Review paper

Colorectal cancer and microbiota: systematic review

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Abstract

Introduction: The gut microbiome maintains the mucus membrane barrier's integrity, and it is modulated by the host's immune system.

Aim: To detect the effect of microbiota modulation using probiotics, prebiotics, symbiotics, and natural changes on colorectal cancers (CRCs).

Material and methods: A PubMed search was conducted to retrieve the original and in vivo articles published in English language from 2010 until 2021 containing the following keywords: 1) CRCs, 2) CRCs treatment (i.e. surgical, chemotherapy, radiotherapy and/or immunotherapy), and 3) microbiota probiotic(s), prebiotic(s), symbiotic(s), dysbiosis and/or nutritional treatment. A total of 198 PubMed records/articles were initially identified. 108 articles were excluded at the initial screening, and another 29 articles were excluded after reviewing the abstracts, and finally 61 studies were analysed for this systematic review.

Results: The gut microbiota metabolites and (SCFAs) short-chain fatty acids (i.e. acetate and butyrate) have a protective effect against CRCs. SCFAs reduce the inflammatory cytokines, inhibit colonocyte proliferation, and promote malignant cell apoptosis. Butyrate maintains the integrity of the mucus membrane barrier and reduces intestinal mucosal inflammation. Reduced butyric acid level and increased inflammatory cytokines were observed after reduced Bacteroides fragilis and Bacteroides vulgatus species in the colon. Akkermansia muciniphila bacterium decreased in patients with CRCs.

Conclusions: Prebiotics (i.e. inulin and resistant starch, SCFAs producers) and consumption of unprocessed plant products are useful for developing and maintaining healthy gut microbiota. The pro-, pre- and/or symbiotics may be useful when carefully selected for CRC patients, to restore beneficial gut microbiota and support treatment efficacy.

Introduction

Approximately 10–20% of colorectal cancer (CRC) patients have a family history of the same disease [1], and 5–7% of CRCs have a clear genetic origin [2]. Hereditary CRC syndromes are divided into CRC with polyposis and CRC without polyposis (i.e. Lynch syndrome) [3]. Risk factors for CRCs include inflammatory bowel disease (i.e. Chron's and ulcerative colitis) [4].

The chronic inflammation (i.e. Chron's and ulcerative colitis) is associated with release of inflammatory cytokines with subsequent chronic DNA and cell damage [3]. The chronic DNA/cell damage and/or genetic mutations predispose to the development of premalignant polyps or lesions [5]. The premalignant polyp can be further differentiated into either adenoma-carcinoma (70–90%) or serrated CRC (10–20%). The non-polyposis CRC had lower incidence than the polyposis type [3].

The microbiome includes microorganisms found in the host's epithelial and/or mucus membrane barriers, acquired since birth by vertical transmission, modulated throughout the life of the host by the environment, and reacting with the host in a complex way [6, 7].

The microbiome maintains the health of the epithelial and/or mucus membrane barriers, involved in the development of diseases and it is modulated by the host's immune system [8]. The gut microbiota me-

tabolites, short-chain fatty acids (SCFAs) [9] (i.e. acetate and butyrate) [10] produced by the bifidobacteria have a protective effect against CRC [11]. SCFAs reduce the inflammatory cytokines [11], inhibit colonocyte proliferation, and promote malignant cell apoptosis [12].

Butyrate maintains the integrity of the mucus membrane barrier, regulates the occlusion of the mucosal cell junction, and reduces intestinal mucosal inflammation [13].

Butyrate-producing bacteria such as genus *Butyricicoccus*, can protect against colitis in irritable bowel syndrome [14]. SCFA-producing bacteria are essential for healthier microbiota profiles [15].

Reduced butyric acid level and increased inflammatory cytokines were observed after reduced *Bacteroides fragilis* and *Bacteroides vulgatus* species in the colon [16]. *Akkermansia muciniphila* bacterium decreased in patients with ulcerative colitis [17] and in those with CRC [18].

Dysbiosis means a pathological change and/or imbalance of intestinal microbiota composition, which is associated with tumour development [19, 20]. Intestinal microbiota imbalance (decreased beneficial microbiota and increased pathogenic organisms) is frequently observed in CRC patients, caused by intensive use of antibiotics [21].

Chronic inflammation and disruption of the intestinal mucosal are the most important risks for CRC [22]. H_2S-producing bacteria are associated with CRC development. H_2S-producing bacteria can oxidize and reduce local intestinal SCFAs [23].

H_2S is toxic to colonocytes, it oxidizes the butyrate, damages intestinal mucosal epithelium, and promotes chronic inflammation with a subsequent DNA damage [24]. Additionally, H_2S disrupts the balance between cell proliferation and apoptosis [25]. High H_2S concentrations were observed during stool examination of 100 patients with CRCs [26]. Other studies reported increased *Fusobacterium nucleatum* species (H_2S-producing species) in colonic tumour tissue [27, 28].

The bacterial species associated with development of CRCs include *B. fragilis*, *E. coli* (*Escherichia coli*), *Peptostreptococcus* spp., *Streptococcus bovis*, and *Enterococcus faecalis* [29, 30]. *B. fragilis* and *E. coli* produces local onco-toxins (i.e. *B. fragilis* toxin and colibactin) [31], which increased the tumour growth and mortality from CRCs in animal studies [31].

Although the value of nutrition is frequently underestimated, the available data show that nutrition is crucial in shaping the gut microbiota. The type of food is the main way to interact and modify gut microbiota [32]. Nutritional diseases such as malnutrition and obesity produce major alternations in gut microbiota. A plant-based food can change our microbiota faster than other therapeutic measures. The Mediterranean diet increases the beneficial gut microbiota and the SCFAs [33]. The high-fibre diet decreases the risk of CRCs through increased gastrointestinal motility and decreased contact of pro-cancerous metabolites/toxins to the gut mucosal barrier, and production of SCFAs when fermented by the gut bacteria [34].

Probiotics are "living bacteria that have a beneficial health effect when given in suitable amounts" [35]. The benefits of probiotics range from the maintenance of intestinal mucosal barrier integrity to the prevention of irritable bowel disease [36]. Probiotics modify the gut microbiota, reduce inflammatory cytokines, and secrete anti-cancer metabolites [37]. Additionally, probiotics modulate T-lymphocyte and dendritic cell activities [38]. *In vitro* [39] and clinical studies [40–42] reported beneficial health effects of probiotics. *Akkermansia muciniphila* (*A. muciniphila*), is one of the probiotics that has a beneficial health effect on obesity [43] and/or epithelial tumours [44].

Moreover, lactic acid-producing bacteria have been used for their immunomodulatory effect [45] and *Lactobacillus* salivary and *Lactobacillus fermemtum* combined with *Lactobacillus acidophilus* reduced CRC cell proliferation in experimental studies [46, 47].

Prebiotics are defined as "substances utilized by the host's organism that have a beneficial health effect" [48]. Inulin is an example of the prebiotics and dietary fibres (i.e. inulin-type fructans) found in garlic, onion, and asparagus [49]. Inulin-type fructans are not digested in the small intestine and are fermented in the colon to produce lactic acid and SCFAs [50, 51] from the CRC protective bacteria (i.e. *Bifidobacteria* [52], *Bacteroides* [53], and *A. muciniphila*) [43].

Resistant starch is another example of prebiotic (not digested in the small intestine and fermented in the colon), found in cereals, legumes, vegetables, and seeds. Resistant starch produces protective SCFAs (butyrate) and reduces the colonic PH [54].

Symbiotics are "a mixture of living bacteria (probiotics) and substances utilized by the host's organism (prebiotics), and both have a beneficial health effect" [55].

An example of a symbiotic associated with decreased incidence of CRC includes a combination of *Bifidobacterium animalis* subspecies *lactis* (*B. lactis*) as a probiotic and resistant starch (prebiotic) [55].

The role of microbiota has been studied with different cancer treatments, including radiotherapy [56], chemotherapy [57], and immunotherapy [58]. Most studies have focused on the microbiota's role in immunotherapy because of its promising role in immune response modulation [58].

Paulos *et al.* [56] reported the microbiota's role in immune response modulation. Paulos *et al.* [56] found that the Gram-negative bacteria lipopolysaccharide

(LPS) increases the activity of dendritic cells and TCD8+ lymphocytes, with subsequent melanoma regression after radiotherapy.

