.g., mutations) changes. For example, IBD is characterized by large, chronically inflamed mucosa regions that are susceptible to neoplastic transformation, whereas the sporadic form of CRC is typified by discrete small lesions with dysplastic changes (adenomas, serrated polyps). Field cancerization is the term used to describe this phenomenon (Alatab *et al.*, 2017) (Seyedian *et al.*, 2019) (Shah *et al.*, 2022).

Initiation, Promotion, and Progression are the three stages in the development of CRC and starts with initiation, which is defined as irreversible genetic damage that makes impacted intestinal mucosal epithelial cells more vulnerable to later neoplastic transformation (Tanaka *et al.*, 2009). During the promotion phase, initiated cells undergo proliferation, results in aberrant growth and the emergence of cancer. During the progression stage, benign cancer cells change into malignant ones, developing aggressive characteristics and the capacity to spread (Gandomani *et al*, 2017). The presence of a benign precursor lesion called a polyp, an abnormal growth on the colon mucosa within its lumen, is a critical factor in the carcinogenesis of CRC. Lesions in the lumen of the large intestine have been identified as adenomatous polyps (adenomas) and

serrated polyps, which are direct precursors to the majority of cancers (Rawla *et al.*, 2019) (Rosty *et al.*, 2013). Compared to non-advanced adenomas, advanced adenomas have a significantly higher risk of cancer progression (30 to 50%), especially if their diameter is ≥1 cm and they have diversity. The transition rates to cancer increase with age, particularly in advanced adenomas (Brenner *et al.*, 2007) (Aust *et al.*, 2010).In addition to adenomas, other types of preneoplastic lesions observed in the colon include hyperplastic polyps, serrated adenomas, flat adenomas, and dysplastic lesions (Tanaka *et al.*, 2009). In humans, colorectal cancer is histologically classified as adenocarcinoma (Machado *et al.*, 2016).

Adenomatous polyps develop in the epithelium as the first step is relatively slow process of CRC, carcinogenesis, which eventually results in the formation of an adenocarcinoma (Sabit *et al.*, 2019). The slow accumulation of mutations and genetic changes, which usually take ten to fifteen years, is what propels this process. But in some circumstances, like Lynch syndrome patients, the progression might happen more quickly (Zauber *et al.*, 2007).

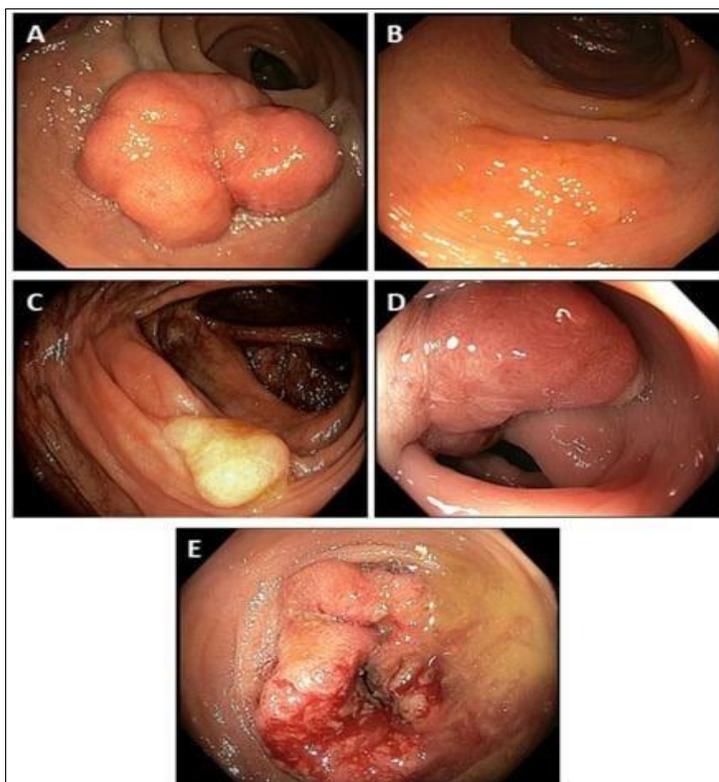**Fig. 2: Selected endoscopic images of adenomas and CRC at different stages. (A)—Tubular adenoma; (B)—tubulo-villous adenoma; (C)—sedentary serrated adenoma (SSA) without dysplasia; (D)—tubular adenocarcinoma, grade 1 and (E)—tubular adenocarcinoma, grade 2. (Sawicki *et al*, 2021)**
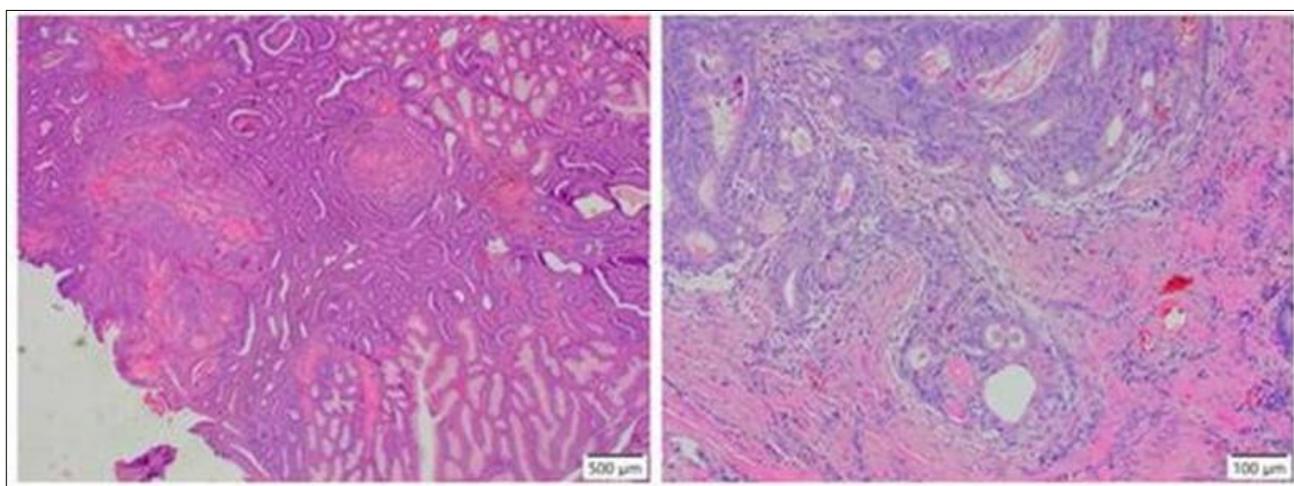

Fig 3: Representative histopathological appearance of adenocarcinoma in the colon (Sawicki *et al*, 2021)

ETIOLOGY

Colon cancer (CCA) has three potential causes: inherited syndromes (10%), familial clustering (20%), and sporadic cases (70%). While a small proportion of individuals with a true inherited pattern have a higher risk at an earlier age (under 50 years old), the majority of sporadic CCA patients (the remaining 20%) exhibit familial clustering without a discernible inherited syndrome. Environmental factors are the primary cause of sporadic CCA patients, who are typically diagnosed after the age of fifty. Familial adenomatous polyposis coli (FAP) and Lynch syndrome, also referred to as hereditary nonpolyposis colorectal cancer (HNPCC), are the two most common hereditary syndromes that predispose individuals to colorectal cancer. These hereditary syndromes together account for about 5% of colorectal cancer cases, but up to 10% to 15% of patients with unselected colorectal cancer may have a high-risk mutation unrelated to FAP or HNPCC (Allen *et al.*, 2019) (Celind *et al.*, 2019).

HNPCC, an autosomal dominant disease, brought on by mutations in the genes that repair mismatches, which causes mistakes in DNA during cell division. The proteins that these genes encode are in charge of correcting mismatched DNA. While mutations in other genes, such as MSH6, MLH3, TGBR2, PMS1, and PMS2, can also cause HNPCC, MLH1 and MSH2 mutations account for the majority of HNPCC cases. By the age of fifty, those with HNPCC have a twenty percent chance of getting CRC, and by the age of eighty-five, their risk rises to eighty-five percent. (Win *et al.*, 2014) (Sehgal *et al.*, 2014) (Kolligs *et al.,* 2016) (Rawla *et al.*, 2019) (Valle *et al.*, 2019).

