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A Systematic Review of Reducing the Burden of Colorectal Cancer through Microbiome Alteration

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Abstract

Background: The gastrointestinal tract microorganisms play a very crucial role in colorectal cancer (CRC). While certain bacteria can actually promote cancer growth, there are also beneficial microbes that can help reduce the risk and slow down the progression of CRC. Research has consistently highlighted a strong connection between the types of gut bacteria present and the likelihood of being diagnosed with CRC.

Methods: Following PRISMA 2020 guidelines, this systematic review examined 20 years of peer-reviewed research (PubMed, Google Scholar) on microbiome-altering strategies, such as probiotics and symbiotics, for reducing the risk of colorectal cancer (CRC).

Findings: Probiotics greatly enhanced gut health and decreased inflammation. They sped up recovery after CRC surgery by reducing the risk of diarrhoea and other digestive problems.

Conclusion: Probiotics containing Lactobacillus and Bifidobacterium improve the gut health of patients with colorectal cancer after surgery without causing significant adverse effects. Future studies ought to concentrate on their capacity for prevention.

Keywords: Colorectal cancer, Probiotics, prebiotics, Microbiota, microbiome, gut microbes.

Introduction

Cancer is a complex illness marked by unchecked cell division and expansion that results in tumour development and metastasis[1]. In the year 2020, 1.9 million Colorectal cancer (CRC) cases have been reported worldwide[2]. Approximately 10% of individuals with stage IV colon cancer survive for five years after diagnosis; colorectal cancer claimed the lives of 900,000 people worldwide.[3] Based on the study, a mutation in the TP53 gene is associated with colorectal cancer [4]. Males record a mortality rate of 11.0 due to CRC, whereas that of females is 7.2. This is closely related to lifestyle changes, such as diet, alcohol consumption and smoking[5]. When instances recorded in developed nations are more than those recorded in developing nations, the role of lifestyle changes is evident. The rate of incidence is 7.2 in countries with a lower Human Development Index (HDI) and 20.4 in countries with higher HDI.[6] Cancer research has come a long way, and we're starting to see some exciting new discoveries[7]. The cancer treatment timeline showcases the remarkable journey of therapies over the last 170 years [8]. These days, oncology is all about creating cancer nanomedicines that are both safe and effective [9]. Diving into the role of the microbiome in cancer has become a crucial area of research [10]. The human intestine holds trillions of bacteria plays a key role in bodily functions [11]. Tumor microenvironment is a multifaceted structure comprising other cell types in addition to the cancer cells [12]. The tumor microenvironment helps in cancer progression by creating a complex interaction between cancer cells and the various cellular and acellular components that surround them [13]. Thus, the knowledge about different microbiota-host interactions can enhance precision in the application of CRC prevention measures [14]. Previous studies suggest a link between a specific gut microbiome and CRC progression. This can occur via neoplastic cell transformation or immune system compromise due to reduced gut bacterial diversity. [15]. Our human microbiome is a fascinating mix of bacteria, viruses, archaea, fungi, and protozoa that resides on our epithelial barriers [16]. This complex ecology is key to our well-being and has a great effect on disease. Treatment for dysbiosis, a change in the gut microbiome, are many. [4]. Intestinal microbes are pivotal in controlling mucosal inflammation and supporting systemic immunity [17]. In addition, the use of probiotics and prebiotics offers another possible approach to altering dysbiosis. Lastly, recommending specific changes in lifestyle can also help to alter the equilibrium of the gut microbiota [18]. In the early diagnosis cancer or recognizing potential threats in patients, Faecal Microbiota Transplantation (FMT) can serve as a good treatment regime [19]. FMT was found to have suppressed the progression of the tumour and reduced the tumour cells[20]. This treatment can be planned along with immunotherapy or chemotherapy for better efficacy [21]. Many studies suggested personalised gut microbiota-based CRC treatments. Research indicates *that F.* nucleatum interacts with a protein called DHX15 for people with KRAS gene mutations; this can be neutralised by other bacteria called *P.* distasonis, which can slow the progression of CRC in people [22]. Some studies suggest that gut bacteria, Fusobacterium nucleatum, Bacteroides fragilis and Escherichia coli, can cause tumours[23]. Fusobacterium nucleatum nucleatumcreates hypoxic tumour microenvironments through biofilms and creates inflammation to sustain its growth [24]. The control of this bacterium needs external antibiotics and oral hygiene to control the development of this bacteria[25]. Enterotoxigenic Bacteroides fragilis produces toxins that cause inflammation and use gut mucosa for dysbiosis. High-fat diets in humans can promote the growing environment for these bacteria [26]. The main control strategies include probiotics and low-fat diets for patients [27]. Some bacteria damage DNA through genotoxins or metabolites, which promote tumorigenesis in patients. Bacteria like Escherichia coli and Bilophila wadsworthia produce colibactin or hydrogen sulphide, which attacks epithelial cells' DNA, causing damage. Consuming dietary fibre and probiotics can help control these bacteria and its proliferation. [28]. Gut reduced diversity also leads to the growth of some bacteria, which causes CRC risk. Some species of bacteria such as Porphyromonas and Bilophila wadsworthia flourish in people who consume fat-rich diets with low fibre intake. These bacteria produce tumour-promoting metabolites such as butyrate and hydrogen sulphide, which are involved in inflammation and a greater chance of getting colorectal cancer (CRC) [29]. On other hand, including probiotics and prebiotics, together with a high fibre diet and low-fat intake, can control the overgrowth of these harmful bacteria [30].