Immunotherapy is still ineffective in a large proportion of CRCs, due to the host's genetics and/or cancer phenotype [59]. Immunotherapy induces the host's immune response through T-lymphocytes. Therefore, it is important to identify the ideal microbiota to improve the efficacy of immunotherapy during CRC treatment. The beneficial microbiota during immunotherapy treatments for epithelial tumours include *Clostridiales*, *Ruminococcacae*, *Enterococci*, *Collinsella*, *Alistipes*, *A. muciniphila*, *B. fragilis*, and *Bifidobacteria* [60].

The aim of surgeries in CRC is total tumour resection with safety margins around. The risk of tumour recurrence significantly decreases if the CRC is totally resected with tumour-free margins around [61].

However, the incidence of local recurrence in CRCs is 15%, which is due to the histological and biological characteristics of the primary tumour and/or the degree of deep invasion [62, 63]. Mostly the tumour recurrence occurs at the anastomosis site due to loss of the intestinal mucosal barrier's integrity and the presence of collagenolytic organisms [64]. A high-fat diet increases the recurrence of CRCs at the anastomosis site in preclinical studies [65] due to overproduction of collagenolytic organisms at the anastomosis site [65]. Therefore, low collagenolytic organisms after CRCs surgeries is a healthy colonic microbiota for successful CRC surgeries and prevention of recurrence.

Although, the value of nutrition is frequently underestimated in medical fields, the available data showed that nutrition is crucial in shaping the gut microbiota.

Aim

This systematic review aimed to detect the effect of microbiota modulation using probiotics, prebiotics, symbiotics, and natural changes on CRCs.

Material and methods

Inclusion criteria: A PubMed search was conducted to retrieve the original and *in vivo* articles published in English language from 2010 until 2021 containing the following keywords: 1) CRCs, 2) CRCs treatment (i.e. surgical, chemotherapy, radiotherapy, and/or immunotherapy), and 3) microbiota probiotic(s), prebiotic(s), symbiotic(s), dysbiosis, and/or nutritional treatment.

Exclusion criteria: *in-vitro* studies, commentaries, letters to the editor or correspondence, editorials comments, duplicate publications, retractions, and reviews (narrative, systematic, and/or meta-analyses) were excluded.

Results

A total of 198 PubMed records/articles were initially identified. 108 articles were excluded at the initial screening because of the article type (i.e. commentaries, letters to the editor or correspondence, editorials comment, duplicate publications, retractions, reviews). After reviewing the abstracts, another 29 articles were excluded due to cancers other than CRCs, *in vitro* studies, non-English language, and conferences presentations. Finally, 61 studies were eligible and were analysed for this systematic review (Figure 1).

Table I contains a summary of the reviewed studies including authors and publication year, cancer origin, type of the study, intervention, effect of intervention on

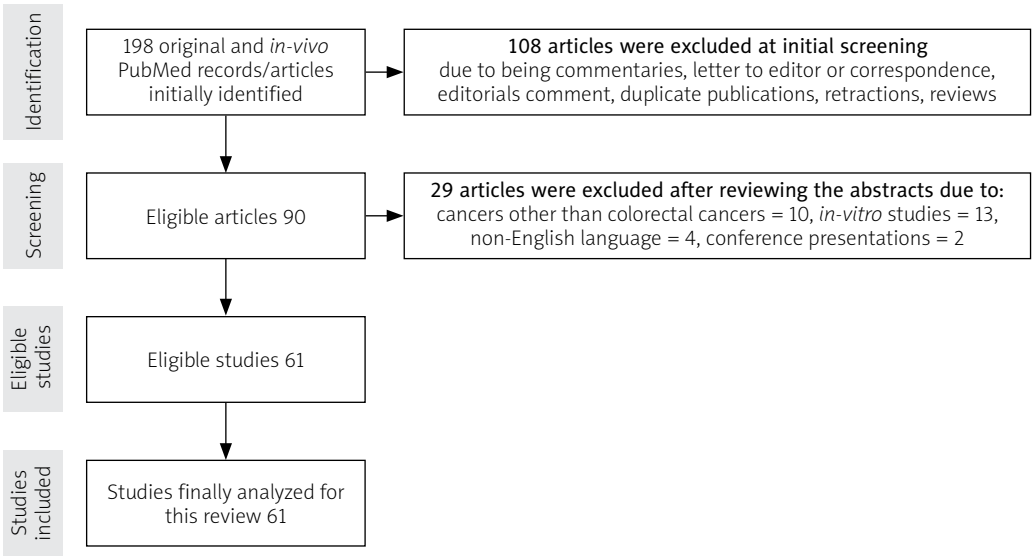

Figure 1. The PRISMA flow chart

Table I. Summary of the reviewed studies

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Preclinical probiotics studies:						
Shi *et al.* 2020 [75]	CRC model	Mice injected subcutaneously with CT26 cells (colorectal carcinoma cell line) ± IL-2	*A. muciniphila*	Increased Akkermansia, Allstipes, and *Lactobacillus* (L)	Decreased tumour volume and increased survival rate	Increased tumour necrosis and apoptosis and decreased tumour proliferation. Increased interferon-γ and IL-2 in the tumour and increased interferon-α in serum
Arthur *et al.* 2013 [71]	CRC model associated with colitis	129/SvEv mouse strain deficient in IL-10 treated with AOM	VSL#3 (contains, *L. plantarum*, *L. delbrueckii*, *L. bulgaricus*, *L. paracasei*, *L. acidophilus*, *B. breve*, *B. longum*, *B. infantis* and *Streptococcus salivarius*)	Increased mucosal proteobacteria. Decreased Bacteroidetes in feces	Increased tumour penetration, multiplicity, and histological grade	Decreased clostridium in the mucous membrane
Zhuo *et al.* 2019 [38]	CRC with colitis	Male BALB/C mice strain treated with AOM and DSS	*L. acidophilus* lysates (*Phylum firmicutes*)	Decreased *Proteo-bacteria*	Decreased tumour volume and increased survival rate	Increased lymphocytes (CD3+ CD4+), interferon-γ and macrophages in mesenteric lymphoid
Chandel *et al.* 2019 [94]	Early colon carcinogenesis	Male rats treated with DHM	*L. rhamnosus* and *L. plantarum*	Increased lactic acid producing-bacteria	Decreased aberrant intestinal crypts	Decreased weight loss, and liver transaminases
Song *et al.* 2018 [67]	CRC with colitis	C57BL/6 mice strain treated with AOM and DSS	*E. faecalis*, *B. longum* and *L. acidophilus*	Increased *Lactobacillus*. Decreased Desulfovibrio, and *Mucispirillum*	Decreased number and volume of tumours	Decreased IL-1β, IL-6 and TNF-α
Wang *et al.* 2020 [18]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	*A. muciniphila* or its membrane protein (Amuc_1100)	Increased *A. muciniphila*	Decreased malignancy score	Increased cytotoxic CD8+ lymphocytes and TNF-α in mesenteric nodules
Xu *et al.* 2021 [113]	CRC associated with colitis	6-C57BL/6NCrSlc mice strain treated with AOM and DSS	*L. rhamnosus* (M9)	Increased *Akkermansia*, L. and *Bifidobacterium*	Decreased number, size of the tumour, and inflammatory markers	Decreased CD68+ and CD163+
Chang *et al.* 2020 [114]	CRC associated with colitis	CRC in animal model treated with DHM	*Butyricicoccus pullicaecorum*	*Butyricicoccus pullicaecorum*	Decreased tumour infiltration, bleeding, and carcinoembryonic antigen (CEA) levels	Increased SLC5A8 and GPR43

