Synbiotics in Gastroesophageal Cancer

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15.1 Introduction

The advancement of sequencing technology has increased our understanding of the human stomach microbiome, which is now known to show a promising role in maintaining a self-sustained balance and that changes in microbial community composition can encourage the development of gastric disorders. The carcinogenic consequences of the stomach microbiome have recently gotten a lot of attention. The most frequent occurring is gastric cancer (GC) having a significant fatality rate worldwide. *Helicobacter pylori* infection is a well-known GC risk factor. Apart from bringing some novel technology and technique for the diagnosis and therapy of gastrointestinal (GI) cancers, certain other factors are becoming increasingly significant, such as maintaining health and preventing malignancies through the use of human nutrition enriched with probiotics and prebiotics. Probiotics are live bacteria that carry the host's health advantages, when taken in adequate amounts (Indian Council of Medical Research Task Force et al. 2011). The fundamental advantage of probiotics is that they assist the host in maintaining intestinal microbial balance, reducing pathogenic gastrointestinal microbes, improving bowel regularity, and restoring intestinal microbial balance with antibiotic-related diarrhea. Moreover, probiotics have been shown to have potential role in the prevention of cancer and its treatment via modulation in microbiota and immune system and reducing

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bacterial translocation, improving gut barrier activity, anti-inflammatory and anti-pathogenic function, and different impacts on tumor formation and metastasis in several studies (Servin 2004; Cotter et al. 2005). Probiotics and gastrointestinal neoplasms have primarily been studied in concern with colorectal cancer (CRC) and gastric cancer associated with Helicobacter pylori (*H. pylori*) (Russo et al. 2014; Rasouli et al. 2017; Khoder et al. 2016; Taremi et al. 2005; Sanders et al. 2013; Ghosh et al. 2019). In addition, chemotherapy commonly causes severe diarrhea and oral mucositis in cancer patients, which has an impact on their treatment. Probiotics, when taken orally, give a therapeutic option for overcoming these limits. These findings suggest that probiotics could be used as dietary supplements to protect against neoplastic predisposition by influencing the immune system of the host (Zhang et al. 2011; Zuccotti et al. 2008; De Preter et al. 2011; Kumar et al. 2010; Liong 2008; Ghosh et al. 2019).

Lactic acid bacteria (LAB) from the Lactobacillus and Bifidobacterium genera are found in the majority of probiotic products now on the market (Holzapfel et al. 2001). Most of the probiotic microbes are Gram-positive, with Lactobacillus and Bifidobacterium being the most occurring species utilized in the treatment of gastrointestinal diseases (Marco et al. 2006). Some Gram-negative bacteria, on the other hand, are employed as probiotics. The most well-known member of this category is Escherichia coli Nissle 1917 (EcN) (12, commonly called "Mutaflor,"which has been recently used in the treatment of chronic constipation and colitis in Germany (Mollenbrink and Bruckschen 1994; Schutz 1989). Streptococcus thermophilus and Lactococcus lactis are two of the major economically important LAB that also show a major role in dairy products.

The current descriptive review highlights the most recent information on probiotic effects and mechanisms in GI malignancies. In addition, we have given a comprehensive evaluation of the evidence from clinical research employing probiotics to prevent or cure GI malignancies.

15.2 Probiotics

Probiotics are living bacteria that have health benefits when consumed by the body. They are found in yogurt, some fermented foods, and also in dietary additives and cosmetics. Probiotics involve a broad category of microorganisms among which bacteria from the Lactobacillus and Bifidobacterium genera are the most occurring ones. Similarly, other bacteria and some yeasts such as Saccharomyces boulardii can be used in probiotics. Probiotics have a wide number of structures where each has some specific advantages. It can be illustrated by taking an example of Lactobacillus. If one type of Lactobacillus prevents an illness, it doesn't mean that some other type of Lactobacillus or any type of Bifidobacterium probiotics will also prevent the same illness. The first requirements of probiotic strains are the safety and functionality for human and animal health along with their technical fitness, in accordance with World Health Organization (WHO), Food and Agriculture Organization (FAO), and European Food Safety Authority (EFSA). For the safety of any strain, there

