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Chapter 17

Prebiotics, Probiotics, Synbiotics and Functional Foods in Control and Treatment of Type II Diabetes Mellitus and Colorectal Cancer

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Additional information is available at the end of the chapter

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Abstract

Prebiotics, probiotics and synbiotics are components that enhance human health by several mechanisms. Patients suffering from type II diabetes mellitus (T2DM) and colorectal cancer have seen benefits when treated with a prebiotic, probiotic or synbiotic therapy. These benefits include the improvement of their lipid profile, oxidative stress status, as well as the modulation of the inflammatory and immune responses. The associated benefits of prebiotic, probiotic or synbiotic functional foods have been studied, showing promising results into the prevention or control of diabetes and colorectal cancer. This novelty research provides new evidence that the use of functional foods along with medical therapy could be used to further enhance patient's health.

Keywords: prebiotics, probiotics, synbiotics, T2DM, colorectal cancer

1. Introduction

Prebiotics, probiotics and synbiotics provide several health benefits to its consumer, such as better control of the glycemic index, blood triglycerides (TG) reduction, prevention of cancer, improvement of mineral absorption, among others [1–3]. Prebiotics, probiotics and synbiot-

ics have been added to food products in order to develop functional foods that confer additional health benefits besides the nutritional ones. Due to the health benefits they provide, the market for functional foods has increased in the previous years, growing up to a 47.6 billion US$, and it is expected to continue growing during the following years [4].

The objective of this chapter was to show some of the latest work done regarding the use of prebiotics, probiotics and synbiotics in prevention and treatment of type II diabetes mellitus (T2DM) and colorectal cancer, along with clinical studies showing that functional foods enriched with at least one of these components show a health benefit to patients.

2. Diabetes

Diabetes is a disease in which the body cannot regulate the amount of sugar in blood, being two major types of the disease:

- Type I: there is little or none insulin production, and insulin injections are needed daily.
- Type II: insulin resistance is present and glucose is unable to enter the cells to be used stored or used as energy.

Symptoms of both types include fatigue, blurry vision and slower healing in bladder and kidney infections. For type I, insulin injection is currently the only treatment, as for type II, medication is used when needed. These therapeutic drugs include α-glucosidase inhibitors, sulfonylureas, biguanides, among others. However, for most cases of T2DM, weight loss, healthy diet as well as exercise are enough to control or put into remission the disease [5]. Due to the nature of T2DM, this type poses a real possibility of overcoming the disease and where most of research is done in order to prevent, control and cure the disease.

The epidemics of diabetes is growing alarmingly, and it is estimated that by 2030, 342 million people (4.8% world's population) will be suffering from this disease [6]. It is estimated that 4 million people die from its complications each year, costing around 3.9 billion US$ for Brazil, 0.8 billion US$ for Argentina, 2.0 billion US$ for Mexico, and up to 44 billion US$ for USA in 1994; in 2012, it was 245 billion US$ for USA [7,8].

2.1. T2DM prebiotic, probiotic and synbiotic clinical therapy

2.1.1. Proposed molecular mechanisms

The molecular mechanisms on how probiotics or prebiotics work is not fully understood yet; however, few proposed or suggested mechanisms have been presented. Since T2DM is at a higher risk of cardiovascular complications, improvement or control of the lipid profile associated with prebiotics and probiotics has been studied, and it has been suggested that this improvement is done by the production of short-chain fatty acids (SCFA), which act as inhibitors of lipid synthesis in liver [9].

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Probiotics have also shown the ability to reduce reactive oxygen species (ROS) which, among other harmful effects, damage the intestinal barrier and allow bacterial translocation, which might lead to different infections and inflammation. *Bifidobacterium* has been associated with control of mild chronic inflammation, since it has been found that when levels of *Bifidobacterium* decrease, bacterial lipopolysaccharides (LPS) increase, and this is a characteristic of endotoxemia which leads to a higher concentration of pro-inflammatory cytokines [10]. Also, it has been shown that probiotic *Lactobacillus casei* regulates the release of LPS into blood via liver GlyRs upregulation [11].

Another proposed mechanism is that probiotics have the ability to modulate Th1 and Th2 pro-inflammatory responses, aiding in prevention of development of T2DM. Probiotic regulation of expression of *FoxA2* gene, whose product affected inulin sensitivity, has also been found. Also, a probiotic effect in Cl secretion and chloride channel protein expression in small intestine was determined. Chloride channel protein expression modulation has the effect of maintaining the normal function of tight junction barrier, decreasing bacterial translocation. All these results were observed in *L. casei*; further studies would be needed in order to associate similar effects for other probiotic strains [11]. However, these results show possible molecular mechanisms in which probiotics act on immune response.

