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The Administration of Probiotics and Fermented Products Containing Lactic Acid Bacteria Exert Beneficial Effects Against Intestinal and Non-Intestinal Cancers

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Abstract

Probiotic microorganisms and fermented foods containing lactic acid bacteria have been growing in popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers.

There are many reports about the anticarcinogenic effect of probiotic strains and fermented products against intestinal and non intestinal tumors. Different mechanisms of action can be involved in these beneficial effects, being the modulation of the host's immunity one of the most important properties reported using in vitro assays and also in animal models. However, there are few human trials in which the application of probiotics as biotherapeutics against cancer were tested. These assays are very important before the medical community can accept the addition of probiotic or fermented milks as supplements for cancer patients.

This review summarizes some of the relevant research with probiotics and fermented products containing lactic acid bacteria in cancer prevention and / or treatment with emphasis on the possible mechanisms involved. Colon cancer is one of the types of cancer for which there are more researches and will be discussed separately from the non intestinal tumours.

Keywords: Colon cancer; Non-intestinal tumors; Probiotics; Fermented milk; Anti-tumor mechanisms

Introduction

The population tends to consume foods that in addition to their nutritional values can offer some additional benefits to their health.

Lactic acid bacteria (LAB) represent a heterogeneous group of microorganisms that are present in the normal diet of many people and also in the gastrointestinal and urogenital tract of animals, and some of these claimed to be probiotics. Probiotic microorganisms and fermented foods containing LAB were growing in their popularity due to increasing numbers of studies proving that certain strains present health promoting properties, among them the prevention or treatment in the early stages of some types of cancers [1,2].

It is know that many factors can be involved in the development of cancer such as some genetic, environmental and dietary factors. It is also important to considerer that probiotic characteristics are strain dependent meaning that a strain with effects against a type of cancer will not necessarily exert a beneficial effect against another types of tumour.

The use of experimental animal models has a number of advantages in that the environmental conditions and genetics can be either controlled or defined. The value of the models is the insight they can provide into the complex, multi faceted processes and mechanisms that can result in cancer development. In vitro assays are also important to understand the mechanisms of action involved in the LAB effects. However, the application of probiotics as a biotherapeutic against cancer needs to be ultimately tested in human trials.

This review summarizes some of the relevant researches about probiotics and fermented products containing LAB in cancer prevention and/or treatment with emphasis in the possible mechanisms involved. Colon cancer is one of the types of cancers for which there have been more studies performed in this area and will be discussed separately from the non intestinal tumours.

Effects in Colon Cancer Prevention and Treatment

Colorectal cancer (CRC) is one of the most common cancers worldwide, being its incidence rates higher in the Western world. The effects of probiotics and fermented products on intestinal disorders have been the most extensively studied considering that these microorganisms enter the organism orally and can positively modulate the intestinal microbiota involved in many of these disorders. The benefits of probiotics on the gut immune system in the prevention of cancer has also been previously described [3-5].

There are many different mechanisms by which probiotics and fermented products containing viable LAB may lower the risk of colon cancer; among them, the modulation of the intestinal microbiota, the inactivation of carcinogenic compounds, anti-oxidant effects and the modulations of the host's immune response.

Modulation of the Gut Microbiota

The gut microbiota plays an important function in the balance between health and disease [6]. In this sense, there are differences in the gut microbiota of healthy hosts and those suffering some intestinal pathologies. For example, the stool of CRC patients showed increased *Bacteroides–Prevotella* populations compared to healthy controls [7]. This article also demonstrated that changes in the composition of the microbiota of colon cancer patients can impact on themucosal immune response. Marchesi et al. also reported that the phylogenetic core of human microbiota was significantly different in the stools of patients with CRC compared to those of individuals with normal colonoscopy [8].

All these results suggest that modifications in the gut microbiota

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have an important role in the development and/or maintenance of colorectal carcinogenesis. Considering this fact, probiotics can be used as a tool to modify the altered microbiota and restore its balance, which could be related with their anti-carcinogenic effects.

