Original Article

Colorectal Cancer In Young Adults: Epidemiology, Risk Factors, Development, Symptoms, Traditional Herbal Therapy And Prevention

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Abstract

Colorectal cancer is a formidable health problem worldwide. In men, it's the third most prevalent cancer, while in women; it's the second most common. Colorectal cancer occurrence has been on rise in patients younger than age 50, often referred to as early-onset disease. The main aim of the present work was to provide an overview of medicinal plants effective on colon cancer with respect to risk factors and prevention. The surge in colorectal cancer incidence in young adults is particularly alarming as the overall colorectal cancer frequency has been decreasing. Colorectal cancer, year by year, shows an increasing tendency in terms of both morbidity and deaths. Many factors may be responsible for the development of this disease, including genetic as well as environmental and lifestyle-related major risk factors like lack of physical activity, obesity, alcohol intake and smoking. Lifestyle factors are significant because of the potential for improving our understanding of the disease. Physical inactivity, obesity, smoking and alcohol consumption can also be addressed through therapeutic interventions. Treatment of young adults with colorectal cancer represents an unmet clinical need, especially as late diagnosis in this population might lead to the greatest loss of years of life. In this context, herbal plants like Allium sativum has a relevant role, and Sophoridine has found to have potential anti-colorectal carcinoma effect when tested on mice with tumorxenograft of SW480 cells subcutaneously in the mice armpit. Recent research indicates that grape, soybean, green tea, garlic, and pomegranate are the most effective plants against colon cancer.

Keywords: Colorectal cancer, Familial colorectal cancer, Risk factor, Young adult, Colorectal cancer symptom, Epidemiology

Introduction

Colorectal cancer (CRC) is a malignant neoplasm arising from the lining of the large intestine including colon and rectum [1]. CRC is a multifactorial disease process, with aetiology encompassing genetic factors, environmental exposures (including diet), and inflammatory conditions of the digestive tract [2]. CRC contributes for more than 9%

of all cancer cases [3,4]. CRC is the world's third most frequent cancer and the fourth leading cause of death. [3]. Men and women are approximately equally affected by CRC, including over 1 million new cases documented in 2002 [5]. The main risk factor for colorectal cancer is age: past the fifth decade of life, the risk of developing CRC is markedly increased, while the onset of colorectal cancer below the age of fifty is rare (except inherited cancers [6]. In addition to age, there are other inherent risk factors that cannot be modified. A personal history of colorectal cancer or inflammatory bowel disease (IBD)-the risk in patients with ulcerative colitis is increased by 3.7% [7], while people suffering from Crohn's disease have a 2.5% higher risk of developing colorectal cancer [8]. Another risk factor that can be included in this group is the presence of a positive familial history of CRC in relatives, especially those relatives under fifty years of age at diagnosis. An increased risk due to familial history can be derived from inherited mutations or the environment factors [9]. Modern day life style and dietary habit of the person constitute the important risk factor for CRC. Colorectal cancer risk is substantially influenced by diet, and dietary adjustments could reduce the burden of cancer by up to 70% [10]. High-fat diets, particularly animal fat diets, are a strong risk factor for colon cancer [4]. The choice of treatment for CRC patients currently involves a multimodal approach based on tumour-related characteristics (e.g., number and localization of metastases, tumour progression, presence or absence of biochemical markers, etc.) and patient-related factors (e.g., co-morbidity, prognosis, etc.) [11,12].

