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Classification and Antitumor Activities of Postbiotics from the Biotic Family

Biyotik Ailesinden Postbiyotiklerin Sınıflandırılması ve Antitümör Aktiviteleri

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ABSTRACT

Cancer is the second leading cause of death worldwide, and although the prognosis for patients has improved, it is still poor in a significant proportion of cases. Complex and inconclusive approaches to anticancer treatment in the human body motivate the search for new ways to create an anticancer environment. Studies have shown that probiotics, prebiotics, synbiotics and postbiotics are effective in their use as adjunctive therapy in cancer treatment. Postbiotics, from the biotic family, are health-promoting microbial metabolites offered as a functional food or dietary supplement. They directly affect the body's signaling pathways or indirectly manipulate the metabolism and composition of the intestinal microflora. The administration of postbiotics is an effective complementary strategy to fight cancer. In this review, studies including the antitumoral effects of postbiotics and their role in metastatic cancers were examined and the main findings showing the usefulness of postbiotic sources in tumor cells were summarized. Postbiotics can be considered as adjunctive therapy in cancer treatment and may help reduce the side effects caused by treatment methods. In addition, more in vivo and in vitro studies are needed to evaluate the effects of postbiotics on cancer in detail.

Keywords: Antitumor agents, cancer, metastasis

Makale Bilgisi

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ÖZ

Kanser, dünya çapında önde gelen ikinci ölüm nedenidir ve hastaların prognozunun iyileşmesine rağmen, vakaların önemli bir kısmında hala kötüdür. İnsan vücudunda antikanser tedavisine yönelik karmaşık ve sonuç alınamayan yaklaşımlar, antikanser ortamı yaratmanın yeni yollarını aramaya motive etmektedir. Probiyotikler, prebiyotikler, sinbiyotikler ve postbiyotiklerin, yapılan çalışmalar ile kanser tedavisinde yardımcı tedavi olarak kullanımında etkili olduğu gösterilmektedir. Biyotik ailesinden olan postbiyotikler, fonksiyonel bir gıda veya gıda takviyesi olarak sunulan ve sağlığı destekleyen mikrobiyal metabolitlerdir. Doğrudan vücudun sinyal yollarını etkilerler ya da dolaylı olarak bağırsak mikroflorasının metabolizmasını ve bileşimini manipüle ederler. Postbiyotiklerin uygulanması, kanser ile savaşmak için etkili bir tamamlayıcı stratejidir. Bu derlemede, postbiyotiklerin antitümöral etkilerini ve metastatik kanserlerdeki rolünü içeren çalışmalar incelenmiş ve tümör hücrelerinde postbiyotik kaynaklarının yararlılığını gösteren temel bulgular özetlenmiştir. Postbiyotikler, kanser tedavisinde yardımcı tedavi olarak değerlendirilebilir ve tedavi yöntemlerinin neden olduğu yan etkilerin azaltılmasına yardımcı olabilir. Ayrıca postbiyotiklerin kanser üzerindeki etkilerini detaylı olarak değerlendirmek için daha fazla in vivo ve in vitro çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Antitümör ajanlar, kanser, metastaz

