

Probiotics, Prebiotics, Synbiotics: Is There Enough Evidence to Support Their Use in Colorectal Cancer Surgery?

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Key Words

Probiotics · Synbiotics · Colorectal cancer · Surgery · Review

Abstract

Background/Aims: Pro-/pre-/synbiotics supplementation seems to provide beneficial effects in various aspects of abdominal pathology. Skepticism exists with respect to their effects on colorectal cancer (CRC) patients. This review presents the potential clinical applications of pro-/pre-/synbiotics in CRC surgery. **Methods:** A literature search of electronic databases was conducted and all studies published on 'probiotics', 'prebiotics' and 'synbiotics' were collected. Among them, the ones referring to CRC and which had any clinical relevance offering information on perioperative parameters were used. **Results:** Incorporation of pre-/pro-/synbiotic formulations in the preoperative mechanical bowel preparation cannot be supported by the current evidence. Limited clinical studies may be promising in supporting their potentially protective role against postoperative infectious complications. Encouraging are the results on their protective role against adjuvant (chemo)radiation-induced diarrhea. Such supplementation may also hold promise to improve

postcolectomy gastrointestinal related quality of life. **Conclusions:** Despite the positive results and plethora of agents, bacterial combinations and concentrations, the inconsistency in administration, the inhomogeneity of comparison groups and lack of stringent clinical endpoints remain obstacles in the effort to establish a definitive clinical strategy at this time. Further work is warranted to gain a keen understanding of their clinical value in CRC patients.

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Introduction

The human large intestine is recognized as one of the most metabolically active organs with an extremely complex and dynamic resident living bacteria ecosystem [1–3]. Recent evidence supports the important role of diet and colonic microflora in the etiology of colorectal cancer (CRC), which has led to an intense interest in factors that can modulate the gut microflora and their metabolism, such as probiotics, prebiotics and synbiotics [4].

A probiotic, as defined by Fuller [5], is a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance. Ex-

amples are lactic acid-producing lactobacilli, a number of Gram-negative *Escherichia coli* strains and *Saccharomyces boulardii* [5]. A prebiotic, as defined by Gibson and Roberfroid [6], is a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that have the potential to improve host health. Examples include inulin-type fructans and oligofructose [7, 8]. The term synbiotics is used to determine the combination of probiotics and prebiotics which is believed to be more efficient compared to probiotics and prebiotics alone in terms of gut health and function [6]. It is now widely accepted that regular ingestion of probiotics, prebiotics or synbiotics can modify the population of gut microflora, thereby modifying intestinal function, macroscopic and microscopic structure, immune response, inflammatory procedures, and susceptibility to CRC [9].

Pro-/pre-/synbiotics' potential anticancer activity has been mainly supported by a number of laboratory studies [10, 11]. Alteration of the intestinal microflora composition/competition with the consumption of probiotics, reduction of intestinal inflammation (as well as of the mutagenic, carcinogenic and genotoxic compounds), elevation of immune response and increased short-chain fatty acid production have been proposed as potential chemopreventive mechanisms [12]. In addition to the exploration of their potential chemopreventive role, several researchers have focused on the beneficial clinical role pro-/pre-/synbiotics may have at the different stages of CRC management, such as preoperatively as an adjunct to the mechanical bowel preparation, perioperatively in an attempt to reduce infectious complications, and postoperatively as gut-protective agents during adjuvant treatment administration. This review presents the potential clinical applications of pro-/pre-/synbiotics in CRC surgery.

Search Strategy

This review is based on the results of bibliographic searches of PubMed, EMBASE, Cochrane Library and Google Scholar. Searches from the literature, unrestricted by language, until April 2012 were performed applying combinations of the following terms: 'probiotics', 'prebiotics', 'synbiotics', 'colorectal cancer', 'bowel preparation', 'infection', 'chemotherapy', 'radiotherapy', 'quality of life' and 'gastrointestinal function'. In addition, we identified relevant trials from the reference list of each selected article.

All studies published on 'probiotics', 'prebiotics' and 'synbiotics' were collected and, from these, the ones that referred to CRC and had any clinical relevance were used for analysis in the present review. Due to the limited information on this matter, all studies offering clinical information on perioperative parameters and which referred to patients treated by colorectal resection for cancer were included irrespectively of their nature, i.e. randomized clinical trials, nonrandomized prospective comparative studies, observational prospective studies, etc. Data referring to the type of pro-/pre-/synbiotic used, the mode of supplementation, the comparison groups and the endpoints of the trials were extracted from each study and are analytically presented in the present review. Exclusion criteria for the colorectal studies were based on the type of study (i.e. review), indication (i.e. inflammatory bowel disease) and study population (i.e. radiation for extrarectal pelvic malignancies). When multiple articles for a single study were present, we used the latest publication and supplemented it with data from the previous publications. Relevant information from selective studies and reviews, either experimental (i.e. animal models) or referring to extracolonic abdominal pathologies and being connected to the perioperative parameter discussed in each of the review's sections, were included in order to clarify and accentuate pertinent conclusions from CRC studies, which remained the main scope of this review. Neither publication status nor language of publication was an exclusion criterion. Main results and conclusions derived from the included studies are depicted in table 1.

