Diet-Derived Phytochemicals Modulate the Gut Microbiome

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Diet-derived phytochemicals modulate microbiome that is found to offer significant protective effects against colorectal cancer (CRC). The person's lifestyle and the eating pattern have significant impacts on the CRC in a positive and/or negative way. Phytochemicals are a concoction of various bioactive compounds directing various cell signaling pathways that altered gut microbiota composition. This may support to destroy malignant cells with minor risks of emerging drug resistance. The effectiveness of CRC can be reduced by the use of various dietary phytochemicals or modulating microbiome that reduces or inverses the progression of a tumor, which could be promising and efficient in reducing the burden of CRC. Phytochemicals with modulation of gut microbiome continue to be auspicious investigations in CRC through noticeable anti-tumorigenic effects, which provides new openings for cancer inhibition and treatment.

Phytochemicals Gut microbiota modulation Eubiosis Colorectal cancer therapy

1. Gut microbiota

The microbiome is the main inhabitants in the human gut, comprises 100 trillion microbes with diverse actions that maintain the integrity of healthy colon [1]. Undigested dietary residues in the colonic lumen are the prime energy sources for the gut microbiota, which digest those dietary residues resulting in the formation of several active metabolites with favorable functions. Imbalance of gut microbiota or dysbiosis can lead to several pathologies, including infectious diseases, gastrointestinal cancers, inflammatory bowel disease, and even obesity and diabetes. Dysbiosis may cause chronic inflammation, recognized as one of the prime causes of CRC. Earlier, our publications have also summarized the functions of gut microbiota, particularly, short-chain fatty acid synthesis with their benefits to the hosts in regulating various diseases such as diabetes, cardiovascular diseases, and cancer [2-4]. Dietary interventions or the consumption of phytochemicals is the beneficial components, proved as effective in treating CRC [5-12]. Taken into the account, we aimed to review in-depth analysis of various diet-derived phytochemicals mediated gut microbiome and its role in CRC prevention and treatment.

Earlier studies suggested the gut microbiota (*Bacteroides fragilis*, *Escherichia coli* strain NC101, *Desulfovibrio, Helicobacter hepaticus*, *Clostridium ramosum*, Fusobacterium, Campylobacter*, Prevotella*, etc.) in humans play a significant role and alter the immune function through pro-carcinogenic markers resulting in the etiology of CRC [4]. Altering the immune system in the gut normally enhances tumor microhabitats, and inflammation, ensuing the CRC development [3]. In recent research has also recommended genetically reformed colon bacteria, which are beneficial and are currently employed in experimental cases that outcomes are promising [13]. Furthermore, they

can be greatly beneficial to the host as probiotics that inhibit CRC through alterations of microbiota and colon environment.

The consumption of natural products produces essential bioeffects in the body through multifaceted relations with gut microbiota [14,15]. Natural phytochemicals normally have fiber-rich glycosides that exist as complex molecules with the properties of lower bioavailability and lesser solubility [16]. The nature of the phytochemicals could be altered during microbial fermentation in the colon, ensuring high quantities of various byproducts with greater pharmacological activity [17]. Numerous metabolites that derived from gut microbiota may further be subject to various enzymatic cleavage by methylation, glucuronidation, glycination, or sulfation in the hepatocytes, which are then trafficked into the tissues and finally excreted into the gut [16,18]. Gut microbiota converts glucuronides to aglycones by β-glucuronidases, which can be immediately reabsorbed in the colon. Thus, the synthesis of microbial β-glucuronidase and its enterohepatic passage have possible steps to extend the holding period of phytochemicals in the host [16,18]. Rising data suggested the dietary phytometabolites derived from gut microbiota, which are capable of enhancing the bioavailability, antioxidant properties, detoxification of xenobiotics, and prebiotics function [18,19]. Furthermore, these compounds can eliminate gut pathogenic organisms, reduce oxidative DNA damage and pro-inflammatory mediators, and thus regulate normal cell division and apoptosis [20,21]. The effects of phytochemicals on gut microbiota and their anti-inflammatory effects are presented in **Table 1.**

Table 1. Effects of phytochemicals on gut microbiota and their anti-inflammatory effects.