Similar to HNPCC, FAP is inherited autosomally dominantly and is caused by gene abnormalities linked to adenomatous polyposis coli (APC). The APC gene, which is classified as a tumour suppressor, produces a protein that is essential for controlling DNA replication and cell division. In their mid-teens, people with FAP usually begin to develop hundreds or even thousands of colon polyps, with a high chance that these polyps will progress to cancer. It is predicted that almost everyone with untreated and undiagnosed FAP syndrome will be diagnosed with colorectal cancer before the age of 35 to 40. (Kolligs *et al.*, 2016) (Rawla *et al.*, 2019) (Valle *et al.*, 2019) (Yang *et al.*, 2020).

PATHOPHYSIOLOGY

Since 1990, significant progress has been made in unravelling the molecular mechanisms and genetic model for CRC tumorigenesis (Fearon *et al.*, 1990). The identification of accumulating mutations in key genes like K-ras, APC, tumor protein P53 (TP53), and deleted in colorectal carcinoma has provided insights into the progression from normal mucosa to adenoma to carcinoma. However, these mutations alone cannot fully explain all cases of CRC. The pathogenetic pathway of CRCs is diverse, characterized by two primary tumorigenic pathways as proposed by (Delattre *et al.*, 1989).

- ***Instability Chromosome:***

    This particular mutation, present in 85% of colorectal cancers, affects important genes such as APC, TP53, K-ras, allelic loss of 18q, and induces aneuploidy. It also results in proto-oncogene mutations and the loss of heterozygosity in tumor suppressor genes (Vacante M *et al.*, 2018). People with conditions like familial adenomatous polyposis FAP have a 90% chance of developing cancer without a colectomy and a higher risk of extracolonic cancers, particularly if they have 10–99 adenomas at diagnosis. (Ballester V *et al.*, 2016). Over 60% of the mutations in the APC gene, a prominent "housekeeping" gene, are concentrated in the five′ ends of the exons on the 5q21 chromosome. These mutations include frameshift and microdeletions (Li H *et al.*, 2017).

- ***Microsatellite Instability:***

    This mutation, which accounts for 15% of colorectal cancers, is primarily caused by errors in the mismatch repair system (MMR) of the DNA damage repair system. These errors arise from a breakdown in base complementarity. Short sequences expand in tandem with this breakdown, leading to an increase in the number of mutations. Seven genes make up the MMR system: hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. To date, more than five hundred different mutations have been found in these genes (De' Angelis *et al.*, 2018). For example, this mutation causes Lynch syndrome (LS), which develops into cancer with a 70% lifetime risk of colorectal cancer (CRC) (Ballester V). For path MLH1, MSH2, and MSH6 carriers, the cumulative incidence of colorectal cancer at 75 years is 46%, 43%, and 15%, respectively (Møller P *et al.*, 2018)

- ***Epigenetic*** (**DNA Methylation**)

    Methylation of CpG islands occurs in sporadic CRC 15%, and also it affects the expression of DNA repair genes or Mismatch genes. (Abbaszadegan *et al.*, 2018)

RISK FACTORS

Table 1: List of risk factors of colorectal cancer and their proposed mechanism

PARAMETERS	PROPOSED MECHANISM
Epidemiology	
• Old age	Acquired colonocyte mutations accumulate with age.
• Living in highly nations	Dietary and environmental carcinogens
Diet	
• Low fruit and consumption	Anticarcinogenic substances in fruits and vegetables (eg, folic acid)
• Obesity	Carcinogens in an unhealthy diet or role of abnormal insulin levels in carcinogenesis
Social habits	
• Smoking cigarettes	Carcinogens present in tobacco.
• Alcohol	May promote cell proliferation and inhibit DNA repair.
Genetics/family history	Develops hundreds of adenomatous colonic polyps. Inevitably develops colon cancer resulting from small but significant risk for malignant transformation in each adenoma.
• FAP	
• Gardner's syndrome	Variant of FAP.
• HNPCC (Lynch syndrome)	Mutant mismatch repair gene leads to accumulation of genetic mutations, including mutations of tumor suppressor genes.
• Peutz-Jeghers syndrome	Syndromic hamartomatous polyps occasionally may transform to adenomas.
• Juvenile polyposis	Syndromic juvenile polyps can transform to adenomas and then cancers over time.
• Family history of nonsyndromic colon cancer	Postulated shared genetic factors leading to mild susceptibility to colon cancer and possibly shared environmental factors.
• Hyperplastic polyposis	Genetic mutation in hyperplastic polyposis seems to predispose to colon cancer.
Inflammatory bowel disease	
• Chronic ulcerative colitis	Dysplasia and genetic mutations associated with mucosal injury and repair.
• Chronic Crohn's colitis	Dysplasia and genetic mutations associated with cell injury and repair
Other	
• Pelvic radiation	Carcinogenic effects resulting from radiation induced mutations.
• Streptococcus bovis bacteremia	May promote colonocyte proliferation.
• Ureterosigmoidostomy	Carcinogens excreted in urine or colonic mucosal proliferation during repair after Urine induced mucosal injury.
• Acromegaly	Growth hormone promotes proliferation of preexisting colonic adenomas and cancers.
Physical inactivity	Physical activity may stimulate immunosurveillance and stimulate intestinal peristalsis to decrease mucosal contact with faecal carcinogens.
Low calcium	Calcium binds to bile acids that otherwise are potentially colonotoxic.
High fat	Various theories (eg, increased bile secretion)

High red meat	Animal fat in red meat or carcinogens (eg, nitrosamines) in cooked meat.
Low selenium	Selenium can help neutralize toxic free radicals due to antioxidant effects.
Low folate	Folate needed for DNA synthesis and repair.
Low carotenoid diet	Carotenoids can help neutralize free radicals resulting from antioxidant effects.
Low fiber diet	Dilution of carcinogens in stool due to increased stool bulk and stool water with a high fiber diet.
Breast cancer	Shared reproductive hormonal or environmental factors.
Diabetes mellitus	Insulin may modulate colonocyte proliferation.
Prior cholecystectomy	Continuous colonic exposure to potentially carcinogenic bile acids after cholecystectomy.

CURRENT GLOBAL EPIDEMIOLOGY OF COLORECTAL CANCER

Colorectal cancer ranks as the third most prevalent cancer in men and the second most common cancer in women. In 2017, it caused 896,000 deaths worldwide. Slovakia, the Netherlands, and New Zealand reported the highest standardized incidence rates that year, while Greenland, Hungary, and Slovakia had the highest standardized death rates (Tran *et al.*, 2017). In 2018, there were 1,849,518 colorectal cancer cases globally, constituting 10.2% of all cancers, and resulting in 880,792 deaths (Goodarzi *et al.*, 2019).

Estimates for 2020 indicate 1.93 million new cases and ninety-four million deaths from colorectal cancer worldwide, representing 10% of global cancer incidence (totalling 19.29 million new cases) and 9.4% of all cancer-related deaths (totalling 9.96 million deaths) (Xi Y *et al.*, 2015). In 2020, there were over 1.9 million new cases (Arnold M *et al.*, 2015) (Bray *et al.*, 2021). CRC stands as the second most common cause of cancer-related deaths, estimated to be responsible for nearly 935,000 deaths (Arnold *et al.*, 2015). Globally, it is among the cancers with increasing incidence, comprising 11% of all cancer diagnoses (Wong *et al.*, 2020). According to GLOBOCAN 2020 data, there is significant geographic variation in colorectal cancer incidence and mortality among countries worldwide (WHO, 2016).
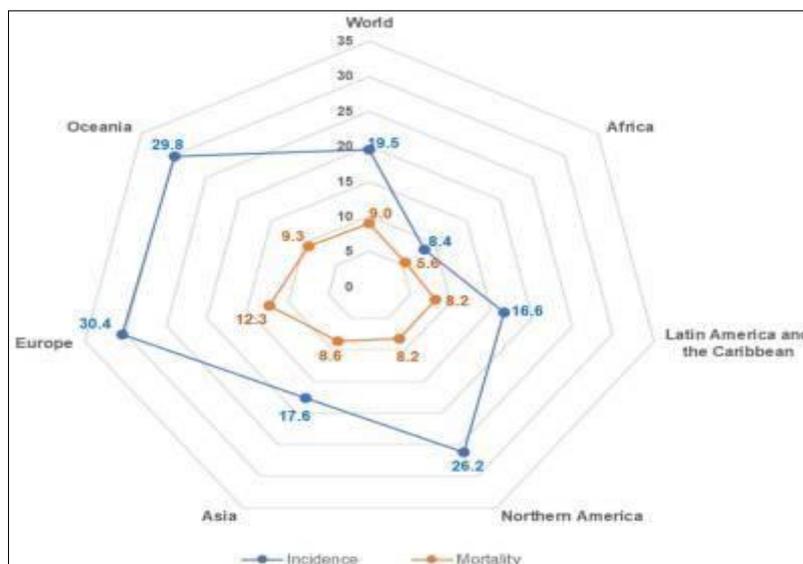

