Submitted: 04 February, 2024 Accepted: 30 May, 2024 Published: 30 November, 2024 DOI:10.22514/jomh.2024.180

REVIEW

JOMH Journal of Men's Health

A potential target for the prevention and therapy of colon cancer: focused on men's clinical features

Yeonhee Pyo[1], Ki Han Kwon[2,*]

[1]Department of Beauty Cosmetics, College of Biomedical and Health Science, Konkuk University, 27478 Chungju, Republic of Korea
[2]College of General Education, Kookmin University, 02707 Seoul, Republic of Korea

***Correspondence**
kihan.kwon@kookmin.ac.kr
(Ki Han Kwon)

Abstract

Colon cancer (CCa) is a prevalent malignancy among men and ranks among the leading causes of cancer-related deaths globally, highlighting the critical need for the development of natural therapeutics for both its treatment and prevention. In this regard, the pharmacological properties of medicinal plants have been extensively studied, revealing their potential in exhibiting anti-cancer, anti-oxidant, anti-mutagenic, anti-inflammatory and anti-angiogenic activities relevant to colon cancer prevention and therapy. Current pharmacologic strategies for colorectal cancer (CRC) treatment are under active investigation, yet a universally accepted gold standard remains elusive. The identification of cancer stem cell (CSC) markers plays a pivotal role in enhancing cancer treatment strategies. It enables the customization of therapeutic approaches and is closely linked with the treatment outcomes and prognosis in CCa patients, particularly concerning cell resistance. 5-Fluorouracil (5-FU), a key component in chemotherapy regimens for CRC, is known for its severe side effects and the potential for developing chemoresistance. Research has shown that Portulaca oleracea extract can inhibit the proliferation of HT29 cancer stem cells at concentrations ranging from 0.07 to 2.25 μg/mL, enhancing the sensitivity of these cells to 5-FU. Moreover, the extract may regulate the growth of CCa stem cells by suppressing the expression of Notch1 and β-catenin genes, thereby interfering with the Notch signaling pathway. This review summarizes the findings of clinical trials involving medicinal plants with promising effects against CRC in men. Given the pharmacological efficacy of these plants, their extracts hold promise as viable alternative treatments for CCa.

Keywords

Colon cancer; Anti-cancer; Anti-oxidant; Anti-inflammatory; Pharmacological plants

1. Introduction

Colon cancer (CCa) represents a significant health issue in men, attributed to a combination of environmental, genetic and nutritional factors [1]. Current interventions, including surgery, radiation and chemotherapy, are not without limitations and adverse effects [2]. Additionally, an upward trend in CCa incidence among younger populations has been observed, correlating with poor dietary habits and high consumption of meat and alcohol, suggesting the urgent need for the development of novel alternative treatments and anti-cancer agents [3]. In this context, pharmacotherapy emerges as a less detrimental option, particularly in the management of CCa. Notably, over 50% of these pharmacotherapeutic agents are derived, either directly or indirectly, from medicinal plants, highlighting their potential as a source for innovative treatments [4]. Compounds isolated from medicinal plants have demonstrated anti-tumor and anti-apoptotic properties, offering promising avenues for the prevention and treatment of colorectal cancer (CRC) through new pharmacological approaches. These effects are attributed to phytochemicals capable of activating signal transduction pathways and influencing various cancer-related signaling mechanisms. Consequently, natural substances derived from plants are gaining recognition for their potential in cancer treatment and risk reduction [5].

For CCa, the World Health Organization emphasizes the importance of practicing natural medicine and developing natural drug products for cancer treatment because the implementation of natural medicines is safer than conventional drugs, and researchers hope to find effective and less toxic CCa drugs based on anti-CCa activity from plants [6]. Therefore, this review focuses on plant extracts that have been shown to prevent and treat CCa and discusses data concerning plants that offer potential as natural pharmacological alternatives, specifically for men.

2. Materials and methods

A literature search for this review was conducted in November 2023, with a supplementary search in January 2024 across five databases: PubMed, SCOPUS, Google Scholar, Web of Science, and EMBASE. The search terms included "colorectal

cancer", "colon cancer", "colon cancer prevention", "colon cancer treatment", "targeted therapy for colon cancer" and "targeted therapy for crystal cancer". A systematic search of peer-reviewed and non-peer-reviewed studies (including gray literature) was conducted between 10 January and 17 January, 2024. Forward and reverse citation tracking was also employed up to January 2024. Searches combined free-text and title queries, designed to encompass all relevant studies on CCa and cancer stem cells (CSC). Duplicate records and studies that could not be identified were removed. The abstracts of the remaining studies were then reviewed. Two independent reviewers screened all titles and abstracts to determine study eligibility. There were no exclusions based on sample type, review nature, internet article status, editorial content, protocol, perspective, commentary, position paper, report, or publication language, provided the content was available in English. Studies were excluded if they lacked full-text availability or access, did not present raw data, were off-topic, or were not pertinent to the primary focus of this review. The full texts of potentially eligible studies were further assessed by two researchers based on the previously mentioned criteria. During the detailed screening phase, reasons for exclusion were documented. We also manually searched the reference lists using academic search alerts to perform pre- and post-qualifying expert citations to identify all relevant studies.

3. Results

3.1 Prevalence of CCa

CCa is a major contributor to cancer-related deaths among men worldwide, making it a significant health concern alongside lung, prostate, and breast cancer. This highlights the urgency of enhancing disease treatment methodologies and advancing drug development efforts [7]. Globally, CCa is the most frequently diagnosed cancer, with a wide range of onset ages [8]. The etiology and pathogenesis of CCa are complex and not fully elucidated. Most colon tumors are found on the left side of the colon, whereas tumors on the right side tend to expand into the intestinal lumen. Risk factors for developing CCa include age, diet, genetic factors, lifestyle choices, and environmental exposures. Diets high in fats and animal products, combined with smoking and alcohol consumption, significantly increase CCa risk. Moreover, insulin levels are implicated in CCa risk, with excessive alcohol intake, especially when combined with low levels of micronutrients such as folate and methionine, contributing to a higher incidence of CCa. Smoking at an early age further elevates this risk. While certain substances, including aspirin and sex hormones, have been explored for their chemopreventive effects against CCa, they may also pose potential adverse impacts on the disease [9].