Commonly used chemotherapeutic drugs for the treatment of colorectal cancer includes fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI). The FOLFOXIRI regimen was associated with a significantly higher response rate, progression-free survival and overall survival compared to the FOLFIRI regimen [13]. Currently targeted drugs like bevacizumab, ziv-aflibercept, cetuximab, panitumumab, ramucirumab are also used as treatment modalities for the management of colorectal cancer (Targeted drugs work differently from chemotherapy drugs). They sometimes work when chemo drugs don't, and they often have different side effects. They can be used either along with chemo or by themselves if chemo is no longer working [14]. The main problems associated with these medicines are high and dangerous untoward effects due to this decreased patient compliance are reported [15]. On the other hand herbal medicines have lower adverse effects and are relatively safe as compared to modern medicines which are a well established fact. Chinese herbal medicine (CHM) has a long history in China and is gaining popularity as a form of complementary and alternative medicine. Currently, CHM has been widely accepted and used in the adjuvant therapy of various cancers in China. CHM formulas also have been increasingly used as an adjuvant therapy to manage chemotherapy-induced side effects and improve the completion rate of chemotherapy [16,17]. Current evidence from preclinical studies also suggests that CHM is beneficial in preventing or alleviating chemotherapy-induced side effects [18]. Moreover, some researches have shown that CHM may plays a significant role in tumorigenesis, reduction of toxicity, alleviating clinical symptoms, prolonging survival time and decreasing the risk of CRC recurrence and metastasis [19]. Considering all the aspects, we made efforts to systematize the available literature data in terms of epidemiology, risk factors, pathogenesis, nature of symptoms, prevention for colorectal cancer, with attention paid to herbal therapy.

Epidemiology

Colorectal cancer accounts for 9.4% of all cancer cases in males and 10.1% of all cancer cases in women in the world.Colorectal cancer, on the other hand, is not universally prevalent. The worldwide reach of colorectal cancer differs greatly by geography. Colorectal cancer is mostly a problem in developed nations with a Western culture [4]. Australia, New Zealand, Canada, the United States, and parts of Europe are among the highest incidences. China, India, sections of Africa, and South America are among the nations with the lowest risk. [4]. In India National Cancer Registry Programme-2013 (NCRP-2013) reported the highest annual incidence rates (AAR) in men for CRCs in Thiruvananthapuram (4.1%) followed by Banglore (3.9%) and Mumbai (3.7%). The highest AAR in women for CRCs was recorded in Nagaland (5.2%) followed by Aizwal (4.5%) [20]. The age standardized rate (ASR) for CRC in India is low at 7.2 per 100,000 population in males and 5.1 per 100,000 population in women [21]. However, studies on Indian immigrants from countries with a high prevalence of CRC like the USA and Singapore show that CRC incidence is lower in Indians than in the native population but higher than that observed from the Indian registries [22].

Risk factors

CRC is a multifactorial disease process, with aetiology encompassing genetic factors, environmental exposures (including diet), and inflammatory conditions of the digestive tract. Numerous risk factors can contribute for the development of CRC.

Age

The main risk factor for colorectal cancer is age: past the fifth decade of life, the risk of developing CRC is markedly increased, while the onset of colorectal cancer below the age of fifty is rare (except cases of inherited cancers) [6]. In the United States and elsewhere, the CRC incidence pattern is characterized by a strong birth cohort effect [23,24].

Body weight

A strong birth cohort effect indicates population-level changes in behavioral factors that influence cancer risk. Major established modifiable risk factors for CRC are excess body weight [25]. Remarkably, this increased risk is linked to both food intake and increased levels of visceral adipose tissue (VAT), a hormonally active component of total body fat that can promote the development of colorectal cancer through the secretion of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), which leads to an inflammatory situation in the colon and rectum, insulin resistance and modulation of metabolic enzymes such as adiponectin or lectin [26]. The risk of EO-CRC among U.S. women was recently shown to have increased by 20% for every 5- unit increase in body mass index and by 69% for more than 14 hours per week of television watching [27,28].

Lifestyle

Cigarette smoking [29], and heavy alcohol consumption [30] is the leading cause of CRC in the present situation. Although there is a well-established link between tobacco smoking and lung cancer, smoking is also exceedingly damaging to the colon and rectum. According to research, smoking is responsible for 12% of colorectal cancer fatalities [31]. Regular intake of alcohol, including smoking, has been linked with an increased risk of colorectal cancer. Consumption of alcoholic beverages is linked to the beginning of colorectal cancer at a relatively young age [32], as well as a risk for disproportionate increase of tumors in the distal colon [33]. In case of alcohol consumption, acetaldehyde (the main metabolite of ethanol) has been described as carcinogenic by increasing the risk of developing colorectal cancer among populations depending on polymorphisms of alcohol metabolysing enzymes [34]. Physical inactivity is also risk factors for developing CRC [35].