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Hradicka *et al.* 2020 [115]	Early colon carcinogenesis	CRC in rates treated with DHM	*L. plantarum* (VD23, C28 and MS18). *L. salivarius* (MS3, MS6 and MS16)	NR	Decreased proliferation, size, and number of tumours	Increased IL-18
Silveira *et al.* 2020 [95]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	*L. bulgaricus*	*L. bulgaricus*	Decreased tumour mass and size	Decreased IL-6, IL-17, IL-23 and TNF-α. Increased interferon-γ in healthy and tumour tissue
Yuan *et al.* 2018 [66]	Syngeneic CRC model	BALB/c mice strain injected subcutaneously with CT26 cells (colorectal carcinoma cell line)	L. and *Bifidobacterium*	Increased *Alloprebotella,* Citrobacter, *Roseburia, Thalassospira, Erysipelatoclostridium, Bacteroides_chinchillae Helicobacter_* Ganmani. Decreased *Escherichia coli*, and *Bacteroides vulgatus*	No change in tumour volume	NR
Chang *et al.* 2018 [72]	Syngeneic CRC model	BALB/c mice strain injected subcutaneously with CT26 cells (colorectal carcinoma cell line) and treated with FOLFOX	*L. casei* variety rhamnosus (Lcr35)	Increased *Firmicutes and Bacteroidetes*	Unchanged	Decreased diarrhea, mucous membrane inflammation, TNF-α and IL-6
Bindels *et al.* 2018 [116]	CRC model with cachexia	Mice injected subcutaneously with CT26 cells (colorectal carcinoma cell line)	*Faecalibacterium prausnitzii*	NR	Decreased tumour volume (insignificant)	Improvement parameters of the intestinal barrier (insignificant)
Jacouton *et al.* 2017 [73]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	*Lactobacillus casei* BL23	Increased *Lactobacillus zeae*	Decreased tumour volume, and number	Decreased Ki67
Gao *et al.* 2017 [74]	CRC associated with colitis	BALB/c mice strain treated with AOM and DSS	*Lactobacillus reuteri*	NR	Decreased tumour numbers	Decreased tumour IL-22, IL-6, IL-1-α and TNF-α
Chung *et al.* 2017 [70]	CRC associated with colitis	BALB/c mice strain treated with AOM and DSS with Western diet and metformin	VSL#3	NR	Metformin + VSL#3 decreased number of tumours	Metformin + VSL#3 decreased Ki67
da Silva Duarte *et al.* 2020 [117]	Early colon carcinogenesis	BALB/c mice strain treated with DHM	*L. paracasei* *L. rhamnosus*	Increased *Ruminiclostridium* and fecal acetic acid and SCFAs	Unchanged	Decreased IL-6. Increased TNF-α, interferon-γ and the P-53 (tumour suppressor gene)

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Mendes *et al.* 2018 [69]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	*L. acidophilus*, *L. rhamnosus* and *Bifidobacterium bifidum*	Increased L., B., *Allobaculum*, and *Clostridium*	Decreased number of tumours	Decreased colitis, and TNF-α. Increased IL-10
Preclinical prebiotics studies:						
Donohoe *et al.* 2014 [34]	CRC model with colitis	BALB/C mice strain treated with AOM and DSS	Fructooligosac charide/inulin	NR	Decreased histological grade, volume number	Increased histone 3 and decreased Ki-67
Zhang *et al.* 2021 [81]	Syngeneic model of colon cancer	C57BL/6 WT mice strain injected with colon cancer (MC38) cells, treated with humanized microbiota from healthy humans or patients, anti-PD-1 treatment	Pectin	Increased *Lactobacillaceae, Bifidobacteriaceae, Ruminococcaceae*, and *Faecalibacterium. Increased acetate* and *butyrate*	Decreased tumour volume and size	Increased lymphocytes CD4+, TCD8+ and interferon-γ
Li *et al.* 2020 [83]	Subcutaneously transplanted colon cancer cells (MC-38)	Syngeneic C57BL/6 mice strain	Mucin and inulin	Increased *Clostridium cluster* XIVa	Inulin decreased tumour volume. Tumour volume unchanged with mucin	Increased CD40+ and TLR3 and TLR7
Zhu *et al.* 2021 [118]	CRC with colitis	C57BL/6 mice strain treated with HFD, AOM and DSS	Evodiamine	Increased *Campylobacter*, B., and *L. Decreased E. faecalis* and *E. coli*	Increased survival and apoptosis. Decreased tumour diameter and proliferation	Decreased IL-1, IL-6 and circulating TNF-α and in colonic tissue
Terasaki *et al.* 2021 [100]	CRC associated with colitis	ICR mice strain treated with AOM and DSS	Fucoxanthin	Increased *Lachnospiraceae* and decreased *Bacteroides* and *Rikenellaceae*	Decreased size and number of colorectal adenomas	Increased caspase 3
Luo *et al.* 2021 [119]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	Menthol	Increased butyrate producing bacteria	Decreased the number of 1–3 mm adenomas in a dose-dependent manner	Decreased expression of Ki67, IL-6 and TNF-α. Increased IL-10 in the distal colon
Liu *et al.* 2020 [120]	Subcutaneous transplanted colon cancer (MC-38)	Mice	Chitosan and LMW citrus pectin encapsulating bilberry anthocyanins	Increased *Lachnospiraceae* (*Clostridiales*) and diversity	Decreased tumour volume	Increased of SCFAs and T lymphocytes (CD4+ and TCD8+)

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Zhang *et al.* 2019 [89]	CRC associated with colitis	C57BL/6 mice strain treated with AOM, DSS and HFD	Canmei formula	Increased *Bacteroides, Bacteroidaceae, Faecalibaculum, Erysipelatoclostridium* and *Staphylococcus*	Decreased tumour incidence	Decreased serum IL-17
Khan *et al.* 2019 [92]	Prevention of CRC of genetic origin	Mice	Polysaccharides and saponin	Increased SCFAs producing bacteria	Decreased number and size of polyp	Shift from M1 to M2 macrophages. Reversal of Ecadherin/N-cadherin ratio and decreased oncogenic signaling
Li *et al.* 2020 [83]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	α-ketoglutarate	Increased *Akkermansia, Butyricicoccus, Clostridium* and *Ruminococococcus*. Decreased *Escherichia* and *Enterococcus*	Decreased tumour size and stage	Decreased IL-1, IL-6, IL-22, and TNF
Fernandez *et al.* 2018 [121]	CRC associated with colitis	Rats treated with AOM and DSS	Lactulose derived Galacto-oligosaccharides	Increased B., *Bacteroidaceae, Prevotellaceae, Acidaminococcaceae, Bifidobacteriaceae*, and *Peptococcaceae*. Decreased *Lachnospiraceae, Eubacteriaceae, Acholeplasmataceae*	Decreased number and volume of polyps	Increased cecum length
Mudd *et al.* 2020 [122]	CRC associated with dysbiosis	Mice inoculated with *Bacteroides fragilis*	Anthocyanidins	NR	Decreased number of tumours	Increased liver phase I enzymes CYP1A1 and CYP1B1
Wu *et al.* 2018 [87]	CRC associated with colitis	Males ICR mice strain treated with benzo[a]pyrene and DSS	Polymethoxyflavones	Increased *Sphingobacteriaceae, Gammaproteobacteria*, and *Ruminococcaceae*. Decreased *Bacilli, Parabacteroides, L. ruminis*	Decreased hyperplasia, adenoma, and adenocarcinoma	Decreased hepatic and renal toxicity. Decreased Inflammation and metastasis genes. Increased antioxidants
Wang *et al.* 2019 [15]	CRC associated with colitis	FVB/N mice strain treated with benzo[a]pyren e and DSS	Epigallocatech in gallate	Increased L., *Fusobacterium, Ruminococococcus*. Decreased *Bacteroides*	Decreased volume and number of tumours and pre-cancerous lesions	NR
Chou *et al.* 2017 [90]	CRC associated with colitis	ICR mice strain treated with AOM and DSS	Boswellia serrata resin extract	Increased *Clostridiales* spp. and decreased *Bacteroidales*	Decreased number of tumours	Decreased TNF-κB. Increased colon length