The incidence of CCa in men has been linked to an increased prevalence of diabetes. Data from the Tumor Epidemiology Database (IQVIA) involving 80,193 cancer patients across Europe and Asia revealed a high co-occurrence of CCa and diabetes, with a prevalence rate of 15.5% and is most pronounced in Europe and Asia, indicating a significant overlap between CCa patients and those suffering from diabetes in these regions [10]. Further, an analysis by EUROREVAL on the prevalence of CCa post-diagnosis was conducted among 243,471 CCa patients registered in the 36 European population-based Lombardy Cancer Registry (LCR). Cures and cases of relapse or death were analyzed, and the results showed that the overall prevalence was 89% in the LCR, 91% in Italy and Europe, while the prevalence was 11% (LCR) and 9% (Italy, Europe), indicating the need for continued treatment for CCa [11].

Approximately 50% of CCa patients experience tumor recurrence [12]. Particularly in the terminal stages of CCa, more than one-third of patients did not receive adjuvant chemotherapy (ACT), and this rate was found to increase with age. Despite the demonstrated positive effects of ACTs on survival, their application alongside continuous drug therapy remains limited. Therefore, it is recommended that ACTs be administered to patients of advanced age and even in late-stage CCa to enhance patient outcomes [13].

3.2 Signs and symptoms of CCa

CCa manifests with various abdominal signs and symptoms. Notably, 99.4% of CCa cases present with rectal bleeding, while the presence of fecal occult blood in the stool (FOBT) or anemia, indicative of gastrointestinal bleeding, exhibits a sensitivity of 57.5%. Other common symptoms include abdominal pain, constipation, and bloating [14]. Early detection of CCa might reveal symptoms such as rectal blood loss or bleeding with bowel movements, though some cases may remain asymptomatic. Research provided pooled positive likelihood ratios (PLRs) for CRC indicators, showing that symptoms and signs such as weight loss (PLR: 2.79, confidence interval (CI): 2.00–3.90), change in bowel habit (PLR: 1.92, CI: 0.54–3.57) and severe anemia (PLR: 3.67, CI: 1.30–10.35) are more prevalent in individuals aged 60 and above [15]. A prospective cohort study involving CCa patients from Norway, Denmark, Scotland, Sweden, Belgium and the Netherlands, involving consultations with 6802 CCa patients, found that 6264 experienced abdominal symptoms. Rectal bleeding showed a significant gender association, with age and gender-dependent variations observed in symptoms like macroscopic hematuria, rectal bleeding, and involuntary weight loss. Annually, the UK reports more than 37,000 new CRC cases [16]. Symptoms predominantly appear in the primary stage, with abdominal pain present in 3.3% of cases, anemia in 9.7%, and either weight loss or changes in bowel habits. The majority of CCa symptoms include abdominal pain, diarrhea, or constipation accompanied by rectal bleeding, with single symptoms being associated with a slightly lower risk in primary care settings [17]. deep learning (DL) algorithms are significantly enhancing the accuracy and efficiency of diagnostic processes in CRC. DL, a sophisticated analytical technique, accelerates CRC diagnoses and minimizes diagnostic errors [18–20]. However, DL systems are subject to limitations related to the protection of patient data privacy and economic factors, which may necessitate greater computational resources [21]. As for staging CCa, computed tomography imaging is considered the gold standard, with a sensitivity of approximately 80%, surpassing that of endoscopy or pathology in identifying staging ranges [22, 23].

3.3 CCa cells

Recent advancements in cellular immunotherapy for CCa involve the use of T cells, natural killer (NK) cells, macrophages, or stem cells to selectively target tumor cells or CSCs [24]. The immune system plays a critical role in both cancer development and its treatment, with chronic infections and inflammation known to elevate cancer risk. As tumors evolve, there is an ongoing interaction between the tumor microenvironment (TME) and the tumor cells themselves. This often leads to increased immunosuppression and the induction of immune cell death (ICD). Cellular immunotherapy aims to manipulate this dynamic by using a combination of biomarkers to identify and utilize anti-tumor agents effectively, counteract the immunosuppressive nature of the TME, activate T cells and enhance adaptive immunity, achieve sustained tumor control and induce ICD, thereby harnessing the body's immune response to fight cancer more effectively [25].

CSCs are a small subset of cells in a tumor that have characteristics such as self-renewal, differentiation, and tumor heritability. CSCs have been identified as therapeutic targets due to their roles in tumor recurrence, metastasis, and resistance to conventional treatments. Selectively targeting CSCs aims to halt the spread of tumor cells and impede overall tumor growth [26]. The concept of the cancer stem cell model was first introduced in 1997 for hematologic malignancies. This model posits that specific cells within the tumor possess pluripotency, the capability for self-renewal, and an enhanced capacity for initiating distant metastasis. Identified markers for CCa stem cells include cluster of differentiation (CD)133, CD44, CD166, aldehyde dehydrogenase 1 family member A1 and leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) [27]. These markers facilitate the application of CSC marker expression in CRC for personalized treatment strategies, significantly impacting the management and prognosis of patients with cellular resistance [28]. In the context of CCa prevention and treatment, recurrence and resistance to chemotherapy drugs are prevalent in the disease's advanced stages. These phenomena are attributed to adenosine triphosphate (ATP)-citrate lyase (ACLY), the rate-limiting enzyme in the first step of lipid synthesis. ACLY interaction stabilizes the beta-catenin 1 (CTNNB1) protein, and the resulting complex promotes CTNNB1's cytoplasm-to-nucleus translocation, enhancing CTNNB1 transcriptional activity and facilitating CCa cell migration and invasion. Elevated expression levels of ACLY and CTNNB1 proteins are positively associated with CCa metastasis, contributing to the improved efficacy of CCa treatments [29].

