Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives

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Colorectal cancer (CRC) is the third most common form of cancer. Diverse therapies such as chemotherapy, immunotherapy and radiation have shown beneficial effects, but are limited because of their safety and toxicity. Probiotic formulations have shown great promise in CRC as preventive and early stage therapeutics. This review highlights the importance of a balanced intestinal microbiota and summarizes the recent developments in probiotics for treating CRC. Specifically, this report describes evidence of the role of probiotics in modulating the microbiota, in improving the physico-chemical conditions of the gut and in reducing oxidative stress. It also discusses the mechanisms of probiotics in inhibiting tumour progression, in producing anticancer compounds and in modulating the host immune response. Even though some of these effects were observed in several clinical trials, when probiotic formulations were used as a supplement to CRC therapies, the application of probiotics as biotherapeutics against CRC still needs further investigation.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in western countries (Kumar et al., 2010). According to the Canadian Cancer Society and the National Cancer Institute, in 2012, an estimated 23,300 Canadians and 143,460 Americans were diagnosed with CRC and 9,200 and 51,690, respectively, died of it. CRC develops by the accumulation of mutations, starting in stem cells at the base of the crypts (Barker et al., 2009), and usually begins as a non-cancerous polyp (Jemal et al., 2011). CRC incidence can be associated with a number of genetic factors such as germline mutations in the mismatch repair genes (Silva et al., 2009) and adenomatous polyposis coli (APC) gene (de Miranda et al., 2009). In addition to genetic predispositions, environmental factors such as lifestyle and diet play an important role in CRC risk (Steffensen et al., 1997). Researchers agree that a diet rich in red meat and processed food with a low consumption of fruits and vegetables increases CRC incidence (Ahmed, 2007; Kono, 2011). This lifestyle and diet also leads to disturbances in the intestinal environment, including the luminal content and microbiota (Zhu et al., 2011). The microbiota plays a role in generating biochemical and physiological conditions that may increase the number of colonic pre-neoplastic lesions (Rowland, 2009; Uronis et al., 2009). Interestingly, consumption of beneficial bacteria can modulate the micro-organisms of the gastrointestinal (GI) system (Prakash et al., 2011). Modulation of the unbalanced gut microbiota can provide a therapeutic and preventive effect by downgrading carcinogenic stimulating events in the colon (Rafter, 2001).

Probiotics are ‘live microorganisms which, when administered in an adequate amount, confer a beneficial health effect to the host’ (Ochman´ski & Barabasz, 1999; FAO/WHO, 2006). Although probiotics have been used to manage a number of GI disorders such as diarrhoea, infection and inflammation (Ehlers & Kaufmann, 2010), their role in preventing and treating CRC is still under extensive investigation. In this context, probiotic bacteria should have potential features relevant to the development of CRC biotherapeutics. For example, lactic acid bacteria (LAB) have shown protective effects against CRC by reinforcing and modulating the host’s natural defence mechanisms (Klaenhammer et al., 2012). LAB may also modify luminal secretions, reinforce the mucosal barrier (Tlaskalova´-Hogenova´ et al., 2011), affect epithelial cell proliferation (Grimoud et al., 2010) and reduce the exposure to toxic and carcinogenic compounds in the colon (Olejnik et al., 2010). This review will highlight the effects of probiotics on the modulation of the gut microbiota, the reinforcement of gut integrity and the physico-chemical conditions. It will
describe the relevance of probiotics in preventing neoplastic formation within the large intestine by decreasing the generation and levels of carcinogens and by the production of anti-carcinogenic and antioxidant metabolites. The review will describe the relationship between the mechanisms of actions of probiotics and the attenuation of CRC risk factors (Table 1). It will subsequently discuss recent studies of the mechanisms of action of probiotics and the efficacy of the different doses and treatments used in preclinical and clinical studies. Then, it will discuss recent findings about immunoregulatory properties of probiotics. Finally, the use of probiotic treatments as supplements to reduce the complications associated with conventional CRC treatments will be described.

Probiotics and their role in modulating CRC-associated intestinal microbiota and gut integrity

Unbalanced gut microbiota in CRC

The normal human GI tract usually maintains a delicate balance of the microbiota with about $10^{12}$ bacteria per gram of luminal content and over 1000 species (Qin et al., 2010). The gut microbiota is responsible for metabolizing nutrients, producing vitamins, endogenous hormones and toxic products (e.g. carcinogens), especially in the large intestine (Guarner & Malagelada, 2003). The microbiota is responsible for degrading organic compounds including food additives, bile salts and cholesterol (Cummings, 1975; Pavlovic et al., 2012). In CRC, the gut microbiota has been

