Review Article

Probiotics as a Preventive and Therapeutic Strategy in Colon Cancer: A Narrative Review

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Abstract

The colorectal cancer (CRC) is a significant global health problem, with rising incidence, particularly in Asia. Lifestyle factors and gut microbiota dysbiosis are implicated in its development, prompting investigation into novel therapeutic approaches. The present review was aimed with the objective of exploring the role of probiotics and post biotics in CRC management, specifically focusing on their potential in cancer therapy, its prevention, and the mechanisms through which they exert these beneficial effects. A descriptive mapping methodology was employed, utilizing various databases such as Web of Science, Scopus, PubMed, etc. To conduct this, review of articles published between 2018 and 2024 were analysed, focusing on objectives, methods, research findings, and gaps. It was found that the probiotics, particularly Lactobacillus and Bifidobacterium, modulate gut microbiota, enhance barrier function, and produce anticancer metabolites, showing promising role in mitigating chemotherapy side effects and potentially preventing CRC, though clinical trial results varied. Finally, it was concluded that the probiotics and postbiotics hold potential as adjuncts in CRC management, but further research is needed to establish standardized protocols, identify optimal strains and dosages, and fully understand their interactions with cancer treatment, leading to improved clinical patient outcomes.

Keywords: *Bifidobacterium* spp., colorectal cancer, *Lactobacillus* spp., probiotics

Introduction

Colorectal cancer (CRC) stands today as the second most prevailing cancer detected in women and third among men. Recent advancements in epidemiological studies have shown an increase in the incidence of CRC in Asia, impacting the health of both male and female populations. This rise in the cases creates an awareness and improved preventive measures across the region to address the growing public health challenge posed by CRC.[1]

The majority of colon cancer cases can be attributed to lifestyle factors and the ageing process. A smaller proportion of risk factors arise due to genetic disorders and mutations. In addition, the other factors contributing are dietary habits and the composition of gut microbiota. These factors collectively influence the risk and progression of the disease, and therefore the need for prevention strategies that address lifestyle changes, diet, and genetic alterations.[2]

In addition, the gut microbiota contributes by generating anticancer immune responses and signals. CRC, which originates in the colon or rectum, is commonly detected through a range of symptoms, including changes in bowel, bleeding of the rectum, and abdominal pain. Earlier detection and understanding of the complex relation between genetic and environmental factors were crucial for effective prevention and exact treatment of the disease.[3] Despite of progress in treatments such as surgery, chemotherapy, and radiation therapy, the prognosis for advanced-stage CRC remains less favorable and is not determined. This ongoing challenge has led to a growing interest in exploring novel treatment strategies,

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including the potential role of probiotics and postbiotics. CRC is linked to a wide range of risk factors, such as low physical activity, obesity, a high body mass index, diets rich in fat and low in fiber, alcohol consumption, smoking, the use of nonsteroidal anti-inflammatory drugs, and genetic predispositions.

In recent years, alongside established surgical methods, there has been an increasing focus on investigating probiotics as a promising area for therapeutic intervention in solid tumors, offering additional impact for improving treatment outcomes of the disease.[4] Historically recognized for their role in promoting gut health, recent research has expanded our understanding of probiotics to encompass their potential impact on cancer treatment, including CRC. The most common probiotics organisms are lactic acid bacteria, with *Lactobacillus* spp. and *Bifidobacterium* spp. being the most prevalent. These probiotics are naturally present in the intestinal microbiota and have demonstrated effectiveness in managing various gastrointestinal conditions, including acute diarrhea, antibiotic-associated diarrhea, functional digestive disorders, and inflammatory bowel diseases. Their therapeutic benefits are largely attributed to their influence on the intestinal microbiota, maintenance of the intestinal epithelial system, and modulation of the intestinal ecosystem.[4]