Probiotics can modify the intestinal microbiota and as result of this action by reducing the level of certain enzymes such as β-glucuronidase, nitroreductase, among others, which convert pro-carcinogens to carcinogens in the intestine [9-11]. The products of these enzymatic reactions are known to be mutagenic and carcinogenic and their activities were correlated with the number of certain bacteria in the intestine. The consumption of *Lactobacillus* (*L.*) *acidophilus* in experimental animal models reduced the activity of fecal enzymes such as β-glucuronidase, azoreductase and nitroreductase [12,13]. Goldin and Gorbach studied the effect of feeding two *L. acidophilus* strains on the activity of these bacterial enzymes in 21 healthy volunteers [11]. It was also demonstrated using an induced colon cancer model in mice that animals injected with DMH and fed cyclically with yogurt presented lower enzyme activity levels in the intestinal content than the tumor control group, which increased the activity of these microbial enzymes contributing in this way to the cancer development [14]. Probiotics *L. rhamnosus* GG and *L. acidophilus* suppresse DMH-induced pro-carcinogenic fecal enzymes and pre-neoplastic aberrant crypt foci in early colon carcinogenesis in Sprague Dawley rat [15].

Modifications in the gut microbiota can also be related with change in the presence of short chain fat acids (SCFA) produced by bacterial fermentation of undigested carbohydrates. It was reported that the different incidences of CRC between certain populations could be related to the diet. Studies provided by O'Keefe et al. demonstrated that high dietary intakes of animal products may alter the gut microbiota and therefore play a key role in carcinogenesis of African Americans [16]. It was also reported that microbe-derived SCFAs (such as butyrate) regulate host gene expression involved in intestinal homeostasis as well as carcinogenesis through modulation of microRNAs [17]. Butyrate was also associated with induction of differentiation, suppression of proliferation, and enhanced apoptosis *in vitro* [18].

Using animal models, it was demonstrated that the probiotic mixture VSL#3 was able to convert linoleic acid into conjugated linoleic acid (CLA) inducing the up-regulation of PPARγ, a reduction in colonic tumor cells viability, and the induction of apoptosis [19]. The symbiotic combination of resistant starch (RS) and *Bifidobacterium* (*B.*) *lactis* significantly protected against the development of CRC in a rat model, which was in part due to an increase in the SCFA by RS intake [20].

These studies showed that one of the possible mechanisms by which probiotics can prevent CRC is by fermentation of indigestible food; however, further investigations are needed.

Inactivation of Cancerogenic Compounds

A meta-analysis of 15 prospective studies showed an increase in the relative risk of developing CRC for the people with a higher consumption of red meat, compared to people who eat red meat in lower quantities [21]. Among the hypotheses proposed to explain this relationship are the presence of heterocyclic aromatic amines (HCA), resulting from cooking meat at high temperatures [22,23]. LAB and other commensal bacteria can bind or metabolize several carcinogens, including HCA and N-nitrous compounds, which was correlated with the reduction in mutagenicity observed after exposure of HCA to the bacterial strains [24]. Sreekumar and Hosono demonstrated that strains of *L. gasseri* and *B. longum* strongly bound 3-amino-1,4-dimethyl-5H-pyrido-[4,3-b]índole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido[4,3-b]indoleTrp-P-2 [25,26]. Mice given *L. acidophilus* NCFB1748 and *B. longum* BB536 decreased the bioavailability of Trp-P-2 in their gastrointestinal tracts and other tissues [27]. It was also reported that cell fractions of *L. acidophilus* and *Bifidobacterium* spp. bond Trp-P-1 and decreased its genotoxicity [28].

All these results show that the detoxification of cooked food mutagenic compounds, especially from the Western meat-rich diet, may be another of the main mechanisms by which LAB prevent CRC.

Improvement of the Host's Immune Response

There are several studies using animal models that suggest that probiotics have potential to prevent CRC by modulation of the host's immune system, especially the cellular immune response. *L. casei* strain Shirota (LcS) has been demonstrated to have beneficial effects in carcinogenesis animal models, via host immune modulation [29]. A possible mechanism of carcinogenesis prevention is the proliferation and activation of NK and T-cells [30]. Lee et al. reported that the administration of *L. acidophilus* SNUL, *L. casei* YIT9029 and *B. longum* HY8001 increased the survival rate of mice injected with tumor cells, which was correlated with an increase in cellular immunity (total T cells, natural killer (NK) cells and Major histocompatobility complex (MHC) class II$^+$ cells, and CD4$^-$CD8$^+$ T cells) [31].

