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Gut Microbiome Dynamics and the Therapeutic Potential of Probiotics in Colorectal Cancer: Insights into Progression and Treatment: A Systematic Review

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ABSTRACT:

Objective: This systematic review explores the role of gut microbiome dynamics in colorectal cancer (CRC) development and the therapeutic potential of probiotics.

Methods: Dysbiosis, marked by an imbalance of harmful microbes like Bacteroides and Fusobacterium, and a reduction in beneficial bacteria, contributes to CRC progression by promoting inflammation and oxidative stress.

Results: Probiotic interventions, such as Bifidobacterium longum and Lactobacillus acidophilus, have shown promise in rebalancing the gut microbiome, improving intestinal barrier function, and mitigating CRC-related inflammation. Randomised controlled trials show that probiotics can improve gastrointestinal symptoms caused by chemotherapy and reduce pro-inflammatory cytokines such as IL-6.

Conclusion: The results are promising but there are challenges like small sample sizes and variation in probiotic formulations. Future research should target large scale trials in order to refine probiotic use and to understand its mechanistic impact on CRC better. Probiotics offer potential as a complementary therapy in CRC management, improving patient outcomes and quality of life.

1. INTRODUCTION

The second largest cause of cancer-related fatalities globally and the third most frequently diagnosed malignancy is colorectal cancer (CRC) [1]. Colorectal cancer development is associated with both controllable and non-modifiable risk factors. Individuals have little control over their medical history, including inflammatory bowel disease (IBD) history, adenomatous polyp history, age, race, or family history. The variables that can be changed have to do with personal habits or ways of living [2]. In practically every region of the world, the number of people born after the early 1950s who have colorectal cancer (CRC) has increased. [3]. The human digestive system contains billions of microbes, including a highly diverse gut microbiota that is shaped at birth and whose composition is largely determined by a multitude of genetic, nutritional, and environmental factors [4]. Human homeostasis is maintained in significant part by the gut microbiota, which is acknowledged as the largest endocrine organ [5]. The intestinal mucosa may experience dysregulation and chronic inflammation as a result of gut microbial dysbiosis, which can foster the development of colorectal cancer [6]. Our gut microbiome, or gut system, is home to at least 100 trillion bacteria. With

a biomass of roughly 1.5 kg, the human gut microbiota is a complex ecology. Additionally, the microbes in the ascending colon, distal colon, proximal ileum, and jejunum have different compositions. These microbes are essential for maintaining our homeostasis and general health, which includes food digestion, vitamin biosynthesis, behavioural responses, and pathogen defence [7]. It is believed that colorectal carcinogenesis is influenced by oxidative stress and inflammation in the colonic epithelium. Furthermore, if the colonic barrier is compromised, colonocytes may be exposed to a greater amount of toxins from the colonic environment, which may aggravate inflammatory processes and the release of reactive oxygen species (ROS). There is also a growing awareness of the aetiological significance of the gut microbiome and its composition in the development of colorectal cancer (CRC). These factors are smoking, physical inactivity, obesity, and the consumption of processed meats, red meats, and alcoholic beverages [8]. In patients with colorectal cancer the probiotic intervention improves intestinal permeability, tight junction function, and enzyme activity it releases antimicrobials and anticarcinogenic compounds it helps to remove carcinogens and it improves the microbiota [9]. This systematic review emphasises the importance of gut microbiota in the aetiology of colorectal cancer (CRC). Dysbiosis, or imbalance in the gut microbiota, disrupting intestinal homeostasis, is a significant contributor to the development of colorectal cancer. In addition, the review focuses on the therapeutic potential of probiotics in slowing down the progression of CRC, providing a promising approach to manipulate the gut microbiome to improve patient outcomes.

MATERIALS AND METHODS

STUDY DESIGN:

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was followed in conducting this systematic review.

ELIGIBILITY CRITERIA

We incorporate observational research (cross-sectional, case-control, cohort) and interventional studies (randomised controlled trials, non-randomized trials). The search only included studies that were published in English. Included were only research articles released between January 2015 and May 2024.

Case reports, case series, editorials, commentaries, and letters to the editor were excluded. Studies with pregnant women, animals as models, and children under eighteen years were excluded. Excluding purely theoretical studies or those that do not demand empirical evidence.

SEARCH STRATEGY AND INFORMATION SOURCES

Based on the described P.I.C.O. (Population, Intervention, Comparison, Outcome) paradigm, the research search was conducted.