### Table 1. Probiotic potential mode(s) of action in mitigating the factors responsible for CRC

<table>
<thead>
<tr>
<th>Factors linked to CRC</th>
<th>Potential mode(s) of action of probiotics in mitigating factors of CRC</th>
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<tr>
<td><strong>Unbalanced gut microbiota:</strong></td>
<td>Modulation of gut microbiota:</td>
</tr>
<tr>
<td>↑ Bacteroides, Eubacterium, Fusobacterium,</td>
<td>↑ Bifidobacterium, Lactobacillus,</td>
</tr>
<tr>
<td>Proteobacteria, Salmonella and Prevotella</td>
<td>↓ Escherichia, Staphylococcus</td>
</tr>
<tr>
<td><strong>Disrupted colonic physico-chemical conditions:</strong></td>
<td>Improvement of colonic physico-chemical conditions:</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>↓ pH,</td>
</tr>
<tr>
<td>Water absorption in the colon</td>
<td>Improve fermentation</td>
</tr>
<tr>
<td>Incomplete fermentation</td>
<td>↓ Putrefactive products:</td>
</tr>
<tr>
<td>Genotoxic faecal water content</td>
<td>Putrescine, cadaverine and tryptamine</td>
</tr>
<tr>
<td><strong>Damaged epithelial barrier:</strong></td>
<td>Reinforce gut epithelial barrier:</td>
</tr>
<tr>
<td>Normal epithelial cell death</td>
<td>↑ Defensins and mucus production by goblet cells</td>
</tr>
<tr>
<td>↑ Permeability</td>
<td>↑ Cytoprotective heat-shock proteins</td>
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<tr>
<td>Tight junction protein rearrangement</td>
<td>↑ Normal epithelial cell survival</td>
</tr>
<tr>
<td>Pathogen translocation</td>
<td></td>
</tr>
<tr>
<td>↑ Harmful bacterial enzymes:</td>
<td>↓ Bacteria producing harmful enzymes:</td>
</tr>
<tr>
<td>β-Glucuronidase, β-glucosidase, azoreductase, nitroreductase,</td>
<td><em>Bacteroides, Clostridium, Enterococcus, Salmonella, Enterobacter, Streplococcus, Citrobacter, Escherichia and Staphylococcus</em></td>
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<tr>
<td>alcohol dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>↑ Carcinogenic products:</td>
<td>Binding, deactivation of carcinogens:</td>
</tr>
<tr>
<td>IQ, tryptophanase, urease, acetaldehyde, MNNG, AFLB1, TrpP-1,</td>
<td>↑ Detoxifying enzymatic antioxidants:</td>
</tr>
<tr>
<td>N-nitroso compounds, aromatic amines, sodium azide, benzo(α)pyrene, transformed secondary bile salts, aglycones hydrogen sulfide and indoles</td>
<td>GTS, glutathione, glutathione reductase, Glutathione peroxidase, superoxide dismutase and catalase</td>
</tr>
<tr>
<td>↑ DNA damage:</td>
<td>↑ Anti-carcinogenic metabolites:</td>
</tr>
<tr>
<td>↑ Abnormal cell growth:</td>
<td>SCFAs, CLAs, phenols</td>
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<tr>
<td>Dysplasia, tumour formation</td>
<td>↑ Apoptosis</td>
</tr>
<tr>
<td><strong>Intestinal inflammation:</strong></td>
<td>↑ Differentiation in cancer cells</td>
</tr>
<tr>
<td>↑ NF-κB, IL-8, IL6</td>
<td></td>
</tr>
<tr>
<td>↓ Immune response against tumour cells</td>
<td>↓ Intestinal inflammation:</td>
</tr>
<tr>
<td></td>
<td>↓ TLR-4, ↑ IL-10, IL-8 secretion, NF-κB activation</td>
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<td></td>
<td>Immune response against tumour cells</td>
</tr>
<tr>
<td></td>
<td>↑ TNF and NO production in epithelial cells</td>
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<td></td>
<td>↑ Regulatory T-cell activity</td>
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<td></td>
<td>↑ Bactericidal phagocytic activities of neutrophils</td>
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<td></td>
<td>↑ IL-12, stimulation of DCs and NK cells</td>
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</table>
shown to be compromised and unbalanced (Frank et al., 2007). Studies comparing human stool samples of healthy and CRC patients found a significant difference in bacterial genera (Sobhani et al., 2011). Several Lactobacillus species from the intestinal flora were present in lower counts (Wong et al., 2006), while Fusobacterium (Castellarin et al., 2012; Kostic et al., 2012), Bacteroides, Eubacterium, Proteobacteria and Prevotella (Shen et al., 2010; Sobhani et al., 2011), some Salmonella (Schiffman et al., 1989) and Clostridium species (Scanlan et al., 2008) were in higher counts in CRC patients.

Colon microbial carcinogenesis is a process that involves increased counts of CRC-causing bacteria such as enterotoxigenic Bacteroides fragilis that have been shown to induce colon tumour formation in multiple intestinal neoplasia (Min) mice (Sears & Pardoll, 2011). It has, therefore, been suggested that a colon microbial imbalance may increase the proliferation of carcinogenic bacteria that enhance the production of carcinogenic compounds, secondary bile acids and cholesterol metabolites, driving oncogenic transformations in the epithelium and CRC pathogenesis (Arthur & Jobin, 2011). However, further investigations are needed to establish this hypothesis.

**Transient modulation of gut microbiota by probiotic bacteria**

An unbalanced microbial composition can provide favourable conditions for colonic carcinogenesis (Rescigno, 2008). It has been reported that a daily consumption of specific probiotic strains can improve human health, restore the microbiota balance (Lee et al., 2009) and inhibit intestinal colonization by pathogenic micro-organisms (Fig. 1). In a study using 1,2-dimethylhydrazine (DMH)-induced CRC rats, Lactobacillus rhamnosus GG administration reduced the number of coliforms and significantly elevated the count of lactobacilli (Bertkova et al., 2010). According to a recent trial on goats, a mixture of Lactobacillus reuteri DDL 19, Lactobacillus alimentarius DDL 48, Enterococcus faecium DDE 39 and Bifidobacterium bifidum DDBA, significantly modified the faecal microbiota by reducing faecal enterobacteria and increasing bifidobacteria and LAB counts (Apas et al., 2010).

In a clinical trial of CRC patients, the oral administration of probiotic treatment increased the counts of Bifidobacterium, Lactobacillus and Enterococcus and decreased the counts of Escherichia coli and Staphylococcus aureus (Zhang et al., 2012; Zhu et al., 2012). In addition, formulations of Lactobacillus and/or Bifidobacterium strains such as Lactobacillus gasseri OLL2716:LG21 (Ohara et al., 2010) and Bifidobacterium lactis Bb12 (Worthley et al., 2009) have increased Bifidobacterium and Lactobacillus in the faecal flora and decreased pathogen counts, including Clostridium perfringens.

For a better understanding of the action of probiotics on oncogenic/pathogenic bacteria further investigations were required. It was found that probiotic bacteria, delivered to the gut, rely on their antimicrobial, competitive, adhesive and anti-invasive properties to act on other microorganisms and regulate gut microbial activity (Prakash et al., 2011; Jones et al., 2013). In addition, probiotics can provide intestinal and epithelial haemostasis, specifically improving epithelial barrier integrity (Rafter, 2003). Probiotics were found to produce antimicrobial substances, such as bacteriocins, lactic acid, reuterin, hydrogen peroxide and deconjugated bile acids, providing mechanisms for inhibition of pathogenic and carcinogenic microbes (Sušković et al., 2010). Some probiotic bacteria can bind or compete with pathogens for nutrients/molecules, adhere to epithelial cells and block the adherence of pathogens (competitive exclusion) (Prince et al., 2012; Ranadheera et al., 2012), and outcompete pathogens by forming biofilms (Hancock et al., 2010).

