IJTMGH International Journal of Travel Medicine and Global Health

Int J Travel Med Glob Health. 2026 Jun;14(2):112-118 doi 10.30491/ijtmgh.2025.528756.1492
http://ijtmgh.com

Review Article Open Access

Anticancer Effects of Synbiotics: Bridging Hypothesis and Reality

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Received 2025-06-06; **Accepted** 2025-08-16; **Online Published** 2026-06-01

Abstract

Introduction: One of the main causes of death in the world is cancer. This disease is caused by genetic and epigenetic changes that lead to the unlimited proliferation of cells and eventually lead to tumor formation. The potential anticancer effects of synbiotics, combinations of probiotics and prebiotics, have garnered increasing attention in recent years, transitioning from theoretical frameworks to practical applications in cancer research.

Methods: This review explores the mechanisms through which synbiotics may exert protective effects against various types of cancer, focusing on their ability to modulate gut microbiota, enhance immune function, and reduce inflammation. We examine the existing preclinical and clinical studies that support the hypothesis of synbiotics as effective adjunctive therapies in cancer prevention and treatment. Key findings indicate that synbiotics can influence tumor microenvironments, inhibit cancer cell proliferation, and promote apoptosis, thereby offering a multifaceted approach to cancer management. Additionally, we discuss the challenges and limitations in current research, including variability in synbiotic formulations, dosage considerations, and the need for standardized clinical protocols.

Results: By synthesizing current evidence and identifying gaps in knowledge, this review aims to provide a comprehensive overview of synbiotics' anticancer potential, highlighting their role in bridging the gap between hypothesis and reality.

Conclusion: Future research directions are proposed to further validate the therapeutic applications of synbiotics in oncology, paving the way for innovative dietary interventions in cancer care.

Keywords: Cancer, Synbiotics, Anticancer, Probiotics, Prebiotics, Microbiota

Citation: Nejadasdollah Z, Abbasi L, Rahmanzadeh S , Nemati KH , Gorzin Matayi F , Mokabberi S. Anticancer Effects of Synbiotics: Bridging Hypothesis and Reality. Int J Travel Med Glob Health, 2026;14(2):112-118. Doi: 10.30491/ijtmgh.2025.528756.1492

Introduction

One of the main causes of death in the world is cancer. The World Health Organization predicts that cancer diagnoses will increase by 45% between 2008 and 2030. The main causes of cancer include smoking, poor diet, physical inactivity and environmental pollution. In 2018, the most common cancers included lung, colorectal, prostate, skin and stomach cancer.[1] The financial burden of cancer is also very heavy, estimated at approximately $16 trillion in 2010. Cancer is defined as uncontrolled growth of cells and is known as malignant neoplasm. This disease is caused by genetic and epigenetic changes that lead to the unlimited proliferation of cells and eventually lead to tumor formation.[2] Cancer cells can metastasize to other parts of the body through the blood or lymphatic system. Cancer treatment depends on the type and stage of the disease and includes options such as chemotherapy, radiotherapy, surgery, immunotherapy and monoclonal antibody therapy. Despite recent advances, chemotherapy is still the mainstay of cancer treatment.[3]

Chemotherapy

Chemotherapy, introduced by Paul Ehrlich in the early 1900s, was used as a treatment for cancer in the 1940s and 1950s. This method is known as an essential part in cancer treatment, and the development of anti-cancer drugs is one of the main fields of pharmaceutical research. Chemotherapy is usually the only option for the treatment of metastatic cancers, but its main drawback is its

