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Herbal Approaches to the Treatment of Colon Cancer: A Comprehensive Review

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Abstract

Although early identification through thorough screening can prevent colon cancer, one of the major causes of cancer-related deaths, current statistics show an alarming rise in incidence and mortality among young persons under 50. Drug resistance and serious adverse effects frequently restrict the efficiency of recognized basic therapies, such as chemotherapy with 5-fluorouracil (5-FU). New developments in targeted and customized treatments, including as immunotherapy, anti-angiogenesis, and creative radiation methods, hold out hope for overcoming these obstacles. Age, family history, and chronic inflammatory bowel disease (IBD) are major risk factors for colon cancer, which is caused by a complex combination of genetic and environmental factors. Every stage of colon cancer development, from localized polyps to advanced carcinoma, necessitates a different approach to treatment. Herbal extracts from tea plants, ginger, turmeric, and garlic are examples of natural items that have demonstrated promise in lowering cancer cell growth and triggering apoptosis, providing an alternative or supplementary strategy to traditional treatments. The effectiveness of current formulations such as cetuximab, capecitabine, and Avastin in treating metastatic colorectal cancer (mCRC) is still being investigated. It is anticipated that the prevalence of colon cancer would increase worldwide, highlighting the necessity of ongoing research and development in prevention, early detection, and treatment approaches.

Keywords: Antiangionetic, Chemotherapy, Herbal Drugs, Colon Cancer (CC), Nutraceuticals, Genetic Alteration 5-Fluroauracil, Avastin, Polyphenol

Introduction

One prevalent cancer that can be prevented is colon cancer. The incidence and fatality rates of colon cancer have dropped in the treated population since Western nations began implementing comprehensive colon cancer screening. However, during the past 25 years, young adults under 50 have seen an increase in both the incidence and death of colorectal cancer. Benefits differ, for example, in that screening colonoscopy lowers the chance of death for both left- and right-sided colon cancer. Numerous steps have been attempted to reduce this inequality, and the cause may be complex [1]. One of the most deadly cancers is colon cancer, which can spread to the ovaries, liver, lungs, and other gastrointestinal organs. Historically, patients with colon cancer have been treated with 5-fluorouracil (5-FU), a drug that inhibits the creation of deoxyribonucleic acid (DNA). Anti-cancer medications made of synthetic chemicals frequently produce unanticipated side effects. Nutraceuticals and phytochemicals are currently being used to treat colon cancer because of these investigations. GLOBOCAN 2020 projects that 1.15 million new cases of colon cancer will occur globally in 2020. These figures are expected to rise to 1.92 million in 2040 with additional growth [2].

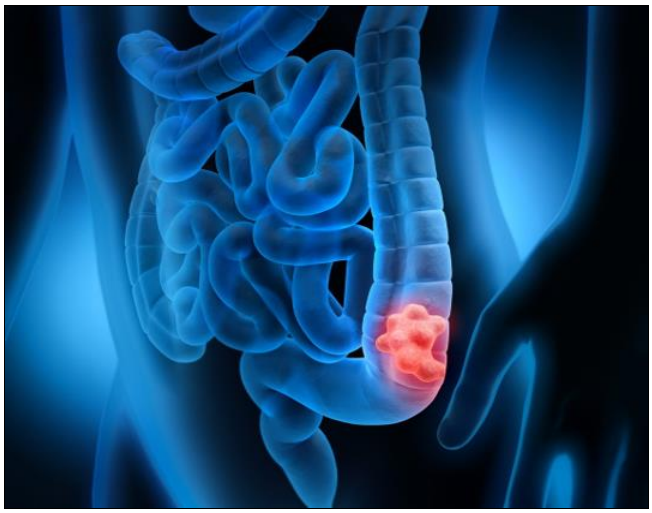

Fig 1: Colon Cancer

There are two levels of risk for CRC development: Ordinary and high. Those without polyposis syndrome, hereditary colorectal cancer syndrome, chronic IBD, or a personal or family history of colorectal cancer or advanced colon cancer are considered to be at average risk. The majority of people at average risk develop colorectal cancer (CRC) after the age of fifty. High-risk individuals must adhere to a particular screening and surveillance program because they develop colorectal cancer (CRC) at a young age. They are as follows: 1) Family history of colorectal cancer (CRC): Two first-degree relatives with CRC or advanced adenomas at any age, or one first-degree relative with CRC or advanced adenoma (adenoma > 1 cm in size, or with high-grade dysplasia or villous histology) detected before the age of 60.2) Up until the time of the colectomy, patients with classical (germline mutation of the APC gene) should undergo annual colonoscopy or flexible sigmoidoscopy as a screening for colorectal cancer. Polyposis typically manifests at age 16, and colorectal cancer typically develops around age 39 [1]. A combination of genetic alterations brought on by several environmental variables accounts for about 60–65% of sporadic cases of colon cancer. 15. Age is the biggest risk factor for colon cancer; people over 50 are more likely to have it [3].