Fig. 4: Incidence and mortality rates for CRC in 2020/100,000

INCIDENCE

The global incidence of colorectal cancer exhibits regional variations, with the highest rates observed in Australia and New Zealand, Europe, and North America, and the lowest rates in Africa and South-Central Asia. These differences seem to be linked to

varying dietary and environmental exposures, lower socioeconomic status, and limited CRC screening, all set against a backdrop of diverse susceptibility (Macrae *et al.*, 2017).

In the United States, CRC incidence rates had been decreasing at a rate of about 2 percent per year, but this decline slowed to approximately 1.2 percent per year during the period from 2014 to 2018 (Cronin *et al.*, 2022). In contrast, there has been a rapid increase in CRC incidence rates in areas historically at low risk, including Spain, as well as several countries in Eastern Asia and Eastern Europe (Jemal *et al.*, 2011) (Center *et al.*, 2009).

Specific factors contribute to the increase in CRC incidence globally, including a more sedentary lifestyle, obesity, the consumption of highly processed

foods, alcohol, red meat, and an overall rise in life expectancy (Sawicki *et al.*, 2021).

STAGES AT DIAGNOSIS

The staging system employed for colorectal cancer is the tumour–node–metastasis classification, originating from the original work by Dukes in 1932. The 'T' component indicates the depth of tumor invasion into various layers of the bowel wall, The N component refers to the number of lymph nodes involved (Sobin *et al.*, 2009). Recently, a distinct nodal category, N1c, was introduced to denote the presence of tumor deposits without lymph node metastases, sparking considerable debate in the literature (Nagtegaal *et al.*, 2012), adding complexity to treatment decisions. The M component signifies the presence of distant metastasis.

Table 2: Stages of colon cancer and its characteristics

STAGE CHARACTERISTICS
Tumor
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through muscularis propria into subserosa or mesocolic
T4 Tumor directly perforates to another organs
Regional nodal metastasis
NX Regional lymph nodes cannot be assessed
N0 No involved lymph nodes
N1 Metastasis in 1–3 mesocolic nodes
N1c (special category) Tumor deposits are evident in the absence of lymph node metastases.
N2 Metastasis in four or more mesocolic nodes
N3 Metastasis to atypical node
Distant Metastasis
MX Distant metastasis presence is currently indeterminable.
M0 No distant metastasis
M1 Distant metastasis

The T, N, and M stages collectively form the stage classification for CRC. The stages are as follows: Stage I represents early-stage cancer confined to the bowel wall (T1, T2) without lymph node metastases. Stage II entails cancer without lymph node involvement, encompassing T3–T4 tumours. Stage III involves cancer without distant metastases but with lymph node metastases. Finally, Stage IV signifies cancer with

distant metastases (M1) diagnosed at the outset. It is crucial to note that the T, N, and M stages are interrelated; as the T stage increases, the risk of lymph node and distant metastases rises. Similarly, with an advancing N stage, the risk of distant metastases also increases. The term Tis, denoting carcinoma in situ, is not considered cancer but is regarded as high-grade neoplasia (Bosman *et al*, 2010).
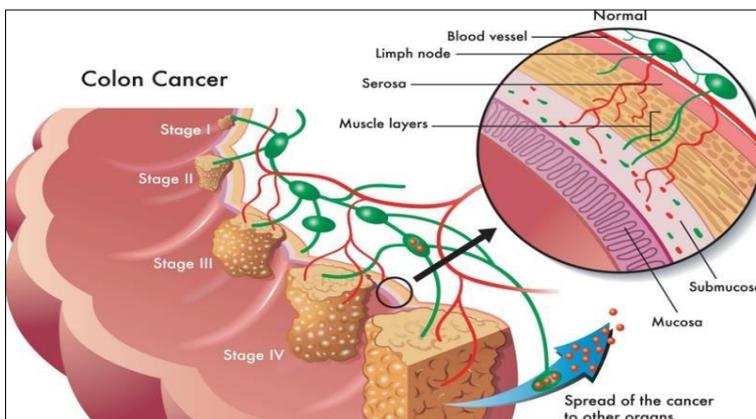

Fig. 5: Different stages of colon cancer (Lakkim, V *et al.*,2017)

TREATMENT

1. Current Surgical Treatment Strategies for Colorectal Cancer

A number of risk factors determine the best surgical strategy for patients with Lynch syndrome and colon cancer, including total abdominal colectomy and segmental colectomy with ileorectal anastomosis. In deciding which course of action is best, patient surgical preferences—especially taking into account their age and capacity for close observation—are crucial (Maeda *et al.*, 2010).

Lymph node dissection has a significant influence on the long-term prognosis following colorectal cancer surgery and entails the en bloc excision of the tumor's lymphatic drainage as well as any related lymph nodes. A greater number of lymph nodes examined, usually between 11 and 25, has been linked to better survival, according to several studies (Lykke *et al.*, 2015) (Le Voyer *et al.*, 2003) (Swanson *et al.*, 2003). Standardized excision techniques, such as complete mesocolic excision (CME) and total mesorectal excision (TME) in rectal cancer, within the mesocolic plane with central vascular ligation, can help achieve this optimal range (West *et al.*, 2010).

The CME concept entails high ligation of the vascular supply at its origin and complete removal of the intact mesentery (Kontovounisios *et al.*, 2014). Numerous studies have shown that, when compared to other approaches, routine CME implementation results in increased lymph node harvest, decreased morbidity, lower rates of locoregional recurrence, and longer cancer-specific survival (Willaert *et al.*, 2014). This approach may lead to upstaging patients, identifying more individuals for whom chemotherapy is indicated.
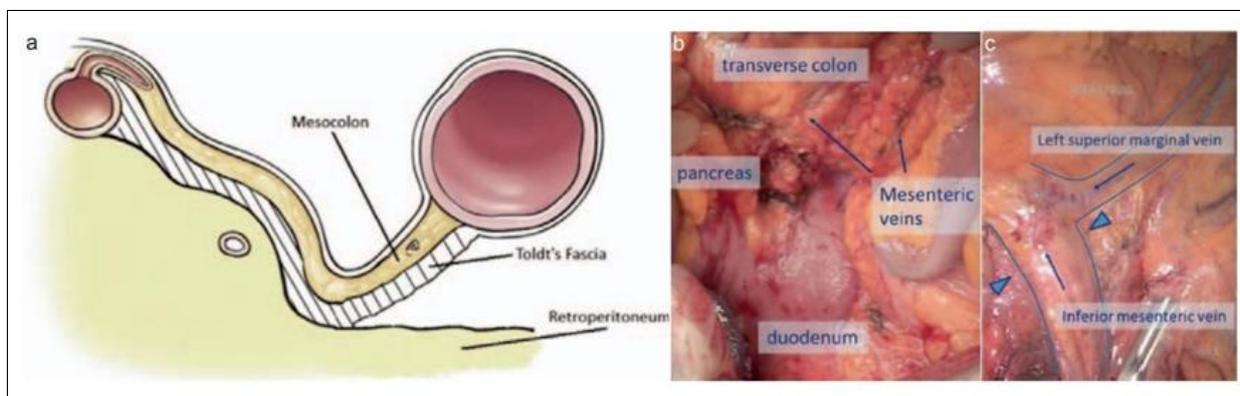

Fig. 6: a) Schematic illustration of the anatomic plane for complete mesocolic excision (CME) in right-sided hemicolectomy
b) Crucial intraoperative step for CME in right-sided hemicolectomy. Mesocolon and mesoileum have to be mobilized along Toldt's fascia to the duodenum and lower edge of the pancreas. The vascular trunks of the middle (transverse) colon and ileal artery/vein are the dissection margins to the left. (Rentsch, M *et al.*,2016)

Hand-Assisted Laparoscopic Colectomy (HALC)

This technique involves entails maintaining pneumoperitoneum while inserting the surgeon's non-dominant hand through a specialized hand port into the abdomen. A hand inside the abdomen facilitates safe finger dissection and retraction, improves hand-eye coordination, and restores tactile sensation. The combined effect of these factors results in a notable decrease in operating time. Furthermore, in laparoscopic colonic resection, the incision made at the start of the procedure can be strategically used to retrieve the resected colon at the end of it (Meshikhes *et al.*, 2011).