unwanted cytotoxicity, which cannot distinguish between cancer and normal cells.[4] However, cancer cells are usually more sensitive to chemotherapy drugs. The main goal of chemotherapy is to reduce the population of cancer cells to the minimum possible level, and treatment protocols are designed based on the hypothesis of fractional cell killing for different types of cancers.[5] The effectiveness of cancer treatment depends on the drug dose and the number of chemotherapy courses. Each cycle of chemotherapy kills only a limited number of cancer cells, and assuming 99% of the cells are killed in each cycle, the size of the tumor can be reduced to less than one cell. The timing of chemotherapy cycles depends on the ability of the normal tissues to heal and is usually between three and four weeks. Chemotherapy drugs mostly affect dividing cells, and some of them act at specific stages of the cell cycle.[6] Also, newer treatments such as targeted therapy, which targets specific molecules in cancer cells, are becoming more widely used and have been shown to be effective in many cancers. Monoclonal antibodies and small molecule inhibitors are the two main types of targeted therapy in cancer. Monoclonal antibodies work by various mechanisms, such as stimulating the immune system or killing target cells with toxins, and are administered intravenously.[7] In contrast, small molecule tyrosine kinase inhibitors are taken orally and can be administered for longer periods of time than conventional chemotherapy. Both types of treatment may have side effects that can be used as indicators of treatment effectiveness. Cancer treatment usually includes chemotherapy, which helps reduce toxicity and the risk of drug resistance. Most cancer patients undergo this treatment, but this method is associated with complications such as mucositis, pain, inflammation, bleeding, risk of infection, and diarrhea.[8] Chemotherapy toxicity is one of the main concerns that can reduce the quality of life of patients and thus may lead to drug dose reduction, which itself can affect the survival of patients. Currently, different types of chemotherapy agents with different side effects are being used. [9] Chemotherapy is an important part of cancer treatment, but it has many side effects for patients. Attempts have been made to reduce these complications, but they have not been completely successful. Recent research has shown that the gut microbiota can have a positive effect on cancer and the side effects of chemotherapy. This review examines the effectiveness of maintaining or changing intestinal microbiota in reducing the side effects of chemotherapy and its effect on cancer. [10] The gut microbiota consists of 10-100 trillion microorganisms, including bacteria, fungi, and viruses, that live primarily in the large intestine. This microbiota includes about 1000 species of bacteria and plays an important role in the metabolism, immunity and overall health of the body. The gastrointestinal tract acts as an interface and barrier between the gut microbiota and the major organs of the body and secretes essential hormones that are involved in functions such as digestion and neuromodulation. [11] The hormonal secretions of this device change under the influence of the internal environment of the body and psychological or physiological stress, and these changes can affect the composition of the intestinal microbiota. Also, gut microbes produce bioactive molecules that help modulate immunity, metabolism, and maintain gut barrier integrity.[12] Some gut bacteria, such as Bifidobacterium and Bacteroidetes, help produce important micronutrients such as vitamin K and B, as well as signaling molecules such as GABA and histamine. These bacteria can also convert inactive polyphenols and primary bile acids into active compounds and secondary bile acids. Gut microbiota produces conjugated linoleic acid, which has antidiabetic properties, and also produces short-chain fatty acids (SCFAs) by fermenting dietary fibers, which are an energy source for colon cells and control carbohydrate and lipid metabolism. [13] The gut microbiota and its host have a two-way relationship, and maintaining the balance and appropriate number of microbes is essential for the host's metabolic and immune functions. Any change in this balance can lead to dysbiosis, which is associated with various diseases, including cancer. The gut microbiome, which includes the microbial genome, contains more genomic information than the human genome.[14] Metagenomics studies allow researchers to examine the diversity and richness of the gut microbiome and determine the effect of microbial species on the host. In the past decade, advanced techniques such as next-generation sequencing and analysis of 16S rRNA amplicons have been used to study microbiota, revealing the impact of microbiome diversity on human health.[15] It is possible to modulate the gut microbiota using beneficial bacteria, especially through the consumption of probiotics, prebiotics and synbiotics. Probiotics are live microorganisms that have benefits for human health when consumed in sufficient quantities. In the early 1900s, Eli Metchnikoff proposed that human health could be improved by modifying the microbial composition of the gut.[16] Research has shown that probiotics not only affect the gut microbiota population, but also stimulate physiological and metabolic changes in the host. Yogurt and fermented foods contain natural bacteria that can be considered probiotics, including Lactobacillus and Bifidobacterium, as well as non-pathogenic yeasts such as Saccharomyces boulardi.[17] The use of probiotics is recommended to control intestinal dysbiosis and maintain