**Effects on the gut epithelial barrier**

In the intestinal epithelium, the cells form an impermeable barrier (Amsheh et al., 2009) and are covered with a mucus layer (Mennigen et al., 2009). This barrier protects the intestinal wall from physical and chemical damage, as well as from pathogens (Watson et al., 2005). If pathogenic bacteria penetrate the intestinal epithelium, an inflammatory response is initiated at the site and in the adjacent intestinal mucosa causing damage to this epithelial barrier, increasing CRC risk (Karin et al., 2006). It has been found that probiotic consumption can reinforce the epithelial barrier by preventing tight junction protein rearrangement (Worthley et al., 2009) and by increasing the production of defensins and mucus by goblet cells (Kleessen & Blaut, 2005), as well as reducing the leakage of harmful solutes, micro-organisms and antigens (Fig. 1) (Watson et al., 2005; Mennigen et al., 2009). A recent study indicated that components of E. coli strain Nissle 1917 decreased the permeability of 14C-mannitol by restoring a disrupted epithelial barrier (Stetinova et al., 2010). Preparations of L. rhamnosus GG and B. lactis Bb12, tested on CRC patients, also significantly improved epithelial integrity (Ko et al., 2007; Karczewski et al., 2010). Probiotics prevented epithelial barrier damage by inducing the production of cytoprotective heat-shock-proteins in stressed epithelial cells to maintain haemostasis (Yan & Polk, 2012) and promote cell survival (Mennigen et al., 2009; Khalilova et al., 2010). Interestingly, the epithelial cell signalling implicated is not only stimulated by bacterial metabolites but also by whole bacteria formulations (Madsen, 2012).

**Effects on the gut physico-chemical conditions**

Physico-chemical properties of digesta in the colon such as bulking, water retention, pH, viscosity and levels of bile acids were disrupted in CRC subjects (Ohara et al., 2009; Roessler et al., 2011; Clark et al., 2012). This environment can be altered by probiotics to increase the resistance to carcinogenesis. As demonstrated by Lan et al., upon exposure to probiotic propionibacteria short chain fatty acids (SCFAs, propionate and acetate), an acidic
extracellular pH shifts cancer cell death from apoptosis to necrosis (Lan et al., 2007). Moreover, a slight change in pH conditions (a lower pH in the faeces) can block harmful enzymatic activity of the commensal bacteria and its binding to the surrounding epithelial cell wall and molecules (Wollowski et al., 2001). The toxicity of faecal water content (Prescott, 1912; Grishina et al., 2011) and the degree of water absorption by the colon are one of the first signs of irritation of the colonic mucosa (Jensen et al., 1976). Rats consuming *Bifidobacterium adolescentis* SPM1207 had less faecal water content than did control rats, decreasing colon toxicity, due to reduced exposure to soluble toxic compounds (Wollowski et al., 2001; Lee et al., 2009). A clinical trial on the daily consumption of *L. gasseri* OLL2716: LG21 for 12 weeks in CRC patients demonstrated a decrease in alkalosis in stool and faecal product synthesis (oxidized products from incomplete fermentation) such as putrescine, a cancer marker (Apás et al., 2010; Ohara et al., 2010). Thus, mounting evidence suggests that the improvement of colonic environment by probiotic bacteria is strongly linked to a decrease in colonic irritation and lesions that cause inflammation and abnormal cell growth.

**Effect of probiotics on metabolic and carcinogenic compounds**

**Activity of bacterial enzymes in CRC**

An unbalanced gut microbiota may favour the secretion of bacterial enzymes such as β-glucuronidase, β-glucosidase, azoreductase (Gorbach & Goldin, 1990) and nitroreductase, which produce carcinogens (Kim et al., 1994; Hambly et al., 1997; Ohno et al., 2001). These harmful enzymes generate toxic metabolites such as aromatic amines (Gorbach & Goldin, 1990; Roldán et al., 2008), transformed secondary bile salts (McGarr et al., 2005), hydrogen sulfide (Ramasamy et al., 2006), aglycones (McBain & Macfarlane, 1998), acetaldehydes (Seitz & Becker, 2007) and reactive oxygen species (ROS) (Kumar et al., 2007). β-Glucosidase, for example, can hydrolyse the detoxifying compound glucuronide, and produce other carcinogens.

Bacterial β-glucuronidase produced by *Clostridium perfringens* (Fujisawa & Mori, 1996) increases the genotoxicity of food mutagens, such as 2-amino-3-methylimidazo[4,5-f] quinolin (IQ) in the colon (Abdelali et al., 1995). The bacterial enzymes azoreductase and nitroreductase, produced by...
bacteria such as Bacteroides, Clostridium, Enterococcus, Salmonella and Staphylococcus (Chung et al., 1992), metabolize colourants, drugs and aromatic nitro compounds to generate toxic aromatic amines (Gorbach & Goldin, 1990). Enterobacter, Enterococcus, Streptococcus, Citrobacter and Escherichia increase alcohol dehydrogenase activity and the production of acetaldehyde, a carcinogen (Azcárate-Peril et al., 2011).

Inhibition of harmful enzymatic activity

In CRC patients, bile acids and cholesterol are converted to microbial products faster in the colon, leading to a disrupted enzymatic activity of the faecal flora and the generation of harmful enzymes (Mal et al., 2012). These are reduced by the administration of probiotic formulations. Interestingly, several studies showed that Bifidobacterium or Lactobacillus consumption may limit the formation of toxic metabolites by decreasing the dehydroxylation of primary bile acids and reducing faecal deoxycholic acid concentrations (De Preter et al., 2011). L. rhamnosus GG significantly decreased the activity of β-glucuronidase (Bertkova et al., 2010). Indeed, the activity of harmful bacterial enzymes can be reduced by certain LAB, as observed with Butyrivibrio fibrisolvens supplementation in a mouse CRC model (Ohkawara et al., 2005) and with Lactobacillus plantarum given to rats with DMH-induced CRC (Bertkova et al., 2010). Furthermore, B. adolescentis SPM1207 (Lee et al., 2009) and B. adolescentis SPM212 (Kim et al., 2008) reduced intestinal β-glucosidase, and β-glucuronidase (Kekkonen et al., 2011), as well as tryptophanase and urease, producers of putrefactive products linked to higher incidence of CRC, such as indoles and ammonia (An et al., 2010, 2011).

