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Improving colorectal cancer treatment: integrating synbiotics therapy with various treatment approaches

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Abstract

Introduction: Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide. Despite advancements in conventional therapies, there is a critical need for innovative strategies to enhance treatment efficacy and patient outcomes. Various growth factors and novel nutrients, including probiotics and prebiotics, have been tested in experimental models to combat mucositis. Prebiotics are non-digestible compounds that selectively stimulate the growth and activity of beneficial microbes in the gut microbiota and provide health benefits to the host. Synbiotics are symbiotic combinations of probiotics and prebiotics that can have better effects than either of these agents alone. This paper explores the potential of integrating synbiotics therapy—comprising prebiotics and probiotics—into existing CRC treatment regimens. Synbiotics may improve gut microbiota balance, enhance immune response, and mitigate treatment-related side effects, thus offering a complementary approach to conventional therapies such as chemotherapy, radiation, and targeted therapies. We review current evidence on the role of synbiotics in CRC management, highlighting their mechanisms of action, potential benefits, and clinical applications. Additionally, we discuss challenges and future directions for research in this field. By synergizing synbiotics therapy with diverse treatment modalities, we aim to pave the way for more effective, personalized approaches to colorectal cancer care.

Keywords: Colorectal cancer, Synbiotics, Treatment integration, Probiotics, Prebiotics, Treatment efficacy

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Introduction

Cancer is a malignant neoplasm that is caused by the abnormal growth of cells and can metastasize to surrounding tissues through the lymphatic system or blood.[1] Different types of cancer include bladder, lung, breast, colon and rectal cancer, non-Hodgkin's lymphoma, endometrium, pancreas, kidney, prostate, blood and thyroid. Treatment methods include surgery, chemotherapy, radiation therapy, immunotherapy, and treatment with monoclonal antibodies.[2] Gastrointestinal toxicity in this context is known as mucositis. Mucositis is a common side effect of cancer chemotherapy that leads to painful inflammation and ulceration of the mucous membranes of the gastrointestinal tract.[3] This condition is caused by a disorder in normal cells such as enterocytes and can affect the entire digestive system as well as the mouth. Depending on the dose and type of chemotherapy drug, between 40% and 100% of patients may experience various stages of mucositis.[4]

Chemotherapy

Chemotherapy-induced intestinal damage occurs due to the death of normal cells and changes in intestinal microbial communities.[5] This damage leads to an increase in intestinal permeability and the entry of pathogenic bacteria into the blood, which causes inflammation and the release of pro-inflammatory cytokines. Also, oxidative stress contributes to the exacerbation of intestinal damage.[6] Cancer patients undergoing chemotherapy

commonly experience symptoms such as abdominal distension, nausea, weight loss, and malnutrition, and in severe cases, it may lead to death.[7] Chemotherapy-induced mucositis consists of five stages, the understanding of its pathophysiology is important to reduce the severity of the disease.[8] The first "initiation" phase begins with an increase in reactive oxygen species and DNA damage. In the second stage, "message regulation and generation", transcription factors are produced and the mucosa becomes more fragile, leading to pain in the patient.[9] The third stage is "signaling and amplification," in which levels of tumor necrosis factor-α(TNF- α) and other factors increase and further tissue damage occurs.[10] The fourth stage "wound and inflammation" is associated with bacterial colonization and the production of pro-inflammatory cytokines, which can lead to bacteremia and violation of mucosal integrity.[11] Finally, the fifth stage is "healing", in which the intestinal epithelium is restored and the homeostasis of the intestinal microbiota is restored[12] The treatment of mucositis, especially in the mouth, has received more attention, while research on the treatment of gastrointestinal mucositis is less.[13] Current therapeutic approaches are focused on identifying agents that can protect the mucosa and promote the healing process without compromising the cytotoxic effects of chemotherapy.[14]