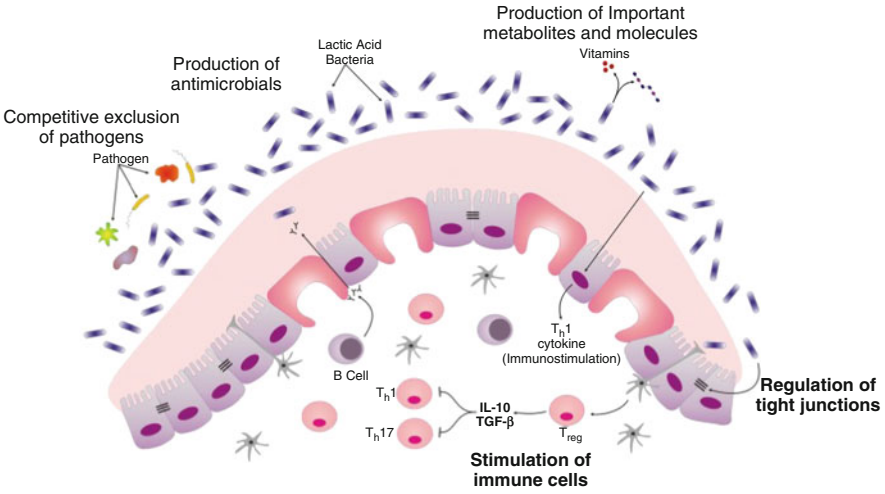

Fig. 15.1 Figure displaying different mechanism by which probiotic manifest their beneficial role in intestine. Figure reproduced with permission from Ghosh et al. (2019)

should be absence of connection between pathogenic cultures and the antibiotic resistance profile. The microorganisms which are employed as probiotics must satisfy the requirements of GRAS (Generally Regarded as Safe) and QPS (Qualified Presumption of Safety). Their survival in the gastrointestinal tract and its safety effects are determined by functional characteristics (Anadon et al. 2006; Gaggia et al. 2010). Because of the probiotic market's rapid growth, it's critical that probiotics survive and maintain their qualities throughout the storage and distribution process (Markowiak and Slizewska 2017) (Figs. 15.1, 15.2, and 15.3).

15.3 Prebiotics

Prebiotics, which are found naturally in some foods, can help our bodies create good bacteria. A prebiotic, in this case, is a substrate that is used selectively by host bacteria to provide health benefits. Prebiotics withstand hydrolytic behavior of the digestive enzymes in the stomach and small intestine, allowing them to transit to the colon. They're fermented here, which boosts the number of good bacteria in our gut. Many prebiotics are also classified as dietary fiber. Though not all fibers are prebiotics, insoluble fiber (the kind that adds bulk to the stool) is often poorly fermented by our gut bacteria and is therefore not considered a real prebiotic. Insulin, galactooligosaccharides, and fructooligosaccharides are the most studied prebiotics, which are also kinds of soluble fiber. Soluble fiber varies from insoluble fiber in which it forms a gel with water, trapping specific dietary components and slowing digestion. Insoluble fiber, on the other hand, adds bulk to the stool and aids in the faster passage of food through the stomach and intestine.

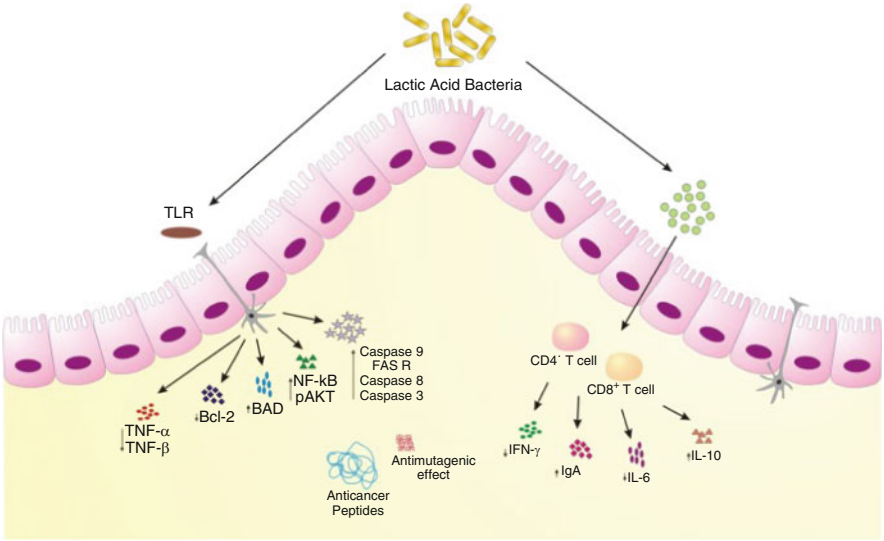

Fig. 15.2 Schematic diagram displaying different methods by which probiotic prevents intestinal cancer. Figure reproduced with permission from Ghosh et al. (2019)

15.4 Synbiotics

The term "synbiotics" was recently coined to describe a food that contains probiotics as well as prebiotics having a functional and health-promoting values (Schutz 1989). The main focus of synbiotics product is moving towards functional evidence such as infection resistance, antibacterial activity, and better immunological status (Schutz 1989). Though there have been a number of studies on biotic products that focus on a healthy colonic microbiota, there have been little studies on the actions of intestinal digesting enzymes. The impact of synbiotics which is a blend of probiotics and prebiotics, on the ecology of gut microbes and digestive enzyme behavior in rats, as well as the role of enteric feeding and the microenvironment in cancer must be studied thoroughly in upcoming days.