Removal of carcinogenic products by probiotics

Carcinogenic compounds in the gut. In CRC cases, high oxidative and genotoxic levels in the gut have been observed (Mai et al., 2009; Boleij & Tjalsma, 2012). In fact, high levels of bile acids in the aqueous phase of faeces were detected. Bile acids can exert cytotoxic effects on the colonic epithelium and increase malignant cell proliferation (Fotiadis et al., 2008). Bile acids (e.g. deoxycholic acid and lithocholic acid) are potentially carcinogenic and are negatively correlated with the levels of antineoplastic products in the colon, such as SCFAs (Ou et al., 2012). The colonic mucosa is exposed to cancer-causing compounds (Nancey et al., 2001; Nau, 2011) that are mutagens and pro-mutagens such as N-methyl-N’-nitro-N-nitrosoguanidine (MNNG), IQ, benzo(a)pyrene and sodium azide (Cheah, 1990; Schiffman et al., 1990; Pearson et al., 2009). Also, a high level of food-borne generated compounds (Cross & Sinha, 2004), such as aflatoxin B1 (AFBL1) and 3-amino-1,4-dimethyl-5H-pyrido (4,3-b) indole (TrpP-1), a fungal dietary contaminant, can increase gut genotoxicity (Nancey et al., 2001; Nau 2011). Carcinogens such as N-nitroso compounds and indoles, generated from the intestinal metabolism of proteins, may increase faecal mutagenicity and increase CRC risk (Kelloff et al., 1996; Davis & Milner, 2009).

Recent studies have demonstrated that probiotic bacteria can reduce carcinogen levels by deactivation or mechanical sequestration, reducing the impact on epithelial cells (Fig. 1) (Bomba et al., 2012).

Binding of carcinogens. L. rhamnosus GG and L. rhamnosus LC-705 were shown to bind carcinogens such as indole and AFLB1 and excrete them in the faecal matter (Eaton & Gallagher, 1994; El-Nezami et al., 1998). It was also demonstrated that Bifidobacterium longum, Lactobacillus acidophilus and Streptococcus salivarius strains could bind and cause the release in faeces of heterocyclic amines and mutagens such as 2-amino-3,4-dimethylimidazo [4,5-f] quinoline (MeIQ), 2-amino-3-methyl-3H-imidazo [4,5-f] quinoline (MHIQ), and 5-phenyl-2-amino-1-methylimidazo [4,5-f] pyridine (PhMIP) (Bolognani et al., 1997). The administration of L. reuteri DDL 19, L. alimentarius DDL 48, Enterococcus faecium DDE 39 and B. bifidum DBBA, to animals, and L. gasseri, to CRC patients, decreased mutagen faecal concentrations such as putrescine (Apás et al., 2010), cadaverine and tryptamine (toxic amines) (Ohara et al., 2010). Better methodology for the investigation of binding capacity of probiotic bacteria as well as their effects on mutagens is still required.

Inactivation of carcinogens. LAB can decrease the activity of carcinogens such as MNNG and DMH by scavenging reactive intermediates and producing carcinogen-deactivating and antioxidative enzymes such as glutathione-S-transferase (GST), glutathione, glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase (Liong, 2008). Remarkably, the treatment of colon cells with a supernatant from bacterial fermentation increased GST activity, an enzyme considered as having chemopreventive potential (Scharlau et al., 2009). The probiotic suppression of DMH-induced rat CRC can be related to the detoxifying effect of antioxidative enzymes (Kumar et al., 2012).

Anti-carcinogenic and antioxidant metabolites produced by probiotics prevent CRC

Probiotics enhance the fermentation of dietary fibres (Borowicki et al., 2011) and increase the levels of antitumour compounds such as SCFAs, conjugated linoleic acids (CLAs) or phenols, with potential therapeutic effects against CRC (Wollofski et al., 2001; Le Leu et al., 2010). SCFAs are an energy source for colonocytes (Floh, 2010) and promote acidosis and apoptosis of CRC cells (Pufulete, 2008). B. lactis increased the production of SCFAs promoting an acidic environment that is problematic to the formation of high levels of secondary bile acids (Zampa et al., 2004) and lowering the incidence and multiplicity of colonic neoplasms (Le Leu et al., 2010). A number of probiotic bacteria produce, from lactic fermentation, phenols with antioxidant capacity (Lai et al., 2013) and bioactive fatty acids such as CLAs...
(Mladenova et al., 2011), a group of isomers of linoleic acid, that possess anti-inflammatory and anti-carcinogenic properties (Bertkova et al., 2010). During growth, *Pediococcus pentosaceus* 16:1, *L. plantarum* 2592 and *Lactobacillus paracasei* F19 produce antioxidants corresponding to almost 100 mg of vitamin C (Kruszewska et al., 2002). This antioxidant capacity may inhibit peroxidation and scavenge free radicals, preventing tumour formation (Kumar et al., 2012). On the other hand, Watson has stated in his recent review that the antioxidant nutritional supplements may cause more cancers than they prevent (Watson, 2013). It is clear that more research is needed in this field.

Several anti-carcinogenic and antioxidant probiotic products potentially repress and prevent colon neoplastic growth (Pufulete, 2008) by the acceleration of apoptosis (Borowicki et al., 2011) and the inhibition of cancer cell proliferation. In addition, probiotic bacteria and their metabolites were found to promote cell differentiation (Linsalata & Russo, 2008; Linsalata et al., 2010) and reduce DNA damage in the colonic epithelium (Table 2) (Gozuacik & Kimchi, 2004; Kim et al., 2010).

**Probiotics favourably modulate the host immune response to reduce CRC risk**

Probiotics can both suppress and enhance the intestinal and systemic immune response, offering therapeutic and preventive options against inflammatory diseases and CRC (Takagi et al., 2008; Elmadfa et al., 2010). Probiotics affect immunological and cellular responses by enhancing the epithelial barrier and stimulating the production of anti-inflammatory, antioxidant and anti-carcinogenic compounds. Increasing evidence suggests that probiotics, interacting via Toll-like receptors (TLRs), induce anti-inflammatory cytokine production, initiate NF-κB production in epithelial cells, inhibit NFκB production in macrophages and influence the production of IL-8 needed for the recruitment of neutrophils (Fig. 2) (Gareau et al., 2010). Some strains of lactobacilli can also promote regulatory T-cell activity, stimulate bacterial phagocytic activities of neutrophils in peripheral blood and natural killer (NK) cell activity involved in the suppression of tumorigenesis (Fig. 2) (Ohara et al., 2009).