Phytochemicals	Compounds	Model	Effect on gut microbiota	Anti-inflammatory effect	References
Anthocyanins	Anthocyanins	C57BL/6 J mice	Feces of gut microbiota-deficient mice showed an increase in anthocyanins and a decrease in their phenolic acid metabolites, while a corresponding increase was observed in jejunum tissue	Decreased the inflammatory status of mice	[22]
Anthocyanins	Anthocyanins	C57BL/6 J mice	Treatment modified the gut microbiota	Effectively reduced the	[23]

			composition	expression levels of IL-6 and TNFα genes, markedly increased SOD and GPx activity	
Catechins	Epigallocatechin-3-gallate	C57BL/6 J mice	The Firmicutes/Bacteroidetes ratio significantly lowered in HFD + EGCG, but higher in control diet + EGCG	Potential use for prevention, or therapy, for oxidative stress-induced health risks	[24]
Catechins	Epigallocatechin-3-gallate	C57BL/6 J mice	Maintained the microbial ecology balance and prevented dysbiosis	Suppressed the activation of NF-κB and decrease expression of iNOS	[25]
Catechins	Epigallocatechin-3-gallate	Wistar rats	Affected the growth of certain species of gut microbiota	Suppressed the activation of NF-κB	[26]
Catechins	Quercetin	C57BL/6 J mice	Increased Firmicutes/Bacteroidetes ratio and gram-negative bacteria and increased Helicobacter. Regulated gut microbiota balance	Reverted dysbiosis-mediated TLR-4, NF-κB signaling pathway activation, and related endotoxemia, with	[27]

				subsequent inhibition of inflammasome response and reticulum stress pathway activation	
Catechins	Quercetin	Wistar rats	Attenuated Firmicutes/Bacteroidetes ratio, inhibiting the growth of bacterial species associated with diet-induced obesity (Erysipelotrichaceae, Bacillus, *Eubacterium cylindroides*). Quercetin was effective in lessening high-fat sucrose diet-induced gut microbiota dysbiosis	Suppressed the activation of NF-κB	[28]
Catechins	Quercetin	Fischer 344 rats	Exerted prebiotic properties by decreased pH, increased butyrate production, and altered gut microbiota	Suppressed the activation of NF-κB	[29]
Catechins	Kaempferol	3 T3-L1 adipocytes	Treatment modified the gut microbiota composition	Reduced LPS pro-inflammatory action, promoted anti-inflammatory and antioxidant effects	[30]

Flavonones	Baicalein	C57BL/6 J mice	Firmicutes/Bacteroidetes ratio significantly lowered and regulated dysbiosis	Suppressed the activation of NF-κB and decreased the expression of iNOS and TGF-β	[31]
Organosulfur compounds	Garlic essential oil and Diallyl disulfide	C57BL/6 mice	Treatment modified the gut microbiota composition	Significantly decreased the release of pro-inflammatory cytokines in the liver, accompanied by elevated antioxidant capacity via inhibition of cytochrome P450 2E1 expression	[32]
Phenolic acid	Curcumin	Mice	A direct effect of bioactive metabolites reaching the adipose tissue rather than from changes in gut microbiota composition	Nutritional doses of *Curcuma longa* decreased proinflammatory cytokine expression in subcutaneous adipose tissue	[33]
Phenolic acid	Curcumin	LDLR−/− mice	Improved intestinal barrier function and prevented the	Significantly attenuated the Western diet-induced	[34]

			development of metabolic diseases	increase in plasma LPS levels	
Phenolic acid	Curcumin	Human IEC lines Caco-2 and HT-29	Modulated chronic inflammatory diseases by reducing intestinal barrier dysfunction despite poor bioavailability	Significantly attenuated LPS-induced secretion of master cytokine IL-1β from IEC and macrophages. Reduced IL-1β-induced activation of p38 MAPK in IEC and subsequent increase in the expression of myosin light-chain kinase	[35]
Polyphenols	Polyphenols	C57BL/6 J ApcMin mice	Bacterial diversity was higher in the bilberry group than in the other groups	Attenuation of inflammation in cloudberry-fed mice	[36]
Stilbenes	Resveratrol	Kunming mice	HF microbiomes were different from those in CT and HF-RES mice. After treatment, Lactobacillus and Bifidobacterium were significantly increased, whereas *Enterococcus faecalis* was significantly decreased, resulting in a	Decreased the inflammatory status of mice	[37]