Aim: The goal of this systematic review is to thoroughly evaluate how well probiotics, prebiotics, and other microbiome modification techniques lower the risk of colorectal cancer (CRC). The main aim is to assess how well these therapies can improve gut health and reduce the risk of colorectal cancer in at-risk groups. This research will also highlight the benefits and drawbacks of these methods, particularly in relation to CRC surgery and recovery after the operation.

Materials and Methods

The systematic review process involved identifying the present research problem, developing a plan for carrying out a literature search, searching the literature and identifying articles, extracting data, analyzing, and appraising the evidence found.

Research Question

Studies investigate the relationship between the gut microbiome and colorectal cancer, with the potential of modulating the microbiome to minimize cancer risk and development. Probiotics, prebiotics, dietary changes, and fecal microbiota transplantation (FMT) show promise in preventing and treating colorectal cancer. These options provide new ways to lessen the impact of this disease. The research question is "What is the efficacy of probiotics, prebiotics, and other microbiome modification strategies in mitigating the risk of colorectal cancer?"

PICO

- **Population:** participants with cancer and undergoing cancer treatment
- **Intervention:** microbiome alteration
- **Comparison:** placebo
- **Outcome:** reducing the risk of colorectal cancer

Eligibility Criteria

This review brings together findings from English-language randomized controlled trials conducted over the last ten years, specifically looking at microbial changes in patients with colorectal cancer. We left out studies that didn't use cancer cell lines, focused on non-cancer pathways, or were published in other languages when there were restrictions.

Search Strategy

The study conducted an extensive search on three important databases, such as Google Scholar, PubMed, and Web of Science, to find the related articles using the various keyword combinations "CRC treatment AND probiotics", "CRC treatment AND RCT AND probiotics", and "CRC treatment AND symbiotic". The studies are sorted into years of publishing, and the most relevant articles are selected. Only research papers published in the past 10 years that have control double-masked studies are taken into consideration.

Discussion

Using cytokine levels as a gauge, Zaharuddin L et al. (2019) performed a double-blind RCT on CRC patients to evaluate the effects of probiotics. The probiotics, which contained strains of Lactobacillus and Bifidobacterium, showed an anti-inflammatory effect by lowering IFN-γ and inflammatory cytokines (TNF, IL-6, 10, 12, 17A, 17C, and 22). Since no adverse effects were noted, probiotics containing these strains might be appropriate for the treatment of colorectal cancer. However, the study's small sample size necessitates more investigation.[31]

Hibberd et al. (2017) looked into how probiotics affect the microbiota in both cancerous (ER) and non-cancerous control groups. They discovered unique microbial patterns among colon cancer patients. Interestingly, the group taking probiotics had fewer butyrate-promoting microbes. The study indicated that probiotics didn't cause any side effects and might actually enhance treatment outcomes for patients with gut cancer. [32].

The effect of symbiotic supplements (probiotics and prebiotics) on the balance of the gut microbiota was examined in a study by Komatsu et al. (2018). For seven to eleven days following surgery, participants were given either a placebo or Lactobacillus casei and Bifidobacterium breve. The supplement group's samples contained ten times as many bacterial cells per gram, according to the results. Additionally, their blood showed fewer bacteria that promote cancer and a greater percentage of good bacteria.[33].

Yang et al. (2015) carried out a placebo-controlled study involving sixty cancer patients at stages 0-III to explore the effects of probiotics on infections. In this trial, thirty patients were given probiotics (specifically Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis), while the other thirty received a placebo made of sucrose. Although there were no notable changes in bowel movements, the use of probiotics led to a 50% reduction in diarrhea frequency, highlighting their impressive role in balancing the microbiome.[34].