Robotic Surgery:

The inaugural robotic-assisted colectomy took place in the USA in 2002 (Weber PA *et al.*, 2002). Robotic surgery provides benefits like motion scalability, stereoscopic vision, tremor filtration, and wristed instrument use, which improve the surgeon's dexterity and allow for accurate lymph node dissection and intracorporeal anastomoses (Giulianotti *et al.*, 2003). Based on cohort studies, patients with stage I–III colon cancer may have a better long-term prognosis if they undergo partial or total colectomies using robotic techniques rather than laparoscopic ones (Mirkin *et al.*, 2018). However, there are still a number of significant disadvantages to robotic colectomy in colon cancer, including longer operating times, higher costs, and steeper learning curves (Isik *et al.*, 2017). The precise role of robots in colon cancer surgery remains uncertain.

On the other hand, for rectal cancer, minimally invasive transanal and robot-assisted laparoscopic TME appear to have potential for enhancing the prognosis for both distal and mid-rectal cancer (Jayne *et al.*, 2017) (Ma B *et al.*, 2016). According to a meta-analysis, robotassisted surgery for rectal cancer may have similar oncological outcomes and a more favourable therapeutic effect than laparoscopic surgery. (Wang X *et al.*, 2020).

Radiotherapy:

For patients with stage II and III rectal cancer or unresectable residual tumors (positive margins), preoperative hypo fractionated radiation therapy in

conjunction with chemotherapy is recommended. This suggestion is based on the anatomopathological results that were documented in the surgical specimen (Wang *et al.*, 2018). Interestingly, radiotherapy is only used as palliative care in a limited number of metastasis cases, mostly involving the brain and bones (Yu J *et al.*, 2019).

Targeted Therapy:

Individuals with colorectal cancer have shown notable improvements in overall survival when using targeted therapy, which is a novel approach. This advancement has been made possible by novel drugs that block multiple immune pathway checkpoints at a never-before-seen pace, such as the anti-EGFR (epidermal growth factor receptor) drug cetuximab and the anti-angiogenesis drug bevacizumab (Xie *et al.*, 2020).

Many of the identified checkpoints, such as the immune checkpoint (T cell), VEGF/VEGFR, EGF/EGFR, hepatocyte growth factor (HGF), mesenchymal-epithelial transition factor (cMET), insulin-like growth factor/insulin-like growth factor 1 receptor (IGF/IGF-1R), transforming growth factor (TGF), Wnt/β-catenin, Notch, and Hedgehog, have the potential to be targeted therapeutic interventions for CRC (Xie *et al.*, 2020).

Immunotherapy Drugs	Receptor	Type of protein
Cetuximab	EGFR	Transmembrane protein
Bevacizumab	EGFR, VEGF/VEGFR	Transmembrane/signalling protein
Panitumumab	EGFR, VEGF/VEGFR	Transmembrane/signalling protein
Zif-aflibercept	VEGF/VEGFR	signalling protein
Regorafenib	VEGF/VEGFR	signalling protein
Ramucirumab	VEGF/VEGFR	signalling protein
Pembrolizumab	Block PD-1	Programmed cell death protein one
Nivolumab	Block PD-1	Programmed cell death protein one
Ipilimumab	Block PD-1	Programmed cell death protein one

Chemotherapy

The Food and Drug Administration (FDA) in the United States has approved numerous medications for the treatment of colorectal cancer. During treatment, your doctor might suggest one or more of them at various points. These are occasionally mixed with medications for targeted therapy (Lotfollahzadeh *et al.*, 2017). 5-FU alone; 5-FU with leucovorin (folinic acid); a vitamin that improves the effectiveness of 5-FU; Capecitabine, an oral form of 5-FU, FOLFOX: 5-FU with leucovorin and oxaliplatin; FOLFIRI: 5-FU with leucovorin and irinotecan; Irinotecan alone; FOLFOXIRI: 5-FU with leucovorin, oxaliplatin, and irinotecan; XELOX/CAPEOX: Capecitabine with oxaliplatin; Use of a targeted therapy in combination with chemotherapy may be recommended: bevacizumab (Avastin), cetuximab (Erbitux), or panitumumab (Vectibix).

Chemotherapy-Related Toxicities and Complications

Hematologic, Neutropenia, Thrombopenia, Anemia, Gastrointestinal, Diarrhea, Nausea/vomiting, Oropharyngeal, Mucositis, Stomatitis, Gingivostomatitis, Dermatological Dermatitis, Alopecia, Hand and foot syndrome, Neurologic, peripheral neuropathy (Aoullay *et al.*, 2020).

Gene Therapy

Gene therapy is a therapeutic approach that utilizes genetic components, such as DNA or RNA, to address various diseases, including cancer, by substituting or repairing malfunctioning genes. This method can trigger an immunological response or function as an independent treatment. Mutations and gene aberrations are important factors in the development of CRC. Adjusting and fixing these defective genes, along with avoiding the overexpression of certain genes, may be able to inhibit colorectal cancer. Many genes have changed during the course of colon cancer's evolution, due to a variety of causes including point mutations, the emergence of oncogenes, the disruption or elimination of protooncogenes, and the reduction of suppressor-oncogene interaction (Armaghany *et al.*, 2012).

Of the 50,000–100,000 genes found in the human body, only a small number are involved in the cell cycle. As at least 30% of colon cancers are caused by faulty genes, which are known to play a major role in CRC. Certain faulty genes have also been connected to familial cases of colon cancer. Transferring specific genes to targeted tumor cells is the main benefit of gene therapy, as it suppresses the aberrant function of mutant genes and slows the growth of tumors (Zhang *et al.*, 2015) (Takami *et al.*, 1995) (Cho *et al.*, 1992).

Immunotherapy

Researchers are interested in using tumor immunotherapy to treat CRC because of its promising therapeutic potential. Numerous immunotherapies, such as immune checkpoint inhibitors, adoptive cell therapy, complement inhibition, cancer vaccines, monoclonal antibody (MAb) therapy, and cytokine treatment, are being studied in humans with colorectal cancer as part of ongoing clinical trials. (Zahavi *et al.*, 2020). Numerous research studies have reported encouraging outcomes for these approaches, many of which are undergoing phase I or II clinical trials. Over forty clinical trials that are actively recruiting patients or are in the process of doing so are currently underway, and over twenty-four clinical studies that have examined immunotherapy for human

colorectal cancer have been completed to date (Hossain *et al.*, 2022).

A) Monoclonal Antibody Therapy

Treatment for metastatic colorectal cancer involves the use of humanized antibodies, such as cetuximab and panitumumab that are specifically made to target the epidermal growth factor receptor (EGFR). A number of MAbs are being studied in ongoing clinical trials for CRC. These include pemtumomab, which targets mucins, labetuzumab, which targets carcinoembryonic antigen (CEA), and adecatumumab, which targets the epithelial cell adhesion molecule (EpCAM) (Cunningham *et al*, 2004).