Moving on to prebiotics, inulin, the most widely studied prebiotic, has shown the effect of glycemic index control by reducing the absorption rate of glucose and lipid profile control by decreasing the amount of serum triglycerides through the inhibition of glycerol-3-phosphate acyltransferase and fatty acid synthase as well as key enzymes in *de novo* lipid synthesis [12].

Extensive work has been done regarding the study of molecular mechanisms in which both prebiotics and probiotics function. Still, further studies are needed in order to establish a better understanding of the molecular mechanisms in which both enhance human health.

2.1.2. Recent studies done with T2DM

Several studies had been made with the use of prebiotics, probiotics or synbiotics into the treatment of T2DM. One of the first most recent studies uses probiotics as an aid in the treatment in diabetic rats along with gliclazide, an antidiabetic drug. Forty rats were divided into four groups: healthy, healthy probiotic, diabetic and diabetic probiotic. In the last two, diabetes was induced by alloxan solution injection (30 mg/kg). A mixture of *Lactobacillus acidophilus*, *B. lactis* and *Lactobacillus rhamnosus* was prepared in a formulation and administered along with the pharmaceutical to both healthy and diabetic male Wistar rats in a concentration of 10^{11} cells/g and 20 mg/kg, respectively. Probiotics were administered through gavage twice daily for 3 days for both health and diabetic groups and, after taking a baseline blood sample, gliclazide was administered by gavage as a single sample, taking blood sample doses from 5 min up to 600 min. Insulin concentrations in blood and blood glucose levels were measured for analysis. HPLC and MS were used to determine gliclazide serum concentration using a non-compartmental model. Parameters such as maximum

concentration, time to maximum concentration, half-life and mean residence time were evaluated by an analysis of variance (ANOVA). The study showed that in groups with probiotic treatment, there was no difference in glucose levels in healthy rats, but there was a significant reduction in diabetic ones from 23.8 ± 3 mmol/l to 12.6 ± 4 mmol/l. The bioavailability of gliclazide in both healthy and diabetic rats was studied, and results showed that there was a reduction in bioavailability in healthy rats from $(1.06 \pm 0.30) \times 10^4$ μg/mL to $(0.45 \pm 0.14) \times 10^4$ μg/mL and an increase in diabetic ones from $(0.80 \pm 0.15) \times 10^4$ μg/mL to $(1.00 \pm 0.23) \times 10^4$ μg/mL [13]. However, alloxan-induced diabetes is considered to be suffering from type I diabetes.

A different study used oligofructose-enriched inulin in order to evaluate the effect on several T2DM markers such as triglycerides (TG), total cholesterol (TC), malondialdehyde (MDA), low-density lipoprotein cholesterol (LDL-C), among others. A randomized, triple-blind, placebo-controlled trail was conducted for 8 weeks in 70 diabetic female volunteers whose ages range from 25 to 65 years old and having diabetes diagnosed for more than 6 months; however, only 52 patients completed the study. Maltodextrin was used as placebo in the control group, while the oligofructose-enriched inulin for the intervention group, both doses consisted of 5 g of supplement to be eaten during breakfast and 5 g at dinner. An Analysis of Covariance (ANCOVA) was performed to identify differences between the two groups. Results show that there was a general decrease in lipid levels, such as TC, from 203.1 mg/dL to 175 mg/dL, and LDL-C from 116.3 mg/dL to 94.3 mg/dL. There was no significant decrease in TG, from 216.8 mg/dL to 176.9 mg/dL, nor in MDA which values ranged from 4.3 nmol/mL to 2.6 nmol/mL [14]. This study suggests that these prebiotics have potential in improving the lipid profile of patients with T2DM, and this would lead to a decrease in the cardiovascular risk associated with the disease.

Impaired glucose tolerance is a major risk factor involved in T2DM, and a study was made assessing the effect of a probiotic in a preventive and/or ameliorating way in male Sprague Dawley rats. *L. casei* was administered on a 10^9 CFU/d to 50 rats divided into five groups: normal control (NC), *L. casei* preventive (LP), *L. casei* therapeutic (LT), hyperinsulinemia model group at 9 weeks (HMI) and hyperinsulinemia model group at 13 weeks (HMII). During the course of the study, 14 weeks, they evaluated parameters such as blood glucose level, total bile acids levels and liver glycogen content along with the composition of intestinal predominate bacteria. The statistical analysis was performed using an ANOVA and Fisher's least significant difference (LSD) to compare among groups. This study suggests an increase in glucose tolerance as well as the number of *Lactobacillus* and *Bifidobacterium* present in colon, while decreasing *Clostridium. L. casei* ameliorated glucose tolerance in rats, and this is suggested by the decrease in glycogen content in liver, stopping an excessive stress with an increase in liver's glucose uptake due to the fact that over 70% of dietary fructose is metabolized by the liver leading to an improvement in health [15].