Various studies have shown that proprotein convertases (PCs) play a crucial role in the malignant transformation of CCa cells, presenting a novel therapeutic strategy by influencing the maturation and expression of various molecules. Despite the tumor-reducing effects of 5-FU treatment, an increased rate of CCa recurrence has been observed, hinting that cells exhibiting mesenchymal stem cell traits might rely on oxidative phosphorylation (OXPHOS) for tumor growth [30]. Conversely, cells resistant to 5-FU treatment have shown reduced activity of pyruvate kinase M1 (PKM1) and PKM2. This reduction leads to decreased levels of nicotinamide adenine dinucleotide phosphate (NADPH), diminished anti-oxidant defense, oxidation of PKM2, and a stem-like cell phenotype. Thus, combining 5-FU with OXPHOS inhibition could offer a sustainable and effective therapeutic strategy for CCa [31]. 5-FU remains a staple in chemotherapy regimens for treating colorectal cancer (CRC) despite its association with significant side effects and chemoresistance. A potential solution to these challenges is the use of 17β-estradiol (E2), which has been shown to arrest the CCa cell cycle and induce apoptosis when used alone [32]. Our research demonstrates that microRNA (miR-302) significantly counteracts 5-FU-induced apoptosis and cell viability in CCa cell lines, including HCT116 and HT26. This suggests that targeting the insulin-like growth factor-1 receptor (IGF-1R) with 5-FU treatment could represent an innovative therapeutic approach for CCa [33].

3.4 CCa surgery

The risk of CCa increases with age, and individual patient characteristics, such as age, are linked to a higher likelihood of postoperative complications. Specifically, an assessment of a patient's immune function can predict the risk of recurrence or death from CCa [34]. Surgery remains the cornerstone of CCa treatment, with laparoscopy serving as a critical method for diagnosis and staging. Despite its benefits, laparoscopic resection of abdominal tumors, including adrenalectomy and CCa resection, is infrequent. The complications associated with laparoscopic surgery underscore the need for careful consideration in its application for palliative care in abdominal cancers [35]. In the United States, over 100,000 individuals are diagnosed with CCa annually, with more than 90% undergoing surgery primarily aimed at curative resection. Yet, recurrence occurs in 30–50% of cases, with tumor characteristics significantly impacting survival rates. The selection of surgical techniques and procedures, including laparoscopic and other minimally invasive methods, alongside the management of cancers originating from polyps and the treatment of metastatic disease, are crucial factors in determining surgical outcomes. This highlights the importance of ongoing surveillance post-surgery [36].

Anastomotic fistula (AF) is one of the severe significant complications that may develop after CCa surgery. A study analyzing data from 163 patients who underwent CCa surgery identified 22 cases of AF. Risk factors associated with AF included diabetes ($p = 0.04$), smoking ($p = 0.01$), hypoalbuminemia ($p = 0.01$), preoperative hemoglobin levels below 10 g/dL ($p < 0.01$), AF location at the left colonic angle ($p = 0.02$), postoperative blood transfusion ($p < 0.01$), and surgical duration exceeding 180 minutes ($p = 0.04$) [37]. Furthermore, visceral obesity has been linked to increased postoperative complications in CCa surgery. An examination of data from 610 CCa resection patients showed a correlation between the peri-renal fat surface area (PRF) and the risk of postoperative complications. Patients with a PRF $\geq$40 cm^2 experienced longer intermediate complications compared to those with PRF $<$40 cm^2, with the absolute risk of complications being comparable between men and women with a PRF $\geq$40 cm^2 [38]. Surgical resection, while the primary treatment modality for

CCa, can negatively impact survival due to postoperative complications. In this context, a higher pan-immune-inflammation value (PIV) has been associated with an increased rate of postoperative complications and has been found to influence survival outcomes [39]. Surgical site infection (SSI) is the most common complication after colorectal surgery, leading to patient distress, increased healthcare costs, prolonged hospital stays, readmissions, sepsis, and mortality. An investigation into the relationship between SSI and CRC recurrence post-surgery revealed that SSI was linked to a higher likelihood of CRC recurrence and significantly poorer outcomes in terms of 5-year recurrence-free survival (RFS) and overall survival (OS) [40]. As a result, various strategies, including antibiotic prophylaxis, maintaining normoglycemia, and adhering to standardized surgical protocols, have been employed to reduce the risk of SSIs [41].

3.5 Plant-derived CCa treatment

Plants used in the pharmacological treatment of CCa are rich in bioactive chemicals, such as flavonoids, polyphenolic compounds, caffeic acid, saponins, catechins, triterpenoids, polysaccharides, glycosides, phenols, alkaloids, luteolin, quercetin, kaempferol, carnosic acid, rosmarinic acid, oleanolic acid, eugenol, emodin, and anthricin. These compounds have demonstrated efficacy in treating cancer due to their ability to induce cancer cell death through various mechanisms. They can reduce tumor cell proliferation and possess anti-cancer, anti-oxidant, anti-mutagenic, anti-inflammatory, and anti-angiogenic properties. However, despite these promising qualities, the precise sources and the complete understanding of these natural ingredients derived from plants remain areas that require further exploration [42].

Polyphenols in plants are primarily anti-oxidants that offer health benefits. Despite the underappreciation of plants' pharmacological effects, extracts with significant anti-oxidant and phenolic content demonstrate anti-cancer activity by influencing biological properties. Specifically, certain plants have been shown to possess anti-cancer properties against CCa cell lines, mediating the expression of cytokines, vascular endothelial growth factor-1 (VEGF-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which lead to anti-proliferative effects [43]. Polyphenols, beneficial against bacterial and viral infections, cancer, inflammation, and a range of gastrointestinal and metabolic diseases, act as potent inhibitors of cancer cell growth. They disrupt bacterial metabolism and impede growth [44]. However, polyphenols can also have adverse effects, particularly due to their inhibition of digestive enzymes and impact on the gut microbiome. The consumption of polyphenols may alter the composition of food components reaching the gut [45, 46], and their bacterial inhibitory effect is not limited to pathogens but extends to all bacteria [47]. Resveratrol, a well-known polyphenol, has established anti-inflammatory, anti-oxidant, and neuroprotective properties. Nonetheless, a placebo-controlled trial involving 62 patients with autism spectrum disorder (ASD) did not show significant benefits, revealing no substantial difference in the number and severity of adverse events between the treatment and control groups, except for a minor improvement in patient hyperactivity [48], underscoring the importance of cautiously using phytopharmaceuticals in clinical practice, taking into consideration individual responses and potential side effects.

