



# Synbiotics: Promising Approach for the Therapeutic Management of Cancer

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## 3.1 Introduction

Cancer is a disease represented by an uncontrolled growth and proliferation of cells due to evasion of central endogenous control mechanisms as well as the acquisition of metastatic properties. Typically, the upregulation of oncogenes and the downregulation of tumour suppressor genes can lead to dysregulated cell cycle progression and inhibited cell apoptotic mechanisms. In contrast to benign tumours, malignant tumours acquire metastasis, which involves the deactivation of cell adhesion receptors that are necessary for tissue-specific and cell to cell attachment, as well as the activation of receptors that induce cell motility. Activation of membrane metalloproteases also facilitates the spreading of metastatic tumour cells (Sarkar et al. 2013; Adjiri 2016). As such, managing cancer is highly challenging

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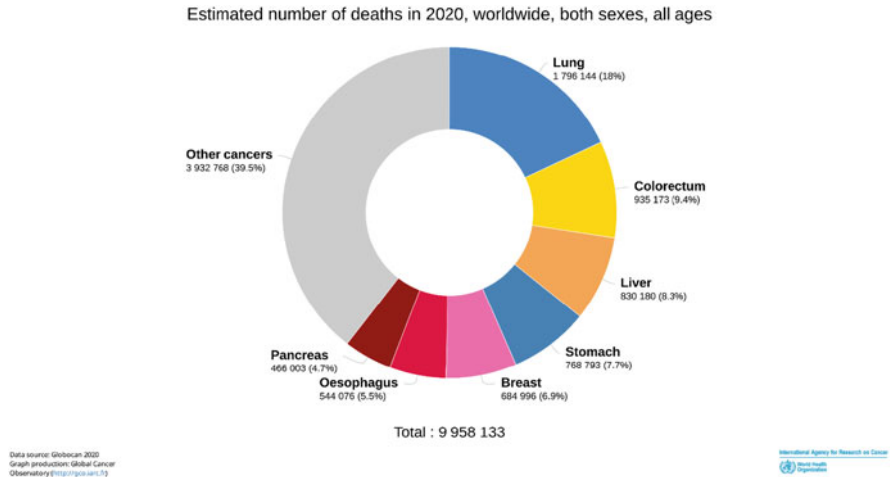
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**Fig. 3.1** Estimated number of cancer-related deaths worldwide in the year of 2020 for both sexes and across all ages. (Reproduced from Cancer Today, 2020 ([https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode\\_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population\\_group=0&ages\\_group%5B%5D=0&ages\\_group%5B%5D=17&nb\\_items=7&group\\_cancer=1&include\\_nmsc=1&include\\_nmsc\\_other=1&half\\_pie=0&donut=1](https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=1)), with permission from the International Agency for Research on Cancer, World Health Organization)

and complex, in which chemotherapy, radiotherapy, and surgery are the most common types of cancer treatment strategies available nowadays. These conventional cancer therapies have been documented throughout history by ups and downs not only due to their poor efficacy, therapeutic resistance, and associated adverse effects, but also in many cases, by hope and the reality of complete cancer remission and cure (Arruebo et al. 2011; Debela et al. 2021). Over the recent years, advancement in oncology research has also led to the discovery and development of novel therapeutic strategies such as immunotherapy, stem cell therapy, targeted therapy, chemodynamic therapy, sonodynamic therapy, and nanomedicine (Debela et al. 2021; Falzone et al. 2018; Chu et al. 2020). Despite that, cancer remains as one of the leading factors of death, and it is a significant barrier to an increased life expectancy across the world. According to the International Agency for Research on Cancer, World Health Organization (WHO), there was an estimated total of 9.9 million deaths globally in the year of 2020 with lung cancer being the leading factor of cancer-related deaths, responsible for nearly 1.8 million mortalities across both sexes (Fig. 3.1). The burden brought upon by cancer is expected to grow in the coming years, exerting immense emotional, physical, and financial strain on suffering individuals, their families, communities, as well as global health systems (WHO n.d., 2020; Sung et al. 2021). In addition, during the progression of cancer, tumours often become highly heterogeneous, thereby producing a mixed population of tumour cells that are characterized by varying molecular features and therefore, diverse responsiveness to therapies and it is the primary factor responsible for the development of multiple resistant cancer phenotypes (Pucci et al. 2019). Although

huge resources have been devoted into oncology research, healthcare professionals and medical researchers are still struggling as most of the existing therapies are not entirely effective, and there is still a long journey ahead to a complete eradication of this disease that continues to kill numerous individuals each year (Adjiri 2016). Hence, a new revolution in the field of medical oncology is necessary not only to evade the development and/or progression of cancer, but also to optimize the efficacy and/or minimize adverse effects associated with existing anticancer therapeutics.

Every exposed human body surface such as the skin, as well as the respiratory, genitourinary, and gastrointestinal tracts are known to be heavily colonized by more than trillion of microorganisms that include fungi, archaea, bacteria, and viruses. Over the recent years, studies have identified commensal microorganisms as the key determinants of a host's homeostasis and health. For this instance, the gut microbiota is the most extensively populated, in which the human gastrointestinal tract is populated by a complex ecosystem of microorganisms that are commensal and undergo symbiotic co-evolution throughout the course of life of the host (Vivarelli et al. 2019; Markowiak and Ślizewska 2017). Generally, the gut microbiota represents a highly dynamic system whereby its density and composition can be influenced by exogenous factors such as environmental factors, drug use, diet, and infections, as well as endogenous factors such as genetic features of the host, age, and gender. Among these, diet has been evidenced to be key factor in dictating the composition and evolution of the gut microbiota over time (Ferraris et al. 2020; Hills et al. 2019). The production of advantageous micronutrients, strengthening gut integrity, harvesting energy, and modulation of a normal immunological response towards invading pathogens are among the essential functions exerted by beneficial intestinal microorganisms. However, there is potential for these functions to be disrupted due to an altered gut microbial composition, leading to the expansion of several microbiota subpopulations that produce high level of toxins (Hills et al. 2019; Thursby and Juge 2017; Vivarelli et al. 2019). As such, it has been widely proven that disruption in normal gut microbiota, known as microbiota dysbiosis, is implicated in the development of multiple chronic diseases ranging from inflammatory bowel disease, cardiovascular diseases, type 2 diabetes to various cancers (Hills et al. 2019; Olas 2020; Scott et al. 2018). The degree of gut microbiota dysbiosis is also direct causative factor in disease progression and prognosis (Shimizu et al. 2013). In terms of cancer, it is becoming increasingly well established that gut microbiota dysbiosis can contribute to almost all aspects of tumorigenesis ranging from susceptibility to cancer, cancer progression, development of co-infections, as well as the host's response to cancer therapeutics. Several microorganisms are also found to be specifically associated with cancer development and progression. For instance, *Helicobacter pylori* has been classified as a class I carcinogen by the WHO and plays a role in gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. On the other hand, *Escherichia coli*, *Chlamydia trachomatis*, and *Salmonella enterica* are also linked to colorectal, cervical, and gallbladder cancers, respectively (Vivarelli et al. 2019; Khan et al. 2022). Therefore, achieving, restoring, and sustaining a favourable equilibrium in the gut environment, as well as the

activity of intestinal microorganisms is necessary to enhance the health condition of the host.

