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Review Article

The Role of Probiotics in the Prevention and Complementary Treatment of Colorectal Cancer.
Part 2: Therapeutic Mechanisms, Probiotic Strains, and Naturopathic Interventions.

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Abstract

Building upon the microbiological foundations established in Part 1, this article evaluates the therapeutic potential of probiotics as adjuncts in the prevention and clinical management of col-orectal cancer (CRC). We detail the specific mechanisms through which beneficial strains—primarily from the Lactobacillus and Bifidobacterium genera—modulate the immune re-sponse, strengthen the intestinal barrier, and produce anti-cancer metabolites such as butyrate. The paper further contrasts the role of pathogenic bacteria, like Fusobacterium nucleatum, with the protective effects of next-generation probiotics. Additionally, we explore a holistic naturopathic framework, integrating dietary modifications and targeted supplementation to mitigate the side effects of conventional treatments like chemotherapy. Ultimately, this review advocates for an integrative oncological approach to improve clinical outcomes and enhance the quality of life for CRC patients.

Keywords: Probiotics; Complementary Therapies; Colorectal Cancer; Naturopathy.

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Background

The term "probiotic" is derived from the Greek, meaning "for life". It was first used by Lilly and Stillwell in 1965 [1] and has since received many conceptual designations [2].

However, the current definition, formulated by the Food and Agriculture Organization (FAO) and the WHO, maintains that probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [3-6].

This definition emphasises that the efficacy of probiotics depends on both the viability of the microorganisms and the dose administered, highlighting the crucial role these microorganisms can play in promoting intestinal health and preventing disease [7]. They are bacteria or yeasts that help maintain digestive health, strengthen the immune system, and can prevent or treat pathologies related to the gastrointestinal tract. Probiotics are found in foods or dietary supplements. Table 1 schematically presents the classification, types, and sources where probiotics can be found.

Mechanisms of Probiotics in the Treatment and Prevention of Colorectal Cancer

Probiotics have emerged as a promising approach in the prevention and supportive treatment of CRC. Studies suggest that by balancing the gut microbiota and improving intestinal health, probiotics can help reduce risk factors associated with CRC

development, such as chronic inflammation and the production of carcinogenic compounds. Through diverse mechanisms, including the regulation of the immune system and the maintenance of intestinal barrier integrity, probiotics present significant therapeutic potential in the fight against this disease [12,13].

Table 1. Probiotics' type, source and examples in food.

	Types	**Sources**	Food Examples	**References**
Probiotics	*Lactobacillus*	Among the lactic acid bacteria belonging to the genus *Lactobacillus*, the following stand out: *Lb. acidophilus, Lb. helveticus, Lb. casei* (subsp. *paracasei and subsp. tolerans), Lb. paracasei, Lb. fermentum, Lb. reuteri, Lb. johnsonii, Lb. plantarum, Lb. rhamnosus* and *Lb. salivarius*.	*Yoghurt*; Sour cream; *Kombucha*; Sourdough breads; Some beers; *Sauerkraut*; Most cheeses; Types of cheeses such as *Kefir* and cottage.	8-11
	Bifidobacteria	Among the bacteria belonging to the genus *Bifidobacterium*, the following stand out: *B. bifidum, B. breve, B. infantis, B. lactis, B. animalis, B. longum* and *B. thermophilum.*		

The mechanisms of probiotics include:

