Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/17/20240627

Flavonoids and the gut microbiota: A promising frontier for colorectal cancer prevention and intervention

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Abstract. Colorectal cancer (CRC) is a formidable global health challenge, with increasing incidence rates and significant mortality. Flavonoids, known for their antioxidant properties, a class of polyphenolic compounds found in various dietary sources, exert multifaceted effects on gut microbiota composition, short-chain fatty acids (SCFAs) production, inflammation mitigation, and gut barrier enhancement. Moreover, they demonstrate promise in countering DNA damage induced by microbial toxins and modulating metabolic processes. Animal studies and clinical trials revealed changes in gut microbiota composition in CRC. However, the translational application of flavonoids to treat CRC through modifying gut microbiota requires further research. This review paper delves into the intricate relationship between flavonoids, and gut microbiota, with a particular focus on their potential in CRC prevention. This paper discusses the complex mechanisms through which flavonoids influence CRC development and highlights their potential in shaping dietary strategies for cancer prevention. In the midst of the rising CRC burden, flavonoids offer a hopeful link between dietary choices and improved health outcomes, paving the way for a healthier, cancer-free future.

Keywords: Flavonoids, Gut Microbiota, Colorectal Cancer.

1. Introduction

Colorectal cancer, identified as colon cancer or rectal cancer, originates in the colon or rectum, components of the digestive system. Its inception often traces back to the growth of abnormal cells called polyps along the colon or rectum's inner lining. With time, some of these polyps may undergo a malignant transformation. This once seldom-seen cancer is now the fourth most fatal globally, resulting in almost 900,000 deaths each year [1]. Several factors, including an aging population, unhealthy dietary practices, obesity, physical inactivity, and smoking, elevate the risk of its occurrence. While advancements in comprehension and treatment have enhanced survival rates, the most essential point lies in early detection. Colorectal cancer constitutes roughly 10% of cancer cases worldwide, with more substantial prevalence in developed nations. Though screening and lifestyle modifications have curbed or reversed the trend in these countries, a disconcerting surge in cases among individuals under 50, particularly involving rectal and left-sided colon cancer, poses a partially unexplained challenge [2].

Flavonoids, a class of polyphenolic compounds found in plants, have a vital role in shielding against various threats, including ultraviolet radiation, microbes, and oxidative stress [3]. These compounds adhere to a specific carbon structure delineated by the International Union for Pure and Applied Chemistry [4], characterized by three rings (C6-C3-C6) adorned with different molecular substitutions.

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Impressively, the world of flavonoids encompasses over 10,000 distinct compounds, organized into subcategories like flavanols, flavanones, flavonols, flavones, and anthocyanins. Additionally, some references consider isoflavones as part of this group. Flavonoids are prominently present in a wide range of dietary plants and herbs, including citrus fruits, green tea, and grapes [5]. Scientific investigations have unveiled their potential to bestow various health benefits, spanning from anticancer properties to antihypertensive and antithrombotic effects. Particularly intriguing is their capacity to combat cancer, which is closely associated with their ability to influence oxidative stress.

The progress in sequencing technology has brought to light the crucial involvement of these microorganisms in both cancer development and its treatment. It underscores the possibility of adjusting the composition of the gut microbiota to amplify the efficacy of cancer therapies. This potential arises from the interplay between gut microbes, the environment, and different cancer treatments, including immunotherapy, chemotherapy, radiation therapy, and surgery [3]. Microbes contribute to cancer development in several ways. When the delicate balance of microorganisms in the gastrointestinal tract is disrupted, leading to a less stable and more pathogenic microbiota, it results in a condition known as gut dysbiosis. This can adversely affect the host's physiological processes, potentially contributing to various health issues, including cancer. Microbes can influence cancer through various mechanisms. One approach is through contact-dependent effects, which occur locally at mucosal surfaces or within the tumor microenvironment (TME). Another avenue is contact-independent effects, where harmful microbial molecules, such as lipoteichoic acid (LTA) and deoxycholic acid (DCA), enter the bloodstream through capillaries. This can facilitate cancer development in distant areas or promote cancer progression by compromising the host's antitumor immunity. In summary, microbes play a complex role in cancer development, impacting it through various dimensions and mechanisms, both locally and systemically.

