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How do tumours outside the gastrointestinal tract respond to dietary fibre supplementation?

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ABSTRACT

Cancer remains one of the leading causes of death worldwide, despite advances in treatments such as surgery, chemotherapy, radiotherapy and immunotherapy. The role of the gut microbiota in human health and disease, particularly in relation to cancer incidence and treatment response, has gained increasing attention. Emerging evidence suggests that dietary fibre, including prebiotics, can modulate the gut microbiota and influence antitumour effects. In this review, we provide an overview of how dietary fibre impacts the gut–tumour axis through immune and non-immune mechanisms. Preclinical evidence shows that β-glucan or inulin effectively suppress extraintestinal tumour growth via immunomodulation. Other fibres such as resistant starch, modified citrus pectin and rye bran may confer antitumour effects through metabolic regulation, production of metabolites or downregulation of the insulin/insulin-like growth factor 1 axis. Additionally, we highlight the potential for dietary fibre to modify the response to immunotherapy, chemotherapy and radiotherapy, as shown by inulin increasing the abundance of beneficial gut bacteria, such as *Bifidobacterium*, *Akkermansia*, *Lactobacillus* and *Faecalibacterium prausnitzii*, which have been associated with enhanced immunotherapy outcomes, particularly in melanoma-bearing mice. Furthermore, certain types of dietary fibre, such as psyllium, partially hydrolysed guar gum, hydrolysed rice bran and inulin plus fructooligosaccharide, have been shown to mitigate gastrointestinal toxicities in patients with cancer undergoing pelvic radiotherapy. Despite the proven benefits, it is noteworthy that most adults do not consume enough dietary fibre, underscoring the importance of promoting dietary fibre supplementation in patients with cancer to optimise their treatment responses.

INTRODUCTION

Cancer remains a significant global health challenge, with 9.6 million deaths attributed to it in 2018, making it the second leading cause of mortality worldwide after cardiovascular disease.[1] Despite advancements in anticancer treatments such as surgery, chemotherapy, radiotherapy and immunotherapy, patients with advanced-stage cancer often have a poor prognosis due to inadequate treatment responses.

The gut microbiota encompasses the diverse community of bacteria, fungi, viruses, archaea and protozoans, that constitute the normal physiology of the gut. Recently, evidence has suggested that the bacteria colonising the gut (the gut microbiota) may have roles in both altering the risk of developing cancer and treating cancer, including colorectal cancer (CRC)[2] and cancers outside the intestine.[3] For example, a comprehensive meta-analysis of 526 faecal metagenome samples from diverse cohorts identified seven bacteria that were enriched in patients with CRC.[2] Furthermore, the baseline gut microbiota has been shown to play a crucial role in influencing the response to immunotherapy[4] and chemotherapy drugs, including cyclophosphamide,[5] chemoradiation[6] and radiotherapy[7] in both preclinical models and human studies.

Dietary fibre has been shown to impact gut microbiota composition, diversity and richness. A study conducted by David *et al* demonstrated a positive correlation between long-term fibre intake and the baseline *Prevotella* genus abundance in human.[8] Additionally, they found a significant rise in β diversity after just 2 days of transitioning to a nearly zero-fibre (animal-based) diet. The microbiota in the colon feed on dietary fibres, leading to the selection of beneficial bacteria through different types of fibres. This process results in the breakdown of dietary components and the fermentation of metabolites that regulate host physiology, including gut barrier function, metabolic and immune homeostasis.[9] Dietary fibre deprivation has been shown to cause the consumption of host-secreted mucous glycoproteins by the gut microbiota, leading to the erosion of the colonic mucosal barrier and lethal

colitis, with evidence of invasion of *Citrobacter rodentium* in gnobiotic mice colonised with human gut microbiota.[10] In addition, the Western-style diet, low in dietary fibre, decreases microbial diversity and increases the risk of chronic inflammatory diseases such as cardiovascular disease, diabetes, CRC and obesity.[11]

This article aims to review preclinical and human studies concerning the gut barrier, the gut microbiota and dietary fibre, to discuss the mechanisms by which dietary fibre supplementation can suppress extraintestinal tumour growth, and to consider how fibre supplementation may improve outcomes from cancer treatments.

ANATOMY AND IMMUNOLOGICAL FUNCTION OF THE GUT BARRIER

The mucosal epithelium of the gastrointestinal tract provides a large area of luminal interaction between host and external environments and plays a pivotal role in regulation of the immune system.[9] The gut mucosa forms a selectively permeable barrier to enable transport of dietary nutrients, electrolytes, water and certain microbial metabolites into the blood stream, and protects against pathogenic microorganisms, food antigens and environmental toxins entering the gut lumen, both physically and immunologically.[9]

The gut barrier is made up of three interconnected layers which include the luminal mucus layer, the gut epithelial layer and the submucosal layer, which forms the mucosal immune system. The outer mucus layer acts as the first line of physical defence met by extrinsic molecules on arrival at the gut lumen and some gut microbiota are contained within it. The inner mucus layer contains antimicrobial proteins and secretory immunoglobin A (sIgA), synthesised in the lamina propria, which act as immune-sensing and regulatory proteins. Highly glycosylated mucin proteins are essential in the formation of this layer and, in the small intestine and colon, mucin 2 (MUC2) is found in large amounts.[12] This abundant gel-forming mucin attaches firmly to the epithelium, preventing the direct adhesion of bacteria to the intestinal lining.[13] The thickness of the inner mucus layer varies across the gastrointestinal tract: it is particularly thick in the colon and lacks bacteria,[13] while it is thinner and discontinuous in the small intestine.[14] B cell-deficient mice and mice deficient in the receptor necessary for sIgA transport to the lumen have increased activation of innate responses in gut epithelial cells in the small intestine and colon, demonstrating that the innate immune system compensates for the lack of adaptive responses and highlighting the importance of maintaining efficient immune protection in this area of the body.[15] SIgA also provides protection against the adhesion of pathogens and their infiltration into the barrier.[12]