3.6 Anti-cancer and anti-oxidant properties

Ginkgo biloba extract (EGB 761) is a pharmacological plant renowned for its anti-cancer and anti-oxidant effects and has been utilized for thousands of years in treating various diseases, including cancer. It has been demonstrated that EGB 761 mediates anti-cancer effects against CCa cell lines HT29 and HCT116 [49]. Additionally, EGB 761 stabilizes E-cadherin protein in CCa with the relative expression of lincRNA-p21, potentially playing a functional role in cancer therapy. *Angelica dahurica Radix* possesses anti-cancer and anti-oxidant activities, impacting cell viability, apoptosis, and necrotic activity against HT29 CCa cell lines. Its extract has been shown to significantly reduce the gene expression of p53, Bcl and Bax and induce apoptosis through the caspase cascade and cell cycle arrest, thereby contributing to its anti-cancer effects [50]. *Musa balbisiana* (bananas), *Punica granatum L* (pomegranate), *Glycine max* (Soybean), *Brassica oleracea L var. italica Plenck* (Broccoli), *Hibiscus rosa-sinesis* and *Hibiscus sabdariffa* (hibiscus) have been associated with the development and progression of CCa. They demonstrate potential as natural anti-oxidants in Chinese medicine, including polyphenols and carotenoids that inhibit the oxidation of lipids, proteins, and nucleic acids, initiating oxidative chain reactions. These bioactive compounds are considered vital dietary supplements [51]. *Vaccinium myrtillus L.* (bilberry) contains much higher levels of phenolic compounds than fruits and is characterized by bioactive phytochemicals with anti- has significantly higher levels of phenolic compounds than other fruits and features bioactive phytochemicals with anti-bacterial and anti-cancer effects. It has been shown to inhibit the growth of breast (MCF-7) and cervical (HeLa) cancers, as well as HT-29, and is recognized as a potential source for anti-cancer drug development due to its non-genotoxic properties [52]. Ornithogalum narbonense L. (OR), utilized in folk medicine and as food in the Şanlıurfa region of Turkey, has shown strong anti-cancer and anti-oxidant effects through its methanolic extract from the buds. Its high phenolic content, notably cosmocyin, followed by cinnamic acid, p-coumaric acid, and quinic acid, rich in anti-oxidants, has been demonstrated to cause apoptosis in cancer cells [53]. Melissa officinalis (MO), known as lemon balm and a popular herbal tea ingredient, has attracted attention for its diverse pharmacological effects, including anti-cancer activity against CCa. A study identified 3465 quantitative proteoforms from a total of 24,348 peptides, suggesting that MO hot water extract exerts anti-tumor effects in CCa cells by inducing a reactive oxygen species (ROS)-mediated oxidative stress response, with decreased protein expression and interference with mitochondrial membrane potential (MMP) [54].

Lavender oil is recognized for its biologically and pharmacologically active properties, including anti-mutagenic and anti-cancer effects. It exhibits anti-cancer activity across six human cancer cell lines: hepatocellular carcinoma (HepG2),

prostate cancer (PC3), lung cancer (A549), skin cancer (A431), breast cancer (MCF7), and colorectal cancer (HCT116) [55]. The methanolic extract from the leaves of Petasites japonicus Maxim (PJ) demonstrates anti-mutagenic effects. Notably, the PJ extract significantly reduced both spontaneous beta-galactosidase activity and beta-galactosidase activity induced by the mutagenic induced chromosomal rearrangement (ICR) in *Salmonella typhimurium* TA 1535/plasmid stabilization kinase1002. Importantly, the PJ extract exhibits a significant cytotoxic effect on cancer cells, particularly affecting stomach, colon, and uterine cancer cells [56]. Spearmint (*Mentha spicata*), commonly used as a food flavoring agent, has shown anti-mutagenic activity in *Salmonella* assays. *In vivo* studies reveal that spearmint water extract (2%; w/v), when administered to rats as their sole drinking water source before, during, and after exposure to quinoline (IQ) for two weeks, significantly inhibited the formation of colonic abnormal *foci* at eight weeks ($p < 0.05$ compared to rats treated with IQ alone). These findings suggest that spearmint extract may offer protection against IQ and other heterocyclic amines by inhibiting carcinogen activation and exerting direct effects on activated metabolites [57].

Yerba Mate (*Ilex paraguariensis St. Hill., Aquifoliaceae*) is a South American native tree known for its bioactive compounds that can potentially treat CCa through diet. Studies have shown that *Yerba Mate* positively affects cell proliferation, the invasive ability of tumor cells, and angiogenesis, suggesting its use as an ingredient in traditional Chinese medicine or functional foods, making it a promising healthy food source. Additionally, *Yerba Mate* induces apoptosis and could serve as a therapeutic agent for CCa, especially when the extract is administered orally at a dose of 1.6 g/kg/day in a murine synthetic tumor model [58]. *Acacia catechu Willd*. heartwood extract (AC) is noted for its gastrointestinal health benefits, particularly due to its high catechin content. It has an apoptosis-enhancing effect on human colon adenocarcinoma human colon adenocarcinoma cell line, showing potential for CRC treatment by reducing mitochondrial membrane potential (MMP) and increasing caspase-9 and -3 activities [59]. *Portulaca oleracea* extract has been shown to inhibit the proliferation of HT29 cancer stem cells treated with 5-FU, ranging from 0.07 to 2.25 μg/mL, enhancing HT29 cancer stem cell sensitivity. It may also modulate the growth of CCa stem cells by inhibiting the expression of Notch1 and β-catenin genes, affecting the Notch signaling pathway [60]. The Notch signaling pathway is essential for various biological processes, including cardiovascular health and tumor microcirculation. It is implicated in the increase of blood pressure induced by tyrosine kinase inhibitors (TKI), leading to vascular proliferation and migratory tube formation, and is being explored as a novel endothelial cell-based therapy during tumor angiogenesis [61, 62]. In the Notch signaling pathway, Notch proteins, acting through transmembrane receptors on the cell surface, mediate crucial cellular functions. This signaling cascade is integral to cell differentiation, proliferation, and apoptosis, with its proteins and ligands, including extracellular endothelial growth factor (EGF)-like repeats [63]. The pathway also promotes interaction with Notch and C promoter-binding factor 1/suppressor of hairless/lymphoid enhancer-binding factor 1 analog (CSL) proteins, resulting in the translocation of Notch to the nucleus [64].