*Lactobacillus* and *Bifidobacterium* have been shown to decrease the expression of TLR-4, IL-8 secretion and NF-κB activation (Grimoud et al., 2010), potentially caused by the release of bacterial products such as proteins, flagellin and LPS, and to decrease the expression of peroxisome proliferator-activated receptors (PPAR) γ, a ligand for CLAs (Bassaganya-Riera et al., 2002; Ewaschuk et al., 2006; Bassaganya-Riera & Hontecillas, 2010). SCFAs have immunomodulatory functions that affect the inflammatory response, in some cases through interactions with G-protein-coupled receptors in the gut (Kimura et al., 2011). Recent animal and human studies have discussed the cellular and immunological effects of bacterial cells and products of recent probiotic formulations.

**Animal studies**

*Lactobacillus fermentum* FERM P-13857 and *Lactobacillus casei* shirota elicited IL-12 production in bone marrow cell-derived dendritic cells (DCs) in mice (Takagi et al., 2008), which stimulates DCs and activates NK cells, involved in tumour-immune surveillance (Takagi et al., 2008). Also, *L. rhamnosus* GG and *B. adolescentis* bacterial extracts, given to rats, induced macrophage activation and significantly increased the production of TNF-α (Bertkova et al., 2010) and nitric oxide (NO) by macrophages (Lee et al., 2008), which can be cytotoxic or cytostatic to tumour cells (Switzer et al., 2011). Potential immunomodulatory and anti-tumorigenic properties of microencapsulated *L. acidophilus* (Urbanska et al., 2009) and *Saccharomyces boulardii* (Chen et al., 2009) in a yogurt formulation administered to ApC (Min/+) mice was demonstrated. There was a correlation between the reduction of intestinal tumour growth, dysplasia and inflammation with the oral administration of probiotics (Urbanska et al., 2009). The mechanisms involved were related to the downregulation of extracellular-signal-regulated kinases (Erk)1/2 activities through the inactivation of growth receptors such as EGFR (epidermal growth factor receptor) and EGFR-Erk pathways (Chen et al., 2009).

**Human studies**

In a recent animal study, *L. gasseri* OLL2716: LG21 increased IL-1β, a cytokine that plays a central role in the regulation of immune responses, and enhanced NK cell activity in the blood (Ohara et al., 2010). The daily ingestion of fermented milk containing *L. casei* shirota for 3 weeks restored NK cell activity in healthy subjects. Peripheral blood mononuclear cells (PBMCs) from healthy humans were cultured in the presence of heat-killed *L. casei* shirota, which increased the activity of NK cells (Nanno et al., 2011), which play a role in tumour-immune surveillance (Uccello et al., 2012). *L. rhamnosus* GG, *B. lactis* Bb12 and/or inulin enriched with oligofructose demonstrated immune stimulatory effects by inducing the maturation of DC (Roller et al., 2007), reinforcing the immune response against tumour cells (Elmadfa et al., 2010). This formulation has shown anti-inflammatory effects by the activation of IL-10-secreting cells linked to the induction of apoptosis in colon cancer and suppressing pro-carcinogenic factors (Ewaschuk et al., 2006; Zhu et al., 2011).

**Application of probiotics as a supplement to advanced-CRC treatments**

Based on their anticancer properties, probiotics can be used in combination with conventional CRC therapies (such as surgery and chemotherapy) (Baldwin et al., 2010). Data obtained, although based on a limited number of patients and samples, suggest an effective approach for achieving clinical benefits in immune-compromised hosts by improving their intestinal environments (Wada et al.,
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<th>CRC model and treatment</th>
<th>Effects</th>
<th>Potential mechanisms</th>
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<td><strong>Enterococcus faecium</strong> RM11 and <strong>L. fermentum</strong> RM2</td>
<td>Caco-2 cells; live probiotic cells and supernatant</td>
<td>↓ Cell viability</td>
<td>↑ Adherence</td>
<td>Thirabunyanon et al. (2009)</td>
</tr>
<tr>
<td><strong>Saccharomyces boulardii</strong></td>
<td>HT-29, SW-480 or HCT-116; probiotic cells</td>
<td>↓ Colony formation and induction of apoptosis</td>
<td>↑ Adherence, ↑ Apoptosis, ↑ Pan-caspases, ↑ EGFR-Erk and EGFR-Akt pathways, ↑ EGFR and receptor tyrosine kinase signalling</td>
<td>Chen et al. (2009)</td>
</tr>
<tr>
<td><strong>Apc (Min/+) mice</strong></td>
<td>Oral administration of probiotic cells</td>
<td>↓ Intestinal tumour growth and dysplasia</td>
<td>↓ HER-2, HER-3, and insulin-like growth factor-1 receptor</td>
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<tr>
<td><strong>L. delbrueckii</strong> CU/22</td>
<td>HT-29 cells; probiotic supernatant</td>
<td>↑ Apoptosis and necrosis</td>
<td>↑ Bacterial hydrogen peroxide and superoxide radicals</td>
<td>Strus et al. (2009)</td>
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<tr>
<td><strong>L. acidophilus</strong> 606 EPS</td>
<td>HT-29 cells; isolated cell-bound exopolysaccharides (cb-EPS)</td>
<td>↑ Tumour cell death via autophagy</td>
<td>↑ Beclin-1 and GRP78</td>
<td>Kim et al. (2010)</td>
</tr>
<tr>
<td><strong>L. rhamnosus</strong> GG and <strong>B. lactis</strong> Bb12 (aleurone (+))</td>
<td>HT29 and LT97 cells; fermentation supernatant</td>
<td>Alteration of cell morphology</td>
<td>↓ Bcl-2 and Bax regulation, ↑ Cell cycle arrest in G0/G1 and alkaline phosphatase activity, ↑ Apoptosis and p21 and WNT2B BAX translocation, cytochrome c release, and caspase-9 and -3 cleavage</td>
<td>Borowicki et al. (2011)</td>
</tr>
<tr>
<td><strong>B. lactis</strong> and <strong>L. rhamnosus</strong></td>
<td>Caco-2 cancer cell line; live probiotic bacteria</td>
<td>↑ Apoptosis</td>
<td>↑ Apoptosis and p21 and WNT2B BAX translocation, cytochrome c release, and caspase-9 and -3 cleavage, ↑ ErbB receptor-dependent pathway</td>
<td>Altonsy et al. (2010)</td>
</tr>
<tr>
<td><strong>Bacillus polyfermenticus</strong></td>
<td>Colon, breast, cervical and lung cancers and azoxymethane-treated NCM-460 colonocytes; bacterial cell-free supernatant</td>
<td>↓ Colony formation on soft agar</td>
<td>↓ ErbB2 and ErbB3 protein and mRNA expression, ↓ E2F-1-dependent transcriptional regulation of cyclin D1</td>
<td>Ma et al. (2010)</td>
</tr>
<tr>
<td><strong>L. paracasei</strong> subsp. <strong>paracasei</strong> M5, <strong>L. paracasei</strong> subsp. <strong>paracasei</strong> X12, <strong>L. fermentum</strong> K11, <strong>L. fermentum</strong> K14 and <strong>L. casei</strong> X11</td>
<td>Colon, breast, cervical and lung cancers and azoxymethane-treated NCM-460 colonocytes; bacterial cell-free supernatant</td>
<td>Tumours implanted in the skin of nude mice; Injection of bacterial cell-free supernatant</td>
<td>Carcinogen-induced colony formation by normal colonocytes, ↓ Tumour growth</td>
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<tr>
<td><strong>L. plantarum</strong> AS1 CRC induced by DMH in rats</td>
<td>HT-29 cells; cell walls and cytoplasm extracts</td>
<td>↓ Cell proliferation</td>
<td>↑ Apoptosis</td>
<td>Wang et al. (2012)</td>
</tr>
<tr>
<td><strong>S. thermophilus</strong> 14085 and <strong>Bifidobacterium infantis</strong> 14603</td>
<td>HT-29 and Caco-2 cells; extracts from fermented soymilk with organic solvents CRC induced by DMH in rats; pre- and post-treatment with 1 ml containing 10^9 c.f.u. of <strong>L. plantarum</strong> AS1 in saline day^-1</td>
<td>↓ Cell proliferation</td>
<td>S-phase accumulation, ↑ Apoptosis</td>
<td>Lai et al. (2013)</td>
</tr>
<tr>
<td><strong>L. plantarum</strong> AS1</td>
<td>↓ Mean tumour volume diameter and total number of tumours</td>
<td>↑ Antitumour bioactive compounds from bacterial fermentation, Altering lipid peroxidation and antioxidant enzyme activities in the colon and in the plasma</td>
<td>Lai et al. (2013)</td>
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<td><strong>Propionibacterium freudenreichii</strong></td>
<td>HGT-1 cells; fermented milk supernatant</td>
<td>↑ Cytotoxicity of camptothecin, a drug used in chemotherapy</td>
<td>↑ Chromatin condensation and formation of apoptotic bodies, ↑ DNA laddering and cell cycle arrest</td>
<td>Kumar et al. (2012)</td>
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<td>Kumar et al. (2013)</td>
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*Probiotics in colorectal cancer*