15.5 Anticancer Mechanism of Synbiotics

Probiotics have numerous anticancer properties as well as significant impact on the gut microbiota's quantitative and/or qualitative changes. One major cause for the development of GI cancer is the toxic and genotoxic bacterial metabolites from intestinal microbiota. These metabolites can cause mutations due to its binding to certain receptors of the cell surface and altering transductions of intracellular signals, which can lead to mutations. *Streptococcus bovis*, *Bactericides*, *Clostridia*, and *H. pylori* are among the bacteria that cause the development of cancer (Kasmi

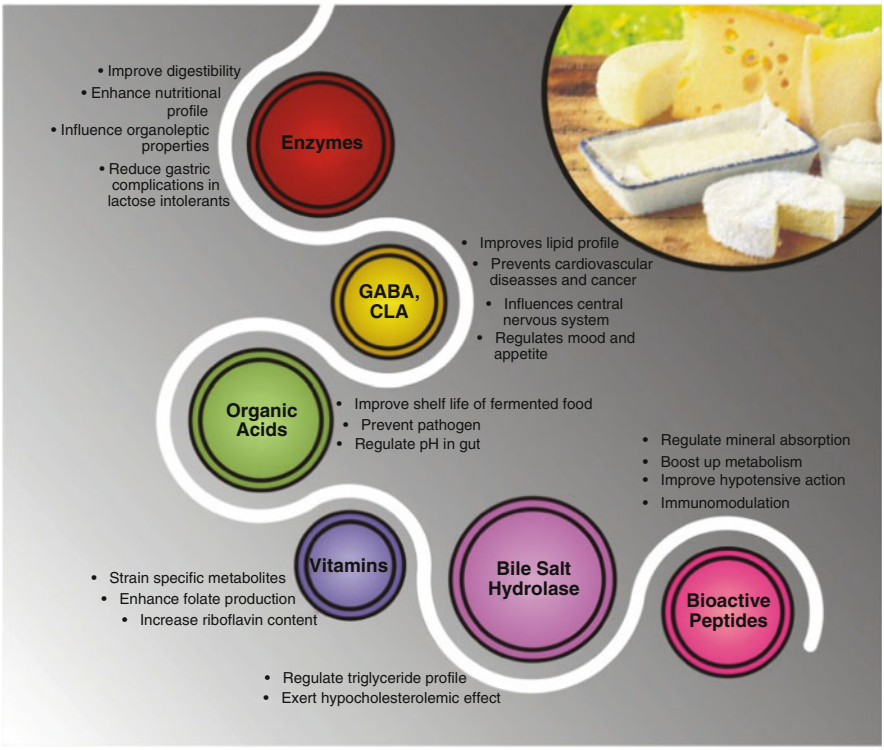

Fig. 15.3 Schematic diagram displaying health benefits of metabolites present in the fermented food. Figure reproduced with permission from Ghosh et al. (2019)

et al. 2011; Nakamura et al. 2002; Strofilas et al. 2012). As a result, the balance between "harmful" and "useful" bacteria has significance in the development of cancer. It has been observed that changing the number of microorganisms can affect carcinogen bioactivation and consequently cancer risk. Dietary components (prebiotics) are increasingly shown to have a substantial impact on this equilibrium. Furthermore, probiotics alter intestinal microbiological compositions, which has positive impact on the host by increasing intestinal barrier integrity, decreasing pathogen development, and reducing pro-carcinogenic chemical metabolism.

15.6 Role of Synbiotic in GI Cancer

The probiotic therapy can be used in the prevention and treatment of a variety of GI problems, such as irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), and the pathogenic bacterial or viral infection and antibiotic-related diarrhea, which has piqued the scientific community's attention (Zuccotti et al. 2008; De Preter et al. 2011). Probiotics have also been shown to protect against cancer in