Yoghurt feeding inhibited tumor growth in a CRC model in mice. The administration of yogurt to DMH injected mice resulted in an increase in the number of IgA secreting cells and CD4+ T lymphocytes in the lamina propria of the large intestine together with a decrease in the IgG + and CD8+ cells [32]. The increase in the number of IgA secreting cells, but not of IgG + cells, in the large intestine of the mice fed with yogurt could limit the inflammatory response, since IgA is considered as an important barrier in colonic neoplasia [33]. The analysis of cytokines suggested that yogurt feeding could modulate the immune response by stimulating cytokine production when this was required; or inducing down-regulation of the immune cells to avoid an exacerbated immune response. This effect would occur mainly through the regulatory cytokine IL-10, which was increased in the tissue of the mice given yoghurt during all the assayed periods [34,35].

Considering the host immunity, it is also important to note that chronic inflammation was associated with several malignant diseases [36], and this relationship would be mediated by cytokines [37] or by reactive oxygen species generated by inflammatory phagocytes that can cause injury to target cells, thus contributing to cancer development [38]. It is known that patients with persistent ulcerative colitis have a 5 to 7 times greater incidence rate of colon cancer development [39]. In this sense, probiotics that exert beneficial effects on inflammatory bowel disease (IBD) models could also exert a preventive effect against CRC.

Pretreatment with the probiotic VSL#3 attenuated various inflammatory-associated parameters, delaying transition to dysplasia and cancer, offering a potential therapeutic use in patients with long-standing colitis [40]. A comparative study between yoghurt consumption (before and after DMH injection) and indomethacin treatment was carried out in a DMH induced CRC model in mice.

Mice treated with indomethacin showed that the immune cells infiltrating into the large intestine were fewer than the same observed with yogurt feeding where a great increase in the number of immune cells infiltrating the lamina propria was observed [35]. It was also observed that indomethacin treatment maintained the effects until the administration was stopped due to cachexia produced in the animals; after that, the tumor developed with the same characteristics as in the control without treatment. However, when the yogurt feeding was stopped at the end of the experiment (6 months), the animals were observed over a 9-month period and did not develop tumors. The same model of DMH-induced CRC was used to find out at which stage of the tumor process yogurt acted (initiation, promotion or progression of tumor growth). The results obtained showed that yogurt feeding for 10 days previous to DMH injections was not enough to inhibit the tumor in the initiation stage and only delayed tumor appearance [35]. Unlike this, mice that did not receive yogurt previous to DMH injection but were fed cyclically with yoghurt after tumor induction did not develop tumor demonstrating that yogurt exerted its antitumor activity by the inhibition of tumor progression and that this effect was achieved by long-term cyclical yogurt consumption.

Anti-Oxidant Effects

Oxidative stress and epithelial damage are normally linked to pathologies of the gastrointestinal tract such as IBD, so another mechanism by which LAB could prevent certain types of cancer is through the production of antioxidant enzymes that can degrade reactive oxygen species (ROS) or impair their formation. The normal intestinal mucosa is equipped with a network of antioxidant enzymes that neutralize ROS. However, the levels of these enzymes in IBD patients are frequently depleted [41,42], highlighting the potential for increasing the local levels of these enzymes to function as a therapeutic.

Since the majority of LAB are not well equipped with enzymes to detoxify oxygen derived compounds, genes coding for antioxidant enzymes (such as catalases or superoxide dismutase, SOD) were inserted in LAB as an anti-inflammatory strategy. Rochat et al. introduced the *B. subtilis* heme catalase *KatE* gene into *Lactococcus* (*Lc.*) *lactis* obtaining a strain capable of producing active catalase that can provide efficient antioxidant activity [43]. This genetically modified strain was evaluated in an experimental DMH-induced colon cancer model and its capacity to prevent tumor appearance was demonstrated [44]. The catalase producing *Lc. lactis* strain used in this study was able to slightly increase catalase activity in the intestines of mice treated with DMH; however, it was sufficient to reduce H_2O_2 levels in the large intestines.

Other LAB strain genetically modified to produce anti-oxidant enzymes showed their anti-inflammatory properties using IBD models in mice [45] and have a potential to be tested in CRC models.