Results

Bowel Preparation

Scientific Background

There is no clear evidence that mechanical bowel cleaning significantly reduces the mortality and morbidity in patients undergoing elective colorectal surgery [13]. The intestinal microbiota and their products may affect a patient's clinical outcome by influencing the immunologic, endocrine and barrier functions of the gastrointestinal track [14]. Preoperative mechanical cleaning and intestinal starvation can cause overgrowth of pathogenic bacteria, such as Gram-negative bacteria including Enterobacteriaceae, predisposing to intestinal inflammation, ulceration and microbial translocation [15–18]. Gastrointestinal microflora may be modulated by prebiotics and probiotics by the competitive inhibition of pathogenic strains' colonization [19, 20].

Table 1. Cardinal results and conclusions derived from CRC-related studies included in this review

| Author | Type of action | Number of patients | Comparison | Immune response/gut barrier/microbiological data | Clinical outcome | Remarks/conclusions |
|----------------------|--|---|--|--|--|---|
| Horvat et al. [21] | bowel preparation | 68 | synbiotics vs. prebiotics + heat-deactivated probiotics vs. MBP | higher IL-6 (72 h) and fibrinogen (24 h) in the synbiotic group | no difference in postoperative complications | probiotics can stimulate the immune response |
| Reddy et al. [22] | bowel preparation | 92 | MBP vs. neomycin + MBP vs. synbiotics + neomycin + MBP vs. synbiotics + neomycin | decreased enterobacteria-positive samples and lower bacterial translocation in synbiotics + neomycin + MBP group | no difference in septic morbidity | decreased bacterial translocation may lead to decreased incidence of postoperative sepsis |
| McNaught et al. [43] | prevention of postoperative infections | 129 | pre- and postoperative <i>Lactobacillus</i> 299v + oat fiber vs. placebo | no difference in mesenteric lymph nodes translocation | no difference in infection rates | limiting factors: short period of administration, potential sensitivity of probiotics in acidic stomach environment, inhomogeneity and lack of stratification |
| Anderson et al. [47] | prevention of postoperative infections | 144 | synbiotics (<i>L. acidophilus</i> La5, <i>B. lactis</i> Bb-12, <i>S. thermophilus</i> , <i>L. bulgaricus</i> + oligofructose) vs. placebo | no difference in bacterial translocation | no difference in infection rates | |
| Rayes et al. [48] | prevention of postoperative infections | 90 (mixed population including colectomies) | enteral nutrition+ nasojejunal probiotic + inulin vs. enteral nutrition + inulin vs. parenteral nutrition | no data | decreased infection rates in synbiotic groups | |
| Liu et al. [57] | prevention of postoperative infections and effect on HRQoL and GI function | 100 | probiotics (<i>L. plantarum</i> , <i>L. acidophilus</i> and <i>B. longum</i>) vs. placebo | increased transepithelial resistance, reduced bacterial translocation, decreased blood enteropathogenic bacteria and increased fecal bacterial variety in the probiotics group | decreased postoperative infectious complications; decreased central line, respiratory and urinary infections; lower diarrhea incidence, shorter time to defecate; lower incidence of abdominal cramping and distension in the probiotics group | results are attributed to the restriction of bacterial translocation and maintenance of intestinal flora – improvement of HRQoL and GI function with probiotics |
| Zhang et al. [26] | prevention of postoperative infections | 60 | probiotics (<i>B. longum</i> , <i>L. acidophilus</i> , <i>E. faecalis</i>) vs. placebo | lower levels of endotoxins, IL-6, CRP, higher sIgA and inversion of <i>Bifidobacterium/Escherichia</i> ratio in the probiotics group | decreased rates of postoperative bacteremia and septicemia | results are attributed to the restriction of bacterial translocation and maintenance of intestinal flora |
| Giannoti et al. [58] | prevention of postoperative infections | 31 | <i>B. longum</i> (BB536), <i>L. johnsonii</i> (La1) vs. placebo | decreased number of Enterobacteriaceae and less active dendritic cells in patients colonized by La1 | no data | dose and time of administration are the key factors in obtaining the results |
| Rafter et al. [63] | prevention of CRC | 80 (37 colon cancer and 43 polypectomized) | synbiotics (prebiotic SYN1 and probiotics <i>B. lactis</i> Bd12 and <i>L. rhamnosus</i> GG) vs. placebo | decreased <i>C. perfringens</i> strains, reduced colorectal proliferation, improved epithelial barrier, decreased IL-2 secretion and increased INF- γ in the synbiotics group | no data | synbiotic intervention can favorably modulate colon cancer biomarkers |
| Roller et al. [64] | prevention of CRC | 80 (34 colon cancer and 40 polypectomized) | synbiotics (inulin + oligofructose + <i>L. rhamnosus</i> + <i>B. lactis</i>) vs. placebo | increased IL-2 and INF- γ in the synbiotics group | no data | synbiotics have minor stimulatory effects on the systemic immune system |

