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Chemopreventive Potential of Probiotics and Prebiotics

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Abstract

Utilization of probiotics and prebiotics in food products and in the diet supplemental form continues to gain interest because of their health benefits. Cancer is the leading cause of death and strategies for chemoprevention are important to reduce mortality and morbidity. Probiotics are gaining attention to use as preventive agents. Efficacy of their use as chemopreventive agents was established through research. This review focused on the mechanisms of prebiotics and probiotics action against cancer. Benefits of probiotics against cancer are attributed to competitive exclusion of pathogenic bacteria, direct physical binding to carcinogens, altering intestinal environment to modulate the production enzymes, antioxidant activity and immune modulation. Prebiotics are indigestible food components that could promote the growth of probiotics. Chemopreventive properties of prebiotics are due to their production of short chain fatty acids and enhancing the immunity of the host. Anticarcinogenic properties of pre- and probiotics result from a combination of events rather from a single event.

Keywords

Prebiotics, Probiotics, Cancer, Microbiota, Oligosaccharides

1. Introduction

Cancer continues to be a major health problem despite of the progress in treatment and prevention. Cancer is one of the leading causes of death in developed countries including the United States. In 2014, there will be an estimated 1,665,540 new cancer cases diagnosed and 585,720 cancer deaths in the United States [1]. In 2013 the World Cancer Research Fund estimated that up to one-third of the cancer cases that would occur in United States that year would be related to overweight or obesity, physical inactivity, and/or poor nutrition, and could be prevented. There are 14.5 million survivors of cancer in US and are expected to reach to 18.1 million by the year 2020

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(ACS, 2014) incurring huge health care costs. The overall costs of cancer in 2009 were $216.6 billion: $86.6 billion for direct medical costs (total of all health expenditures) and $130.0 billion for indirect mortality costs [2]. It is estimated that the best case scenario for cancer medical costs to increase to $157.77 billion with a worst case scenario of costs to exceed $207 billion in 2020 [2].

Functional foods provide health benefits beyond nutrition and are gaining attention and popularity among consumers as demand for such products are increasing at faster pace. Food products fortified with special constituents that possess advantageous physiological effects [3] [4] are marketed with labelled health benefits. Marketing potential for such products has increased because of the health awareness of individuals, willingness to adopt healthy life styles, and need for alternate sources of prevention of chronic diseases.

A very diverse group of microorganisms comprising bacteria, archaea, viruses, and unicellular eukaryotes resides within the gastrointestinal tract. Bacterial concentration in the colon may be as high as 10^{12} cfu/mL in the colon and contribute to 60% of the fecal mass [5]. Among the bacterial population, the two major phyla are gram-positive *Firmicutes* and gram-negative *Bacteroidetes*, with other phyla to a minor concentration as *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Cyanobacteria* in minor proportions [6]. Symbiosis between host and microbes of the gut is evident from the generation of energy from undigested food of host through fermentation for use as a metabolic fuel. In turn, commensal bacteria reduce infections by enteric pathogenic organisms by competing for nutrition and producing bactericidal factors forming a colonization resistance [7]. They assist host immune system regulation, process drug metabolites affecting their pharmacokinetics and adverse effect profile, and importantly synthesize vitamins such as biotin, folic acid, and vitamin K essential for the host [8]. Environmental and genetic factors disrupt the symbiosis by altering microbiota composition, distribution and the metabolic activity which may lead to dysbiosis, a contributing factor for the onset and progression many chronic diseases including cancer. Interindividual differences of micobiota of host are related to both host genetics and environmental factors such as diet, smoking, physical activity, stress, drugs, illness, and antibiotics [9]-[12].

Probiotics is a term defined by a United Nations and World Health Organization Expert Panel as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (FAO/WHO, 2002) [13]. Probiotic organisms used in food must be able to survive passage through the gut; *i.e.*, they must have the ability to resist gastric juices and exposure to bile. Furthermore, they must be able to proliferate and colonize the digestive tract. Possibly the most important is that they must be safe and effective while maintaining their effectiveness and potency for the duration of the shelf-life of the product. Most commonly used microbes in probiotic preparations are *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus*, *Bacillus* and *Streptococcus*. Some fungal strains belonging to *Saccharomyces* have also been used [13]-[16]. *Lactobacillus* is common in fermented milk products, and *Bifidobacteria* and *Streptococcus* are common in cheese and other drinks.