The central cellular monolayer of gut epithelium contains specialised epithelial cells, including Paneth cells and enteroendocrine cells, which collectively work to maintain the integrity of the barrier and separate the lumen from the lamina propria (a layer of connective tissue lying beneath the intestinal epithelium), through junctional complexes.[9] Beneath the gut epithelium, the lamina propria and the gut-associated lymphoid tissues (GALT; the Peyer's patches, the isolated lymphoid follicles and the mesenteric lymph nodes) are also parts of the mucosal immune system.[12] Innate (macrophages, dendritic cells, plasma cells, neutrophils) and adaptive (B cells and T cells) immune cells reside in the lamina propria,[16] while dendritic cells travel through the lymphatics to transport antigens and present them to T cells in GALT and initiate immune responses.

THE GUT MICROBIOTA AND ITS ROLE IN GUT PHYSIOLOGY

In early development, the gut microbiota lacks diversity and is mostly made up of two phyla: Actinobacteria and Proteobacteria.[17] By age 30 months, the infant microbiota's composition and functional capacity reflects the adult microbiota.[18] The composition and population size of the microbiota are affected by chemical, nutritional and immunological gradients throughout the gut.[19] Due to higher concentrations of acid, oxygen and antimicrobials, and a shorter transit time, the small intestine is home to fewer bacteria than the colon. The latter can better support bacterial growth as bacteria survive by fermentation of some, but not all, dietary fibres.[19]

Firmicutes and Bacteroidetes are the two most abundant colonic bacterial phyla. Both break down ingested fibre, which can then inhibit the growth of pathogenic microorganisms in the gastrointestinal tract by colonisation resistance to maintain the diversity and stability of gut microbiota and aid in processes such as gut motility and insulin sensitivity.[20] Colonisation resistance is the phenomenon of maintaining stable and diverse expansion of commensal gut microbiota while resisting the invasion of the pathogenic bacteria.[20] The mechanisms of colonisation resistance include nutrient competition, niche exclusion (space competition), changes of the gut physiological environment (pH alteration), production of toxic substances (such as bacteriocins, secondary bile acids, and proteinaceous toxins) and metabolite production between commensals and pathogens.[21] Additionally, host immune responses, including the gut barrier and innate immunity, also play an important role in colonisation resistance.[21] Diet is a major factor shaping the composition and diversity of gut microbiota, and fibre-rich diets and 'prebiotics' ('substrates that are selectively utilised by host microorganisms conferring a health benefit')[22] are associated with beneficial impacts on gut microbiota.

Gut microbiota translocation is the process by which bacteria spread through the gut epithelial layer, which can occur physiologically or pathologically due to disruption of gut barrier integrity and uptake by antigen-presenting cells.[23] For example, dendritic cells carried *Enterobacter cloacae* to the mesenteric lymph nodes, triggering the production of IgA by antibody-secreting plasma cells (terminally differentiated B cells).[23] Both chemotherapy[5]

and radiotherapy[24] can disrupt gut barrier integrity, facilitating the translocation of gut microbiota and thereby enhancing antitumour immune responses.

DIETARY FIBRE

Dietary fibres come from foods such as fruits, vegetables, oats, barley, wheat bran and seeds and include non-digestible oligo/polysaccharides (carbohydrates that cannot be absorbed by the body because humans lack the enzymes required for their digestion) and lignin.[11] They can be categorised as soluble and insoluble.[11] Insoluble fibres cannot be fermented as they are insoluble in water; insoluble fibre remains relatively intact throughout the colon and acts to bulk faecal material.[11] Soluble fibres are metabolised by bacteria in the colon to short-chain fatty acids (SCFAs). More recently, dietary fibre is often categorised more comprehensively based on physicochemical characteristics, especially fermentability.[11] For example, cellulose exhibits low solubility and fermentability, while β-glucans and pectins are soluble and fermentable.[11] Resistant starch, on the other hand, demonstrates low solubility and slow fermentability.[11] Fructans (fructooligosaccharides (FOS) and inulin) and galactans (galactooligosaccharides) are the dominant dietary fibre categories that promote the abundance and activity of beneficial gut microbiota.[25]

Short chain fatty acids

Fermentation of dietary fibres can produce metabolites, including SCFAs which may be involved in tumour suppression through the systemic circulation.[11] The major SCFAs identified as metabolites produced during bacterial fermentation of dietary fibre are acetate, propionate and butyrate, comprising two, three and four carbon fatty acids, respectively. SCFAs are absorbed directly into colonocytes or the portal vein and hence may enter the systemic circulation.[11] Cummings *et al* confirmed systemic bioavailability in a study measuring the concentration of acetate, propionate and butyrate in the colon, portal vein (total SCFA of~375 µM), hepatic vein (after uptake by liver, ~148 µM) and peripheral (~79 µM) circulation of people who were recently deceased.[26] While the concentration of SCFAs were reduced, acetate (in greatest proportion), propionate and butyrate were present in the peripheral circulation, implying availability for uptake in tissues and cells outside the colon.[26]

