Phytochemicals and Gastrointestinal Cancer Progression

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Gastrointestinal (GI) cancer is a prevailing global health disease with a high incidence rate which varies by region. It is a huge economic burden on health care providers. GI cancer affects different organs in the body such as the gastric organs, colon, esophagus, intestine, and pancreas. Phytochemicals are non-nutritive bioactive secondary compounds abundantly found in fruits, grains, and vegetables. Consumption of phytochemicals may protect against chronic diseases like cardiovascular disease, neurodegenerative disease, and cancer. Multiple studies have assessed the chemoprotective effect of selected phytochemicals in GI cancer, offering support to their potential towards reducing the pathogenesis of the disease.The aim of this review is to summarize the current knowledge addressing the anti-cancerous effects of selected dietary phytochemicals on GI cancer and their molecular activities on selected mechanisms, i.e., nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B), detoxification enzymes, adenosine monophosphate activated protein kinase (AMPK), wingless-related integration site/-catenin (wingless-related integration site (Wnt)-catenin, cell apoptosis, phosphoinositide 3-kinases (PI3K)/ protein kinase B AKT/ mammalian target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK). Overall, phytochemicals improve cancer prognosis through the downregulation of -catenin phosphorylation, therefore enhancing apoptosis, and upregulation of the AMPK pathway, which supports cellular homeostasis. Nevertheless, more studies are needed to provide a better understanding of the mechanism of cancer treatment using phytochemicals and possible side effects associated with this approach.

Keywords: phytochemical ; gastrointestinal cancer ; intestinal cancer ; apoptosis ; anti-cancerous effects

1. Gastrointestinal Cancer and Phytochemicals

1.1. Gastrointestinal Cancer

Cancer is a leading cause of death worldwide, being responsible for approximately 7.9 million deaths (13% of all deaths) [1]. The rate of cancer-related death is expected to rise to an estimated 12 million deaths by 2030 [2]. Gastrointestinal cancer (GI) is the second most common cause of cancer-related death in the world [3]. Statistical results obtained in 2008 showed that GI cancer is the fourth most common cancer in men and the fifth most common cancer in women [4]. GI cancer is a malignant condition which affects the gastrointestinal tract and accessory organs such as the colon, esophagus, and intestine [5]. The carcinogenesis of GI cancer occurs due to the accumulation of genetic variation of multiple genes such as tumor suppressors, mismatch repair genes, and oncogenes [6]. Imbalance between cellular proliferation and apoptosis leads to the pathogenesis of GI cancer [7]. Internal and external factors such as genetic, obesity, alcohol consumption, and *Helicobacter pylori* infection contribute to the pathogenesis of GI cancer [8]. Although patients with GI cancer become symptomatic after they have advanced lesions with either local or distant metastasis, commonly presented findings include bloating, epigastric pain, and palpable epigastric mass [9]. Though the incident rate of GI cancer is declining, it remains a major health problem and a huge burden on health care providers [10]. The prognosis of GI cancer is variable between patients depending on its progression at the time of detection. Early detection of GI cancer improves the outcomes of patients. Treatments of the disease include surgery, radiation, and administration of chemotherapy components such as cisplatin, mitomycin, and docetaxel injection [11].

1.2. Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common malignant tumor in the world, with an incidence of 1.2 million new cases and over 600,000 death cases [12]. CRC is the second most common cancer in women and the third most common cancer in men worldwide [10]. As CRC is a so-called westernized disease, the highest incidence rates are found in Australia, New Zealand, North America, and Europe [13]. Although advance treatments are available to improve the survival rate of the disease, CRC remains an incurable disease [14]. While the rate of CRC in adults aged 50 and above decreases, an increase in disease incidence is observed in adults younger than 50 [15]. This suggest that factors such as physical activity, gut microbiome composition, and diet may underline the development of the disease [16]. Like most cancers, CRC is driven by an accumulation of genetic mutations in tumor suppressors such as adenomatous polyposis coli (APC), Smad4 and p53, and oncogenes such as K-ras [17]. These mutagenic accumulations lead to a stepwise progression from normal intestinal epithelial cells to pre-malignant tumor development/adenoma to adenocarcinoma [18]. Etiologically, CRC may be sporadic (more than 80% of cases are sporadic), hereditary, or be related to a history of inflammatory bowel disease [19]. Signs of colon cancer include change in bowel dietary habits and blood in stools [20].