epidemiological studies (Kumar et al. 2010). Probiotics have been shown to have anti-proliferative effects in the cancers of GI tract, with colonic as well as gastric cancer cells being the most widely examined (Liong 2008; Rafter 2004). Several research on the health impacts of fermented milk by using *Lactobacillus casei* and *Lactobacillus acidophilus* have been conducted, and the obtained results show that these probiotics have a good influence on tumor cell death (Lee et al. 2004; Baldwin et al. 2010). Previous research has shown that *L. rhamnosus* GG strain has anti-proliferative properties in both colon and gastric cancer cells of human (Russo et al. 2007; Orlando et al. 2009; Orlando et al. 2012), and there is an another probiotic product called *Bifidobacterium adolescentis* SPM0212 inhibited the proliferation of three human colon cancer cell lines: HT-29, SW 480, and Caco-2 (Kim et al. 2008). *Bacillus polyfermenticus* (Ma et al. 2010), *L. acidophilus* 606 (Kim et al. 2010), LGG/Bb12 (Borowicki et al. 2011), and *LGG/Bifidobacterium animalis subsp*. lactis were among the probiotic products or strains that showed anticancer activity for cancer cells of human colon (Stein et al. 2012). Cousin et al. also found that fermented milk containing *Propionibacterium freudenreichii* increased the cytotoxicity of camptothecin, a stomach cancer chemotherapy drug (Cousin et al. 2012). With the emergence of *H. pylori*-resistant strains, the efficacy of *H. pylori* eradication regimens involving two antibiotics (clarithromycin plus amoxicillin or metronidazole) and a proton pump inhibitor (PPI) has decreased in recent years. According to a recent meta-analysis, supplementing antibiotic therapy with probiotics is particularly effective in eradicating *H. pylori* (Tong et al. 2007; Losurdo et al. 2018; Zhu et al. 2014).

We further reviewed the findings of a research where clinical trials on the effect of probiotics and antibiotic combination in the eradication of *H. pylori* colonization. Probiotic addition during antibiotic treatment for *H. pylori* eradication reduces undesirable adverse effects which results in higher compliance and in some circumstances, enhanced eradication rates, according to the findings of these studies. Furthermore, after effective eradication, a stomach tumor that was stimulating lymphoid tissue development vanished (Gisbert and Calvet 2011; Kokkola et al. 1996). A postulated reason for probiotic treatment is due to the presence of microorganisms in the stomach though they remain there for a short period of time, thereby increasing the overall immune response and reducing the inflammation effect on the gastric mucosa of host cells due to *H. pylori* (Du et al. 2012).

Among frequently occurring disease in the world, colorectal cancer (CRC) is listed as third most frequent disease with over one million new cases diagnosed each year and over 500,000 people dying from it (Bhandari et al. 2017). Taking probiotics has been found to be a supportive and protective strategy for the maintenance of a healthy gut flora while also lowers the risk associated with colon cancer (So et al. 2017). Despite numerous in vivo and in vitro investigations in animal models and human cancer cell lines, few randomized placebo-controlled trials (RCTs) have reported on the efficacy of probiotics to prevent and inhibit in carcinogenesis the intestine (Hatakka et al. 2008; Worthley et al. 2009; Ohara et al. 2010).

To prevent intestinal malignancies is not only the benefit of probiotics but can also help patients who are having colon cancer surgery avoid symptoms and consequences.

Unlike several studies on CRC and GC, some studies have suggested a role for probiotics to prevent and treat other GI cancers of pancreas and liver.

Pancreatic cancer is the world's 12th most prevalent malignancy, with 338,000 new cases per year, and the 7th most common cause of death, with 331,000 fatalities per year; however, the cause is still unclear (Ferlay et al. 2017; Pourhoseingholi et al. 2017; Javanmaed et al. 2018). Previous research suggests that probiotics play a multidimensional role to prevent pancreatic cancer by modifying pancreatitis as well as other associated risk factors such diabetes, pancreatic necrosis, inflammation, and obesity (Olah et al. 2007; Olah et al. 2002; Besselink et al. 2008). Probiotics had no significant influence on the clinical benefits of patients with SAP, according to the results of a meta-analysis of six clinical trials (Gou et al. 2014). Because of only few trials and their heterogeneity, the existing data are insufficient to conclude the impacts of probiotics in pancreas and colon-associated cancer.

15.7 Conclusion

Various studies till this date have supported that synbiotics are supplementary diet-based strategies and has positive effect to prevent or treat GI cancer. In addition, synbiotics have proven to tackle cancer through several mechanisms like anti-carcinogenic effect, activation of the host immune system, alteration of tumor gene expression, and inhibition of proliferation of bacteria that changes pro-carcinogens to carcinogens. However, detailed clinical trials sufficiently proving advantageous role of synbiotics on GI cancer, mode of treatment and information on aftermath treatment are still insufficient. Hence in upcoming future additional evidence-based trial and thorough analysis of synbiotic in increasing the survival of patients with GI cancer must be performed.

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