			higher abundance of Bacteroidetes and a lower abundance of Firmicutes		
Stilbenes	Resveratrol	Glp1r−/− mice	Treatment modified the gut microbiota composition	Decreased the inflammatory status of mice	[38]
Stilbenes	Resveratrol	Wistar rats	Trans-resveratrol supplementation alone or in combination with quercetin scarcely modified the gut microbiota profile but acted at the intestinal level, altering mRNA expression of tight-junction proteins and inflammation-associated genes	Altered mRNA expression of tight-junction proteins and inflammation-associated genes	[28]
Stilbenes	Resveratrol	Adipocytes	Treatment modified the gut microbiota composition	Resveratrol opposed the effect induced by LPS, functioning as an ameliorating factor in disease state	[39]
Stilbenes	Resveratrol	Human	Steroid metabolism of the affected gut microbiota was studied	-	[40]

Stilbenes	Piceatannol	C57BL/6 mice	Altered the composition of the gut microbiota by increasing Firmicutes and Lactobacillus and decreasing Bacteroidetes	Decreased the inflammatory status of mice	[41]
Stilbenes	Piceatannol	Zucker obese rats	It did not modify the profusion of the most abundant phyla in gut microbiota, though slight changes were observed in the abundance of several Lactobacillus, Clostridium, and Bacteroides species belonging to Firmicutes and Bacteroidetes	Showed a tendency to reduce plasma LPS by 30%	[42]

Abbreviation: Caco-2—human epithelial colorectal adenocarcinoma cells; CT—control diet; EGCG—Epigallocatechin-3-gallate; GPx—glutathione peroxidase; HF-RES—high-fat diet supplemented with resveratrol; HFD—high-fat diet; IEC—intestinal epithelial cells; IL 6—interleukin 6; iNOS—inducible nitric oxide synthase; LPS—lipopolysaccharides; MAPK—mitogen-activated protein kinase; mRNA—messenger ribonucleic acids; NF-κB—nuclear factor kappa B; SOD—superoxide dismutase; TGF β—*transforming growth factor-beta;* TLR-4—toll-like receptor 4; TNFα—tumor necrosis factor-alpha; P450 2E1—cytochrome *P450 2E1*

2. Dietary Polyphenols

Polyphenols are one of the prime classes of chemicals in plants, extensively studied for their health-promoting properties [7-10,12,43-46]. Human diets contain varieties of polyphenols and have significant protective activities against various cancer types. Scavenging of free radicals and reducing oxidative stress are the key mechanisms by which a polyphenol can achieve [38]. Several studies confirmed the actions of polyphenols on CRC inhibition, which often interconnected with the relationship of gut microbiota [47-49]. For instance, an animal study was conducted related to cranberry polyphenols on *Akkermansia* (mucin-degrading bacterium), which protected the host from obesity, diabetes, and gut inflammation. In this study, the mice were administered with high fat and sugar diet and cranberry extract (CE) (200 mg/kg/day) for eight weeks, and the various gut microbiota were analyzed by the methods of 16S rRNA and 454 pyrosequencing. The outcomes of the study revealed the administration of CE reduced body weight, visceral fat obesity, triglyceride accumulation, and inflammation, and elevated antioxidant

properties and insulin sensitivity. Furthermore, the metagenomics study of CE treatment exhibited an increased percentage of *Akkermansia* [48].

The anti-carcinogenic properties of the gut microbiota are generally attributed based on the two properties, (a) either by improving the host's immune system or (b) by generating the metabolites, which can interfere with the pathways involving CRC formation. A study demonstrated that the presence of amines, bile acids, and high consumption of meat can reduce some bacterial growth such as *Clostridium,* which inhibits the development of CRC [49]. By using the alimentary metabolites, gut microbiota produces biologically active short-chain fatty acids. The *Rosburia faecis* and *Eubacterium rectale* group of bacteria can normally produce the butyrate, which involves reducing cell apoptosis and diversity [47]. A study showed the polyphenol metabolites modulated microbiota that directly restricted the growth/proliferation of CRC [50]. Another study has also related intestinal metabolites, quercetin, chlorogenic, and caffeic acids to interfering in cyclooxygenase-2 expression resulting in the prevention of DNA damage in the colon [51]. The polyphenols-mediated gut microbiota changes are a potential technique for inhibiting colon cancer, although insufficient trials have been piloted, in which, wine [52], blueberry [53], and cocoa [54] displayed a bifidogenic outcome.