- Modulation of the gut microbiota: They promote a balance between beneficial and pathogenic bacteria, thereby reducing intestinal dysbiosis [14].
- Production of Short-chain fatty acids (SCFAs): Probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium*, produce SCFAs through the fermentation of dietary fibres. Butyrate, in particular, possesses anti-cancer properties, including the promotion of tumour cell apoptosis and the reduction of intestinal inflammation [15].
- Strengthening the Intestinal Barrier: Probiotics help maintain the integrity of the intestinal barrier, preventing the translocation of toxins and pathogens into the systemic circulation. Dysfunction of this barrier is associated with chronic inflammation and CRC development [16].
- Immune System Modulation: Probiotics stimulate the immune system, increasing the activity of Natural Killer (NK) cells and macrophages, which are vital in the defence against tumour cells. Furthermore, they can reduce chronic inflammation, which is linked to cancer risk [17,18].
- Production of Anti-cancer Compounds: Certain probiotics can inhibit intestinal bacterial enzymes, such as β-glucuronidase, which are associated with the production of carcinogenic compounds. Genera such as *Lactobacillus* and *Bifidobacterium* can reduce the production of these carcinogens [19-21].
- Reduction of Chronic Inflammation: Probiotics decrease inflammation by regulating the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [22].
- Interference with Cell Signalling Pathways: Studies demonstrate that probiotics can influence cell signalling pathways related to cell proliferation and apoptosis, such as the β-catenin and NF-κB pathways, which are frequently dysregulated in cancer [23-25].

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Bacteria Associated with Colorectal Cancer

The tumour microenvironment of colorectal carcinoma is a complex community of genomically altered cancer cells, non-neoplastic cells, and a diverse collection of microorganisms. Each of these components can contribute to carcinogenesis. However, the role of the microbiota remains the least understood [26].

Studies have shown that the microbiota of CRC patients, when compared to healthy controls, is enriched with opportunistic pathogenic and pro-inflammatory bacteria. These can inhibit, disrupt, or exaggerate the host's normal response, leading to abnormal apoptosis, cell proliferation, and inflammation [27-29].

The bacteria associated with CRC development include *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *Escherichia coli* [30]. *F. nucleatum* is a Gram-negative anaerobic bacterium found in the oral and gastrointestinal microbiota. While typically located in the mouth and associated with periodontal diseases, it can also establish itself in other areas of the intestine [31]. A study demonstrated that *F. nucleatum* is linked to increased tumour cell proliferation through the modulation of the *β-catenin* signalling pathway [32]. Additionally, it interferes with the host's immune response, promoting an inflammatory environment that favours CRC development [26].

Bacteroides fragilis is a common Gram-negative anaerobic bacterium of the gastrointestinal tract (GIT). However, certain strains produce toxins (enterotoxins) that can trigger chronic intestinal inflammation, leading to the activation of oncogenic signalling pathways, such as the Wnt/β-catenin pathway, and an increased risk of CRC [26].

Escherichia coli and *Salmonella*: Some strains of *E. coli*, especially those producing toxins such as *colibactin*, are associated with CRC. *Colibactin* induces DNA damage, leading to mutations and cancer development [33].

Beneficial Bacteria in the Treatment and Prevention of CRC

Probiotics may be useful in cancer prevention and can serve as adjuncts during treatment [34]. Beneficial bacteria, such as Lactobacillus and *Bifidobacterium*, have been extensively studied for their potential in CRC treatment due to their ability to modulate the immune system, reduce inflammation, and produce anti-cancer metabolites, such as SCFAs. These metabolites promote tumour cell apoptosis and inhibit cellular proliferation. Furthermore, these microorganisms play a role in restoring the gut microbiota, which is frequently disrupted by treatments such as chemotherapy and radiotherapy; this restoration can improve both the patient's response to treatment and their quality of life [35].

The efficacy of microorganisms from the genus Lactobacillus—including *L. casei*, *L. paracasei*, *L. rhamnosus*, *L. plantarum*, and *L. acidophilus*—as well as other genera such as *B. lactis* and *B. longum*, has been investigated in CRC patients. Results revealed a reduction in the proliferation and growth of cancer cells, alongside a decreased inflammatory response.