Prebiotics are defined as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon" [17]. At the present time, all prebiotics described are short-chain carbohydrates with a degree of polymerization between two and about sixty, and are thought to be non-digestible by human, or animal digestive enzymes not including bacterial enzymes.

The food industry is utilizing the results of scientific literature and promoting products by making claims suggesting that consuming foods containing prebiotics and probiotics will be beneficial to health. Dairy products fermented with lactic acid bacteria, such as *Bifidobacterium* and *Lactobacillus* strains, sugar fortified with FOS (fructo-oligosaccharides) or inulin, or food supplements containing probiotic bacteria are already on the food market.

2. Probiotics Mechanisms of Action

Colonization of facultative bacteria via disymbiosis is common in disease states, especially cancer. Antibiotics may have been used to reduce the tumor burden in such cases. However, treating with broad-spectrum antibiotics may disrupt the homeostasis of gut biota composition in quantity and quantity of microbes and may lead to increased risk for developing chronic diseases such as obesity, asthma, diabetes, cancer and allergies [18]. Administration of probiotics and prebiotics may offer protection against cancer while maintaining healthy microbiome. Probiotics effect carcinogenesis indirectly or directly at all stages of initiation, promotion and progression. Mixed results have been reported with the consumption of fermented products in offering protection against cancer in epidemiological studies [19] [20].

3. Production of Short Chain Fatty Acids (SCFA)

Probiotics ferment undigested carbohydrate residues preferentially in the proximal colon resulting in high levels of short chain fatty acids (SCFAs) and gases like hydrogen and methane.

Undigested protein residues from the gut are also fermented more distally in the colon and produce branched SCFAs, hydrogen sulfide, ammonia, and several phenolic and indolic compounds [21] [22]. The major SCFAs produced are acetate, propionate, and butyrate. Among these SCFA, butyrate is most abundant and transported to the colonic epithelium for the production of energy [23]. Butyrate is preferred by colonic cells over circulatory glucose or glutamine, to obtain up to a 70% of energy needs. Butyrate is an important tumor suppressant molecule formed during fermentation and exerts selective functions in normal and tumor colon cells [24]-[26]. It promotes growth in normal cells, while inhibiting growth in colon tumor cells by promoting apoptosis and suppressing proliferation. Unlike normal cells, tumor cells utilize glucose as an energy source leading to the accumulation of unmetabolized butyrate. Accumulation of butyrate results in histone acetylation and up regulates cell proliferation, cell differentiation and apoptotic genes [27]. Infusion of butyrate in the distal colon reduced the formation of tumors in azoxymethane induced rats by more than 60% compared to untreated rats [28].

4. Altering Intestinal Environment

Production of SCFAs by probiotics in colon results in acidic environment that is not conducive for the growth of pH-sensitive pathogenic bacteria. Feeding *B. longum* resulted in a significant change for cecal pH and weight in rats [29]. Secondary bile acids and carcinogenic compounds, exert cytotoxic and proliferative effects on colonic epithelium and increase tumor formation. A lower pH or acidic environment in the colon inhibits the enzymatic conversion of primary bile acids to carcinogenic secondary bile acids [30]. Fermented wheat aleurone enriched with the probiotics *Lactobacillus rhamnosus* GG or *Bifidobacterium animalis lactis* reduced deoxycholic acid concentration by more than 84% in *in vitro* [31]. In addition, free calcium in an acidic environment in the presence of probiotics enhanced the binding of free bile acids thereby decreasing their solubility and ultimately the carcinogenic potential [32].

Bacterial enzymes such as *β*-glucuronidase, nitroreductase and azoreductase are involved in the in the process of carcinogenesis by forming carcinogens in the intestinal lumen [33]. Carcinogenic compounds are detoxified in the liver and released into intestine with bile after glucoronic acid conjugation. In the colon, these conjugates are activated or decojugated by pathogenic bacterial *β*-glucuronidase enzyme and regains carcinogenic potential [34]. A high level of fecal *β*-glucuronidase activity was found in colon cancer patients and also in individuals at higher risk for colon cancer [34] [35]. *Lactobacillus* bacteria reduced the activity of *β*-glucuronidase by 76.0% (*Lb. paracasei* 0908) in the fecal water of children, and by 82.0% (*Lb. paracasei* 0919) in the elderly after incubating with 2-amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IQ) [36]. Continuous feeding of probiotics is needed to reduce the activity of harmful enzymes. A reversal in increased enzyme activity was found with a halt in feeding *Lactobacillus* for 10-30 days in 21 healthy volunteers [37].