The discovery of SCFAs as molecular signalling ligands for G-protein-coupled receptors found throughout the body, on cells such as enteroendocrine and immune cells, led to studies of the mechanisms of molecular signalling between gut microbiota and host.[27] Butyrate binds to GPR109A and GPR41, acetate to GPR43, propionate to both GPR41 and GPR43.[28] GPR41 and GPR43 are expressed on the renal epithelium and on various cells in the gut, including enteroendocrine cells, sympathetic ganglia, immune cells and adipocytes.[29] When GPR109A is absent, butyrate is unable to bind and initiate second messenger pathways. Absence of GPR109A has been linked to the development of CRC and other inflammatory processes.[30] GPR43 was found to be absent in metastatic cells and colon tumours, implying a role in carcinogenesis. When GPR43 expression was restored in adenoma cell lines, appropriate cell cycle signalling and apoptosis occurred.[29]

SCFAs can also confer antitumour effects through their properties as histone deacetylase (HDAC) inhibitors.[31] Wei *et al* showed that butyrate inhibited tumour growth in a subcutaneous lymphoma mouse model and further demonstrated that histone acetylation increased in cancer cells.[32] In normal colonocytes, butyrate acts as the primary energy source.[33] However, in cancer cells, accumulation of butyrate in the nucleus, caused by Warburg effect, leads to the inhibition of histone deacetylase enzymes.[34] Additionally, butyrate can be metabolised to acetyl-CoA, an essential co-factor that stimulates the activity of histone acetyltransferase enzyme,[31] resulting in increased histone acetylation. This alteration in histone acetylation can affect gene expression patterns and contribute to the antitumour effects of butyrate.

DIETARY FIBRE AND SYSTEMIC ANTITUMOUR EFFECTS

Dietary fibres can either manipulate the microbiota or cause tumour suppression via other mechanisms. The anticancer effects of dietary fibre have been widely investigated in CRC, including the local tumour suppressive effects of SCFAs.[35] High dietary fibre consumption, especially cereal fibre and whole grains, was associated with a lower risk of CRC in a systematic review.[36] O'Keele *et al* showed significant beneficial changes after a 2-week dietary shift from a high-fat, low-fibre Western-style diet to a high-fibre, low-fat African-style diet.[37] This transition led to decreased levels of proliferative and inflammatory biomarkers and an increase in faecal butyrate levels. Additionally, there was an increase in butyrate-producing gut bacteria, including *Roseburia intestinalis, Eubacterium rectale, Clostridium symbiosum, Saccharomyces cerevisiae.*

However, there have also been reports of systemic antitumour effects of dietary fibre on extraintestinal tumours in rodents and humans (tables 1 and 2). Both immune and non-immune mediated mechanisms have been described.[38–42] In some instances, metabolites from bacterial fermentation of dietary fibre mediate tumour-suppressive activity.[42 43] For example, β-glucan from *S. cerevisiae* yeast has been shown to decrease tumour growth of prostatic adenocarcinoma[44] and reduce metastatic melanoma in the lungs, associated with activation of monocytes,[45] in mice. Modified citrus pectin (MCP) can also inhibit tumour growth, angiogenesis and spontaneous metastasis in a preclinical immunocompromised breast cancer model.[46] Additionally, Taper *et al* found that inulin and pectin can suppress breast and liver tumour growth.[47]

Table 1 Animal studies on tumour suppressive effects of dietary fibre supplementation

Animal model	Cancer	Dietary fibre[references]	Main findings
BALB/c, C57BL/6, BALB/c nude mice	Lymphoma	High-fibre(8%) versus low-fibre (<0.3%)[32]	↓ tumour growth and ↑ survival in mice on high-fibre diet; ↑ butyrate levels in serum and mouse lymphoma tumour; ↑ histone H3 acetylation level; ↑ FAS, p21, p27 and Bax expression
BALB/c mice	Melanoma	β–1,3 glucan (50, 100 and 200 g) versus PBS[39]	↓ tumour weight, lung metastasis and mortality;↑NK cell-mediated antitumour activity
Athymic nude mice	Urinary bladder cancer	Modified citrus pectin (350 and 700 mg/kg body weight) versus vehicle[41]	↓ tumour burden; ↓ galectin-3 and Ki67 expression (cell proliferation marker); ↑ cleaved caspase-3 (cell apoptosis marker)
C57BL/6 mice	Melanoma	Mucin (3% in drinking water) or inulin (15% supplemented in chow) versus standard chow[42]	↓ tumour growth and ↑ antitumour immunity with total $CD45^+$ cells, effector $CD4^+$ and $CD8^+$ T cells, and total DCs; ↑ expression of chemokines, inflammasome-related and antigen presentation-related genes; Inulin: ↓ melanoma resistance to MEK inhibitor
Copenhagen rats	Prostate adenocarcinoma	1,3–1,6 β-D-glucan (50 mg/kg/daily orally)[44]	↓ tumour growth and ↓ malondialdehyde (oxidative stress marker) levels
C57BL/6J mice	Pulmonary metastatic melanoma	Yeast-derived β-glucan (1 mg intraperitoneally) versus PBS[45]	↓ lung metastasis and ↓ gene expression of tyrosinase; ↑ monocyte-dependent antitumour immunity; ↑ levels of TNF-α and G-CSF in lung and plasma
NCR nu/nu mice	Metastatic breast cancer	Modified citrus pectin (1% (w/v) in drinking water) versus regular autoclaved water[46]	↓ tumour growth, angiogenesis and spontaneous metastasis
Sprague-Dawley rats	Breast cancer	Inulin, oligofructose or pectin (15 g of fibre in 100 g basal diet) versus basal diet[47]	↓ tumour growth
C57BL/6 mice	Mammary cell/ Lewis lung cancer	Yeast-derived whole β-glucan particles (800 µg daily) versus PBS[62]	↓ tumour weight and splenomegaly; ↓ polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC)
Nu/Nu nude mice	Pancreatic cancer	Engineered resistant starch (Hi Maize 260) versus standard diet[66]	↓ tumour growth; ↓ acetylcarnitine, arginine, aspartic acid, hypoxanthine, inosine, and xanthine; ↑ glutamine
Copenhagen rats	Pulmonary metastatic prostate cancer	Modified citrus pectin (0.0%, 0.01 %, 0.1% or 1.0% (w/v) in drinking water)[69]	↓ lung metastasis in rats given 1.0% MAP
BALB/cABom nude mice	Prostate adenocarcinoma	Rye bran (30 g/100 g diet) or soy protein (22.5 g/100 g diet)[74]	↓ tumour growth and weight; ↓PSA secretion and ↑ cell apoptosis

