

## A Contemporary Review of Prebiotics in Colorectal Cancer

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### Abstract

**Introduction:** The concept of prebiotics was first introduced by Glenn Gibson and Marcel Roberfreud in June 1995. prebiotics include non-digestible food substances that help improve the health of the host by stimulating the growth and activity of specific bacteria in the large intestine. Colorectal cancer (CRC) is a significant global health concern, necessitating innovative strategies for prevention and treatment. This contemporary review examines the role of prebiotics in CRC management, focusing on their potential to modulate gut microbiota, enhance immune responses, and reduce inflammation. Prebiotics, dietary fibers that promote the growth of beneficial gut bacteria, may play a crucial role in maintaining gut health and preventing tumorigenesis.

**Methods:** We analyze recent studies that highlight the mechanisms by which prebiotics exert their effects, including the production of short-chain fatty acids (SCFAs) and their impact on cellular signaling pathways. Additionally, we explore the synergistic potential of prebiotics when combined with conventional therapies, assessing their role in improving treatment outcomes and mitigating side effects.

**Results:** This review aims to provide a comprehensive understanding of the current evidence regarding prebiotics in the context of colorectal cancer, emphasizing their potential as a complementary approach in CRC prevention and therapy.

**Conclusion:** Future research directions are suggested to further elucidate the clinical applications of prebiotics in CRC management.

**Keywords:** CRC, Tumorigenesis, Prebiotics, Microbiota, Dietary fibers.

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### Introduction

The concept of prebiotics was first introduced by Glenn Gibson and Marcel Roberfreud in June 1995. Prebiotics include non-digestible food substances that help improve the health of the host by stimulating the growth and activity of specific bacteria in the large intestine. Since then, the definition of prebiotics has changed continuously and there is still no clear consensus among different bodies. In 2007, the Food and Agriculture Organization of the United Nations described prebiotics as non-digestible food components that contribute to host health and microbiota modulation.<sup>1</sup> Also, this year, the market of prebiotics included more than 400 food products, and today the number of these products has reached more than 1300. There are different definitions for prebiotics, the most recent of which is from the International Scientific Association of Probiotics and Prebiotics. According to this definition, prebiotics are

substrates that are selectively used by host microorganisms and are beneficial to health.<sup>2</sup> The World Digestive Organization also considers prebiotics to be live microorganisms that are used in various products and help maintain the body's natural microflora. The concept of prebiotics is evolving and the Roberfroid criteria for their definition are widely accepted. These criteria include lack of hydrolysis and absorption in the upper gastrointestinal tract, being selective for beneficial bacteria in the colon, altering the colonic flora in favor of a healthier composition, and inducing beneficial effects on the health of the host. Roberfroid also identified fructo-oligosaccharides, inulin, and galacto-oligosaccharides as "true" prebiotics. Finally, a prebiotic must meet three main criteria: resistance to hydrolysis and absorption, selective growth or activity in the gut, and fermentation by gut flora.<sup>3</sup> In June 2018, the FDA identified eight non-

digestible carbohydrates as dietary fiber. Among these fibers, inulin fructans and galacto-oligosaccharide (GOS) have been accepted as prebiotics recognized by the scientific community. Mysonhimer et al. conducted clinical trials on the tolerance and side effects of these carbohydrates. The results showed that inulin and GOS are well tolerated up to 5 grams and 20 grams, respectively. Mixed cell wall beta-glucans are not well tolerated at doses as low as 3 g, while pectin is well tolerated up to 36 g. Arabinoxylan (up to 15.1 g), alginate (up to 3.75 g), polydextrose (up to 12 g), and maltodextrin/resistant dextrin (up to 12 g) are well tolerated. Higher doses often lead to the side effects of bloating and diarrhea, but doses in the right range help maintain healthy stool viscosity and bowel frequency.<sup>4</sup>

### Methods

Recent studies that highlight the mechanisms by which prebiotics exert their effects, including the production of short-chain fatty acids (SCFAs) and their impact on cellular signaling pathways were analyzed. Additionally, the synergistic potential of prebiotics when combined with conventional therapies, assessing their role in improving treatment outcomes and mitigating side effects were explore.