As mentioned earlier, it is suggested that lipid profile and oxidative stress are improved by probiotics. A single-blinded clinical trial was performed with 40 T2DM patients studying the

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effect of probiotics *L. acidophilus, Lactobacillus bulgaricus, L. casei* and *L. bifidum* in 1500 mg capsules twice daily during 6 weeks, while control group receives 1000 mg magnesium stearate capsules. Lipid profile and oxidative stress biomarkers such as TC, TG, LDL-C, among others were evaluated. For statistical analysis, paired *t*-test samples were used to compare continuous variables within groups, while comparison between different groups was done through two independent-samples *t*-tests. In the absence of normal distribution, Wilcoxon and Mann–Whitney *U*-tests were used. There was not any significant difference found between control group and probiotic treated group, and authors argue that it might have been due to the sample size or the short duration of the study [6]. These results pose controversial evidence between health enhancement properties of prebiotics, probiotics and synbiotics; however, further analyses into the sample size, duration of each trial, and dosage have to be taken into account in order to establish an objective conclusion as well as the duration of the study.

Further studies have been done in the topic of T2DM; however, there is no an extensive amount of literature available. A short summary of these is presented in **Table 1**.

Authors	Component	Host	Dosage/ length	Study's design
[16]*	Several *Bifidum* and *Lactobacillus* strains	T2DM patients	4 g sachets daily intake (2.5×10^9 CFU/g) 26 weeks	Single-center, double-blinded, randomized, placebo-controlled study with 60 patients
[11]	*L. casei*	Sprague Dawley Rats	4×10^9 CFU/d rat 2 weeks	1. Sixteen rats divided into high-fat fructose diet (HFS) and normal control (NC) 2. Twenty-seven rats divided into three groups: HSF, NC, and HSF with probiotics ANOVA followed by LSD
[17]*	Inulin oligofructose	Pre-diabetic patients	10 g daily 6.5 months	Randomized crossover controlled trial Kolmogorov–Smirnov goodness-of-fit test, Pearson correlation, and ANOVA
[18]	Several *Bifidum* and *Lactobacillus* strains	T2DM patients	Range from 1.5×10^9 to 7×10^9 CFU 15 months	Randomized double-blinded controlled clinical trial Kolmogorov–Smirnov test, Paired sample *t*-test, Student's *t*-test
[19]*	Inulin	Pre-diabetic patients	10 g inulin daily 6 weeks	Double-blinded, placebo-controlled, parallel group design Multiple-sample repeated-measures analysis of variance, ANCOVA
[20]	*L. acidophilus Bifidobacterium*	T2DM patients	10^9 CFU/day 7 months	Randomized double-blinded parallel group placebo-controlled trial Shapiro–Wilk

Authors	Component	Host	Dosage/ length	Study's design
	animalis			test, Student's *t*-test
[21]	*B. animalis* Polydextrose Antidiabetic drugs	Mice	10^9 CFU Polydextrose 0.25 g/day 4 weeks	1. Forty mice divided into four groups: diabetic control, *B. animalis* (B420) intake, metformin, metformin + B420 2. Forty-eight mice divided into six groups: non-diabetic control, diabetic control, sitagliptin (SITA), SITA + polydextrose (PD), SITA + B420, SITA + PD + B420 2 × 2 Factorial, Shapiro–Wilk, ANOVA, Tukey's HSD

* To our knowledge, results of clinical trial have not been published to the date of writing.

Table 1. Recent studies done with prevention or treatment of T2DM using prebiotics, probiotics or synbiotics.

2.2. Functional foods in T2DM

As mentioned above, T2DM can be controlled by a healthy diet. This has been used as a novelty approach into the treatment of the disease using prebiotic, probiotic or synbiotic functional foods, while evaluating the health benefits provided. Most of the functional foods studied are either yoghurts or breads.

A probiotic yogurt with *L. acidophilus* and *B. lactis* was used to evaluate the effect on the lipid profile of T2DM patients. This was a double-blinded randomized controlled clinical trial in which a total of 64 subjects were assigned to either a control group or a treatment group. Three-hundred grams of either control or probiotic yoghurt were consumed daily during the 6-week period the study lasted. It was determined that an average of 4.14×10^6 CFU/g for *L. acidophilus* and 3.61×10^6 CFU/g for *B. lactis* was the concentration on probiotic yoghurts when consumed by patients. For statistical analysis of the parameters measured, different tests were measured such as Kolmogorov–Smirnov, *t*-tests, chi-squared tests and Mann–Whitney *U*-test. It was found a decrease of 4.54% of total cholesterol and 7.45% decrease in LDL-C, while no significant effect was found on triglycerides and in high-density lipoprotein cholesterol (HDL-C). However, authors discussed certain limitations such as the short duration time and the lack of a control group who did not consumed yogurt at all [22]. This study suggests that the consumption of a probiotic yoghurt might help reduce cardiovascular risk in patients with T2DM.