The search terms [“gut microbiota” OR “intestinal flora”] AND [“CRC”] were used in four databases: PubMed, EMBASE, Scopus, and Web of Science. Medical Subject Headings (MeSH) terms were used when conducting searches on PubMed, whereas Embase Subject Heading (Emtree) terms were used for searches on EMBASE.

STUDY SELECTION AND DATA EXTRACTION

Data given from each study that were manually retrieved from the full text publications included the following: first author, year of publication, study type, diagnostic criteria, specimen type, study sample size for both CRC and controls, gut microbiome dysbiosis, and probiotic therapy. After a careful review of abstracts, full texts, and titles, publications that discussed the pathophysiology of gut microbiota and colorectal cancer (CRC) as well as the association between probiotic and synbiotic consumption and CRC, were deemed eligible for inclusion. We were able to manually search the reference lists of the included research and review papers. To ensure no important details were missed, a thorough check of the references in the included papers was also conducted.

ASSESSMENT OF RISK OF BIAS

All of the results that were provided were arranged in tables that demonstrated the pathophysiology, metabolic implications, influence of gut dysbiosis on colorectal cancer, and function of probiotics on colorectal cancer.

RESULTS

Table 1: Gut Microbiota Dysbiosis and Colorectal Cancer

STUDY AUTHOR (YEAR)	SAMPLE SIZE	POPULATION CHARACTERISTICS	GUT MICROBIOME DYNAMICS
Deepak Bamola et.al., (2022)	24	12 healthy volunteer, 12 colorectal cancer patient	In comparison to the healthy group, we found that the colon cancer group had a noticeably higher abundance of Bacteroidetes. Actinobacteria and the phylum Firmicutes were much more prevalent in the healthy group.
Iradj Sobhani et.al., (2011)	179 patients	60 with colorectal cancer 119 with normal colonoscopy	This discrepancy was caused by the higher concentration of Bacteroides/Prevotella bacteria in cancerous groups as compared to normal groups. The Bacteroides/ Prevotella group levels were unaffected by the patient's age, body mass index, the purpose for the colonoscopy, or if they had a family history of polyps or cancer.
Jinho Yang et.al., (2019)	250	161 healthy individuals (85 females and 76 males) 89 patients with colorectal cancer (37 women and 52 men)	Twelve genera were found to be substantially changed in CRC patients, according to this investigation. Among these were higher prevalences of Bacteroides, Fusobacterium, Dorea, and Porphyromonas and lower carriage of Pseudomonas, Prevotella, Acinetobacter, and Catenibacterium.
Tingting Wang et.al., (2012)	102	56 healthy volunteers 46 with colorectal cancer	The gut microbiota of CRC patients had one OTU that was highly associated with Bacteroides fragilis, whereas the gut microbiota of healthy volunteers had three OTUs associated with Bacteroides vulgatus and Bacteroides uniformis. Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus, and Peptostreptococcus were the genera with the highest number of OTUs (11 total) in the gut microbiota of CRC patients compared to the genus Roseburia and other butyrate-producing bacteria in the Lachnospiraceae family.
Zhiguang Gao et.al., (2015)	61	30 healthy volunteers 31 CRC Patients	Patients with colorectal cancer had higher abundances of the genera Lactococcus Fusobacterium, Escherichia-Shigella, and Peptostreptococcusten, but lower abundances of the following genera: Psychrobacter, Pseudomonas, Stenotrophomonas (Gammaproteobacteria), Pedobacter, Sphingobacterium (Sphingobacteria), Caulobacter, Brevundimonas, Sphingomonas, Sphingomonas (Alphaproteobacteria), Acidovorax, Janthinobacterium (Betaproteo-bacteria), Buttiauxella, Rahnella, Acinetobacter, Janthinobacterium, Psychrobacter, and Propioni-bacterium (Actinobacteria).

Table 2: Gut Microbiota Treatment and Colorectal Cancer

STUDY AUTHOR (YEAR)	STUDY TYPE	SAMPLE SIZE	POPULATION CHARACTERISTICS	PROBIOTICS (TREATMENT)
Yongzhi Yang et.al., (2016)	Randomized controlled trial	60	30 Control Group, 30 Probiotics group	Enterococcus faecalis, Lactobacillus acidophilus, and Bifidobacterium longum (1:1:1) with a minimum of 1.0x107 CFU/g viable cells, three times a day, for a five-day daily dose of 6.0x107 CFU.
Babak Golkhalkhali et.al., (2017)	Randomized controlled trail	140	70 placebo Group, 70 Probiotics Group	When L. acidophilus, L. casei, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium longum and Bifidobacterium infantis and omega-3 fatty acids were administered, the level of IL-6 decreased whereas it increased in the placebo group.
Feng Huang et.al., (2023)	Randomized, single-blind, placebo-controlled prospective study	100	50 placebo Group, 50 Probiotics Group	E. fecalis, B. cereus, L. acidophilus, and B. babies. Giving probiotics might help mitigate the gastrointestinal side effects of chemotherapy, especially diarrhoea.