Dietary habit

High consumption of red and processed meat, and low fibre intake are the most relevant risk factors for developing CRC [36]. Red meat releases heme groups in the intestine, which enhance the formation of carcinogenic N-nitroso compounds as well as cytotoxic and genotoxic aldehydes by lipoperoxidation [37]and meat cooked at high temperatures produces heterocyclic amines and polycyclic hydrocarbons after digestion, both of which are considered to be potential carcinogens [38]. Lamb consumption is also reported to be associated with increased risk of CRC [39].

Family history

Inherited genetic risk accounts for 5 to 10% of colorectal cancers in families with a history of the disease [3]. Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), often known as Lynch syndrome, are the most prevalent inherited disorders.The genes that cause various types of hereditary colorectal cancer have been identifiedHNPCC is linked to mutations in DNA-repair genes, specifically the MLH1 and MSH2 genes, which are the causative mutations in HNPCC patients [40,3]. Known hereditary cancer-predisposing syndromes or familial CRC is higher among EO-CRCs [41].

Other risk factors

There are various other risk factors well known to play a more important role in the development of CRC among young individuals. Inflammatory bowel diseases increase two- to threefold risk of CRC, especially if diagnosed in early age [42]. Low adherence to specific screening programs in individuals with known cancer syndromes or familial CRC is also a major point in countries with a private health system or among populations with a low socioeconomic level [15]. Colorectal adenomas, ovarian cancer and colorectal cancer are all linked to the development of CRC. [41,43,44].

Barriers to care

Beyond increasing appropriate screening and surveillance, there is an immediate opportunity to reduce mortality through earlier diagnosis. One single-institution study found a median time from onset of rectal cancer symptom to treatment of 217 days for patients younger than age 50 compared with 29.5 days for those older than age 50, largely because of patient delays in presentation to the initial physician [45]. Some of these delays are caused by misdiagnoses [46]. Diagnosis can be delayed because symptoms are attributed to a low index of suspicion on the part of treating providers, who focus on more common conditions in young adults [47]. A recent study found that, among 52% of patients with EO-CRC who experienced rectal bleeding, the average time from onset of bleeding to diagnosis was 271.17 days [48].This challenge can be addressed by working with primary care setting to educate the community care provider about the changing incidence of this entity. Primary care setting physicians and other clinicians can have a dramatic impact on the morbidity and mortality of EO-CRC by ruling out serious causes ((rectal bleeding, abdominal pain, change in bowel habits, and anemia)of these symptoms in young patients [49].

Development of colorectal cancer

Colorectal cancer was rather rare in 1950, but has become a predominant cancer in Western countries, now accounting for approximately 10% of cancer-related death. Reasons explaining this increased incidence include population ageing and the preponderance of poor dietary habits, smoking, low physical activity and obesity in western countries. The change in incidence is not only apparent in the rates of sporadic disease, but also in some familial cancer syndromes (49,50). Colorectal cancer is now the predominant presentation of Lynch syndrome (a hereditary non-polyposis type of colorectal cancer), whereas carriers of this syndrome used to be predominantly affected by gastric cancer [51].