One year later, results from another similar study were published in which a probiotic yogurt containing *L. acidophilus* and *B. lactis* was used to assess the effect on oxidative stress biomarkers of T2DM patients. Similarly, this was a double-blinded randomized controlled clinical trial, conformed by 64 patients in which patients were randomly assigned either a control or an intervention group. During 6 weeks, patients consumed 300 g a day of either a probiotic or conventional yoghurt. Probiotic yoghurt contained an average of 1.85×10^6 CFU/g of *L. acidophilus* and 1.79×10^6 CFU/g. of *B. lactis*. Some of the parameters measured were the

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glutathione peroxidase activity, MDA serum concentration and hemoglobin A1c. Several statistical tests were used such as Kolgomorov–Smirnov, independent-samples *t*-test, chi-square and Mann–Whitney *U*-tests. It was shown that the consumption of this yogurt decreased fasting blood glucose and increased erythrocyte superoxide dismutase and glutathione peroxidase activity. These results show the improvement in the oxidative stress status of patients and that this probiotic yogurt is a promising agent for diabetes management [23].

On another study, the evaluation of the lipid profile of T2DM patients while consuming a synbiotic bread containing *Lactobacillu sporogenes* and inulin was made. This study was a randomized double-blinded controlled clinical trial in which 78 subjects were randomly assigned to three groups: a control group consuming bread, a probiotic bread consuming probiotic bread with a bacteria concentration of 1×10^8 CFU and a synbiotic bread containing the probiotic and 0.07 g inulin per 1 g of bread. One hundred-twenty grams of bread were consumed daily for 8 weeks. For statistical analysis, tests such as Kolmogorov–Smirnov and ANOVA were used to identify significant differences. The best results were obtained with the synbiotic bread in which triacylglycerols (TAG), very low-density lipoprotein cholesterol (VLDL-C) and the ratio between total cholesterol and HDL-C were decreased significantly compared to the control group and the probiotic one. However, there was no effect on the fasting plasma glucose (FPS), total cholesterol (TC), LDL-C and non-HDL-C. These results show that this synbiotic bread enhances patient's health even further than probiotic or prebiotic ones [24].

On a different approach, *L. sporogenes* with inulin were used as synbiotic components in a different study. This clinical trial consisted of a randomized double-blinded crossover in which 62 patients consumed the product during 6 weeks. The dosage consumed by subjects daily was of 27×10^7 CFU and 1.08 inulin. Statistical analysis of the assessed variables was evaluated through Kolmogorov–Smirnov and paired *t*-tests. The assessed variables were consistent with other studies regarding the lipid profile. It was found that there was a significant decrease in insulin levels, serum hs-CRP, while there was an increase in uric acid levels, but no significant effect on LDL-C, serum triglycerides and HDL-C in patients with T2DM. These results also suggest that synbiotics have a positive effect in glycemic control [25]. However, the high dosage of probiotics should be taken into account when comparing with similar studies, and this dosage was the highest found in consulted literature.

In a different study, another synbiotic functional food was developed enriched with β-carotene, and this food contained inulin as a prebiotic and *L. sporogenes* as a probiotic. This was double-blinded controlled crossover clinical trial in which 102 patients were randomly allocated to a control food group or a synbiotic one for 6 weeks. Their daily dosage was 3×10^7 CFU, 0.3 g of inulin and 0.15 g β-carotene. Results show a decreased insulin's concentration, triglycerides, VLDL-C and TC/HDL-C, improving the lipid profile of patients and lower cardiovascular disease associated with T2DM; however, β-carotene should be taken into account when considering these results, and authors suggest a mechanism in which β-carotene impacts gene expression and gut microbiota–SCFA–hormone axis [26]. Nonetheless, previ-

ous studies show the health enhancing properties of probiotics and prebiotics, so this should not take any credit for these results.

To conclude with T2DM and functional foods, another synbiotic bread was developed using *L. sporogenes* and inulin to evaluate its effect of nitric oxide (NO) and MDA, biomarkers of oxidative stress and liver enzyme activities. A randomized double-blinded, placebo-controlled clinical was done, and 81 patients were divided into three groups: Group A consuming synbiotic bread, Group B consuming probiotic bread and Group C consuming control bread. All three groups consumed 120 g/day of bread, and dosages for treatment groups consisted of 3×10^8 CFU and 0.21 g inulin per day. Statistical analysis was done using Kolmogorov–Smirnov and ANOVA tests. It was observed that there was a significant increase in NO and MDA levels, while there was no effect on plasma total antioxidant capacity, plasma glutathione (GSH) and serum liver enzymes, among others. This study shows that the consumption of the synbiotic bread had positive effects on NO and MDA levels, improving the oxidative stress status of T2DM patients [27]. These results support the idea that functional foods might be useful as an aid in the treatment of T2DM. There were no significant differences in other variables such as GSH activity, blood pressure, serum liver enzymes, among others, which must be considered when taking a control of T2DM using functional foods.