**Table 2. Inhibition of cancer cell proliferation and prevention of malignant transformation: effects and mechanisms of probiotics**
The administration of probiotics along with CRC treatment may alleviate the secondary effects related to chemotherapy (Osterlund et al., 2007). Moreover, clinical reports show that probiotics can improve the integrity of the gut mucosal barrier and decrease infectious complications in surgical CRC patients (Liu et al., 2011). Some of the recent applications of probiotic strains in CRC are summarized in Table 3.

With chemotherapy
Recent studies showed the ability of LAB to enhance the apoptosis-induction capacity of 5-fluorouracil (5-FU), a chemotherapeutic agent (Baldwin et al., 2010). According to Osterlund et al., L. rhamnosus GG supplementation reduced several undesirable effects of 5-FU-based chemotherapies such as the frequency of severe diarrhoea and abdominal discomfort (Osterlund et al., 2007). Patients receiving L. rhamnosus GG along with 5-FU-based regimens needed less hospital care, had less bowel toxicity, received fewer chemotherapy doses and suffered less from abdominal pain and diarrhoea than patients with no probiotic administration (Osterlund et al., 2007). Nagata et al, concluded from their study that the enteral administration of Bifidobacterium breve Yakult to cancer patients on chemotherapy was shown to prevent infections and particularly improve the faecal microbiota; the frequency of fever and the use of intravenous antibiotics were also reduced (Wada et al., 2010).

**Effects on complications related to surgery**
In patients with CRC, supplementation with viable probiotics, before surgery, can improve bacterial dysbiosis (Zhang et al., 2010). L. casei shiratai was given to patients whose colonic polyps were surgically removed in order to

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**Fig. 2.** Potential mechanisms of action of probiotic bacteria in the improvement of the physico-chemical conditions and the microbiota balance in the colon while producing beneficial metabolites and reducing toxic compounds. (1) Enhancing mucus production from goblet cell. (2) Reinforcing intercellular integrity by increasing the intercellular integrity of apical tight junctions and producing beneficial metabolites that improve the growth of epithelial cells. (3) Antimicrobial activity by blocking pathogen entry into the epithelial cells and also by producing antimicrobial compounds. (4) Reducing carcinogens production by inhibiting the activity of harmful enzymes that generate potential carcinogens from bile salts, food and other products. (5) Detoxification of toxic compounds by decreasing faecal putrefaction, degrading and binding certain molecules. (6) Inhibiting cancer cell proliferation by producing anti-carcinogenic metabolites that suppress malignant growth and induce apoptosis in cancer cells. (7) Decreasing oxidative stress and genotoxicity by producing antioxidants that scavenge free radicals, such as reactive oxygen species, and reduce DNA damage in colon cells.
suppress the recurrence of CRC (Nanno et al., 2011). Infection following abdominal operation, considered as a factor affecting the morbidity of patients, was reduced using preoperative administration of probiotics. Patients who received daily encapsulated treatment containing B. longum BL-88, L. acidophilus La-11 and L. plantarum CGMCC No. 1258, before and after their operation, had better recovery of peristalsis, lower incidence of diarrhoea (Liu et al., 2011) and reduced infection-related complications (Liu et al., 2011). Likewise, Zhang and colleagues found that the preoperative use of viable Bifidobacterium stabilized the immune status and prognosis of patients undergoing CRC resection and diminished postoperative septic complications (Zhang et al., 2010). Probiotic mixtures supported the intestinal barrier function following CRC surgery, which may have prevented cancer recurrence (Xia et al., 2010). Polypectomized patients and CRC patients who have undergone curative resection while receiving B. lactis and L. rhamnosus had greater PBMCs producing IFN-γ and IL-2, both cytotoxic to cancer cells (Roller et al., 2007).