Although treatment of CRC depends on the time of diagnosis and the stage of the disease, common treatments used include surgery, radiation, immunotherapy, and chemotherapy [21].

1.3. Esophageal Cancer

Esophageal cancer is a serious malignancy which accounted for more than 400,000 deaths worldwide in 2005 [22]. Although the incidence rate of other types of cancer is expected to decrease by 2025, the prevalence of esophageal cancer is expected to increase by 140% [23]. The two predominant histological subtypes of esophageal cancer are adenocarcinoma and squamous cell carcinoma, with these having unreliable racial and geographical distribution [24]. Although squamous cell carcinoma remains the most common type of esophageal cancer globally, adenocarcinoma has become the leading type in Western countries due to the higher incidence of obesity and Barrett's esophagus [25]. Treatment of esophageal cancer includes surgery, radiation, and chemotherapy [26].

1.4. Diet and Microbial Metabolites

The gastrointestinal tract in the human body has the highest population of different microbes, such as in the microbiome. They play a critical role in the well-being of the host [27]. It is estimated that the human gut contains between 30 trillion to 400 trillion micro-organisms [28]. The interaction between the microbiome with different parts of the human gut (mucus layer, epithelial cells, and immune cells) helps in determining the health or disease status of the host [29]. Changes in the gut microbiota due to environmental exposure, host genetics, and diet are known to affect human physiology, prevalence of disease, and nutrition [30]. The gut composition of people lacking *Helicobacter pylori* infection has identified 128 phylotypes within 8 bacterial phyla of which Proteobacteria, Firmicutes, Bacteroidetes, Fusobacteria, and Actinobacteria are the most abundant [31]. Epidemiological studies have indicated that a diet with high fiber and low red meat and fat content reduces the risk of CRC due to the presence of colonic microbiota [32]. They enhance the host's health by promoting the metabolism of fiber to produce short chain fatty acids (SCFAs) such as butyrate which downregulate pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-12 (IL-12) [33].

2. Anti-Cancerous Effects of Selected Phytochemicals

2.1. Carotenoids

Carotenoids are pigments found in plants, bacteria, algae, and fungi [34]. The family of carotenoids (tetraterpenes) contains 500 compounds, 50 of which exhibit provitamin A activity [35]. While only 40 carotenoids have been identified in the human diet, human blood and tissue contain 20 carotenoids [36]. Carotenoids are well recognized for their antioxidant activities, regulation of cellular growth, immune response, and modulation of gene expression [37]. Pre-dominant carotenoids include lutein, lycopene, and β-carotene, which are abundantly found in egg yolk, tomato, and carrot [38].

2.1.1. Lutein

Lutein in an abundant fat-soluble xanthophyll with a singular molecular formula ($C_{40}H_{56}O_2$) [39]. It is found abundantly in egg yolk, oranges, yellow fruits, and green leafy vegetables [40]. Lutein is one of the two carotenoids that accumulates in fovea in the human retina [41]. It is a major constitute of macular pigment which is responsible for fine feature vision [42]. Recently, lutein has gained public health attention due to its putative role in protection against degenerative eye conditions and cancer [43]. A study performed on a Korean population showed an association between dietary lutein and the risk of colorectal cancer [44]. Lutein has considerable antioxidant function, which regulates apoptosis [45]. Administration of lutein in animal models has been observed to decrease the concentration of K-ras and AKT in tumors, resulting in cell cycle arrest [46]. Mice treated with lutein have been found to significantly inhibit aberrant crypt foci (ACF) development in the colon, reducing cellular proliferation [47]. Additionally, administration of lutein has been observed to reduce β-catenin concentration, hyperplasia, and adenocarcinoma in colonic samples [48]. It also acts as an effective blocking agent by reducing the concentration of specific protein-like β-catenin involved in cellular proliferation and apoptosis (Figure 2) [49]. Moreover, lutein plays a role in reducing reactive oxygen species and oxygen radicals while enhancing DNA damage repair (Table 1) [50].