3. Colorectal cancer

As any other cancer, colorectal is characterized by uncontrolled proliferation of cells which lead to the formation of tumors. Symptoms involve blood in stool, either diarrhea or constipation, fatigue, frequent gas pain cramps, among others. Colorectal cancer is the third most common cancer worldwide in men, just below lung and prostate cancers, and second most common in women just below breast cancer. There were 1.3 million new diagnosed cases of colorectal cancer in 2012 and it is expected that this figure will keep growing [28].

The cost of colorectal cancer in 2010 in the US was of 14.14 billion US$, while worldwide it is estimated to be of 99 billion US$ annually [29, 30].

3.1. Colorectal cancer prebiotic, probiotic and synbiotic clinical therapy

3.1.1. Proposed molecular mechanisms

Several molecular mechanisms in which probiotics and prebiotics work and help prevent as well as ameliorate health in colorectal cancer patients have been proposed, some are presented here. Probiotics cause the acidification of pH which has been shown to inhibit *Escherichia coli* and clostridia, subsequently causing the decrease in bacterial enzymes linked to conversion of procarcinogens into carcinogens such as β-glucuronidase. Probiotics isolated from "idly," a traditional cereal pulse from India, had the ability to exert desmutagenicity in various mutagens such as heterocyclic amines and aflatoxins. Also, bifidobacteria have shown binding properties on the carcinogens such as methylazoxymethanol and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole and the ability of removing them physically through feces, reducing the

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amount of absorption of this carcinogens in lumen and thus reducing the probabilities of developing cancer. Furthermore, *Bifidobacterium longum* showed reduction in expression of *ras*-p21 oncoprotein, and mutations in *ras* genes have been found to be present in colon adenomas, carcinomas and tumors. A general summary of mechanisms can be seen in **Figure 1** [31].

