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Cancer Prevention by Synbiotics Effect of Fiber-Rich Sourdough Fermentation

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ABSTRACT

Sourdough is a very complex biological system, which obtained from water and cereal fermentation. Sourdough fermentation usually consists of combinations of probiotic lactobacilli starters and prebiotic dietary fibers called synbiotics which have a synergistic effect, greater than that of either the probiotic or prebiotic administered individually. Preliminary research suggests that synbiotics offer anti-cancer benefits to the human body. The risk of lung, colon, liver, breast and bladder cancer may be reduced with the help of synbiotic effects. The most promising research is the ability of synbiotics to improve the health of cancer patients undergoing radiation therapy. Proposed mechanisms of action of probiotics lactobacilli starters and prebiotics dietary fibers in cancer include binding of carcinogens, alteration in gut microbiota formation and metabolism of carcinogens, stimulation suppression of carcinogenesis, improvement in epithelial barrier function, anti-inflammatory effects, inductance of apoptosis, and inductance of protective enzymes. Briefly these mechanisms and synbiotics effect of fiber-rich sourdough fermentation in cancer prevention will be discussed in this mini review.

Keywords: Sourdough fermentation, cancer prevention, Symbiotic effect, probiotic lactobacilli starters, prebiotic dietary fiber.

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Cancer is the main lead-in cause of death in highly-developed countries and over the past decade it has become clear that nutrition plays a major role in cancer prevention. The fact that incidence has been rising in parallel with economic development indicates that environmental factors such as diet might play a role in the causation of cancer. It has been evaluated by the world cancer research fund that 30 to 40% of all cancers can be prevented by diet and proper body weight management. Prevention of cancer remain also the most promising strategy for reducing its incidence of this disease. For more than ten years, findings from basic research and clinical trials have informed the development of proper lifestyle and medical approaches to cancer prevention (1).

Data have pointed to nutrition as one of the most relevant external factors involved in cancer prevention. There is no need to adopt a foreign dietary scheme in order to protect oneself against cancer. Traditional western diets also have their good factors that should be regular constituents in our foods. Lignans from traditionally made sourdough rye bread, linseed/flaxseed and berries are sources of potentially cancer protective factors.

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Furthermore, indole-3-carbinol rich cabbage species can contribute to cancer protective covering, too. But, clear cut recommendations for single nutrients or secondary plant metabolites are not yet possible, lacking sufficient data on individual bioavailability, safety and long term outcome. Cancer prevention by dietary means therefore relies on an individually tailored mixed diet, rich in basic meals and traditional manufacturing and preparation methods (2). Nowadays, there is growing producer interest in health aspects of food, including functional and synbiotic food products with specific physiological functions of health relevance.

The term synbiotic has been proposed for combinations of prebiotic ingredients and probiotic microorganisms that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and activating the metabolism of one or a limited number of health-promoting microorganisms, and thus improving host welfare. The probiotic originates from the ancient Greek words *pro* and *biotica*, meaning "for life" and the most acceptable definition of a probiotic is a living microorganism which upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition. A probiotic should be non-pathogenic, non-toxic and also resistant to low pH and bile salts to improve its survival in the

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Most probiotics are members of two genera of lactic acid bacteria (LAB), *Lactobacillus* and *Bifidobacterium*. A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of microorganisms in the colon that have the potential to improve host health. A number of poorly digested carbohydrates fall into the category of prebiotics, including certain fibers and resistant starches, but the most widely described prebiotics are non-digestible oligosaccharides and microbial exopolysaccharides. Combinations of probiotic microorganisms and prebiotic ingredients (synbiotics) can result in additive or synergistic effects on gastrointestinal function (3).
The definition for probiotic microorganisms has gradually changed with increasing understanding of the mechanisms by which they influence human life. Health effects related to changes in the intestinal microflora also related to adhesion and immune system effects, competitive exclusion or metabolic and nutritional effects, with an increasing array of other potential modes of action. Most clinically documented and validated health effects have been investigated using either fermented milks containing viable pure cultures. Specific targets for the future include controlled studies comparing foods containing viable strains to those containing non-viable strains and to assess the combined effects of multiple probiotic microorganisms(4).