B) Immune Checkpoint Inhibitors Therapy:

T-cell activation is inhibited in part by CTLA-4, an immune checkpoint molecule that binds to CD80/CD86 structures on antigen-presenting cells. Programmed death receptor ligand one-half (PD-L1/L2) binds to the PD-1 receptor on T-cells and is normally stimulated by different ligands expressed on either tumor cells (e.g., PDL1/L2PD-1) or APCs (e.g., CD80/86 CTLA-4; PD-L1/L2PD-1). This negatively regulates the function of T-cells. Critical are the immune checkpoint signals triggered by PD-1 and CTLA-4. In the context of colorectal cancer, there is an ongoing phase II clinical study evaluating the efficacy of the single medication Nivolumab as well as a combination of dual therapies, such as Nivolumab + Ipilimumab (Sharma *et al*, 2015).

C) Cancer Vaccines

Cancer vaccines are designed to deliver antigens to antigen-presenting cells (APCs), like dendritic cells (DCs), in order to stimulate antigen-specific T- or B-cell activity against cancer. Additionally, some vaccines contain ingredients like DC vaccination and OncoVAX that are meant to activate pulsated DCs with antigens and guide them to a nearby lymph node (Hu *et al.*, 2018).

Cytokine Therapy:

Particularly in colorectal cancer, where the inflammatory process and immunogenic responses are what propel tumor development, cytokines are crucial elements of tumor immunology. TNF and interleukin-6 play a crucial role in CRC by stimulating nuclear factor-B and inducer of transcription 3 (STAT3), two important oncogenic factors, in intestinal cells to promote proliferation and resistance to apoptosis (West *et al.*, 2015).

Traditional Medicine and Medicinal Plants for Colon Cancer

Grapes, which are high in flavonoids and procyanidins, help slow down the growth of cancer cells by raising the levels of dihydroceramides, p53, and p21 (a protein that acts as a gatekeeper for the cell cycle). Furthermore, nuclear factor erythroid 2-related factor 2 (Nrf2), a transcriptional factor, was activated by grape extracts to cause an antioxidant response. (Signorelli *et al.*, 2015).

Soybean is another plant that produces saponins. Colon cancer cells were exposed to soy extract for 72 hours, and it was discovered that this extract reduced the expression and activity of cyclooxygenase-2 (COX-2) and protein kinase C (H.Y. Kim *et al.*, 2004). After being exposed to the soy extract, the density of the cancer cells dramatically dropped. Additionally, soybeans can lower the quantity of cancer cells and raise their death rate; this effect may be brought on by higher levels of the protein Rab6 (Q. Zhu *et al.*, 2002).

In both in vitro and in vivo experiments, green tea leaves, which contain high levels of catechins, enhanced apoptosis in colon cancer cells and decreased the expression of vascular endothelial growth factor (VEGF) and its promoter activity. In comparison to the control group, the extract increased apoptosis, or programmed cell death, in tumor cells by 1.9 times and in endothelial cells by three times (Y.D. Jung *et al.*, 2001). Green tea leaves can be effective in the inhibition of matrix metalloproteinase 9 (MMP-9) and in inhibiting the secretion of VEGF (M. W. Roomi *et al.*, 2005).

Allicin and organosulfur compounds are found in garlic roots. Stops the proliferation of cancer cells and triggers apoptosis by blocking the phosphoinositide 3-kinase/Akt pathway.

Additionally, they have the ability to decrease the expression of Akt and p-Akt and increase the expression of phosphatase and tensin homolog (PTEN) (M.Dong *et al.*, 2014). Sallylcysteine and S-allylmercaptocysteine, found in garlic roots, are known to have anticancer effects (Y.D. Jung *et al.*, 2001).

Possible mechanisms suggested for the anticancer effects of the garlic extract are both the increase of detoxifying enzyme soluble adenylyl cyclase (SAC) and an increased activity of glutathione S-transferase (GST). The results suggest that the garlic extract stimulates mouse spleen cells, causes the secretion of cytokines, such as interleukin-2 (IL2), tumor necrosis factor-α (TNF-α), and interferon-γ, and increases the activity of natural killer (NK) cells and phagocytic peritoneal macrophages (Tanaka *et al.*, 2006).

A variety of phytochemicals found in pomegranate fruits, including punicalagins, ellagitannins, ellagic acid, and other flavonoids like quercetin, kaempferol, and luteolin glycosides, suggest that this extract has anticancer properties by reducing p65 subunit phosphorylation and subsequently inhibiting nuclear factor-κB (NFκB). Moreover, it suppresses the Akt-induced TNF receptor activity, which is necessary for NFκB activity. Fruit juice has a significant inhibitory effect on cancer cells' expression of TIPA, a protein that

induces TNF-α in the COX-2 pathway. (L.S. Adams *et al.*, 2006). Flavonoids, polyphenol compounds like caffeic acid, catechins, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, and phenols like luteolin and quercetin, as well as kaempferol and luteolin glycosides, are the active and significant components found in pomegranates. By stopping cells in the G1 phase, the extract made from Annona muricata leaves inhibits the growth of colon cancer cells and triggers apoptosis (Moghadamtousi *et al.*, 2014). They can also prevent the progress of the G1/S phase in cancer cells (J. Linet *et al.*, 2014). In general, the herbal extracts reported here have been able to stop cancer cells at various stages, such as G2/M, G1/S, S phase, G0/G1, and G1 phase, and could prevent their proliferation and growth.

Eugenol, a naturally occurring component derived from honey, can be found in extracts from balm plants, citrus, clove oil, cinnamon, and Flos Magnolia. The novel medicinal applications of eugenol may be beneficial for a variety of chronic diseases. It causes colon cancer cells to undergo more apoptosis (Seeram *et al.*, 2006). Eugenol has been promoted as a natural colon cancer therapy. Eugenol stimulates sub-G1 cell division, which, in turn, triggers apoptosis in a way that is time-dependent. In its role as a signal transducer for apoptosis, it is responsible for regulating the production of matrix metallo-proteins (MMP) and non-protein thiols. Eugenol induced p53 activation and the cleavage of proline-rich acidic protein (PRAP) in colon cancer cells (Jaganathan *et al.*, 2015).

Curcumin has a wide range of pharmacological effects, such as anti-inflammatory, antibacterial, and potential free radical scavenging (Shehzad *et al.*, 2010). Furthermore, curcumin exhibits anti-neoplastic properties. On the healthy cells, the curcumin treatment had no negative effects. In contrast, p53 mutant COLO 320 DM cells experienced a cell cycle arrest in the G1 phase, which resulted in a decrease in the number of cells in the S phase and death. (Jayaprakasha *et al.*, 2010) (Dasiram *et al.*, 2017) Curcumin suppressed the CaCo-2 human CRC cell line's growth via triggering apoptosis and activating caspase-3/7 (Sakuma *et al.*, 2014).

Panax quinquefolius, Ginsenosides, also known as triterpenoid saponins, are an essential bioactive molecule having anti-inflammatory properties that can aid in the prevention of CRC (Y. Jin *et al.*, 2010). They are an important bioactive molecule with anti-inflammatory qualities that were extracted from dried roots and may help prevent colorectal cancer. HT29 cell lines were treated with BST204, a fermented ginseng extract. It halts the cell cycle in the G1 phase and causes changes in the expression of tumor genes, including a rise in the CDK inhibitor p53 and a fall in the expression of G1-S transition proteins like CDK2, cyclin E, and cyclin D1. (J.W. Park *et al.*, 2011). Numerous studies have demonstrated that the antineoplastic activity of

Oleuropin, a phenolic molecule found in the wild olive tree cultivar Olea europaea var. Sylvestris, is caused by this cultivar. The capacity of human CRC cell lines HT29 and SW260 to divide and multiply was significantly reduced. The drug's ability to stop cell growth by making the p53 gene more active and reducing the expression of the HIF1α gene at the same time resulted in apoptosis. (Shamshoum *et al.*, 2017).