### Prebiotics

The prevalence of prebiotics and the reasons for their use are increasing rapidly due to the importance of gut microbiota diversity in society's health. The use of prebiotics and probiotics in the United States quadrupled from 2007 to 2012, becoming the third most commonly used dietary supplement. This growth is due to increasing consumer awareness of the health benefits of prebiotics and their use in the food industry. The consumption of prebiotics is related to the modulation of the intestinal microbial population, and probiotic bacteria produce short-chain fatty acids, vitamins, and help in the metabolism of drugs.<sup>5</sup> Their immune effects are also being researched and have been shown to stimulate the production of immunoglobulin A and anti-inflammatory cytokines. The composition of intestinal flora has a direct effect on the growth of pathogenic bacteria. Probiotic microbes compete with pathogens and some of them can kill pathogenic bacteria. It is important to maintain the balance of microbiota. The simultaneous consumption of prebiotics and probiotics acts as a source of energy for living microorganisms and facilitates their reproduction. This combination is known as synbiotics and is defined as a mixture of living microorganisms and substrates that are selectively used by host microorganisms.<sup>6</sup> Synbiotics help the growth of beneficial microorganisms in the gut and can be divided into two categories: synergistic and complementary. In vivo studies have shown that

synbiotics have anticarcinogenic and antimutagenic properties. These benefits are related to stimulation of beneficial bacteria, production of SCFAs, regulation of nutrient absorption, and modification of the immune response.<sup>7</sup> Studies have shown that the consumption of date fruit, which contains oligosaccharides and polyphenols, has great effects on the intestinal microbiota of healthy people, also, the polyphenols in these fruits prevent the proliferation of cancer cells. These food sources have been noted for their nutritional and colon cancer-fighting properties. Supplements are regulated by the FDA under the DSHEA Act, but their safety and efficacy are not tested before they go on the market, and minor side effects such as cramping, nausea, and bloating may occur.<sup>8</sup>

### Colorectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer death in the United States and the third most common type of cancer worldwide. Despite advances in screening and treatment, an estimated 52,980 people in the United States died from the disease in 2021. Screening is recommended for people with inflammatory bowel disease, Lynch syndrome, or a family history of CRC after age 50 or earlier. In the last 40 years, the overall incidence of CRC has decreased, but in people under 55 years of age, the incidence of the disease has increased by 9%. The exact cause of this trend is unclear, but factors such as processed foods, obesity, and toxins from alcohol and tobacco may play a role.<sup>9</sup> Also, research shows that dairy products and beef may contain viral DNA particles that play a role in causing cancer. With the new changes, it is necessary to re-evaluate CRC screening criteria. Colonoscopy is known as the best screening tool and in addition to diagnosis, it also provides the possibility of polyp removal and sampling. There are other tests, such as blood tests to detect SEPT9 gene mutations and stool samples to detect blood, but these tests cannot replace a colonoscopy. Normally, cell division and reproduction are under strict controls, but cancer occurs when abnormal cells escape these controls and multiply uncontrollably.<sup>10</sup> In CRC, polyps form in the lining of the colon or rectum. Adenomatous polyps, which account for 96% of colorectal cancers, are detected when they are non-malignant. Hyperplastic and inflammatory polyps are also usually benign. Polyps originate from the inner lining of the intestine, and abnormal cells in them may become cancerous and grow into other layers. Disease progression is classified according to the TNM staging system, which includes tumor size, spread to lymph nodes, and the presence of metastasis. Disturbances in gene regulation play a role in CRC carcinogenesis, and studies have been conducted on the effect of prebiotics on the expression of genes associated with programmed cell death