3. Dietary Flavonoids

Flavonoids are mainly present in fruits, vegetables, seeds, and various beverages such as tea, coffee, and red wine. Several medicinal herbs are amongst the richest sources of flavonoids. They are grouped into the following sub-classes-flavonols (quercetin, rutin), flavanols (catechin, epicatechin, and epigallocatechin), flavones (luteolin, apigenin), anthocyanidins (malvidin, cyanidin, and delphinidin), isoflavones (daidzein, genistein, glycetin, and formanantine), and flavanones (naringenin, hesperetin) [55-58]. A hypothesis stated that the presence of beneficial phytochemicals in diets attributes an anticancer property to the respective food. The flavonoids present in the food prevent CRC development by exerting various mechanisms: alleviating DNA damage, reducing the effects of gene mutation, regulation of phase I, and phase II enzymes via modulation in cell signaling pathways, suppressing oncogene expression and regulating inflammatory responses [59-63]. In a recent clinical trial, a flavonoid mixture of 20 mg apigenin along with 20 mg epigallocatechin gallate was given to CRC patients daily for long-term interventions that showed the reduction of CRC relapse [64]. The greater quantities of polymeric flavonoids and the non-absorbed flavonoids passed into the colon region where they underwent breakdown and gut microbiota facilitate converting these flavonoids into simple phenolic acids [65].

The digestion of flavonoids is often mediated by gut microbiota, which is a similar pattern to other phytochemicals. Gut microbiota facilitates converting a large group of flavonoids into simple active metabolites (aromatic catabolites and small phenolic acids) by oxidation and demethylation [66,67]. These active products augment physiological activity and perform various roles in the regulation of the host's immune system. One best instance for the gut microbiota-mediated metabolite is daidzein-isoflavones, which serves various benefits to the host. Daidzein is found in numerous plants and predominantly occurs in soybeans; daidzein is transformed by bacterial flora into the most active compound equol. In vitro and clinical trials showed that equol is more bioactive than daidzein (food precursor), and the biological effect is significantly improved in patients who produced equol after isoflavone

consumption [68]. This result strongly suggested that gut microbiota aid a pivotal function in regulating the biological effects of ingested phytochemicals.

We recognize that the impacts of the gut bacterium on the flavonoids and the effects of flavonoids on the gut microbiota are bidirectional. Flavonoids can change the organization and roles of gut microbiota, and similarly, gut microbiota can enhance the flavonoid breakdown. A case pilot study with 178 elderly people showed the habitual diet, which contributed to bacterial alterations resulted in the improvement of frailty and inflammation [69]. Another fascinating study revealed that 15 women with a two-month dietary intervention connected to alterations of gut microbiota including, Gammaproteobacteria and Erysipelotrichi [70]. A study on the impacts of grape extract (GE) on experimental animals showed the reduction of the Firmicutes-to-Bacteroidetes ratio and an increasing of *Akkermansia muciniphila*. Supplementation of GE along with gut microbiota significantly reduced inflammatory response and improved insulin sensitivity. These findings offered noteworthy support in favor of colonic bacteria and their substantial role in facilitating the flavonoids on health impacts, which reduced inflammatory response as well as improved the metabolic function. Another interesting clinical study demonstrated that the feeding stable isotope-labeled anthocyanins were ingested by gut microbiota, which yielded high quantities of diverse active metabolites [1,71]. These colonic bioactive phytometabolites exert greater anti-inflammatory functions and maintain vascular integrity when compared to the normal colonic metabolites [72]. This statement complements the belief of the effect of increased activities of phytochemicals on host health, which are the utmost prospective study related to gut microbiota.