the balance of intestinal microbiota. Research has shown that the consumption of certain probiotics can reduce the colonization of pathogenic microbes such as Clostridium difficile and Staphylococcus aureus. Probiotics prevent the colonization of pathogens by competing for nutrients and adhering to epithelial cells, and also contribute to antimicrobial activity and pH change by producing bacteriocins and metabolites such as acetic and lactic acid to prevent the growth of pathogens.[18] Probiotics can have different effects on the immune system, including reducing colonic inflammation or increasing immune surveillance, depending on the type of probiotic strain. Strains such as Bifidobacterium infantis and Bifidobacterium bro activate intestinal dendritic cells by interacting with Toll receptors and inducing retinoid acid metabolism, leading to the production of regulatory T cells and the release of IL-10. In contrast, some strains may induce a pro-inflammatory immune response by increasing the activity of natural killer cells and the ability of phagocytosis . [19] Probiotics have positive effects on the intestinal mucosa by strengthening the integrity of the intestinal barrier and increasing the production of butyrate. By promoting the expression of tight junction proteins, probiotic strains such as Lactobacillus rhamnosus and Escherichia coli Nissl 1917 improve intestinal barrier function and stimulate mucin production, which leads to reduced epithelial inflammation.[20] Prebiotics are defined as non-digestible food substances that selectively promote the growth of beneficial bacteria in the gut and improve health. These compounds mainly include carbohydrates and fiber, but other substances such as unsaturated fatty acids and polyphenols also have prebiotic potential. The effects of prebiotics on probiotics were first investigated using culture models, but new technologies have been able to provide a better understanding of their effects on gut microbes. Research has shown that the consumption of prebiotics can increase the abundance of beneficial bacteria and also help reduce pathogen colonization and inflammatory responses in patients with chronic intestinal inflammation.[21] Gut bacterial fermentation of prebiotics produces SCFA such as acetate, propionate, and butyrate. Butyrate is used as an energy source for colonocytes, while propionate and acetate are taken up by the liver and muscles to produce glucose and energy. Butyrate improves epithelial barrier function, and propionate and acetate reduce colon inflammation and intestinal infection. Prebiotics can also directly affect the gut and prevent pathogens from adhering.[22] Prebiotic oligosaccharides with the same structure as glycoconjugates can interact with pathogenic bacteria and prevent them from binding to epithelial cells. Also, prebiotics can be taken up by intestinal cells and modulate gene expression, which in an animal study showed increased production of IFN-γ and IL-10 in CD4+ T cells. Probiotics are usually taken together with prebiotics, which is called a synbiotic combination. These compounds help to improve the survival of beneficial microorganisms in the intestine and increase the resistance of bacteria against adverse conditions. [23]

Synbiotics

Synbiotics work more effectively than probiotics and prebiotics alone and modulate intestinal metabolic activity by improving intestinal integrity, regulating immunity, and increasing fiber fermentation. Also, the use of synbiotics helps to reduce the accumulation of unwanted metabolites and increase the production of some useful substances. [24] Clinical data show that synbiotics are effective in reducing the severity of some intestinal pathological conditions. A meta-analysis of five studies in children with acute diarrhea found that synbiotics were more effective in reducing diarrhea and hospitalization compared to probiotics alone. Also, a study on patients with nonalcoholic steatohepatitis showed that synbiotics were associated with a decrease in intrahepatic triglycerides at six months. In another study on patients with nonalcoholic fatty liver disease, synbiotic supplementation led to inhibition of nuclear factor-κB and decreased TNF production, indicating reduced inflammation. [25] Synbiotic therapy has been investigated as a nutritional approach to reduce the side effects of chemotherapy and radiotherapy, especially gastrointestinal problems such as intestinal dysbiosis and mucositis. These complications can lead to oral and esophageal ulcers, abdominal pain, and diarrhea, which ultimately lead to dehydration and malnutrition in patients with solid organ tumors. The use of prebiotics and probiotics, especially β-glucans obtained from various sources such as bacteria and plants, helps to strengthen the gut microbiota and reduce side effects. β-glucans have anti-cancer, anti-inflammatory and immunomodulatory properties and can help the growth of probiotics. [26] A clinical study showed that beta-glucan-rich durum wheat flour and whole-wheat pasta can increase the population of beneficial gut microbes, as well as reduce the number of Firmicutes and Fusobacteria. Another study of 62 patients with colorectal cancer showed that beta-glucan had no significant effect on the reduction of leukocyte and neutrophil cells compared to chemotherapy alone, but could reduce the incidence of diarrhea and oral mucositis. The beneficial effect of beta-glucan on chemotherapy and killing tumor cells is difficult to interpret. [27] Since ancient times, honey has been used as a treatment for digestive diseases, and some of its types have antibacterial and anti-