Table 1. (continued)

| Author | Type of action | Number of patients | Comparison | Immune response/gut barrier/microbiological data | Clinical outcome | Remarks/conclusions |
|-----------------------|-------------------------------------|---|---|--|---|---|
| Osterlund et al. [68] | adjuvant treatment-related toxicity | 150 | <i>L. rhamnosus</i> GG vs. fiber | no data | reduced diarrhea, abdominal distention, borborygmi, flatulence and abdominal discomfort in the probiotic group, decreased chemotherapy-related toxicity | probiotic supplementation can reduce chemotherapy-related bowel toxicity |
| Urbancsek et al. [72] | adjuvant treatment-related toxicity | 206 | <i>L. rhamnosus</i> vs. placebo | no data | decreased diarrhea and better feces consistency in the probiotic group | probiotic supplementation can reduce radiation-related toxicity |
| Delia et al. [73] | adjuvant treatment-related toxicity | 190 (100 rectal cancer) | freeze-dried living bacteria compound (VSL/3) vs. placebo | no data | decreased GI toxicity in the probiotic group | probiotics can prevent the occurrence of postradiation diarrhea |
| Delia et al. [74] | adjuvant treatment-related toxicity | 490 (mixed gynecological and rectal cancer) | high-potency probiotic preparation VSL#3 vs. placebo | no data | reduced diarrhea and increased mean time to use loperamide in probiotics group | probiotics may benefit the prevention of enteritis and colitis associated with adjuvant radiation for abdominal and pelvic cancer |
| Timko [75] | adjuvant treatment-related toxicity | 42 (mixed abdominal and pelvic cancer) | Probiotic preparation '5' Strain Dophilus vs. preparation Hylak Tropfen Forte | no data | decreased diphenoxylate and antibiotics requirements in the probiotic group | prophylactic probiotic therapy produces highly favorable benefit/risk score |
| Ohigashi et al. [79] | HRQoL and GI function | 77 | <i>B. natto</i> and <i>L. acidophilus</i> (Guard) no placebo group | no data | improvements of HRQoL based on EORTC QLQ-C30, SF-36 and Wexner incontinence scale | improvement of HRQoL especially in patients with right colectomy and loss of ileocecal valve |

MBP = Mechanical bowel preparation; GI = gastrointestinal; INF = interferon; CRP = C-reactive protein.

Clinical Studies

Horvat et al. [21] conducted a prospective double-blind randomized placebo-controlled trial comparing the efficacy of synbiotics (n = 20 patients) or prebiotics and heat-deactivated probiotics (n = 28 patients) to standardized preoperative mechanical bowel cleaning (n = 20 patients) in terms of systemic inflammatory response and clinical outcome in patients undergoing colorectal surgery. The researchers used interleukin 6 (IL-6), fibrinogen at 24 h, leukocyte count, C-reactive protein and the lymphocyte/granulocyte ratio as indicators of the inflammatory response. Based on the significantly higher values of IL-6 72 h after the operation in the symbiotic group (p = 0.025) and the increase of fibrinogen at 24 h postoperatively (p = 0.030), they concluded that probiotic bacteria in the uncleaned bowel may stimulate the inflammatory response more than a patient's own flora

plus prebiotics. No clinical advantage was evident since there were no differences in postoperative complications and hospital stay between the groups [21].

Reddy et al. [22] compared the effect of synbiotics, neomycin and mechanical bowel cleaning in gut microflora, gut barrier function, bacterial translocation and inflammatory response after elective colorectal surgery. Based on the polymerase chain reaction in fecal samples and cultures of nasogastric aspirates, the researchers observed a decrease in Enterobacteriaceae-positive samples in patients who had received the combination of synbiotics, neomycin and mechanical bowel cleaning while the same patients had a significantly lower incidence of bacterial translocation after bowel mobilization. However, gut barrier function, severity of systemic inflammatory response and septic morbidity were found to be similar between patients who had the above com-

combination, the combination of neomycin and mechanical bowel cleaning, the combination of neomycin and synbiotics and mechanical bowel cleaning only [22]. Diminishing the occurrence of bacterial translocation may lead to a decreased incidence of postoperative septic events, and synbiotics may indirectly contribute to decreased postoperative morbidity and mortality by strengthening the gut barrier [23]. Further studies are required to determine their benefits as an adjunct or substitution to mechanical bowel preparation on clinical outcomes.

Postcolectomy Infections

Scientific Background

A significant number of patients who have undergone colectomy for cancer have experienced postoperative infections [24–27]. The decreased postoperative intestinal motility, the antibiotics leading to small bowel bacterial overgrowth, the loss of mucosal barrier function due to malnutrition and the suppression of the gut immune system by blood products and operative trauma are the most important factors predisposing the patient to translocation from pathogenic bacteria [28–32]. The use of broad-spectrum antibiotics in order to eliminate potential pathogenic bacteria has been shown to reduce bacterial colonization of the gut, but had no impact on overall infection rates and mortality [33–35]. It is obvious, therefore, that there is a need for alternatives that target the restriction of bacterial translocation and which aim at protecting the mucosal barrier in order to protect patients who undergo abdominal operations from postoperative infections.