The old age quote by the father of modern medicine, Hippocrates, “Let food be thy medicine and medicine be thy food” represents the ideology of today’s health-conscious population. There is a plethora of foods, plants, and herbs that has served as the backbone of traditional healing systems and has been integrated as part of global culture and history since the ancient times. Nutraceuticals, derived from “nutrition” and “pharmaceutical”, are products with medicinal properties for disease prevention and treatment, as well as nutritional properties that aid in promoting physical health, maintaining proper body function, and improving longevity (Chan et al. 2021; Pandey and Naik 2015). Throughout these years, the roles of functional foods in maintaining good body health and the advantages of nutritional supplements in preventive healthcare have received increasing recognition and are being promoted around the world as a promising strategy to protect the body against various chronic diseases, in which extensive research have been focused on identifying and ascertaining health benefits of these products. Namely, probiotics and prebiotics are examples of nutraceuticals and functional foods that can positively alter, modify, and restore a normal gut microbiota (Pandey and Naik 2015; Alamgeer et al. 2018; Santana et al. 2016; Chanda et al. 2019). According to the Food and Agriculture Organization of the United Nations (FAO) and WHO, probiotics are defined as “live strains of strictly selected microorganisms which, when administered in adequate amounts, confer a health benefit on the host”, whereas prebiotics are metabolic substrates defined as “non-digestible food supplements which exert advantageous health effects on the host through the induction of growth and/or activity of one or more gastrointestinal microorganisms” (Aponte et al. 2020). They are often utilized as substrates for probiotics, whereby galacto-oligosaccharides, fructo-oligosaccharides, and trans-galacto-oligosaccharides are the most utilized prebiotics currently. As such, synbiotics are essentially probiotics and prebiotics mixtures that are employed to synergistically influence the gut microbiota in which the prebiotic compound(s) can selectively favour the probiotic microorganism(s) (Davani-Davari et al. 2019; Davani-Davari et al. 2018). As a therapeutic strategy in cancer, synbiotics have the potential to exert onco-suppressive effects by repairing the gut microbiota and maintaining the native gut environment and intestinal barrier function, thereby improving health and overall human well-being. For instance, synbiotics can facilitate the detection and degradation of potential carcinogens and production of signalling molecules that influence cell death and proliferation. At the same time, synbiotics can prevent the conversion of non-toxic pro-carcinogen into toxic, harmful, and highly reactive carcinogens. Besides, synbiotics also influence the production of anti-inflammatory cytokines that can affect the process of tumorigenesis while activating phagocytes for the elimination of early-stage tumour cells (Scott et al. 2018; Górška et al. 2019; Gurry 2017; Raman et al. 2013). Moreover, when used as adjuncts in the treatment of cancer, synbiotics can also enhance the efficacy as well as minimize any adverse effects and complications brought upon by radiotherapy, chemotherapy, surgery, and other anticancer therapeutics (Scott et al. 2018; Shimizu et al. 2013). In this chapter, we

offer an overview into the potential anticancer properties of synbiotics. We also compiled some of the recent studies performed in this research area, which could serve as the basis for further research into the application of synbiotics as a novel therapeutic strategy and/or adjunctive therapy to existing therapeutics in the management of various cancers.

## 3.2 Potential Anticancer Properties of Synbiotics

### Highlights

- Gut microflora dysbiosis predisposes an individual to cancer as it promotes tumour cells development, progression, and metastasis.
- An altered gut microbial composition induces genomic instability and mutations by genotoxins, promotes angiogenesis, sustains oncogenic pathways, as well as stimulates tumour-promoting inflammatory state by excessive production of inflammatory factors.
- Synbiotics modify the gut microbial ecosystem by increasing the population of beneficial microorganisms and reducing the population of harmful microorganisms.
- A healthy gut microflora also ensures mucosal integrity and normal cell processes, generating a protective microenvironment.
- A healthy gut microbiome primes the immune response, thereby promoting an anti-inflammatory and anti-oxidative state by regulating hormone levels and inducing immune infiltration into tumour cells.
- Synbiotics, when compared with prebiotics or probiotics alone, are more effective due to synergistic action in which prebiotic enhances colonization, growth, survival, and activity of probiotic strains.

### 3.2.1 Anti-inflammatory

Inflammation represents a natural reaction of the human immune system that can be stimulated by pathogens as well as infected cells and tissues. Therefore, inflammatory processes are part of the body defence mechanism that is essential in maintaining good health through the removal of injurious stimuli and facilitation of healing processes of damaged tissues (Greten and Grivennikov 2019; Chen et al. 2017). Typically, an inflammatory response is self-limiting, with its duration influenced by multiple molecules with dual anti-inflammatory and pro-inflammatory activities. As such, the resolution of an inflammatory response is a highly regulated process that involves spatially and temporally regulated secretion of mediators where chemokine gradients are diluted over time (Chen et al. 2017). Generally, the restoration of homeostasis involves the termination of tissue neutrophils infiltration, spent neutrophils apoptosis, counter-regulation of cytokines and chemokines, transformation of macrophages from classically to alternatively

activated cells, and lastly healing initiation. Effective resolution of inflammatory processes can prevent their progression into chronic inflammation, which ultimately prevents augmented damage of tissues and the progression of chronic inflammatory condition into chronic diseases (Chen et al. 2017; Neurath 2019). In the contrary, if an acute inflammatory response fails to restore tissue homeostasis, or if one or more steps of the inflammatory resolution process is/are dysregulated, it can lead to non-resolving and persistent chronic inflammatory process that is characterized by the presence of abnormal lymphocytes and macrophages which constantly secrete growth factors and cytokines (Chen et al. 2017; Zappavigna et al. 2020; Sugimoto et al. 2016).

In terms of cancer, it has been established that chronic inflammation can lead to cancer development and predisposes an individual to all stages of tumorigenesis (Greten and Grivennikov 2019). The relation between inflammation and tumorigenesis is generally driven through both intrinsic and extrinsic pathways. Intrinsic pathway is generally stimulated via biological alterations, which then lead to inflammation and invasive carcinoma. These transformations can include activation of proto-oncogenes, amplification, and rearrangement of chromosomes, as well as inactivation of tumour suppressor genes. An inflammatory microenvironment generated by inflammatory mediators from transformed cells has been reported to further promote the activation of oncogenes, damage of DNA and proteins, and the release of reactive oxygen species (ROS). In the contrary, extrinsic pathway is mediated via infections or inflammation which increase the chances for developing cancer in organs, such as the skin, pancreas, prostate, lung, and colon. Both intrinsic and extrinsic pathways interrupt tumour cells and modulate various signalling pathways. These include p53, mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF- $\kappa$ B), leading to an increased production of pro-inflammatory factors. These pro-inflammatory molecules further recruit and activate various leucocyte populations into the tumour microenvironment, whereby such a concerted action will lead to a more remarkable generation of inflammatory mediators and triggers a positive amplification loop that stimulates tumour growth and invasiveness (Greten and Grivennikov 2019; Multhoff et al. 2012; Zhao et al. 2021).

As mentioned earlier, the progression and development of cancer is typically a result of chronic inflammation aggravated by a lack of resolution to the underlying inflammatory processes (Hart et al. 2020). The body's homeostasis and tissue integrity are affected when tumours grow and metastasize, thereby signalling the body to initiate an acute phase inflammatory response. Several markers can be employed to detect the presence of inflammation and serve as prognosis indicator for chronic diseases including cancer. For instance, C-reactive protein (CRP) is the primary protein of the acute phase response reflecting the presence of tissue injury (Shrotriya et al. 2015). In general, the blood level of CRP reflects an ongoing inflammatory response and is frequently used as a minimally invasive indicator for several diseases including cancer. As such, the accumulation of CRP in blood often suggests the presence of an unresolved and advancing disease, such as cancer. For instance, high blood CRP level is directly correlated with the mortality of patients

with colorectal cancer, as well as hepatocellular carcinoma aggressiveness in patients with liver cancer. Besides, elevated levels of CRP in non-small cell lung cancer corresponds to tumour size and staging. In breast cancer, increased CRP levels are also associated with a higher mortality and declination of survival rate. For cancers involving the gastrointestinal tract, disease progression and advanced stage metastatic cancer with low survival were observed in patients with high blood CRP values (Hart et al. 2020; Shrotriya et al. 2015; Allin and Nordestgaard 2011; Fang et al. 2017; Xiao et al. 2019). Interleukin (IL)-6 is another example of major pro-inflammatory cytokines present in the tumour microenvironment. Dysregulation of IL-6 is often shown in tumours and overproduction of IL-6 has been discovered in almost every type of tumours, in which IL-6 overexpression is often observed in the tumour microenvironment suggesting a high correlation between carcinogenesis and inflammation. Namely, IL-6 enhances the process of tumorigenesis via modulation of specificities of tumours and various signalling pathways, which include survival, proliferation, apoptosis, angiogenesis, metastasis, invasiveness, as well as the metabolism of tumour cells. Furthermore, IL-6 facilitates the induction and restoration of countersignalling pathways thus shielding the cancer cells from therapeutic agents that induce apoptosis, oxidative stress, and DNA damage. As such, therapeutic agents that can potentially inhibit IL-6 and/or its associated signalling pathways presents great potential in cancer therapy (Kumari et al. 2016; Chonov et al. 2019).