inflammatory properties. Honey can act as a prebiotic and increase the beneficial microbial population in the gut, which helps relieve symptoms of constipation and ulcerative colitis. Studies have shown that honey can be effective in reducing oral mucositis caused by radiotherapy and chemotherapy and also prevent this complication. However, honey has no effect on reducing the severity of mucositis. [28] Probiotics are used as a way to enrich the gut microbiome and reduce the side effects of chemotherapy, including diarrhea and mucositis. Administering probiotics to cancer patients can help improve the function of intestinal bacteria and reduce digestive complications. However, there are concerns about the risk of opportunistic infections and antibiotic resistance in immunosuppressed patients. Probiotics can improve the composition of healthy gut microbiota and help reduce treatment-related complications. [29] Probiotic supplements, especially Lactobacillus species, have been recommended for the prevention of gastrointestinal complications in patients with pelvic malignancies. Several research studies are investigating the therapeutic effect of probiotics on gut microbiota in cancer patients. A 2010 clinical trial showed that probiotics can improve gut microbiota composition and regulate immune system function . [30] Also, in 2014, a study found that 35% of patients receiving probiotics did not suffer from radiation-induced diarrhea, compared to 17% in the placebo group. Also in 2015, another study reported a reduction in the incidence of diarrhea in patients receiving probiotics compared to the placebo group. These results indicate the therapeutic potential of probiotics in cancer patients. Studies show that the use of probiotics in patients undergoing chemotherapy and radiotherapy has conflicting results. In one study, enterocolitis was not observed in the probiotic group, and in another study, a decrease in inflammatory cytokines was reported in patients with colorectal cancer.[31] However, probiotic interventions appear to be useful in preventing enterotoxicity and do not have significant side effects. According to the MASCC/ISOO guidelines, probiotics can help prevent diarrhea in patients undergoing chemotherapy, but ESPEN believes there is insufficient evidence to support this use. Recent research has focused on the effect of synbiotics on symptoms caused by anticancer treatment. The administration of synbiotics, including a combination of Bacillus coagulans and prebiotic sugarcane flour, has shown a significant reduction in the severity of the disease and colon inflammation in the IBD mouse model. Also, another study using a synbiotic containing the probiotic Lactobacillus fermentum and the prebiotic fructo-oligosaccharide has reported a reduction in inflammation in the small intestine of mice. [32] In 2016, a clinical study showed that synbiotics can reduce the risk of postoperative complications, such as irritable bowel syndrome, in cancer patients. In 2017, another study found that intraoperative use of a synbiotic formulation could significantly reduce the rate of postoperative infections in colon cancer patients. In 2018, a clinical study showed that administration of a synbiotic formulation containing several types of probiotic bacteria and FOS for seven days before surgery in patients with colorectal cancer reduced inflammation, complications, and the use of antibiotics, as well as Hospitalization has helped.[33] In another clinical trial, patients were divided into three groups: a prebiotic group, a synbiotic group, and a mechanical bowel cleansing group. Although no significant difference was observed in the systemic inflammatory response after surgery, the synbiotic group had more lactic acid-producing bacteria, indicating a positive effect of the synbiotic on the intestinal microbiota. Patients undergoing chemotherapy may experience complications such as colon infection, mucositis, and diarrhea. The use of synbiotics can help reduce these symptoms. Various clinical studies have shown that synbiotics can reduce chemotherapy-induced lymphopenia and diarrhea. However, due to limitations in the number and variety of studies, it is difficult to draw definitive conclusions .[34] More and more well-designed clinical studies are needed to better understand the effect of synbiotics on the side effects of chemotherapy. This research can contribute to the development of microbiota-based interventions. Cancer patients undergoing chemotherapy are susceptible to infections that can cause complications such as sepsis and organ failure. These complications may lead to hospitalization and reduced patient survival. Although various approaches have been investigated to prevent the side effects of chemotherapy, they have not yet been clinically validated. One of the new methods to reduce these complications is to prevent intestinal dysbiosis and repair the intestinal mucosa through the manipulation of intestinal microbiota. [35] Gut microbiota is essential for gut health, but disease treatments such as antibiotics and chemotherapy can affect its composition. Chemotherapy damages the intestinal mucosa and leads to the loss of beneficial microbiota and dysbiosis. Current research seeks to develop methods to restore intestinal mucosal integrity and reduce dysbiosis to reduce the harmful gastrointestinal side effects of chemotherapy, radiation, and immunotherapy. The use of probiotics during anti-cancer treatment helps to maintain intestinal microbial balance and shows positive clinical results. [36] Patients who take probiotics during chemotherapy have fewer