3.7 Anti-inflammatory effect

Resistance, negative side effects or toxicity, and the potential for recurrence and drug-drug interactions are significant concerns with radiochemotherapy [65, 66]. In contrast, the use of medicinal plants offers a promising alternative, as various phytochemicals present in these plants provide anti-bacterial and anti-fungal activities. These plants are increasingly recognized for their specific medicinal properties and are being used to treat a wide range of diseases, highlighting the potential of medicinal plants as an alternative to conventional pharmaceuticals for treating human diseases, leveraging their natural availability and long-standing use in traditional medicine [67, 68]. Research involving both *in vivo* and *in vitro* studies on human subjects has underscored the anti-fungal activity of *Candida albicans* extract from *G. glabra*. These findings support the use of *F. religiosa* and *P. major* as anti-fungal agents and in mouthwashes, owing to their potent, naturally occurring components that offer efficacy comparable to synthetic agents [69].

Cactus (*Opuntia spp*) is a plant used in traditional medicine in the United States, India, Mexico and Korea due to its anti-cancer and anti-inflammatory properties against cancer cells. Its extract, rich in phenolic and flavonoid compounds, demonstrates cytotoxic effects on human CCa cells (SW480) by downregulating the anti-apoptotic protein Bcl2, indicating its potential in CCa therapy [70]. Similarly, *Inula viscosa*, a perennial herb native to the Mediterranean basin and utilized in folk medicine, exhibits promising anti-inflammatory activities. The ethanol extract of *Inula viscosa* (EIV) shows significant inhibitory effects on the growth of CCa cells (HT29) with a half maximal effective concentration of 62.39 μg/mL, at a concentration of 369.88 μg/mL, without exhibiting cytotoxicity towards fused Caco-2 cells. This highlights its potential role in the management of inflammatory bowel disease and as a preventive measure against CCa [71]. Examples of medicinal plants with potential effects on the prevention and treatment of CCa are shown in Table 1.

4. Conclusions

CCa, a common cancer affecting men, has one of the highest mortality rates worldwide, with a widely varying age of onset, thereby highlighting the urgent need for developing natural therapeutics in disease therapy. Thus, with the growing interest in the pharmacological effects of medicinal plants and phytochemical-rich foods, it is essential to identify specific information about their anti-cancer, anti-oxidant, anti-mutagenic, anti-inflammatory, and anti-angiogenic mechanisms for CCa prevention and treatment. This review provides an extensive list of plants, demonstrating their potential as alternative agents for CCa treatment based on plant extracts.

TABLE 1. Plant extracts that may prevent and treat CCa.

Sr#1	Plant	Efficacy	Properties	Common name	Reference
1	*Ginkgo biloba*	E-cadherin protein inhibition in CCa	Anti-cancer and anti-oxidant	Ginkgo	Chang *et al.* [49]
2	*Angelica dahurica Radix*	Decreased gene expression of *p53*, *Bcl* and *Bax*, caspase cascades and cell cycle arrest, and induction of apoptosis	Anti-cancer	Angelica	Zheng *et al.* [50]
3	*Musa balbisiana*	Oxidation inhibition and oxidative chain reaction of lipids, proteins and nucleic acids	Anti-oxidant	Banana	Macharia *et al.* [51]
4	*Punica granatum L*			Pomegranate	
5	*Glycine max*			Soybean	
6	*Brassica oleracea L var. italica Plenck*			Broccoli	
7	*Hibiscus rosa-sinesis* and *Hibiscus sabdariffa*			Hibiscus	
8	*Vaccinium myrtillus L.*	Inhibits cancer growth against breast (MCF-7) and cervical (HeLa) cancers	Anti-bacterial and anti-cancer	Bilberry	Ginovyan *et al.* [52]
9	*Ornithogalum narbonense L.*	High phenolic content leads to apoptosis of cancer cells	Anti-cancer and anti-oxidant	Ornithogalum	Koyuncu *et al.* [53]
10	*Melissa officinalis*	Induces ROS-mediated oxidative stress responses, inhibiting protein expression and interfering with MMP's potential	Anti-cancer	Lemon balm	Kuo *et al.* [54]
11	*Lavanduia officinalis*	Anti-cancer activity of six human cancer cell lines: CCa (HCT116), hepatocellular carcinoma (HepG2), prostate cancer (PC3), lung cancer (A549), skin cancer (A431), and breast cancer (MCF7)	Anti-mutations and anti-cancer	Lavender	Fahmy *et al.* [55]
12	*Petasite japonicus maxim*	Strong cytotoxic effects on colon and uterine cancer cells	Anti-mutations	Butterbur	Kang *et al.* [56]
13	*Mentha spicata*	Protection against IQ and other heterocyclic amines for inhibition of carcinogen activation and active metabolites	Anti-mutations	Spearmint	Yu *et al.* [57]
14	*Ilex paraguariensis St. Hill. Aquifoliaceae*	Cell proliferation, invasive ability of tumor cells, angiogenesis and apoptosis	Anti-angiogenic	Yerba Mate	Garcia-Lazaro *et al.* [58]
15	*Acacia catechu Willd. Heartwood*	Reduces MMP with apoptosis-enhancing effects	Anti-angiogenic	Senegalia catechu	Chiaino *et al.* [59]
16	*Portulaca oleracea*	Modulatory effect on CCa stem cell growth	Anti-angiogenic	Purslane	Jin *et al.* [60]
17	*Opuntia spp*	Downregulates the anti-apoptotic protein Bcl2 against cytotoxicity and human CCa (SW480)	Anti-cancer and anti-inflammatory	Cactus	Kim *et al.* [70]
18	*Inula viscose*	Manage inflammatory bowel disease and prevent CCa	Anti-inflammatory	Dittrichia viscosa	Kheyar *et al.* [71]