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Introduction

The composition of each person's gut microbiota is different, but the functions of the microbiota are quite similar. The microbiota in humans is responsible for the conversion of indigestible food components into absorbable forms, minimizing contact with ingested bacteria, reducing the growth and proliferation of pathogenic flora, and regulating the immune system (Vrzáčková et al., 2021). An imbalance or a disorder in the gut microbiota, called dysbiosis, adversely affects the overall health of the host (Sartor, 2012). Because microbial metabolites absorbed into the circulation are responsible for projecting beyond the gut onto the whole body signal transduction, including the brain (Vrzáčková et al., 2021). This causes us to feel the damage occurring in the intestines in a different area outside the intestine. The positive or negative situation occurring in our intestines affects brain functions due to the gut-brain axis, and the intestines are described as our second brain (Sartor, 2012). Dysbiosis has been associated with serious chronic diseases such as obesity, autoimmune diseases, psychiatric disorders, allergies and even cancer (Vrzáčková et al., 2021). Postbiotics can repair the intestinal microbiota, stabilize and increase the effectiveness of the intestinal barrier function in cancer patients, and promote anticarcinogenic, anti-inflammatory, antimutagenic or other biologically important biochemical pathways with high specificity against tumor cells (Kvakova et al, 2022). For these reasons, manipulation of the intestinal microbiota is suggested to be a powerful strategy in the fight against cancer and other diseases (Sartor, 2012). In this review article, Google Scholar, PubMed and ScienceDirect scientific databases were searched in the form of an advanced search by typing the keywords 'postbiotic', 'postbiotic and antitumor'. In November 2022, all studies on postbiotics covering the last 20 years were examined. It is aimed to gain a perspective for the future by bringing together the definition of known postbiotic compounds and their effects on cancer, as well as research on these effects.

Postbiotics

Postbiotic is a term derived from the Greek words 'post' meaning 'after' and 'bios' meaning life. Also, the 'biotic' family of terms (probiotics, prebiotics, synbiotics, and postbiotics) is related to microorganisms (or their substrates) (Vinderola et al., 2022). Probiotics, prebiotics and synbiotics consisting of a combination of these two components play an effective role in maintaining microbiota homeostasis. Postbiotics produced by living microorganisms are defined as microbial non-viable metabolites, microbial fractions or cell lysates (Açar & Kaya, 2021). The production of functional proteins, short-chain fatty acids (SCFAs), secreted polysaccharides, microbial fractions, extracellular polysaccharides, cell lysates, pilus-type structures, teichoic acid and peptidoglycan-derived muropeptides, known as postbiotics, is caused by many beneficial bacteria in the microbiota (Aguilar-Toalá et al., 2018). Postbiotics are assumed to include all non-prebiotic substances of bacterial or fungal origin that do not meet the definition criteria of probiotics that have beneficial effects on their host (Fig. 1) (Żółkiewicz et al., 2020).

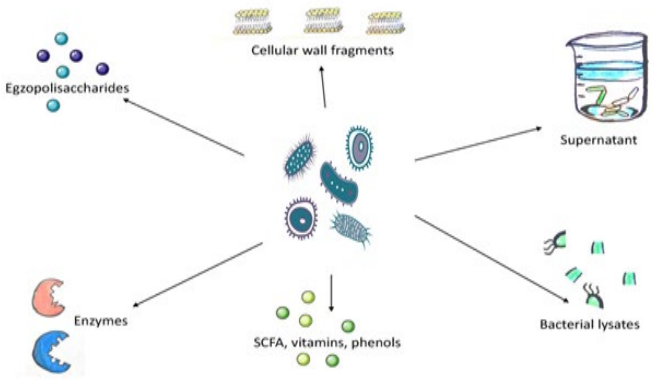

Figure 1. Methods of Acquisition of Postbiotics *SCFA, short-chain fatty acids (Żółkiewicz et al., 2020).

Classification of Postbiotics

Cell-Free Supernatants

Cell-free supernatants (CFSs) containing active metabolites are typically prepared by centrifugation of microbial cultures followed by filtration to maintain sterility. These solutions produced through filtration have anti-inflammatory, antioxidant, antibacterial, anti-infectious and anticancer effects (Żółkiewicz et al., 2020).

A study has been published that found a relationship between CFS and cancer cell invasion. In this study, they used two strains of CFS made on the human colorectal cancer cell line HCT-116 and tested in vitro. These CFSs are *Lactobacillus casei* and *Lactobacillus rhamnosus* GC. The striking point of this study was that CFS had a positive effect on the metastasis-forming activities of cancer cells. Both CFSs have been shown to reduce HCT-116 metastatic cancer cell invasion in vitro by decreasing the activity of metalloproteinases and increasing the level of zona occluded protein (Escamilla et al., 2012). Studies have hypothesized that cell-free supernatants may have clinically beneficial effects in preventing cancer due to their ability to reduce in vivo oxidative stress and provide direct antitumor activity (Escamilla et al., 2012; Amaretti et al., 2012).