Other Mechanisms Involved in the Antitumor Effect of LAB and Yogurt in CRC Models

Anti-proliferative effects via regulation of apoptosis and cell differentiation is another mechanism that can be involved in the antitumoral effect of probiotic LAB. In many types of cancer, a reduction in the ability to trigger apoptosis is an important pathogenetic event [46].

Apoptosis induction and the relationship between mitosis and apoptosis were studied in a model of DMH induced CRC in mice that received yogurt administration. An increase in mitosis during the first 4 weeks of tumor growth was observed in the animals treated with the carcinogen DMH. Mice that received yoghurt showed a moderate cell proliferation with a significant increase in the number of apoptotic cells [47]. In another work, the symbiotic combination of resistant starch and *B. lactis* exerted a pro-apoptotic action in response to the carcinogen using rodent studies [48].

Effects in the Prevention and/or Treatment of Non-Intestinal Tumours

The oral administration of certain substances such as probiotic microorganisms can influence mucosal sites different to the intestine due to the existence of the common mucosal immune system. In this sense, after intestinal stimulation, both B and T cells can migrate from Peyer's patches to mucosal membranes of the respiratory, gastrointestinal and genito-urinary tract, as well as to exocrine glands such as the lacrimal, salivary, mammary and prostatic glands [49].

The effects of probiotic LAB were reported for non-intestinal tumors. *L. casei* CRL 431 is a probiotic strain with several studies showing its modulator effects on the mucosal immune system. The oral administration of *L. casei* CRL 431 to mice induced an immune stimulation not only at the intestinal level, but also in bronchus and mammary glands [50]. The antitumor activity of *L. casei* CRL 431 was studied against a fibrosarcoma induced by methylcholantrene in mice. The administration of the probiotic strain inhibited tumor growth in a dose-dependent form [51,52], stimulated the immune system with high levels of macrophage activation (the main infiltrative cells in the tumor), high levels of TNFα and with a remarkable decrease in tumor volume.

In addition to containing LAB, fermented milks can possess non-bacterial components produced during fermentation that may contribute to their immunogenicity and to properties such as their anti-tumor activities [53]. Thus, cultured dairy products were proposed to inhibit the growth of many types of cancers, including breast tumors.

Table 1 summarizes the effect of LAB or fermented products containing these microorganisms in non-intestinal tumours reported during the last three years (2011-2013). Results were obtained searching the words "probiotc and cancer" in PubMed database. Results about colon cancer were not added because the table refers to non-intestinal tumours; however they were discussed with more details previously in this review. The relationship between LAB administration and breast cancer will be discussed in the next paragraphs, and were not included in Table 1.

Breast cancer is another type of tumour in which there are reports about the beneficial effects of probiotic administration. Breast cancer is the second cause of death in women after lung and bronchus pathologies, and more than 200,000 new cases of invasive breast cancer were expected to occur in the United States during 2013 [54]. It is known that there is a relationship between nutrition and certain types of cancers [55,56]. There are also reports that relate certain diets with lower risks of breast cancer. Soya based products and especially soy isoflavones were analyzed because they can bind and compete with estrogens to the estrogen receptors, in particular to the beta-subtype, in target organs such as breast [57-59]. There are other works in which soy isoflavone ingestion was studied accompanied with the co-administration of probiotic bacteria, and it was observed that high

Table 1: Examples of non-intestinal cancer (animal models, in vitro assays and some human trial) that have demonstrated that LAB exert beneficial effects.