PSA, prostate-specific antigen.

The gut–tumour axis

The concept of a 'gut–tumour axis' is analogous to the well-established gut–brain, gut–liver, gut–lung and gut–heart axes, illustrating how the gut microbiota can communicate with extraintestinal sites. For example, in the gut–brain axis, gut microbiota can interact with central nervous system (CNS) by breaking down dietary fibres into SCFAs, whose levels in the brain and cerebrospinal fluid are related to the severity of CNS diseases, and by synthesising neurotransmitters.[48] In the gut–lung axis, feeding mice with 30% pectin leads to decreased pulmonary inflammation due to the anti-inflammatory effect of gut microbiota-producing SCFAs.[49] In the gut–heart axis, gut microbiota-produced trimethylamine-*N*-oxide promoted atherosclerosis in mice, which is related to an enhancement of platelet hyperactivity and thrombosis risk.[50] Furthermore, C57BL/6 mice fed high amylose starch or acetate showed decreased blood pressure and left ventricular hypertrophy compared with controls fed normal chow.[51]

The existence of a gut–tumour axis has been shown in various cancers (figure 1). Patients with pancreatic cancer who responded to chemotherapy had a higher level of the microbiota-derived tryptophan metabolite, indole-3-acetic

Table 2 Human studies on tumour-suppressive effects of dietary fibre supplementation

Study type (size)	Cancer	Dietary fibre[reference]	Main findings	Fibre dose and duration of supplementation
Phase II clinical trial (n=10)	Relapsing prostate cancer	Modified citrus pectin[70]	↑ prostate-specific antigen (PSA) doubling time	14.4 g per day for 12 months
Phase II clinical trial (n=59)	Non-metastatic relapsing prostate cancer	Modified citrus pectin[71]	↑ PSA doubling time	14.4 g per day for 6 months
Randomised controlled trial (n=17)	Prostate cancer	Rye whole grain and bran versus refined wheat grain with added cellulose (control)[75]	↓ PSA plasma concentration; ↓ low-grade inflammation and endothelial function markers including tumour nuclear factor receptor-2, e-selectin and endostatin in plasma	485 g of rye and bran products or refined wheat products with added cellulose per day for 6 weeks
Randomised controlled crossover study (n=17)	Prostate cancer	Rye whole grain and bran versus refined wheat grain with added cellulose (control)[76]	↓ PSA plasma concentration; ↓ fasting plasma insulin and 24 hours urinary C-peptide excretion	485 g of rye and bran products or refined wheat products with added cellulose per day for 6 weeks

acid, which enhanced the efficacy of chemotherapy in mice.[52] Additionally, the gut microbiota has been associated with response to radiotherapy in patients with hepatocellular carcinoma.[53] A preclinical study further demonstrated that antibiotics could diminish radiotherapy efficacy, associated with T cell immune responses via stimulator of interferon genes (STING) signalling.[53] Gut microbial β-glucuronidase enzymes can deconjugate oestrogen into its free, active form, allowing oestrogen to be reabsorbed into the bloodstream and oestrogen

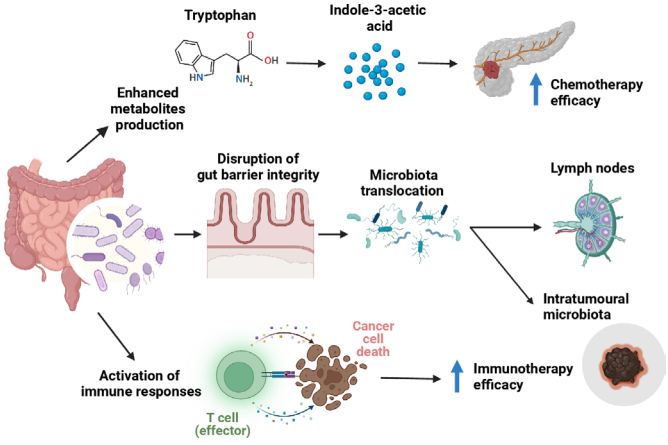

Figure 1 Evidence for the gut–tumour axis. The gut microbiota interacts with the tumour microenvironment in various ways, collectively summarised in the gut–tumour axis. For example, high levels of the gut microbiota-derived tryptophan metabolite, indole-3-acetic acid, improve chemotherapy efficacy in patients with pancreatic cancer. Additionally, following disruption of the gut barrier integrity, the microbiota can translocate to lymph nodes or tumour sites, as observed in melanoma. Gut microbiota can also enhance immunotherapy efficacy via activation of antitumour immune responses. Figure created with biorender.com.