Certain probiotic interventions have shown promise in selected clinical conditions where aberrant microbiota have been reported, such as dermatitis, enterocolitis, pouchitis and possibly irritable bowel syndrome. However, no studies have been conducted that can causally link clinical improvements to changes of probiotic-induced microbiota. Whether a pattern of disease-prone microbiota can be remodelled to a more robust, resilient and disease-free state by probiotic administration remains a key unanswered question. Progress in this area will be facilitated by optimising strain, dose and product formulations, including protective commensal species, matching these formulations with selectively responsive subpopulations and identifying ways to manipulate diet to modify microbial profiles and metabolism (5).

The prebiotic ingredients and probiotic microorganisms area is a fast evolving field that attracts significant interest by both the industrial and academic communities. Therefore, many researches are generated every year. The target of many probiotics and prebiotics is the prevention and treatment of disorders associated with the gastrointestinal tract and suggested as therapeutic materials. An increasing amount of evidence from in vitro and in vivo researches suggests that they are effective in the prevention of allergies and may have potential anti-carcinogenic effects. In addition to the above, there has been considerable interest in extra-intestinal application of probiotic microorganisms and prebiotic ingredients, such as in urogenital infections and oral health. Because factors involved in the initiation and promotion of cancer might be separated in time from actual tumor development, it is difficult to choose outcomes or end points that are definitive indicators of efficacy of probiotic starters or prebiotic materials. Studies that have showed the cause-effect relationship directly have used usually animal models (6, 7).

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Current cancer treatments including chemotherapy, radiotherapy and surgery are all associated with a high risk of complications and are not always successful, highlighting the need to develop new treatment ways. The ingestion of synbiotics represents a novel new therapeutic option. Probiotics and prebiotics act to alter the intestinal microflora by increasing concentrations of beneficial microorganisms, and reducing the levels of pathogenic agents. This strategy has the potential to inhibit the development and progression of neoplasia via mechanisms including decreased intestinal inflammation, enhanced immune function and anti-tumorigenic activity, binding to potential food carcinogens such as toxins found in some food products, and a reduction in microbial enzymes which hydrolyse pre-carcinogenic compounds. There is substantial experimental evidence to suggest that probiotic starters and prebiotic ingredients may be beneficial in the cancer prevention and treatment, however to date there have been few conclusive human trials (8).

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Epidemiological studies have shown that regular consumption of meals based on whole-grain cereals and their products is associated with reduced risks of various types of degenerative chronic diseases. Food proteins are considered an important source of nutraceutical peptides and amino acids that can exert biological functions to promote health and prevent different disease and cancers. There are several reports on peptides with anti-tumour activity. Plant-derived peptides, such as lunasin have received main attention (9). Intake of whole grain foods is increasingly reported to be associated with health benefits, including improved regulation of blood glucose levels, decreased risk of diabetes, cardiovascular disease, and certain cancers. Sourdough fermentation has also proven useful in improving the texture and palatability of whole grain and fiber-rich products, and it may stabilise or increase the levels of bioactive compounds. The production of prebiotic compounds by LAB also is an interesting possibility (10).

Furthermore, there is several health or nutritional benefits possible from some species of LAB such as improved nutritional value and digestion of lactose, control of intestinal infections, some types of cancer and serum cholesterol levels. Some potential benefits may result from growth and action of the probiotic bacteria during the manufacture of cultured foods. Some may result from growth and action of certain species of the probiotic LAB in the intestinal tract following ingestion of foods containing these microorganisms. In selecting a culture for specific benefit it is necessary to consider not only the wide variation among species of the LAB but also that among strains within a given species (11). LAB are a diverse group of bacteria that produce lactic acid as their major fermented product and most of them are normal flora of human being and produce myriad beneficial effects for human including alleviation of lactose intolerance, diarrhea, peptic ulcer, stimulation of immune system, antiallergic effects, antifungal actions, preservation of food and prevention of colon cancer (12). While a myriad of healthful effects have been attributed to the probiotic LAB, perhaps the most controversial remains that of anticancer and anti-carcinogenic activity (13).