This paper focuses on the influence of flavonoids on gut microbiota and their potential in colorectal cancer prevention. It introduces flavonoids, found in foods like citrus fruits, green tea, and cacao, emphasizing their well-known antioxidant properties. The paper explores how flavonoids possess the capability to combat reactive oxygen species (ROS) and inhibit ROS-generating enzymes, showcasing their potential in preventing and treating cancer. It further underscores their role in shaping the composition of gut microbiota, stimulating beneficial short-chain fatty acids (SCFAs) production, reducing inflammation, and strengthening the integrity of the gut barrier. The paper also discusses the significance of gut microbiota in colorectal cancer, including the association between specific microorganisms and CRC.

2. Modulation of gut microbiota by flavonoids

A striking facet of flavonoids' interaction with gut microbiota is their capacity to influence microbial composition. Investigations reveal that specific flavonoids present in apples, tea, and red wine, among others, stimulate the proliferation of beneficial bacteria, including *Bifidobacteria* and *Lactobacilli*, while concurrently inhibiting the growth of potentially harmful pathogens. These alterations in microbial composition contribute to a healthier gut milieu, which, in turn, is associated with a reduced risk of colorectal cancer [6].

2.1. SCFAs production

Flavonoids exert a compelling impact on gut microbiota by promoting the production of short-chain SCFAs. SCFAs, which encompass butyrate, propionate, and acetate, emerge as metabolic byproducts of bacterial fermentation within the colon. Their established role in preserving gut health aligns with a reduced risk of colorectal cancer when they are present. Flavonoids serve as substrates for specific gut bacteria, instigating increased SCFA production. Notably, butyrate, in particular, garners attention for its ability to inhibit the growth of colorectal cancer cells and facilitate apoptosis [6].

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2.2. Anti-inflammatory effects

Chronic inflammation stands as a recognized contributor to colorectal cancer development. In this context, flavonoids unveil their anti-inflammatory capabilities, partially attributable to their influence on gut microbiota. By modulating the composition of gut microbiota and promoting the growth of anti-inflammatory bacteria, flavonoids cultivate an environment that mitigates chronic inflammation, thus diminishing the risk of colorectal cancer [6].

2.3. Enhancement of gut barrier function

The integrity of the gut barrier assumes paramount importance in preventing the translocation of harmful substances and pathogens into systemic circulation. Flavonoids make substantial contributions to this defense mechanism by supporting the proliferation of mucus-producing goblet cells and augmenting the expression of tight junction proteins. Collectively, these effects fortify the health of the gut lining, thereby minimizing the risk of inflammation-associated colorectal cancer [6].

To summarize, the intricate interplay between flavonoids and gut microbiota emerges as a pivotal component in colorectal cancer prevention. Flavonoids' capacity to modulate microbial composition, stimulate SCFA production, mitigate inflammation, and enhance gut barrier function constitutes a robust arsenal for reducing the risk of colorectal cancer. While extant research has shed light on these interactions, further investigations are warranted to dissect specific molecular mechanisms and establish precise dietary recommendations that harness the potential of flavonoids in colorectal cancer prevention. Nevertheless, the current body of evidence underscores the importance of integrating flavonoid-rich foods into one's diet as a natural, accessible strategy for diminishing the risk of colorectal cancer (table 1) [6].

Table 1. Common dietary flavonoids and their potential health benefits.

Flavonoid Type	Food Sources	Potential Health Benefits
Flavanols	Green tea, dark chocolate, apples	Antioxidant properties, cardiovascular health support
Flavanones	Citrus fruits (e.g., oranges, lemons)	Anti-inflammatory, immune system support
Flavonols	Onions, kale, broccoli, apples	Anti-cancer, anti-inflammatory, neuroprotective
Flavones	Parsley, celery, chamomile tea	Antioxidant, anti-inflammatory, allergy relief
Anthocyanins	Berries (e.g., blueberries, strawberries)	Anti-aging, cognitive function, heart health
Isoflavones	Soy products (e.g., tofu, soybeans)	Hormone regulation, bone health, menopausal relief

2.4. Role of flavonoids on TME

In recent years, the spotlight has turned toward microorganisms as substantial contributors to cancer biology, contributing to over 15% of newly diagnosed cancer cases, including gastric, hepatocellular, and cervical cancers. Inside the TME, a microbial community recognized as the microbiota has garnered significant acknowledgment as an indispensable environmental factor in various cancers, particularly CRC. This complex relationship springs from extensive interactions between the colorectum and myriad microorganisms, wielding considerable influence over gastrointestinal physiology and immune function. Furthermore, perturbations in the relative abundance of gut microbiota have demonstrated links to a range of conditions, spanning from cardiovascular and metabolic diseases to neuropsychiatric disorders and inflammatory bowel disease [6]. Contemporary research efforts have increasingly zoomed in on the gut microbiota's role in the genesis of colorectal cancer, embarking on mechanistic investigations

DOI: 10.54254/2753-8818/17/20240627

through both animal and human studies. This section will plunge into the interplay between gut microbiota and CRC, embarking on a quest to explore potential clinical applications while shedding light on key mechanistic insights [6].