dysregulation is one of the main risk factors for breast and endometrial cancer development.[54]

Gut microbiota translocation from the gut to lymph nodes or distal organs can also be part of the gut–tumour axis, including melanoma, which is typically considered aseptic.[55] This indicates that gut bacteria can access extraintestinal tumours via the proposed disruption of gut barrier integrity.[56] Gut microbiota can enhance the responses of extraintestinal tumours to cyclophosphamide via stimulation of T helper cell immune responses associated with translocation of gut bacteria to secondary lymphoid organs.[5 57] Choi *et al* and Paulos *et al* further showed that immune checkpoint blockade[55] and total body irradiation[24] cause gut microbiota translocation and hence stimulates the antitumour T cell responses of extraintestinal tumours.

Immune-mediated mechanisms of extraintestinal tumour suppression by dietary fibre

The tumour microenvironment is known to exhibit strong immune suppression, allowing cancer cells to escape immunosurveillance.[58] Therefore, enhancing immune responses through dietary fibre, such as β-glucans and inulin, has been shown to be beneficial for tumour control.[39 42] β-glucans are polysaccharides found in the cell walls of yeast, mushrooms and cereals and they possess immune-modulatory effects.[59] One particular β-glucan mimetic, known as (1→6)-β-glucose-branched poly-amido-saccharides, has been shown to activate immunoregulatory signalling pathways by binding to pattern recognition receptors, such as toll-like receptor 4 (TLR-4) and Dectin-1 (figure 2).[38 60 61] Additionally, a study has demonstrated that insoluble β-glucan derived from yeast can enhance antitumour immunity associated with stimulation of natural killer (NK) cells, resulting

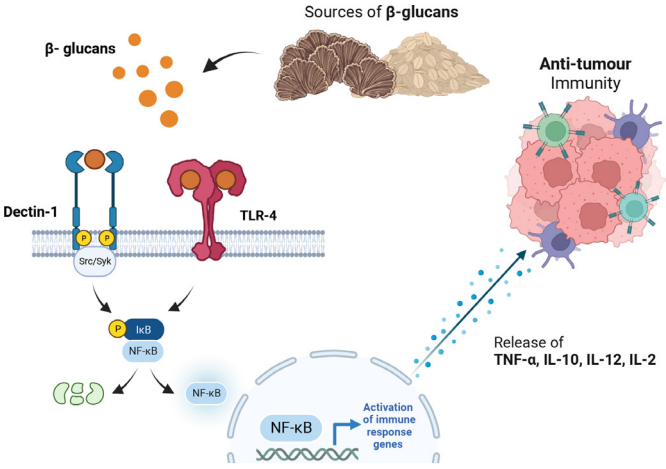

Figure 2 β -glucans generate antitumour immunity. A β-glucan mimetic, known as (1→6)-β-glucose-branched poly-amido-saccharides activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling, via dectin-1 and toll-like receptor 4 (TLR-4) binding. Binding to dectin-1 dimers results in phosphorylation and activation of Src and Syk kinases, which ultimately leads to phosphorylation and degradation of IκB and nuclear translocation of NFκB. Binding to TLR-4 has the same outcome but involves different mediator proteins. In the nucleus, NFκB acts as a transcription factor, resulting in expression of immune response genes. Cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-10, IL-12 and IL-2 are released and cytotoxic natural killer and $CD8^+$ T cells are activated within the tumour microenvironment, leading to antitumour immunity.[60 61] Figure created with biorender.com.

in reduced melanoma lung metastasis in a preclinical model.[39] Another study showed that yeast-derived whole β-glucan particles (WGP) reduced tumour weight and immunosuppressive polymorphonuclear myeloid-derived suppressor cells in mouse models of lung carcinoma and mammary cell carcinoma.[62] The antitumour properties of lentinan, a β-glucan from Shiitake mushrooms, have been extensively described and, in China and Japan, lentinan is clinically used as an adjuvant to cancer chemotherapy for lung, colorectal, ovarian, gastric and pancreatic cancer.[63] β-glucans derived from fungi, such as maitake (soluble in water), lentinan (soluble), WGP (insoluble) and yeast (insoluble) have glycosidic linkages of β-(1→3, 1→6), while β-glucans from higher plants, such as barley (soluble) and oat (soluble) have glycosidic linkages of β-(1→3, 1→4).[64]

In addition, inulin suppressed tumour growth and induced antitumour immunity by stimulating $CD4^+$ and $CD8^+$ T cells in a preclinical melanoma model,[42] by stimulating dendritic cells to express more MHC class I and II, thereby increasing antigen presentation.[42] The antitumour effect of inulin was also shown in an immunocompetent breast cancer rat model.[47] Furthermore, our research has demonstrated that a combination of psyllium and inulin can delay bladder tumour growth, and this effect was associated with increased cytotoxic T cells.[65] However, human studies of inulin supplementation for cancer suppression are lacking and more research is needed on their mechanism of action.