Effects on inflammation
Lactobacillus johnsonii La1, given orally pre- and post-operatively, adhered to the colonic mucosa, reducing the counts of potentially pathogenic bacteria in the stool (enterobacteria and enterococci). Gianotti and colleagues used L. johnsonii La1 in a formulation with B. longum BB536 and demonstrated the increased expression of naive and memory lymphocyte subsets while reducing dendritic phenotypes, dampening an overinflammatory response at the intestinal and distant sites in case of surgery (Gianotti et al., 2010). In addition to alleviating several undesirable complications associated with CRC treatments, the administration of probiotics to patients may prevent cancer recurrence and improve their quality of life (Xia et al., 2010). On the other hand, a mixture of probiotic bacteria: Pediococcus pentosaceus, Leuconostoc mesenteroides, L. paracasei subsp. paracasei and L. plantarum, with bioactive plant fibres β-glucans, inulin, pectin, resistant starch, postoperatively elevated the levels of the anti-inflammatory cytokine IL-6 and prevented mild wound infection with faecal secretion. In this case, the probiotic formulation did not have an anti-inflammatory effect, probably due to absence of bowel cleaning (Horvat et al., 2010). As described, specific probiotic strains administered in different ways (mixture, period, dose) were effective to a certain extent in bringing clinical benefits to CRC patients. However, more investigations are needed to improve probiotic formulations for better efficacy.

Significance and future directions of probiotic formulations in CRC
Very few reports demonstrate any limitations and negative aspects of probiotic oral supplementation. Some studies suggest that an increased bacterial translocation was related to mortality after supplementation with Lactobacillus delbrueckii UFV-H2b20 and B. lactis Bb12 in mice with DMH-induced injuries. These findings alert us to the potentially severe side-effects associated with the use of probiotics under stressful situations, such as change in environmental and experimental conditions (Liboredo et al., 2010). The variability observed in the documented benefits of probiotics in humans was shown to be dependent on the concomitant therapies and the health baseline status of the patient, the dosing and the addition of prebiotics or many strains into the formulation. Many reports brought to attention another important player minimizing the efficacy of orally administrated probiotics which is the loss in the viability of probiotics reaching the large intestine (Tomaro-Duchesneau et al., 2012b). Subsequently, microencapsulation, defined as the entrapment of viable cells in a polymer matrix, has been suggested to improve cell viability during GI transit (McConnell et al., 2008; Del Piano et al., 2010; Prakash et al., 2011). Microencapsulation of probiotics can confer a significant resistance to gastric juice, thus protecting the bacterial cells during gastric and duodenal transit (Kailasapathy, 2002; Del Piano et al., 2011). Indeed, the use of artificial cell microcapsules allows for a ‘pH controlled delivery’ of the probiotic bacteria through the gut. Concurrently, it allows the diffusion of oxygen, nutrients and metabolites while preventing white lymphocytes, antibodies and cytokines from accessing the microcapsule (Sultana et al., 2000; Kailasapathy, 2002; Tomaro-Duchesneau et al., 2012a). As supported by previous research, this technology may assume a lot of importance in the near future for the development of active probiotic bacterial preparations in treating many diseases, including CRC.

Concurrently, recent research continues to support the idea that probiotic consumption may reduce tumour growth, modulate the host immune response and re-establish healthy gut conditions in CRC subjects. Recent studies continue to provide evidence that probiotic formulations have the potential to protect the gut and colon epithelial cells against toxic substances digested or produced within the intestine, reactive metabolites and from compromising activity of pathogens or endogenous commensal bacteria (Iacono et al., 2011; Circu & Aw, 2012). Several studies have shown the immunomodulatory impact of probiotics on the inhibition of tumour growth by the modulation of cytokines production and signalling pathways related to carcinogenesis initiation and epithelial cell growth (Azcárate-Peril et al., 2011; Ullman & Itzkowitz, 2011; Zhu et al., 2011). Research in this field still has to progress towards a solid understanding of the molecular interactions of the micro-organisms with both healthy and compromised hosts (Kleerebezem & Vaughan, 2009). The current treatments of CRC include invasive procedures and toxic drugs that not only attack cancer cells but also affect normal cells (Siegel et al., 2012). As a current view, it seems challenging to portray probiotics as a therapy that can replace these treatments, but, the emerging outcomes of
Table 3. Clinical applications of probiotic formulations in CRC patients