DISCUSSION

This review provides a comprehensive overview of the potential of probiotics to act as a therapeutic strategy to modulate the dynamics of the gut microbiome, highlighting their critical role in the pathogenesis of colorectal cancer. Some studies included in this review show a characteristic dysbiosis in CRC patients compared to healthy subjects. The potential contribution of changes in microbiome composition to the development of CRC has been reported. Significant differences include the enrichment of pathogenic bacteria (e.g. Bacteroides, Fusobacterium, Escherichia/Shigella and Enterococcus) and the depletion of beneficial bacteria (e.g. Roseburia and butyrate-producing strains).

CRC and the gut microbiome:

Studies reviewed consistently demonstrate that CRC patients have significant alterations in gut microbial composition with higher abundance of pro-inflammatory and possibly carcinogenic microorganisms. In CRC patients, Bacteroides and Fusobacterium have been detected to enhance tumourigenesis through increasing inflammation, oxidative stress and altering immune responses. But in healthy people, microbiomes usually are more balanced with a higher proportion of beneficial, anti-inflammatory bacteria, like Roseburia and Lachnospiraceae, which are involved in butyrate production, a key short-chain fatty

acid that protects against CRC .

Gut dysbiosis either by altered composition or disturbed microbial balance also appears to be an important factor in CRC development and progression via increased intestinal permeability and production of toxic compounds . These findings underscore the importance of further studies to better understand the causation and molecular processes that link dysbiosis and CRC aetiology.

Probiotics as a Treatment Strategy:

Several studies have shown the therapeutic potential of probiotics, including modification of the gut flora, restoration of balance, and retardation of CRC progression. The probiotic treatments studied in the research were mainly aimed at rebalancing the microbiota, improving the integrity of the intestinal barrier, and reducing the inflammatory responses that lead to CRC

formation. importantly, Bifidobacterium longum, Lactobacillus acidophilus and Enterococcus faecalis showed positive results in randomised controlled trials (RCTs) for gastrointestinal symptoms and immunological responses Specifically, probiotics have been reported to decrease chemotherapy-related adverse effects such as diarrhoea, indicating a wider therapeutic potential in the management of CRC.

Moreover, studies on the effects of probiotics in association with anti-inflammatory drugs and omega 3 fatty acids, suggest that these therapies can reduce pro-inflammatory cytokines such as IL-6, often elevated in CRC patients . The results suggest that probiotics can be effective in a synergistic way with traditional drugs to increase efficacy and to decrease side effects . Limitations and Future Research

Nevertheless, although the results are excellent, many caveats must be pointed out. Many of the studies included in the study had small sample sizes which could have impacted the generalisability of the findings. First, there is the issue of the range of probiotic strains and dosages used in the trials, making it difficult to draw firm conclusions about the optimal probiotic formulation for CRC treatment. Besides, the long-term effects of probiotics on prevention and recurrence of colorectal cancer are still unknown and needed more study.

Future studies should be conducted on large sample sizes and multicenter trials to find out therapeutic benefits of probiotics and the most beneficial strains and dosage. Moreover, further detailed studies are needed to clarify the molecular mechanisms of probiotics in regulating gut microbiome and influencing CRC progression. Knowledge of the cross-talk between probiotics, host immunity and gut microbiota is essential for the development of personalised microbiome-based therapies for CRC patients.

CONCLUSION

In summary, this systematic review demonstrates the importance of gut microbiome dynamics in colorectal cancer and suggests that probiotics may be a promising complementary therapeutic approach to CRC. Further studies are warranted to confirm these results and optimise the administration of Probiotics. Preliminary findings are in line with the potential of Probiotics to modulate gut microbiome, reduce inflammation and improve CRC patient outcomes. Hence, probiotics may be a useful tool in CRC management, possibly exerting preventive and therapeutic effects by restoring microbial equilibrium and reinforcing gut defence mechanisms.

CONFLICTS OF INTEREST

There are no Conflicts of interest

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AUTHOR CONTRIBUTION

Dr. Palur Ramakrishnan Anandvijayakumar – Conceived the idea.
Dr. Dhivyaprasath Palaniappan – Prepared the Article.
Dr. Velavan.K – Reviewed the Article.
Dr. K. Kavi Shankar - Reviewed the Article.
Dr. Angelin Grace T – Edited.
All authors read and finalised the manuscript.