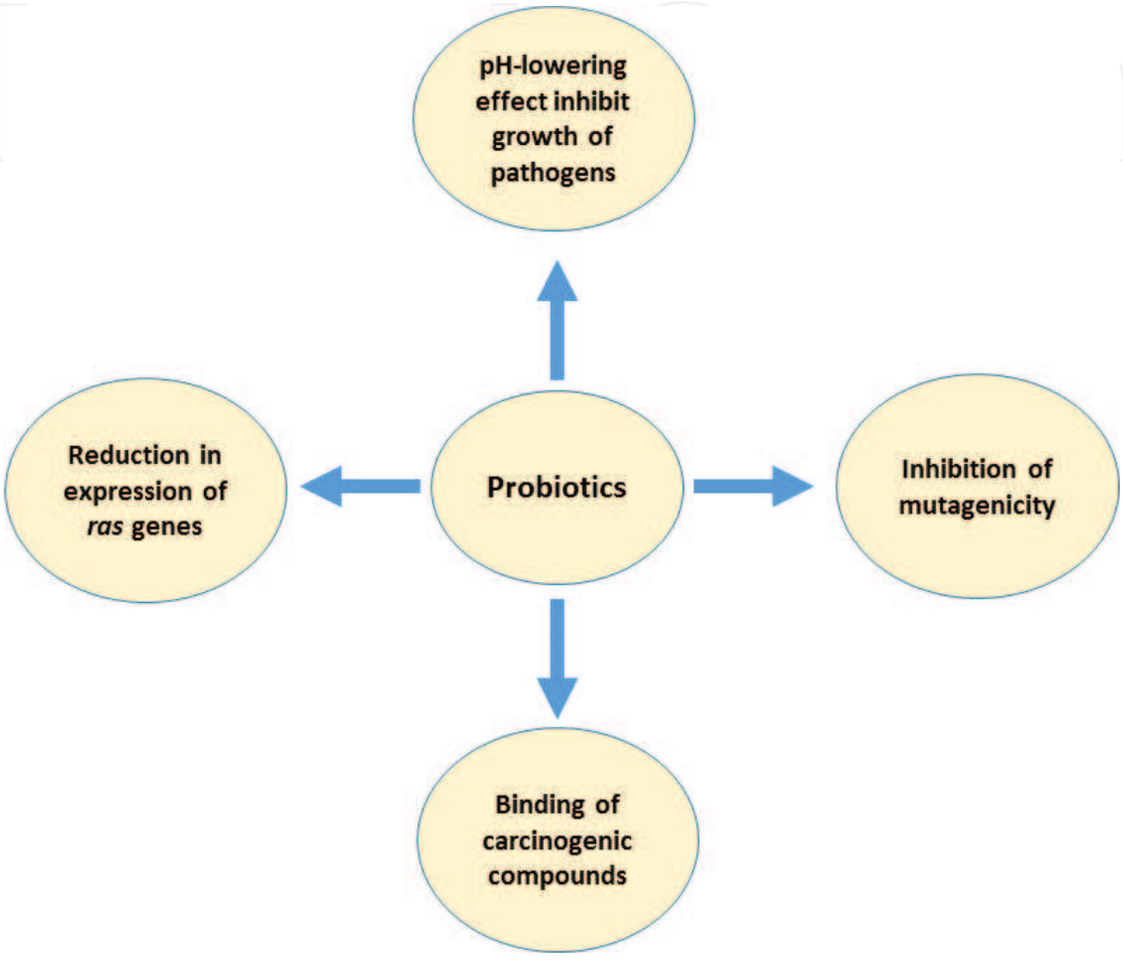

Figure 1. General anti-carcinogenic probiotic mechanisms in colorectal cancer.

Most of the studies done on the mechanism of prebiotics have been on oligofructose prebiotics such fructooligosaccharides and inulin. Oligofructose-enriched inulin has shown a decrease in the expression of enzymes linked to colorectal cancer such as glutathione S-transferase and nitric oxide synthase. Also, cyclooxygenase 2, an enzyme upregulated in cancers was in lower in prebiotic rats than in control rats. Fermentation in colon generates SCFA, butyrate being one of them. Sodium butyrate has been found to be a grown inhibitor and inducer of phenotype differentiation and apoptosis, reducing the risk factors of developing cancer [31].

While there are several proposed mechanisms with evidence suggesting them, for both probiotics and prebiotics, further studies must be done in order to provide uncontroversial

evidence on the established pathways and provide better understanding of the molecular dynamics followed in the human colon.

3.1.2. Recent studies done with colorectal cancer

Several studies have been made in order to evaluate the effect on several variables associated with colorectal cancer. In a randomized double-blinded placebo-controlled trial, a synbiotic treatment containing *L. rhamnosus, B. lactis* and inulin was used in a study evaluating the effects on several markers of immune functions. During 12 weeks, 34 patients were randomly placed on either the control group or the treatment one. Control or placebo group consumed daily encapsulated maltodextrin and a 10 g sachet of maltodextrin, while the treatment group consumed 1×10^{10} CFU *L. rhamnosus* and 1×10^{10} CFU of *B. lactis* along with a 10 g sachet of inulin. Several parameters such as burst activity of monocytes and neutrophils, lytic activity of natural killer cells and production of interleukins (IL)-2, IL-10 and IL-12, among others were evaluated. The statistical analysis was done using Kolgomorov–Smirnov, ANOVA and Dunnett's tests. The synbiotic therapy only showed significant effect on an increased capacity of peripheral blood mononuclear cells to produce IFN-γ. These results do not show promising evidence, but it should be noted that authors measured immune response factors in blood. Authors even suggest future studies should aim gut-associated immune system. The main contribution of this study was to determine that the immune effects of a synbiotic treatment are kept in human colon [32].

A different approach has also been taken, and *Bifidobacterium adolescentis* extracts were used in a study to evaluate the antiproliferative effects on three human colon cancer cells: Caco-2, HT-29 and SW480, measuring the production of tumor necrosis factor-α (TNF-α) and NO. This study consisted in the isolation of *B. adolescentis* from 20 healthy Koreans 20–30 years old. Extracts were prepared in several concentrations ranging from 12.5 μg/mL up to 200 μg/mL and incubated with the different cell lines mentioned earlier. There was a significant decrease in the proliferation of the three human colon cancer cells, correlated with the increase in TNF-α and NO production, from 25 μg/mL to 200 μg/mL in a dose-dependent manner. There are no data shown for the increase in NO production. The increase in both of these immune response markers as well as the decrease in cancer cell proliferation show the potential of including *B. adolescentis* in therapy or diet diminishing cancer advance; however, studies should be done *in vivo*, without using an extract, and also in clinical trials before reaching a definitive conclusion [33].

Fructans and soybean meal (SM) were used to evaluate the effect on tumors. Some of the variables measured in colorectal cancer-induced rats with azoxymethane were GST activity and bacterial enzyme activity. Ninety Fisher 344 male rats were randomly assigned to nine groups, which difference was the diet. Control groups rats were fed with American Institute of Nutrition-93 Growth/Maintenance (AIN-93G/M) diet, and the eight groups were fed with the following diets: prebiotics 5%, prebiotics 10%, SM 5%, SM 10%, prebiotics 5% + SM 5%, 10% + SM 10%, 5% + SM 10% and 10% + SM 5%. Tumors present in control group were bigger in size than those fed with either fructans, soybean meal or both. GST activity was increased in two- to fourfold in rats fed with treatment diets compared to the control group, and β-

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glucosidase activity showed no significant difference between control group and treatment one, with the exception of a significant increase in rats fed with prebiotics 10% and rats fed with prebiotics and SM 10% + 5%. Overall there were better results obtained in prebiotics + SM consumption [34]. These results suggest that prebiotics can be used in treatment of colorectal cancer.