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Treatment</th>
<th>Trial design and CRC conditions</th>
<th>Clinical study outcomes</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td><em>L. rhamnosus</em> GG <em>LGG</em> and <em>B. lactis</em> Bb12</td>
<td>$10^{10}$ c.f.u. of <em>L. rhamnosus</em> GG <em>LGG</em> and <em>B. lactis</em> Bb12 + 10 g of oligofructose-enriched inulin In a capsugel Orally; daily for 12 weeks</td>
<td>Randomized, double-blinded, placebo-controlled trial For 12 weeks 37 CRC and 43 polypectomized patients</td>
<td>↑ Faecal <em>Bifidobacterium</em> and <em>Lactobacillus</em> ↓ <em>Clostridium perfringens</em> ↓ CRC proliferation ↓ Faecal water-induced necrosis in cancer cells ↓ Exposure to genotoxins ↓ Secretion of IL-2 ↑ Production of IFN-γ</td>
<td>Rafter <em>et al.</em> (2007)</td>
</tr>
<tr>
<td><em>L. rhamnosus</em> GG and <em>B. lactis Bb12</em></td>
<td>$10^{10}$ c.f.u. of <em>L. rhamnosus</em> GG and $10^{10}$ c.f.u. of <em>B. lactis</em> Bb12 + 10 g of inulin enriched with oligofructose Encapsulated Orally; daily for 12 weeks</td>
<td>Randomized double-blinded, placebo-controlled trial 34 CRC patients with curative resection and 40 polypectomized patients</td>
<td>↑ IL-2 secretion by activated PBMCs ↑ Capacity of PBMC to produce IFN-γ Minor stimulatory effects on the systemic immune system</td>
<td>Roller <em>et al.</em> (2007)</td>
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<tr>
<td><em>B. longum</em> BB536 and <em>L. johnsonii</em> La1</td>
<td>$10^7$ or $10^8$ c.f.u. of a mixture of <em>B. longum</em> BB536 and <em>L. johnsonii</em> La1 Orally; two daily doses for 3 days preoperatively and 5 days postoperatively</td>
<td>Randomized, double-blinded 31 subjects with elective resection for CRC</td>
<td>Probiotic adherence to the colonic mucosa ↓ Pathogens ↓ Dendritic phenotypes CD83-123, CD83-HLADR; CD83-11c</td>
<td>Gianotti <em>et al.</em> (2010)</td>
</tr>
<tr>
<td><em>Pediococcus pentosaceus</em>, <em>Leuconostoc mesenteroides</em>, <em>L. paracasei</em> 19 and <em>L. plantarum</em> 2362</td>
<td>$10^8$ c.f.u. of each probiotic + 10 g fibre Orally; every 8 h, 2 days preoperatively and at day 2 postoperatively till day 4</td>
<td>Prospective double-blinded randomized placebo-controlled trial 68 patients having mechanical bowel cleaning preoperatively</td>
<td>↑ IL-6 after 72 h ↓ Mild wound infection with faecal secretion</td>
<td>Horvat <em>et al.</em> (2010)</td>
</tr>
<tr>
<td><em>L. plantarum</em> CGMCC No. 1258, <em>L. acidophilus</em> La-11 and <em>B. longum</em> BL-88</td>
<td>$2 \times 10^{11}$ c.f.u. <em>L. plantarum</em> CGMCC No. 1258, $1 \times 10^{10}$ c.f.u. of <em>L. acidophilus</em> La-11 and $5 \times 10^{10}$ c.f.u. of <em>B. longum</em> BL-88 Daily Encapsulated formulation 6 days preoperatively and 10 days postoperatively</td>
<td>100 patients with CRC</td>
<td>↑ Transepithelial resistance ↓ Transmucosal permeation of horseradish peroxidase and lactulose/mannitol ratio ↓ Ileal-bile acid binding protein Positive rate of blood bacterial DNA ↑ Mucosal tight junction protein expression ↓ Blood enteropathogenic bacteria Post-operative recovery of peristalsis Improved infectious-related complications</td>
<td>Liu <em>et al.</em> (2011)</td>
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**Table 3. cont.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><em>L. rhamnosus</em> LGG</td>
<td>$2 \times 10^{10}$ c.f.u. of <em>L. rhamnosus</em> LGG</td>
<td>150 patients having 5-FU-based regimens</td>
<td>↓ Incidence of diarrhoea, ↓ Frequency of severe diarrhoea and abdominal discomfort, ↓ Chemotherapy dose</td>
<td>Osterlund <em>et al.</em> (2007)</td>
</tr>
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<td></td>
<td>Daily for 24 weeks on cycle days 7–14, for 8 days/month</td>
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<td>↓ Abdominal discomfort and diarrhoea, ↓ Risk infection</td>
<td>Wada <em>et al.</em> (2010)</td>
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<tr>
<td><em>B. breve</em> Yakult</td>
<td>Enteral</td>
<td>42 CRC patients on chemotherapy</td>
<td>Improved faecal micro flora and intestinal environments, ↓ Frequency of fever, ↓ Intravenous antibiotics use, ↓ Recurrence of CRC with moderate/severe atypia</td>
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<tr>
<td><em>L. casei</em> Shirota</td>
<td>After surgery</td>
<td>Patients with surgically removed colonic polyps</td>
<td>↓ Pathogens</td>
<td>Nanno <em>et al.</em> (2011)</td>
</tr>
<tr>
<td><em>L. johnsonii</em> La1 and <em>B. longum</em> BBS36</td>
<td>$2 \times 10^7$ <em>L. johnsonii</em> La1 and $2 \times 10^9$ c.f.u. day$^{-1}$ <em>B. longum</em> BBS36, Orally for 3 days pre- and 6 days postoperatively</td>
<td>21 CRC patients</td>
<td>↑ Expression of naive and memory lymphocyte subsets, ↓ Expression of dendritic phenotypes, ↓ Postoperative <em>Bifidobacterium</em>/E. coli (B/E) ratio as compared to preoperative B/E ratios, ↑ Both preoperative and postoperative B/E ratios, ↑ Stool SIgA, while ↓ serum IgG, IgM, IgA, IL-6, CRP</td>
<td>Zhang <em>et al.</em> (2010)</td>
</tr>
<tr>
<td><em>Bifidobacterium</em></td>
<td>Administration of viable bacteria with routine enteral nutrition</td>
<td>60 patients undergoing CRC resection</td>
<td>↑ Expression of naive and memory lymphocyte subsets, ↓ Expression of dendritic phenotypes, ↓ Postoperative <em>Bifidobacterium</em>/E. coli (B/E) ratio as compared to preoperative B/E ratios</td>
<td>Zhang <em>et al.</em> (2010)</td>
</tr>
<tr>
<td>n/a</td>
<td>1 day bowel preparation with probiotics for 3 days</td>
<td>60 patients with colonic surgery</td>
<td>Maintain the intestinal barrier function after surgery CRC</td>
<td>Xia <em>et al.</em> (2010)</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em> M-74</td>
<td>For 3 months</td>
<td>60 CRC patients with colonic adenoma</td>
<td>↑ Biopsies with intracellular bacteria in adenoma and carcinoma group, ↑ Intraepithelial bacteria in patients with large bowel adenoma and carcinoma</td>
<td>Mego <em>et al.</em> (2005)</td>
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</table>
probiotic applications in CRC or other diseases (e.g. IBS, diabetes, allergies) (Collado et al., 2009) suggest the consideration of probiotics for therapeutic and prophylactic purposes. Probiotics have shown clinical latency as a supplement for CRC patients especially when administrated prior/post surgery or during prolonged hospitalization to manage symptoms related to the severity of the disease or the side-effects and other complications related to the treatments. Still, further human studies are needed to guide the decision of their establishment as complementary treatment in CRC.

Acknowledgements

This work was supported by funding from the Canadian Institutes of Health Research (CIHR) MOP 64308 to S.P. The authors wish to acknowledge a McGill Internal scholarship from the George G. Harris Fellowship Program to I.K. and a Doctoral Alexander Graham Bell Canada Scholarship from NSERC to C.T.-D.

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