Beyond their well-established effects on gastrointestinal health, probiotics are emerging as potential agents in cancer treatment. Evidence suggests that probiotics can enhance both the quantity and quality of the intestinal microbiota, potentially reducing chronic inflammation and the production of carcinogenic compounds associated with intestinal dysbiosis.[5] Probiotics can influence cancer development and progression through several mechanisms, including competition for adhesion sites on the intestinal mucosa, production of microbicidal agents such as bacteriocins, enhancement of intestinal permeability, release of bioactive metabolites, and modulation of immune responses. These actions collectively contribute to reducing tumor development and promoting overall intestinal health.[6]

The main objective of this review was to explore the role of probiotics in cancer therapy and prevention, further to evaluate their potential to improve outcomes in cancer treatment, prevention of cancer recurrence, and elucidate the underlying mechanisms through which they exert their effects to control proliferation of colon cancer and to minimize side effects of chemotherapy.

Materials and Methods

The review was carried out by using a descriptive (mapping) methodology. It was conducted on original research articles published and using different search engines, various databases, and journals. The main source of references was databases as Web of Science, Scopus, PubMed, Google Scholar, ResearchGate, J-Gate, MDPI, and JSTOR. The period of articles was from the year 2018 to 2024. The criteria for selection of research articles were based on a detailed study of objectives, research methods, key findings, and research gaps identified by the researchers [Figure 1].

Results

The 21 studies[7-27] were included in this review. The evidences from literature indicate that probiotics, particularly belonging to the genus *Lactobacillus* and *Bifidobacterium* species, play a very crucial role in altering or changing the gut microbiota, and this is a key factor in CRC development.

Mechanisms of action

Modulation of gut microbiota

The human gut microbiota, a complex and dynamic community of microorganisms, plays a crucial role in maintaining gastrointestinal health and overall well-being. This microbial ecosystem supports various physiological functions, including digestion, immune system modulation, and defense against pathogenic organisms. Dysbiosis, or an imbalance in the gut microbiota, has been implicated in the development and progression of several diseases, including CRC. Evidence suggests that a well-balanced microbiota can mitigate the risk of CRC by delaying its onset. Probiotics, as live microorganisms offering health benefits, play a significant role in modulating the gut microbiota. They impact cellular and immunological processes by interacting with specific receptors and producing metabolites that influence the intestinal environment. Probiotics can enhance the integrity of the intestinal epithelial barrier, modulate immune responses, and regulate signaling pathways that contribute to a balanced immune response and reduced cancer risk.[10,17]

Probiotics and gut microbiota balance

Probiotics help restore and maintain the balance of the gut microbiota, particularly in cases of dysbiosis. Their beneficial effects are mediated through several key mechanisms:

Promotion of beneficial bacteria growth

Probiotics can colonize the intestinal tract and support the growth of beneficial bacteria while inhibiting the colonization of pathogenic microorganisms. They achieve this by competing for nutrients and adhesion sites, enhancing the intestinal barrier's integrity, modulating immune responses, inducing apoptosis in cancer cells, and producing beneficial metabolites. For instance, strains such as *Lactobacillus* and *Bifidobacterium* are particularly effective in promoting a healthy balance of gut bacteria. These probiotics compete with pathogenic microorganisms for adhesion sites on the intestinal mucosa, thereby inhibiting the growth and establishment of harmful bacteria.[11,17,18]

In addition, *Lactobacillus gallinarum* has been implicated in CRC prevention by remodeling the gut microbiota and inhibiting tumor cell viability. This strain appears to exert its protective effects by altering the intestinal microbial community and directly affecting cancer cell survival. Probiotic strains such as *Lactobacillus acidophilus, L. gallinarum, L. casei, L. fermentum, L. gasseri, L. johnsonii, L. paracasei, L. plantarum,* *L. rhamnosus, and L. salivarius* have shown promise in gastrointestinal cancer contexts due to their beneficial effects on gut health and cancer prevention.[9]