Moreover, these probiotics improved the integrity of the intestinal mucosa, exerted stimulatory effects on the immune system, and prevented metastasis. *L. casei* inhibits atypical colorectal tumours, while *L. rhamnosus* reduces abdominal pain in CRC patients undergoing chemotherapy with 5-fluorouracil. Other studies conducted with L. acidophilus, *L. plantarum*, *L. rhamnosus*, *B. longum*, *B. bifidum*, *B. tetragenous*, and *E. faecalis* demonstrated a reduction in surgical site and postoperative infections, as well as intervention-associated septicaemia. Conversely, an increase in protective antibody levels, specifically IgG and sIgA, was observed [16].

The administration of probiotic strains can mitigate the adverse effects of antitumour therapy, particularly following surgical procedures, chemotherapy, and radiotherapy. Radiotherapy often causes diarrhoea in these patients, known as radiation-induced diarrhoea. In a double-blind, placebo-controlled study, it was demonstrated that the administration of *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *B. longum*, *B. breve*, *B. infantis*, and *S. thermophilus* could reduce the risk of diarrhoea in patients receiving radiotherapy after CRC surgery [36].

Next-generation probiotics, such as *Bifidobacterium* spp. and *Bacteroides fragilis*, have opened new therapeutic perspectives for CRC. Certain *Bifidobacterium* strains may enhance the efficacy of antitumour therapies based on immunotherapy. Currently, these next-generation strains are considered a novel therapeutic strategy for CRC treatment. However, further studies are required to clarify their mechanisms of action and explore potential treatment hypotheses [36,37].

The ability of probiotics to prevent the proliferation of cancer cells may stem from the acidification of the colonic pH promoted by *Bifidobacteria*, which inhibits enzymes capable of converting pre-cancerous cells into malignant ones. At a molecular level,

probiotics such as *Bifidobacteria* exhibit anti-cancer activity by affecting the function of the cytochrome P450 enzyme, which is involved in the conversion of azoxymethane from a pre-cancerous to a cancerous state, suggesting they possess CRC-suppressive characteristics [38].

Naturopathic Treatment of Colorectal Cancer

The naturopathic approach to CRC involves the use of natural and complementary medicine practices to restore the body's balance holistically during conventional cancer treatments, such as chemotherapy and surgery. Although this approach does not replace traditional medical treatments, it is regarded by many as a means to improve quality of life, strengthen the immune system, and reduce the side effects of conventional therapies. Naturopathy employs several methods to restore the body's natural balance, including:

Diet: Nutrition plays a significant role in the development of CRC. The focus is on diets rich in fibre, vegetables, fruits, and whole grains, which can assist in the prevention of CRC [39,40].

Supplementation: Supplements may be used to support CRC treatment. For instance, studies suggest that Vitamin D may help regulate cellular growth and reduce inflammation [41,42]. However, dosage must be carefully managed, taking the patient's clinical status into account [41]. Furthermore, one study demonstrated that after adjusting for inflammatory markers, there was no significant change in this association [43].

Other Interventions: Supplements such as vitamins, minerals, and antioxidants must be used with caution to avoid potential interactions with prescribed medications. Acupuncture may help reduce the side effects of chemotherapy, such as nausea and fatigue [44]. Other recommended practices include stress management, physical exercise, yoga, meditation, *Qigong*, and massage [45-49].

Conclusion

The evidence presented in this study highlights the therapeutic potential of probiotics, particularly strains of *Lactobacillus* and *Bifidobacterium*, as vital adjuncts to conventional therapies. By producing anti-cancer metabolites such as butyrate, strengthening the intestinal barrier, and modulating the immune response, probiotics not only inhibit carcinogenesis but also mitigate the adverse effects of chemotherapy and radiotherapy, thereby enhancing patient quality of life.

Furthermore, integrating these microbial strategies within a holistic naturopathic framework—emphasising high-fibre nutrition, targeted supplementation, and lifestyle modification—offers a comprehensive approach to cancer care. While the current results are promising, further clinical research is essential to fully elucidate the molecular mechanisms of next-generation probiotics and to refine their application in personalised oncology.

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