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Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Fukuda *et al.* 2011 [123]	CRC associated with colitis	AOM-treated rats	Germinated barley extract	NR	Decreased aberrant crypts	Decreased TLR4 and COX2
Preclinical symbiotics studies:						
Zheng *et al.* 2020 [91]	Subcutaneous and orthotropic model of CRC	CRC model in mice	Clostridium butyricum and prebiotic dextran	Increased *Muribaculaceae, Bacteroides, Mucispirillum, Alloprebotella, Lachnospiraceae*, and *Ruminococcaceae*	Decreased tumour size in combination with Diclofenac	Increased iso-butyrate, butyrate, and isovalerate, propionate
Oh *et al.* 2020 [96]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	*Lactobacillus* gasseri 505 and leaf extract of Cudrania tricuspidata (CT) in fermented milk	Increased *Lactobacillus*, *Bifidobacterium*, and Akkermansia associated with SCFAs	Decreased incidence of tumours and dysplasia	Decreased TNF-α, interferon-γ, IL-1β, IL-6
Preclinical food studies:						
Gaines *et al.* 2020 [65]	Model of CRC recurrence after surgery	BALB/c mice strain inoculated with CT26 cells (colorectal carcinoma cell line) after resection and anastomosis	Western diet, antibiotics, and *Enterococcus faecalis*	Western diet associated with increased proteus, *Akkermansia* and *Trabulsiell*a. Decreased in *Bacteroides, Roseburia* and *Ruminococcus*	Increased distant metastasis with Western diet	NR
Rudd *et al.* 2019 [98]	CRC genotoxic	C57BL/6 mice strain treated with AOM	Selfish *Muricidae* 1. Marine extract (NE) 2. Metabolite of the extract 6-bromoisatin (6-Br)	NR	6-Br decreased the number of aberrant crypts and tumours. NE decreased number of tumours	6-Br decreased tumour proliferation. NE decreased proliferation and increased apoptosis
Zhang *et al.* 2021 [81]	CRC associated with colitis	BALB/c mice strain treated with AOM and DSS	Extract of 55 different foodstuffs	Decreased *Desulfovibrio* and *Ruminococcaceae*. Increased *Bacteroides, Ruminiclostridium_6* and *Allobaculum*. Increased acetic, ascorbic, palmitic, and branched amino acids	Decreased number and size of tumours. Increased survival rate	Improved intestinal barrier and body weight. Decreased IL-6 and TNF-α
Piazzi *et al.* 2019 [104]	CRC genotoxic	CRC in mice model treated with AOM	LFD HFD A mixture of one of them with MD	MD improves dysbiosis with an HFD	MD decreased incidence of CRCs	MD increased apoptosis especially in LFD. MD increased EPA, especially in LFD

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Li *et al.* 2015 [101]	Prevention of CRCs of genetic origin	CRCs in mice model	Nutmeg	NR	Decreased tumour volume and number of tumours	Decreased cresol sulphate and phenyl sulphate in urine. Decreased serum IL-6, liver transaminases and amylase
Chen *et al.* 2018 [93]	CRC associated with colitis	C57BL/6 mice strain treated with AOM and DSS	Anthocyanin extract from blackberries	Decreased *Eubacterium rectale, Faecalibacterium prausnitzii Lactobacillus*, Desulfovibrio and *Enterococcus* spp.	Decreased number of tumours	Decreased IL-1β, IL-6, IL-10 and TNF-α
Fernandez *et al.* 2018 [121]	CRC associated with colitis	Rats treated with AOM and DSS	Anthocyanin extracted from strawberries and blackberries	Decreased *Bilophila wadsworthia*	Decreased number of tumours	Improved plasma reducing capacity
Wang *et al.* 2019 [15]	CRC associated with colitis	Mice treated with AOM, DSS and HFD	American Ginseng	Improving dysbiosis	Decreased number of tumours and histological grades	NR
Hu *et al.* 2016 [88]	CRC associated with colitis	Rats treated with AOM and DSS	Green tea extract (EGCG) and resistant starch	Increased *Parabacteroides, Barnesiella, Ruminococcus, Marvinbryantia* and *Bifidobacterium*. Increased *acetate*, and *butyrate*	Resistant starch decreased number of adenocarcinomas	Decreased TNF-α and IL-1β
Yu *et al.* 2015 [124]	Prevention CRCs of genetic origin with a Western diet	Mice on HFD	American Ginseng	NR	Decreased tumour volume and number	Decreased IL-1α, IL-1β, IL6 and TNF-α
Clinical probiotics studies:						
Gao *et al.* 2017 [74]	CRCs patients underwent radical surgery and scheduled for further surgery	RCT Placebo (n = 11) Probiotic (n = 11) Controls (n = 11)	*Bifidobacterium longum*, *L. acidophilus* and *Enterococcus faecalis*	Increased *Enterococcus*. Decreased *Peptostreptococcus* and *Fusobacterium*	NR	NR
Zhang *et al.* 2012 [105]	CRCs patients scheduled for surgery	RCT Placebo (n = 30) Preoperative probiotic (n = 30)	*Bifidobacterium longum*, *L. acidophilus* and *Enterococcus faecalis*	Increased preoperative ratio of *Bifidobacterium/ E. coli*	Decreased incidence of post-surgery infections	Increased IgG in serum. Decreased endotoxins, IL-6, and CRP

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Aisu *et al.* 2015 [107]	CRCs patients scheduled for surgery	Clinical study Control (n = 81) Probiotic (n = 75)	*Enterococcus faecalis* (T110), *Clostridium butyricum* (TO-A) and *Bacillus mesentericus*	NR	NR	Decreased incisional infections and reduced post-surgical acute inflammation
Liu *et al.* 2011 [106]	CRCs patients scheduled for surgery	Randomized double-blind clinical study. Placebo (n = 50) Probiotic (n = 50)	*L. plantarum*, *L. acidophilus* and *Bifidobacterium longum*	Increased *Bifidobacterium* and *Lactobacilli*. Decreased *Enterobacteriaceae, Pseudomonas* and *Candida*	NR	Increased claudin-1, and occludin
Gianotti *et al.* 2010 [125]	CRCs patients scheduled for surgery	Randomized double-blind clinical study. Placebo (n = 10), Probiotic at a dose of 107 (n = 11) Probiotic at a dose of 109 (n = 11)	*Bifidobacterium longum* (BB536) and *L. johnsonii* (La-1)	La-1 increased La-1 in mucosa and feces. Decreased *Enterobacteriaceae*	NR	Increased lymphocytes CD3+, CD4+, and CD8+
Bajramagic *et al.* 2019 [42]	Stage III CRCs	RCT of 78 patients with CRCs who undergo for surgery	*L. acidophilus*, *L. casei*, *L. plantarum*, *L. rhamnosus B. lactis, B. bifidum, B. breve* and *Streptococcus thermophilus*	NR	NR	Decreased number of complications associated with CRCs surgeries
Clinical prebiotics studies:						
Zhu *et al.* 2021 [118]	CRCs patients	CRCs versus healthy patients undergoing colonoscopies	Evodiamine	Increased *E. faecalis* and *E. coli*. Deceased *Campylobacter, Bifidobacterium* and L in CRCs	Decreased proliferation, p-STAT3 after incubation with evodiamine in cancer cells	Increased pSTAT3 in cancerous versus peritumour biopsies
So *et al.* 2021 [108]	Patients at high risk of CRCs	Randomized, double-blind, controlled trial (placebo group 19 and treatment group 20)	Rice bran	Increased *Firmicutes* and *Lactobacillus*	NR	NR
Xie *et al.* 2019 [109]	CRCs patients requiring radical surgery	Randomized double-blind clinical study for CRCs (control 70 and prebiotics 70)	Fructo-oligosaccharides, xylo-oligosaccharides, and polydextrose	Increased *Bifidobacterium* and *Enterococcus*, and decreased *Bacteroides* before surgery. Increased *Escherichia-Shigella*, and decreased *Enterococcus* after surgery	NR	Increased IgG, IgM before surgery. Increased IgG, T lymphocytes CD3+, CD8+ and B lymphocytes CD19+ after surgery

Table I. Cont.

Authors and publication year	Origin of cancer	Type of the study	Intervention	Effect of intervention on microbiota	Effect of intervention on tumour	Possible mechanism that explains the effect of intervention
Clinical symbiotics studies:						
Polakowski *et al.* 2019 [110]	CRCs stages I-III scheduled for surgery	Double-blind, randomized, placebo-controlled clinical study (placebo 36 and treatment 37)	Maltodextrin as placebo and treatment with Simbioflora® (fructo-oligosaccharide, plus *L. acidophilus*, *L. rhamnosus*, *L. casei* and *B. lactis*)	NR	3 deaths in the control group and no death in the treatment group	Decreased plasma IL-6, post- surgery infections, antibiotic use and hospital stay
Hibberd *et al.* 2017 [84]	Stage I–III CRCs undergoing surgery	Clinical trial (21 healthy controls, 15 CRCs 8 non-intervention 7 probiotic)	*B. lactis*, *L. acidophilus* and inulin	Increased *Firmicutes*, *Clostridiales* spp. and *Faecalibacterium*	NR	NR
Clinical pre-, pro- and symbiotic studies:						
Worthley *et al.* 2009 [126]	CRCs prevention in healthy subjects	Randomized double-blind clinical study with crossover treatments	Prebiotic (resistant starch) probiotic (*Bifidobacterium lactis*) or combination of both (symbiotic)	Symbiotic increased *Lachnospiraceae* spp.	NR	No changes in fecal ammonium, SCFAs, cytokines and/or epithelial changes
Clinical food studies:						
Brown *et al.* 2017 [127]	CRCs patients undergoing surgery	Randomized clinical study (controls 10 and normal controls 9)	Rice bran	NR	NR	Increased carbohydrate, lipid, amino acid, and vitamin metabolism
Nunez-Sanchez *et al.* 2017 [111]	CRCs patients scheduled for surgery	Randomized clinical study (controls 10 and patients 35)	Pomegranate extract with high ellagitannin content	NR	NR	Decreased CD44+ in adjacent both malignant and healthy tissue
Nunez-Sanchez *et al.* 2015 [112]	CRCs patients scheduled for surgery	Randomized double-blind clinical study (controls pomegranate extract #1 and pomegranate extract #2)	Pomegranate extract with high ellagitannin content	NR	NR	Modulation of miRNAs