Exopolysaccharides

Growing microorganisms also produce biopolymers with different chemical properties. These biopolymers are called exopolysaccharides (EPS) and these EPSs are assumed to move outside the bacterial cell wall, forming a heterogeneous group of substances. Those consisting of a single type of carbohydrate polymer are called homopolysaccharides, those containing two or more carbohydrate polymers are called heteropolysaccharides and are used as fermentable substrates by commensal intestinal bacteria. They play a role in modulating the activity, functionality and composition of the gut microbiota, promoting the production of metabolites that benefit the host (Wegh et al., 2019).

Studies say that EPS has intestinal health-promoting and disease-preventing, cholesterol-lowering, ulcer-preventing, anticarcinogenic and immune-regulating effects on health (Wegh et al., 2019; Żółkiewicz et al., 2020). EPS of *L. plantarum* C70 isolated from camel milk showed antioxidant and cytotoxic activities in colon cancer and breast cancer lines (Ayyash et al., 2020).

Dectin-1 receptors on the surface of macrophages can interact with another class of EPS, β-glucans, and this interaction can activate them. As a result, β-glucans can have a therapeutic effect by increasing the cellular immune response of the organism against viruses, parasites, bacteria and cancer cells (Żółkiewicz et al., 2020).

Enzymes

Microorganisms have developed defense mechanisms against reactive oxygen species (ROS), protecting lipids, proteins, carbohydrates and nucleic acids from possible harmful effects. Microorganisms provide their defense mechanisms against ROS, especially with antioxidant enzymes such as glutathione peroxidase (GPx), NADH-oxidase, peroxide dismutase (SOD) and catalase (Kullisaar et al., 2002). *Lactobacillus lactis*, a genetically engineered enzyme that expresses catalase, has been shown to inhibit colon cancer induced in mice (de LeBlanc et al., 2008).

Antioxidant enzymes such as catalase, peroxide dismutase and glutathione peroxidase fight against reactive oxygen species. Antioxidant properties of *L. plantarum* postbiotics were observed with the increased concentration of glutathione peroxidase in serum (Izuddin et al., 2020).

Cell Wall Fragments

In microorganisms, a number of components of the bacterial cell wall are immunogenic and elicit a specific immune response. Lipoteichoic acid (LTA) induces cytokine production and is found in the cell walls of gram-positive bacteria and can be released extracellularly (Żółkiewicz et al., 2020).

Reports presented in some studies show that LTA reduces by blocking IL-12 production and stimulates the production of cytokines with immune regulatory activity (eg, IL-10). In contrast, others have shown that LTA does not attenuate its inflammatory effects and primarily damages tissues in the gut. Also, due to LTA's anti-inflammatory and anti-cancer potential, it may have broader benefits (Żółkiewicz et al., 2020).

In a study, it was observed that lipoteichoic acid found in the cell wall of *Staphylococcus aureus* induced inflammatory cytokines such as interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). It has also been reported that lipoteichoic acid is recognized by Toll-like receptor 2 and contributes to the development of immunity (Kang et al., 2016).

Despite these beneficial activities, LTA can cause adverse effects in living organisms and cause a high inflammatory response. Therefore, further security considerations are warranted for the LTA (Żółkiewicz et al., 2020). Apart from the compiled studies, new studies on humans should be conducted in order to evaluate in detail the positive and negative consequences of some components of the bacterial cell wall in microorganisms.

Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are metabolic products formed by the fermentation of dietary carbohydrates by bacteria in the gastrointestinal tract. Thanks to these properties, they show postbiotic properties (Rautiola, 2013). In many studies, the most studied postbiotics are SCFA, and especially acetate, propionate and butyrate were used from SCFA in the studies. These postbiotic molecules are products from the fermentation of dietary fiber and are formed by intestinal microorganisms, primarily *Faecalibacterium prausnitzii* and *Eubacterium rectale* (Kim et al., 2008).