Probiotics may prevent overgrowth of potential pathogens by direct antimicrobial effects, such as lactic acid production [36]. They also preserve and/or reinforce the mucosal gastrointestinal barrier function through a variety of mechanisms, such as prevention of bacterial adherence to the epithelial lining by competitive exclusion, inhibition of pathogenic-induced alterations of epithelial permeability and regulation of enterocyte gene expression involved in maintenance of the mucosal barrier [37, 38]. Furthermore, specific probiotic strains inhibit the local proinflammatory reactions in enterocytes after stimuli such as pathogenic bacterial adhesion or ischemia/reperfusion injury [39]. Probiotics are also thought to have regulatory effects on the systemic immune system after abdominal surgery through a number of different pathways, such as induction of IL-10 secretion by monocytes and lymphocytes and reduction of the production of the proinflammatory cytokine IL-6 [40, 41].

In a recent review, Bengmark [42] supported that probiotics and synbiotics appear to be effective when they are administered in health-concerned individuals to prevent disease, especially in elective surgical procedures. Immune modulatory formulas appeared to increase the secretion of anti-inflammatory cytokines while *Lactobacillus* strains (e.g. *L. paracasei* and *L. plantarum*) are believed to reinforce the immune response in many different ways. Older studies incorporating a mixed abdominal surgery patients, including colectomies, did not show a significant positive effect of synbiotics in postoperative outcome [22, 43]. On the other hand, Pitsouni et al. [44], in a recent meta-analysis of 733 abdominal surgery patients, demonstrated decreased postoperative infection frequency in patients receiving pro-/synbiotics than in the control group, while the mortality rate was the same between these two groups. The major benefit of supplementation seemed to be related to inhibition of bacterial translocation. Interestingly, this meta-analysis suggested that the length of antibiotic therapy and hospital stay were significantly shorter in patients receiving pro-/synbiotics [44]. According to the meta-analysis of 13 randomized controlled trials by Kinross et al. [45], the administration of probiotics reduced the infective complications (pneumonia, sepsis, wound infection, urinary tract infections) after elective abdominal surgery. The addition of synbiotics seems to strengthen the outcome especially in terms of shorter hospital stay and antibiotic therapy. Jeppsson et al. [46] also concluded that the effects of nutrients in colorectal surgery are not so significant compared to hepatobiliary and upper gastrointestinal tract surgery because the number of mucosa-associated bacteria is far greater in the lower gastrointestinal tract. In these conditions it is much more difficult to control the microbial balance, and the role of immune modulation is less prominent. A longer period of administration and higher doses of probiotics may be required to establish a statistically significant result in terms of infective complications prevention [46]. Complementing the remarks derived from the aforementioned meta-analysis and reviews, and in agreement with the concept of the present review, the clinical studies involving or focusing only on CRC patients are discussed below.

Clinical Studies

One group of researchers has performed three consecutive studies. Initially, 64 patients treated pre- and postoperatively with 107 *L. plantarum* 299v plus oat fiber (ProViva; Skanemejerier, Malmö, Sweden) were com-

pared to a control group of 65 patients [43]. No significant differences regarding bacterial infection rates (13 vs. 15%) and degree of bacterial translocation in mesenteric lymph nodes (12 vs. 12%) were demonstrated [43]. Following that, the perioperative treatment of 72 patients with a synbiotic combination containing *Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb-12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* (Trevis; Christen Hansen, Denmark) and oligofructose did not result in a decrease of infectious complications (32 vs. 31%) and bacterial translocation (12 vs. 11%) [47]. However, in the third study, where only colorectal surgical patients (n = 88) were included and received mechanical bowel preparation alone, neomycin plus mechanical bowel preparation, neomycin plus mechanical bowel preparation plus synbiotics (Trevis) or neomycin plus synbiotics, it was revealed that synbiotics significantly reduced bacterial translocation (21, 5, 0 and 18%, respectively) and the amount of fecal Enterobacteriaceae, but this was not associated with a reduction in serum levels of C-reactive protein and IL-6 or septic morbidity (21, 18, 15 and 14%, respectively) [22]. The relatively short postoperative period of administration, the potential sensitivity of probiotics in the acidic environment of the stomach and the unavoidable inhomogeneity of the operations due to the mixed populations and the unstratified risk for development of operative infections may all account for the lack of effectiveness of these studies.

On the other hand, in their first study performed with synbiotics, Rayes et al. [48] included a mixed population of surgical patients (colectomies, hepatectomies, gastrectomies and pancreatectomies) and used early enteral nutrition plus nasojejunal administration of one probiotic (*L. plantarum* 299) and inulin as fiber, which was compared with enteral nutrition plus inulin alone or parenteral nutrition without synbiotics. A beneficial effect of synbiotics was proven as the infection rate decreased from 30% in the parenteral group to 10% in the rest of the synbiotic-treated patients [48]. Again lack of stratification, the short period of synbiotic administration (5 days) and the mode of nutrition are limiting factors to making definitive conclusions on the real value of synbiotics in infectious complication prevention after colectomies. It has to be stressed, though, that probiotic and synbiotic treatment has been beneficial in pylorus-preserving pancreatoduodenectomy, conventional pancreatectomy, acute pancreatitis, hepatobiliary resections, multisystem trauma and intensive care unit patients [49–56].