Non-immune-mediated mechanisms of extraintestinal tumour suppression by dietary fibre

Dietary fibres can impact tumours through non-immune mechanisms. Resistant starch (Hi Maize 260) has been shown to modulate the control of pancreatic cancer xenografts through regulating miRNA, affecting not only inflammatory responses but also cell migration, metastasis and synthesis of carbohydrates, glucose metabolism disorder,[66] and ERK1/2 and mTOR pathways.[67] In our study, a combination of psyllium and resistant starch (Hi Maize 260) delayed bladder tumour growth after irradiation and this was positively correlated to caecal isoferulic acid levels.[65] Citrus pectin can be modified in the laboratory to improve gastrointestinal absorption (MCP).[68] MCP decreased bladder cancer xenograft growth by reducing galectin-3 levels and inactivating the Akt signalling pathway in an immunocompromised mouse model,[41] lowered incidence of prostate cancer lung metastases in rats[69] and increased prostate-specific antigen (PSA) doubling time in patients with prostate cancer.[70 71] Notably, galectin-3 levels have been found to correlate with cancer aggressiveness and metastasis,[72] and it is also expressed in endometrial cancer.[73] These findings underscore the potential of dietary fibre, such as MCP, in the treatment of various extraintestinal cancers.

A preclinical study showed that consumption of rye bran and soy protein led to a decreased take rate of subcutaneous prostate tumours and a reduction in PSA secretion in nude mice,[74] while rye and whole grain-rich diets impacted on biomarkers in low-grade prostate cancer[75] potentially involved in slowing disease progression (see table 2). Furthermore, a randomised controlled study confirmed that patients with prostate cancer who consumed rye whole grain and bran had significantly lower levels of plasma insulin and PSA compared with those who consumed refined wheat products with added cellulose.[76] It is known that activation of the insulin-STAT-5 pathway can promote hepatic production of insulin-like growth factor 1 (IGF-1).[77] Therefore, the reduced insulin secretion by dietary fibre may lower IGF-1 levels, potentially leading to antitumour effects.[78]

There is very limited direct evidence linking gut bacterial metabolites produced from dietary fibre to tumour suppression, with most of these findings limited to SCFAs or in vitro studies.[79] Wei *et al* showed that compared with low-fibre diet, an unspecified high-fibre diet increased tumour and plasma butyrate levels and suppressed the tumour growth of subcutaneous lymphoma xenografts in mice.[32] An indirect association was observed with dietary barley leaf supplementation, which increased gut microbiota-derived inosine levels,[80] while Magel *et al* found that the bacterial metabolite inosine can promote the immunotherapy response against intestinal, bladder and melanoma cancer in mice.[81]

ADJUVANT DIETARY FIBRE IN CANCER THERAPY

Immunotherapy

The gut microbiota is involved in therapeutic responses to immune-checkpoint inhibitors, which have revolutionised the treatment landscape for various cancers, including non-small cell lung cancer, renal cell carcinoma and melanoma.[82] Sivan *et al* found that oral administration of *Bifidobacterium* alone had a similar degree of improved tumour control as anti-programmed death-ligand 1 (PD-L1) therapy, and combined treatment even conferred stronger effects in melanoma mice.[83] Therefore, dietary fibres, like inulin, which have been shown to increase the *Bifidobacterium* and *Faecalibacterium prausnitzii* abundances,[84] have the potential to enhance the efficacy of immunotherapy via activation of antitumour immune responses by these key commensal bacteria. There is both preclinical and clinical evidence supporting the beneficial role of dietary fibre in anticancer treatments (table 3).[85] In a melanoma mouse model, Han *et al* demonstrated that inulin, when formulated as a colon-retentive orally administered gel, amplified the antitumour activity of anti-PD-1.[86] Inulin has been shown to increase *Akkermansia* and *Lactobacillus*, which were associated with enhanced tumour control when combined with anti-PD-1, and to activate cytotoxic T cells in colon tumour-bearing mice.[86] *Bifidobacterium pseudolongum* enhanced melanoma and bladder response to immunotherapy via gut translocation of bacteria-produced inosine and activation antitumour T cells in a preclinical study.[81] Additionally, the gut bacteria-produced inosine from dietary barley leaf supplementation mitigated perturbation of gut microbiota and dextran sulfate sodium-induced colitis,[80] implying the

Table 3 Animal and human studies on anticancer treatments with dietary fibre supplementation/intake

Animal model/ study type (size)	Cancer	Dietary fibre and anticancer treatments[reference]	Main findings	Fibre dose and duration of supplementation
BALB/c and C57BL/6 mice	Colorectal carcinoma and melanoma	Orally administered inulin gel along with anti-PD-1 immune checkpoint inhibitors[86]	↑ the relative abundances of important commensal microbes and SCFAs; ↑ interferon-γ cytotoxic T cells; ↑ establishment of stem-like T-cell factor-1$^+$ PD-1$^+$ CD8$^+$ T cells	60 mg/dose inulin gel started 7 days after tumour inoculation, followed by anti-PD-1
C57BL/6 mice	Melanoma	Inulin along with anti-PD-1 therapy[85]	↑ the abundance of *Bifidobacterium*; ↓ tumour growth; ↑ Th1-polarised CD4$^+$ and CD8$^+$ αβ T cell-mediated antitumour response	7.2% inulin in drinking water started 15 days before tumour inoculation; anti-PD-L1 was injected intraperitoneally on days 4, 7 and 10 post-tumour inoculation
Observational study (n=128)	Melanoma	Dietary fibre intake and immunotherapy (anti-PD-1, anti-CTLA1)[87]	↑ progression-free survival was associated with higher dietary fibre intake in 128 patients received immunotherapy	Sufficient (>20 g/day) versus insufficient (<20 g/day) dietary fibre intake
Randomised controlled trial (n=38)	Gynaecological cancer	Inulin and fructooligosaccharide, and pelvic radiotherapy (52.2 Gy)±brachytherapy[90]	↓ number of days with watery stool	12 g mixture of fibre (50% inulin and 50% FOS) per day vs 12 g maltodextrin per day
Randomised controlled trial (n=60)	Prostate or gynaecologic cancer	Psyllium and pelvic radiotherapy (mean of 68 Gy)[91]	↓ incidence and severity of diarrhoea	Psyllium (dose: not specified)
Randomised controlled trial (n=166)	Pelvic cancer	Nonstarch polysaccharide (NSP) and pelvic radiotherapy (mean of 54 Gy)[95]	High-fibre group has a small change of Inflammatory Bowel Disease Questionnaire–Bowel Subset (IBDQ-B) score between the start and end of radiotherapy compared with the habitual-fibre group	High-fibre (≥18 g NSP/day), habitual-fibre (control), low-fibre (≤10 g NSP)/day] diet
Randomised controlled trial (n=141)	Advanced head and neck squamous cell carcinoma (HNSCC)	1,3–1,6 β-D-glucan and concurrent chemotherapy (cisplatin, tegafur, uracil, leucovorin) and radiotherapy (65–75 Gy)[105]	↓ concurrent chemoradiotherapy-associated adverse events; ↑ global quality of life scale score	1 g Maitake mushroom extract per day, 1 hour before meals during CCRT