Bifidobacterium species, which belong to the phylum Actinobacteria, third most prevalent phylum in the human gut microbiota, including strains such as *Bifidobacterium adolescentis, B. angulatum, B. bifidum, B. breve, B. catenulatum, B. dentium, B. longum, B. pseudocatenulatum,* and *B. pseudolongum.* These species are integral to maintaining a balanced gut microbiota and are commonly found in the human gastrointestinal tract. Both *Bifidobacterium* and *Lactobacillus* species are well-documented for their effects on patients with CRC. Other microorganisms such as *Lactococcus, Streptococcus, Enterococcus, Bacillus, and Saccharomyces* are also utilized as probiotics in various diseases, including CRC. These microorganisms contribute to the modulation of gut microbiota and may offer therapeutic benefits in CRC management.[9,10]

Inhibition of pathogenic bacterial enzyme activity

Probiotics exert antimicrobial effects through the production of substances such as bacteriocins and lactic acid, which inhibit the growth of pathogenic bacteria. This antimicrobial activity is crucial for reducing the colonization of harmful bacteria and pathogens within the gut. Endogenous toxic compounds, such as N-nitroso compounds, cresol, aglycones, and phenols, are known to contribute to CRC development by participating in anti-apoptotic pathways. Pathogenic bacterial enzymes, such as 7-β-dehydroxylase, nitroreductase, β-glucuronidase, β-glucosidase, and azoreductase, can exacerbate the carcinogenic potential of these compounds. For example, pathogenic bacteria such as *Staphylococcus aureus, Enterococcus*, and *Salmonella* produce azoreductase, which metabolizes dyes and drugs into toxic aromatic amines. Polyketide synthase (pks) islands in specific *Escherichia coli* strains encode the genotoxin colibactin, which induces DNA damage and increases mutation rates. Enterotoxigenic Bacteroides fragilis has also been linked to CRC initiation through toxin production that promotes carcinogenic processes. Probiotic supplementation may suppress bacterial enzyme activity, with studies showing that *Lactobacillus* can reduce primary bile acid levels and β-glucuronidase activity. However, certain strains such as *L. acidophilus A1, L. plantarum 299V*, and *L. rhamnosus DR20* have not shown a decrease in glucuronidase activity in healthy subjects.[9-11,20]

Enhancement of gut barrier function

Probiotics contribute to strengthening the intestinal barrier by increasing the production of mucins and tight junction proteins. A robust gut barrier prevents pathogen and toxin translocation into the bloodstream, thereby reducing inflammation and cancer risk. Recent studies have linked colibactin, a genotoxin of unknown structure produced by *E. coli*, to CRC development. Colibactin's exact mechanism is still under investigation, but it is associated with increased DNA damage and mutations. Probiotics, such as *L. reuteri* strains ATCC PTA 6475 and ATCC 53608, have demonstrated the ability to reduce infection by enteropathogenic *E. coli*, potentially through competitive exclusion and binding to the mucus layer, which enhances the physical barrier against pathogen infection.[15]

Modulation of immune responses

Cancer cells often express tumor-associated antigens targeted by T lymphocytes, but immune regulatory molecules can suppress these responses. Recent advancements in immunotherapy have focused on disrupting immune checkpoints to improve patient outcomes. Probiotics can modulate the host's immune system by interacting with gut-associated lymphoid tissue.