(apoptosis).<sup>11</sup> BCL-2 and Bax genes play a role in this process, and caspases and Survivin also help to regulate apoptosis. As one of the main regulators of the cell cycle, p53 protein helps suppress tumor formation by regulating cell death and cell arrest at G1 and G2 checkpoints. In cancer treatment, the goal is to increase cell death and decrease apoptosis inhibitors in cancer cells. Risk factors for colorectal cancer include modifiable factors such as physical inactivity, smoking, and alcohol consumption, as well as nonmodifiable factors such as race and family history. Exercise and a diet rich in fruits, vegetables and whole grains prevent cancer due to increased fiber consumption.<sup>12</sup> Currently, known prebiotics include inulin, FOS, oligofructose, and GOS, which are classified as fibers and are not absorbed or digested in the small intestine. Inulin, FOS and oligofructose are known as fructans and GOS are known as galactans. Also, new types of prebiotics such as protein-oligosaccharide combinations, human milk oligosaccharides and non-carbohydrate molecules such as polyphenols and lipids have been identified to promote the growth of beneficial bacteria. Fructans are oligosaccharides that are mainly composed of fructose units and are resistant to human digestive enzymes due to beta bonds. This group includes inulin, FOS and oligofructose prebiotics. Inulin has the longest chain with 3 to 60 fructose monomers, and FOS and oligofructose have shorter chains, respectively. These prebiotics move through the digestive system and are fermented in the colon. Research has shown that these compounds can help improve problems such as constipation and weight loss, and are mainly fermented by bifidobacteria in the large intestine.<sup>13</sup> These microbes have enzymes to break beta bonds, and the byproducts of this process are short-chain fatty acids. Also, the use of inulin supplements has increased the growth of bifidobacteria in the human intestine.

Galactans are oligosaccharides composed of galactose and glucose and include GOS prebiotics. GOS is divided into two types: alpha-GOS (natural) and beta-GOS (synthetic). These prebiotics are resistant to digestion and are fermented by microbes in the large intestine. Bifidobacteria are known as the main consumers of GOS, and their consumption increases the population of the gut microbiome. Also, the number of lactobacilli increases after consuming GOS. Fructans and galactan prebiotics are available as isolated supplements or naturally in whole foods. Prebiotics are listed on supplement labels as "dietary fiber" or specific ingredients. These components include substances such as chicory root, garlic, onion and banana, which are known as prebiotics based on their inulin/FOS content. Alpha-GOS is found naturally in legumes and grains, while beta-GOS is produced through an enzymatic reaction with lactose and can be added to foods or taken as a

supplement.<sup>14</sup> Prebiotics are food sources with diverse nutritional benefits, but their dosage varies. Supplements allow fine-tuning of dosages and help consumers better evaluate their beneficial effects. Effective doses for FOS, inulin, and  $\beta$ -GOS are 10, 5-2.5, and 7 g/day, respectively, which increase bifidobacteria and SCFA in the colon. However, doses above 40 to 50 grams may cause side effects such as diarrhea and nausea. Also, side effects such as bloating and gas production are also common.<sup>15</sup> HMOs (human milk oligosaccharides) are a group of 200 carbohydrate compounds known as novel prebiotics that are abundant in human milk. These compounds are not digested in the digestive tract and reach the large intestine, where they shape the gut microbiota. HMOs are especially present in colostrum with a concentration of 20-25 g/L and decrease to 10-15 g/L in milk. These compounds help improve intestinal compliance and reduce the incidence of necrotizing enterocolitis in infants, and can also cover microbial pathogens and prevent infection and inflammation. HMOs are divided into three main categories, and their synthetic production technologies have led to industrial applications in foods and supplements. Some companies are developing HMOs. HMOs may be effective in the prevention or treatment of cancer and have shown anti-proliferative and growth-arresting effects in cancer cells. The mechanism of these effects is related to the interaction of HMOs with epidermal growth factor receptors and the activation of related signaling pathways.<sup>16</sup> HMOs support the growth of bifidobacteria (*B. infantis*) and lactobacilli, which metabolize HMOs and produce SCFA. One study showed that HMO consumption increased the growth of *B. infantis* in the microbiome of more adults and increased faecal butyrate levels. Also, in mouse models, *B. infantis* suppresses enteropathogens. Protein-oligosaccharides are one of the new classes of prebiotics that are created through covalent bonding of proteins to prebiotic fibers. These compounds can increase the bioavailability of proteins and act as an energy source for probiotic strains. Studies have shown that protein-oligosaccharide conjugates are resistant to gastrointestinal digestion and can promote the growth of beneficial bacteria. For example, one study showed that the conjugate of GOS and lactoferrin caused a two-fold increase in the growth of *Lactobacillus casei*.<sup>17</sup> Also, soy protein isolate with oligosaccharides has also had a positive effect on the growth of beneficial bacteria and the reduction of pathogenic bacteria. These compounds can be used as synbiotics to modulate the human microbiome, but there is a need for in vivo experiments to evaluate their effectiveness in the gut environment. Plant polyphenols have received attention due to their positive effects on the microbiome and gut health. These plant metabolites, which are resistant to degradation in the digestive system,