Stages of Colon Cancer

Four developmental stages can be used to characterize the progression of colon cancer. The tumour first develops in the "polyp," or inner layers of the colon, during stages 0 and 1. When cancer reaches stage 2, it passes through the colon's walls and begins to grow in the outer layers, but it does not spread to the lymph nodes, where it is identified as "adenomas." In stage three, the tumour spreads to the lymph nodes and develops into a "carcinoma [4]."

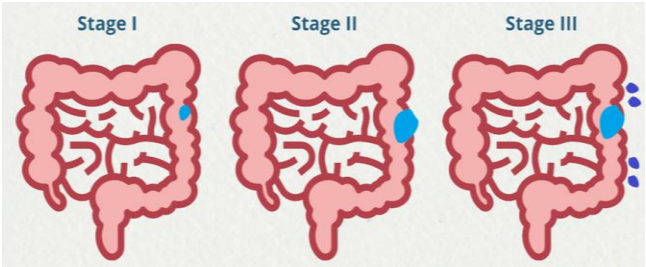

Fig 2: Stages of Colon Cancer

Stage I: Research on tumours is still ongoing, and they have the potential to drastically lower the risk of problems, which is typically 20% for patients having traditional surgical excision. Surgeons can now execute colectomy with far fewer difficulties and a quicker recovery time for patients thanks to the tremendous growth of robots and the spread of laparoscopy. Generally speaking, surgical resection has three objectives: Resecting obvious malignant disease, excising the colon wall tumour, and removing the lymph nodes in the tumour drainage basin [5].

Stage II: Colon cancer in stage II There hasn't been any clear evidence of a strong survival benefit by AC in stage II CC patients, despite a number of randomized trials and meta-analyses. Significant prognostic variability within this patient group (5-year survival rate of 66.5%) is one of the obstacles to demonstrating a definite advantage with AC in stage II patients. Stage migration in T3N0 tumours compared to 37.3% in T4bN0 tumours due to advancements in lymph node sampling over time.

Stage III: Colon cancer Clinical trials using three main schedules of 5-FU and LV combinations were carried out over the following decades after the NSABP C-01 trial showed that 5-FU-based AC improved survival in patients with resected Duke B and C colon cancer and that leucovorin (LV) enhanced the antitumor activity of 5-FU [83]. (1) Mayo Clinic regimen of monthly bolus 5-FU and LV; (2) Weekly bolus FU and LV, six weeks out of eight weeks [5].

Treatments of colon cancer

Chemotherapy: Adjuvant fluorouracil (5-FU) and leucovorin are administered for six months as part of the current standard regimen for colon cancer, which is known to dramatically lower relapse rates and mortality risks from resected colon cancer. The three-year disease-free survival rate is greatly increased by this regimen. But just 26% of patients react. Drug resistance is a significant issue that restricts chemotherapy's efficacy, and some patients find it difficult to endure its systemic adverse effects. A condition known as multidrug resistance (MDR) allows cancer cells to avoid the cytotoxic effects of chemotherapy drugs. Although it can happen in a variety of ways, it frequently correlates with the overexpression of intracellular or membrane molecular proteins, which can lead to changes in drug targeting, processing of drug-induced damage, evasion of apoptosis, increased drug efflux, decreased drug influx, or drug inactivation [6].

Immunotherapy: The third therapeutic option for colon cancer is immunotherapy. There are several strategies being researched that use vaccines and antibodies as adjuvant therapy.

The immune system can be activated by TAA, which is expressed by colon tumour cells [6].

Anti- angiogenesis: Because anti-angiogenic therapy is less harmful than traditional chemotherapy and has a lesser chance of developing drug resistance, it is a prospective treatment option for colon cancer. Additionally, anti-angiogenic medicines have the ability to temporarily "normalize" the aberrant form and function of the tumour vasculature, improving medication delivery and boosting the effectiveness of traditional treatments [6].

Radiation therapy: Most colon cancer patients receive adequate treatment through surgery, adjuvant systemic therapy, or both. the regular application of radiation as an

adjuvant treatment for colon cancer has no known function. Following R0 resection, an intergroup study (0130) assessed the use of levamisole and 5-fluorouracil (5-FU) with or without adjuvant radiation in patients with colon cancer patients with T3N+ malignancies of the ascending or descending colon, as well as those with tumour adhesion or invasion of adjacent structures, were eligible. The dose of radiation was 45–50 [7].

Herbal drug used in Colon Cancer

Phytochemicals found in plants can prevent the growth of tumours. Flavonoids, polyphenols, carotenoids, anthocyanins, genistein, resveratrol, caffeic acid, epigallocatechin, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, phenols, quercetin, luteolin, rosmarinic acid, carnosic acid, emodin, eugenol, kaempferol, and luteolin glycosides are among the numerous phytochemicals and bioactive substances found in medicinal plants. The seeds, fruits, roots, and leaves of the plants are the source of these phytochemicals. By activating caspase and/or releasing cytochrome C, they can trigger apoptosis via the mitochondrial route [8].