Disease	Results	LAB	Ref.
Cervical cancer	Women with an HPV+low-grade squamous intraepithelial lesion diagnosis in their PAP smear that received daily a probiotic drink had a twice as high chance of clearance of cytological abnormalities. Pilot study that suggested that probiotic promotes the clearance of HPV-related cytological abnormalities.	NE	[73]
Cervical cancer	Common vaginal lactobacilli exerted cytotoxic effects on cervical tumour cells, but not on normal cells, and this cytotoxicity was independent of pH and lactate.	Vaginal lactobacilli	[74]
Cervical cancer	Non-genetically modified lactic acid bacteria displaying E7 antigen at their surface protected mice against human papillomavirus type 16-induced tumors	*Lc. lactis* and *L. casei* displaying E7 antigen	[75]
Ductal carcinoma	Daily intake of *L. casei* improved the immune responses in mice bearing invasive ductal carcinoma. LAB administration significantly increased the production of IL-12 and IFN-γ and increased the NK cytotoxicity in spleen cells culture of mice.	*L. casei* ssp *casei*	[76]
Head and neck cancer	Oral nutritional supplement enriched with omega-3 fatty acids, micronutrients, and probiotics improved body weigh as well as serum albumin and pre-albumin levels in patients with head and neck cancer cachexia.	NE	[77]
Hepatocellular carcinoma	The administration of probiotic fermented milk and chlorophyllin reduced pre-carcinogenic events in AFB1 induced liver carcinogenesis in rats, and this effect could be attributed to an increased antioxidant status and decreased expression of oncogenes.	*L. rhamnosus* GG *L. casei* strain Shirota	[78,79]
Oral cancer	Oral administration of probiotic LAB or its secretions suppressed 4NQO-induced oral carcinogenesis in rats. Probiotic administration significantly decreased the expression of proliferating cell nuclear antigen and induced apoptosis in a dose-dependent manner.	*L. salivarius* REN	[80]
Skin carcinogenesis	The administration of maesil (a member of the genus *Rosaceae*) fermented with probiotics suppressed the development of DMBA-TPA induced skin carcinogenesis in mouse, enhancing total antioxidant capacity and phase II detoxifying enzyme.	*L. acidophilus* KCTC 3155	[81]

*Microbial abbreviations: *L.* (*Lactobacillus)*; *Lc.* (*Lactococcus);* NE = not specified

concentrations of probiotics may alter the metabolism of isoflavones [60].

Biffi et al. studied *in vitro* milks fermented by different LAB strains (*B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei*) and reported the inhibition of the growth of a breast cancer cell line [61]. Other studies performed in humans, by Le et al., showed a negative association between yogurt consumption and breast cancer development [62]. van't Veer et al. showed similar results in The Netherlands, suggesting that these effects would be related to changes in the intestinal microbiota (which could alter the metabolism of estrogen) and to the modulation on the immune system [63].

It was reported that milk fermented by *L. helveticus* R389 (a strain with high proteolytic activity) was able to delay tumour growth in an experimental breast cancer model using BALB/c mice [64,65]. This effect was related to the immunoregulatory capacity of this fermented milk that decreased IL-6 levels, which are very important in oestrogen-dependent tumours, modulating the relationship between immune and endocrine systems. This fermented milk was compared to milk fermented by the proteolytic deficient mutant. The study of the cytokines showed that the consumption of both fermented milks diminished IL-6. The increase of IL-10 in mice fed with milk fermented by *L. helveticus* R389 could explain the important difference between both fermented milks, attributed principally to the components released into the milk after the fermentation with the proteolytic strain, where the regulation of the immune response was observed in serum, mammary gland and also in the tumour infiltrating immune cells.

Kefir was another fermented product also evaluated in a breast cancer model in mice. Kefir and its cell-free fraction (KF) possess several substances that can exert beneficial effects on the immune system and prevent certain types of cancer [66-68]. It was observed that mice receiving 2 days cyclical feeding with whole kefir diminished tumour growth, and the same cyclical feeding with KF showed the most significant delay of the tumour growth [69]. This effect was related principally to a decrease in IL-6. KF caused not only a decrease of this cytokine but also a regulatory response with increased levels of IL-10 in all the samples studied. The results also demonstrated that the most important effect in this tumour model was due to substances released during milk fermentation (and not the microorganisms themselves) [70].

Recently, it was reported that other LAB, *L. acidophilus* isolated from traditional home-made yogurt and also from neonatal stool induced a significant decrease in breast tumour growth pattern using a mouse model [71]. The aadministration of selenium nanoparticle-enriched *L. plantarum* induced an efficient immune response in 4T1 breast cancer bearing mice. This effect was caused by the elevation of the pro-inflammatory cytokines IFN-γ, TNF-α and IL-2 levels and increased NK cell activity [72].

Conclusions

There are many reports about the anticarcinogenic effect of probiotic strains and fermented products that contain these microorganisms against intestinal and non intestinal tumors. Different mechanisms of action can be involved in these beneficial effects, being the modulation of the host's immunity one of the most important mechanisms reported using in vitro assays and also in animal models. However, there are not enough human trials where the application of probiotics as biotherapeutics against cancer was tested. These assays are very important before the medical community can accept the addition of probiotic or fermented milks containing LAB as supplements for cancer patients.

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