Fermented cereal foods are an essential component of the daily diet. Nutritionally, they are an important source of carbohydrates, protein, dietary fiber, many vitamins and components not essential for growth but with potential biological functions. Recent findings have indicated a protective

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role of especially fermented whole grain foods against several Western diseases (14, 15). Dietary fiber was long considered the major health protective component of these grains. There is now increasing evidence also of other protective compounds, such as oligosaccharides, phytochemicals and bioactive peptides which together with dietary fiber are concentrated in The levels and also bioavailability of carbohydrates and various bioactive compounds (compounds effecting human physiological reactions with health relevance) can remarkably be influenced by food processing chain (16).

Sourdough fermentation especially in whole cereal grains is one of the oldest food biotechnologies, which has been studied and rediscovered for its effect on the sensory, structural, functional, nutritional and shelf life properties of leavened baked goods. Acidification, proteolysis and activation of some enzymes as well as the synthesis of microbial metabolites cause several changes during this fermentation, which affect the dough and baked product matrix and influence its functional quality (17). A common trend of sourdough fermentations is the unique symbiosis of certain hetero and homo fermentative probiotic LAB with certain yeasts. The most relevant bacteria isolated from different sourdoughs belong to the genus *Lactobacillus*. Some of the reported benefits of sourdough on quality of final product may be based on the formation of exopolysaccharides by certain probiotic LAB, whereas most of the beneficial properties attributed to sourdough are determined by the acidification activity of these microorganisms (18).

In principle, the whole grain or fractions of cereal grain can be modified by LAB sourdough fermentation to improve nutritional value or promote healthiness of cereal foods. Whole meal flour is rich in fiber, minerals, vitamins and many phytochemicals or bioactive compounds such as phenolic compounds, sterols, tocopherols, tocotrienols, lignans and phytic acid. However, whole meal products are not always in the market, because of the lack of palatable taste and appealing mouth feel. With LAB sourdough processes the mouth feel and palatability of whole meal cereals can be improved without removing any nutritionally important components. Sourdough fermentation also improves texture and flavour of bran-rich products (19).

The changes during LAB sourdough fermentation in cereal products potentially leading to improved nutritional quality are numerous. These are including acid production, suggested to retard starch digestibility and to adjust pH to a range which favours the action of certain endogenous

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enzymes, thus changing the bioavailability pattern of minerals and bioactive compounds. This is especially beneficial in rich bran products to deliver minerals and potentially protective compounds in the blood system.

The action of enzymes during LAB sourdough fermentation also causes hydrolysis and solubilisation of grain macromolecules, such as proteins and cell wall polysaccharides. This changes product structure, which may affect nutrient and non-nutrient absorption. New bioactive compounds, such as prebiotic exopolysaccharides or other metabolites, may also be formed in cereal fermentations by LAB sourdough (10, 20).

Recently the potential of sourdough LAB to release lunasin as an anti-tumour peptide during fermentation of cereal and nonconventional flours was investigated by (21). The peptidase activities of a large number of sourdough LAB were analyzed using synthetic substrates. Selected probiotic LAB were used as sourdough starters to ferment whole meal wheat, soybean, barley, amaranth, and rye flours. Proteinase activity during sourdough fermentation was characterized and after fermentation, lunasin from the water-soluble extracts was quantified and purified. Compared to control doughs, the concentration of lunasin increased up to 2–4 times during sourdough fermentation. Lactobacillus curvatus SAL33 and Lactobacillus brevis AM7 synthesized the highest concentrations of lunasin in all the flours. Besides the presence of the entire lunasin sequence, fragments containing the immunoreactive epitope were also determined. This study showed that fermentation by sourdough LAB increased the concentration of lunasin to levels that would suggest new possibilities for the biological synthesis and for the formulation of functional foods.