AI USE STATEMENT

No artificial intelligence (AI) or AI-assisted tools were used in the writing, data analysis, or creation of figures for this manuscript.

ETHICAL APPROVAL

PROSPERO NO: CRD42024629224

ABBRIVATION

CRC - Colorectal Cancer.

IBD - Inflammatory Bowel Disease.

IL-6 - Interleukin 6.

ROS - Reactive Oxygen Species.

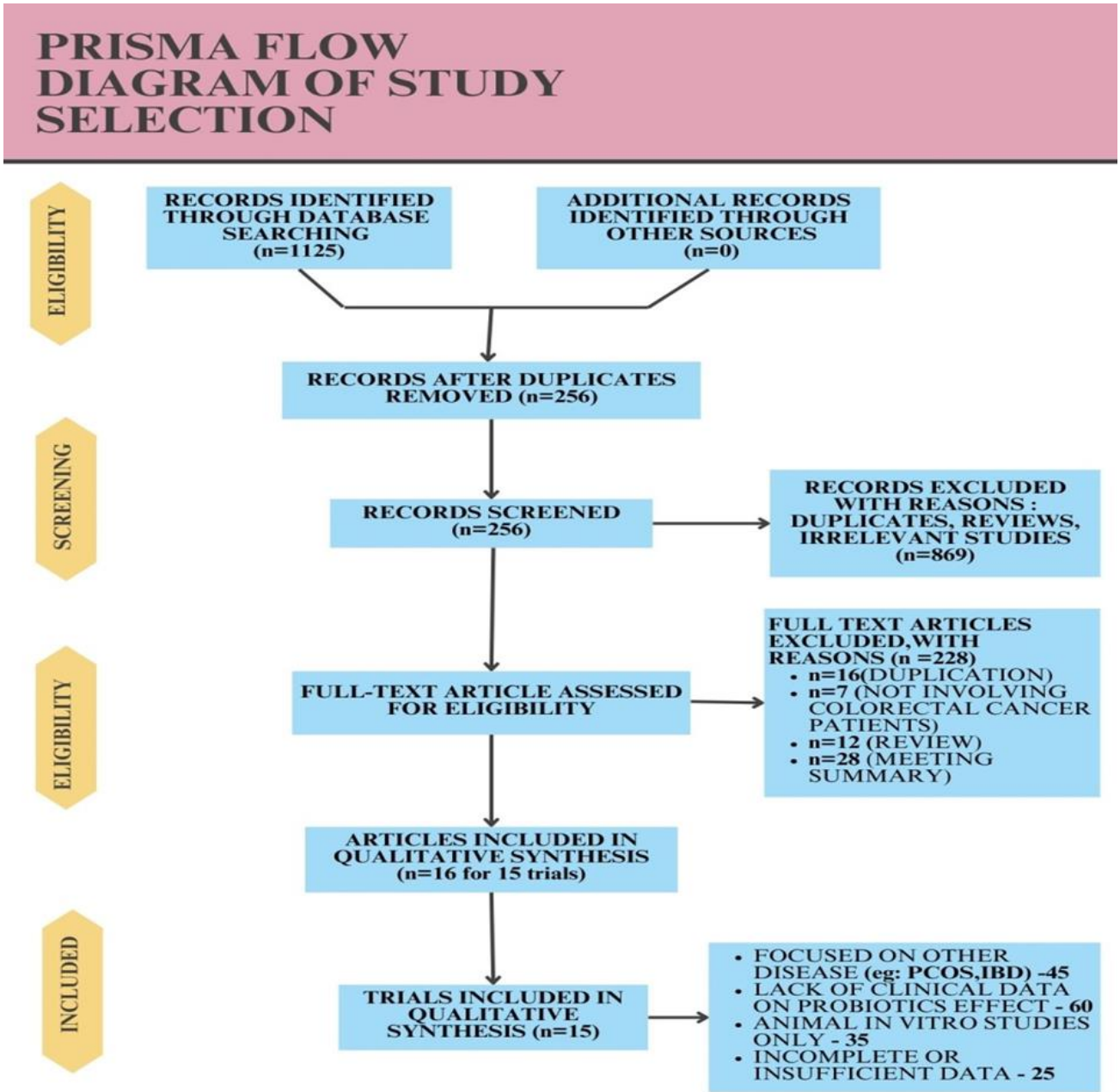

FIG.1: Flow Chart of the Systematic Review

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