Due to the strong correlation between inflammation and cancer, agents that can effectively suppress inflammatory responses may also be effective for the management of cancer. For instance, there have been several research that demonstrated the potential of synbiotics in suppressing inflammatory responses.

- A double-blind, randomized controlled trial evaluated the impact of administering preoperative synbiotic in colorectal cancer patients subjected to colorectal resection. Patients were randomized to either the synbiotics group where Simbioflora comprising the probiotics *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Lactobacillus casei*, as well as 6 g of fructo-oligosaccharide were given to patients preoperatively or placebo group where patients received maltodextrin. The study was carried out for a duration of 7 days and all patients received nutritional assessments and evaluation of CRP and IL-6 levels. Results showed that IL-6 ( $163.2 \pm 19.5$  versus  $138.8 \pm 12.5$ ) and CRP levels ( $10 \pm 5.2$  versus  $7.17 \pm 3.2$ ) were decreased significantly in the group taking synbiotic after 7 days. There were no substantial changes seen in the placebo group for IL-6 levels ( $154.2 \pm 18.3$  versus  $160.9 \pm 18.6$ ) and CRP ( $10.6 \pm 6.18$  versus  $10.4 \pm 6.1$ ). This study concluded that oral synbiotics supplementation given to patients preoperatively managed to attenuate the body's inflammatory state (Polakowski et al. 2019).
- One study assessed the impact of perioperative oral supplementation of synbiotics upon systemic inflammatory responses in patients undergoing high-risk hepatobiliary resection. One hundred and one biliary cancer patients with planned combined liver and extrahepatic bile duct resection with hepaticojejunostomy were randomly assigned to group A, where patients received enteral feeding with



synbiotics after the operation, or group B, where they received synbiotic treatment before and after the operation. The synbiotic supplementation consisted of one 100-mL bottle of Bifiel containing *Bifidobacterium breve* strain Yakult, one 80 mL bottle of Yakult 400 containing *Lactobacillus casei* strain Shirota; and 15 g/day of galacto-oligosaccharides. Group B patients received synbiotics administration for continuously 2 weeks before hepatectomy, whereby patients in Group A did not. It was found that preoperative IL-6 levels of patients in group B decreased significantly while levels of IL-6 in group A patients remained unchanged (5.1 vs 11.0 pg/dL). White blood cell counts, CRP levels and postoperative serum IL-6 levels of patients in group B showed a significant reduction when compared to those of group A patients. Thus, this study concluded that synbiotics can alter systemic inflammatory responses (Sugawara et al. 2006).

- A double-blind, randomized controlled trial was performed to evaluate the effect of synbiotics on inflammatory markers in type 2 diabetes mellitus patients. 44 subjects were randomly assigned to take either one synbiotic tablet daily or one placebo tablet daily for 8 weeks. It was found that there was a substantial reduction in the serum CRP levels ( $4.15 \pm 1.96$  vs  $4.94 \pm 2.36$  mg/L), IL-6 ( $8.12 \pm 5.02$  vs  $9.19 \pm 5.97$  ng/L), and tumour necrosis factor (TNF)- $\alpha$  ( $7.36 \pm 2.61$  vs  $8.03 \pm 2.73$  ng/L) in patients receiving synbiotic at the end of 8 weeks when compared with baseline. Such a reduction was highly significant in contrast to the placebo group, in which no remarkable changes were reported in the placebo group. These findings indicate that synbiotic supplementation can reduce serum markers of inflammation (Akram Kooshki et al. 2015).
- A double-blind, randomized controlled trial assessed the potential of synbiotic in improving inflammatory markers and gastrointestinal wellness in middle-aged individuals. The researchers demonstrated that synbiotic containing *Bifidobacterium animalis* subsp. *lactis* and fructo-oligosaccharides decreased inflammatory status in these subjects. In the study, individuals were randomly assigned to take either placebo or synbiotic for 30 days and the levels of plasma pro-inflammatory cytokines were evaluated. It was showed that the levels of interferon (IFN)- $\gamma$ , IL-8, IL-6, and IL-17a were remarkably lowered after synbiotic supplementation for 30 days which effects were not observed in the placebo group and were independent of gut barrier function. Notably, IL-6 was particularly suppressed among other pro-inflammatory markers (Neyrinck et al. 2021).
- An in vivo study examined the anti-inflammatory potential of preventive administration of synbiotics containing *Lactobacillus plantarum* and inulin in chronic inflammatory rats upon *N,N*-dimethylhydrazine administration. It was showed that administration of *N,N*-dimethylhydrazine stimulated the production of various pro-inflammatory mediators, including cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and NF- $\kappa$ B, and the pro-inflammatory cytokines IL-2, IL-17, IL-6, and TNF- $\alpha$ . Notably, these inflammatory processes in the jejunal mucosa were attenuated upon 28 weeks supplementation with synbiotic and the synthesis of the anti-inflammatory cytokine IL-10 was stimulated. These findings indicate that synbiotic can suppress chronic inflammation by



downregulating various inflammatory factors and their underlying signalling pathways (Štofilová et al. 2015).

In short, the above studies clearly demonstrated the positive impact of synbiotics in attenuating the body's inflammatory states. Given the close relationship between inflammation and cancer, synbiotics have great potential for application in cancer prevention and treatment.

### 3.2.2 Anti-oxidative

Oxidative stress arises when the production of reactive metabolites and free radicals such as hydroxyl radicals, hydrogen peroxide, superoxide radicals, and singlet oxygen collectively known as ROS, exceeds the detoxification ability of the body on these reactive products (Pizzino et al. 2017). ROS are redox messengers that are generated as metabolic by-products by the biological system when there is a partial reduction of molecular oxygen. Several key biological processes including the activation of transcriptional factors, protein phosphorylation, cell differentiation and apoptosis, as well as immunity rely on well-regulated production of ROS in which the presence of ROS should be kept at a low but optimal level within cells. When ROS is present at low levels, their negative effects can be safely neutralized by the body's natural antioxidant defences. Among which, catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) are examples of enzymes responsible for protecting cells from the deleterious effects of ROS (Pizzino et al. 2017; Bhattacharyya et al. 2014). Conversely, when normal cellular homeostasis could not cope due to an excessive accumulation of ROS, it can result in oxidative stress and cellular dysfunction. Namely, a prolonged and long-term exposure to pro-oxidant factors can induce structural defects at the level of mitochondrial DNA while altering the functions of enzymes and cellular structures, resulting in aberrant gene expression. Thus, oxidative stress is often responsible for the initiation and progression of various chronic diseases such as respiratory diseases, cardiovascular diseases, neurodegenerative diseases, diabetes, and cancer (Sharifi-Rad et al. 2020).