Dietary interventions for preventing cancer have recently attracted increased attention from researchers and clinicians. The probiotic microorganisms have emerged as potential therapeutic agents but are also regarded as healthy dietary supplements for functional and health applications. The metabolome of probiotic may interfere with various cellular and molecular processes, including the onset and progression of colon cancer. The metabolites of probiotic bacteria may lead to the modulation of diverse cellular signal transduction and metabolic pathways. The gut microbial metabolites such as organic acids, bacteriocins and other peptides have been noted to interact with multiple key targets in various metabolic pathways that regulate cellular proliferation,

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Progress in this field suggests that epigenetic alterations will be widely used in the near future to cancer prevention and treatment (22). Fiber-rich sourdough fermentation usually consists of synbiotic combinations of probiotic lactobacilli starters and prebiotic dietary fibers. The precise mechanisms by which this synbiotic effect may inhibit cancer might include alteration of the metabolic activities of intestinal microflora and physicochemical conditions in the colon, binding and degrading potential carcinogens, alterations in the intestinal microflora incriminated in producing putative carcinogens and promoters production of anti-tumourigenic or anti-mutagenic compounds, enhancing the host's immune response and effects on physiology of the host. The mechanisms of these abilities have been discussed briefly in next paragraphs

Main Mechanisms by Which Synbiotic Fermentation May Inhibit Cancer

Considering the increasing incidence of cancer disease, the last decade has seen much attention directed towards understanding possible prevention and treatment strategies. Efforts to study the intestinal microbiota and its interaction with the host have underlined that disbiosis in colonic microbial composition is a risk factor for colon cancer. Modulation of the composition of intestinal microorganisms through the use of probiotic, prebiotic and synbiotic products could therefore represent a strategy for prevention of cancer development. Wide spectrum impact of probiotic bacteria and prebiotic compounds on the host health has been proved. These microorganisms have been confirmed to boost immunity, aid in digestion, eliminate pathogens, inflammatory bowel diseases, moderate side effects of antibiotic therapy, lower cholesterol and blood glycemic index and produce vitamins. Researchers are in universal agreement with the critical role of probiotic LAB in getting rid of mutagens, delaying the onset of tumors, alleviating the side effects, pepping up chemotherapy, easing the postoperative complications, foiling remission and lifting the spirit of survivors (23). anti-mutagenic ingredients and short chain fatty acids, binding of mutagens, suppression of bacteria that convert pro-carcinogens into carcinogens, immune system stimulation, elevating the hosts' immune response and altering the hosts' physiology and reduction in level certain intestinal bacterial enzymes that promote carcinogen formation (24, 25).

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The reported anti-cancer mechanisms of probiotic bacteria encompass intraluminal, systemic, and direct effects on intestinal mucosa. Intraluminal effects include competitive exclusion of pathogenic intestinal microflora, alteration of intestinal microbial enzyme activity, reduction of carcinogenic secondary bile acids, binding of carcinogens and mutagens, and increasing short chain fatty acids production. Reduction of DNA damage and suppression of aberrant crypt foci formation have been well demonstrated as direct anti-cancer effects of probiotic microorganisms on intestinal mucosa. Existing evidence clearly support a multifaceted immuno modulatory role of probiotic LAB in cancer, particularly its ability to modulate intestinal inflammation, a well known risk factor for cancer. The effectiveness of probiotic bacteria in cancer prevention is dependent on the strain of the microorganism, while as indicated by several studies, viability may not be a prerequisite for certain probiotic anticancer mechanisms. Emerging data suggest synbiotic as a more effective approach than either prebiotic microorganisms or probiotic compounds alone. More in vivo especially human studies are warranted to further elucidate and confirm the potential role of viable and non-viable probiotics, prebiotics and synbiotics in cancer prevention (26).