CCa, colon cancer; IQ, quinoline; MMP, mitochondrial membrane potential; ROS, reactive oxygen species.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YP and KHK—conceptualization; validation; writing-review. YP—methodology, software; formal analysis, investigation, resources, data curation, writing-original draft preparation; editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Esmeeta A, Adhikary S, Dharshnaa V, Swarnamughi P, Ummul Maqsummiya Z, Banerjee A, *et al*. Plant-derived bioactive compounds in colon cancer treatment: an updated review. Biomedicine & Pharmacotherapy. 2022; 153: 113384.

[2] Yaghoubi A, Khazaei M, Avan A, Hasanian SM, Soleimanpour S. The bacterial instrument as a promising therapy for colon cancer. International Journal of Colorectal Disease. 2020; 35: 595–606.

[3] Fabregas JC, Ramnaraign B, George TJ. Clinical updates for colon cancer care in 2022. Clinical Colorectal Cancer. 2022; 21: 198–203.

[4] Nelson VK, Sahoo NK, Sahu M, Sudhan HH, Pullaiah CP, Muralikrishna KS. *In vitro* anticancer activity of Eclipta alba whole plant extract on colon cancer cell HCT-116. BMC Complementary Medicine and Therapies. 2020; 20: 355.

[5] Islam MR, Akash S, Rahman MM, Nowrin FT, Akter T, Shohag S, *et al*. Colon cancer and colorectal cancer: prevention and treatment by potential natural products. Chemico-Biological Interactions. 2022; 368: 110170.

[6] Revathi S, Hakkim FL, Ramesh Kumar N, Bakshi HA, Sangilimuthu AY, Tambuwala MM, *et al*. *In vivo* anti cancer potential of pyrogallol in murine model of colon cancer. Asian Pacific Journal of Cancer Prevention. 2019; 20: 2645–2651.

[7] Labianca R, Beretta GD, Kildani B, Milesi L, Merlin F, Mosconi S, *et al*. Colon cancer. Critical Reviews in Oncology/Hematology. 2010; 74: 106–133.

[8] Mansour-Ghanaei F, Varshi G, Joukar F, Ashoobi MT, Esmaeilpour J, Gharibpoor A, *et al*. Prevalence of pre-cancerous colon lesions in referred patients under patronage of a local relief foundation in Guilan province. JML Journal of Medicine and Life. 2019; 12: 133–139.

[9] Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterology Clinics of North America. 2002; 31: 925–943.

[10] Roderburg C, Loosen SH, Hoyer L, Luedde T, Kostev K. Prevalence of diabetes mellitus among 80,193 gastrointestinal cancer patients in five European and three Asian countries. Journal of Cancer Research and Clinical Oncology. 2022; 148: 1057–1062.

[11] Gatta G, Capocaccia R, Berrino F, Ruzza MR, Contiero P. Colon cancer prevalence and estimation of differing care needs of colon cancer patients. Annals of Oncology. 2004; 15: 1136–1142.

[12] Gupta R, Bhatt LK, Johnston TP, Prabhavalkar KS. Colon cancer stem cells: Potential target for the treatment of colorectal cancer. Cancer Biology & Therapy. 2019; 20: 1068–1082.

[13] Hines RB, Bimali M, Johnson AM, Bayakly AR, Collins TC. Prevalence and survival benefit of adjuvant chemotherapy in stage III colon cancer patients: comparison of overall and age-stratified results by multivariable modeling and propensity score methodology in a population-based cohort. Cancer Epidemiology. 2016; 44: 77–83.

[14] Kostev K, Krieg S, Krieg A, Luedde T, Loosen SH, Roderburg C. In-hospital mortality and associated factors among colorectal cancer patients in Germany. Cancers. 2024; 16: 1219.

[15] Olde Bekkink M, McCowan C, Falk GA, Teljeur C, Van de Laar FA, Fahey T. Diagnostic accuracy systematic review of rectal bleeding in combination with other symptoms, signs and tests in relation to colorectal cancer. British Journal of Cancer. 2010; 102: 48–58.

[16] Holtedahl K, Borgquist L, Donker GA, Buntinx F, Weller D, Campbell C, *et al*. Symptoms and signs of colorectal cancer, with differences between proximal and distal colon cancer: a prospective cohort study of diagnostic accuracy in primary care. BMC Primary Care. 2021; 22: 148.

[17] Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. British Journal of General Practice. 2011; 61: e231–e243.

[18] Bousis D, Verras GI, Bouchagier K, Antzoulas A, Panagiotopoulos I, Katinioti A, *et al*. The role of deep learning in diagnosing colorectal cancer. Przeglad Gastroenterologiczny. 2023; 18: 266–273.

[19] Mulita F, Tepetes K, Verras GI, Liolis E, Tchabashvili L, Kaplanis C, *et al*. Perineal colostomy: advantages and disadvantages. Przeglad Gastroenterologiczny. 2022; 17: 89–95.

[20] Beniwal SS, Lamo P, Kaushik A, Lorenzo-Villegas DL, Liu Y, MohanaSundaram A. Current status and emerging trends in colorectal cancer screening and diagnostics. Biosensors. 2023; 13: 926.

[21] Pacal I, Karaboga D, Basturk A, Akay B, Nalbantoglu U. A comprehensive review of deep learning in colon cancer. Computers in Biology and Medicine. 2020; 126: 104003.

[22] Yu C, Helwig EJ. The role of AI technology in prediction, diagnosis and treatment of colorectal cancer. Artificial Intelligence Review. 2022; 55: 323–343.