In a more recent randomized double-blind clinical study, Liu et al. [57] evaluated the effects of probiotic sup-

plementation as a part of preoperative bowel preparation compared to placebo. One hundred patients with CRC were randomly divided into a control group (n = 50) and a probiotics group (n = 50). Patients in the probiotics group received daily encapsulated bacteria (Institute of Life Science, Shanghai Jiao Tong University, Shanghai, China), containing *L. plantarum*, *L. acidophilus* and *Bifidobacterium longum*. The probiotics were given orally for 6 days preoperatively and 10 days postoperatively. The authors used intestinal flora profiles, gut barrier function and systemic immune responses to estimate the risk for postoperative infection and related complications. Compared with the control group, the probiotics group had increased transepithelial resistance ($p < 0.05$), reduced transmucosal permeation of horseradish peroxidase and lactulose/mannitol ratio, reduced bacterial translocation ($p < 0.05$), decreased ileal bile acid-binding protein ($p < 0.05$) and a positive rate of blood bacterial DNA ($p < 0.05$), and an enhanced mucosal tight junction protein expression. They had decreased blood enteropathogenic bacteria and increased fecal bacterial variety. The clinical significance of the results lies at the decreased postoperative occurrence of infectious complications (14% for the probiotics group vs. 46% for the control group, $p < 0.05$), which was translated to decreased central line, respiratory and urinary infections, but a nonsignificant difference in intra-abdominal and incisional infections. It seems that these effects can be attributed to the maintenance of the intestinal flora and restriction of bacterial translocation from the intestine [57].

In a recently published single-center prospective randomized control study, Zhang et al. [26] randomly equally assigned 60 patients undergoing colorectal resection to preoperative (from the 5th to the 3rd day prior to the operation) administration of 3 oral bifid triple viable capsules, containing *B. longum*, *L. acidophilus* and *Enterococcus faecalis* (Shanghai Sine Wangxiang Pharmaceutical Co., Shanghai, China), 3 times a day or placebo treatment. A postoperative significant increase of *Bifidobacterium* counts, along with a decrement of *Escherichia* counts ($p < 0.05$) and an inversion of the *Bifidobacterium/Escherichia* ratio, but lower levels of endotoxins, D-lactic acids, serum IL-6 and C-reactive protein, and higher levels of serum IgG and sIgA ($p < 0.05$) were all noted in the probiotics group compared to controls. The overall significant decrease of postoperative infections in the probiotics group (10.0 vs. 33.3%, $p < 0.028$) was due to the lower incidence of septicemia and bacteremia in the colectomized patients who had received probiotics, while the differences of pneumonia, surgical site and intra-abdom-

inal infections did not reach statistical difference, a fact that may be related to the power of this study. Again, the maintenance of the intestinal flora and restriction of bacterial translocation were attributed as the possible mechanisms for the enhancement of systemic/localized immunity and the concurrent attenuation of the systemic stress response [26].

Gianotti et al. [58] evaluated the potential adherence of probiotic bacteria to the colonic mucosa and their role on the inhibition of pathogenic bacteria and the stimulation of the gut immune response. The researchers used *B. longum* and *Lactobacillus johnsonii*, but only the latter was able to adhere to colonic mucosa and colonize feces. This finding was correlated with a reduction of potentially pathogenic bacteria and decreased stimulation of dendritic cells. In particular, dendritic cells isolated from patients colonized with *Lactobacillus* appeared to be less active and not able to respond to a second inflammatory challenge, such as lipopolysaccharides, leading to a decreased inflammatory response. Finally, according to the researchers, the dose of probiotics and the time of administration with respect to the operation seem to be key factors in obtaining these results [58].

The effect of synbiotics in surgical patients depends on a variety of factors, including the exact type of operation, the concentration of probiotics and the time of therapy. Specifically, it seems that probiotic therapy should be long enough, especially postoperatively, to prevent infections. It is clear that the use of synbiotics in order to decrease the risk for infections following abdominal surgery must be carefully tested and evaluated in new randomized controlled clinical studies.

Postcolectomy and Postpolypectomy Prevention of CRC Scientific Background

Accumulating evidence from animal studies support that probiotic strains may prevent CRC and, in some cases, may treat established tumors [4, 10]. Even though the mechanisms involved are not well defined, evidence exists for a few of them. One is the alteration of the intestinal microflora composition: the significant reduction of fecal putrefactive bacteria (i.e. coliforms) and the increment of commensal bacteria (i.e. *Lactobacillus* and bifidobacteria) following the consumption of probiotic organisms has been associated with a reduced incidence of colonic adenocarcinoma in IL-10 knockout mice treated with a strain of *Lactobacillus salivarius* [59]. Another is the reduction of mutagenic and carcinogenic compounds, such as bacterial enzymes: *Lactobacillus* and *Bifidobacterium* strains have been demonstrated to decrease the ex-

tent of 1,2-dimethylhydrazine-induced DNA damage in rats, while they may possess significant antigenotoxic effects in vitro [60, 61]. Finally, there is evidence for an elevation of immune response, e.g. the cytoplasmic fraction of *Lactobacillus* and *Bifidobacterium* strains were able to significantly reduce tumor proliferation in vitro, increase survival rate in mice injected with tumor cells and promote antitumor activity via increased cellular immunity [62].