The de novo SCFA production potential of four probiotic bacterial strains was evaluated in vitro. Significant amount of propionate of *L. rhamnosus* GG; It has been reported that *B. Bifidobacterium bifidum* MF 20/5 and *Bifidobacterium longum* SP 07/3 can produce acetate. It was determined that *B. longum* SP 07/3, *L. gasseri* PA 16/8 and *B. bifidum* MF 20/5 produced significant amounts of propionate (LeBlanc et al., 2017).

In a non-cancerous cell in the Krebs cycle, butyrate is metabolized with the use of Acetyl-CoA and via β-oxidation. In cancer cells, the main energy source is glucose, which is metabolized to lactate by glycolysis; this conversion is called the Warburg effect and is a phenomenon associated with inhibition of β-oxidation. Therefore, butyrate molecules assemble in the cancer cell cytoplasm and move towards the nucleus where they can inhibit cancer cell proliferation as suppressors of histone deacetylases (HDACs) (Vrzáčková et al., 2021).

Bacterial Lysates

The clinical use of bacterial lysates (BLs) is associated with the functional link found between the immune system of the gut and the respiratory system. Bacterial lysates (BLs) are formed by the chemical or mechanical change of Gram-positive

bacteria and Gram-negative bacteria of different species and large numbers in the environment. (Feleszko et al., 2007). A meta-analysis study of more than 4800 children in 2018 found a significantly lower incidence of respiratory infections in the case group compared to the control group using a commercially available BL preparation (Yin et al., 2018).

Therapeutic Benefits of Postbiotics

Although the mechanisms related to their beneficial effects on health have not been fully elucidated, studies have reported that postbiotics have antimicrobial, anti-inflammatory, antiobesogenic, antihypertensive, hypocholesterolemic, antiproliferative, antioxidant and immunomodulatory properties. It has been shown that these properties can positively affect microbiota homeostasis, physiological, immunological and metabolic reactions (Figure 2.) (Kvakova et al, 2022; Sharma & Shukla, 2016).

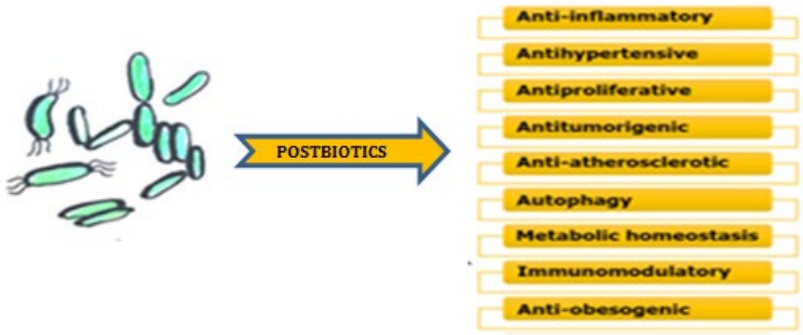

Figure 2. Examples of Postbiotics and Their Proposed Activity (Kvakova et al., 2022)

It has been proven that postbiotics provide health benefits with their immunomodulatory, anti-inflammatory and antibacterial properties, exhibiting local effects on certain tissues of the intestinal epithelium, and also exhibit systemic effects by affecting multiple organs or tissues in addition to preventing celiac disease, anticarcinogenic, antiproliferative benefits (Sharma & Shukla, 2016).

Certain postbiotics exert antitumor activity, including selective cytotoxicity against tumor cells suggesting their therapeutic potential (Figure 2.) (Fong et al., 2020).

Antitumor Effects of Postbiotics

Inflammation is inextricably linked with carcinogenesis, and therefore any agent that blocks inflammation is also assumed to play an anti-cancer role (Cousin et al., 2012). For example, SCFAs are well-known inhibitors of the epigenetic enzymes histone deacetylases, which play an effective role in gene regulation; thus SCFAs have the effects of inducing cell cycle arrest or cell apoptosis in multiple cancer cell pathways (King et al., 2021). Indeed, one study showed that SCFA propionate (produced by propionibacterium freudenreichii) selectively induces apoptosis in gastric cancer cells (Cousin et al., 2012).