[23] Hann A, Troya J, Fitting D. Current status and limitations of artificial intelligence in colonoscopy. United European Gastroenterology Journal. 2021; 9: 527–533.

[24] Luna JI, Grossenbacher SK, Murphy WJ, Canter RJ. Targeting cancer stem cells with natural killer cell immunotherapy. Expert Opinion on Biological Therapy. 2017; 17: 313–324.

[25] Ruan H, Leibowitz BJ, Zhang L, Yu J. Immunogenic cell death in colon cancer prevention and therapy. Molecular Carcinogenesis. 2020; 59: 783–793.

[26] Garza Treviño EN, Quiroz Reyes AG, Rojas Murillo JA, de la Garza Kalife DA, Delgado Gonzalez P, Islas JF, *et al*. Cell therapy as target therapy against colon cancer stem cells. International Journal of Molecular Sciences. 2023; 24: 8163.

[27] Sanders MA, Majumdar AP. Colon cancer stem cells: implications in carcinogenesis. Frontiers in Bioscience. 2011; 16: 1651–1662.

[28] Kozovska Z, Gabrisova V, Kucerova L. Colon cancer: cancer stem cells markers, drug resistance and treatment. Biomedicine & Pharmacotherapy. 2014; 68: 911–916.

[29] Wen J, Min X, Shen M, Hua Q, Han Y, Zhao L, *et al*. ACLY facilitates colon cancer cell metastasis by CTNNB1. Journal of Experimental & Clinical Cancer Research. 2019; 38: 401.

[30] Gerovska D, García-Gallastegi P, Descarpentrie J, Crende O, Casado-Andrés M, Martín A, *et al*. Proprotein convertases blockage up-regulates specifically metallothioneins coding genes in human colon cancer stem cells. Biochimica et Biophysica Acta-Molecular Cell Research. 2021; 1868: 118912.

[31] Denise C, Paoli P, Calvani M, Taddei ML, Giannoni E, Kopetz S, *et al*. 5-fluorouracil resistant colon cancer cells are addicted to OXPHOS to survive and enhance stem-like traits. Oncotarget. 2015; 6: 41706–41721.

[32] Mahbub AA. 17β-estradiol enhances 5-fluorouracil anti-cancer activities in colon cancer cell lines. Medical Sciences. 2022; 10: 62.

[33] Liu N, Li J, Zhao Z, Han J, Jiang T, Chen Y, *et al*. MicroRNA-302a enhances 5-fluorouracil-induced cell death in human colon cancer cells. Oncology Reports. 2017; 37: 631–639.