2.5. Other microbial realms in CRC

The microbiota present in CRC transcends beyond the boundaries of bacteria alone; it encompasses viruses and fungi. Research has shed light on the presence of cytomegalovirus, John Cunningham (JC) virus, human papillomavirus, and alterations within enteric viromes in CRC samples. These findings have hinted at intricate microbial interactions that bridge different kingdoms, such as correlations between bacteriophages and the loss of oral bacteria, as well as fungi-bacteria co-exclusive correlations observed in CRC [7].

2.6. Gut microbiota in colorectal adenoma

Colorectal adenomas, which serve as precursors to the majority of CRC cases, also exhibit distinct profiles of microbiota. These studies have unveiled global shifts in composition, heightened ecological richness, and changes in microbial taxonomies, notably featuring an overabundance of Fusobacterium [7]. Specific bacterial species, including *Fusobacterium nucleatum* and *Solobacterium moorei*, as well as fungal phyla like Basidiomycota, demonstrate shifts in abundance linked to various stages of adenoma development. These alterations in the microbiota hold promise as potential biomarkers for the early detection of adenomatous lesions [7].

3. Effects of flavonoids on CRC through regulating gut microbiota

3.1. Mechanisms underpinning carcinogenesis

The intricate process of colorectal carcinogenesis entails numerous mechanisms that are influenced by genetic and environmental factors. Microbiota-associated components play pivotal roles in navigating this intricate path [7].

Chronic inflammation, a well-established risk factor for CRC, particularly prevails in patients with inflammatory bowel disease. Several bacterial species, including Fusobacterium nucleatum and Bacteroides fragilis, have the capacity to induce pro-inflammatory responses in the gut, creating a milieu conducive to the progression of CRC. Pattern recognition receptors like Toll-like receptors and nucleotide-binding oligomerization-like receptors also come into play in the context of colitis-associated carcinogenesis [7].

The metabolic functions of the gut microbiota exert considerable influence on the risk of CRC. Dietary factors, such as red and processed meat, are firmly linked to CRC risk. Some dietary components, such as dietary fiber and resistant starch, undergo fermentation by gut bacteria, giving rise to SCFAs, which can wield both anti-inflammatory and pro-inflammatory effects, contingent upon the context. Bile acids, originating from the liver and undergoing metabolic transformations by gut bacteria, also bear a connection to the risk of CRC [7].

Specific bacteria, including Escherichia and Campylobacter species, have the capability to produce genotoxins like cryptolectal distending toxin (CDT) and colibactin, which possess the potential to instigate DNA damage and heighten the risk of CRC. Toxins from B. fragilis and ROS emanating from *E. faecalis* are likewise associated with DNA damage and genomic instability. Strategies aimed at inhibiting the production of these toxins or therapeutically targeting them hold promise for the prevention and treatment of CRC [7].

The intricate web of factors contributing to CRC development encompasses a myriad of environmental, genetic, and epigenetic elements. Recent years have cast the spotlight on the gut microbiota as an integral environmental player in the complex pathogenesis of CRC. Investigating the nuanced alterations within the gut microbiota and its intricate relationship with CRC development has risen to the forefront of research endeavors. The potential influence of flavonoids in modulating several mechanisms includes controlling DNA damage, regulating metabolism, and signaling pathways [7].

DOI: 10.54254/2753-8818/17/20240627

3.2. Antioxidant effects

ROS, highly reactive oxygen-containing molecules generated within cellular organelles including mitochondria, peroxisomes, and the endoplasmic reticulum, play a dual role in cancer progression. On one hand, they can inflict DNA damage, promote mutagenesis, and initiate metabolic shifts conducive to carcinogenesis. On the other hand, an excess of ROS can trigger anti-cancer mechanisms, leading to cell cycle arrest and cell death through apoptosis, autophagy, and necroptosis.