Probiotics

Various growth factors and novel nutrients, including probiotics and prebiotics, have been tested in experimental models to combat mucositis.[15] Also, probiotic-derived factors and antioxidant and anti-inflammatory compounds in plant extracts and animal oils also seem promising in the prevention of mucositis[16] Studies show that due to the diversity of these factors, the severity of mucositis can be reduced through different paths. The use of strategic combinations including probiotics, probiotic-derived factors and plant extracts can be more effective in protecting mucositis than the use of individual factors.[17] Probiotics, particularly *lactobacilli* and *bifidobacterial*, are live microorganisms that confer health benefits to the host when administered adequately. Other species such as *Lactococcus*, *streptococcus* and some non-pathogenic strains may also be effective in this regard.[18] Probiotics have been studied for decades as beneficial agents for maintaining the intestinal microbiota and reducing the severity of digestive disorders, diabetes and atopic diseases.[19] These compounds are especially used in the treatment of inflammatory bowel disease in some countries such as Germany. The mechanisms of action of probiotics include adhering to the intestinal surface, competing with pathogens, strengthening the mucosal barrier, and improving immune responses.[20] Based on these characteristics, some new probiotic strains may be effective in reducing chemotherapy-induced intestinal damage. Scientist reviewed the evidence for the use of probiotics for the prevention and treatment of chemotherapy-induced mucositis.[21] Mucin binding proteins from probiotics such as *Bifidobacteria bifidium* and *Lactococcus lactis* ssp. lactis BGKP1 have been identified, contributing to the binding properties in vivo and in vitro.[22] Also, some species of Lactobacillus and *Bifidobacterium* spp. Tests have shown that they can inhibit the growth of intestinal pathogens such as *Escherichia coli* (E. coli) and *Salmonella*. Therefore, probiotics can compete with pathogens for binding sites and nutrients and reduce the likelihood of pathogenic infections and secondary infections caused by chemotherapy.[23] Chemotherapy can change the composition of microbiota towards pathogenic species, so that beneficial species such as *Clostridium* and *Lactobacillus* are reduced and harmful species such as E. coli are increased.[24] In a study on mice, the administration of probiotics (*Bifidobacterial and Lactobacillus*) after colorectal cancer surgery helped to improve the stool microbiota and increased the number of beneficial species and decreased harmful species. These results show that probiotics can help restore and normalize gut microbiota under the influence of chemotherapy[25] Maintaining the intestinal barrier in cancer patients undergoing chemotherapy is a serious challenge. Chemotherapy can disrupt the secretion of mucin and tight junction proteins and increase the risk of bacterial infection. Certain probiotics, such as *Lactobacillus plantarum* can modulate tight junction proteins and reduce intestinal permeability.[26] These probiotics can also help regulate mucin secretion and restore microbiota composition and mucosal immunity. In addition, some probiotics can help improve the condition of patients by regulating the homeostasis between apoptosis and cell proliferation. Finally, the consumption of probiotics may help restore the balance between apoptosis and proliferation of enterocytes affected by chemotherapy.[27] Probiotics can enhance innate immunity by increasing the number and activity of immune cells and regulating inflammation. Also, these substances may improve adaptive immune function by modulating specific antibodies.[28] For example, administration of *Lactobacillus Delbruck* in elderly subjects increased natural killer cells and immature T cell subsets. Also, the administration of *Clostridium botulinum* led to a decrease in the expression of pro-inflammatory cytokines in mice. Similar results have been observed in gastrointestinal diseases and

alcohol-induced inflammation.[29] In addition, consumption of probiotics in colorectal cancer patients improved the levels of IgA, IgG, IgM and interleukin-2, indicating a positive effect of probiotics on adaptive immune modulation.[30] Probiotic-derived factors include proteins and other molecules released from live probiotics that can confer health benefits to the host. Investigating these factors will help achieve therapeutic benefits and reduce the risks associated with the administration of live bacteria and provide a better understanding of the mechanisms of action of probiotics.[31] These factors can compete with pathogens; For example, bacteriocins and protein molecules prevent adhesion and survival of intestinal pathogens. Lactobacillus acidophilus ATCC 4356 and other strains can inhibit pathogenic activity and reduce the likelihood of infection, especially in the setting of chemotherapy.[32] It is important to maintain the intestinal barrier by modulating the mucosal layer and the tight junctions of the intestine by probiotic agents. These factors can improve intestinal damage caused by chemotherapy. In one study, the administration of *Lactobacillus rhamnosus* to alcohol-treated rats caused changes in intestinal tight junction proteins and increased mRNA levels of some factors.[33] Also, this probiotic prevented the dysfunction of Caco-2 cells. Protein factors extracted from *Clostridium botulinum* also increased the expression of A20 in HT-29 cells. These results indicate the potential of probiotic agents in maintaining the intestinal barrier after damage caused by chemotherapy.[34] p75 and p40 proteins promote proliferation of epithelial cells and prevent apoptosis induced by TNF- α. Also, p75, renamed Major secreted protein 1 (Msp1), is an O-glycosylated protein, whose glycosylation plays an important role in the communication between microbes and hosts. Furthermore, supernatants from *Lactobacillus rhamnosus* and E. coli Nissl 1917 significantly reduced caspase 3/7 activity in IEC-6 cell line after challenge with chemotherapy, indicating their ability to prevent enterocyte apoptosis induced by It is chemotherapy.[35] Metabolites released from *Bifidobacterium* breve and *Streptococcus* thermophilus have the ability to inhibit TNF- α and activate nuclear factor kB. Also, Lactobacillus reuteri biofilms reduce TNF- α production in monocytoid cells.[36] Caco-2 cells treated with supernatants of *Lactobacillus plantar*um 2142 decrease interleukin 8 synthesis and heat shock protein 70 expression. Also, the probiotic Lactobacillus paracasei CNCM I-4034 has similar effects in reducing TNF- α and chemokine MCP-1 in Salmonella-challenged human dendritic cells.[37] Factors derived from the probiotic *Bifidobacterium bifidum* LMG13195 can act as immune regulators in vitro. These factors increased the number of high CD4þCD25 cells in human blood mononuclear cells after culture with HT29 cells. Therefore, these factors can reduce inflammation and restore immunity in conditions affected by chemotherapy by modulating immune cells.[38]