[34] Hartwig MFS, Gögenur I. Colon cancer surgery in the high-risk

patient. Journal of the Danish Medical Association. 2020; 182: V10190572. (In Danish)
[35] Ramshaw BJ. Laparoscopic surgery for cancer patients. CA: A Cancer Journal for Clinicians. 1997; 47: 327–350.
[36] Rossi H, Rothenberger DA. Surgical treatment of colon cancer. Surgical Oncology Clinics of North America. 2006; 15: 109–127.
[37] Zouari A, Masmoudi A, Khanfir F, Ketata S, Rejab H, Bouzid A, *et al*. Predictive factors for anastomotic leakage after colon cancer surgery. The Pan African Medical Journal. 2022; 42: 129. (In French)
[38] der Hagopian O, Dahlberg M, Heinius G, Nordberg J, Gustafsson J, Nordenvall C, *et al*. Perirenal fat surface area as a risk factor for perioperative difficulties and 30-day postoperative complications in elective colon cancer surgery. Colorectal Disease. 2018; 20: 1078–1087.
[39] Seo YJ, Kim KE, Jeong WK, Baek SK, Bae SU. Effect of preoperative pan-immune-inflammation value on clinical and oncologic outcomes after colorectal cancer surgery: a retrospective study. Annals of Surgical Treatment and Research. 2024; 106: 169–177.
[40] Koike T, Mukai M, Kishima K, Yokoyama D, Uda S, Hasegawa S, *et al*. The association between surgical site infection and postoperative colorectal cancer recurrence and the effect of laparoscopic surgery on prognosis. Langenbeck's Archives of Surgery. 2024; 409: 40.
[41] Hatharaliyadda B, Schmitz M, Mork A, Osman F, Heise C, Safdar N, *et al*. Surgical site infection prevention using "strike teams": the experience of an academic colorectal surgical department. Journal for Healthcare Quality. 2024; 46: 22–30.
[42] Esmeeta A, Adhikary S, Dharshnaa V, Swarnamughi P, Ummul Maqsummiya Z, Banerjee A, *et al*. Plant-derived bioactive compounds in colon cancer treatment: an updated review. Biomedicine & Pharmacotherapy. 2022; 153: 113384.
[43] Prakash MD, Stojanovska L, Feehan J, Nurgali K, Donald EL, Plebanski M, *et al*. Anti-cancer effects of polyphenol-rich sugarcane extract. PLOS ONE. 2021; 16: e0247492.
[44] Keyvani-Ghamsari S, Rahimi M, Khorsandi K. An update on the potential mechanism of gallic acid as an antibacterial and anticancer agent. Food Science & Nutrition. 2023; 11: 5856–5872.
[45] Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, Tuohy K. Gut microbiota functions: metabolism of nutrients and other food components. European Journal of Nutrition. 2018; 57: 1–24.
[46] Bié J, Sepodes B, Fernandes PCB, Ribeiro MHL. Polyphenols in health and disease: gut microbiota, bioaccessibility, and bioavailability. Compounds. 2023; 3: 40–72.
[47] Duda-Chodak A, Tarko T. Possible side effects of polyphenols and their interactions with medicines. Molecules. 2023; 28: 2536.
[48] Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. Microbiome. 2019; 7: 91.
[49] Chang L, Liu T, Chai Z, Jie S, Li Z, Liu M, *et al*. lincRNA-p21 mediates the anti-cancer effect of ginkgo biloba extract EGb 761 by stabilizing E-Cadherin protein in colon cancer. Medical Science Monitor. 2018; 24: 9488–9496.
[50] Zheng YM, Shen JZ, Wang Y, Lu AX, Ho WS. Anti-oxidant and anti-cancer activities of Angelica dahurica extract via induction of apoptosis in colon cancer cells. Phytomedicine. 2016; 23: 1267–1274.
[51] Macharia JM, Mwangi RW, Rozmann N, Zsolt K, Varjas T, Uchechukwu PO, *et al*. Medicinal plants with anti-colorectal cancer bioactive compounds: potential game-changers in colorectal cancer management. Biomedicine & Pharmacotherapy. 2022; 153: 113383.
[52] Ginovyan M, Babayan A, Shirvanyan A, Minasyan A, Qocharyan M, Kusznierewicz B, *et al*. The action mechanisms, anti-cancer and antibiotic-modulation potential of *Vaccinium myrtillus* L. extract. Discovery Medicine. 2023; 35: 590–611.
[53] Koyuncu I, Gönel A, Akdağ A, Yilmaz MA. Identification of phenolic compounds, antioxidant activity and anti-cancer effects of the extract obtained from the shoots of Ornithogalum narbonense L. Cellular and Molecular Biology. 2018; 64: 75–83.
[54] Kuo TT, Lin LC, Chang HY, Chiang PJ, Wu HY, Chen TY, *et al*. Quantitative proteome analysis reveals melissa officinalis extract targets mitochondrial respiration in colon cancer cells. Molecules. 2022; 27: 4533.
[55] Fahmy MA, Farghaly AA, Hassan EE, Hassan EM, Hassan ZM, Mahmoud K, *et al*. Evaluation of the anti-cancer/anti-mutagenic efficiency of Lavandula officinalis essential oil. Asian Pacific Journal of Cancer Prevention. 2022; 23: 1215–1222.
[56] Kang HG, Jeong SH, Cho JH. Antimutagenic and anticarcinogenic effect of methanol extracts of Petasites japonicus Maxim leaves. Journal of Veterinary Science. 2010; 11: 51–58.
[57] Yu TW, Xu M, Dashwood RH. Antimutagenic activity of spearmint. Environmental and Molecular Mutagenesis. 2004; 44: 387–393.
[58] Garcia-Lazaro RS, Lamdan H, Caligiuri LG, Lorenzo N, Berengeno AL, Ortega HH, *et al*. *In vitro* and *in vivo* antitumor activity of Yerba Mate extract in colon cancer models. Journal of Food Science. 2020; 85: 2186–2197.
[59] Chiaino E, Micucci M, Durante M, Budriesi R, Gotti R, Marzetti C, *et al*. Apoptotic-induced effects of *Acacia Catechu* willd. Extract in human colon cancer cells. International Journal of Molecular Sciences. 2020; 21: 2102.
[60] Jin H, Chen L, Wang S, Chao D. Portulaca oleracea extract can inhibit nodule formation of colon cancer stem cells by regulating gene expression of the Notch signal transduction pathway. Tumor Biology. 2017; 39: 1010428317708699.
[61] Wang W, Li G, Ma J, Fan X, Lu J, Sun Q, *et al*. Microvascular rarefaction caused by the NOTCH signaling pathway is a key cause of TKI-apatinib-induced hypertension and cardiac damage. Frontiers in Pharmacology. 2024; 15: 1346905.
[62] Kwak M, Southard KM, Kim WR, Lin A, Kim NH, Gopalappa R, *et al*. Adherens junctions organize size-selective proteolytic hotspots critical for Notch signalling. Nature Cell Biology. 2022; 24: 1739–1753.
[63] Takahashi H, Sakakibara-Konishi J, Furuta M, Shoji T, Tsuji K, Morinaga D, *et al*. Notch pathway regulates osimertinib drug-tolerant persistence in EGFR-mutated non-small-cell lung cancer. Cancer Science. 2023; 114: 1635–1650.
[64] Johnson SE, Barrick D. Dissecting and circumventing the requirement for RAM in CSL-dependent Notch signaling. PLOS ONE. 2012; 7: e39093.
[65] Lewtak K, Fiołka MJ, Czaplewska P, Macur K, Kaczyński Z, Buchwald T, *et al*. Sida hermaphrodita seeds as the source of anti-Candida albicans activity. Scientific Reports. 2019; 9: 12233.
[66] Negri M, Salci TP, Shinobu-Mesquita CS, Capoci IR, Svidzinski TI, Kioshima ES. Early state research on antifungal natural products. Molecules. 2014; 19: 2925–2956.
[67] Baba H, Onanuga A. Preliminary phytochemical screening and antimicrobial evaluation of three medicinal plants used in Nigeria. African Journal of Traditional, Complementary and Alternative Medicines. 2011; 8: 387–390.
[68] Singh P, Singh VK, Singh AK. Molecular docking analysis of candidate compounds derived from medicinal plants with type 2 diabetes mellitus targets. Bioinformation. 2019; 15: 179–188.
[69] Sharma H, Yunus GY, Agrawal R, Kalra M, Verma S, Bhattar S. Antifungal efficacy of three medicinal plants Glycyrrhiza glabra, Ficus religiosa, and Plantago major against oral Candida albicans: a comparative analysis. Indian Journal of Dental Research. 2016; 27: 433–436.
[70] Kim J, Jho KH, Choi YH, Nam SY. Chemopreventive effect of cactus (Opuntia humifusa) extracts: radical scavenging activity, pro-apoptosis, and anti-inflammatory effect in human colon (SW480) and breast cancer (MCF7) cells. Food & Function Journal. 2013; 4: 681–688.
[71] Kheyar N, Bellik Y, Serra AT, Kheyar F, Bedjou F. *Inula viscosa* phenolic extract suppresses colon cancer cell proliferation and ulcerative colitis by modulating oxidative stress biomarkers. BioTechnologia. 2022; 103: 269–281.

How to cite this article: Yeonhee Pyo, Ki Han Kwon. A potential target for the prevention and therapy of colon cancer: focused on men's clinical features. Journal of Men's Health. 2024; 20(11): 1-8. doi: 10.22514/jomh.2024.180.