potential protective effects of inosine in colitis induced by anticancer treatments.

A recent study by Spencer *et al* reported that in a cohort of 128 patients undergoing anti-PD-1 therapy, those who reported high-fibre diets had significantly improved progression-free survival than those who reported low-fibre diets.[87] Intriguingly, sufficient intake of dietary fibre without probiotics, defined as 'live microorganisms that confer a health benefit on the host',[88] had a better outcome compared with those with probiotics in patients receiving melanoma immunotherapy.[87] Their preclinical melanoma model further demonstrated that high dietary fibre enhanced the T cell receptor signalling pathway and T cell activation of tumour-infiltrating lymphocytes, while low fibre or probiotics decreased interferon-γ (IFN-γ) $^{+}$ cytotoxic T cells in tumours in the setting of treatment with anti-PD-1.[87]

Radiotherapy and chemotherapy

In England, 27% of all patients with cancer received radiation therapy and 28% received chemotherapy[89] between 2013 and 2016, so maximising efficacy of these treatments and moderating side effects is important. A body of research suggests that dietary fibre may be useful in ameliorating radiotherapy-induced toxicity[90 91] but there is limited research on the potential antitumour effects of dietary fibre in combination with radiotherapy.[92 93] In an immunodeficient mouse model, we showed that 10% inulin enhanced bladder tumour responses to irradiation, which was associated with an increased abundance of the gut commensal *Bacteroides acidifaciens*.[92]

In terms of radiotherapy-induced toxicities, oat bran has been demonstrated to reduce the levels of systemic proinflammatory cytokines raised by radiotherapy in the colorectal region of mice.[94] Randomised controlled trials conducted on patients undergoing pelvic radiotherapy revealed that a high-fibre diet (with a daily intake of≥18 grams of non-starch polysaccharide),[95] Metamucil (psyllium husk),[91] partially hydrolysed guar gum,[96] hydrolysed rice bran[97] and inulin combined with 50% FOS[90] were also found to be beneficial in mitigating diarrhoea in patients with cancer receiving pelvic or abdominal radiotherapy. A recent systematic review, which included 23 randomised controlled trials, reported that biotic supplements, particularly probiotics and synbiotics, can lower the risk of diarrhoea in patients undergoing pelvic radiotherapy.[98] This finding contradicts previous recommendations that advised a low-fibre diet in similar situations.

In the context of chemotherapy, Taper *et al* showed that dietary oligofructose or inulin with chemotherapeutic drug increased the lifespan of ascitic liver tumour-bearing mice.[99] Additionally, a systemic review revealed that lentinan significantly improved clinical effectiveness, including complete response and partial response rates, as well as quality of life, in patients with non-small cell lung cancer (NSCLC) who received cisplatin.[100] Moreover, meta-analyses demonstrated that the use of lentinan in combination with chemotherapy increased overall survival in patients with unresectable gastric cancer[101] and significantly improved objective response rates in patients with NSCLC.[102] Furthermore, a randomised controlled trial showed that the use of Imprime PGG, a soluble fungal-derived 1,3–1,6 β-glucan immunomodulator, in combination with carboplatin, paclitaxel and cetuximab, resulted in improved objective response rate in patients with advanced NSCLC.[103]

Chemoradiotherapy (CRT), referring to the simultaneous use of chemotherapy and radiotherapy, is often used to treat patients with advanced head and neck squamous cell carcinoma. The maitake D-fraction, a β-glucan extracted from maitake mushroom that is a biological response modifier like lentinan, has immunomodulatory effect of increasing NK cell activity as well as antitumour activity.[104] Additionally, a randomised control trial showed that maitake D-fraction administration during CRT improved overall survival (p=0.017) of patient and conferred a protective effect against radiation toxicity, reducing radiotherapy-induced side effects and thus improved quality of life.[105] A preclinical experiment also demonstrated that Maitake D-fraction administration suppressed tumour growth of mammary carcinoma tumour, implanted in the axillary region, via an increase IFN-γ^{+}CD4^{+} cells in the inguinal lymph node and the production of IL12 p70 and TNF-α of whole spleen cells.[106]