Mutations in specific genes can lead to onset of colorectal cancer, as happens in other types of cancer. Those mutations can appear in oncogenes, tumour suppressor genes and genes related to DNA repair mechanisms [52]. Genomic instability is an important feature underlying colorectal cancer.Depending on the origin of the mutation; colorectal carcinomas can be classified as sporadic, inherited, and familial. The pathogenic mechanisms leading to this situation can be included in three types, namely chromosomal instability (CIN), microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) [53]. The CIN pathway, which is also considered to be the classical pathway since it represents the cause of up to 80%–85% of all CRC cases [54]. [, is characterized by imbalances in the number of chromosomes, thus leading to aneuploydic tumours and loss of heterozygosity (LOH). The mechanisms underlying CIN include alterations in chromosome segregation, telomere dysfunction and DNA damage response, which affect critical genes involved in the maintenance of correct cell function, such as APC, KRAS, PI3K and TP53 amongst others. APC mutations cause the translocation of β-catenin to the nucleus and drive the transcription of genes implicated in tumourigenesis and invasion, whereas mutations in KRAS and PI3K lead to a constant activation of MAP kinase, thus increasing cell proliferation. Finally, loss-of-function mutations in TP53, which encodes for p53, the main cell-cycle checkpoint, cause an uncontrolled entry in the cell cycle [55].

Symptoms

CRC often grows slowly, and generally does not produce symptoms until reaching a considerable size of several centimeters, which may block the passage of feces and lead to cramping, pain, or bleeding that can present as visible bleeding with bowel movements or, rarely, dark “tarry” stools. Most colon tumors develop via a multistep process involving a series of histological, morphological, and genetic changes that accumulate over time [56]. Approximately 41% of all colorectal cancers occur in the proximal colon, with approximately 22% involving distal colon and 28% involving rectum [57].

Because early-stage colon cancer is typically asymptomatic, screening plays a major role in the diagnosis of curable cancerous lesions, as well as the detection of precancerous lesions (adenomatous colon polyps). In patients younger than 50 years old age group that is experiencing rising rates of colorectal cancer - a study that used data from England's Clinical Practice Research Datalink found that abdominal pain was the most common presenting symptom of colorectal cancer. Compared with other age groups, these younger patients had the lowest percentage of typical ‘red-flag’ signs and symptoms (i.e, rectal bleeding, anemia, change in bowel habits, diarrhea and abdominal mass). Instead, these patients were more likely to have presented to their primary care provider, in the year before diagnosis, with nonspecific symptoms [58]. Patients with EO-CRC can present with characteristic symptoms, including abdominal pain, weight loss, and fatigue, but tend to have a higher rates of left-sided related symptoms at presentation, including rectal bleeding and changes in bowel habits [59,60]. The most common symptoms in young patients are rectal bleeding, abdominal pain, change in bowel habits, and anemia [61,62]. Approximately 20% of individuals who are diagnosed with CRC have metastatic disease on presentation. Metastasis occurs by lymphatic spread, hematogenous spread, contiguous or transperitoneal spread. Most common sites of metastases from CRC include regional lymph nodes, liver, lung and peritoneum. Depending on the site of metastases, symptoms may include abdominal pain, perforation and abscess due to direct extension, jaundice and right upper quadrant pain (Liver), supraclavicular lymphadenopathy, periumbilical nodules and dyspnea [63].

Management of CRC

The choice of treatment for CRC patients currently involves a multimodal approach based on tumour related characteristics (e.g., number and localization of metastases, tumour progression, presence or absence of biochemical markers, etc.) and patient-related factors (e.g., co-morbidity, prognosis, etc.). In practice, all these aspects are used to classify CRC patients into one of four different risk groups that will be used to guide the treatment strategy [11,12]:

Group 0: Patients with no metastatic disease or with resectable liver or lung metastases and lack of poor prognostic signs (e.g., relapse during adjuvant treatment). In this case, the recommended treatment consists of surgical resection of the metastasis. Chemotherapy has not been found to provide a great advantage in the overall survival of this group;

Group 1: Patients with potentially respectable metastatic disease. These patients are initially treated with induction chemotherapy to reduce the number and size of the metastases and enable subsequent surgical resection. Recommended chemotherapy for these cases comprises cytotoxic doublet or triplet, which may be combined with anti-VEGF or anti-EGFR strategies in KRAS wild-type tumours.