In terms of cancer, oxidative stress influences with all three major stages of the disease, namely, initiation, promotion, and progression. During the initiation stage, excessive ROS may induce DNA damage through the introduction of structural alterations and gene mutations. Namely, ROS can result in an abnormal gene expression to modulate second messenger systems and cell-to-cell communications during the promotion stage (Reuter et al. 2010). For instance, the oxidation of negative feedback loop controllers can be attributed to an increased ROS level, thereby dictating the behaviour of multiple signalling pathways underlying the growth of tumours and programmed cell death via the MAPK and phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) pathways, which leads to the induction of cell proliferation and reduced apoptosis of the initiated cell population. Besides, the accumulation of ROS in tumour cells also leads to the downregulation of phosphatase and tensin homolog (PTEN), which in turn upregulates PI3K/PKB signalling

that further induces tumour cells proliferation (Arfin et al. 2021; Saha et al. 2017). Finally, the rise in ROS levels may exploit the underlying mutagenesis and genomic variability in tumour cells to stimulate the progression of cancer. Further DNA alterations may also be added to the initiated cell population, thereby accelerating the progression of the disease (Reuter et al. 2010; Arfin et al. 2021; Saha et al. 2017). Apart from that, ROS is also involved in the crosstalk between chronic inflammation and cancer. One important feature of tumour promoters is their capability to recruit and activate inflammatory cells while inducing them to generate ROS. Therefore, such an accumulation of inflammatory cells within the tumour microenvironment can result in an overproduction of ROS through the activation of oxidant-generating enzymes, such as iNOS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and myeloperoxidase, as well as the stimulation of lipoxygenase (LOX) and COX-2 (Reuter et al. 2010; Aggarwal et al. 2019). At the same time, ROS can influence the type, presence, and the levels of inflammatory factors such as peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , NF- $\kappa$ B, activator-protein (AP)-1, p53, inflammatory chemokines and cytokines, hypoxia-inducible factor (HIF)-1 $\alpha$ , as well as growth factors. Thus, the abundant accumulation of ROS along with inflammation-modulating factors causes an elevation in mutation load, signal transduction defects, and apoptosis deactivation (Aggarwal et al. 2019). In addition, increased ROS also facilitates tumour cell angiogenesis and metastasis. Studies have shown that ROS can promote the generation of new blood vessels to improve oxygen and nutrient supplies for meeting increased metabolic needs of proliferating tumour cells. As for tumour cells metastasis, it has been documented that ROS promote epithelial mesenchymal transition by stimulating the activity of matrix metalloproteinases that mediate proteolytic degradation of components of the extracellular matrix (Aggarwal et al. 2019; Aboeella et al. 2021). In a nutshell, oxidative stress is undoubtedly a major influence of the hallmarks for cancer development. Hence, reduction and/or attenuation of oxidative stress represents one of the vital strategies in the prevention and/or treatment of cancer.

Evidences have affirmed the anti-oxidative properties of synbiotics, in which several studies have documented a decrease in ROS and/or other oxidative stress markers upon synbiotics supplementation.

- One study assessed the impact of synbiotic supplementation consisting of the probiotic bacteria *Lactobacillus casei* and inulin prebiotic on the antioxidant properties of human plasma. Thirty-two healthy volunteers were randomized to either control or synbiotic groups, and their blood samples were collected prior to synbiotic supplementation and after 7 weeks at the end of the study. Antioxidant markers, namely, GPx activity, SOD, CAT, and the ferric reducing ability of plasma (FRAP) in human plasma were measured before and after synbiotics supplementation. Generally, SOD, CAT, and GPx are antioxidant enzymes that can neutralize oxidants in the intestinal tract whereas FRAP is a sensitive indicator of the biological fluid's total antioxidant status. SOD can be found in three forms, namely, manganese SOD, copper-zinc SOD, and extracellular SOD. It

catalyses the reaction of superoxide anion dismutation and such activity shields cells from oxidative stress. Another antioxidant enzyme that interacts closely with SOD is CAT. CAT decomposes hydrogen peroxide into oxygen and water. The reduction of CAT activity is often seen in oxidative stress-induced diseases including cancer. GPx acts by reducing hydrogen peroxide and organic peroxides in the presence of reduced glutathione (GSH). Results from the study showed that the FRAP values and CAT activity were increased significantly in the synbiotics group following synbiotics administration and the increase in SOD and GPx activity is insignificant compared to controls. The study concluded that synbiotics may have a positive impact on the activity of selected antioxidant enzymes and human plasma antioxidant capacity (Kleniewska et al. 2016).

- One study assessed the effect of synbiotic containing *L. casei* and inulin on the parameters of oxidative stress, such as hydrogen peroxide, concentrations of malondialdehyde (MDA), free sulfhydryl groups content, and glutathione. Thirty-two healthy volunteers were randomized to either control or synbiotic groups. One capsule of synbiotic was provided to the synbiotic group every day for 7 weeks. Blood sample of the subjects were collected prior to synbiotic supplementation and after 7 weeks at the end of the study (Kleniewska and Pawliczak 2017). MDA is an important marker of antioxidant status and oxidative stress in patients with cancer. It is one of the final products of polyunsaturated fatty acid peroxidation in cells and its overproduction is the result of increased free radicals (Ayala et al. 2014). Glutathione, on the other hand, is a major antioxidant in the body in which glutathione disulphide (GSSG) represents the oxidized form of glutathione. The levels of GSSG often increase when there is an increase in intracellular oxidative stress associated with disease states (Sadhu et al. 2016). Results showed that there is a significant decrease in MDA, hydrogen peroxide, and GSSG concentrations in the synbiotic group in contrast to control, as well as a remarkable increase in the concentrations of total glutathione, GSH, and free sulfhydryl (-SH) group content in the synbiotic group in contrast to control. Thus, this study concluded that synbiotics could positively impact selected markers of oxidative stress (Kleniewska and Pawliczak 2017).
- One double-blind, randomized controlled trial assessed the impact of synbiotics supplementation on oxidative markers in breast cancer survivors. Eighty-eight subjects were randomized to take either synbiotic supplement containing *L. rhamnosus*, *L. casei*, *L. bulgaricus*, *L. acidophilus*, *S. thermophilus*, *B. longum*, *B. breve*, and fructo-oligosaccharides, or a placebo for 10 weeks. GPx, MDA, SOD concentration, and serum total antioxidant capacity were evaluated at the end of the study. It was demonstrated that serum MDA levels were remarkably reduced whereas serum SOD concentration was significantly increased after 10 weeks of synbiotic supplementation in contrast to placebo (Navaei et al. 2020).
- One study has reported that synbiotics present greater antioxidant properties than prebiotics alone. The researchers prepared yogurt with either the probiotics *L. fermentum* and *L. plantarum* alone, or with the prebiotic fructo-oligosaccharides. It was demonstrated that the supplementation of fructo-

oligosaccharides promoted the growth of both probiotic strains. Besides, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity was also remarkably greater in synbiotic yogurt with a highest total phenolics and ferric reducing power as compared with prebiotic and control yogurt. Such findings suggest that application of synbiotics as an antioxidant may offer added advantages due to the synergistic effect of both probiotics and prebiotics (Madhu et al. 2012).

To sum up, the above studies demonstrated that synbiotics can shield the body from oxidative stress. Since oxidative stress is closely related to cancer, synbiotics can be considered for application in cancer prevention and/or treatment.

### 3.2.3 Immunomodulatory

The human immune system and cancer are closely related, and its link has been widely acknowledged over the last decade. The basis for the connection between immunity and cancer involves three fundamental principles on defence mechanism of our immune system and how it can protect an individual (Pardoll 2015; Pandya et al. 2016). Namely, the immune system detects foreign antigens from malignant cells or pathogens, possesses effector functions that can specifically target and eliminate malignant cells or pathogens for host protection, and activates the adaptive immune response to develop immunological memory for subsequent defence mechanisms. Such a multifaceted mechanism provides effective immune surveillance that can contribute to elimination of any attack against the host or injury. For this instance, the ability of tumour cells to evade immune surveillance represents one of the most established cancer hallmarks, thereby giving rise to the paradigm of treatments within the context of immunomodulation (Pandya et al. 2016; Hoos and Britten 2012; Gonzalez et al. 2018).