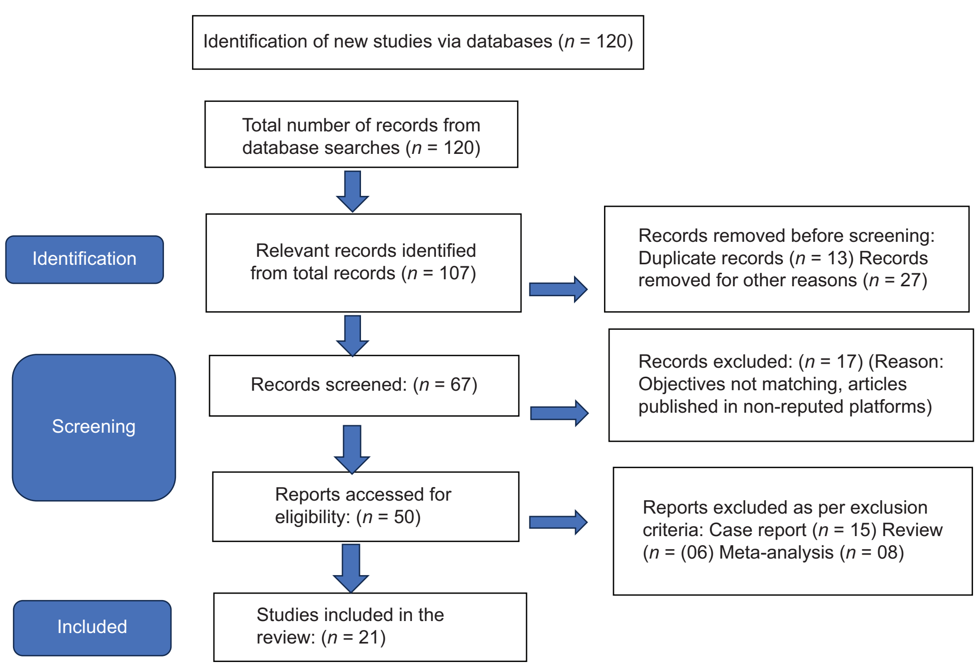

Figure 1: Flowchart demonstrating the selection of articles

They stimulate the production of anti-inflammatory cytokines, regulate immune cell activity, and balance immune responses, which can protect against chronic inflammation and cancer. The link between commensal bacteria and immune response regulation is well-documented, with microbes and their metabolites influencing immune function. Immunomodulatory properties vary by probiotic strain; factors such as survival and persistence in the gastrointestinal tract, dosage, and specific strain characteristics can affect their efficacy in modulating immune responses. Probiotics may also enhance cancer vaccine efficacy, particularly in CRC patients.[20]

Production of metabolites with anticancer properties

Probiotics can produce beneficial metabolites, such as short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, through fermentation of dietary fibers. Butyrate, in particular, plays a crucial role in maintaining colon health. It promotes apoptosis in cancer cells, inhibits cell proliferation, and reduces inflammation by regulating gene expression related to the cell cycle and apoptosis. Butyrate acts through multiple pathways: activating G protein-coupled receptor 43 (GPR43), inhibiting histone deacetylases, inducing apoptosis via caspase activation, and enhancing intestinal barrier integrity by promoting tight junction formation. Other metabolites produced by probiotics, such as lactic acid and propionic acid, also have been shown to influence cancer cell behavior and support gut health.[11,18,20]

Probiotics in cancer therapy

Adjuvant therapy

Probiotics have gained attention as adjuncts to traditional cancer therapies, including chemotherapy and radiotherapy. For example, probiotics have been investigated for their ability to reduce chemotherapy-induced diarrhea, a common and distressing side effect of many cancer treatments. Studies suggest that probiotics may improve gut microbiota balance, support mucosal health, and reduce the incidence of diarrhea, thereby improving patient quality of life.[20]

Chemotherapy-induced diarrhea

Chemotherapy-induced diarrhea is a frequent adverse effect of cancer treatments, leading to dehydration, malnutrition, and diminished quality of life. Probiotics have been studied for their potential to mitigate this side effect by restoring gut microbiota balance, enhancing mucosal barrier function, and reducing inflammation. Strains such as *L. rhamnosus* GG and *Saccharomyces boulardii* have shown promise in reducing diarrhea associated with chemotherapy.[14,17]

Enhanced efficacy of chemotherapy

Probiotics may also enhance the efficacy of chemotherapy by modulating the gut microbiota, which influences drug metabolism and effectiveness. Some studies suggest that probiotics can improve the absorption and metabolism of chemotherapeutic agents, potentially leading to better therapeutic outcomes. For instance, research indicates that probiotics may enhance the efficacy of doxorubicin, a widely used chemotherapeutic agent, by modulating gut microbiota and reducing treatment-related side effects. However, more research is needed to establish definitive benefits and optimal probiotic strains for enhancing chemotherapy efficacy.[24]

Chemotherapy-induced mucositis

Chemotherapy-induced mucositis is a common and debilitating side effect characterized by inflammation and ulceration of the mucous membranes in the gastrointestinal tract. Probiotics have been investigated as potential interventions to alleviate mucositis symptoms by supporting gut health, reducing inflammation, and promoting mucosal healing.