More specifically, flavonoids structural attributes, marked by the presence of hydroxyl groups on ring B and a 2,3-double bond combined with the 4-oxo functionality, equip flavonoids to counteract a spectrum of ROS such as hydroxyl, peroxyl, and peroxynitrite radicals (figure 1) [6]. This counteraction involves intricate one-electron transfer reactions influenced by factors like the arrangement and quantity of hydroxyl groups, the existence of catechol moieties, glycosylation, and methylation [6]. Furthermore, flavonoids impede ROS-generating enzymes like xanthine oxidase, cyclooxygenase (COX), and NADPH oxidase (NOX) through molecular interactions, with hydroxyl groups at precise positions and the 2,3-double bond in ring C playing pivotal roles. Their ability to chelate trace metals such as iron and copper, fundamental to ROS production, also depends on specific structural attributes that enhance their chelation capacity [6].

The therapeutic potential of regulating ROS, particularly through natural products like flavonoids, holds immense promise in cancer treatment. Intriguingly, this promise aligns with the dietary habits of populations consuming a diet rich in fruits and vegetables, which inversely correlates with cancer incidence and progression. Flavonoids, owing to their multifaceted antioxidant properties, have thus garnered substantial attention as agents capable of modulating oxidative stress—a foundational factor in cancer prevention and treatment [6].

In recent years, intensified research has delved into the intricate interplay between flavonoids and gut microbiota, with a particular focus on colorectal cancer prevention. Emerging evidence paints a multifaceted picture of how flavonoids shape gut microbiota to exert protective effects [6].

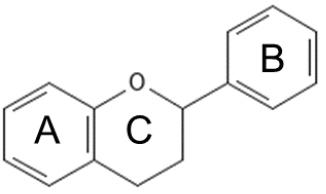

Figure 1. Chemical structures of flavonoid. Modified from [3]. Figure credit: original.

3.3. DNA damage

A pivotal mechanism by which the gut microbiota contributes to CRC revolves around the induction of DNA damage. Toxins derived from bacteria, such as colibactin produced by members of the Enterobacteriaceae family, have the capacity to directly inflict DNA damage, initiating a cascade of oncogenic mutations that serve as the genesis of colorectal carcinogenesis. Within this context, flavonoids, abundantly present in various dietary sources, showcase their antioxidant prowess, potentially countering the genotoxic effects of these bacterial toxins. Unraveling the mechanisms through which flavonoids may mitigate DNA damage induced by toxins from the gut microbiota stands as a vital avenue of research [7].

3.4. Metabolism

The gut microbiota is a prolific generator of diverse metabolites that play pivotal roles in the etiology of CRC. Flavonoids, in their multifaceted role, may exert influence over the metabolism of the gut microbiota and the subsequent production of metabolites. Notably, flavonoids may play a role in modulating the production of SCFAs, a group of compounds known for their dualistic nature, possessing both anti-inflammatory and pro-inflammatory effects. Dissecting how flavonoids impact the production

DOI: 10.54254/2753-8818/17/20240627

of metabolites linked to CRC risk holds paramount importance in elucidating their contribution to cancer prevention [7].

3.5. Regulation of signaling pathways

The gut microbiota wields the power to influence signaling pathways intimately associated with cell proliferation, migration, and invasion—key players in the landscape of CRC development. Flavonoids, with their recognized potential to intervene in signaling pathways [8], including those entangled with inflammation and cancer, emerge as intriguing subjects of investigation [9]. The quest to uncover whether flavonoids can modulate these pathways within the context of gut microbiota-driven CRC represents an area of compelling interest.

In summary, the intricate interplay between flavonoids and the gut microbiota emerges as a fertile field of exploration in the realm of CRC prevention. The antioxidant attributes of flavonoids, coupled with their potential to shape the metabolism of gut microbiota and regulate critical signaling pathways, position them as captivating candidates for further scrutiny. The endeavor to unravel how flavonoids might mitigate the impact of gut microbiota on CRC development promises valuable insights into dietary strategies for cancer prevention. The need for further research to delve deeper into these intricate interactions remains imperative [9].

4. Translational applications

4.1. Translational applications

The gut microbiota is progressively being recognized as a potential treasure trove for applications related to CRC. It presents the potential to serve as a biomarker for screening, diagnosing, and prognosticating CRC. Fecal markers, encompassing microbial gene markers and specific bacterial abundances, such as *F. nucleatum*, show promise in distinguishing CRC patients from healthy individuals and detecting adenomas. Moreover, markers present within the oral microbiota and blood, such as *S. gallolyticus*, are undergoing exploration for their diagnostic utility. Furthermore, microbial metabolites present in fecal extracts, including SCFAs and bile acids, may serve as promising markers for CRC screening [7].