Group 2: Refers t o patients with disseminated unresectable disease. Treatment selected for this group of patients will be palliative rather than curative, with the main intention of reducing the symptoms, aggressiveness and extension of the disease. As such, the first-line treatment selected should induce metastatic regression in a short time. To that end, the preferred option usually comprises a cytotoxic doublet in combination with a targeted agent (anti-VEGF or anti-EGFR strategies). In oligometastatic patients who respond to treatment, additional ablative methods may be considered to increase the progression-free interval. If ablative methods cannot be used, de-escalation of the initial combination should be studied as a maintenance treatment. In certain cases, complete discontinuation of the treatment can be considered

Group 3: Patients with unresectable disease and lack of intensive or sequential treatment: In patients lacking symptoms with low risk of deterioration, the purpose of the treatment will be to prevent tumour progression and increase treatment-free life. The most commonly used strategies comprise a fluoropyrimidine as cytotoxic agent combined, or not, with a biological targeted agent

Traditional herbal therapy for CRC

Shikonin and its derivatives

For many years, Shikoninand its derivatives have been used in TCM for the prevention and treatment of various diseases, including cancer. One of the derivatives, β,β-demethylacrylshikonin (DA), a major component of the lithospermumerythrorhizon roots, was identified as a potential inhibitor of hepatocellular carcinoma growth [64]. A study reported that DA displays even more pharmacologic properties, such as anti-inflammatory, antioxidant, and antiplatelet [65]. Yingying, Fan Y, Jin S, He J, Shao Z, Yan J and Feng T showed that systemic therapy with DA can inhibit tumor growth in animals, which was demonstrated by using HCT-116 xenografts in mice. Once HCT-116 cells were injected subcutaneously into upper left flank region of mice, the animals were divided into 4 groups and treated daily with DA (0.3, 0.6, and 1.2 mg/kg) or saline as a negative control. All mice were sacrificed on Day 13 after inoculation with HCT-116 cells. Treatment with DA significantly reduced tumor growth and exhibited no toxicity, measured by body weight decrease. The mechanism of DA action is arguably associated with inducing apoptosis of tumor cells; the authors found that DA decreased the expression of anti-apoptotic protein Bcl-2 and increased expression of pro-apoptotic Bax protein [66].

Shikunshito-Kamiho

Shikunshito-Kamiho (SKTK) is a TCM preparation composed of 8 crude drugs (Ginseng radix, Hoelen, AtractylodisRhizoma, Glycyrrhizae Radix, Prunellae Spica, OstreaeTesta, LaminariaThallus and Sargassum), which serves as a cure for CRC in oriental medicine. Yoo BH, Lee BH, Kim JS, Kim NJ, Kim SH and Ryu KW investigated the anticarcinogenic effect of SKTK on 1,2-dimethylhydrazine (DMH)- induced CRC in mice. The animals received injections of carcinogen (DMH) once a week for 10 weeks while being fed with diet containing 0.5% or 1.5% extracts of SKTK. The water extracts of SKTK were provided to the diet for 5 weeks after last injection of DMH [67].Eventually, the authors evaluated fecal enzymes, such as β-glucuronidase, tryptophase and urease, and the aberrant crypt foci (ACF) formation in murine colon. β-Glucuronidase and tryptophanase were reduced in both groups, whereas the level of urease was significantly reduced only in mice fed with 1.5% SKTK. The number of ACF in the colon, which are regarded as putative preneoplastic lesions of rodent and humans, was significantly decreased in the group fed with both concentrations of SKTK, compared with positive control (no SKTK) [68].