Probiotic LAB appear to have three general ways to fight cancer. First, certain strains of probiotics can eliminate substrates that can be turned into carcinogens and promote the development of cancer. Such a substance is called a pro-carcinogen and an example of pro-carcinogen is nitrite that is unstable compound or ion. Probiotics in the intestinal tract convert pro-carcinogens like nitrites into neutral ingredients. *Lactobacillus acidophilu*s is an example of a probiotic strain that can neutralize these problem substrates in our body. Other species may also have this ability. Second, probiotic LAB can stop enzymes which help turn pro carcinogens into carcinogens. These enzymes are secreted by undesirable bacteria, such as *Clostridium* and *Bacteriodes*, which are normally found in our gut and particularly live in our lower intestine. With fewer enzymes to create cancer-causing chemicals, the body is less likely to develop cancer disease. *Lactobacillus acidophilus* is particularly effective at neutralizing harmful enzymes that promote cancer expansion. This may be the most important contribution of probiotic LAB to cancer prevention .The third way probiotic bacteria appear to have anti-cancer effects in the body is less direct. . We already know there is a positive interaction between probiotic LAB and our immune system. Probiotic bacteria support and stimulate the immune system in many positive ways. However, probiotic LAB also help the immune system by lightening its load. Probiotic bacteria promote a healthy intestinal lining. This reduces the ability of undesirable microorganisms that we eat from entering into our bloodstream.

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With fewer undesirable microbes in our blood that our immune system has to trap and eliminate, the less work it has to do. Thus, our immune system can focus on its main role and helping cells that are damaged and prevent these cells from becoming cancer. In general, healthy colonies of probiotic bacteria in the intestinal tract can support the immune system, leaving it more energy and resources to focus on cancer prevention. Probiotic LAB by their properties may help strengthen homeostasis and thus reduce side effects associated with cancer treatment. Experimental evidence suggests that probiotic microorganisms might have also beneficial effect on the toxicity of anticancer therapy (27).

The relationship between cancer, diet, and gut microflora is very complex. The substrates entering the colon from the ileum and the resident microbiota represent key determinants of colon physiology. The ability of the colonic microorganisms to generate a wide variety of mutagens, carcinogens and tumor promoters from dietary precursors is well documented. A major role for the intestinal bacteria has been identified in the metabolism of some bile acids, which are thought to possess tumor-promoting activity. Other potential tumor-promoters are also generated by deamination of some amino acids by these bacteria (28).

There are a large number of reports describing the adsorption or binding in vitro by probiotic LAB and other intestinal bacteria, of a variety of food-borne carcinogens including the heterocyclic amines formed during cooking of food, Aflatoxin B1, benzopyrene and some food contaminants. In several of these researches, a concomitant decrease in mutagenicity was reported. The extent of the binding was dependent on the mutagen and bacterial strain used usually greatest binding was seen with the heterocyclic amines and least with Aflatoxin B1.

The adsorption appeared to be a physical phenomenon, but binding represents a plausible mechanism for the inhibition of genotoxicity and mutagenicity by probiotic LAB in vitro, it does not appear to have any influence in vivo (29).
In general, species of Bifidobacterium and Lactobacillus, have low activities of enzymes involved in carcinogen formation and metabolism by comparison to other major anaerobe bacteria in the gut such as bacteroides, eubacteria and clostridia.
This suggests that increasing the proportion of probiotic LAB in the gut could modify, beneficially, the levels of xenobiotic metabolizing enzymes. Studies have been carried out in laboratory organisms in order to acquire a greater understanding of the way in which administration of specific probiotic bacteria and prebiotic compounds affect gut microbiota metabolism (30)

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Studies demonstrate that the increase in concentration of probiotic LAB as a consequence of consumption of these bacteria leads to decreases in certain bacterial enzymes purported to be involved in synthesis or activation of carcinogens, genotoxins and tumor promoters. This would appear to be due to the low specific activity of these enzymes in probiotic LAB. Such changes in enzyme activity or metabolite concentration have been suggested to be responsible for the decreased level of preneoplastic lesions or tumors seen in carcinogen-treated rats given probiotic bacteria and prebiotic ingredient. Although a causal link has not been demonstrated, this remains a plausible hypothesis. There is considerable focus currently on synbiotics, the theory being that, the metabolites of the fermentation of the prebiotic compounds by the probiotic bacteria will have anti-cancer activity. Anti-inflammatory effects have been also reported for some probiotic LAB. For example, Borruel et al. (33) observed decreases in cancer cells in human ileal specimens obtained from patients with Crohn’s disease and treated ex vivo with *Lactobacillus casei* DN114001 and *Lactobacillus bulgaricus* LB10. The establishment of oral tolerance within the host in the long term may mean that modulation of host immunity is a temporary event, confined to early intake of probiotic bacteria.