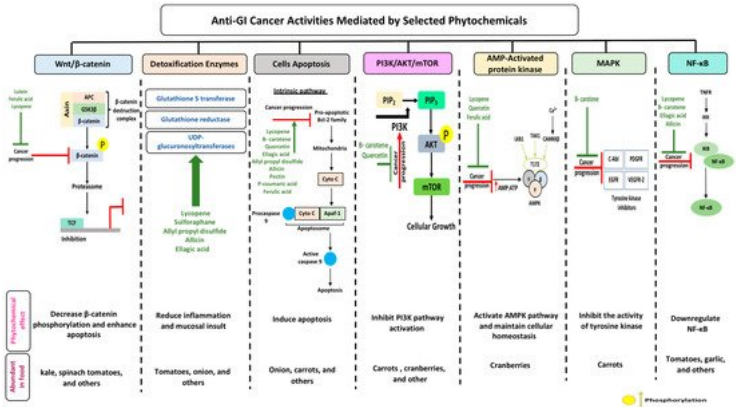


Figure 2. Phytochemicals as anti-GI cancer agents: mode(s) of action, aberrant signaling pathways (Wnt/β-catenin, detoxification enzymes, cellular apoptosis, PI3K/AKT/mTOR, AMPK, MAPK, and NF-κB), and pathway components targeted by phytochemicals (highlighted in green). Phytochemicals have a wide range of anti-cancerous actions through which one could target multiple mechanisms. These phytochemicals can enhance or suppress (green and red lines, respectively) the mechanisms through several activities. (see text for detailed mode(s) of action for phytochemicals mentioned).

2.1.2. Lycopene

Lycopene is a lipophilic pigment and the main component of-red colored fruits and vegetables such as tomatoes [51]. Lycopene is structurally similar to β-carotene with the molecular formula $C_{50}H_{56}$, a hydrocarbon chain, and no functional groups [52]. The concentration of lycopene in tomatoes ranges 0.9 to 9.27 mg/g [53]. Lycopene is a potent antioxidant which can counteract reactive oxygen species like peroxyl radicals [54]. The expression of lycopene's antioxidant activity is due to (i) the detoxification process through the production of enzymes like glutathione peroxidase (GPx), glutathione-S-transferase (GST), and glutathione reductase (GR); (ii) the inhibition of cytochrome P450 2E1, which is critical for the conversion of xenobiotics in cancer; and (iii) the suppression of carcinogen progression (Figure 2) [55]. In addition, lycopene exerts both anti-inflammatory and anti-cancer activity specifically against colorectal cancer [56]. Administration of lycopene using gold nanoparticles as a vehicle has been found to reduce the expression of pro-caspase 3, 8, and 9 and enhance Bcl-2-associated X protein (BAX) expression, thus enhancing the apoptotic pathway [57]. A one-day cultured colon cancer cell with 10 µm of lycopene showed a reduction in cellular growth by reducing the expression of Hmg Co-A reductase and enhancement in Ras translocation from the plasma membrane to cytosol [58]. Lycopene is reported to inhibit the expression of NF-κB and c-Jun N-terminal kinases (JNK), which (i) leads to a decreased tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and IL-6 and (ii) inhibits the expression of cyclooxygenase 2 (COX-2) and NO production (Table 1) [59]. In a gastric-induced carcinogens model, lycopene has been found to block the activity of carcinogenic cells through the upregulation of a reduced glutathione (GSH) dependent hepatic detoxification system, thus protecting cells from oxidative damage [60].

2.2. Proanthocyanidins

Proanthocyanidins, also known as condensed tannins, result from flavanol condensation [61]. They are abundantly found as polymers and oligomers in fruits, barriers, seeds, leaves, and flowers [62]. Recent interest in proanthocyanidins has been stimulated due to their potential health benefits which arise mainly from their antioxidant activity [63]. The effectiveness of proanthocyanidins are determined by gut microbiome composition [64]. Additionally, they have anticancer properties via the reduction of tumor development by inducing apoptosis or inhibiting cellular proliferation [65].

2.2.1. Quercetin

The cranberry (*Vaccinium macrocarpon*) is a fruit which has been used as a functional food due to its health benefits [66]. It is a rich source of polyphenols, which exerts anti-inflammatory, antiviral, antibacterial, antioxidant, anticarcinogenic, and antimutagenic activities [67]. It has a complex and rich phytochemical composition, consisting predominantly of A-type procyanidins (PACs), flavan-3-ols, anthocyanins, ursolic acid, quercetin, and benzoic acid [68]. Recently, the cranberry has received attention as a result of its effects related to lowering the risk of cancer [69]. Animal studies have reported the chemoprotective effect of cranberry to suppress the growth of several types of cancer cells, including colon, lung, prostate, oral, and ovarian [70]. Administration of 20% cranberry juice in water to rat models demonstrated a reduction in the total number of ACF [71]. Cranberry extracts have been reported to reduce proinflammatory interleukins and C-reactive protein [72]. $APC^{min/+}$ mice fed with 20% (*w/w*) freeze dried whole cranberry powder for 12 weeks showed a significant prevention of intestinal tumor formation (33.1%) due to induced cellular apoptosis and reduced cellular proliferation [73]. Also, it is reported that cranberry consumption inhibits the activation of the PI3K, AKT, and COX-2 signaling pathway (Table 1) [74]. Administration of cranberries has shown an activation in the AMPK pathway which helped maintain cellular homeostasis [75].