4. Phytochemicals modulate Gut microbiome that regulates Wnt/β-catenin signaling pathways

The initiation of colon tumorigenesis is frequently determined by mutations in the Wnt signaling. Wnt is generally a secreted signaling protein. Conversely, the loss of function of adenomatous polyposis coli or gain of function of *β*-catenin cause the balance of unrestricted β-catenin that provides abnormal Wnt signaling leads to tumorigenesis [73]. Notably, mutation triggering of the Wnt pathway in G-protein-coupled receptor ($Lgr5^+$) cells contributes to intestinal tumors with high competence than other colonic cell tumors [74]. According to the CSC hypothesis, the populace of colon cells can propagate tumor generation, measured as multipotent resulting in the cell of cancer [74,75]. Current data shows that multiple CSC hierarchies occur in the colon, facilitate cell fate in the account for various extrinsic factors including, diet, inflammation, and body anxiety [76]. Additionally, a function of diet in the maintenance of colon CSC has also described [77]. The Wnt signaling generally occurs in an upstream of the β-catenin pathway [78] (**Figure 1**). Briefly, Wnt ligands largely fix with the complex of Frizzled/LRP co-receptor, which triggers the canonical pathway. Axin, a Wnt signaling inhibitor protein is employed to the cell membrane, resulting in the inactivation of the adenomatous polyposis coli complex succeeding in the equilibrium of β-catenin. When Wnt is triggered, β-catenin is instantly soothed, allowing transfer to the nucleus and fixes with T cell factor and eventually elicits the expression of target genes. Among them, Leucine-rich repeat-containing $Lgr5^+$ genes participated in stem cell proliferation [79]. The adenomatous polyposis coli is normally a tumor-suppressor protein that is mutated in almost 80% of CRC. Thus, the stimulation of Wnt/*β*-catenin is a primary biomarker of colitis-related CRC [80]. Diet-derived phytochemicals balance the microbiome status (Eubiosis), which inhibits Wnt/*β*-catenin signaling pathways and successively prevent intestinal infection and inflammation [81,82].

Figure 1. Diet-derived phytochemicals stabilize the microbiome status (Eubiosis) that inhibit Wnt/*β*-catenin signaling pathways successively prevent intestinal infection and inflammation.

Gut microbiota is chiefly affected by the dietary phytochemicals that can disturb its physiological relations in the host [3]. Through their alimentary canal route, phytochemicals are digested by colonic bacteria and produce several by-products [14]. These phytochemicals are rich in various active principles comprising polyphenols and flavonoids that upsurge the *Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria*, which alters the pH of the colon environment and maintains the balance of the colonic microbiome [4]. Therefore, the effect of colonic bacteria on the dietary phytochemicals targeting dietary intervention which may contribute to host well-being [3,4]. The phytochemicals facilitate colonic bacteria, which may influence as adjuvants to treat cancer, obesity, diabetes, and chronic inflammatory diseases and prove as potentially prophylactics and candidates for the treatment of these diseases [2-4].

5. Concluding Remarks and Prospective

Several matters urgently require to explain before phytochemicals can be successfully transferred from bench to bed. Concerning the good source of bioactive compounds, the succeeding features ought to be measured: (a) they acquire directly from dietary or pharmacological sources (b) can be employed alone or combined with other existing medicine (c) bioavailability and optimization of the individual bioactive compound, which impacts on gut

microbiota (d) require adequate clinical trials based on the underlying gastrointestinal inflammatory conditions. (e) Standardize the feasible nutraceutical preparations (methodology and chemical composition) (f) the dosage fixation and route of infusion of the drugs. The existing cumulative data associated with in vitro and animal studies that strongly propose the promising effects of the wide spectrum of phytochemicals related to various gut-associated disease conditions. However, it remains inadequate to achieve in the human trials due to lacking validation of phytochemicals on the gut microbiome. More investigations are highly recommended to focus on the analysis of different diet-derived phytochemicals metabolized by gut microbiota and their impacts on human health. Nevertheless, dietary phytochemicals and their analogs modulate gut microbiota, which can be offered the advancement of better quality drugs and provide the resolution to eradicate various gut-associated diseases. Dietary phytochemicals induced gut microbiota is continued to be an encouraging and dynamic research niche in the upcoming days with evident anti-tumorigenesis effects and propose novel opportunities for CRC prevention and treatment.

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