Review Article

Probiotics and Cancer

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Abstract

Probiotics are live microbial food supplements or components of bacteria, which have been shown to have beneficial effects on human health. Probiotic bacteria are used to treat or prevent a broad range of human diseases. Cancer is one of the most important deaths causing in the world and many factors as chemicals, rays, viruses and genetic factors may influence it. There are many studies that have been suggested using of probiotic products as cancer risk reducer. The aim of this review is to consider the current evidence on the effects of probiotics on human health and decrease cancer.

Keywords: Probiotic; Cancer; Ames Test; Human Health; Gut Microflora

1. Introduction

Cancer is one of the most important deaths causing in the world [1]. Cancer can take over 200 distinct forms, including lung, prostate, breast, ovarian, hematologic, skin, and colon cancer, and leukemia, and both environmental factors (tobacco smoke, alcohol, radiation, and...
chemicals) and genetic factors (inherited mutations and autoimmune dysfunction) are associated with an increased risk of developing cancer. Bacterial and viral infections are also strongly associated with some types of cancer (stomach cancers and cervical cancer, respectively). The most common type of cancer in men and women is prostate and breast cancer [2]. The enormous numbers and diversity of the human gut microflora is reflected in a large and varied metabolic capacity, particularly in relation to xenobiotic biotransformation, carcinogen synthesis and activation. The metabolic activities of the gut microflora can have wide ranging implications for the health of the host, resulting in both beneficial and detrimental effects [3]. Probiotics are defined as the viable microorganisms that exhibit a beneficial effect on the health of the host by improving its intestinal microbial balance. The term probiotics was first coined by Lilly and Stillwell in 1965 in reference to substances produced by protozoa, which stimulated the growth of other organisms [4, 5]. A probiotic organism should be nonpathogenic and non-toxic, and also resistant to low pH and to bile salts to improve its chances of survival in the gastrointestinal tract. Probiotics have been used to treat a wide range of diseases, ailments, and conditions that affect humans and animals [6]. Table 1, contains a partial list of human diseases and conditions that probiotics have been used to prevent and/or treat [7]. Most probiotics are members of two genera of lactic acid producing bacteria (LAB), Lactobacillus and Bifidobacterium, but Saccharomyces and Enterococcus are also used [8]. The aim of this review is to consider the current evidence on the effects of probiotics on human health and decrease cancer.

Table 1. Medical applications of probiotics

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Probiotics</th>
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<tbody>
<tr>
<td>Lactose maldigestion</td>
<td>LAB and <em>Streptococcus salivarius</em> subsp. <em>thermophilus</em></td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>LAB or <em>S. boulardii</em></td>
</tr>
<tr>
<td>Traveler's diarrhea</td>
<td>LAB</td>
</tr>
<tr>
<td>Allergies</td>
<td>LAB</td>
</tr>
<tr>
<td><em>Clostridium difficile</em>–induced colitis</td>
<td>LAB</td>
</tr>
<tr>
<td>Dental caries</td>
<td>LAB</td>
</tr>
<tr>
<td>Inflammatory bowel disease or</td>
<td>LAB and <em>Bifidobacterium</em> species, <em>S. boulardii</em> and drug, <em>S. boulardii</em> alone, or LAB alone</td>
</tr>
<tr>
<td>irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>LAB</td>
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</table>

Evidence that probiotics can influence carcinogenesis is derived from a variety of sources:
- Effects on bacterial enzyme activities.
- Antigenotoxic effects in vitro and in vivo.
• Effects on pre-cancerous lesions in laboratory animals.
• Effects on tumour incidence in laboratory animals.
• Epidemiological and experimental studies in humans [8].

2. Lactic Acid Bacteria

Most probiotic microorganisms belong to Lactic Acid Bacteria (LAB), such as *Lactobacillus* spp., *Bifidobacterium* spp. and *Enterococcus* spp. The yeast *Saccharomyces boulardii* has been studied extensively and also other bacterial species, like *Bacillus* spp. and *Clostridium butyricum* [9].

2.1. *Lactobacillus*

Lactobacilli are Gram-positive bacteria, unable to sporulate, occurring as rods or cocco-bacilli, with a GC composition of the genome usually below 50% (low GC bacteria). They are fastidious microorganisms, requiring rich media to grow, and microaerophilic. The genus *Lactobacillus* belongs to the Phylum Firmicutes, Class Bacilli, Order Lactobacillales, Family Lactobacillaceae and its closest relatives, being grouped within the same Family, are the genera Paralactobacillus and Pediococcus. Some *Lactobacillus* cultures used as probiotic are *Lactobacillus Acidophilus*, *L. casei*, *L. delbrueckii*, *L. plantarum*, *L. rhamnosus* [10].