are not more than 90% absorbed and reach the large intestine to be processed by microbes. Studies have shown that polyphenols can stimulate the production of short-chain fatty acids (SCFA) by probiotic bacteria and also have antioxidant and anti-cancer effects. In particular, the polyphenol hydroxy afluor yellow A (HSYA) from the safflower plant has been shown in mice to prevent dysbiosis induced by a high-fat diet and reduce permeability by strengthening the intestinal barrier. Also, an increase in SCFA-producing bacteria has been observed in these mice.<sup>18</sup> In a preclinical study, Messaoudene et al identified the polyphenol castalagin in camu-camu berries as an anti-PD-1 immunotherapy enhancer. In this research, mice bearing sarcoma and breast cancer were treated with CC extract and anti-PD-1 antibodies. The results showed that the mice that received this combination had a significant reduction in tumor volume and a high correlation was observed between this treatment and the activation of CD8+ cytotoxic T cells in the tumors and spleen. Antitumor effects were specifically attributed to castalagin, and tumor size reduction was dependent on gut microbiome changes.<sup>19</sup> Also, treatment with castalagin increased the concentration of taurine-conjugated bile acids, which prevents colon adenoma. These findings indicate the influence of the gut microbiome on the efficacy of anti-PD-1 immunotherapy and suggest the need for further research in clinical models and other tumor types. SCFAs, which include acetate, butyrate, and propionate, are significantly associated with the fermentation of prebiotics by gut microbes and have positive effects on host metabolism and immunity. By lowering the pH of the intestinal lumen, SCFAs reduce the survival of enteropathogenic species and increase the proliferation of beneficial bacteria such as lactobacilli and bifidobacteria. This process can help reduce acute and chronic inflammation, thereby reducing DNA damage and the risk of CRC. Also, some pathogenic microbes may show specific responses to SCFAs that can lead to tissue damage, while others protect against inflammation by downregulating the expression of their invasive genes. SCFAs are also involved in modulating anti-inflammatory mechanisms and interacting with the host immune system.<sup>19</sup> The interaction between probiotic bacterial strains and intestinal epithelium and underlying immune cells is important. Immune cells such as dendritic cells sample the gut to recognize antigens, and these processes are influenced by Toll-like receptors and pattern recognition receptors. Microbial adhesion to the intestinal epithelium facilitates immune interactions and various immune responses are generated when pathogens attack the epithelium. These responses can lead to the production of inflammatory cytokines and chronic inflammation, possibly leading to the development of CRC. Studies