In a study by Park et al. (2020), researchers looked into how probiotics can affect bowel issues, inflammation, and overall quality of life after colon surgery. Patients took a probiotic powder—featuring Bifidobacterium animalis subsp. lactis, Lactobacillus casei, and Lactobacillus plantarum—four times a day for four weeks. While there was a notable improvement in ARS scores, the patients didn't see a significant change in their overall quality of life. The findings indicate that a longer-term study would be beneficial for gaining deeper insights.[35]

A study conducted in 2023 by Mohebian F and colleagues revealed that combining yogurt with probiotics can significantly alleviate chemotherapy-related diarrhea (CRD). Patients who took this combination saw a remarkable drop in their daily bowel movements, going from an average of 4.63 to just 2.26. They also reported a decrease in diarrhea intensity, which fell from 1.47 to 0.16 by the sixth day, along with better stool consistency.[36]

Huang, F. et al. (2023) looked into how a combination of four probiotics—Lactobacillus acidophilus, Enterococcus faecalis, Bacillus cereus, and Bifidobacterium infantis—could help ease gastrointestinal issues caused by chemotherapy in patients with colorectal cancer (CRC). Their findings indicated that these probiotics were effective in reducing abdominal pain and diarrhea while also boosting fatty acid production. However, one downside is that the study's findings may not apply broadly, as it focused on a specific age group and demographic.[37]

Conclusion

Probiotics, especially Lactobacillus and Bifidobacterium strains, show significant promise in managing CRC both before and after surgery. They improve gut health by boosting beneficial bacteria and reducing inflammation, thereby alleviating chemotherapy side effects like diarrhea and pain, and potentially reducing CRC risk. Symbiotic approaches (prebiotics + probiotics) also appear beneficial across cancer stages. However, concerns about reduced butyrate-producing bacteria with some probiotic interventions necessitate careful analysis before broad implementation. Future research should address current limitations like small sample sizes and limited diversity, and explore dietary probiotic treatments.

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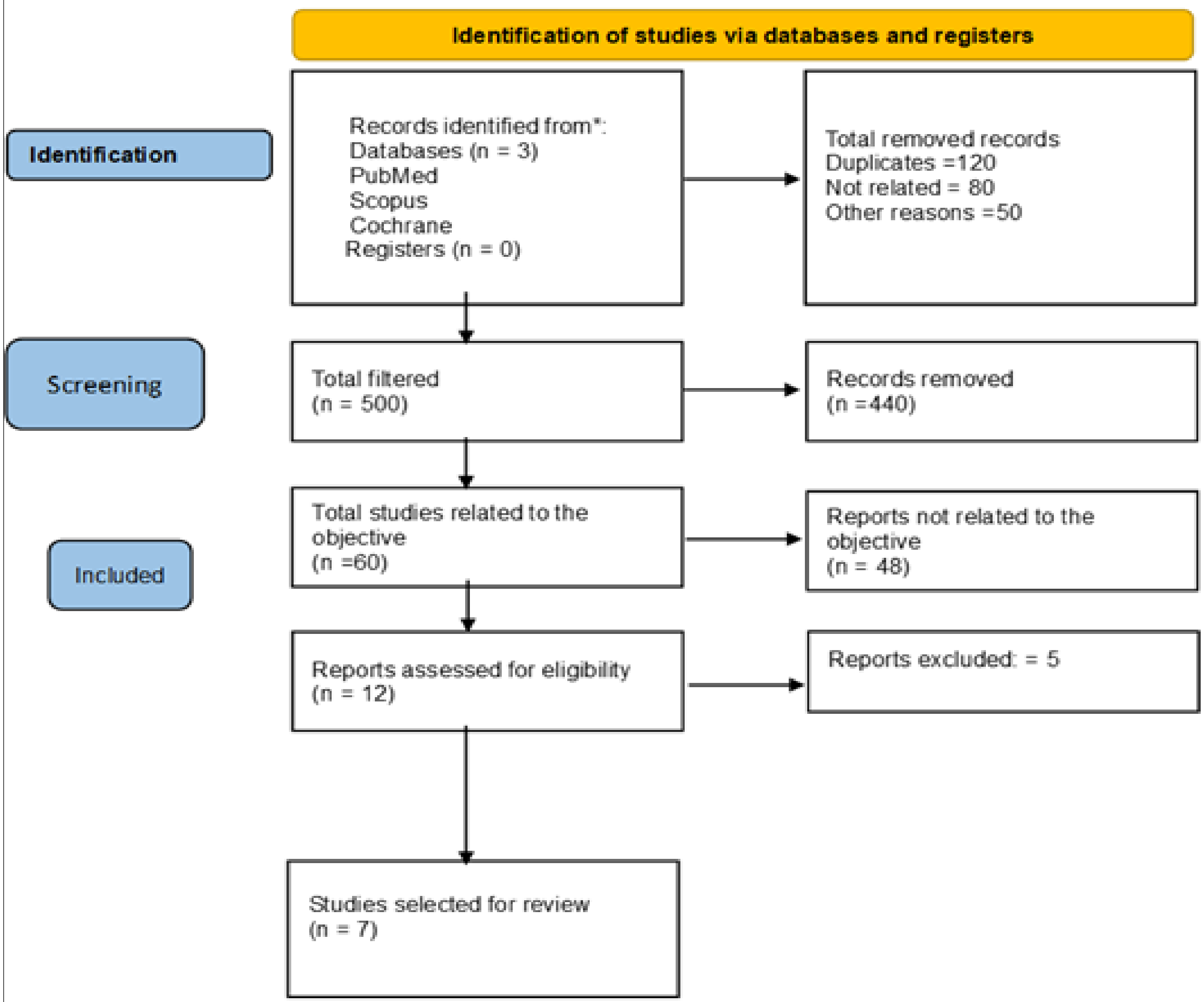
39. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Office of Health Assessment and Translation (OHAT)