A. muciniphila – Akkermansia muciniphila, AOM – azoxymethane, APC – adenomatous polyposis coli, B. – Bifidobacterium, CEA – carcinoembryonic antigen, CD44+ – multifunctional cell surface molecule involved in cell proliferation, COX-2 – cyclooxygenase-2, CRCs – colo-rectal cancers, CRP – C-reactive protein, CYP – Cyp-Express-1A1 or 1B1-Cytochrome P450, DHM – dihydromyricetin, DSS – dextran sodium sulfate, E. – Enterococcus, EPA – eicosapentaenoic acid, FOLFOX – 5-fluorouracil, leucovorin, and Lactobacillus casei oxaliplatin, GPR43 – G-protein-coupled receptor-43, HFD – high fat diet, Ig – immunoglobulin, IL-2 – interluekin-2, Ki-67-positive cells – is often correlated with the clinical course of cancer, L. – Lactobacillus, LFD – low fat diet, MD – Mediterranean diet, miRNAs – micro-RNAs that act as epigenetic regulators, LMW – low molecular weight, NR – not reported, PD-1 – programmed cell death protein-1, pSTAT3 – over expression of STAT3protein and is associated with poor prognosis, PUFA – polyunsaturated fatty acids, RCT – randomized controlled trial, SCFAs – short chain fatty acids, SLC5A8 – carrier family 5 member 8, TLR4 – Toll-like receptor 4, TNF – tumour necrosis factor.

the microbiota and tumour, and possible mechanisms that explain the effect of intervention.

The quality of the reviewed studies was assessed using the CONSORT and STROBE checklists. The CONSORT checklist is a 25-item checklist focusing on the article/study design, analysis, and interpretation. The STROBE checklist is a 22-item checklist evaluating different sections/parts of the observational studies.

Discussion

The microbiota works as a natural defence, and it modulates the host's immune response against tumour development and progression [8]. Although the value of nutrition is frequently underestimated, the available data showed that nutrition is crucial in shaping the gut microbiota. Therefore, this systematic review aimed to detect the effect of microbiota modulation using probiotics, prebiotics, symbiotics, and natural changes on CRCs.

Lactobacillus combined with *Bifidobacterium* is one of the most studied probiotic combinations in CRCs.

Although Yuan *et al.* [66] found that the combination of *Bifidobacterium* and *Lactobacillus* cannot improve the response to 5-FU treatment in CRCs, *Lactobacillus acidophilus* combined with *Bifidobacterium longum* and *Enterococcus faecalis* (Bifico cocktail) was approved in China in preclinical studies for reduction of colon tumour growth [67, 68].

Moreover, the combination of 3 strains of *Lactobacillus* with one strain of *Bifidobacterium* decreased the incidence of CRCs in a preclinical study [69].

The use VSL#3 (*Lactobacillus*, *Bifidobacterium*, and *Streptococcus*) with a Western diet and metformin decreased the development of CRCs in a murine model [70] compared to VSL#3 alone [71].

Chang *et al.* [72] reported improved microbiota and inflammatory parameters when *Lactobacillus casei* was used in combination with FOLFOX (5-FU, leucovorin, and oxaliplatin) in CRCs associated with colitis in an animal model, Chang *et al.* [72] found that *Lactobacillus casei* inhibits healthy intestinal epithelial death while FOLFOX increases malignant cell apoptosis.

Lactobacillus casei BL23 strain were protective against CRCs in a mouse model, it downregulates inflammatory cytokines (interleukin-22), and it has an immunomodulatory and anti-proliferative effect [73].

Gao *et al.* [74] found the *Lactobacillus reuteri* (i.e. a histamine-producing probiotic) reduced the cancer-associated inflammatory cytokines and the number and size of CRCs in an animal model.

The therapeutic effect of interleukin-2 (IL-2) as an immunotherapy was significantly augmented by the oral use of *Akkermansia muciniphila* (*A. muciniphila*) in CRC-bearing mice [75].

Shi *et al.* [75] found that tumour volume decreased and survival rate increased in mice with CRCs after the use of IL-2 and *A. muciniphila*. Therefore, the SCFAs producing probiotics and *A. muciniphila* could have a useful therapeutic effect for patients with CRCs.

Pectin is SCFAs producing prebiotic [76], reduces the ammonia [77], and improves glucose metabolism [78]. Pectin is a metabolite derived from plant wall metabolite, which serves as an energy source for SCFA-producing bacteria after fermentation in the colon [79]. Moreover, pectin is protective against colorectal, prostate, and breast cancers [80]. Pectin increases the SCFA-producing bacteria (i.e. acetate) and increases the expression of interferon-γ-producing TCD8+ [81].

Galacto-oligosaccharides that are originated from lactulose reduced the CRC development and modulated the microbiota in preclinical studies [82]. Fructo-oligosaccharides (inulin) reduced the volume of implanted colonic tumours in an animal model [83]. They inhibit the tumour development through butyrate production and microbiota modulation [84].

The normal colonocytes use butyrate as the main energy source [85, 86]. Additionally, butyrate inhibits histone deacetylase and increases malignant colonocytes apoptosis [34].

Wu *et al.* [87] found that polymethoxyflavones were effectively prevent carcinogen-induced CRCs in an animal model through modulation of gut microbiota and increased butyrate-producing bacteria.

Hu *et al.* [88] found that resistant starch was able to protect against colitis-associated CRCs in rats by increasing SCFA-producing bacteria. Zhang *et al.* [89] found that Canmei herbal formula (containing Mume sieb, Marci Hieronymi, and more than 41 active ingredients – mainly DL-arginine, L-carnitine, and L-tyrosine) reduced the colitis associated with CRCs in an animal model through modulation of the colon microbiota.

Symbiotics can increase the efficacy of CRC treatments. They decrease the invasiveness of CRCs and increase the SCFA-producing microbiota [90].

Zheng *et al.* [91] found that symbiotics containing dextran and *Clostridium butyricum* (*C. butyricum*) regulate the gut microbiota and increase the SCFA-producing microbiota. Further studies regarding the ideal symbiotic and its proper therapeutic dose for CRCs are warranted.

Prebiotics can be extracted from mushrooms, green tea [92], and fruits [93]. Probiotics can be extracted from fruit [94], dairy products (i.e., yogurt, milk, and cheese) [95], and dairy products fermentation [96]. A high-soluble-fibre diet can inhibit intestinal mucosal erosions, decrease its degradation, and enhance the intestinal mucosal barrier [3]. Anthocyanins (i.e. blackberries) decrease local colonic inflammation, improve

the gut microbiota, and reduces the incidence of CRCs [93, 97].

Marine extract containing certain shellfish may have anticarcinogenic effects [98, 99]. Terasaki *et al.* [100] found that fucoxanthin (algae-derived product) present in *Undaria pinnatifida* decreased the number of CRC-adenocarcinomas in an animal model. Nutmeg can decrease the development of adenomatous polyposis coli-induced CRCs (API-induced CRCs) [101].

The Mediterranean diet prevents certain types of cancer [102] and reduces the incidence of CRCs by 11% [103]. The Mediterranean diet combined with a high-fat diet improves the gut microbiota [104].

Bajramagic *et al.* [42], in a randomized controlled trial (RCT) including 78 patients, studied the effect of probiotics in reducing the post-operative side effects after surgeries for stage III adenomatous CRCs. They found that the probiotics mixture containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* strains decreased the common post-operative side effects after CRC surgery, especially post-operative paralytic ileus.

Zhang *et al.* [105] found that a probiotic mixture containing *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* in CRCs decreases the *Fusobacterium* (Gram-negative, anaerobic bacteria) associated with CRCs and decreases post-operative infection after CRC surgeries.

The probiotic containing *L. plantarum*, *L. acidophilus*, and *Bifidobacterium longum* reduces post-operative diarrhoea, fever, and infection [106].