show that prebiotics in HMOs can act as adhesion inhibitors of microbial pathogens and prevent them from binding to host cells. By reducing the expression of TLR-4 and pattern recognition receptors, these compounds limit inflammatory responses and help maintain tolerance to gut microbes.<sup>20</sup> Prebiotics show anti-inflammatory activity by being converted to short chain fatty acids (SCFA) by probiotics. SCFAs, such as propionic and butyric acid, prevent the release of chemokines and adhesion of pathogens to the intestinal epithelium, and also reduce the production of inflammatory cytokines and increase anti-inflammatory cytokines. These acids bind to specific receptors in dendritic cells and activate the immune system. Dendritic cells help reduce inflammation by releasing IL-10 and IL-8 and stimulate B cells to produce IgA antibodies. However, the exact mechanism of these interactions and the effect of the microbiome on IgA secretion are still unclear.<sup>21</sup> Studies have shown that metabolites of probiotic bacteria, especially exopolysaccharides (EPSs), affect the growth of colon cancer cells. These metabolites act as antioxidants and can be effective in cancer treatment. EPSs have time-dependent anti-proliferative effects on colon cancer cells, and the effect of 48 and 72 hours on genes related to cell death is greater than that of 24 hours. Bcl-2 gene expression and Bax gene expression increase, which indicates the inability of Bcl-2. In inhibiting Bax and causing cell death. And the expression of caspase 3 and 9 increases and the expression of Survivin decreases.<sup>22</sup> The results of Qamar et al. for the treatment of aberrant crypt foci (ACF) of mice using 1,2-dimethylhydrazine dihydrochloride (DMH) or azoxymethane showed that treatment groups with galacto-oligosaccharides (GalOS) produced by *Limosilactobacillus reuteri*, against Weight gain caused by DMH shows resistance and prevents the occurrence of ACF in the colon, and it has been proven that CRC can be prevented in the early stages by using prebiotics. Also, in the results of Qamar et al., SCFAs were shown in higher concentrations in mice treated with prebiotics and caused changes in harmful bacterial enzymes. A lower content of nitroreductase,  $\beta$ -glucuronidase and azoreductase enzymes was observed in the GalOS and inulin-treated groups, while these enzymes increased with the high-beef diet.<sup>23</sup> Changes in the intestinal bacterial population have been investigated. Beneficial bacteria such as bifidobacteria and lactobacilli increased, while harmful bacteria such as clostridia decreased in the GalOS and inulin-treated groups. In one study, GalOS-Lu has been shown to decrease total body weight and increase cecum weight, which has been attributed to the stimulation of the bacterial population and the fermentation process. Changes in the intestinal microbiota also include an increase in Bacteroides and a decrease in Firmicutes, and the Bacteroides/Firmicutes

ratio is associated with obesity and type 2 diabetes. An increase in bacteria and a decrease in Firmicutes have been used as metabolic markers to identify healthy individuals. Fernandez et al observed a significant difference in the number of polyps between the control group and rats in the GalOS-Lu group. The GalOS-Lu group showed a 57.5% reduction in the number of polyps and a 50.4% reduction in the average tumor area.<sup>24</sup> A study by Lin et al investigated the effects of sprouted brown rice (GBR) prebiotics and *Lactobacillus acidophilus* and *Bifidobacterium animalis subsp lactis* on DMH- and DSS-treated rats. The results showed that the consumption of GBR alone or together with probiotics leads to an increase in the expression of pro-apoptotic proteins p53 and Bax and a decrease in the expression of Bcl-2. Also, the group that received the combination of GBR and *L. acidophilus* had the greatest inhibition in ACF formation. These results suggest that prebiotics in combination with probiotics may prevent the formation of colon cancer. Also, it was emphasized that the quality and selection of prebiotic products is important to achieve the best results.<sup>25</sup> A study by Milosevic and colleagues showed that the balance in mucins can influence the development of colorectal cancer. Also, research by Lin et al showed that the combination of GBR and probiotics significantly reduced the number of SiM-ACF, whereas GBR alone reduced the number of mucin-depleted foci. These results suggest that prebiotics can be used alone or in combination with probiotics to prevent the development of carcinogenesis. Also, treatment with DMH decreased the activity of the antioxidant enzyme SOD in colon cells, while the groups treated with GBR and probiotics showed a significant increase in SOD levels.<sup>26</sup> Currently, clinical studies with different objectives and endpoints are being conducted. These studies include examining the response of patients with squamous cell cancer of the anal canal and comparing different treatments, studying the use of corn starch as a daily supplement to prevent colon cancer and examining the effects of eicosapentaenoic acid on the microbiome and immune system, the effect of synbiotic treatment on diarrhea Osmosis in CRC patients and investigating the effect of controlled diet with high fiber on patients with colon adenoma.<sup>27</sup> In a research study by O'Hara et al., the effect of a diet containing *Bifidobacterium longum* alone and in combination with fructo-oligosaccharide on human feces was investigated. The results showed that the consumption of this prebiotic and probiotics is effective in preventing colon cancer and led to a significant increase in total SCFAs and suppression of *Bacteroides fragilis* enterotoxin and putrefactive bacteria. Also, the amount of *Bifidobacterium* in the synbiotic group was higher than the probiotic group, which is explained by the synergism of probiotics in stimulating the growth of beneficial