However, in the rat the inhibition of carcinogenesis correlates with changes to immune activity in response to consumption of probiotic LAB (34). Further work is needed to assess the long term effects of probiotic microorganisms on host immunity in relation to anti-carcinogenesis. The human probiotic Propionibacterium freudenreichii kills colorectal adenocarcinoma cells through apoptosis in vitro via its metabolites, the short chain fatty acids (SCFA). In general, the precise mechanisms, the kinetics of cellular events and the impact of environmental factors such as pH remained to be specified. Investigations demonstrate a major impact of a shift in extracellular pH on the mode of propionibacterial SCFA-induced cell death of cancer cells, in the pH range 5.5 to 7.5 prevailing within the colon. Propionibacterial SCFA triggered apoptosis in the pH range 6.0 to 7.5, a lethal process lasting more than 96 h. Indeed at pH 7.5, SCFA induced cell cycle, followed by a sequence of cellular events characteristic of apoptosis. By contrast, at pH 5.5, the same SCFA triggered a more rapid and drastic lethal process in less than 24 h. This was characterised by sudden mitochondrial depolarisation, inner membrane permeabilisation and drastic depletion in ATP levels, suggesting death by necrosis. Thus, in digestive cancer prophylaxis, the observed pH-mediated switch between apoptosis and necrosis has to be taken into account in strategies involving SCFA production

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by propionibacteria to kill colon cancer cells (35).

The most recent data generated by studies in clinical trials on the role of probiotic LAB in preventing colorectal cancer and the mechanisms proposed have been reviewed (36). Reduction of colonic carcinogenesis has been attributed to controlling colorectal neoplastic progression via an increased proportion of probiotic bacteria with proinflammatory characteristics. Studies in humans have examined the effect of oral administration of yogurt supplemented with probiotic LAB on intestinal microbiota associated with colorectal cancer. A significant decrease in these cells was reported in the probiotic treatment group but not in the milk control group, implying the potential of probiotic bacteria for eliminating microorganisms associated with colorectal An intervention study undertaken in the pouches of patients with familial adenomatous polyposis showed decreased cell proliferation and increased detoxification capacity after treatment with probiotic LAB and prebiotics such as inulin. This mechanism and others were demonstrated experimentally in animals using a rat colon cancer model to examine DNA damage and colorectal tumorigenesis. In the future, with growing understanding of the human microbiome, probiotic LAB may serve as chemoprotective agents for the prevention of cancer.

However, more clinical trials in humans are needed to assess probiotics protective effect. A number of studies have been carried out on the effects of probiotics, prebiotics and synbiotics on human subjects which have included measurement of bacterial enzyme activities. Effects in human researches of prebiotic LAB and synbiotics on toxic bacterial metabolites in feces are few and generally have yielded inconsistent or negative results. More direct evidence for protective properties of probiotic bacteria and prebiotic ingredients against cancer has been obtained by assessing the ability of cultures to prevent DNA damage and mutations as an early event in the process of carcinogenesis in cell cultures or in organisms. Using the technique of single cell microgel electrophoresis, (37) investigated the ability of a range of species of probiotic LAB to inhibit DNA damage in the colon. mucosa of rats treated with the carcinogens. Klinder et al. (38) also showed that prebiotic and synbiotic supplementation (8 months) caused a reduction in the genotoxicity of fecal and cecal samples obtained from azoxymethane. Rafter et al. (39) evaluated the influence of 12 weeks synbiotic supplementation of probiotic *Lactobacillus rhamnosus* GG and probiotic *Bifidobacterium lactis* Bb12 with a commercial fructan as a prebiotic compound on selected cancer biomarkers in polypectomized and cancer patients.