Reduction of mucositis severity

Probiotics may help mitigate mucositis symptoms by enhancing gut barrier function, reducing inflammation, and promoting mucosal repair. Clinical studies have evaluated the efficacy of probiotics in preventing or reducing mucositis severity, with some studies reporting positive outcomes. Strains such as *L. plantarum* and *L. rhamnosus* have been associated with improvements in mucositis symptoms and faster recovery.[10,27]

Prevention of secondary infections

Probiotics may also help reduce the risk of secondary infections associated with mucositis. By supporting a healthy gut microbiota and enhancing mucosal immunity, probiotics can help prevent the overgrowth of pathogenic organisms and reduce the incidence of infections during cancer treatment.

Probiotics in cancer prevention

Mechanistic insights

The potential role of probiotics in cancer prevention is supported by their effects on gut microbiota balance, immune modulation, and production of beneficial metabolites. Probiotics can influence cancer risk through several mechanisms, including modulation of gut microbiota, enhancement of gut barrier function, and production of anticancer metabolites. Specific probiotic strains have been shown to reduce the incidence of cancer in animal models and may offer protective effects in human populations.[17]

Gut microbiota modulation

Probiotics can influence cancer risk by promoting a balanced gut microbiota and reducing dysbiosis. Dysbiosis is associated with chronic inflammation and an increased risk of cancer. Probiotics can restore microbial balance, support a healthy gut environment, and reduce inflammation, thereby potentially lowering cancer risk. Studies have demonstrated that probiotics can modulate the gut microbiota composition and reduce the abundance of pathogenic bacteria associated with cancer development.[24]

Immune system modulation

Probiotics can modulate the immune system, enhancing immune responses and reducing chronic inflammation. By stimulating immune cells, regulating cytokine production, and balancing immune responses, probiotics may contribute to cancer prevention. Probiotics can also enhance the body's ability to recognize and eliminate cancer cells, further supporting their potential role in cancer prevention.[24]

Metabolite production

Probiotics produce beneficial metabolites, such as SCFAs, which have anticancer properties. SCFAs, particularly butyrate, play a key role in maintaining gut health and preventing cancer. Butyrate has been shown to inhibit cancer cell proliferation, induce apoptosis, and reduce inflammation. Other metabolites produced by probiotics may also contribute to cancer prevention by influencing cellular processes and supporting gut health [Figure 2].

Clinical evidence

Some studies have reported reductions in cancer incidence among individuals who regularly consumed probiotics, while others have found no significant effects. The effectiveness of probiotics in cancer prevention may depend on factors such as strain specificity, dosage, and individual patient characteristics.

Reduction in cancer incidence

Clinical trials have explored the effects of probiotic supplementation on cancer incidence, with some studies showing promising results. For example, research has indicated that regular consumption of probiotics may be associated with a reduced risk of CRC and other cancers.[20]

Influence of strain and dosage

The effectiveness of probiotics in cancer prevention may be influenced by specific probiotic strains and dosages used. Different strains of probiotics may have varying effects on gut microbiota and cancer risk.[20]

Discussion

The research on probiotics in colon cancer treatment highlights the role of the gut barrier in human health. It reveals that its loss can lead to various inflammatory conditions. The studies on *L. rhamnosus* CNCM I-3690 have verified its ability to protect intestinal barrier functions and enhance the expression of genes related to healthy gut absorptivity, particularly the SpaFED pili are crucial for these beneficial effects.[28,29] The potential of *Lactobacillus* strains in CRC treatment is also explored that shows their ability to induce apoptosis, modulate immune responses, and hinder tumor metastasis, offering a promising alternative to chemotherapies alone or in combination.[30] The strain-specific influence of *L. reuteri* on *E. coli* adherence to the intestinal epithelium emphasizes the importance of precise probiotic selection, with some strains targeting the epithelium and others the mucus layer. In addition, *L. gallinarum* exhibits significant anti-CRC effects by reducing tumor size and promoting apoptosis.[9,31]