Sophoridine

Sophoridine (SRI) is one of the quinolizidine alkaloids, which were extracted from seeds of Saphoraalopecuroides L [69]. This traditional Chinese herb has been used for clearing heat and removing toxins for hundreds of years. Previous research showed that SRI is one of the most active compounds occurring in this herb and can significantly inhibit the growth of colon adenocarcinoma cells [62]. Liang L, Wang XY, Zhang XH, Ji B, Yan HC and Deng HZexplored a potential anti-colorectal carcinoma effect of sophoridine using mice with tumorxenograft of SW480 cells subcutaneously in the mice armpit. The anti-tumor activity of SRI (15 and 25 mg/ kg, 5 days a week) was compared with 5-fluorouracil (30 mg/kg, 3 days a week), both given through i.p. injection. The experiment in SW480 tumor-bearing mice demonstrated that the higher dose of SRI had a significant effect on tumor inhibition: the average tumor volume in SRI (25 mg/kg) group was significantly lower than in the control group (0.579±0.144 vs 1.149±0.142 cm3, respectively). Based on the in vitro and in vivo experiments, authors concluded that SRI acts as a pro-apoptotic factor in SW480 cells. The immunocytochemistry suggested that SRI may activate caspase-3-dependent pathways, leading to cell apoptosis. Of note, after treatment with SRI there was no change in animal behaviour; the animals ate and defecated normally and their weight increased. The mice treated with 5-fluorouracil (5-FU) ate less throughout the study; they also weighed much less and developed bloody diarrhoea in the later stages of the treatment [62].

Spica prunellae

Spica Prunellae, the fruit spikes of the perennial plant Prunella vulgaris L, are used in TCM to treat poor vision, blood stasis, and edema. They are also believed to possess anti-cancer properties. Lin, Zheng L, Zhuang Q, Zhao J, Cao Z and Zeng J reported that the extract of Spica Prunellae promotes apoptosis of human CRC cells and displays anti-angiogenic activity in vitro [70]. In another study the authors investigated the anti-carcinogenic activity of Spica

Prunellae using a mouse HT-29 cell xenograft model. In the course of the experiment, the animals received the ethanol extract of SP (EESP) at the dose of 6 g/kg or saline (both p.o.) once daily, 5 days a week for 16 days. Body weight and tumor growth were measured every 2 days. EESP treatment significantly reduced both, tumor volume and weight compared with control mice. Moreover, EESP treatment did not affect body weight [67]. These results indicate that EESP effectively suppresses CRC growth in vivo without apparent signs of toxicity. The gathered data indicates that EESP promotes CRC cell apoptosis, as well as inhibits cell proliferation and tumor angiogenesis. According to Lin et al the mechanism of EESPs activity is associated with suppression of the STAT3 pathway activation and regulation of the expression of Bcl-2, Bax, Cyclin D1, CDK4, VEGF-A, and VEGFR-2 in xenograft mice [70].

Allium sativum

Allium sativum root extracts resulted in inhibition of the PI3K/Akt pathway, upregulation of PTEN, and downregulation of Akt and p-Akt expression [71,72]. Allium sativumroots have allicin and organosulfur compounds as their chief chemical constituents. In an in vitro study, they inhibited cancer cell growth and induced apoptosis through the inhibition of the phosphoinositide 3-kinase/Akt pathway. They can also increase the expression of phosphatase and tensin homolog (PTEN) and reduce the expression of Aktand p-Akt (71). Further, garlic roots contain S-allylcysteine and S-allylmercaptocysteine, which are reported to exhibit anticancer properties. The results of a clinical trial on 51 patients, whose illness was diagnosed as colon cancer through colonoscopy, and who ranged in age from 40 to 79 years, suggest that the garlic extract has an inhibitory effect on the size and number of cancer cells. Possible mechanisms suggested for the anticancer effects of the garlic extract are both 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 [73].

Camellia sinensis

Camellia sinensis commonly known as Green tea, the leaf extracts- involved in attenuation of COX-2 expression and modulation of NFκB, AP-1, CREB, and/or NF-IL-6 genes [74,67]. Green teacontains a number of polyphenolic compounds belonging toflavan-3-ol (catechin) family, such as (-)-epigallocatechin (-)-epicatechin, (-)-epigallocatechin-3-o-gallate, (-)-epicatechin-3-o-gallate, (+)-catechins and (+)-gallocatechin. These compounds are known to have a wide spectrum of biological activities such as antioxidant, antiviral, anticancer, anti- bacterial, antifungal, antitoxoplasmal, antitrypanosomal, anticocci-dial, antinematodal and antihelminthic [75]. Green tea leaves have also attracted the researchers' attention in these studies. Green tea leaves, with high levels of catechins, increased apoptosis in colon cancer cells and reduced the expression of the vascular endothelial growth factor (VEGF) and its promoter activity in in-vitro and in vivo studies. The extract increased apoptosis (programmed cell death) by 1.9 times in tumor cells and 3 times in endothelial cells compared to the control group [76,77].