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Synbiotic supplementation resulted in significant reductions in DNA damage in the colonic mucosa of polyp patients. The above results provide evidence that both probiotic LAB and prebiotics may have protective effects against the early stages of colon cancer. There are fewer reports on prebiotic and synbiotics than on probiotics in terms of tumor incidence but overall the studies indicate protective effects.

Jacobson et al (40) compared the incidence of tumors in challenged rats following consumption of FOS or inulin as prebiotics. Significantly less rats developed colon tumors in the FOS group compared to the control diet. The total number of tumors developed per rat was significantly reduced following both prebiotic FOS and inulin supplementation, but supplementation had no effect on the malignancy of the tumors. Femia et al. (41) investigated the protective effects of prebiotic ingredients, probiotic *Bifidobacterium lactis* Bb12 and *Lactobacillus rhamnosus* GG, or synbiotic combination of the two, against induced colon tumors in rats. Prebiotic and synbiotic fed groups resulted in lower adenoma and adenocarcinoma incidence than in the rats not given prebiotic (probiotic and control). Prebiotic and synbiotic groups had in fact nine cancers over 84 tumors (11%), while controls and probiotic groups had 19 cancers over 83 tumors (23%). the number of rats with induced colon tumors, as well as the number of tumors per rat. Amer et al., isolated novel lactobacilli probiotic strains from human feces and screen them for the presence of two valuable antitumor genes for future potential therapeutic application in cancer prevention. (42). Prevention of febrile neutropenia by probiotic *Enterococcus faecium* M-74 enriched with selenium in leukemic patients was also studied by Mego et al., (43). Febrile neutropenia remains a potentially life-threatening complication of anticancer chemotherapy.

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Bacterial translocation via intestinal mucosa is a significant mechanism of febrile neutropenia development. Competitive inhibition of bowel colonization by pathogenic microorganisms by probiotic LAB could be a useful prevention of febrile neutropenia. Results demonstrated the safety of the probiotic strain *Enterococcus faecium* M-74 enriched with selenium in leukemic patients with severe neutropenia. However, its administration was not effective in the prevention of febrile neutropenia, but this does not preclude the protective effect of other probiotic bacteria. An open pilot study carried out by Boutron-Ruault et al. (44) evaluated the influence of short -chain fructo-oligosaccharides on parameters that are indicative of colon cancer in adenoma and adenoma free patients. Interestingly, butyrate concentrations were lower in the adenoma patients compared to the adenoma free patients, although FOS supplementation significantly elevated the butyrate concentrations in ademona patients. Supplementation in adenoma free patients decreased the fecal lithocholic acid whilst cholic acid, ursodeoxycholic acid and total bile acids were all significantly increased. The lack of significant effects in adenoma patients would indicate that FOS supplementation may have a role in the prevention of cancer in healthy humans. New options are given through the genetic manipulation of probiotic LAB, designed to act as a delivery system for anti-cancer factors. Studies in vitro systems and in a wide range of animal models also provide considerable evidence that probiotic bacteria, prebiotic ingredients and synbiotics exert anti-cancer effects. Their consumption may be beneficial in preventing the onset of cancer, but also in the treatment of existing tumors. However, evidence from human studies is still limited. Many researchers have pointed out the need for carefully designed human clinical trials. Furthermore, research is required to identify the probiotics, prebiotics or synbiotics combination that will be more effective for humans.

Conclusion:

Fiber-rich sourdough fermentation usually consists of synbiotic combinations of probiotic lactobacilli starters and prebiotic dietary fibers. Recently the potential of sourdough LAB to release anti-tumour peptide during fermentation of cereal and nonconventional flours was confirmed. Furthermore, new bioactive compounds such as prebiotic oligosaccharides or other metabolites can be formed in cereal fermentations by sourdough. It is clear that probiotic, prebiotic and synbiotics hold great potential as a new strategy for the prevention and treatment of cancer. Fiber-rich sourdough fermentation as future food with ancient history, harboring synbiotic potentials for using as anti-cancer, too.

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