2.2.2. Ellagic Acid

The bilberry (*Vaccinium myrtillus* L) is a rich natural source of anthocyanins [76]. Total anthocyanin content in the bilberry ranges from 300–700 mg/100 g [77]. It is classified by the American Herbal Products Association as a class 1 herb, which means it can be safely consumed when used appropriately [78]. Ellagic acid is a phenolic compound found in bilberry extracts which has potent antioxidant properties and can chelate metal ions and scavenge free radicals [79]. Treatment of rats' hepatocyte primary culture with bilberries has shown a protective effect against oxidative damage [80]. Bilberries have been reported to induce phase II xenobiotic detoxification enzymes, which are critical for cancer prevention [81]. Additionally, bilberry-rich extracts have been observed to inhibit the growth of colon cancer cells but to not affect normal colon cells, thus suggesting a possible protective effect against cancer [82]. Rats with genetic colon adenoma fed concentrated bilberry extract (10% *w/w*) have shown a significant reduction in intestinal adenoma by 15–30% [83]. In a pilot study on 25 patients with colorectal cancer who were given bilberry extract for 7 days, the results showed a significant reduction in tumor cellular proliferation by 7% compared to the results before bilberry administration [84]. Treatment of human monocytic THP-1 cells with bilberry extract showed reduction in pro-inflammatory gene expression, interferon γ (IFN-γ), and cytokine secretion [85]. Moreover, bilberry extract exerts the ability to induce apoptosis and arrest

growth in GI cancer (Figure 2) [86]. Bilberry extract has been reported to diminish topoisomerase catalytic activity in colon carcinoma cells, showing a protective DNA effect [87].

2.3. Organosulfur Compounds

Organosulfur compounds are sulfur-containing organic compounds with beneficial anti-inflammatory, antioxidant, and anti-cancerous effects [88]. Animal and epidemiological studies have shown that administration of organosulfur compounds reduces the risk of colorectal cancer through the induction of mitotic arrest and apoptosis [89][90]. Garlic, onion, asparagus, and cruciferous vegetables are abundant in organosulfur compounds.

2.3.1. Allicin

Attention has been given recently to garlic due to its high content of flavonoids and organosulfur compounds like allicin [91]. Worldwide garlic (*Allium sativum*) has been frequently used as a dietary botanical supplement [92]. Ally sulfur compounds like allicin found in garlic (1% of garlic's dye weight) seems to be responsible for the beneficial effects of garlic [93]. Animal studies have shown that administration of garlic reduces the formation of ACF [94]. The mechanisms by which garlic inhibits the growth of carcinogen cells include reduction of DNA adducts, regulation of cellular arrest, activation of metabolizing detoxification enzymes, and induction of differentiation and apoptosis [95][96]. Organosulfur compounds present in garlic have shown potential for an anti-cancer drug by the modulation of epithelial growth factor receptor (EGFR), which plays a role in cell division [97]. Results obtained from an induced colitis mouse model have shown that administration of diallyl disulfide extracted from garlic is able to prevent the development of colitis-induced colorectal cancer [98]. In addition, garlic has been observed to prevent prolonged inflammation in mice, which supports the chemoprotective effect of garlic in CRC [99]. Moreover, consumption of garlic suppresses the activity of NF-κB by inhibiting phosphorylated P65 translocation (Figure 2) [100]. In xenograft nude mice, administration of S-allylmercaptocysteine (SAMC) in combination with rapamycin (a macrolide compound) was found to enhance anticancer ability by suppressing tumor growth and inducing apoptosis (Table 1) [101]. Administration of aged garlic extract in rat tumor models has been shown to attenuate colon tumor progression effectively by reducing cellular proliferation through the attenuation of NF-κB activity [102]. A meta-analysis study has indicated that the consumption of garlic is associated with reduced gastric cancer with a 95% confidence interval and a 0.53 odd ratio [103].