5. Physical Binding/Inactivation of Mutagenic/Carcinogenic/Genotoxic Compound

A high consumption of red meat is an associated risk factor for cancer development. These associations are mixed within publications but there are known carcinogens (pyrolysis products, mutagens) produced during the processing of meat products; higher consumption rates of these carcinogens have a direct relationship on cancer development. There is a direct relationship with the number of cancer diagnosis as many individuals substitute or reduce the amount of vegetables, fruits, foods with higher fiber content when meat is consumed. Farvid *et al*. (2014) [38] reported that women with lower red meat intake values when compared to those with higher intake values were more likely to have lower body mass index (BMI) values, to have lower energy intake, to be less likely to report smoking. Tavan *et al*. (2002) [39] reported that some carcinogens may be bound to various species of *Lactobacillus* and *Bifidobacterium* and to become inactivated in first steps of colon carcinogenesis. Masood *et al*. (2011) [40] reviews the interaction of milk and fermented milk products on the restriction of initiation of carcinogenesis noting that some organic acids (acetic and butyric, in particular) reduce the mutagenicity of mutagens and promutagens. These organic acids are found in higher concentrations from fermented food products and as they decrease the pH of the system they may reduce the activity of pathogens.

Inactivation of mutagens by binding to probiotics depends on type of mutagen and also the species of probiotic along with the surrounding environment [41]. A comprehensive study conducted by Stidl *et al*., 2008 [42] re-

vealed discrepancies among *Lactobacillus* species in exhibiting detoxification capabilities. Among the tested eight species of *Lactobacillus*, *L. helveticus* and *S. thermophilus* were seven to eight times more effective than *L. kefir* and *L. plantarum* strains in detoxification. The results also found that AAC, heterocyclic amine, was detoxified 3-5 times more efficiently compared to 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) by the bacteria.

Probiotic bacteria also protect against heavy metal induced genotoxicity. Feeding lyophilized probiotic mixture of bacteria (*Lactobacillus rhamnosus*, *L. acidophilus* and *Bifidobacterium longum*) at 5 × 108 cfu/g of food for 5 weeks reduced cadmium induced genotoxicity by 20% in rats [43]. The same study also found that much higher reduction (48%) of genotoxicity by probiotic mixture was observed in *in vitro* hepatocytes. Physical binding of toxins is one of the mechanisms of probiotics in offering protection. Most probiotic cell wall are composed of a thick layer of peptidoglycan, teichoic acid, proteins, polysaccharides and some may secrete exopolysachharides. The carboxyl, hydroxyl and phosphate groups present in these compounds may act as binding sites for toxins and allow them to become inactivated [44] [45].

The ability of probiotics to adhere toxins is site-specific and differs among species [46] [47]. Fractions with glycoproteins from culture free supernatants of *L. plantarum* KLAB21 isolated from Kimchi, a Korean fermented food, exhibited antimutagenic activity against N-methyl-N'-nitro-N-nitrosoguanidine on *Salmonella enterica* serovar *Typhimurium* TA100 cells [48].

6. Immunomodulatory Activity

Inflammation plays an important role in progression of carcinogenesis by promoting cell proliferation and inhibiting apoptosis. Infiltration of macrophages, increased production of cytokines, reactive oxygen species such as nitric oxide, superoxide [49], and elevated conversion of primary to secondary bile acids are seen in bacterial mediated inflammation. Pattern-recognition receptors' (PRRs) have been identified and pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPs) are two groupings where PRRs and probiotics play a major role in immunity. Probiotics influence the immunity of the host by their adhesion, metabolites, and also by cell wall components. They influence both innate and acquired immunity (**Figure 1**). Adhesion of probiotics to gut immune cells may trigger the signal transduction pathway for production of immune response cells. Toll-like-receptor (TLR) signaling is important in innate immunity and effects host microbial composition and functions. TLR was one of the first PRRs identified and was originally found in Drosophila melanogaster [50]. Rachmilewitz *et al*. (2004) [51] evaluated the effects of irradiation and heat treatment on the benefits of probiotics and the TLR system. It was discussed how TLR systems contain specific receptors that recognize and act by different response systems (e.g. TLR2 detects peptidoglycan and lipopeptides, TLR3 recognizes double-stranded RNA, TLR4 binds LPS, TLR5 binds bacterial flagellin, etc.) and that probiotic effectiveness depends upon the system that they trigger. This report specifically focused on colitis and TLR9 as it recognizes unmethylated CpG dinucleotides and is expressed by multiple cells (e.g. dendritic cells) within the immune system. The unmethylated CpG sequences are typically found in the DNA of bacteria and viral, thus it is a valuable identification point for probiotic and pathogen research.