Clinical Studies

Only a few human studies have investigated their immunomodulatory effects of probiotics and prebiotics in patients after polypectomy. Rafter et al. [63] described the first randomized, double-blind, placebo-controlled trial evaluating the antitumor effect of the combination of the prebiotic SYN1 and the probiotics *B. lactis* Bd12 and *L. rhamnosus* GG on polypectomized and colon cancer patients. The researchers used fecal and blood samples which were obtained before, during and after the intervention for the evaluation of intestinal microflora, and colorectal biopsy samples obtained before and after the intervention as biomarkers of CRC. The synbiotic supplement led to significant changes in intestinal microflora. In particular, the *Bifidobacterium* and *Lactobacillus* strains increased while the *Clostridium perfringens* strains were decreased. The examination of the colorectal biopsies showed that the intervention significantly reduced colorectal proliferation and improved the epithelial barrier function. The examination of the blood samples showed that synbiotic consumption inhibited IL-2 secretion from mononuclear cells in the polypectomized patients and stimulated the production of interferon- γ in the cancer patients. The researchers suggested that the synbiotic intervention can favorably modulate a number of CRC biomarkers in polypectomized and colon cancer patients [63].

Roller et al. [64] conducted a randomized double-blind placebo-controlled trial evaluated the effects of the prebiotic inulin enriched with oligofructose in combination with the probiotics *L. rhamnosus* and *B. lactis* Bd12 on the intestinal immune system of polypectomized and CRC patients who underwent curative resection. The researchers measured the phagocytic and respiratory burst activity of neutrophils and monocytes, the lytic activity of natural killer cells, and the production of IL-2, IL-10 and IL-12, as well as tumor necrosis factor- α and interferon- γ produced by activated peripheral blood mononuclear cells prior to intervention, and 6 and 12 weeks after the start of the intervention. They also exam-

ined the concentrations of transforming growth factor- β 1 and prostaglandin E₂ in feces. The results showed that the IL-2 secretion by activated peripheral blood mononuclear cells was increased in the polypectomized patients who received synbiotics while its supplementation resulted in increased interferon- γ production in colon cancer patients at 6 and 12 months after the intervention. The researchers concluded that the intervention with synbiotics after colectomy for colon cancer patients or after polypectomy has only minor stimulatory effects on the systemic immune system [64].

An effort was made to extrapolate the mostly in vitro evidence for antineoplastic effect and potentially chemopreventive role of pro-/pre-/synbiotics, but data for patients after excision of neoplastic lesions remain insufficient, and long-term epidemiologic data to support the routine administration of these agents for preventive purposes is still lacking.

Adjuvant Treatment-Related Toxicity

Chemotherapy: Scientific Background

Although studies in treating chronic IBD are extensive, pro-/pre-/synbiotic therapeutic potential in chemotherapy-induced gastrointestinal toxicity is less well known [65]. In a mouse sarcoma model, dietary fiber chitosan delayed onset of 5-fluorouracil (5-FU)-induced diarrhea and selectively inhibited 5-FU uptake into the small intestine without affecting 5-FU incorporation into the tumor [66]. In a rat model, while *L. plantarum* 299v did not prevent diarrhea or reduce bacterial translocation, it did reduce 5-FU-related anorexia, weight loss and intestinal load of facultative anaerobes [67].

Chemotherapy: Clinical Studies

In one randomized clinical trial, 150 participants received either *L. rhamnosus* GG (ATCC 53103, Gefilus; Valio Ltd., Helsinki, Finland) that was administered at a dose of $1-2 \times 10^{10}$ per day or fiber (11 g guar gum per day) during chemotherapy [64]. *Lactobacillus* supplementation reduced grade 3/4 diarrhea (22 vs. 37%, $p = 0.027$), flatulence, borborygmi and abdominal distension (2 vs. 12%, $p = 0.025$), and any grade of abdominal discomfort (59 vs. 75%, $p = 0.058$). *Lactobacillus* supplementation had no significant effect on the overall toxicity, or the frequency of stomatitis and neutropenia. Twenty-one percent of the patients who received *Lactobacillus* had chemotherapy dose reductions due to bowel toxicity as compared to 47% of those who did not receive *Lactobacillus* ($p = 0.0008$) [68].