Oleaeuropaea

The olive tree also known as Oleaeuropaea L. (OLs), has been cultivated in numerous parts of the world since ancient times [78]. OLs are a rich source of valuable polyphenols, whereas olive fruits are good sources of oleuropeosides, flavonols, and flavones [79]. Oleaeuropaea fruit extracts- increased caspase 3-like activity and were involved in the production of superoxide anions in mitochondria [80]. Numerous studies have documented that the bioactive components in OLs possess beneficial properties, including antioxidant, antimicrobial, and antitumor characteristics [81]. Roy M., Chakrabarty S., Sinha D., Bhattacharya R.K., Siddiqi M. observed changes in viability, proliferation, migration, DNA fragmentation, and gene expression in two cancer cell lines, HT29 and PC3, following treatment with AOLs. Ethanol extracts from Lebanese OLs induced apoptosis in leukemic cells (Jurkat cells) with an IC_{50} of approximately 4 mg/mL at 48 h and 3 mg/mL at 96 h; the OL extracts in their study exibited an anti-proliferative effect with less cytotoxicity [82].

American ginseng and Hibiscus cannabinus

American ginseng and Hibiscus cannabinus concerning HCT116 cells, several plants, such as American ginseng and Hibiscus cannabinus, induced cell cycle arrest in different checkpoints [67]. American ginseng is an obligate shade perennial plant native to eastern north America. The commonly used part of the plant is the root, which is harvested after several years' cultivation. The largest growing area in the US is in Wisconsin. The bioactive constituents of American ginseng are ginsenosides, which are present in the root, leaf, stem and berry of the plant. More than 30 ginsenosides such as Rb1, Rb2, Rc, Rd, Re, Rg1 and Rg3 have been identified in American ginseng [83]. In addition, the extract from American ginseng enhanced the anti-proliferation effect of cisplatin on human breast cancer cells, suggesting that it possesses its own anti-cancer activity (84).

Panax ginseng and Cordycepssinensis

Panax ginseng and Cordycepssinensis have been used for herbal pharmacopuncture (HP) treatment [67]. Ginseng (Panax ginseng C.A. Meyer) has been used widely for thousands of years in traditional Eastern medicine to invigorate and vitalize physical functions. Also, it is claimed to be effective in combating stress, fatigue, oxidants, diabetes mellitus, and cancer (85). Moreover, a randomized, placebo-controlled clinical trial of Panax ginseng has shown its antioxidant effects [86]. In addition, another study concluded that Panax ginseng eases the heart rate, increases lipolysis, reduces plasma lactate concentration, and maintains a good health by reducing stress [87]. Cordycepssinensis has been used in traditional Eastern medicine for respiratory symptoms such as cough, sputum, and bronchial obstruction in asthma, tuberculosis, chronic bronchitis, and other diseases [62]. This HP has been used for the treatment of metastatic pulmonary tumor. Also, Cordycepssinensis have been reported to have antioxidant (88) and anti-tumor effects properties [89].

Grapes

Grapes contain substantial amounts of flavonoids and procyanidins, play a role in reducing the proliferation of cancer cells by increasing dihydroceramides and p53 and p21 (cell cycle gate keeper) protein levels. Additionally, grape extracts triggered antioxidant response by activating the transcriptional factor nuclear factor erythroid 2-related factor 2 (Nrf2). Grape seeds contain polyphenolic and procyanidin compounds, and their reducing effects on the activity of myeloperoxidase have been shown in in vitro and in vivo studies. It has been suggested that grape seeds could inhibit the growth of colon cancer cells by altering the cell cycle, which would lead eventually to exert the caspase-dependent apoptosis [90,91]. Grape seed extract (GSE) is a popular dietary supplement rich in proanthocyanidins and has been reported to have anti-colon cancer properties in a variety of in vitro and in vivo models [92]. As bioactive compounds exist in a complex mixture in fruits and vegetables, laboratory assessment of their biological activity in combination is more relevant to human exposure. In addition, because these compounds have pleiotropic effects, there is the potential that they will exert additive or synergistic chemopreventive actions [93].

