www.journalofcancerology.com PERMANYER J Cancerol. 2016;3:105-8

JOURNAL OF CANCEROLOGY REVIEW ARTICLE

The Role of Probiotics in the Prevention of Colorectal Cancer: Literature Review

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ABSTRACT

Colorectal cancer is one of the most common types of cancer worldwide, being the fifth most common cancer in Mexico. Probiotic bacteria are living microorganisms that, when administered in reasonable quantities, provide the host with health benefits. Several studies have shown the effectiveness of probiotics in the prevention of some diseases such as cancer, infections, allergies, irritable bowel syndrome, and other autoimmune diseases. Regarding the prevention of colorectal cancer, several action mechanisms have been proposed, with a highlight on the sequestration mechanism of mutagens by intestinal bacteria, the bacteria growth suppression that converts pro-carcinogens into carcinogens, the reduction of enzymes β-glucuronidase and β-glucosidase, bile acid de-conjugation, as well as the potentiation of the host immune system. (J CANCEROL. 2016;3:105-8)

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Key words: Colon cancer. Dysbiosis. Lifestyle. Microbiota. Probiotics. Rectal cancer.

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Received for publication: 25-11-2015
Accepted for publication: 18-04-2016

INTRODUCTION

Colorectal cancer (CRC) is one of the most common neoplasms after the age of 50 years[1]. Many authors have reported an increase in the incidence of this cancer in adults under the age of 50 years, calling for the implementation of dietary and lifestyle strategies that could help reduce the current incidence rates[2-4].

At a global level, it represents the third type of cancer in incidence rate, with approximately 1.4 million new diagnosed cases, being the second most common type of cancer in women (9.2%) and the third most common type in men (10%)[5]. In Mexico, cancer is a public health issue as it represents the third cause of deaths, with 71,074 deaths in the year 2008 according to the Health Department of Mexico. Regarding its incidence, it shows a significantly upward trend, going from a rate of 0.9 per 100,000 inhabitants in the year 1980 to 3.1 per 100,000 in 2008. Currently, it is ranked fifth in prevalence[6].

RISK FACTORS

The etiology of CRC is complex because it includes genetic factors as well as environmental factors. The first mentioned factors, responsible for 10-15% of all CRC, include some hereditary conditions such as familial polyposis, hereditary colon cancer or not related to polyposis or Lynch syndrome variants I and II and ulcerative colitis[7]. The second include some changeable factors that have to do with the diet and lifestyle of people[8].

Among the dietary factors identified with the development of CRC, the high consumption of red meat and animal-based fat is worth noting[9], while the high consumption of fruits and vegetables is a protective factor[11]. Lifestyle factors, such as a sedentary lifestyle, alcohol intake, and tobacco use, represent an equal risk[8].

One of the aspects recently studied for its possible influence in the tumorigenesis and development of CRC is the intestinal microbiota[12], defined by some authors as a "group of microorganisms that live in harmony, synthesizing vitamins, contributing to the absorption of nutrients, favoring fiber metabolism, improving digestion, and contributing to neutralizing potentially pathogenic substances[13]." Diet has been identified as playing an important part in the development of dysbiosis (imbalance of protective and pathogenic bacteria of the intestine), a condition that can trigger various chronic diseases[14], among them CRC, with differences being identified between the microbiota of healthy individuals and CRC patients. High levels of certain bacterial species have been detected, such as *Bacteroides fragilis, Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus, Peptostreptococcus, Roseburia* and a reduction of *Lachnospiraceae*[15,16].

Probiotics are living microorganisms that, when administered in suitable quantities, provide the host with health benefits, mainly the immunomodulatory type[17]. Recent studies have shown that probiotic supplements have a beneficial effect on certain types of tumors, among them CRC[18], because they have the potential to modulate the intestinal microbiota through different mechanisms[19].

ACTION MECHANISMS

Several mechanisms of action of the probiotics involved in the anti-carcinogenic activity have been identified as follows.

Intestinal microbiota alteration

Glucuronic acid has the ability to conjugate itself with certain endogenous and exogenous substances, forming a reaction catalyzed by UDP-glucuronyltransferase, a group of compounds collectively named glucuronides. The conjugation of these compounds with glucuronic acid is crucial

for hormonal metabolism, also playing an important role in the inactivation of toxins and endogenous and exogenous carcinogenic compounds[20]. Several enzymes produced by some intestinal bacteria are able to de-conjugate glucuronides, such as β-glucuronidase, which causes the release of aglycones, potentially carcinogenic substances. Other enzymes such as azoreductase and nitroreductase also induce the release of carcinogenic substances[21]. The supplementation of some probiotic species like *L. acidophilus* is related to a reduction in the activity of these three enzymes[19].