L. acidophilus has also shown properties in colon tumor suppression in rats. This probiotic was inoculated into female BALB/cByJ mice during 14 consecutive days at a concentration of 1×10^8 CFU/mouse. After 14 days, cancer cell implantation was done using CT-26 cells in a concentration of 5×10^6. And during the following 3 weeks, 1×10^9 CFU/mouse of *L. acidophilus* was inoculated. After 28 days of tumor induction, mice were killed and several variables were assessed, such as chemokine mRNA expression, tumor size and cell surface phenotypes. For the statistical analysis of results, one-way and two-way ANOVA tests were used. Tumors in rats that were pre-inoculated showed a 50.3% size reduction, and there was an enhanced tumor apoptosis and downregulation of CXCR4 mRNA expressions in colon. These results show that *L. acidophilus* is able to play a role in attenuating tumor growth as well as increasing apoptosis in tumor tissue [35]. This study contributes to the understanding in how probiotics regulate tumor proliferation in an *in vivo* system.

The effect of inulin and lactulose on procarcinogenic biomarkers in 1,2-dimethylhydrazine dihydrochloride (DMH)-induced rats has also been evaluated. Thirty-two male Sprague Dawley rats were divided into four groups: group I which is the control group received a single dose of EDTA saline solution per week, group II received a single dose of DMH per week, group III received a single dose of DMH + inulin 10 mg/0.1 mL and Group IV received DMH + lactulose 14 mg/0.1 mL. All doses were given during the course of 6 weeks. For groups III and IV, prebiotics were administered orally daily and on the 8th day, a single dose of DMH was administered. Three variables were measured among others, and these are as follows: nitroreductase, β-glucosidase and β-glucuronidase activities. Statistical analysis was done using one-way ANOVA and a post hoc LSD tests. Activity of β-glucuronidase (0.045 ± 0.006 μg/h/mg) and β-glucosidase (1.007 ± 0.115 μg/h/mg) was found to be decreased in the inulin + DMH group when compared to control (0.243 ± 0.059 μg/h/mg and 2.219 ± 0.745 μg/h/mg, respectively). Nitroreductase activity was increased in inulin + DMH (0.045 ± 0.005 μg/h/mg) compared to control (0.0162 ± 0.005 μg/h/mg) [36]. These results also suggest the colorectal cancer protection properties of inulin, which could be used in the prevention of developing colorectal cancer.

On similar study, thirty male and female Sprague Dawley rats were divided into three groups: a control group fed only with conventional feed, a DMH group and a DMH + inulin fed group. DMH and DMH + inulin group were treated with DMH at a dose of 21 mg/kg five times in weekly intervals, and DMH + inulin rats were fed with a dose of 80 g/kg of conventional feed during 28 weeks. For statistical analysis of the variables evaluated, a one-way ANOVA test was used. It was found that activity of β-glucuronidase decreased as well as the number of COX-2- and NFκB-positive cells along with a decrease in the expression of IL-2, TNF-α and IL-10. Moreover, there was a significant decrease in β-glucosidase activity (0.03 ± 0.02 μmol/min/g) when compared to the control group (0.08 ± 0.02 μmol/min/g), and also there was

a significant decrease in coliforms (5.96 ± 0.22 $\log_{10}$ CFU/g) when compared to control (6.17 ± 0.56 $\log_{10}$ CFU/g) and DMH group 6.34 ± 0.25 $\log_{10}$ CFU/g). This decrease in coliforms explains the reduction in β-glucuronidase activity. Butyric and propionic acid levels were higher in DMH + inulin group, and these short-chain fatty acids have been associated with apoptosis and metastasis, carcinogen reduction, among others [37].

Several other studies have been made, and these are shown along with a brief summary of each in **Table 2**.

Authors	Component	Organism/cell line	Dosage/length	Study's design
[38]	*L. delbrueckii* fermentation supernatant	Colon cancer SW620	Several protein concentrations ranging from 0 up to 0.75 mg/mL 24 h	*L. delbrueckii* fermented MRS medium. Supernatant was incubated with SW620 cells and evaluated in viability essays Statistical analysis were done using one-way ANOVA and Bonferroni's multiple comparison test
[39]	*L. plantarum* *L. rhamnosus* supernatants	Caco-2 HT-29	2.5, 5 and 10 mg/mL 48 h	Probiotic fermented medium Supernatants was incubated with cancer cells and evaluated viability Statistical data were analyzed using one-way ANOVA
[40]	*L. casei*	C57BL/6 mice	1×10^8 CFU 10 weeks	Mice were administered probiotic and DMH, intestinal damage evaluation, cytokine analysis, gene expression analysis Bonferroni's multiple comparison test
[41]	Xylooligo saccharides (XOS)	Wistar rats	5% and 10% XOS 45 days	XOS diet in rats, bacterial analysis y cecal matter, biochemical assays, proliferation markers One-way ANOVA
[42]	*L. paracasei*	HT-29	0, 10, 50, 100, MOI 48 h	Calculation of multiplicity of infection (MOI), analysis cell distribution, RNA extraction, and semiquantitative RT-PCR One-way ANOVA and Duncan's post hoc tests