2.2. *Bifidobacterium*

The genus *Bifidobacterium*, even if traditionally listed among LAB, is only poorly phylogenetically related to genuine LAB: it belongs to the Phylum Actinobacteria, Class Actinobacteria, Order Bifidobacterales, Family Bifidobacteriaceae, its neighbor genera being Aeriscardovia, Gardnerella, Parascardovia, and Scardovia. The genus includes, at present, 30 species [10]. Bifidobacteria are normal inhabitants of the human and animal gastrointestinal tract and is not surprising to find them in mouth and feces. The intestinal tracts of newborns are colonized with Bifidobacterium within days after birth and the population is influenced by age, diet, antibiotics, and stress. The optimum pH for the growth of Bifidobacteria is 6–7 and virtually no growth at below of 4.5 or above of 8.5. The optimum temperatures of growth are 37–41°C, the minimum are 25–28°C, and the maximum are 43–45°C. Some *Bifidobacterium* cultures used as probiotic are *B. adolescentis*, *B. longum*, *B. infantis*, *B. bifidum* and *B. breve* [11].

3. Mechanisms of Anti-carcinogenicity

3.1. Binding of Carcinogens

There are a large number of reports describing the adsorption or binding in vitro by LAB and other intestinal bacteria, of a variety of food-borne carcinogens including the heterocyclic amines formed during cooking of meat, the fungal toxin Aflatoxin B1, benzo(a)pyrene. In several of these studies, a concomitant decrease in mutagenicity was reported [8].
3.2. Effects on Bacterial Enzymes
The ability of the colonic microflora to generate a wide variety of mutagens, carcinogens and tumour promoters from dietary and endogenously-produced precursors is well. For example, the enzyme β-glucuronidase is involved in the release in the colon, from their conjugated form, of a number of dietary carcinogens, including polycyclic aromatic hydrocarbons. Species of Bifidobacterium and Lactobacillus, have low activities of these enzymes involved in carcinogen formation and metabolism by comparison to other major anaerobes in the gut such as bacteroides, eubacteria and clostridia. This suggests that increasing the proportion of LAB in the gut could modify, beneficially, the levels of xenobiotic metabolising enzymes. Table 2. [8].

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Probiotic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal β-glucuronidase</td>
<td><em>L. acidophilus</em> (10^9-10^10</td>
<td>Decreased the activity of β-glucuronidase by 40-50%</td>
</tr>
<tr>
<td></td>
<td>cells/day)</td>
<td></td>
</tr>
<tr>
<td>β-glucuronidase and β-</td>
<td><em>L. acidophilus</em> or *B.</td>
<td>A significant decrease in enzyme activity for <em>L. acidophilus</em> only</td>
</tr>
<tr>
<td>glucosidase activity</td>
<td>adolescentis* (10^9 cells/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for three days)</td>
<td></td>
</tr>
<tr>
<td>Faecal enzymes and ammonia</td>
<td><em>B. longum</em> (freeze dried)</td>
<td>Significant decrease in β-glucuronidase and ammonia.</td>
</tr>
<tr>
<td></td>
<td>and inulin (5%)</td>
<td></td>
</tr>
<tr>
<td>Faecal levels of enzyme</td>
<td><em>L. acidophilus</em></td>
<td>Animals given <em>L. acidophilus</em> had significantly lower free amines in faeces and 50% less of conjugates</td>
</tr>
</tbody>
</table>

3.3. Production of anti-tumorigenic or antimutagenic compounds
Lactic acid bacteria or a soluble compound produced by the bacteria may interact directly with tumour cells in culture and inhibit their growth. Lactic acid bacteria significantly reduced the growth and viability of the human colon cancer cell line HT-29 in culture, with a significant increase in dipeptidyl peptidase IV and brush border enzymes, suggesting that these cells might have entered a differentiation process. Milk fermented by *B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei* inhibited the growth of the MCF7 breast cancer cell line, the antiproliferative effect not being related to the presence of bacteria. These findings suggest the presence of an ex novo soluble compound produced by lactic acid bacteria during milk fermentation or the microbial transformation of some milk components in a biologically active form [12].

3.4. Enhancement of the host’s immune response
One explanation for tumour suppression by lactic acid bacteria may be that it is mediated via an immune response in the host. Sekine et al, suggested that *B. infantis* stimulates the host-
mediated response, leading to tumour suppression or regression. In addition, there are studies to suggest that lactic acid bacteria play an important role and function in the host’s immunoprotective system by increasing specific and non-specific mechanisms to exert an anti-tumour effect [12, 13].