Prebiotics

Prebiotics are non-digestible compounds that selectively stimulate the growth and activity of beneficial microbes in the gut microbiota and provide health benefits to the host. These compounds include inulin, lactulose and galacto-oligosaccharide. Also, other compounds that have been studied for their prebiotic potential include arabinoxylan-oligosaccharides, keto-oligosaccharides and xylo-oligosaccharides.[39] The role of prebiotics in the treatment of mucositis has been comprehensively reviewed by Wang et al. in 2012. By modulating probiotic bacteria and intestinal microbiota colonization, prebiotics can reduce intestinal dysbiosis caused by chemotherapy and maintain microbiota homeostasis. Also, some prebiotics play a role in the digestion and absorption of nutrients and improve the function of the intestinal barrier. Howarth has also pointed out the importance of inflammasomes in the mediation of inflammation by prebiotics. However, more studies are needed to understand the mechanisms of action of prebiotics in the prevention and treatment of mucositis.[40]

Natural plant extracts

Phenolic compounds, especially flavonoids, are common in plants and are divided into different categories. Flavanols and flavanols (catechins) are among these compounds that are converted to each other by adding hydroxyl groups. Procyanidins, which consist of catechin and epicatechin, are concentrated polymers that are converted to anthocyanidins.[41] Procyanidins and proanthocyanins, as the most important compounds, have the ability to inhibit free radicals and reactive oxygen species. This property is due to antioxidant activities in plant extracts such as grape seed, cat's paw, maca and dragon's blood. The antioxidant ability of these extracts against reactive oxygen species will be explained in the next sections.[42] Reactive oxygen species (ROS) are reactive oxygen-containing molecules that play an important role in oxidative stress in disorders such as rheumatoid arthritis and asthma. Chemotherapy can increase the production of these species and lead to the infiltration of neutrophils and the production of pro-inflammatory cytokines. These processes can lead to the activation of transcription factors and the induction of cell apoptosis, which leads to damage to the intestinal epithelium and clinical manifestations of mucositis.[43] Also, reactive oxygen species can react with intestinal

mucosa macromolecules and cause lipid peroxidation, which contributes to the destruction of the intestinal epithelium. In general, overproduction of these species is implicated in the pathogenesis of chemotherapy-induced intestinal injury. Many studies have investigated the antioxidant properties of phenolic compounds, especially procyanidins. These compounds interact with cell membrane phospholipids and can protect bilayers against oxidative stress.[44] Research has shown that a diet rich in procyanidins in rats increases antioxidant activity in plasma and reduces heart damage. Also, proanthocyanins have the ability to reduce the level of malondialdehyde, which is an indicator of lipid peroxidation, and can reduce the toxicity caused by chemotherapy drugs. These compounds also prevent damage to the vascular endothelium by reducing the induction of adhesion molecules.[45] Procyanidins and proanthocyanins have anti-inflammatory and anti-ulcer effects. Research has shown that procyanidins in wild grape seeds act as a preventive agent by increasing the expression of nuclear factor-related factor E2. This factor helps to express phase II detoxification and antioxidant enzymes that play a role in protecting cells and preventing cancer.[46] Also, proanthocyanins have antithrombotic effects and can improve mucosal blood flow. In a study, these compounds showed anti-ulcer effects on the gastric mucosa of mice by inhibiting the activities of myeloperoxidase and stimulating the activities of superoxide dismutase. Also, proanthocyanins reduce the infiltration of leukocytes and the levels of pro-inflammatory factors, which results support their anti-inflammatory effects.[47] Phenolic compounds have antioxidant, anti-inflammatory and anti-ulcer properties. These properties are due to inhibition of free radicals and effects on apoptosis regulatory genes such as bcl-2 and p53, which affect the production of pro-inflammatory factors. Therefore, plant extracts containing these compounds can be effective in the treatment or prevention of mucositis.[48] Limited studies have investigated the effects of plant extracts on intestinal mucositis. One such study was conducted by Cheah et al., which showed that grape seed extract could protect the intestine of mice from damage caused by the chemotherapy drug 5-fluorouracil. This extract helps to improve the viability of intestinal cells and reduce the inflammation caused by this drug. Also, Golgun et al. reported positive results of proanthocyanidins in reducing intestinal damage caused by methotrexate in rats. These compounds reduce inflammation and related wounds and strengthen the defense system against oxidative stress.[49] Ibrogast (STW5) is a mixture of 9 herbal extracts that include bittersweet, angelica root, milk thistle fruit, celandine plant, black cumin fruit, licorice root, peppermint plant, mummy leaf and chamomile flower. This combination helps to regulate the motility of the digestive system and limit the production of stomach acid and has anti-inflammatory and antioxidant properties. Ibrogast's active compounds, especially flavonoids, are effective in the treatment of digestive diseases such as indigestion and irritable bowel syndrome.[50] Recently, ibrogast was tested in mice to improve mucositis induced by 5-fluorouracil and the results showed that this compound can reduce the severity of mucositis induced by chemotherapy. However, more research is needed on dosage and frequency of administration.[51] Plant extracts such as spinach glycolipid and Eriobotrya japonica seed extract have shown antioxidant and anti-inflammatory effects in rats treated with 5-fluorouracil. These extracts significantly improved mucosal damage and reduced the expression of inflammatory cytokines such as interleukin-1a and TNF- α. Also, the active compounds in spinach extract prevented the production of reactive oxygen species. In a clinical trial, the use of indigo root led to a decrease in the severity of radiation-induced mucositis and a decrease in interleukin-6 levels in patients.[52] In summary, certain plant extracts such as grape seed extract and Iberogast have shown anti-inflammatory and antioxidant effects on chemotherapy-induced mucositis. These plant extracts could be a potential new preventive treatment strategy for intestinal mucositis, although further research is needed. Further studies should focus on the identification of active bioactive components along with the identification of plant extracts that have not yet been tested.[53]