ANTIBIOTIC USAGE IN PATIENTS WITH CANCER

Patients with cancer frequently require antibiotics as part of their treatment, but antibiotic use can influence the gut microbiota. In one study, 45.6% of patients with locally advanced head and neck cancer received antibiotics following CRT, which was associated with poorer progression-free, overall and disease-specific survival.[107] Vancomycin, an antibiotic that eradicates Gram-positive bacteria in the gut, has been shown to enhance radiotherapy efficacy via increasing dendritic cell antigen presentation in preclinical melanoma and lung/cervical tumour models,[7] although an antibiotic cocktail of ampicillin, imipenem, cilastatin and vancomycin reduced tumour response to radiotherapy.[108] These findings suggest that manipulation of the gut microbiota using antibiotics-based approaches in patients undergoing radiotherapy may modulate tumour response. In a murine study, use of antibiotics resulted in tumours resistant to cyclophosphamide,[57] and mice treated with antibiotics have been shown to have poorer responses to CpG-oligonucleotide immunotherapy and platinum chemotherapy.[109]

SUPPLEMENTATION COMPARED WITH DIETARY MODIFICATION

Although the UK's Scientific Advisory Committee on Nutrition recommends a daily intake of over 30 g/day of dietary fibre[110] from sources of fruits, vegetables, whole grains, legumes and other food groups, Gressier and

Frost showed that the average fibre intake in UK adults is 14.9 g/day.[111] Obtaining sufficient amounts of dietary fibre through diet alone would require significant dietary modifications, which may not be feasible shortly before the treatment for many patients with cancer. In fact, a randomised controlled study conducted by Wedlake *et al* also found that only 28% patients were willing to enrol in the study, with reluctance to make dietary changes being a major reason for rejection.[95] Among enrolled patients, 23% were unable to achieve more than 80% compliance with the fibre target. Furthermore, a study in overweight and obese individuals noted significantly increased fibre intake when a psyllium supplement was used compared with heathy eating plus placebo (55 g vs 31 g).[112]

Dietary fibre supplementation is not without side-effects. Patients most frequently reported flatus, belching, bloating, abdominal cramping and altered bowel movement and stool consistency following inulin administration.[113] One study found that patients experiencing dietary fibre side-effects were more likely to reduce their fibre intake or withdraw from the study.[114] However, generally dietary fibres are safe and well tolerated. Recently, a human MRI study conducted by Gunn *et al* revealed that 20 g of psyllium resulted in a decrease in gas production caused by 20 g of inulin, while still maintaining fermentation, as observed through in vitro testing.[115] A clinical trial has also demonstrated the tolerability of other fibres, such as polydextrose and soluble corn fibre, at doses of up to 50 g/day.[116] It is important to state that the majority of these studies were conducted in healthy people, so they may not necessarily reflect what patients with cancer can tolerate. Further studies, similar to those conducted by Murphy *et al* on psyllium[91] and by Garcia-Peris *et al* on inulin and FOS,[90] may be needed to explore maximum dosages within these populations.

The mode of delivering fibre supplementation can vary, as previous studies have used supplementary tablets, powder or bioactive metabolites. This variability is of particular importance when considering soluble fibres, as they may undergo metabolism by the gut microbiota, potentially exerting effects on extraintestinal sites through the modulation of local gut or systemic immunity and the production of metabolites, all within the gut environment.

DIETARY RECOMMENDATIONS IN PATIENTS WITH CANCER

Historically, patients receiving radiotherapy or CRT for pelvic tumour have been recommended a low fibre diet to moderate side effects, particularly diarrhoea, which is the most common issue.[95] However, in 2017, a study conducted by Wedlake *et al* found significantly decreased gastrointestinal toxicity during pelvic radiotherapy at 1-year follow-up in patients given a high-fibre diet during radiotherapy, compared with a control habitual-fibre group, contradicting prior weakly evidenced recommendations.[95] Kenfield *et al* found that higher adherence to the Mediterranean diet (Med-Diet), characterised by its richness in fruits, vegetables and whole grains, in patients with non-metastatic prostate cancer was inversely associated with overall mortality.[117]

The British Nutrition Foundation has also noted an inverse relationship between dietary fibre intake and the risk of developing CRC.[118] Ratjen *et al* found a higher adherence to the Med-Diet after CRC diagnosis was associated with better overall survival.[119] However, they did not explicitly highlight any beneficial relationship regarding dietary fibre and extraintestinal tumours. Promoting the inclusion of dietary fibre in the diets of patients with extraintestinal tumours by dieticians, oncologists and other healthcare professionals, as well as support organisations, may lead to improve outcomes and reduced side effects in patients who are willing to make dietary changes.

CONCLUSIONS

Dietary fibres such as β-glucans, inulin, MCP and resistant starch may exert extraintestinal tumour suppression through immune and/or non-immune mechanisms. There is evidence supporting the benefits of dietary fibre supplementation in conjunction with immune checkpoint inhibitors, with many studies showing increased antitumour T cell responses. Some preclinical studies have shed light on the effectiveness of high-fibre diets in modifying gut microbiota to enhance responses to chemotherapy and radiotherapy. Importantly, certain types of fibres, such as psyllium husk, hydrolysed rice bran, and inulin, may reduce intestinal side effects, particularly those associated with radiotherapy. As many people do not meet the recommended daily fibre intake and it is unrealistic to expect patients with cancer to adopt a new diet, supplementation is therefore a more practical solution. More studies are necessary within these population groups to ascertain the feasibility and tolerability of fibre supplementation.

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