Beyond diagnostic applications, the influence of the gut microbiota extends to the efficacy and toxicity of cancer treatments, spanning chemotherapy and immunotherapy. Modulating the gut microbiota holds the potential as a strategy for enhancing the outcomes of cancer treatment while mitigating adverse effects. Nevertheless, these approaches remain in the early stages of development and require further investigation [7].

4.2. Therapeutic implications for immunotherapy

Immunotherapy has risen to prominence as a cornerstone of cancer treatment, effectively targeting a spectrum of cancer types. Central to this approach are immune checkpoint inhibitors, which dismantle inhibitory signals, thereby empowering tumor-reactive immune responses [7].

4.3. Animal studies

The notion of microorganisms contributing to CRC is far from recent revelation. Studies conducted on animals in the 1960s dropped the first breadcrumbs pointing toward their involvement in CRC development. Impressively, these studies unveiled that intestinal microorganism played a pivotal role in mediating the carcinogenic effects of compounds such as cycasin in conventional rats. Astonishingly, when exposed to the same carcinogen, germ-free rats predominantly remained resistant to the development of tumors [6].

Distinct microbial species, encompassing the likes of Escherichia, Enterococcus, Bacteroides, and Clostridium, came under suspicion for promoting colorectal carcinogenesis in these animal models [10]. Additionally, compelling evidence emerged when stool samples obtained from CRC patients were transplanted into mice, leading to a surge in intestinal cell proliferation in germ-free mice and fostering

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tumor formation in conventional mice, unequivocally underscoring the influential role of microorganisms in the pathogenesis of CRC.

4.4. Clinical trials

Building upon the insights gleaned from animal studies, human research has embraced a metagenomic or metataxonomic approach to unveil the contribution of gut microbiota to CRC. This body of work has unveiled striking disparities between the microbiota residing within CRC patients and that found in healthy individuals [10].

The microbiota associated with CRC manifests higher species richness, a depletion of protective taxa, exemplified by the likes of *Roseburia*, and augmentation of pro-carcinogenic taxa, featuring *Bacteroides*, *Escherichia*, *Fusobacterium*, and *Porphyromonas* [7]. This revelation not only accentuates the shifts in microbial composition but also accentuates the functional significance of this microbial community in the progression of carcinogenesis [7].

Furthermore, researchers have homed in on a potential core group of carcinogenic microorganisms consistently present in CRC, irrespective of population or geographical location. This core comprises species such as *Bacteroides fragilis, Fusobacterium nucleatum, Parvimonas micra, Porphyromonas asaccharolytica, Prevotella intermedia, Alistipes finegoldii,* and *Thermanaerovibrio acidaminovorans* [7].

5. Conclusion

In conclusion, the intricate relationship between flavonoids and the gut microbiota within the context of colorectal cancer offers a promising pathway for prevention and intervention. Colorectal cancer's global significance emphasizes the pressing need to explore innovative approaches. Flavonoids, widely present in various dietary sources, exert a multifaceted influence on the gut microbiota. They shape the composition of microbial communities by fostering the growth of beneficial bacteria while inhibiting the proliferation of detrimental pathogens. They also stimulate the production of beneficial short-chain fatty acids and possess essential anti-inflammatory properties, crucial for combating chronic inflammation—a well-established cancer risk factor. Additionally, flavonoids fortify the integrity of the gut barrier, thereby reinforcing the overall health of the gastrointestinal tract. Furthermore, these compounds exhibit potential in mitigating the DNA damage caused by bacterial toxins and in altering the gut microbiota's metabolic processes, thereby impacting metabolites associated with cancer risk. Moreover, flavonoids have the capacity to intervene in crucial cell signaling pathways that play a pivotal role in cell proliferation and inflammation. While current evidence underscores the significance of incorporating flavonoid-rich foods into one's diet to prevent colorectal cancer, further research is essential to unravel the precise mechanisms involved and explore potential treatment applications, particularly in conjunction with emerging therapies like immunotherapy. In the face of the escalating burden of colorectal cancer worldwide, flavonoids provide a ray of hope—a link between dietary choices and the prospect of improved health outcomes. As ongoing research advances, flavonoids stand out as promising agents for reducing the risk of colorectal cancer, thus contributing to a healthier and cancer-free future.

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