4. Ames Test

Mutation is an important factor in carcinogenesis. Therefore, the incidence of cancer may be reduced by decreasing the rate of mutation. The best way for humans to decrease the rate of mutation is to avoid exposure to or ingestion of mutagens and carcinogens [14]. Each factor that causes removal, inhibition and inactivation of mutagen substances is rewarding. Today, bacteria are being used for the assessment of antimutagenic activities of different compounds in a short-time with excellent results. One of the methods used for assessing the mutation prevention properties of a compound in bacteria is the Ames test. Ames test is a worldwide short-term bacterial reverse mutation test specifically designed for screening a variety of new chemical substances and drugs that can produce genetic damage that leads to gene mutations. The Salmonella strains used in the test have different mutations in various genes in the histidine operon, each of these mutations is designed to be responsive to mutagens that act via different mechanisms (Table 3) [1,15 and 16].

<table>
<thead>
<tr>
<th>Strain</th>
<th>Amino acid marker</th>
<th>Other relevant mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella typhimurium TA97</td>
<td>hisD6610</td>
<td>Frameshift</td>
</tr>
<tr>
<td>Salmonella typhimurium TA98</td>
<td>hisD3052</td>
<td>Frameshift</td>
</tr>
<tr>
<td>Salmonella typhimurium TA100</td>
<td>hisG46</td>
<td>Base pair substitution</td>
</tr>
<tr>
<td>Salmonella typhimurium TA102</td>
<td>hisG428</td>
<td>Base pair substitution</td>
</tr>
</tbody>
</table>

In a comparative study, it was concluded that systems exploiting Salmonella typhimurium TA100 in the assays are most capable in identifying the mutagenic capacity of different chemicals. On the other hand, mouse hepatic homogenate, containing microsomal enzymes including cytochrome P450 has anticancer properties. Cytochrome P450 in liver S9 fraction plays an important role in activating promutagens to proximate and ultimate mutagens. Rat and human liver P450 involved in the activation of some chemical carcinogens have different isoforms. Many researchers suggested that use of Probiotics decrease the risk of cancer [5, 16]. Hosono et al, were the first to report that milk fermented with L. delbrueckii subsp. bulgaricus, Lactococcus lactis subsp. lactis or Enterococcus faecalis exhibited an
antimutagenic activity against NQO [17]. Lankaputhra and Shah, proved that *Lactobacillus spp.* has good activity in decreasing mutagenic substances [18]. Zobel *et al.*, showed that, *L. acidophilus* and its culture extract prevented from DNA damage by MNNG [19]. Heui-dong and Chang- Ho showed that, *L. plantarum* KLAB 21 was isolated from Kimchi can inhibit four mutagenic and carcinogenic agents effects; Aflatoxin B1, NQO, MNNG and NPD. He used two salmonella strains TA100 and TA98. Results showed that the bacterial culture supernatant inhibited mutagenic effects of MNNG (98.4%) in presence of TA100 and NQO (57.3%) in presence of TA98 [20]. Kazemi *et al.*, showed that, *Lactobacillus* species (*L. Plantarum, L. casei, L. brevis*) could inhibit mutagenic agents activity until 40%, that is very good antimutagenic activity [5]. Chalova *et al.*, evaluated the ability of some probiotic bacterial supernatants to decrease the effects of two mutagenic substances benzo[a]pyrene and sodium azide in different growth phases and *Bifidobacterium adolecenti* ATCC 15703 had 48.7% inhibitory in Log phase duration, *L. plantarum* ATCC 8014 showed 59.37% inhibitory function on mutagenic substance benzo[a]pyrene, and *L. plantarum* ATCC 8014 had 54.64% inhibitory on mutagenic substance sodium azide in lag phase duration [21]. Lo *et al.*, showed that, Cells of *Bifidobacterium lactis* Bb-12 and *B. longum* CCRC 14634 showed higher antimutagenic activities than their supernatants [22].

5. Conclusion

Probiotics are found in dairy products, plants, meat products, sewage, manure humans and animals. These kinds of bacteria have positive effects on immune system by inhibition of pathogen attachment to epithelial cells, changing the receptor of bacterial toxins, producing antimicrobial substances such as acid, bacteriocins, fatty acid and aromatic compounds and competition for food. This group of bacteria as gastrointestinal flora cause to decrease absorption of mutagenic and carcinogenic substance. At presence, with increasing of the antibiotic resistance and side effects of chemical drugs, it seems, we need to use alternative remedies.

References