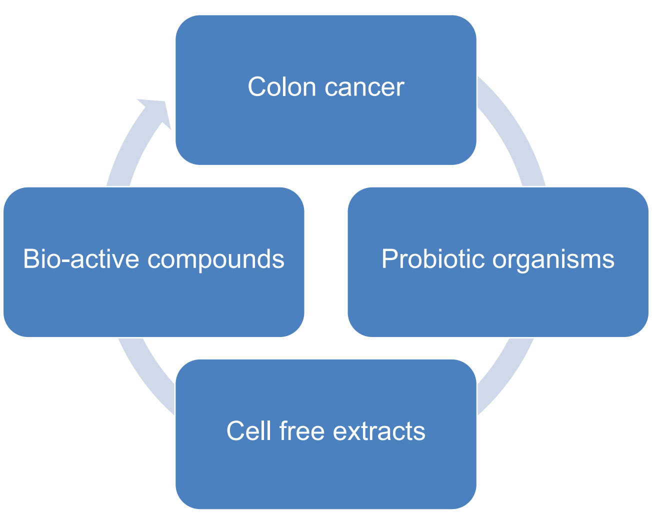

Figure 2: Probiotics in cancer prevention

The gut's microbial balance is very important, as it can contribute to chronic inflammation and even cancer development. Probiotics, like the Bifico cocktail (combination of probiotic organisms) in *in vivo* study, helped to reestablish a healthier gut environment. These organisms work together through a variety of mechanisms. The link between these bacterial changes and the CXCR2 signaling pathway plays a major role in inflammation and cancer. This indicates that probiotics might be able to target specific molecular pathways involved in cancer development, offering a more precise way to prevent or treat the disease.[32,33]

Besides this, studies highlight on how crucial a healthy gut is required for defending against pathogens and preventing diseases like CRC. The research on *Clostridium butyricum* demonstrates how butyrate-producing bacteria can inhibit tumor development by modulating the Wnt/β-catenin signaling pathway and altering gut microbiota composition. The finding that GPR43 knockout reduces the antiproliferative effect of *C. butyricum* and that these receptors are downregulated in CRC progression further underlines the potential of butyrate-producing bacteria in CRC prevention and treatment. Similarly, the investigation of *Lactobacillus* strains as probiotics in CRC reveals their ability to induce apoptosis, modulate immune responses, and hinder tumor metastasis, offering a promising alternative to traditional cancer therapies. These findings underscore the importance of targeted probiotic interventions and the potential of manipulating the gut microbiome to combat serious diseases like CRC.[29,34,35]

Strain-specific variation in exopolysaccharide (EPS) composition and bioactivity shows the importance of strain selection for therapeutic applications. EPS from certain *Lactobacillus* strains, particularly SB27, holds promise as potential therapeutic agents for CRC, acting as inducers of apoptosis. However, further studies are necessary to clarify the precise molecular mechanisms of action, identify the specific EPS components responsible for the observed effects, and evaluate their efficacy in pre-clinical and clinical settings.[36,37]

Probiotics in CRC show distinct variability in clinical trials and their implications as anticancer agents due to differences in the type of probiotic strains, their dosages, and diverse patient populations. While addressing the importance of strain and dosage specificity, it cannot be used for optimal use. The evidence for probiotics in CRC prevention is still under study, requiring more studies and research in this field. Further, individual patient characteristics significantly influence outcomes, thereby complicating the findings.

Conclusion

Probiotics show promise in cancer therapy and prevention by modulating gut microbiota, enhancing gut barrier function, and influencing the immune system. They also produce beneficial metabolites. Preclinical and some clinical data suggest potential benefits, but more research is needed to confirm these effects. Standardized protocols for probiotic use in cancer care are essential. Understanding probiotic-cancer treatment interactions could improve patient outcomes. Ongoing research will provide valuable insights for personalized cancer management.

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Conflicts of interest

There are no conflicts of interest.

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