Soybean

Soybean, an herbal plant that attracted researchers' attention contains saponins as the chief chemical constituent. After 72 hours of exposure of colon cancer cells to the soy extract, it was found that this extract inhibited the activity and expression of protein kinase C and cyclooxygenase-2 (COX-2) [94]. The density of the cancer cells being exposed to the soy extract significantly decreased. Soybeans can also reduce the number of cancer cells and increase their mortality, which may be due to increased levels of Rab6 protein [95]. A high intake of total soy products or dietary isoflavones was associated with a reduced risk for overall colorectal cancer, and the association may be more relevant to distal colon or rectal cancers [83].

Pomegranate

The pomegranate fruit contains numerous phytochemicals, such as punicalagins, ellagitannins, ellagic acid, and other flavonoids, including quercetin, kaempferol, and luteolin glycosides. The effective and important compounds in pomegranate identified in various studies include flavonoids, polyphenol compounds, such as caffeic acid, catechins, saponins, polysaccharides, triterpenoids, alkaloids, glycosides, and phenols, such as quercetin and luteolin, and kaempferol and luteolin glycosides [96]. The results of an in vitro study indicate the anticancer activity of this extract through reduction of phosphorylation of the p65 subunit and subsequent inhibition of nuclear factor-κB (NFκB). It also inhibits the activity of TNF receptor induced by Akt, which is needed for the activity of NFκB. The fruit juice can considerably inhibit the expression of TNF-α-inducing proteins (Tipα) in the COX-2 pathway in cancer cells [97].

Prevention

Primary prevention efforts should include the promotion of physical activity, a major preventive factor for obesity and by itself a major preventive factor for CRC, as well as encouraging healthy dietary habits with limited red and processed meat intake and adequate intake of whole grains, fibres and dairy products [98]. Regular use of aspirin has long been recommended for the secondary prevention of CVD. However, in 2016, the U.S. Preventive Services Task Force (USPSTF) also recommended the use of low-dose aspirin for the primary prevention of CVD and CRC in adults aged between 50–59 years who have a 10% or greater 10-years CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years [99]. Possible mechanisms of chemoprevention of CRC by aspirin include inhibition of the cyclooxygenase (COX) pathway or COX-independent mechanisms, such as the PIK3CA pathway, or therapy-induced senescence of cancer cells (100). Finally, there is a paucity of research focusing on survivorship issues specifically in patients with EO-CRC. Major considerations include surveillance and radiation exposure, recommended lifestyle changes, and preventive modalities for patients with EO-CRC as well as the mental and social implications of survivorship and the impact on family [101].

Conclusion

Colorectal cancer is influenced by interactions of environmental and genetic influences which results in colon polyps that proceed to colorectal cancer. Medicinal plants that contain flavonoids, polyphenol compounds like catechins, polysaccharides, saponins, triterpenoids, alkaloids, caffeic acid, glycosides, and phenols like quercetin and luteolin, as well as kaempferol and luteolin glycosides, can inhibit tumour cell proliferation and induce apoptosis. In recent decades, TCM has been increasingly popular among CRC patients. Traditional herbal drugs like Allium sativum, Camellia sinensis, Oleaeuropaea, American ginseng and Hibiscus cannabinus and Panax ginseng and Cordycepssinensis are among the promising for the future management of CRC. By increasing physical activity, maintaining a healthy body weight, restricting alcohol intake, and cessation of smoking, people can lower their risk of colorectal cancer.

Conflict of Interest

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None

References

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