intestinal bacteria. In another study by Theodoropoulos et al., the effects of probiotics on colectomy patients were investigated in order to evaluate the digestive quality of life and improve intestinal functional symptoms such as diarrhea and constipation.<sup>28</sup> Research on the effect of synbiotics on patients with colorectal cancer showed that the use of Forte Synbiotic formulation, including several types of bacteria and other substances, led to an improvement in the GIQLI score in the group receiving synbiotics compared to the placebo group. Although no significant effect on constipation was observed, the administration of synbiotics helped improve diarrhea in post-colectomy patients. These results suggest that synbiotics may be effective in reducing the symptoms of irritable bowel syndrome as well as in the prevention and treatment of gastrointestinal problems in patients at risk of developing colorectal cancer.<sup>29</sup> Prebiotics, especially when combined with probiotics, can prevent tumor formation. These effects have been observed in animal and human studies and include the inhibition of Crypt foci formation and changes in the expression of apoptosis-related genes. Prebiotics also increase beneficial bacteria and decrease harmful bacteria and enzymes. These compounds are not only effective in preventing colon cancer, but also help to improve the symptoms of patients. However, there are challenges in the selection and regulation of products for consumers, and the need for more research is felt to optimize the use of prebiotics in the treatment of colorectal cancer.<sup>30</sup>

## Conclusion

This contemporary review highlights the significant potential of prebiotics as a valuable component in the management and prevention of colorectal cancer. By modulating gut microbiota and promoting the production of beneficial metabolites, prebiotics can contribute to improved gut health and potentially reduce the risk of tumor development. The evidence presented underscores the mechanisms through which prebiotics exert their effects, including anti-inflammatory properties and enhanced immune responses. As research continues to evolve, the integration of prebiotics into dietary recommendations and therapeutic strategies could offer a complementary approach to conventional CRC treatments. Future studies are essential to further elucidate the clinical implications of prebiotics, optimize dosages, and establish standardized guidelines for their use in colorectal cancer care. Overall, embracing prebiotics as part of a holistic treatment strategy may enhance patient outcomes and contribute to more effective management of this prevalent disease.

## Highlights

### What Is Already Known?

Prebiotics are non-digestible dietary components that selectively stimulate beneficial gut microorganisms, particularly *Bifidobacterium* and *Lactobacillus*. Their fermentation generates short-chain fatty acids (SCFAs), which enhance colonic epithelial integrity, regulate mucosal immunity, and attenuate inflammatory responses. Experimental studies have demonstrated that prebiotic supplementation can reduce oxidative stress, modulate inflammatory pathways, and contribute to the suppression of early markers of colorectal tumorigenesis. Clinical findings suggest potential improvements in gastrointestinal function and shifts in microbial composition; however, outcomes remain inconsistent due to variability in dosage, duration, and individual microbiota profile.

### What Does This Study Add?

This review synthesizes current evidence regarding the biological mechanisms through which prebiotics influence gut microbiota composition and colorectal cancer-related pathways. It integrates findings from preclinical and clinical studies to clarify how SCFA production, modulation of inflammatory mediators, and alterations in microbial profiles may contribute to cancer prevention. The study consolidates the existing literature into a coherent framework, outlining the potential implications of prebiotic use in colorectal cancer risk reduction and highlighting the methodological limitations that should guide future research.

### Authors' Contributions

The acquisition of resources and drafting of the manuscript were conducted by MM, ZM, KT, MRSH, and MR. Critical review and editing of the manuscript were carried out by MM and SM.

The study was supervised by SM. All authors have read, critically reviewed, and approved the final version of the manuscript.

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The authors declare no competing interests.

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