The *Lactobacillus johnsonii* (La1) reduces the pathogenic microorganisms and colonic inflammation after CRC surgeries [5].

The pre-operative use of probiotic mixture containing *Enterococcus*, *Clostridium*, and *Bacillus* significantly reduced post-operative incisional infections after CRC surgeries [107].

The intake of phytochemicals increases the *Firmicutes* and *Lactobacillus* levels and decreases the risk of CRCs [108].

Xie *et al.* [109] in a RCT found that pre-operative use of non-digestible oligosaccharides in patients who underwent radical surgeries for CRCs improved their immune response. Xie *et al.* [109] explained the improved immune response by the positive effect of non-digestible oligosaccharides on the gut microbiota.

The symbiotic (simbioflora®) containing oligosaccharides, *Lactobacillus*, and *Bifidobacterium lactis* strains significantly reduced post-operative infection after CRC surgeries [110].

The *Bifidobacterium*, *Lactobacillus*, and inulin strains improved SCFA-producing microbiota in patients who underwent stage I–III CRC surgeries [84].

Nuñez-Sánchez *et al.* [111, 112] found that intake of pomegranate extract changed the expression of certain genes [111] and microRNAs [112] in CRCs, highlighting the role of diet modification in changing the gene expression in CRCs.

This systematic review found the gut microbiota metabolites, SCFAs (i.e. acetate and butyrate) produced by the lactic acid-producing, and *Bifidobacteria* have a protective effect against CRCs. SCFAs reduce the inflammatory cytokines, inhibit colonocytes proliferation, and promote malignant cell apoptosis. Butyrate maintains mucus membrane barrier integrity, regulates mucosal cell junction occlusion, and reduces intestinal mucosal inflammation. The beneficial effect of pro-, pre-, and/or symbiotics on CRCs should be confirmed in future studies.

Conclusions

Prebiotics (i.e. inulin and resistant starch, SCFA producers) and consumption of unprocessed plant products are useful for developing and maintaining healthy gut microbiota. The pro-, pre-, and/or symbiotics may be useful when carefully selected for CRC patients, to restore the beneficial gut microbiota and support the treatment efficacy. The beneficial effect of pro-, pre-, and/or symbiotics on CRCs should be confirmed in future studies.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Henrikson NB, Webber EM, Goddard KA, et al. Family history and the natural history of colorectal cancer: systematic review. Genet Med 2015; 17: 702-12.
2. Syngal S, Brand RE, Church JM, et al.; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015; 110: 223-62.
3. Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. Lancet 2019; 394: 1467-80.
4. Jones RL. Gut microbiome as a potential biomarker of cancer risk in inflammatory bowel disease. Contemp Oncol (Pozn) 2022; 26: 40-3.
5. Medema JP. Cancer stem cells: the challenges ahead. Nat Cell Biol 2013; 15: 338-44.
6. Stappenbeck TS, Virgin HW. Accounting for reciprocal host-microbiome interactions in experimental science. Nature 2016; 534: 191-9.

7. Zitvogel L, Ma Y, Raoult D, et al. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 2018; 359: 1366-70.
8. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J 2017; 474: 1823-36.
9. Markowiak-Kopeć P, Śliżewska K. the effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients 2020; 12: 1107.
10. Lin Y, Ma C, Liu C, et al. NMR-based fecal metabolomics fingerprinting as predictors of earlier diagnosis in patients with colorectal cancer. Oncotarget 2016; 7: 29454-64.
11. Chen J, Vitetta L. Inflammation-modulating effect of butyrate in the prevention of colon cancer by dietary fiber. Clin Colorectal Cancer 2018; 17: e541-4.
12. Zeng H, Safratowich BD, Wang TTY, et al. Butyrate inhibits deoxycholic-acid-resistant colonic cell proliferation via cell cycle arrest and apoptosis: a potential pathway linking dietary fiber to cancer prevention. Mol Nutr Food Res 2020; 64: e1901014.
13. Zhao Y, Chen F, Wu W, et al. GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3. Mucosal Immunol 2018; 11: 752-62.
14. Eeckhaut V, Machiels K, Perrier C, et al. Butyricicoccus pullicaecorum in inflammatory bowel disease. Gut 2013; 62: 1745-52.
15. Wang G, Yu Y, Wang YZ, et al. Role of SCFAs in gut microbiome and glycolysis for colorectal cancer therapy. J Cell Physiol 2019; 234: 17023-49.
16. Takaishi H, Matsuki T, Nakazawa A, et al. Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. Int J Med Microbiol 2008; 298: 463-72.
17. Vigsnæs LK, Brynskov J, Steenholdt C, et al. Gram-negative bacteria account for main differences between faecal microbiota from patients with ulcerative colitis and healthy controls. Benef Microbes 2012; 3: 287-97.
18. Wang L, Tang L, Feng Y, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurised bacterium blunts colitis associated tumourigenesis by modulation of $CD8^+$ T cells in mice. Gut 2020; 69: 1988-97.
19. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol 2019; 16: 690-704.
20. Peters BA, Dominianni C, Shapiro JA, et al. The gut microbiota in conventional and serrated precursors of colorectal cancer. Microbiome 2016; 4: 69.
21. Dethlefsen L, Huse S, Sogin ML, et al. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol 2008; 6: e280.
22. Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 2012; 482: 179-85.
23. Newton DF, Cummings JH, Macfarlane S, et al. Growth of a human intestinal Desulfovibrio desulfuricans in continuous cultures containing defined populations of saccharolytic and amino acid fermenting bacteria. J Appl Microbiol 1998; 85: 372-80.
24. Carbonero F, Benefiel AC, Gaskins HR. Contributions of the microbial hydrogen economy to colonic homeostasis. Nat Rev Gastroenterol Hepatol 2012; 9: 504-18.
25. Cai WJ, Wang MJ, Ju LH, et al. Hydrogen sulfide induces human colon cancer cell proliferation: role of Akt, ERK and p21. Cell Biol Int 2010; 34: 565-72.
26. Kanazawa K, Konishi F, Mitsuoka T, et al. Factors influencing the development of sigmoid colon cancer. Bacteriologic and biochemical studies. Cancer 1996; 77: 1701-6.
27. Kostic AD, Gevers D, Pedamallu CS, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 2012; 22: 292-8.
28. Castellarin M, Warren RL, Freeman JD, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res 2012; 22: 299-306.
29. Feng Q, Liang S, Jia H, et al. Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 2015; 6: 6528.
30. Garrett WS. The gut microbiota and colon cancer. Science 2019; 364: 1133-5.
31. Dejea CM, Fathi P, Craig JM, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumourigenic bacteria. Science 2018; 359: 592-7.
32. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature 2009; 457: 480-4.
33. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut 2016; 65: 1812-21.
34. Donohoe DR, Holley D, Collins LB, et al. A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumourigenesis in a microbiota- and butyrate-dependent manner. Cancer Discov 2014; 4: 1387-97.
35. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014; 146: 67-75. e5.
36. Sanders ME, Merenstein DJ, Reid G, et al. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol 2019; 16: 605-16.
37. Azcárate-Peril MA, Sikes M, Bruno-Bárcena JM. The intestinal microbiota, gastrointestinal environment and colorectal cancer: a putative role for probiotics in prevention of colorectal cancer? Am J Physiol Gastrointest Liver Physiol 2011; 301: G401-24.
38. Zhuo Q, Yu B, Zhou J, et al. Lysates of Lactobacillus acidophilus combined with CTLA-4-blocking antibodies enhance antitumour immunity in a mouse colon cancer model. Sci Rep 2019; 9: 20128.
39. Nami Y, Haghshenas B, Haghshenas M, et al. The prophylactic effect of probiotic Enterococcus lactis IW5 against different human cancer cells. Front Microbiol 2015; 6: 1317.
40. Kaeid Sharaf L, Shukla G. Probiotics (Lactobacillus acidophilus and Lactobacillus rhamnosus GG) in conjunction with celecoxib (selective COX-2 inhibitor) modulated DMH-induced early experimental colon carcinogenesis. Nutr Cancer 2018; 70: 946-55.
41. Sharaf LK, Sharma M, Chandel D, et al. Prophylactic intervention of probiotics (L. acidophilus, L. rhamnosus GG) and celecoxib modulate Bax-mediated apoptosis in 1,2-dimethylhydrazine-induced experimental colon carcinogenesis. BMC Cancer 2018; 18: 1111.