As discussed earlier, it is known that the gut microbiota has a profound influence on developing a plethora of diseases which include cancer. The gut microbiota regulates human health and primes the body's immune system by regulating both systemic and local immune responses. Therefore, the manipulation of the gut microbiota is a great strategy in cancer prevention and/or treatment as they share a close relationship (Inamura 2021). Generally, local immune responses are triggered by microbes via immune cells interactions that express pattern recognition receptors (PRR) such as Toll-like receptors (TLR). Local dendritic cells (DC) are also activated by microbes via interactions with PRR. Naive T cells' differentiation into effector T cells is induced by the activated DCs, particularly, T helper cells and regulatory T cells when they travel from the gastrointestinal tract to the mesenteric lymph nodes where microbe-derived antigens were presented. Local immune response occurs when a subset of effector T cells travels back to the gastrointestinal tract whereas systemic immunity occurs when the remaining effector T cells enter the systemic circulation. Regulatory T cells release anti-inflammatory cytokines including IL-10, as well as tumour growth factor which will transform the

pro-inflammatory state of the immune system into an anti-inflammatory state. In the contrary, T helper cells transform the immune system from an anti-inflammatory state into a pro-inflammatory state through the secretion of immunostimulatory cytokines such as IL-17, or through the recruitment and activation of neutrophils (Inamura 2021; Ma et al. 2019; Pennock et al. 2013; Kumar et al. 2018; Mellman 2013). Natural killer cells are cytotoxic towards primary tumour cells and inhibits metastasis by preventing proliferation, migration, and colonization of tumour cells to distant tissues. Moreover, natural killer cells modulate adaptive immune responses in the body by producing a large number of cytokines, mainly IFN- $\gamma$ . Natural killer cells are also specific in antitumour cytotoxicity as they could differentiate healthy cells from abnormal cells and thus reducing off-target complications (Wu et al. 2020). In short, DCs, natural killer cells and T cells are the key effectors for the timely detection and deletion of damaged and potentially carcinogenic cells. Hence, increasing beneficial bacteria in the gut via synbiotics supplementation is important for maintaining a normal host defence mechanism as intestinal microflora is vital in providing a natural defence against invading pathogens.

Ideally, probiotics act to increase the population of beneficial microorganisms whereas prebiotics act to boost the formation of resident beneficial intestinal bacteria. Prebiotics provide food for the swallowed probiotics, keeping the flora from being depleted. Dietary carbohydrates that escape digestion/absorption in the small bowel, as well as prebiotics, ferment in the colon, producing short-chain fatty acids that help *Lactobacilli* and *Bifidobacteria* thrive. There have been studies that documented the positive effects of synbiotics in modulating immune responses.

- A randomized study evaluated the impact of a synbiotic containing the probiotic *Lactobacillus casei* with the prebiotic dextran on humans and mice, respectively. For the study involving human subjects, eight healthy adult volunteers received lyophilized *L. casei* and dextran once per day for 7 days. Isolation of peripheral blood mononuclear cells (PBMC) from heparinized venous blood was performed on days 0, 8, and 11 and natural killer cells activities were measured. Results showed that the natural killer cells activity increased significantly from  $28.7 \pm 9.8\%$  on day 0 to  $43.9 \pm 15.9\%$  on day 8 (1 day post-supplementation) and  $41.7 \pm 13.2\%$  on day 11 (4 days post-supplementation). Notably, it was reported that the percentage of natural killer cells in the peripheral blood lymphocyte fractions has the potential for continual increment post-supplementation. These results indicated that oral supplementation of synbiotics increases the ability and number of natural killer cells in humans. The study also investigated the anti-tumour activities of the synbiotic on murine models. BALB/c mice were assigned into four different groups, namely, the synbiotic group, probiotic group, prebiotic group, as well as control. Meth A cells were inoculated intraperitoneally into all mice and the survival rate was tracked for up to 80 days. It was found that the survival rate of the prebiotic and probiotic groups was 33.3%, whereas the control group showed survival rate of only 8.3%. Additionally, the synbiotic group demonstrated remarkable elevation in survival rate of 50% as compared to all the other groups. These results proved that synbiotic supplementation

remarkably elevated anti-tumour activities. In short, the results of both human and animal experiments indicated that host immune functions were enhanced, and antitumour activities were boosted with synbiotics (Ogawa et al. 2006).

- One double-blind, randomized controlled trial has assessed the impact of synbiotic on faecal microbiota and immunity of healthy elderly individuals. Subjects were assigned to consume either synbiotic containing *L. rhamnosus* and soluble corn fibre, or placebo for 3 weeks. Faecal microbiota analyses showed that the synbiotic greatly increased *Parabacteroides* spp. while decreased *Oscillospira* spp. and *Desulfovibrio* spp. This indicated that synbiotic supplementation can facilitate reduction in the population of harmful microorganisms, as *Desulfovibrio* spp. represents a group of sulphate-reducing bacteria that has been implied as one of the key players in the pathogenesis of various gastrointestinal diseases, including colon cancer. Besides, it was also observed that synbiotics consumption enhanced natural killer cells' activity in contrast to control. A positive immunomodulatory effect was further evidenced by a remarkable decline in the level of pro-inflammatory cytokine IL-6, indicating that synbiotic supplementation can be an attractive option for positively enhancing the immune system against various diseases including cancer (Costabile et al. 2017).
- An in vivo study evaluated the potential of synbiotics in altering the colonic microbiome and modulating gastrointestinal immune and inflammatory responses on a spontaneous colitis mice model of inflammatory bowel disease. The combined and individual efficacies of the probiotic *Bacillus coagulans* and the prebiotic sugarcane fibre were evaluated in the study. Gut microbiota dysbiosis, specifically the depletion of both *Bacteroidetes* and *Firmicutes*, has been associated with the development of gastrointestinal diseases. As such, it was found that synbiotic supplementation increased both the levels of *Bacteroidetes* and *Firmicutes*, thereby reversing dysbiosis of the gut microbial community. Besides, the genus *Prevotella* belonging to the phylum *Bacteroidetes* was also enhanced. Such finding was consistent with established evidence that a high fibre diet increases prevalence of *Prevotella*, which is a dietary fibre fermenter for the production of short-chain fatty acids, indicating that the presence of prebiotic within the synbiotic formulation presented synergistic effect in addition to the benefits of probiotic. The results further documented that both probiotic and prebiotic exhibited immunomodulatory effects, however, synbiotic supplementation had the greatest effect in modulating the overall immune profile, namely, innate immune system activation (Shinde et al. 2020).
- One double-blind, randomized controlled trial evaluated the influence of synbiotics on intestinal microbiota and the negative impact of chemotherapy oesophageal cancer patients receiving neoadjuvant chemotherapy. The subjects were randomized to either the group taking synbiotic, where subjects were given 3 g/day of Yakult BL Seichoyaku containing *Bifidobacterium breve* strain Yakult and *Lactobacillus casei* strain Shirota, and 15 g/day of galacto-oligosaccharides, or the control group where they were only given 3 g/day of Biofermin containing *Streptococcus faecalis*. Results showed that on the tenth day of chemotherapy, the number of beneficial bacteria were significantly larger while harmful bacteria

were smaller. Concentrations of propionic acid and acetic acid were also remarkably greater in subjects receiving synbiotic. It was also observed that the occurrence of diarrhoea and severe lymphopenia were reduced significantly. It was concluded that intestinal microbiota could be manipulated by synbiotic supplementation, which is beneficial to cancer patients undergoing chemotherapy in terms of minimized adverse reactions (Motoori et al. 2017).

Given the prominent correlation between the gut microbiota and the human immune system and subsequent oncogenesis, a normal gut microbiota equilibrium is crucial for immune system maturation and to prime an anticancer response. As such, manipulation of the gut microbiota is an advantageous approach in preventing or treating cancer. The microbial ecosystem in the gut can be modified through synbiotic supplementation, in which the beneficial microbes in the gut and their survival can be improved, thereby providing health benefits to the host.