Synbiotics

Synbiotics are symbiotic combinations of probiotics and prebiotics that can have better effects than either of these agents alone. Recent research has shown that synbiotics are effective in maintaining intestinal health and treating important diseases such as septic complications.[54] For example, fermented milk containing two probiotic strains and one prebiotic improved gut health in adults and mice. Also, the combination of Lactobacillus acidophilus and ginger extract in the gastric ulcer environment in rats has shown a significant improvement in the ulcer index and other related parameters.[55] Few studies have investigated the effects of synbiotics on reducing the severity of mucositis. Research by Smith et al showed that a combination of Lactobacillus fermentum BR11 and the prebiotic fructo-oligosaccharide could reduce 5-fluorouracil-induced inflammation in mice, but had no significant effect on mucositis.[56] The need for more studies to investigate the combined effects of probiotics and prebiotics in reducing the severity of mucositis is felt.

Also, the potential of prebiotics in plant extracts is still unknown, but new nutrients could help reduce gut damage and increase the likelihood of achieving positive clinical outcomes. Certain probiotics can reduce mucositis by affecting the bacterial composition of the gut, and certain plant extracts may be more effective in combating chemotherapy-induced oxidative stress.[57] The combination of probiotics and plant extracts can help reduce the severity of mucositis and bring significant clinical improvement. Since most prebiotics are derived from plants, future research should focus on the prebiotic properties of different types of plant extracts. The challenges ahead include identifying specific probiotic and prebiotic combinations with synergistic effects, determining the dosage and frequency of administration, and investigating the bioactive factors and pharmacodynamics associated with them, so that these innovative formulations can be used for the treatment of mucositis.[58]

Conclusion

The integration of synbiotic therapy into colorectal cancer treatment presents a promising avenue for enhancing patient outcomes and improving therapeutic efficacy. By harnessing the beneficial effects of prebiotics and probiotics, synbiotics can potentially restore gut microbiota balance, bolster immune function, and alleviate the adverse effects associated with conventional treatments. As research continues to elucidate the mechanisms underlying these benefits, it becomes increasingly clear that a multi-faceted approach to CRC management—one that combines synbiotics with established therapies—could lead to more personalized and effective treatment strategies. Future clinical trials and studies are essential to validate these findings and establish standardized protocols for incorporating synbiotic therapy into routine care. Ultimately, this integrative approach holds the potential to transform colorectal cancer treatment, offering hope for improved survival rates and quality of life for patients.

Highlights

What Is Already Known?
The effects of each synbiotics have been reviewed separately in original articles.

What Does This Study Add?
This study comprehensively collected the effects of various synbiotics on colorectal cancer

Consent For Publication

Not applicable

Ethics approval

Not applicable

The extent of AI use

Not applicable

Author contributions

F.A and S.M were involved in planning and supervised the work and proof outline M.R, T.A, F.A.B,Kh.H.C and S.M and drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript.

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Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest statement

The authors disclosed no competing interests.

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