Radiotherapy: Scientific Background

Radiation therapy is believed to disturb the colonization resistance of the indigenous gut flora. This is the main mechanism related to the pathophysiology of acute radiation-induced enteritis and colitis. Pelvic radiotherapy in the (neo-)adjuvant setting is required in a respected proportion of rectal cancer patients. Directions on the use of pre-/pro-/synbiotics could be derived from its use in gynecological cancers. *L. acidophilus* either in conjunction with lactulose as a substrate for the bacteria or in combination with *Bifidobacterium bifidum* have been proven to reduce radiation-induced diarrhea in gynecological malignancies [69, 70]. Nutritional intervention, though, with a probiotic drink containing *Lactobacillus casei* did not reduce the incidence of radiation-induced diarrhea in gynecological cancer, but it did have a significant effect on stool consistency [71].

Radiotherapy: Clinical Studies

A Hungarian study in 206 patients suffering from mild-to-moderate diarrhea induced by radiation therapy was performed to determine the efficacy and tolerability of *L. rhamnosus* (Antibiophilus) in comparison to placebo in a double-blind trial design. The number of bowel movements and feces consistency were improved in the Antibiophilus group ($p < 0.1$ and $p < 0.05$, respectively). Diarrhea grade and feces consistency according to patients' self-ratings showed a statistically highly significant treatment-by-time interaction ($p < 0.001$) [72].

A decade ago, an Italian group aimed at determining the ability of a highly concentrated freeze-dried living bacteria compound (VSL#3) to reduce pelvic radiotherapy-induced toxicity in 190 patients, 100 of them having undergone anterior resections for CRC [73]. Gastrointestinal toxicity was found in 50.6% of patients with radiotherapy alone vs. 30.5% of patients receiving VSL#3. Toxicity of degrees 3/4 was found in 28 patients receiving radiotherapy alone versus 7 with VSL#3. These preliminary data suggested the effectiveness of this probiotic compound in preventing the occurrence of postradiation diarrhea [73]. The same group has recently published a double-blind placebo-controlled trial with the same aim on 490 consecutive patients who had received adjuvant postoperative radiation therapy after surgery for sigmoid, rectal or cervical cancers [74]. The patients were randomly assigned to either treatment with VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, Fla., USA), one sachet three times a day, or a VSL#3-identical appearing placebo starting from the first day of radiation therapy

until the end of the scheduled cycles of radiation therapy. Each sachet of VSL#3 contained 450 billion/g of viable lyophilized bacteria, including four strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus*), three strains of bifidobacteria (*B. longum*, *B. breve* and *B. infantis*) and one strain of *Streptococcus salivarius* subsp. *thermophilus*. More patients in the placebo group had radiation-induced enteritis and colitis compared with the VSL#3 group (51.8 vs. 31.6%, $p < 0.001$). Grade 3/4 diarrhea was documented in 55.4% of the placebo-treated patients versus 1.4% of the VSL#3-treated patients ($p < 0.001$). The mean daily number of bowel movements for patients with radiation-induced diarrhea was 14.7 ± 6 and 5.1 ± 3 among placebo and VSL#3 recipients, respectively ($p < 0.05$), and the mean time to the use of loperamide as rescue medication for diarrhea was 86 ± 6 h for patients receiving placebo versus 122 ± 8 h for patients receiving VSL#3 ($p < 0.001$) [74]. The findings of this study reiterated those of the researchers' earlier pilot study and clearly demonstrated the benefits of probiotic therapy with VSL#3 for the prevention and/or reduction of both the incidence and severity of enteritis and colitis associated with adjuvant radiation treatment after surgery for abdominal and pelvic cancer [73, 74].

In a smaller-scale randomized trial of 42 radio-oncology patients who had undergone adjuvant postoperative radiation therapy after abdominal and pelvic cancer, of which only 10 had been treated for CRC, either the probiotic preparation '5' Strain Dophilus (twice per day; L-group) or the preparation Hylak Tropfen Forte (40 drops, three times per day; H-group) were supplemented, starting on the first day and lasting until the end of radiotherapy [75]. The mean daily number of bowel movements was 4.16 in the L-group and 2.52 in the H-group. Abdominal pain was recorded in 25% of the patients in the L-group and 22% of the patients in H-group. Of the patients in the L-group, 27% required diphenoxylate treatment during pelvic radiotherapy, compared with 55% in the H-group. Of the patients in the L-group, 9% required antibiotics administration, compared with 25% in the H-group. The authors concluded that the prophylactic probiotic therapy produced a highly favorable benefit/risk ratio [75]. The few available trials and the presence of significant clinical and statistical heterogeneity limit the potential for robust evidence, but the results are pretty encouraging. More well-performed randomized placebo-controlled studies are required, especially including synbiotic regimens.

Health-Related Quality of Life and Gastrointestinal Function after Colectomy for Cancer Scientific Background

Colectomy for cancer is likely to lead to bowel dysfunction including nausea, vomiting, diarrhea, constipation and abdominal pain which can significantly decrease health-related quality of life (HRQoL). Many recent studies have underlined the importance of HRQoL alterations in the postoperative period in patients with CRC [76–78]. Taking into account the beneficial effects of pro-/pre-/synbiotics in the management of diarrheic syndromes and other gastrointestinal disturbances, postoperative infections and general patient health status, all of which may directly and/or indirectly have a serious effect on HRQoL, their value on this important section of colectomized patients would be worth studying.