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### 3.3 Application of Synbiotics in the Management of Cancer

As discussed above, synbiotics may present positive effects in the management of cancer due to their ability to produce anti-inflammatory, anti-oxidative and immunomodulatory effects. Apart from that, perioperative probiotics, prebiotics, and/or synbiotics supplementation have also been found to contribute to reduced complications, adverse effects, and overall quality of life in cancer patients undergoing treatment. In this section, we have selected some notable studies that demonstrated the potential of probiotics, prebiotics, and synbiotics in alleviating different cancers, their complications, and/or adverse reactions from the use of existing anticancer therapeutics. The key findings from these studies are summarized in Table 3.1.

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### 3.4 Conclusion and Future Directions

The rising prevalence of cancer across the world has prompted the need for the search and development of effective therapies in eradicating the disease. As the causal relationship between cancer and gut microbiota dysbiosis has been observed in various studies, synbiotics have been proposed as the promising agent to restore gut homeostasis and generate a protective microenvironment against various cancers. Nevertheless, the exact differences of the gut microbiota between normal and tumour cells at each step of cancer development and progression is still not yet fully elucidated. Therefore, deciphering the key manifestations of dysbiosis may help researchers to better understand the discrepancies in cancer progression and its response to therapies in patients with similar clinical profiles. Although there have been multiple studies employing probiotics, prebiotics, and/or synbiotics for managing cancer over these years, they are mostly used as adjuvant in addition to existing anticancer strategies as an attempt to minimize adverse reactions and treatment



**Table 3.1** Summary of primary findings from studies employing probiotics, prebiotics, and synbiotics for managing different types of cancers

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
Biliary cancer	Randomized controlled clinical trial: Biliary cancer patients involving hepatic hilus undergoing hepatectomy	2 weeks preoperative	<i>L. casei</i> , <i>B. breve</i> , galacto-oligosaccharides	<ul style="list-style-type: none"> <li>Lymphocyte counts and natural killer cells activity were increased preoperatively while IL-6 was suppressed in patients given synbiotics.</li> <li>Total organic acid concentrations and the numbers of cultured <i>Bifidobacterium</i> colonies and increased significantly in faeces of preoperative patients given synbiotics.</li> <li>Concentration of acetic acids and total organic acids showed remarkably elevation in faeces of postoperative patients given synbiotics.</li> <li>White blood cell counts, CRP, and serum IL-6 were remarkably lower postoperatively in patients given synbiotics.</li> <li>Overall incidences of postoperative infectious complications were 12.1% in patients given synbiotics in contrast to 30.0% in patients of the control group.</li> </ul>	Sugawara et al. (2006)

	<p>Randomized controlled clinical trial: Biliary cancer patients undergoing hepatectomy</p>	<p>14 days postoperative</p>	<p><i>B. breve</i>, <i>L. casei</i>, galacto-oligosaccharides</p>	<ul style="list-style-type: none"> <li>• Synbiotics modified faecal microflora of surgical patients.</li> <li>• Numbers of beneficial microorganisms such as <i>Lactobacilli</i> and <i>Bifidobacteria</i> increased while harmful microorganisms such as <i>Pseudomonas</i>, <i>Enterobacteriaceae</i> and <i>Candida</i> decreased postoperatively in the group taking synbiotic in contrast to control.</li> <li>• Total concentration of organic acids increased in the group taking synbiotic in contrast to control.</li> <li>• Overall infectious complications incidence was 19% in the synbiotic group in contrast to 52% in the control group.</li> </ul>	<p>Kanazawa et al. (2005)</p>
<p>Breast cancer</p>	<p>Double-blind, randomized controlled clinical trial: Overweight and obese breast cancer survivors</p>	<p>10 weeks</p>	<p><i>L. acidophilus</i>, <i>L. casei</i>, <i>B. longum</i>, <i>L. rhamnosus</i>, <i>B. breve</i>, <i>L. bulgaricus</i>, <i>S. thermophilus</i>, fructo-oligosaccharides</p>	<ul style="list-style-type: none"> <li>• Synbiotic supplementation led to a remarkable decline in serum MDA levels as compared with placebo.</li> <li>• Remarkably increased the concentration of serum SOD in the group taking synbiotic in contrast to control.</li> </ul>	<p>Navaei et al. (2020)</p>

(continued)

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
	Double-blind randomized controlled clinical trial: Breast cancer survivors with lymphedema	10 weeks	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. longum</i> , <i>L. rhamnosus</i> , <i>B. breve</i> , <i>L. bulgaricus</i> , <i>S. thermophilus</i> , fructo-oligosaccharides	<ul style="list-style-type: none"> <li>Synbiotic supplementation resulted in a remarkable decline in leptin and TNF-<math>\alpha</math> in contrast to the placebo group.</li> <li>Significantly reduced oedema volume within the synbiotic group post-intervention.</li> </ul>	Vafa et al. (2020)
	In vitro: 4T1 breast cancer cells; in vivo: Female BALB/c mice administered with 4T1 tumour cells	In vitro: 72 h; In vivo: 28 days	Kefir water: <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. lactis</i> (No prebiotic)	<ul style="list-style-type: none"> <li>Kefir water was cytotoxic towards 4T1 tumour cells with an IC<sub>50</sub> value of 12.5 and 8.33 mg/mL at 48 and 72 h, respectively.</li> <li>Animals treated with Kefir water presented remarkable suppression in weight and size of tumour.</li> <li>Remarkable fivefold increment in T helper cells and sevenfold increment in cytotoxic T cells were reported in the Kefir water group.</li> <li>Significant reduction in pro-inflammatory and pro-angiogenic markers were reported in the Kefir water group.</li> </ul>	Zamberi et al. (2016)

<p>In vivo: <i>N</i>-methyl-<i>N</i>-nitrosourea-induced mammary carcinogenesis in female Sprague-Dawley rats</p>	<p>16 weeks</p>	<p><i>L. plantarum</i>, oligofructose-enriched inulin</p>	<ul style="list-style-type: none"> <li>• Remarkable reduction in high to low-grade carcinomas ratio and in the expression of Ki-67 were observed upon synbiotic treatment.</li> <li>• Synbiotic enhanced the infiltration of CD8+ and CD4+ T cells into the tumour.</li> <li>• Synbiotic upregulated CD25+FoxP3+ regulatory T cells in tumours.</li> <li>• Synbiotic administration presented anti-proliferative and immunomodulatory activities.</li> </ul>	<p>de Vries et al. (2006)</p>
<p>Randomized controlled clinical trial: Overweight and obese women with breast cancer-related lymphedema</p>	<p>10 weeks</p>	<p><i>L. acidophilus</i>, <i>L. casei</i>, <i>B. longum</i>, <i>L. rhamnosus</i>, <i>B. breve</i>, <i>L. bulgaricus</i>, <i>S. thermophilus</i>, fructo-oligosaccharides</p>	<ul style="list-style-type: none"> <li>• Significant improvement in quality of life by 39.53% in the group taking synbiotics in contrast to only 1.5% in control.</li> <li>• Remarkable reduction in body mass index by 3.01% in the group taking synbiotic in contrast to control.</li> <li>• Oedema volume reduced remarkably in the group taking synbiotics in contrast to control.</li> </ul>	<p>Vafa et al. (2020)</p>
<p>Triple-blind, randomized controlled clinical trial: Overweight and obese breast cancer survivors</p>	<p>8 weeks</p>	<p><i>L. acidophilus</i>, <i>L. casei</i>, <i>B. longum</i>, <i>L. rhamnosus</i>, <i>B. breve</i>, <i>L. bulgaricus</i>,</p>	<ul style="list-style-type: none"> <li>• Significant decline in serum insulin and insulin resistance were observed in the group taking synbiotics.</li> </ul>	<p>Raji Lahiji et al. (2021)</p>

(continued)