Figure 1:

Figure 1: PRISMA 2020 flow diagram for newly conducted systematic reviews that solely involved database and registration searches



Result

Table 1: Features of study's intervention

S. no	Author details	Participants			Type of Study	Primary outcomes	Secondary outcomes
		Sample size	Age range (years)	Sex			
1.	Zaharuddin L, et al. (2019) NCT03782428	52 (27 in probiotic and 25 in placebo)	18+	Male: 34 Female: 18	Double-blind, randomized control trial	The leading indicators, such as pro-inflammatory cytokines, are reduced in the probiotic group compared to the placebo group.	Introducing probiotic supplements did not affect diarrhoea and infection patterns. No side effects were measured for the supplements.
2.	Hibberd et al., 2017 NCT03072641	36 (15 Cancer and 21 control)	55-75	Male: 10 Female:26	Prospective intervention	The microbiota diversity increases in CRC patients after probiotic intervention. There is an increase in Microbiota like *Faecal bacterium* and *Clostridiales*, which are responsible for butyrate production in patients.	It reduces CRC-enhancing micro bacteria and has therapeutic benefits. It can be used in addition to other treatment techniques.

3.	Komatsu et al (2018) UMIN000003439	72 (synbiotic: 33, Control: 39)	30 - 92	Male: 37, Female: 35	Randomized Control Study	The synbiotic intervention induced a heavy reduction in *Enterobacteriaceae,* which are responsible for postoperative complications.	Synbiotic patients showed a 5% increase in total Enterobacteriaceae compared to the normal population. *Lactobacillus casei* detection also rose in synbiotic groups.
4.	Yang et al. TRC-13003332	60 (30 Probiotics and 30 Control groups)	25 - 80	Male: 27, Female: 33	Double-blind, randomized control trial	The primary endpoint was postoperative diarrhoea, which was 50% lower in the probiotic group, suggesting probiotics help manage CRC by preventing infections.	Probiotics significantly accelerated initial flatus and defecation. While overall bowel movement frequency was comparable, this suggests a positive impact on early bowel function.
5.	Park et al. NCT03531606	60 (29 Probiotic and 31 control)	18 - 75	Male: 32, Female: 28	Double-blind, randomized control trial	Probiotics better improved overall ARS scores, especially flatus control, compared to placebo, although both groups' ARS scores changed post-surgery.	Probiotics increased beneficial bacteria, reduced harmful bacteria and zonulin, and lowered postoperative complications.