Clinical Studies

In a prospective clinical study, Ohigashi et al. [79] examined the functional outcome and the HRQoL after surgery for cancer at different locations (right, left colon and rectum). The Guard (Kowa, Nagoya, Japan), a product containing *Bacillus natto* and *L. acidophilus* as principal probiotics, was provided to 77 patients in doses of three tablets, three times a day (total daily dose 10 mg of *B. natto* and 30 mg of *L. acidophilus*) for a period of 3 months. The Short-Form 36-Item Health Survey (SF-36), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the Wexner incontinence scale were used as the main inquiry tools given to the participants before and after the probiotic treatment. Improvements in the functional outcome and/or HRQoL were observed in all groups after administration of probiotics. Two thirds of them reported improvement in bowel habits, with the right and rectal groups mostly benefited. Patients in the right group exhibited the most marked improvement, with defecation frequency, feeling of incomplete evacuation and global HRQoL on the SF-36 significantly ameliorated. In the left group, the frequency of defecation, role of emotion on the SF-36 and constipation in the EORTC QLQ-C30 were improved; in the rectal group, global HRQoL, constipation and diarrhea in the EORTC QLQ-C30 were improved [79]. The authors speculated that the postoperative changes in the intestinal flora appear to be improved by administration of probiotics, which contributed to improvement of stool frequency, particularly in patients undergoing right colectomy, who had been unavoidably subjected to the loss of their ileocecal valve [79]. While there are adverse effects of symp-

thetic and parasympathetic nerve resection, which are distributed widely throughout the rectum, sigmoid and left colon, probiotics may potentially affect the resulting postoperative intestinal motility disorder [79–81]. The lack of a placebo group was the main drawback of the latter study.

Additive evidence for the potential reversal of the deleterious effect of colectomy on gastrointestinal function comes from the study by Liu et al. [57], in which, compared with the placebo group, the probiotics group had a shorter time to first defecation (3.3 days vs. 4.2 days, $p < 0.05$), a lower diarrhea incidence (10 vs. 30%, $p < 0.05$) and lower incidence of abdominal cramping (26 vs. 38%, $p < 0.05$) and distension (22 vs. 36%, $p < 0.05$).

In an effort to further clarify the potentially beneficial role of synbiotics on gastrointestinal function-related quality of life after colectomy for cancer, our group is in the process of completing a double-blinded prospective randomized trial (NCT01479907), having allocated patients after colectomy for cancer with therapeutic intent to either synbiotics or placebo administration starting on the day they are able to tolerate a postoperative liquid diet and for 15 days thereafter [82]. The primary endpoints of the study are the assessment of gastrointestinal function-related quality of life at 1, 3 and 6 months postoperatively by the use of the validated questionnaire Gastrointestinal Quality of Life Index (GIQLI) and the secondary endpoints are the assessment of functional bowel disorders (diarrhea, constipation, etc.) at 1, 3 and 6 months postoperatively based on the respective domains of the validated instrument EORTC QLQ-C30 [82].

Conclusions

Despite the immense availability of experimental studies and the multitude of tantalizing clinical trials on the potentially positive role of pre-/pro-/synbiotics, a straightforward translation into a clinical evidence-based strategy is not presently possible. Pre-/pro-/synbiotics studies in CRC patients are not only insufficient but, in several aspects, inconclusive. The lack of a systematic and comparative approach, unveiled by the plethora of agents, combinations and concentrations of bacteria used; the inconsistency in duration, timing and the route of their supply; the inhomogeneity of groups for comparison, and the inherent weaknesses of the clinical studies in terms of defining stringent clinical endpoints with value to the surgeon, all remain as obstacles in the effort to assemble this knowledge into a clinical strategy at this time.

Incorporation of pre-/pro-/synbiotics formulations in the preoperative preparation of the CRC patient in lieu of either conventional method of mechanical bowel preparation cannot be supported by the current evidence. Data derived from the limited clinical studies focusing on only CRC patients may be promising in elucidating their potentially protective role against septic complications. Distinct infectious complications, though, need to be specified as separate endpoints in the future with similar clinical studies since intra-abdominal and surgical site infections, which occupy the main part of clinical concern and are closely related to the surgical manipulation, do not seem to be significantly affected. The decrease of bacteremia after treatment with these regimens, although well justified by their biological role, may not be significant enough to reason out their routine perioperative administration in the clinical setting. Until long-term epidemiologic data for the chemopreventive role of pre-/pro-/synbiotics on humans after colectomy for CRC or polypectomy are available, their clinical value on this vital section of CRC posttreatment management may be considered rather limited. As far as for the prevention and treatment of chemotherapy and radiation-induced diarrhea, encouraging results have been observed in human trials. This mode of supplementation may also hold promise to improve postcolectomy gastrointestinal related quality of life. However, it would be interesting for future studies to clearly distinguish the groups of CRC patients who are not only at risk, but also to have the chance to benefit from the administration of pro-/pre-/synbiotics. Further work is warranted to gain a keen understanding of their clinical value in CRC patients.

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