The fruit of Garcinia mangostana, also referred to as the "Queen of Fruits," was discovered to contain xantones, which were demonstrated to be the main bioactive compounds (especially α-and γ-mangostin). Xantones have a variety of pharmacological effects, some of which include cadioprotective, anti-inflammatory, anticancer, and antibacterial properties. (Heber *et al.*, 2004) (J.H. Yoo *et al.*, 2011). When the HCT116 colorectal cancer cell line was treated with a xanthone extract that included α-mangostin (81%) and γ-mangostin (16%), a dosedependent increase in cytotoxicity was seen at an IC50 = 6.5 ± 1.0 μg/ml. After 90 min of treatment, xanthone extract at concentrations of 10 and 20 g/ml enhanced the activity of caspase-3 and caspase-9 but not caspase-8 in cell line cells. The lilac tassel flower, Emilia sonchifolia, is used as a traditional medicine. γ-humulene, a monocyclic sesquiterpene, was identified as one of the main phytochemicals in an Emilia sonchifolia extract by GC-MS analysis (B.S. Shylesh *et al.*, 2000). Numerous investigations have examined the anti-CRC properties of γ-humulene and its likely mechanisms of action. The human colorectal cancer cell line HT29 was used in studies as a therapeutic recipient of Emilia sonchifolia extract (Y.U.H. Lan *et al.*, 2011).

CONCLUSION

Studies on CRC mechanisms have provided many new ideas for CRC prevention and treatment. However, because of individual variations, tumor stages, and crossspecies translation, many challenges remain to be overcome in clinical practice (Wong *et al.*, 2019).

REFERENCES

- Abbaszadegan, M. R., & Moghbeli, M. (2018). Genetic and molecular origins of colorectal Cancer among the Iranians: an update. *Diagnostic Pathology*, *13*, 1-13.
- Adams, L. S., Seeram, N. P., Aggarwal, B. B., Takada, Y., Sand, D., & Heber, D. (2006). Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signalling in colon cancer cells. *Journal of Agricultural and Food Chemistry*, *54*(3), 980-985.
- Alatab, S., Sepanlou, S. G., Ikuta, K., Vahedi, H., Bisignano, C., Safiri, S., & Naghavi, M. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the

Global Burden of Disease Study 2017. *The Lancet gastroenterology & hepatology*, 5(1), 17-30.

- Allen, J., & Sears, C. L. (2019). Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development. *Genome Medicine*, 11, 1-18.

- Aoullay, Z., Slaoui, M., Razine, R., Er-Raki, A., Meddah, B., & Cherrah, Y. (2020). Therapeutic characteristics, chemotherapy-related toxicities and survivorship in colorectal cancer patients. *Ethiopian Journal of Health Sciences*, 30(1).

- Arcos, M. C., & Tirado, M. T. A. (2009). Revisión y actualización general en cáncer colorrectal. In *Anales de Radiología, México*, 8(1), 99-115.

- Armaghany, T., Wilson, J. D., Chu, Q., & Mills, G. (2012). Genetic alterations in colorectal cancer. *Gastrointestinal Cancer Research: GCR*, 5(1), 19.

- Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2017). Global patterns and trends in colorectal cancer incidence and mortality. *Gut*, 66(4), 683-691.

- Aust, D. E., Baretton, G. B., & Working Group GI-Pathology of the German Society of Pathology. (2010). Serrated polyps of the colon and rectum (hyperplastic polyps, sessile serrated adenomas, traditional serrated adenomas, and mixed polyps)—proposal for diagnostic criteria. *Virchows Archiv*, 457, 291-297.

- Ballester, V., Rashtak, S., & Boardman, L. (2016). Clinical and molecular features of young-onset colorectal cancer. *World Journal of Gastroenterology*, 22(5), 1736.

- Bosman, F. T., Carneiro, F., Hruban, R. H., & Theise, N. D. (2010). *WHO Classification of Tumours of the Digestive System* (No. Ed. 4). World Health Organization.

- Bray, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Zanetti, R., & Ferlay, J. (2021). Cancer Incidence in Five Continents Volume XI: Cancer Today. *IARC Scientific Publication*, (166), 5-9.

- Brenner, H., Hoffmeister, M., Stegmaier, C., Brenner, G., Altenhofen, L., & Haug, U. (2007). Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840 149 screening colonoscopies. *Gut*, 56(11), 1585-1589.

- Celind, J., Ohlsson, C., Bygdell, M., Nethander, M., & Kindblom, J. M. (2019). Childhood body mass index is associated with risk of adult colon cancer in men: an association modulated by pubertal change in body mass index. *Cancer Epidemiology, Biomarkers & Prevention*, 28(5), 974-979.

- Center, M. M., Jemal, A., & Ward, E. (2009). International trends in colorectal cancer incidence rates. *Cancer Epidemiology Biomarkers & Prevention*, 18(6), 1688-1694.

- Cho, K. R., & Vogelstein, B. (1992). Genetic alterations in the adenoma–carcinoma sequence. *Cancer*, 70(S4), 1727-1731.

- Cronin, K. A., Scott, S., Firth, A. U., Sung, H., Henley, S. J., Sherman, R. L., & Jemal, A. (2022). Annual report to the nation on the status of cancer, part 1: National cancer statistics. *Cancer*, 128(24), 4251-4284.

- Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., & Van Cutsem, E. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New England Journal of Medicine*, 351(4), 337-345.

- Dasiram, J. D., Ganesan, R., Kannan, J., Kotteeswaran, V., & Sivalingam, N. (2017). Curcumin inhibits growth potential by G1 cell cycle arrest and induces apoptosis in p53-mutated COLO 320DM human colon adenocarcinoma cells. *Biomedicine & Pharmacotherapy*, 86, 373-380.

- Delattre, O., Law, D. J., Remvikos, Y., Sastre, X., Feinberg, A. P., Olschwang, S., & Thomas, G. (1989). Multiple genetic alterations in distal and proximal colorectal cancer. *The Lancet*, 334(8659), 353-356.

- Dong, M., Yang, G., Liu, H., Liu, X., Lin, S., Sun, D., & Wang, Y. (2014). Aged black garlic extract inhibits HT29 colon cancer cell growth via the PI3K/Akt signalling pathway. *Biomedical Reports*, 2(2), 250-254.

- Dukes, C. E. (1980). The classification of cancer of the rectum. *Diseases of the Colon & Rectum*, 23(8), 605-611.

- Dumont, F., Da Re, C., Goéré, D., Honoré, C., & Elias, D. (2013). Options and outcome for reconstruction after extended left hemicolectomy. *Colorectal Disease*, 15(6), 747-754.

- Fearon, E. R., & Vogelstein, B. (1990). A genetic model for colorectal tumorigenesis. *cell*, 61(5), 759-767.

- Gandomani, H. S., Aghajani, M., Mohammadian-Hafshejani, A., Tarazoj, A. A., Pouyesh, V., & Salehiniya, H. (2017). Colorectal cancer in the world: incidence, mortality and risk factors. *Biomedical Research and Therapy*, 4(10), 1656-1675.

- Gian, L. D. A., Lorena, B., Cinzia, A., Gioacchino, L., Federica, G., & Francesca, N. (2018). Microsatellite instability in colorectal cancer. *Acta Bio Medica: Atenei Parmensis*, 89(Suppl 9), 97.

- Giulianotti, P. C., Coratti, A., Angelini, M., Sbrana, F., Cecconi, S., Balestracci, T., & Caravaglios, G. (2003). Robotics in general surgery: personal experience in a large community hospital. *Archives of Surgery*, 138(7), 777-784.

- Goodarzi, E., Beiranvand, R., Naemi, H., Momenabadi, V., & Khazaei, Z. (2019). Worldwide incidence and mortality of colorectal cancer and

---

human development index (HDI): an ecological study. *World Cancer Research Journal*, 6, 8.

- Heber, D. (2004). Vegetables, fruits, and phytoestrogens in the prevention of diseases. *Journal of Postgraduate Medicine*, 50(2), 145-149.

- Hossain, M. S., Karuniawati, H., Jairoun, A. A., Urbi, Z., Ooi, D. J., John, A., & Hadi, M. A. (2022). Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges, risk factors, preventive and treatment strategies. *Cancers*, 14(7), 1732.

- Hu, Z., Ott, P. A., & Wu, C. J. (2018). Towards personalized, tumour-specific, therapeutic vaccines for cancer. *Nature Reviews Immunology*, 18(3), 168-182.

- Isik, O., & Gorgun, E. (2015). How has the robot contributed to colon cancer surgery. *Clinics in Colon and Rectal Surgery*, 28(04), 220-227.