Inactivation of carcinogenic compounds

Several carcinogenic compounds, such as heterocyclic amines and aflatoxin B1 (AFB1), are sequestrated or absorbed by certain probiotic species, thus reducing mutagenicity[22].

Competition with pathogenic microorganisms

The consumption of certain types of food, among them red meat and animal fats, is related to increases in the bacteria produced by biliary salts, which can be cytotoxic and carcinogenic. Diets rich in animal fat and red meat are related to an overgrowth of sulphate-reducing bacteria that produce hydrogen sulfide, which is deemed genotoxic. Some other pathogenic species, like *Bacteroides spp.* and *Clostridium spp.*, are involved in the CRC pathogenesis. Probiotic supplements increase "beneficial" species, such as *Lactobacillus* and *Bifidobacterium*, and reduce *Clostridium perfringens*, and hence, the amount of coliform bacteria is reduced[19].

Improved immune response

Probiotics play an important role in the control of tumor promotion and progression because they interact with antigen-presenting cells, T lymphocytes, B lymphocytes, and natural killer (NK) cells in addition to strengthening the intestinal barrier. Supplements with various species stimulate natural immune responses, whereas others cause a reduced inflammatory response[23]. *In vitro* studies and studies with humans have demonstrated that *Casei Shirota* lactobacilli increase NK cell activity, while inducing the production of interleukin (IL)-12 by monocytes and macrophages[24].

Antiproliferative activity through apoptosis and cell differentiation

Apoptosis is a strictly regulated cell removal physiological process, characterized by a sequence of stereotyped morphological transformations: cell contraction, chromatin condensation, and nuclear and cellular fragmentation, with the formation of apoptotic bodies that are engulfed by near phagocytes before the membrane integrity is lost. Transformations in the regulation of this process are critical for the development of cancer[25,26]. It has been evidenced that probiotic supplements regulate cell proliferation, while promoting apoptosis by activating the signaling pathway of mitogen-activated protein kinases (MAPK)[19].

Fermentation of non-digestible foods

Colonic fermentation of non-digestible carbon hydrates results in the production of short-chain fatty acids, which have an important role in the maintenance of intestinal health, preserving its morphological and functional characteristics. The fatty acids produced are acetic acid, propionic acid, and butyric acid. Butyrate is an energy substrate for colonocytes. At a molecular level, butyrate acts as an inhibitor of histone deacetylase, regulating cell expression and removing DNA-damaged cells. Propionate and acetate induce apoptosis in human cells with CRC[27]. Probiotics have the ability to produce other fatty acids, called conjugated linoleic acids, which are related to anti-inflammatory and anti-carcinogenic activity[19].

Inhibition of tyrosine kinase signaling pathways

Tyrosine kinase receptors have a great physiological importance, mediating vital functions for the cell such as proliferation and differentiation regulation, survival, and modulation of cell metabolism. Human epidermal growth factor (hEGF) is a protein that belongs to the tyrosine kinase receptor family and is represented by four members (EGFR, HER2, HER3, and HER4), which increases the healing rate of wounds and ulcers in different human body tissues. The increased expression of hEGF and structural abnormalities in its receptor or its ligands are involved in tumor development[28].

It has been reported that the supplementation of *Saccharomyces boulardii* regulates the activity of the hEGF receptor, which prevents the formation of cancer cell colonies, reducing the cell proliferation mediated by hEGF, and increases apoptosis[19].

Intestinal pH reduction

Probiotic bacteria produce lactic acid and other short-chain fatty acids, which reduce the load of pathogens, playing a key role in the intestinal homeostasis and in intestinal pH reduction, thus preventing carcinogenesis[27].

CONCLUSIONS

The use of probiotics in the prevention of CRC has gained much attention in recent years due to the positive results found in studies with humans as well as in molecular studies. Various mechanisms have been identified, with an emphasis on their anti-inflammatory action and improved immune response, in addition to alterations in the bacterial species of the intestinal microbiota. However, further experimental studies are necessary, aimed at an accurate understanding of the mechanisms in the host involved in their anticarcinogenic activity.

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