Table 1: Herbal drug used for treatment of colon cancer [9]

S. No	Drug	Sources	Part Used	Cellular effect
1	Allicin	Garlic	Root	induction of cell cycle arrest and apoptosis
2	Anthoxanthin, saponin	Soyabean Plant	Seed	reduction in cell proliferation that is reliant on concentration
3	Flavanol, polyphenol	Tea plant	Leaf	inhibition of HT-29 cell growth.
4	Hydroxychavicol	Bettle leaf	Leaf	Antioxidant capability and increased apoptotic impact induction
5	Curcumin (diferuloylmethane)	Turmeric	Root	prevented the spheroid HCT116 from forming.
6	N Hexane	Spearmint	Leaf	demonstrated antimutagenic properties.
7	Gallic acid	Dragon eye	Seed	Antiangiogenetic properties
8	Gingerol, methyl easter	Ginger	Root	action that inhibits the growth of colorectal cancer
9	geraniol, β-caryophyllene	Mandarin orange	Peel	Cause SNU-C4 human colon cancer cells to undergo apoptosis
10	Anthocyanin, β catenin	Purple fleshed potatoes	Fruits	Induce apoptosis in human colon cancer cells that are SNU-C4.
11	Catechin, epigallocatechin gallate	Teatree shrub	Leaf	Apoptosis of tumour endothelial cells increased.

Formulations available for treatment of colon cancer:

1. **5 - fluorouracil:** Since 1957, 5-fluorouracil (5-FU), an antimetabolite medication, has been used extensively to treat a variety of cancers, including breast and colorectal cancer. 5-FU causes cytotoxicity through either mis incorporating its metabolites into RNA and DNA or interfering with vital biosynthesis by blocking the function of thymidylate synthase (TS) [10].
2. **Cetuximab:** Cetuximab, a chimeric IgG1 antibody, is the first EGFR-targeting monoclonal antibody authorized for mCRC. It efficiently blocks ligand-induced receptor activation by binding to the EGFR Domain III with greater affinity than natural ligands like TGF-α and EGF. Additionally, cetuximab promotes the internalization of EGFR, which helps to downregulate EGFR-dependent signalling [11].
3. **Capecitabine:** In a phase II, single-arm study of patients with mCRC, capecitabine + irinotecan (XELIRI) as first-line chemotherapy showed encouraging effectiveness and safety outcomes. There were no appreciable variations in the overall response rate, PFS, or OS between XELIRI and 5-FU/LV with irinotecan (FOLFIRI) in a meta-analysis of six randomized controlled trials comparing the two regimens for the first-line therapy of patients with mCRC [12].
4. **Avastin:** Formulation F1 to F3 central composite design *in vitro* cytotoxicity The study examined surface-modified nanoparticles (F1 to F3) made using thenanoprecipitation approach as well as polyer-loaded nanoparticles (F1 to F3).Using doses ranging from 10 to 100 µg/mL, the MTT test was utilized to examine thecytotoxicity various polymer ratios and formulations on human cancer. To estimate the percentage vitality of various samples, untreated cancer cells served as a control.Every formulation that contained polymer demonstrated cytotoxicity [13].
5. **Tipiracil:** The initial dose of FTD-TPI was 35 mg per square meter of body surface area, and it was given orally twice a day on days 1 through 5 and on days 8 through 12 every 28 days. Bevacizumab was injected intravenously on days 1 and 15 at a dose of 5 mg per kilogram of body weight. The 28-day course of treatment continued until the condition worsened, there were intolerable side effects, or the patient withdrew their consent. As long as a patient was still receiving FTD–TPI, they were deemed to be receiving treatment; bevacizumab monotherapy was not permitted [14].

Conclusion

Chemotherapy, immunotherapy, anti-angiogenesis therapies, and radiation therapy have all played important roles in the evolution of colon cancer treatment. However, there are frequently drawbacks to these treatments, including systemic adverse effects and drug resistance. Because of their potential to target cancer cells with fewer side effects, nutraceuticals and phytochemicals are becoming more and more popular as adjunct therapy. Natural substances that offer mechanisms such as apoptosis induction, antioxidant effects, and anti-proliferative activity against colon cancer cells, such as allicin from garlic, curcumin from turmeric, and flavonoids from tea, have demonstrated promise in preclinical trials. Formulations including capecitabine, cetuximab, and 5-fluorouracil (5-FU) are still essential parts of current therapy plans. The unmet demand for increased survival and quality of life for patients with colon cancer may be addressed by combining traditional therapy with newly developed herbal medications and formulations to offer more individualized, efficient treatment alternatives. Overall, there is hope that early screening and continued research into natural and synthetic treatments can lessen the incidence of colon cancer and improve patient outcomes for people all over the world.

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Conflict of Interest
The authors declare that no conflict of interest of any financial or other issues.

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