2.3.2. Allyl Propyl Disulfide

Chemical groups found in onions such as flavonoids, alk(en)yl cysteine sulfoxides (ACSOs), and allyl propyl disulfide are associated with the health benefits of onions [104]. The consumption rate of onion (*Allium cepa* L.) has increased worldwide, leading to an increase in the national production of onion by 25% over the last decade [105]. Compounds from onions have been reported to have multiple health benefits, including having antiplatelet, anticarcinogenic, and antithrombogenic activities [106]. Onion extracts have been reported to significantly induce apoptosis and reduce cellular proliferation in colorectal cancer [107]. An in vivo study has indicated that administration of onion in a hyperlipidemic colorectal cancer model plays a similar role to capecitabine in a colorectal cancer model without hyperlipidemia by inhibiting CRC and reducing hyperlipidemia [108]. Human cancer adenocarcinoma cells treated with 200 µm Se-methyl-L-selenocysteine (MSeC) for 24 h have been found to trigger 80% apoptosis in cells through endoplasmic reticulum stress rather than reactive oxygen species stress (Table 1) [109]. The benefit of onions is not limited to reducing or treating GI cancer but also to detecting cancer. One study used carbon nano onion films to develop a capacitive immunosensor for a CA19-9 cancer biomarker detector which succeeded in detecting CA19-9 in whole lysate colorectal adenocarcinoma using the sensor combined with information visualization methods [110].

2.3.3. Asparagusic Acid

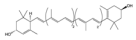
Asparagus species are native medical shrubs which have beneficial medical properties and which belong to the Liliaceae family [111]. Major bioactive compounds found in asparagus include steroidal saponins, asparagusic acid, vitamins (A, B_1, B_2, C, E, Mg, P, Ca, and Fe), folic acid, asparagine, tyrosine, arginine, essential oils, tannin, resin, and flavonoids. The health properties of asparagus include anti-microbial, antioxidant, and cytotoxic activities [112]. Asparagus extracts have illustrated a potent cytotoxic effect against colorectal cancer [113]. Treatment of Myeloid-derived suppressor cells (MDSCs) with asparagus polysaccharide have shown a significant increase in apoptosis through intrinsic pathways and a significant decrease in cellular proliferation [114]. Old stems of asparagus (SSA) tested on colon cancer cells have been found to suppress cellular viability and block cellular migration and invasion through Rho GTPase signaling pathway modulation [115]. In human colon adenocarcinoma, methanolic extracts from white asparagus have demonstrated TRAIL death receptor pathway activation leading to the activation of caspase-8 and caspase-3, and, finally, to cell death. In addition, asparagus extracts have been seen to inhibit cellular pro-inflammatory mediators like MMP7, MMP9, and TNF-α [116].

2.3.4. Sulforaphane

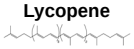
Cruciferous vegetables refer to those which belong to the Brassicaceae family and include cabbage, broccoli, and Brussel sprouts [117]. This family is known for the glucosinolate, a sulfur-containing compound synthesized endogenously in plants derived from amino acid and glucose residues [118]. Upon cellular rupture through vegetable consumption, glucosinolates are hydrolyzed by endogenous enzymes and produce potential compounds such as thiocyanates and nitriles [119]. Cruciferous vegetables contain several phytochemical compounds such as sulforaphane. Studies have shown the

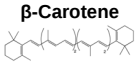
beneficial effects of cruciferous vegetables which have helped inhibit the development of GI cancer [120]. In vivo and in vitro studies have demonstrated the ability of cruciferous vegetables to defend healthy cells against radiation and chemically-induced carcinogenesis [121]. Additionally, these vegetables have been shown to inhibit cellular proliferation, migration, and survival of tumor cells [122]. Cruciferous vegetables demonstrate antioxidant activity as they widely show a protective effect against oxidative stress through the depletion of glutathione [123]. Additionally, these vegetables induce acute oxidative stress through the inhibition of P38 MAPK, which inhibits Nrf2-Keap 1 dissociation (Table 1) [124]. Cruciferous vegetables guard against colorectal cancer through several mechanisms: (i) the modulation of detoxification enzymes (Figure 2), (ii) the induction of cellular apoptosis, and (iii) the controlling of cancer cellular growth through cell cycle arrest [125][126][127]. A meta-analysis study has shown that cruciferous vegetables significantly reduce the risk of gastric and colorectal cancer by 19% and 8%, respectively [128].