Direct adherence of probiotics was found in *in vitro* but not yet established in *in vivo*. For example, it is commonly stipulated that probiotics must adhere to intestinal cells. However, data that support adherence of probiotics are mostly derived from *in vitro* assays, which have limited predictability for the *in vivo* situation. Dendritic cells are cells that identify foreign bodies in the host and present them to the T lymphocytes in host intestine are important to execute the action of probiotics immune activity. Probiotics enter host immune cells by

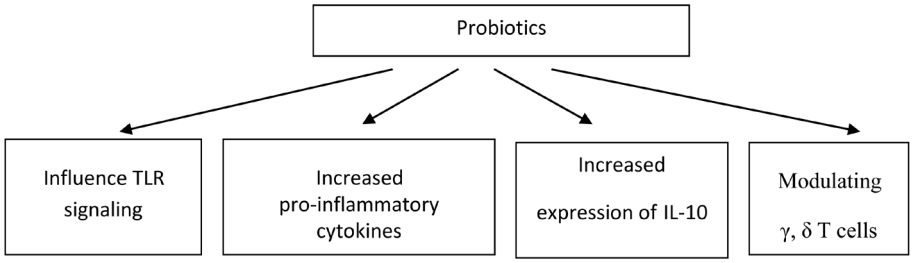

Figure 1. Immnumodulatory activity of probiotics.

either transcytosis of bacteria or internalization [52].

Teichoic acid, a component of the Gram-positive cell wall, of *L. plantarum* is involved in the anti-inflammatory activity of this probiotic. A mutant with enhanced anti-inflammatory capacity incorporated much less D-alanine in its teichoic acids than the wild-type strain and dramatically reduced secretion of pro-inflammatory cytokines by peripheral blood mononuclear cells and monocytes resulting in significant increase in IL-10 production. The effects observed were clearly TLR-2 dependent. This mutant was also more protective in a murine colitis model than its wild-type counterpart [53]. This study elegantly demonstrated the involvement of TLR-2 in the probiotic effect of *L. plantarum* highlighting the importance of TLRs for probiotic actions. A direct anti-inflammatory effect of EcN on human gut epithelial cells (HCT15) could only be demonstrated for live bacteria but without direct contact. Rather a secreted factor mediated this effect by suppressing the TNFα-induced IL-8 transactivation by a mechanism independent of NF-κB inhibition [54]. An oral administration of engineered *Lactobacillus acidophilus* strain, which was unable to synthesize lipoteichoic acid, to mice, resulted in reduction of developed colonic polyps [55].

Some probiotics are able to alter cytokine production by modulating cellular signal transduction. They may either block degradation of the inhibitor IκB by inhibiting the ubiquitination of this inhibitor, by interfering with proteasome function or influencing RelA localization via the receptor γ-dependent signal cascade which in turn is activated through a peroxisome proliferator [56] [57]. Two soluble proteins from *Lactobacillus rhamnosus* GG promote intestinal epithelial cell survival and growth. These proteins inhibit TNF-α-mediated apoptosis by activation of the anti-apoptotic factor Akt and protein kinase B. Furthermore, they inactivate the pro-apoptotic p38 mitogen-activating protein kinase signaling pathway in epithelial cells [58].

7. Prebiotics

Prebiotics, non-digestible oligosaccharides, known to modulate microbiota in the intestine and thereby modulate health. Prebiotics are in use by food industry for their functional and health promoting properties. They are used in many beverage industries because of their individual intrinsic properties such as emulsifying, gel forming, low sweetness, low glycemic index and modulation of viscosity. Prebiotics are produced either by extraction from natural sources or by chemical synthesis [59] [60]. Most common prebiotics are inulin, fructooligosaccharide, lactulose, and resistant starch [61] [62].