- Jaganathan, S. K., Mazumdar, A., Mondhe, D., & Mandal, M. (2011). Apoptotic effect of eugenol in human colon cancer cell lines. *Cell Biology International*, 35(6), 607-615.

- Jayaprakasha, G. K., Murthy, K. N. C., & Patil, B. S. (2016). Enhanced colon cancer chemoprevention of curcumin by nanoencapsulation with whey protein. *European Journal of Pharmacology*, 789, 291-300.

- Jayne, D., Pigazzi, A., Marshall, H., Croft, J., Corrigan, N., Copeland, J., & Brown, J. (2017). Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. *Jama*, 318(16), 1569-1580.

- Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, 61(2), 69-90.

- Jin, Y., Hofseth, A. B., Cui, X., Windust, A. J., Poudyal, D., Chumanevich, A. A., & Hofseth, L. J. (2010). American ginseng suppresses colitis through p53-mediated apoptosis of inflammatory cells. *Cancer Prevention Research*, 3(3), 339-347.

- Jung, Y. D., Kim, M. S., Shin, B. A., Chay, K. O., Ahn, B. W., Liu, W., & Ellis, L. M. (2001). EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. *British Journal of Cancer*, 84(6), 844-850.

- Kahai, P., Mandiga, P., Wehrle, C. J., & Lobo, S. (2017). *Anatomy, Abdomen and Pelvis*: Large Intestine, 1-5.

- Kim, H. Y., Yu, R., Kim, J. S., Kim, Y. K., & Sung, M. K. (2004). Antiproliferative crude soy saponin extract modulates the expression of IκBα, protein kinase C, and cyclooxygenase-2 in human colon cancer cells. *Cancer letters*, 210(1), 1-6.

- Kobaek-Larsen, M., Thorup, I., Diederichsen, A., Fenger, C., & Hoitinga, M. R. (2000). Review of colorectal cancer and its metastases in rodent models: comparative aspects with those in humans. *Comparative medicine*, 50(1), 16-26.

- Kolligs, F. T. (2016). Diagnostics and epidemiology of colorectal cancer. *Visceral Medicine*, 32(3), 158-164.

- Kontovounisios, C., Kinross, J., Tan, E., Brown, G., Rasheed, S., & Tekkis, P. (2015). Complete mesocolic excision in colorectal cancer: a systematic review. *Colorectal Disease*, 17(1), 7-16.

- Lan, Y. H., Wu, Y. C., Wu, K. W., Chung, J. G., Lu, C. C., Chen, Y. L., & Yang, J. S. (2011). Death receptor 5-mediated TNFR family signalling pathways modulate γhumulene-induced apoptosis in human colorectal cancer HT29 cells. *Oncology reports*, 25(2), 419-424.

- Le Voyer, T. E., Sigurdson, E. R., Hanlon, A. L., Mayer, R. J., Macdonald, J. S., Catalano, P., & Haller, D. G. (2003). Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *Journal of Clinical Oncology*, 21(15), 2912-2919.

- Li, H., Zhang, L., Jiang, Q., Shi, Z., & Tong, H. (2017). Identification a nonsense mutation of APC gene in Chinese patients with familial adenomatous polyposis. *Experimental and Therapeutic Medicine*, 13(4), 1495-1499.

- Lin, J., Li, Q., Chen, H., Lin, H., Lai, Z., & Peng, J. (2015). Hedyotis diffusa Willd. Extract suppresses proliferation and induces apoptosis via IL-6-inducible STAT3 pathway inactivation in human colorectal cancer cells. *Oncology Letters*, 9(4), 19621970.

- Lotfollahzadeh, S., Recio-Boiles, A., & Cagir, B. (2017). Colon cancer, 8-15.

- Lykke, J., Jess, P., Roikjaer, O., & Danish Colorectal Cancer Group. (2015). Increased lymph node yield is associated with improved survival in rectal cancer irrespective of neoadjuvant treatment: results from a national cohort study. *Diseases of the Colon & Rectum*, 58(9), 823-830.

- Ma, B., Gao, P., Song, Y., Zhang, C., Zhang, C., Wang, L., & Wang, Z. (2016). Transanal total mesorectal excision (taTME) for rectal cancer: a systematic review and meta-analysis of oncological and perioperative outcomes compared with laparoscopic total mesorectal excision. *BMC cancer*, 16, 1-13.

- Machado, V. F., Feitosa, M. R., Rocha, J. J. R. D., & Féres, O. (2016). A review of experimental models in colorectal carcinogenesis. *Journal of Coloproctology (Rio de Janeiro)*, 36, 53-57.

- Macrae, F. A., Goldberg, R. M., & Seres, D. (2016). *Colorectal Cancer: Epidemiology, Risk Factors, and Protective Factors*, 9.

- Maeda, T., Cannom, R. R., Beart, R. W., & Etzioni, D. A. (2010). Decision model of segmental

compared with total abdominal colectomy for colon cancer in hereditary nonpolyposis colorectal cancer. *J Clin Oncol*, 28(7), 1175-1180.

- Meshikhes, A. W. N., El Tair, M., & Al Ghazal, T. (2011). Hand-assisted laparoscopic colorectal surgery: initial experience of a single surgeon. *Saudi Journal of Gastroenterology*, 17(1), 16-19.

- Mirkin, K. A., Kulaylat, A. S., Hollenbeak, C. S., & Messaris, E. (2018). Robotic versus laparoscopic colectomy for stage I–III colon cancer: oncologic and long-term survival outcomes. *Surgical Endoscopy*, 32, 2894-2901.

- Moghadamtousi, S. Z., Karimian, H., Rouhollahi, E., Paydar, M., Fadaeinasab, M., & Kadir, H. A. (2014). Annona muricata leaves induce G1 cell cycle arrest and apoptosis through mitochondria-mediated pathway in human HCT-116 and HT-29 colon cancer cells. *Journal of Ethnopharmacology*, 156, 277-289.

- Møller, P., Seppälä, T. T., Bernstein, I., Holinski-Feder, E., Sala, P., Evans, D. G., & Capella, G. (2018). Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*, 67(7), 1306-1316.

- Nagtegaal, I. D., Knijn, N., Hugen, N., Marshall, H. C., Sugihara, K., Tot, T., & Quirke, P. (2017). Tumor deposits in colorectal cancer: improving the value of modern staging-a systematic review and meta-analysis. *Journal of Clinical Oncology*, 35(10), 1119-1127.

- Nagtegaal, I. D., Quirke, P., & Schmoll, H. J. (2012). Has the new TNM classification for colorectal cancer improved care? *Nature reviews Clinical oncology*, 9(2), 119-123.

- Park, J. W., Lee, J. C., Ann, S. R., Seo, D. W., Choi, W. S., Yoo, Y. H., & Han, J. W. (2011). A fermented ginseng extract, BST204, inhibits proliferation and motility of human colon cancer cells. *Biomolecules & Therapeutics*, 19(2), 211-217.

- Rawla, P., Sunkara, T., & Barsouk, A. (2019). Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Gastroenterology Review/Przegląd Gastroenterologiczny*, 14(2), 89-103.

- Roomi, M. W., Ivanov, V., Kalinovsky, T., Niedzwiecki, A., & Rath, M. (2005). In vivo antitumor effect of ascorbic acid, lysine, proline and green tea extract on human colon cancer cell HCT 116 xenografts in nude mice: evaluation of tumor growth and immunohistochemistry. *Oncology Reports*, 13(3), 421-425.

- Rosty, C., Hewett, D. G., Brown, I. S., Leggett, B. A., & Whitehall, V. L. (2013). Serrated polyps of the large intestine: current understanding of diagnosis, pathogenesis, and clinical management. *Journal of Gastroenterology*, 48, 287-302.

- Sabit, H., Cevik, E., & Tombuloglu, H. (2019). Colorectal cancer: The epigenetic role of microbiome. *World Journal of Clinical Cases*, 7(22), 36-83.

- Sawicki, T., Ruszkowska, M., Danielewicz, A., Niedźwiedzka, E., Arłukowicz, T., & Przybyłowicz, K. E. (2021). A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. *Cancers*, 13(9), 2025.