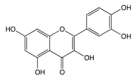
Table 1. Representive Phytochemicals and Their Underlying Anti-Cancerous Effects.

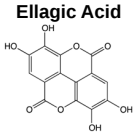
Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
Carotenoids	**Lutein** 	**Egg yolk, kale, spinach, parsley, and peas**	**Oxidation**	**3′-dehydro-lutein**	* Reduces slightly the risk of colorectal cancer * Reduces the risk of colorectal neoplasms in women * Inhibits the growth of carcinoma cells * Decreases the concentration of AKT expression which reduces cellular proliferation * Decreases β-catenin concentration thus enhancing the apoptotic pathway * Regulates miRNA expression through DICER 1 activity * Enhances DNA damage repair * Induces humoral and cell mediated-immune response * Scavenges against oxygen radicals * Quenches reactive oxygen species * Activates MAPK pathway through MAP3K9 interaction * Protects against the formation of	* Sprague-Dawley rats.	* Human colon ep cells * Human adenoca cells

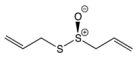
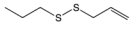
Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
					colonic aberrant crypt foci		

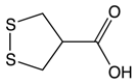
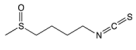
Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
	Lycopene 	**Tomato, guava, papaya, grapefruit, and watermelon**	**Auto-oxidation Radical-mediated oxidation**	**Apo-10′-lycopenoids**	* Suppresses the progression of carcinogenesis through the inhibition of DNA synthesis * Inhibits cell invasion, metastasis, and angiogenesis * Reduces cell migration capacity * Downregulates AKT, NF-κB, MMP-2, MMP-7, and MMP-9 * Decreases β-catenin concentration * Reduces pro-inflammatory mediators and enzymes such as TNF-a and COX-2, respectively * Prevents oxidative damage through scavenging oxygen free radicals * Suppresses the expression of cyclin D1 and PCNA proteins * Inhibits the formation of colonic ACFs * Stimulates the activity of enzymes such as glutathione reductase, glutathione peroxidase, and glutathione S-transferase * Enhances apoptotic	* Induced-colitis rat models * Sprague-Dawely rats * Fischer 344/NSIc rats	* HT-29 c

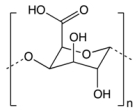
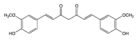
Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
					pathway * Activates MAPK signaling gene * Upregulates p21 cell cycle inhibitor protein * Inhibits the formation of neoplastic tumors * Reduces the number of polyps in the colon * Inhibits pleiotropic cytokines and the NF-κB pathway * Reduces the formation of macroscopic neoplasms by targeting low abundant gut microbiome * Inhibits cellular proliferation through MAPK/ERK and PI3K/AKT pathway inhibition * Enhances p53-dependent apoptosis pathway		
	β-Carotene 	**Carrot**	**Oxidation**	**Falcarindiol 6-methoxymellein**		* Azoxymethane (AOM) treated rats	* HT-29 c * HCT 11 * CCD-33

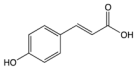
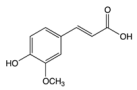
Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
Pro-anthocy-anidins					* Reduces small intestine tumor formation * Reduces inflammatory responses when consumed with fiber * Reduces tumor incidence, multiplicity, burden, and average tumor volume * Reduces colonic inflammatory cytokine expression such as IFN-γ and TNF-α * Inhibits the activation of the PI3K, AKT, and COX-2 signaling pathway * Inhibits cancer cell proliferation and tumor growth * Inhibits VEGF, MMP-2, and MMP-9 expression * Inhibits the incidence of AOM-induced ACF * Induces cellular apoptosis * Increases the number of colonic goblet cells and MUC 2 production * Increases caecal short fatty acids concentration		
	Quercetin 	**Cranberry**	**Sulfation Conjugation**	**3-(4hydroxyphenyl) -propionic acid hippuric acid catechol-O-sulfate**		* Apc(min/+) mice * Male weanling rats	* HCT116 lines * HT-29 c * Cancer encyclo (CCLE)

Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
	Ellagic Acid 	**Bilberry**	**Glucuronidation O-methylation**	**Peonidin-3-galactoside**	* Reduces the expression of proinflammatory cytokines * Reduces inflammation and tumor development * Inhibits cellular proliferation * Inhibits the formation of colonic ACFs * Suppresses the activity of topoisomerase I and II which reduces DNA damage * Induces cellular apoptosis through NF-κB inhibition * Protective activities against colorectal cancer	* Female Balb/c mice	* Intraepit neoplas * HCT-11 line

Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
Organosulfur Compounds					* Inactivates NF-κB localization by inhibiting glycogen synthase kinase 3 (GSK-3) which prevent colitis-induced colorectal cancer * Suppresses cellular proliferation and tumor growth * Induces colon cancer cell apoptosis * Anticancer activity against colorectal cancer through the modulation of epithelial growth factor receptor (EGFR) * Activates antioxidative transcriptor Nrf2		
	Allicin 	**Garlic**	**Oxidation Hydrolysis**	**Allyl methyl sulfide (AMS)** **Allyl methyl sulfoxide (AMSO)** **Allyl methyl sulfone ($AMSO_2$)**		* Xenograft nude mice	* HCT-11 line
	Allyl propyl disulfide 	**Onion**	**Reduction**	**Quercetin 3,4'-diglucoside** **Quercetin 4'-glucoside**	* Reduces cellular proliferation * Reduces migration rate of cancer cells * Reduces tumor growth rate in colorectal cancer * Induces cellular apoptosis * Induces cell cycle arrest at G2/M phase		* Caco-2 * SW620

Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
	Asparagusic acid 	**Asparagus**	**Sulfation**	**Asparagus polysaccharide dimethyl sulfide**	* Cytotoxic effect against human colon cancer cell greater than 5-FU * Reduces cellular proliferation * Inhibits cell motility and cellular growth by targeting Rho GTPase signaling pathway * Induces intrinsic apoptosis through toll-like receptor 4 * Enhances the expression of BAX and Caspase 9		* HCT-11 line * Caco-2
	Sulforaphane 	**Broccoli, cabbage, Brussels sprout, and cauliflower**	**Hydrolysis**	**Thiocyanates Isothiocyanates Epithionitrile nitrile**	* Reduces the risk of adenomatous polyps * Prevents colorectal cancer through miRNA modulation * Protects against Barrett's esophagus * Induces apoptosis and cellular arrest * Induces detoxification enzymes * Cytoprotective effect through the induction of Nrf2 * Scavenges against free radicals		* Squamo carcinor

Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
Other Phytochemicals					* Inhibits cancer cell metastasis of gastrointestinal cancer * Inhibits colon cancer cell proliferation by downregulating ICAM1 expression		
	Pectin 	**Apples, plums, oranges, and gooseberries**	**Colonic fermentation**	**Butyrate**	* Induces apoptosis by downregulating Bcl-xL and Cyclin B * Modulates the expression of signature miRNA * Delivers oral drugs for colon cancer treatment	* BALB/c mice	* HCT116 * Caco-2
	Curcumin 	**Ginger**	**Hydrolysis**	**Curcumin glucuronide** **Curcumin sulfate**	* Suppresses tumor growth by suppressing PPARγ pathway * Prevents cellular proliferation * Induces cellular apoptosis * Upregulates the expression of Caspase-3, cytochrome C, and BAX		* Cancer like cells

Phytochemical Subclass	Phytochemical and Structure	Dietary Source	Conversion Reaction	Metabolites Produced	Mechanism of Action	Model Used	
						In Vivo	In Vitro
	p-Couramic acid 	**Navy beans**	**Hydrolysis**	**N-methylpipecolate 2-aminoadipate Piperidine Vanillate**	* Reduces oxidative stress * Reduces the number of colonic aberrant cypt foci * Anti-tumor activity against colorectal cancer * Increases the abundance of amino acids, phytochemicals, and lipids in stool * Induces cellular apoptosis * Inhibits cellular proliferation, cell cycle progression, and tumor growth * Decreases β-catenin and COX-2 in colon tumors * Increases the production of SCFAs	* FVB/N mice	
	Ferulic acid 	**Rice bran**	**Colonic fermentation**	**Tryptophan α-ketoglutarate γ-tocopherol/β-tocopherol γ-tocotrienol**	* Induces nitric oxide synthase expression, Caspase-3 activation, and NF-κB pathway * Induces cellular apoptosis and lipid peroxidation * Scavenges free radicals * Modifies the composition of intestinal microbiota	* APC (min) mice	* Caco-2 * HAT-29

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