Table 2. Recent studies done regarding colorectal cancer using prebiotics or probiotics.

3.2. Functional foods in colorectal cancer

To the best of our knowledge, only a couple of studies have been made regarding prebiotic, probiotic or synbiotic functional foods for prevention, control or treatment of colorectal cancer.

A synbiotic food using oligofructose-enriched inulin and *L. rhamnosus* and *B. lactis* was developed and evaluated as a potential reduction risk agent in colorectal cancer patients. This

http://dx.doi.org/10.5772/63643

study was a randomized double-blinded placebo-controlled trial in which 37 colon cancer patients were divided into a control group or an intervention one. Intervention patients were given daily a synbiotic food during 12 weeks consisting of 12 g of inulin and 10^{10} CFU of probiotics. For statistical analysis of the data, a generalized linear modeling was used. It was found that the number of *Bifidobacterium* and *Lactobacillus* in feces was increased, while a decrease in the number of *Clostridium* was found. The effect of the synbiotic intervention on DNA damage, as well as the effect on epithelial barrier functions in tumor cell invasion, was also studied. It was found that intervention group had a significant decrease in the level of DNA damage (55.84 ± 21.21 tail lengths) compared to the placebo group (59.18 ± 15.94 tail lengths), but there was no significant difference between control (101.9 ± 6.6) and intervention group (104.9 ± 6.2). A decrease in the level of DNA suggests that there was a decrease in exposure of the colon epithelium to cytotoxic and genotoxic agents, along with decreased cancer cell proliferation. An improvement of the epithelial barrier function is associated with lower cancer risk, while in this study there was no significant difference, it has been seen that probiotics provide a better formation of this layer [43].

A study was done on 56 F344 rats using a probiotic fermented milk with *L. acidophilus*, *L. casei* and *L. rhamnosus*. The rats were divided into seven groups randomly: group 1 served as control by receiving 0.85% saline solution by gavage. Rats in groups 2–7 were injected with DMH 30 mg/kg once a week for 6 weeks; group 2 served as positive carcinogenic control, and groups 3 through 7 were supplemented with 2, 1.5, 1, 0.5 and 0.25 mL of probiotic milk containing at least 50×10^9 CFU during 12 weeks. Variables were observed and evaluated such as the activity of quinone reductase (QR), GST and β-glucuronidase. Statistical analysis of the data was done using one-way ANOVA test. It was found that G4 and G5 improved 154% and 109% compared to control group. QR activity was reduced significantly in all rats treated with DMH when compared to the control group. β-Glucuronidase activity showed a significant decrease by 49% compared to control group. This study shows that there is potential in probiotic functional foods in the prevention, control and treatment of colorectal cancer; however, further studies are needed in order to provide more information about this [44].

4. Conclusions and perspectives

The effect of prebiotics, probiotics and synbiotics over several health markers in T2DM and colorectal cancer patients has been shown through several studies discussed in this chapter. Some of the health benefits presented in this chapter for T2DM are the improvement of lipid and glycemic profile, increase in blood insulin concentration and modulation on the inflammatory response. For colorectal cancer, some of the health benefits presented in this chapter are the modulation of the immune response, antitumor activity and tumor size reduction. However, further research is needed in order to understand completely the specific molecular pathway of each component has.

The use of functional foods for prevention and control of T2DM is a promising opportunity which must be taken into account, after all, and one of the most common causes of this disease

is obesity and poor diet. The design of functional foods with prebiotics, probiotics or synbiotics that will help enhance T2DM patient's health would be an aid in the fight against it; however, the elimination or substitution of antidiabetic drugs is not recommended or endorsed.

There is much to do in the research of prebiotic, probiotic or synbiotic functional foods for the prevention, control or treatment of colorectal cancer. There is evidence suggesting that therapy enhances patient's health, and this should encourage further research into the development of functional foods and their clinical studies in patients. If successful results during the following years are obtained, this could provide as an aid in the fight against colorectal cancer.

The use of functional foods should be used with caution and as a support to clinical therapy, not exclusively as an alternative. This combination could lead to further improvement in patient's health as some studies have found synergistic effect of probiotics along with medical drugs.

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