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
Colorectal cancer	Double-blind, randomized controlled clinical trial: Colorectal cancer patients subjected to colorectal resection	Preoperative: 7 days; Postoperative: 30 days	<i>S. thermophilus</i> , fructo-oligosaccharides  <i>B. lactis</i> , <i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>L. casei</i> , fructo-oligosaccharides	<ul style="list-style-type: none"> <li>Reducing effects on glycaemic profile, IGF-1, and sex hormones was observed; however, these effects were insignificant.</li> <li>Significant suppression in the levels of serum IL-6 and CRP were observed in the synbiotic group after 7 days in contrast to control.</li> <li>Infectious complications occurred postoperatively in 2.8% of patients receiving synbiotics in contrast to 18.9% in control.</li> <li>Mean antibiotic use time in the synbiotic group was <math>1.42 \pm 0.5</math> days compared to <math>3.74 \pm 4.3</math> days in control.</li> <li>Mean hospital stay length in the synbiotic group was <math>3 \pm 1</math> days compared to <math>4 \pm 18</math> days in control.</li> <li>No death was reported among patients receiving synbiotics; however, three deaths were reported in control.</li> </ul>	Polakowski et al. (2019)

<p>Double-blind, randomized controlled clinical trial: Colon cancer patients and polypectomized patients</p>	<p>12 weeks</p>	<p><i>B. lactis</i>, <i>L. delbrueckii</i>, oligofructose-enriched inulin</p>	<p>Rafter et al. (2007)</p> <ul style="list-style-type: none"> <li>• Synbiotic supplementation significantly increased <i>Lactobacillus</i> and <i>Bifidobacterium</i>, whereas <i>Clostridium perfringens</i> reduced in faecal flora.</li> <li>• Synbiotic remarkably suppressed colorectal proliferation and the capacity of faecal water to stimulate necrosis in colonic cells.</li> <li>• Polypectomized patients receiving synbiotics had improved epithelial barrier function.</li> <li>• Genotoxicity assays of colonic biopsy samples of polypectomized patients revealed reduced exposure to genotoxins after 12 weeks.</li> <li>• Synbiotic suppressed the production of IL-2 by peripheral blood mononuclear cells.</li> <li>• Synbiotic induced IFN-<math>\gamma</math> production.</li> </ul>
<p>In vivo: 1,2-dimethylhydrazine dihydrochloride-induced experimental colon cancer in male Wistar rats</p>	<p>7 weeks</p>	<p><i>L. casei</i>, <i>L. acidophilus</i>, <i>L. delbrueckii</i> subsp. <i>bulgaricus</i>, <i>Bifidobacterium</i> spp., <i>S. thermophilus</i>, <i>B. longum</i>, fructo-oligosaccharides</p>	<p>Vagianos et al. (2018)</p> <ul style="list-style-type: none"> <li>• Animals that received synbiotic had 100% survival as compared with only 70% survival in animals that received only carcinogen.</li> <li>• Animals that receive</li> </ul>

(continued)

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
	In vivo: 1,2-dimethylhydrazine-induced colonic tumorigenesis model of male ICR mice	24 weeks	<i>B. longum</i> , <i>L. gasseri</i> (No prebiotic)	<p>synbiotics had remarkably lower percentage of colitis-like lesions, aberrant crypt foci, dysplasia, and inflammation.</p> <ul style="list-style-type: none"> <li>Least pathological lesions in animals that received synbiotics from the beginning of the study (7 weeks) in contrast to the animals which only received synbiotics for 5 weeks.</li> </ul> <ul style="list-style-type: none"> <li>Reduced colon tumour multiplicity and the size of the tumours.</li> <li>Reduced colonic mucosa cellular proliferation rate and inhibited tumour induction by 1,2-dimethylhydrazine.</li> <li>Significantly increased phagocytic activity of peritoneal macrophages.</li> <li>Remarkable upregulation of RAW264.7 macrophages proliferation due to an increased S phase DNA synthesis.</li> <li>Upregulated cyclin A and proliferating cell nuclear antigen.</li> </ul>	Foo et al. (2011)



<p>In vivo: Azoxymethane-induced experimental colon cancer in male Fischer 344 rats</p>	<p>33 weeks</p>	<p><i>L. rhamnosus</i>, <i>B. lactis</i>, oligofructose-enriched inulin</p>	<ul style="list-style-type: none"> <li>• Synbiotic supplementation reversed azoxymethane-induced downregulation of natural cell-like cytotoxicity in Peyer's patches as compared with control animals.</li> <li>• Synbiotic stimulated production of IL-10 in Peyer's patches of rats stimulated with azoxymethane, and in mesenterial lymph nodes of rats not stimulated with azoxymethane.</li> <li>• Synbiotics suppressed the production of IFN-<math>\gamma</math> in Peyer's patches.</li> <li>• Synbiotic suppressed the proliferative responsiveness of lymphocytes in azoxymethane-induced rats.</li> <li>• Synbiotic primarily modulated immune functions in Peyer's patches, thereby reducing the number of colon tumour cells.</li> </ul>	<p>Roller et al. (2004)</p>
<p>In vivo: Azoxymethane-induced experimental colon cancer in male F344 rats</p>	<p>31 weeks</p>	<p><i>B. lactis</i>, <i>L. rhamnosus</i>, oligofructose-enriched inulin</p>	<ul style="list-style-type: none"> <li>• Rats treated with synbiotic had remarkably lower number of tumours as compared to control rats.</li> <li>• Elevated level of caecal</li> </ul>	<p>Femia et al. (2002)</p>

(continued)

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
				<p>short-chain fatty acids was observed in rats treated with synbiotic.</p> <ul style="list-style-type: none"> <li>• Lower level of colonic proliferation was reported in the group taking synbiotics in contrast to control.</li> <li>• iNOS and glutathione S-transferase expressions were suppressed in tumours of rats in the synbiotic group.</li> <li>• Reversed the elevation in the production and expression of COX-2 in the tumours of rats in the synbiotic group.</li> </ul>	
	Randomized controlled clinical trial: Colorectal cancer patients undergoing radical colorectal resection	3 days preoperative	<i>B. longum</i> , <i>L. acidophilus</i> , <i>E. faecalis</i> (No prebiotic)	<ul style="list-style-type: none"> <li>• Remarkable elevation in <i>Bifidobacterium</i> with remarkable suppression in <i>Escherichia</i> on postoperative days 3–5 in patients receiving probiotics.</li> <li>• Lower levels of D-lactic acids, endotoxins, CRP, and serum IL-6 in patients receiving probiotics, but with greater levels of serum IgA and IgG as compared with placebo group.</li> <li>• Overall incidences of</li> </ul>	Zhang et al. (2012)

<p>Hepatic cancer</p>	<p>Randomized controlled clinical trial: Hepatic cancer patients undergoing hepatectomy</p>	<p>14 days preoperative, 11 days postoperative</p>	<p><i>B. breve</i>, <i>L. casei</i>, galacto-oligosaccharides</p>	<p>postoperative infectious complications were 10.0% in the probiotic group in contrast to 33.3% in the placebo group.</p> <ul style="list-style-type: none"> <li>• Less profound postoperative decrease in the activity of serum diamine oxidase was observed in the synbiotic treated group, indicating restoration of intestinal mucosal integrity.</li> <li>• Patients in synbiotic treated group had decreased serum IL-6 and CRP concentrations.</li> <li>• Postoperative infectious complications did not occur in any patients treated with synbiotics in contrast to 17.2% of patients in control.</li> </ul>	<p>Usami et al. (2011)</p>
<p>Lung cancer</p>	<p>Randomized controlled clinical trial: Lung cancer patients undergoing chemotherapy</p>	<p>3 weeks</p>	<p><i>C. butyricum</i> (No prebiotic)</p>	<p>A lower incidence of chemotherapy-induced diarrhoea was reported in the group taking probiotics in contrast to control.</p> <ul style="list-style-type: none"> <li>• Probiotic decreased the ratios of neutrophil to lymphocyte ratio and platelet to lymphocyte, while the ratio of lymphocyte to monocyte</li> </ul>	<p>Tian et al. (2019)</p>