42. Bajramagic S, Hodzic E, Mulabdic A, et al. Usage of probiotics and its clinical significance at surgically treated patients sufferig from colorectal carcinoma. Med Arch 2019; 73: 316-20.
43. Everard A, Belzer C, Geurts L, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci USA 2013; 110: 9066-71.
44. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018; 359: 97-103.
45. Paolillo R, Romano Carratelli C, Sorrentino S, et al. Immunomodulatory effects of Lactobacillus plantarum on human colon cancer cells. Int Immunopharmacol 2009; 9: 1265-71.
46. Kahouli I, Malhotra M, Westfall S, et al. Design and validation of an orally administrated active L. fermentum-L. acidophilus probiotic formulation using colorectal cancer Apc $^{Min/+}$ mouse model. Appl Microbiol Biotechnol 2017; 101: 1999-2019.
47. Zhu J, Zhu C, Ge S, et al. Lactobacillus salivarius Ren prevent the early colorectal carcinogenesis in 1, 2-dimethylhydrazine-induced rat model. J Appl Microbiol 2014; 117: 208-16.
48. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 2017; 14: 491-502.
49. van Loo J, Coussement P, de Leenheer L, et al. On the presence of inulin and oligofructose as natural ingredients in the western diet. Crit Rev Food Sci Nutr 1995; 35: 525-52.
50. Roberfroid MB, Van Loo JA, Gibson GR. The bifidogenic nature of chicory inulin and its hydrolysis products. J Nutr 1998; 128: 11-9.
51. Campbell JM, Fahey GC Jr, Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. J Nutr 1997; 127: 130-6.
52. Fehlbaum S, Prudence K, Kieboom J, et al. In vitro fermentation of selected prebiotics and their effects on the composition and activity of the adult gut microbiota. Int J Mol Sci 2018; 19: 3097.
53. Li K, Zhang L, Xue J, et al. Dietary inulin alleviates diverse stages of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in db/db mice. Food Funct 2019; 10: 1915-27.
54. Faraj A, Vasanthan T. Hoover R. The effect of extrusion cooking on resistant starch formation in waxy and regular barley flours. Food Research International 2004; 37: 517-25.
55. Swanson KS, Gibson GR, Hutkins R, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of symbiotics. Nat Rev Gastroenterol Hepatol 2020; 17: 687-701.
56. Paulos CM, Wrzesinski C, Kaiser A, et al. Microbial translocation augments the function of adoptively transferred self/tumour-specific CD8+ T cells via TLR4 signaling. J Clin Invest 2007; 117: 2197-204.
57. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 2013; 342: 971-6.
58. Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015; 350: 1079-84.
59. Ganesh K, Stadler ZK, Cercek A, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. Nat Rev Gastroenterol Hepatol 2019; 16: 361-75.
60. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumours. Science 2018; 359: 91-7.
61. Alberda WJ, Verhoef C, Schipper ME, et al. The importance of a minimal tumour-free resection margin in locally recurrent rectal cancer. Dis Colon Rectum 2015; 58: 677-85.
62. Manfredi S, Bouvier AM, Lepage C, et al. Incidence, and patterns of recurrence after resection for cure of colonic cancer in a well-defined population. Br J Surg 2006; 93: 1115-22.
63. Naxerova K, Reiter JG, Brachtel E, et al. Origins of lymphatic and distant metastases in human colorectal cancer. Science 2017; 357: 55-60.
64. Shogan BD, Belogortseva N, Luong PM, et al. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. Sci Transl Med 2015; 7: 286ra68.
65. Gaines S, van Praagh JB, Williamson AJ, et al. Western diet promotes intestinal colonization by collagenolytic microbes and promotes tumour formation after colorectal surgery. Gastroenterology 2020; 158: 958-70.e2.
66. Yuan L, Zhang S, Li H, et al. The influence of gut microbiota dysbiosis to the efficacy of 5-fluorouracil treatment on colorectal cancer. Biomed Pharmacother 2018; 108: 184-93.
67. Song H, Wang W, Shen B, et al. Pretreatment with probiotic Bifico ameliorates colitis-associated cancer in mice: transcriptome and gut flora profiling. Cancer Sci 2018; 109: 666-77.
68. Chen CC, Lin WC, Kong MS, et al. Oral inoculation of probiotics Lactobacillus acidophilus NCFM suppresses tumour growth both in segmental orthotopic colon cancer and extra-intestinal tissue. Br J Nutr 2012; 107: 1623-34.
69. Mendes MCS, Paulino DS, Brambilla SR, et al. Microbiota modification by probiotic supplementation reduces colitis associated colon cancer in mice. World J Gastroenterol 2018; 24: 1995-2008.
70. Chung EJ, Do EJ, Kim SY, et al. Combination of metformin and VSL#3 additively suppresses western-style diet induced colon cancer in mice. Eur J Pharmacol 2017; 794: 1-7.
71. Arthur JC, Gharaibeh RZ, Uronis JM, et al. VSL#3 probiotic modifies mucosal microbial composition but does not reduce colitis-associated colorectal cancer. Sci Rep 2013; 3: 2868.
72. Chang CW, Liu CY, Lee HC, et al. Lactobacillus casei Variety rhamnosus probiotic preventively attenuates 5-fluorouracil/oxaliplatin-induced intestinal injury in a syngeneic colorectal cancer model. Front Microbiol 2018; 9: 983.
73. Jacouton E, Chain F, Sokol H, et al. Probiotic strain Lactobacillus casei BL23 prevents colitis-associated colorectal cancer. Front Immunol 2017; 8: 1553.
74. Gao C, Ganesh BP, Shi Z, et al. Gut microbe-mediated suppression of inflammation-associated colon carcinogenesis by luminal histamine production. Am J Pathol 2017; 187: 2323-36.
75. Shi L, Sheng J, Chen G, et al. Combining IL-2-based immunotherapy with commensal probiotics produces enhanced antitumour immune response and tumour clearance. J Immunother Cancer 2020; 8: e000973.