- Seeram, N. P., Adams, L. S., Zhang, Y., Lee, R., Sand, D., Scheuller, H. S., & Heber, D. (2006). Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human cancer cells in vitro. *Journal of Agricultural and Food Chemistry*, 54(25), 9329-9339.

- Sehgal, R., Sheahan, K., O'Connell, P. R., Hanly, A. M., Martin, S. T., & Winter, D. C. (2014). Lynch syndrome: an updated review. *Genes*, 5(3), 497-507.

- Seyedian, S. S., Nokhostin, F., & Malamir, M. D. (2019). A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *Journal of medicine and life*, 12(2), 113.

- Shah, S. C., & Itzkowitz, S. H. (2022). Colorectal cancer in inflammatory bowel disease: mechanisms and management. *Gastroenterology*, 162(3), 715-730.

- Shamshoum, H., Vlavcheski, F., & Tsiani, E. (2017). Anticancer effects of oleuropein. *Biofactors*, 43(4), 517-528.

- Sharma, P., & Allison, J. P. (2015). Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*, 161(2), 205-214.

- Shehzad, A., Wahid, F., & Lee, Y. S. (2010). Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Archiv der Pharmazie*, 343(9), 489-499.

- Shylesh, B. S., & Padikkala, J. (2000). In vitro cytotoxic and antitumor property of Emilia sonchifolia (L.) DC in mice. *Journal of Ethnopharmacology*, 73(3), 495-500.

- Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, 68(1), 7-30.

- Signorelli, P., Fabiani, C., Brizzolari, A., Paroni, R., Casas, J., Fabrias, G., & Caretti, A. (2015). Natural grape extracts regulate colon cancer cells malignancy. *Nutrition and Cancer*, 67(3), 494-503.

- Smereczyński, A., & Kołaczyk, K. (2018). Pitfalls in ultrasound imaging of the stomach and the intestines. *Journal of Ultrasonography*, 18(74), 207-211.

- Sobin, L. H., Gospodarowicz, M. K., & Wittekind, C. (Eds.). (2011). *TNM Classification of Malignant Tumours*. John Wiley & Sons.

- Stanaway, J. D., Reiner, R. C., Blacker, B. F., Goldberg, E. M., Khalil, I. A., Troeger, C. E., & Hay, S. I. (2019). The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Infectious Diseases*, *19*(4), 369-381.

- Swanson, R. S., Compton, C. C., Stewart, A. K., & Bland, K. I. (2003). The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Annals of Surgical Oncology*, *10*, 65-71.

- Takami, K., Yana, I., Kurahashi, H., & Nishisho, I. (1995). Multistep carcinogenesis in colorectal cancers. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *26*, 190-196.

- Tanaka, S., Haruma, K., Yoshihara, M., Kajiyama, G., Kira, K., Amagase, H., & Chayama, K. (2006). Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. *The Journal of Nutrition*, *136*(3), 821S-826S.

- Tanaka, T. (2009). Colorectal carcinogenesis: Review of human and experimental animal studies. *Journal of Carcinogenesis*, *8*.

- Vacante, M., Borzì, A. M., Basile, F., & Biondi, A. (2018). Biomarkers in colorectal cancer: Current clinical utility and future perspectives. *World Journal of Clinical Cases*, *6*(15), 869.

- Valle, L., Vilar, E., Tavtigian, S. V., & Stoffel, E. M. (2019). Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *The Journal of Pathology*, *247*(5), 574-588.

- Verma, R., Kumar, L., & Kurba, V. B. (2014). Green chemistry principles in organic compound synthesis and analysis. *Int. J. Pharmacol. Res*, *4*(1), 01.

- Wang, X., Cao, G., Mao, W., Lao, W., & He, C. (2020). Robot-assisted versus laparoscopic surgery for rectal cancer: A systematic review and metaanalysis. *Journal of Cancer Research and Therapeutics*, *16*(5), 979-989.

- Wang, X., Yu, Y., Meng, W., Jiang, D., Deng, X., Wu, B., & Zhou, Z. (2018). Total neoadjuvant treatment (CAPOX plus radiotherapy) for patients with locally advanced rectal cancer with high risk factors: A phase 2 trial. *Radiotherapy and Oncology*, *129*(2), 300-305.

- Weber, P. A., Merola, S., Wasielewski, A., & Ballantyne, G. H. (2002). Teleroboticassisted laparoscopic right and sigmoid colectomies for benign disease. *Diseases of the Colon & Rectum*, *45*(12), 1689-1696.

- West, N. P., Hohenberger, W., Weber, K., Perrakis, A., Finan, P. J., & Quirke, P. (2010). Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *Journal of Clinical Oncology*, *28*(2), 272-278.

- West, N. R., McCuaig, S., Franchini, F., & Powrie, F. (2015). Emerging cytokine networks in colorectal cancer. *Nature Reviews Immunology*, *15*(10), 615-629.

- Willaert, W., & Ceelen, W. (2015). Extent of surgery in cancer of the colon: is better? *World Journal of Gastroenterology: WJG*, *21*(1), 132.

- Win, A. K., MacInnis, R. J., Hopper, J. L., & Jenkins, M. A. (2012). Risk prediction models for colorectal cancer: a review. *Cancer Epidemiology, Biomarkers & Prevention*, *21*(3), 398-410.

- Wong, M. C., Huang, J., Lok, V., Wang, J., Fung, F., Ding, H., & Zheng, Z. J. (2021). Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. *Clinical Gastroenterology and Hepatology*, *19*(5), 955-966.

- Wong, S. H., & Yu, J. (2019). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nature Reviews Gastroenterology & Hepatology*, *16*(11), 690-704.

- World Health Organization. (2016). *World Health Statistics 2016 [OP]: Monitoring Health for the Sustainable Development Goals (SDGs)*. World Health Organization.

- Xi, Y., & Xu, P. (2021). Global colorectal cancer burden in 2020 and projections to 2040. *Translational Oncology*, *14*(10), 101-174.

- Xie, Y. H., Chen, Y. X., & Fang, J. Y. (2020). Comprehensive review of targeted therapy for colorectal cancer. *Signal Transduction and Targeted Therapy*, *5*(1), 22.

- Yang, J., Gurudu, S. R., Koptiuch, C., Agrawal, D., Buxbaum, J. L., Fehmi, S. M. A., & Samadder, N. J. (2020). American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. *Gastrointestinal Endoscopy*, *91*(5), 963-982.

- Yoo, J. H., Kang, K., Jho, E. H., Chin, Y. W., Kim, J., & Nho, C. W. (2011). α-and γMangostin inhibit the proliferation of colon cancer cells via β-catenin gene regulation in Wnt/cGMP signalling. *Food Chemistry*, *129*(4), 1559-1566.

- Yu, J., Li, N., Tang, Y., Wang, X., Tang, Y., Wang, S. L., & Jin, J. (2019). Outcomes after hypofractionated stereotactic radiotherapy for colorectal cancer oligometastases. *Journal of Surgical Oncology*, *119*(4), 532-538.

- Zauber, A. G., Winawer, S. J., O'brien, M. J., Shi, W., & Bayuga, S. (2007, April). Significant long-term reduction in colorectal cancer mortality with colonoscopic polypectomy: findings of the National Polyp Study. In *Gastroenterology, 132*(4), A50.

- Zhang, J., Kale, V., & Chen, M. (2015). Gene-directed enzyme prodrug therapy. *The AAPS journal*, *17*, 102-110.

- Zhu, Q., Meisinger, J., Thiel, D. H. V., Zhang, Y., & Mobarhan, S. (2002). Effects of soybean extract on

morphology and survival of Caco-2, SW620, and HT-29 cells. *Nutrition and cancer*, *42*(1), 131-140.

- Lakkim, V., Reddy, M. C., Prasad, D. V., & Lomada, D. (2017). Role of STAT3 in colorectal cancer development. *Role of Transcription Factors in Gastrointestinal Malignancies*, 269-298.

- Rentsch, M., Schiergens, T., Khandoga, A., & Werner, J. (2016). Surgery for colorectal cancer-trends, developments, and future perspectives. *Visceral medicine, 32*(3), 184-191.