6.	Mohebian F, et al. IRCT20100911004728N4	66	18 - 65	Male: 21, Female: 45	Placebo-controlled RCT	Yogurt + probiotics significantly reduced defecation frequency, improved stool consistency, and decreased diarrhoea, more so than yogurt alone.	No strong evidence suggests adverse effects from probiotics or yogurt, but yogurt alone might ease post-surgery bowel irritation.
7.	Huang, F., et al. (2023) ChiCTR2000040916	100	40 - 70	Male: 53, Female: 47	Double-blind, randomized control trial	Probiotics significantly reduced chemotherapy-induced diarrhoea, abdominal pain, and constipation compared to the control group..	Probiotics increased beneficial gut bacteria and reduced inflammation-causing bacteria

Table 2: Features of findings from research that were part of systematic review

Sn.	Author details	Intervention	Duration	Measurements	Key results
1.	Zaharuddin L, et al. (2019) [27]	The probiotic group received 30 billion Lactobacillus and Bifidobacteria CFU mixture during morning and evening through pill form daily.	6 Months	The variables such as the status of infection, cytokines in blood and stool pattern in patients.	After six months, the probiotics group showed lower levels of cytokines (TNF, IL-6, 10, 12, 17A, 17C, 22). The study also suggests antibiotics may not be needed due to the supplement's lack of side effects, though probiotics did interact with the anti-tumour agent IFN-γ..($p< 0.05$)
2.	Hibberd et al., 2017 [28]	The supplement contains 14B CFU Bifidobacterium lactis & 7B CFU Lactobacillus acidophilus, releasing slowly over 3 hours.	78 Days	The α and β diversity and the composition of all cancer-causing bacteria.	Tumours exhibit a complex interplay and higher levels of Fusobacterium, Peptostreptococcus, and other bacteria, showing greater α diversity than faeces. ($p <0.05$)
3.	Komatsu et al (2018) [29]	Patients received 2 supplements: 30B Lactobacillus casei + 2.5g galacto oligosaccharides, and 10B Bifidobacterium breve + 1g galacto oligosaccharides.	7-11 days	Sample bacterial group composition, detection rates, and tumour-mycobacterium correlation were analysed.	Synbiotic patients had 10 times more bacteria per gram than controls, with increased detection rates. The study found no link between tumour stage and supplement use ($p = 0.015$)

4.	Yang et al.[30]	A 2g supplement containing Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis is given for 12 days, starting 5 days before and ending 7 days after surgery.	12 Days	The important blood indices, bowel movements, bowel function recovery, and other clinical outcome variables to analyse the results.	Probiotics sped up initial flatus and defecation but didn't impact diet transition or complications. They aid bowel recovery and may improve post-surgery treatment. ($p = 0.0274$)
5.	Park et al. [31]	Participants took a probiotic powder Bifidobacterium animalis subsp, Lactobacillus casei and Lactobacillus plantarum for 4 weeks: 1 week before and 3 weeks after surgery.	4 Weeks	ARS questionnaire evaluated patient symptoms. Faecal microbiome, anti-inflammatory markers, and lifestyle variables were analysed.	Probiotic groups showed a 31% increase in ARS scores vs. the control group. Changing microbiome composition improved the gut microbiome's anti-inflammatory nature. Blood Zonulin decreased by 66%. The probiotic group had very few adverse events/complications compared to the control group ($p=0.030$).
6.	Mohebian F, et al. [32]	The yogurt + probiotic group was given existing probiotics with 4mg of loperamide each day.	7 days	Questionnaire: Participants ranked daily stool consistency, defecation frequency, and diarrhoea	Yogurt plus probiotics best reduced CRD symptoms and improved recovery. Yogurt alone also significantly improved CRD symptoms over the control. ($p > 0.05$)

7.	Huang, F., et al. (2023) [33]	Probiotics were given in tablet form 3 times a day after chemotherapy, containing 4 strains: Enterococcus faecalis, Bacillus cereus, Lactobacillus acidophilus, and Bifidobacterium infantis.	6 Weeks	Nausea, diarrhoea, abdominal pain, distention, and acid reflux were measured. Stool diversity and fatty acid presence were also assessed.	Probiotics significantly reduced post-chemotherapy abdominal complications, increased gut microbiota diversity and beneficial bacteria, and boosted good fatty acid production. (p = 0.008)

Table 3: Quality assessment of all included studies

	Huang et al. (2023)	Zaharuddin et al. (2019)	Hibberd et al. (2017)	Komatsu et al. (2018)	Yang et al. (2016)	Park et al. (2020)	Mohebian et al. (2023)
Sequence creation							
Population assign bias							
Presentation bias							
Detection bias							
Attribution bias							
Reporting bias							
Other bias							
Very low risk of bias							
Low risk of bias							
High risk of bias							
Very high risk of bias							

Table 3 shows the Risk of bias in all the included studies based on the Office of Health Assessment and Translation (OHAT) Assessment tool [38,39]