(continued)

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
Oesophageal cancer	Randomized controlled clinical trial: Advanced oesophageal cancer patients receiving neoadjuvant chemotherapy	2 days prior to chemotherapy and 6 weeks throughout chemotherapy	<i>L. casei</i> , <i>B. breve</i> , galacto-oligosaccharides	<p>was increased.</p> <ul style="list-style-type: none"> <li>A prominent increase in beneficial flora such as <i>Lactobacillus</i> and <i>Clostridium</i> was observed in the probiotic group.</li> <li>Probiotic reduced systemic inflammatory response and promoted homeostasis.</li> </ul> <ul style="list-style-type: none"> <li>The numbers of beneficial bacterial species <i>Bifidobacterium</i> and <i>Lactobacillus</i> were remarkably larger in the group taking synbiotics in contrast to control.</li> <li>The numbers of harmful bacterial species <i>C. difficile</i>, <i>Staphylococcus</i>, and <i>Pseudomonas</i> were remarkably smaller in the group taking synbiotics in contrast to control.</li> <li>Higher levels of acetic acid and propionic acid were observed in the group taking</li> </ul>	Motoori et al. (2017)

	<p>Randomized controlled clinical trial: Advanced oesophageal cancer patients receiving neoadjuvant chemotherapy</p>	<p>3 days prior to chemotherapy and throughout chemotherapy</p>	<p><i>L. casei</i>, <i>B. breve</i>, galacto-oligosaccharides</p>	<p>synbiotics in contrast to control.</p> <ul style="list-style-type: none"> <li>• Remarkably lowered occurrence of diarrhoea and severe lymphopenia was observed in the synbiotic group as compared with control.</li> <li>• Fewer occurrence of febrile neutropenia in the synbiotics group in contrast to control.</li> </ul>	<p>Motoori et al. (2022)</p>
				<ul style="list-style-type: none"> <li>• Incidence of febrile neutropenia was reduced in the group taking synbiotics.</li> <li>• The numbers of <i>Bifidobacterium</i>, <i>Lactocaseibacillus</i>, and <i>Enterobacteriaceae</i> were significantly higher post-chemotherapy in patients receiving synbiotics.</li> <li>• Concentration of acetic acid was remarkably higher in the synbiotic group, leading to reduced severity of diarrhoea and febrile neutropenia.</li> <li>• Synbiotics combined with enteral nutrition was superior to prophylactic antibiotics as supportive therapy.</li> </ul>	<p>(continued)</p>

Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
	Randomized controlled clinical trial: Oesophageal cancer patients undergoing esophagectomy	21 days postoperative	<i>L. casei</i> , <i>B. breve</i> , galacto-oligosaccharides	<p>The postoperative counts of beneficial microorganisms such as <i>Bifidobacterium</i> and <i>Lactobacillus</i>, and harmful microorganisms such as <i>Enterobacteriaceae</i>, <i>Pseudomonas</i>, and <i>Enterococcus</i> were remarkably higher and lower, respectively, in patients receiving synbiotics in contrast to control.</p> <ul style="list-style-type: none"> <li>• Concentration of acetic acid and total organic acid were larger in patients receiving synbiotics in contrast to control.</li> <li>• Intestinal pH was reduced in the group taking synbiotics in contrast to control.</li> <li>• A lower rate of infection at 10% was reported in the group taking synbiotics in contrast to 29.4% in the control group.</li> <li>• Systemic inflammatory response syndrome had a</li> </ul>	Tanaka et al. (2012)

	<p>shorter duration in the synbiotic group as compared with control group.</p> <ul style="list-style-type: none"> <li>• Overall incidence of enteral nutrition interruption due to abdominal symptoms was lower at 6.7% in the synbiotic group in contrast to 29.4% in control.</li> </ul>	<p>Yokoyama et al. (2014)</p>
<p>Randomized controlled clinical trial: Oesophageal cancer patients undergoing esophagectomy</p>	<p>7 days preoperative, 14 days postoperative</p>	<p><i>L. casei</i>, <i>B. breve</i>, galacto-oligosaccharides</p> <ul style="list-style-type: none"> <li>• Significantly higher neutrophil count was observed in control on postoperative days 1, 2, and 7 as compared to the synbiotic group.</li> <li>• More prevalent detection of bacteraemia the day after operation in control as compared with the synbiotic group.</li> <li>• More microorganisms were detected in mesenteric lymph node in control in contrast to the synbiotic group.</li> <li>• Administration of synbiotics lowered the presence of bacteria in mesenteric lymph nodes and blood, thereby reducing inflammatory response</li> </ul>

(continued)



Table 3.1 (continued)

Type of cancer	Type of study	Duration of supplementation	Content	Key findings	Reference
	Randomized controlled clinical trial: Patients requiring neoadjuvant chemotherapy for oesophageal cancer	7 days prior to neoadjuvant chemotherapy	<i>L. casei</i> , <i>B. breve</i> , galacto-oligosaccharides	<ul style="list-style-type: none"> <li>The presence of bacteria was only observed in 2 of 100 blood samples in the symbiotic group in contrast to 16 of 101 samples in control.</li> <li>The presence of bacteria was not detected in any of the mesenteric lymph node samples in the symbiotic group in contrast to 12 of 34 samples in control.</li> <li>Symbiotic increased the concentration of faecal acetic acid thereby lowering faecal pH.</li> <li>Gastrointestinal toxicity rate was reduced in the group taking symbiotics in contrast to control.</li> <li>Symbiotics prevented bacterial translocation and subsequent bacteraemia that may be induced by neoadjuvant chemotherapy.</li> </ul>	Fukaya et al. (2021)
Periapillary neoplasm	Double-blind, randomized controlled clinical trial: Patients undergoing surgery for periampullary neoplasms	14 days	<i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>B. bifidum</i> , <i>L. casei</i> , fructo-oligosaccharides	<ul style="list-style-type: none"> <li>Remarkably lower incidences of postoperative infection at 26.1% was reported in patients receiving symbiotics in contrast to</li> </ul>	Sommecal et al. (2015)

<p>Prostate cancer</p>	<p>Double-blind, randomized controlled clinical trial: Prostate cancer patients undergoing radiotherapy</p>	<p>1-week pre-radiotherapy and 4 weeks post-radiotherapy</p>	<p><i>L. reuteri</i>, soluble fibre</p>	<p>69.6% in the control group.</p> <ul style="list-style-type: none"> <li>• Antibiotic therapy mean duration was shorter at 9 days in patients receiving synbiotics in contrast to 15 days in the control group.</li> <li>• Lower rate of non-infectious complications (6 of 23 patients) in patients receiving synbiotics in contrast to control (14 of 23 patients).</li> <li>• Mean hospital stay length was shorter at <math>12 \pm 5</math> days in patients receiving synbiotics in contrast to <math>23 \pm 14</math> days in control.</li> <li>• Six deaths were reported in control while no deaths were reported in patients receiving synbiotics.</li> <li>• Synbiotics reduced postoperative mortality and incidences of complications.</li> <li>• Synbiotics reduced symptoms of proctitis.</li> <li>• Synbiotics improved the quality of life in radiation-induced acute proctitis in prostate cancer patients undergoing radiotherapy.</li> </ul>	<p>Nascimento et al. (2014)</p>
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complications. As such, future research should focus on employing synbiotics as a cancer therapy that could target and modulate tumour cells directly. The underlying mechanisms of synbiotics in modulating the gut microbiome to exert an anticancer effect should also be thoroughly investigated, which could enable the development of effective strategies for early detection and treatment of tumours by cancer researchers. In a nutshell, with rapid advancement in medical technology and deeper insights into oncology and human microbiome research, it is believed that synbiotics can be translated into a novel cancer prevention and treatment strategy upon successful execution of clinical trials in the near future.

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