76. Bellville JW, Swanson GD, Miyake T, et al. Respiratory stimulation observed following ethanol ingestion. West J Med 1976; 124: 423-5.
77. Shinohara K, Ohashi Y, Kawasumi K, et al. Effect of apple intake on fecal microbiota and metabolites in humans. Anaerobe 2010; 16: 510-5.
78. Schwartz SE, Levine RA, Weinstock RS, et al. Sustained pectin ingestion: effect on gastric emptying and glucose tolerance in non-insulin-dependent diabetic patients. Am J Clin Nutr 1988; 48: 1413-7.
79. Annunziata G, Maisto M, Schisano C, et al. Effect of grape pomace polyphenols with or without pectin on TMAO serum levels assessed by LC/MS-based assay: a preliminary clinical study on overweight/obese subjects. Front Pharmacol 2019; 10: 575.
80. Glinsky VV, Raz A. Modified citrus pectin anti-metastatic properties: one bullet, multiple targets. Carbohydr Res 2009; 344: 1788-91.
81. Zhang SL, Mao YQ, Zhang ZY, et al. Pectin supplement significantly enhanced the anti-PD-1 efficacy in tumour-bearing mice humanized with gut microbiota from patients with colorectal cancer. Theranostics 2021; 11: 4155-70.
82. Bruno-Barcena JM, Azcarate-Peril MA. Galacto-oligosaccharides and colorectal cancer: feeding our intestinal probiome. J Funct Foods 2015; 12: 92-108.
83. Li Y, Elmén L, Segota I, Xian Y, et al. Prebiotic-induced anti-tumour immunity attenuates tumour growth. Cell Rep 2020; 30: 1753-66.e6.
84. Hibberd AA, Lyra A, Ouwehand AC, et al. Intestinal microbiota is altered in patients with colon cancer and modified by probiotic intervention. BMJ Open Gastroenterol 2017; 4: e000145.
85. Warburg O. On the origin of cancer cells. Science 1956; 123: 309-14.
86. Roediger WE. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. Gut 1980; 21: 793-8.
87. Wu JC, Tsai ML, Lai CS, et al. Polymethoxyflavones prevent benzo[a]pyrene/dextran sodium sulfate-induced colorectal carcinogenesis through modulating xenobiotic metabolism and ameliorate autophagic defect in ICR mice. Int J Cancer 2018; 142: 1689-701.
88. Hu Y, Le Leu RK, Christophersen CT, et al. Manipulation of the gut microbiota using resistant starch is associated with protection against colitis-associated colorectal cancer in rats. Carcinogenesis 2016; 37: 366-75.
89. Zhang H, Hui D, Li Y, et al. Canmei formula reduces colitis-associated colorectal carcinogenesis in mice by modulating the composition of gut microbiota. Front Oncol 2019; 9: 1149.
90. Chou YC, Suh JH, Wang Y, et al. Boswellia serrata resin extract alleviates azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colon tumourigenesis. Mol Nutr Food Res 2017; 61. doi: 10.1002/mnfr.201600984.
91. Zheng DW, Li RQ, An JX, et al. Prebiotics-encapsulated probiotic spores regulate gut microbiota and suppress colon cancer. Adv Mater 2020; 32: e2004529.
92. Khan I, Huang G, Li XA, et al. Mushroom polysaccharides and jiaogulan saponins exert cancer preventive effects by shaping the gut microbiota and microenvironment in $Apc^{Min/+}$ mice. Pharmacol Res 2019; 148: 104448.
93. Chen L, Jiang B, Zhong C, et al. Chemoprevention of colorectal cancer by black raspberry anthocyanins involved the modulation of gut microbiota and SFRP2 demethylation. Carcinogenesis 2018; 39: 471-81.
94. Chandel D, Sharma M, Chawla V, et al. Isolation, characterization, and identification of antigenotoxic and anticancerous indigenous probiotics and their prophylactic potential in experimental colon carcinogenesis. Sci Rep 2019; 9: 14769.
95. Silveira DSC, Veronez LC, Lopes-Júnior LC, et al. Lactobacillus bulgaricus inhibits colitis-associated cancer via a negative regulation of intestinal inflammation in azoxymethane/dextran sodium sulfate model. World J Gastroenterol 2020; 26: 6782-94.
96. Oh NS, Lee JY, Kim YT, et al. Cancer-protective effect of a symbiotic combination between Lactobacillus gasseri 505 and a Cudrania tricuspidata leaf extract on colitis-associated colorectal cancer. Gut Microbes 2020; 12: 1785803.
97. Khoo HE, Azlan A, Tang ST, et al. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 2017; 61: 1361779.
98. Rudd DA, Benkendorff K, Chahal C, et al. Mapping insoluble indole metabolites in the gastrointestinal environment of a murine colorectal cancer model using desorption/ionisation on porous silicon imaging. Sci Rep 2019; 9: 12342.
99. Reglero C, Reglero G. Precision nutrition and cancer relapse prevention: a systematic literature review. Nutrients 2019; 11: 2799.
100. Terasaki M, Uehara O, Ogasa S, et al. Alteration of fecal microbiota by fucoxanthin results in prevention of colorectal cancer in AOM/DSS mice. Carcinogenesis 2021; 42: 210-9.
101. Li F, Yang XW, Krausz KW, et al. Modulation of colon cancer by nutmeg. J Proteome Res 2015; 14: 1937-46.
102. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern Med 2015; 175: 1752-60.
103. Bamia C, Lagiou P, Buckland G, et al. Mediterranean diet, and colorectal cancer risk: results from a European cohort. Eur J Epidemiol 2013; 28: 317-28.
104. Piazzi G, Prossomariti A, Baldassarre M, et al. A Mediterranean diet mix has chemopreventive effects in a murine model of colorectal cancer modulating apoptosis and the gut microbiota. Front Oncol 2019; 9: 140.
105. Zhang JW, Du P, Gao J, et al. Preoperative probiotics decrease postoperative infectious complications of colorectal cancer. Am J Med Sci 2012; 343: 199-205.
106. Liu Z, Qin H, Yang Z, et al. Randomised clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery – a double-blind study. Aliment Pharmacol Ther 2011; 33: 50-63.
107. Aisu N, Tanimura S, Yamashita Y, et al. Impact of perioperative probiotic treatment for surgical site infections in patients with colorectal cancer. Exp Ther Med 2015; 10: 966-72.
108. So WKW, Chan JYW, Law BMH, et al. Effects of a rice bran dietary intervention on the composition of the intestinal microbiota of adults with a high risk of colorectal cancer: a pilot randomised-controlled trial. Nutrients 2021; 13: 526.

109. Xie X, He Y, Li H, et al. Effects of prebiotics on immunologic indicators and intestinal microbiota structure in perioperative colorectal cancer patients. Nutrition 2019; 61: 132-42.
110. Polakowski CB, Kato M, Preti VB, et al. Impact of the preoperative use of symbiotics in colorectal cancer patients: a prospective, randomized, double-blind, placebo-controlled study. Nutrition 2019; 58: 40-6.
111. Nuñez-Sánchez MA, González-Sarrías A, García-Villalba R, et al. Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: a randomized clinical trial. J Nutr Biochem 2017; 42: 126-33.
112. Nuñez-Sánchez MA, Dávalos A, González-Sarrías A, et al. MicroRNAs expression in normal and malignant colon tissues as biomarkers of colorectal cancer and in response to pomegranate extracts consumption: Critical issues to discern between modulatory effects and potential artefacts. Mol Nutr Food Res 2015; 59: 1973-86.
113. Xu H, Hiraishi K, Kurahara LH, et al. Inhibitory effects of breast milk-derived Lactobacillus rhamnosus Probio-M9 on colitis-associated carcinogenesis by restoration of the gut microbiota in a mouse model. Nutrients 2021; 13: 1143.
114. Chang SC, Shen MH, Liu CY, et al. A gut butyrate-producing bacterium Butyricicoccus pullicaecorum regulates short-chain fatty acid transporter and receptor to reduce the progression of 1,2-dimethylhydrazine-associated colorectal cancer. Oncol Lett 2020; 20: 327.
115. Hradicka P, Beal J, Kassayova M, et al. A novel lactic acid bacteria mixture: macrophage-targeted prophylactic intervention in colorectal cancer management. Microorganisms 2020; 8: 387.
116. Bindels LB, Neyrinck AM, Loumaye A, et al. Increased gut permeability in cancer cachexia: mechanisms and clinical relevance. Oncotarget 2018; 9: 18224-38.
117. da Silva Duarte V, Dos Santos Cruz BC, Tarrah A, et al. Chemoprevention of DMH-induced early colon carcinogenesis in male BALB/c mice by administration of Lactobacillus Paracasei DTA81. Microorganisms 2020; 8: 1994.
118. Zhu LQ, Zhang L, Zhang J, et al. Evodiamine inhibits high-fat diet-induced colitis-associated cancer in mice through regulating the gut microbiota. J Integr Med 2021; 19: 56-65.
119. Luo L, Yan J, Chen B, et al. The effect of menthol supplement diet on colitis-induced colon tumourigenesis and intestinal microbiota. Am J Transl Res 2021; 13: 38-56.
120. Liu X, Wang L, Jing N, et al. Biostimulating gut microbiome with bilberry anthocyanin combo to enhance anti-PD-L1 efficiency against murine colon cancer. Microorganisms 2020; 8: 175.
121. Fernández J, Moreno FJ, Olano A, et al. A galacto-oligosaccharides preparation derived from lactulose protects against colorectal cancer development in an animal model. Front Microbiol 2018; 9: 2004.
122. Mudd AM, Gu T, Munagala R, et al. Chemoprevention of colorectal cancer by anthocyanidins and mitigation of metabolic shifts induced by dysbiosis of the gut microbiome. Cancer Prev Res (Phila) 2020; 13: 41-52.
123. Fukuda M, Komiyama Y, Mitsuyama K, et al. Prebiotic treatment reduced preneoplastic lesions through the downregulation of toll like receptor 4 in a chemo-induced carcinogenic model. J Clin Biochem Nutr 2011; 49: 57-61.
124. Yu C, Wen XD, Zhang Z, et al. American ginseng significantly reduced the progression of high-fat-diet-enhanced colon carcinogenesis in Apc (Min/+) mice. J Ginseng Res 2015; 39: 230-7.
125. Gianotti L, Morelli L, Galbiati F, et al. A randomized double-blind trial on perioperative administration of probiotics in colorectal cancer patients. World J Gastroenterol 2010; 16: 167-75.
126. Worthley DL, Le Leu RK, Whitehall VL, et al. A human, double-blind, placebo-controlled, crossover trial of prebiotic, probiotic, and symbiotic supplementation: effects on luminal, inflammatory, epigenetic, and epithelial biomarkers of colorectal cancer. Am J Clin Nutr 2009; 90: 578-86.
127. Brown DG, Borresen EC, Brown RJ, et al. Heat-stabilised rice bran consumption by colorectal cancer survivors modulates stool metabolite profiles and metabolic networks: a randomised controlled trial. Br J Nutr 2017; 117: 1244-56.

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