Protective effect of prebiotics against cancer was studied in various studies. In an animal study conducted by Femia *et al.*, (2002) [63], the protective effect of probiotics on azoxymethane-induced carcinogenesis was less when compared to the effects of prebiotics (oligofructose-inulin) might be due to lower colonic proliferation with prebiotics. Most commonly investigated oligosaccharides for cancer prevention are inulins. Feeding inulin and or oligofructan diets to rats suppressed azoxymethane-induced colon tumors at the promotion stage [64], and 1,2-dimethylhydrazine induced colon cancer [65] [66]. A 5% - 15% supplementation of inulin or oligofructose lowered breast tumor incidence in rats and mice and metastasis in the lung [67]. Probiotic (inulin) or prebiotic (*Lactobacillus acidophilus*) treatments to high fat diets significantly reduced formation of aberrant crypt foci formation in rats and no effect was found in reducing ACF in their low fat counterparts [68]. Prebiotics directly or indirectly affect the process of carcinogenesis, colonization and growth of bacteria, modulates proliferation and enhance inflammation.

Fermentation of prebiotics led to production of short-chain fatty acids (SCFA) which provide several effects on colonic mucosa. Inulin-type fructans present in foods such as garlic, onion, artichoke and asparagus increased the levels of *Bifidobacteria* and SCFA concentrations in the intestinal lumen. In an *in vitro* study on human colonic lines L97 and HT29, supernatant fractions of inulin fermentation showed a significant growth-inhibition and apoptosis in human colon tumor cells [69]. Butyrate produced by fermentation has the potential to inhibit the growth of emerging pre-malignant and malignant cells. Preclinical studies have reported that butyrate might be a chemopreventive agent in reducing carcinogenesis process [70] or protector agent against colon cancer by promoting cell differentiation [71]. Butyrate reduces colonic cell proliferation and induces differentiation in colonic epithelial cells [72]. Sodium butyrate was reported as a powerful inhibitor of growth and inducer of differentiation and apoptosis thereby possessing a beneficial effect against colon cancer development [73]. Fermentation by gut bacteria on a high amylose starch diet produced butyrate, which increased the detoxification of electrophilic products associated with oxidative stress [74]. The ability of prebiotic resistant starch type-3 Novelose 330, to reduce the incidence of colon carcinogenesis *via* induction apoptosis in rats was established and the effect was attributed to the increased production of butyrate [75].

Prebiotic consumption has further been shown to convey an anti-tumorigenic effect via an enhancement of the immune response. The consumption of modified arabinoxylan rice bran enhanced the activity of natural killer cells (NK cells) and the binding of NK cells to tumor cells [76] in C57BL/6 and C3H mice, demonstrating the induction of immunity in host. Pro- and prebiotic fermentation products led to an increased integrity of Caco-2 intestinal monolayers treated with the tumor promoter, deoxycholic acid [75].

8. Conclusion

Evidence from *in vitro* and animal studies supports the potential chemopreventive properties of prebiotics and probiotics. However, human studies using pro and prebiotics have not provided consistent results in support of their efficacy in preventing cancer. More randomized controlled human trails need to be conducted with a wide range of population with stringent controls. These control measures are difficult because genetics and immune response potential is varied throughout the population. It is highly recommended that upper and lower gastrointestinal samples be obtained in future studies to better understand the prebiotic utilization, the probiotic viability and the substrate/product kinetics. Probiotics with the abilities to target delivery, provide stronger beneficial properties and maintain stable colonization are needed in order to offer protection against cancer. An integrated approach with inclusion of epidemiological studies with genome studies, microbiome studies would provide more opportunities to understand the complexities of interactions and beneficial properties against cancer.

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Abbreviations

ACS: American cancer society,
WHO: world Health organization,
FAO: Food and Agriculture Organization,
FOS: Fructooligosaccharides,
SCFA: short chain fatty acids,
Lb: Lactobacillus,
AaC,: Amino-a-carboline,
PPR: Pattern-recognition receptors,
PAMP: Pathogen-associated Molecular patterns,
MAMP: Microbe-associated molecular patterns,
TLR: Toll-like-receptor,
LPS: Lipopolysaccharide,
IL: interleukin,
EcN: Escherichia coli Nissle**,**
TNFα: tumor necrosis factor alpha,
NF-κB: Nuclear Factor-kappaB,
ACF: Aberrant crypt foci,
NK: natural killer cells

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