gastrointestinal side effects such as diarrhea and mucositis. This reduction in side effects increases patient compliance with treatment and improves quality of life and prognosis. Combining probiotics with prebiotics, known as synbiotics, can increase efficacy, but its effect on reducing the side effects of chemotherapy has not yet been well studied. Therefore, future studies should focus on human trials to investigate the efficacy of synbiotics in patients undergoing radiation and chemotherapy.[37]

Conclusion

This review highlights the promising anticancer effects of synbiotics, demonstrating their potential as a multifaceted approach to cancer prevention and treatment. By bridging the gap between hypothesis and reality, current research supports the notion that synbiotics can modulate gut microbiota, enhance immune responses, and reduce inflammation, all of which contribute to their anticancer properties. While preclinical and clinical studies provide encouraging evidence, challenges such as formulation variability, optimal dosing, and the need for standardized protocols remain. Future research should focus on addressing these challenges, conducting large-scale clinical trials, and identifying specific synbiotic combinations that yield the most significant therapeutic benefits. By integrating synbiotics into cancer care strategies, we may pave the way for innovative dietary interventions that enhance patient outcomes and improve quality of life. The continued exploration of synbiotics in oncology holds great promise for transforming theoretical concepts into practical applications in cancer management.

Highlights

What Is Already Known?

Synbiotics, combinations of probiotics and prebiotics, have shown promising anticancer properties in previous experimental and clinical studies. Their beneficial effects are mainly attributed to modulation of the gut microbiota, enhancement of immune function, reduction of inflammation, and regulation of tumor growth and apoptosis.

What Does This Study Add?

This review provides a comprehensive synthesis of current evidence on the anticancer potential of synbiotics, highlighting the mechanisms through which they influence cancer development and progression. It also identifies existing research gaps and proposes future directions for integrating synbiotics into cancer prevention and treatment strategies.

Authors' Contributions

S.M. conceived the study, supervised the work, contributed to the interpretation of findings, critically revised the manuscript, and served as the corresponding author.

Z.N.A. performed the literature search, data collection, analysis, and drafted the manuscript.

Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

The authors would like to thank all individuals who contributed to this study. No external funding was received for this work. The authors also acknowledge the support provided by their affiliated institutions for facilitating this research.

Conflicts of Interest Disclosures

The authors declare that they have no competing financial or personal interests that could have influenced the work reported in this manuscript

Consent For Publication

The authors consent to the publication of this manuscript.

Ethics approval

Not applicabel

Funding/Support

Not applicable

The extent of AI use

Not applicable

Conflict of interest statement

The authors disclosed no competing interests.

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