Cell-free supernatants (CFS) of different strains of *Lactobacillus* and *Bifidobacterium* bacteria have been shown to induce apoptosis in cancer cells or inhibit proliferation of CRC cell lines (Escamilla et al., 2012). A study showed that high concentrations of supernatants of *Lactobacillus johnsonii* BCRC17010 and *Lactobacillus reuteri* BCRC14625 strains can damage HT-29 cell membranes by causing high lactate dehydrogenase release. A recent study reported a potent selective cytotoxic effect of postbiotic metabolites from *Lactobacillus plantarum* strains through anti-proliferative effects and

induction of apoptosis in HT-29 cells while sparing normal cells (Chuah et al., 2019; Chen et al., 2017).

Besides the immunomodulatory and anti-inflammatory effects of various *Lactobacillus* strains, anti-cancer effects are also mentioned. In a study with postbiotic *L. paracasei* IMPC2.1 and *L. rhamnosus* GG on cancer cells, it showed anti-proliferative and pro-apoptotic effects. Many different postbiotic *Lactobacillus* fractions, such as heat-inactivated cells, cell wall, peptidioglycan, and cytoplasmic fractions, can exert anti-cancer effects against human cancer cells (Orlando et al., 2012).

Studies have also shown that SCFAs affect the regulation of cancer cell genes oncogenes and cancer cell suppressor genes through epigenetic modifications. It has been reported that the postbiotic *L. rhamnosus* GG cell supernatant increases ZO-1 expression (responsible for cell adhesion and correct structure of tight junctions between cells) and decreases MMP-9 expression (facilitates cancer cell penetration by helping to break down the intercellular matrix). Indeed, differences in ZO-1 and MMP-9 levels caused by exposure to *L. rhamnosus* GG supernatant were effective in arresting colorectal tumor cell proliferation and decreasing activity in an in vitro study (Escamilla et al., 2012).

Cousin et al. (2012) showed that the metabolites consisting of *Propionibacterium freudenreichii* ITG-P9, namely propionate and acetate, induced intrinsic apoptosis of CRC cells by the production and release of SCFAs acting on mitochondria. In addition, CFS or SCFAs in combination with Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), increased proapoptotic gene expression (TRAIL-R2/DR5) and morever decreased the anti-apoptotic gene expression of FLIP and compared to XIAP in HT-29 cancer cells and human healthy intestinal epithelial cells, it showed an antitumor effect by increasing cytotoxicity in CRC cells. Further control studies are required to identify specific molecular targets in these models, as increased toxicity to acidic pH shifts from fermentation remains a potential protective mechanism (Cousin et al., 2012).

Anti-Metastasis Activity of Postbiotics

When we look at the definition of metastasis, it is the spread of cancer cells from the primary tumor to the surrounding tissues and distant organs in various ways. Metastases can develop years after the primary tumor is diagnosed, and this has become the main cause of death for more than 90% of cancer patients. The primary cause of metastasis development is due to the epithelial-mesenchymal transition (EMT) of primary cancer cells in the organism (Mohd Fuad et al., 2022). EMT is a physiological process in which epithelial cells and mesenchymal cells acquire their morphological and physiological characteristics. The stages of metastasis formation are shown (Figure 3) (Hapach et al., 2019).

E-cadherin is a vitally important protein for cell-cell adhesion. *Lactobacillus debrueckii* subsp. *lactis* exhibited a significant increase in E-cadherin levels in human carcinoma of uterine cervix cell lines (HeLa cells). Hence, the increased response of E-cadherin inhibited cancer cell migration (Mohd Fuad et al., 2022). Other than that, *Lact. reuteri* GMNL-89 and *Lact. paracasei* GMNL-133 treatment has been proven to reduce the expression of EMT-related markers in pancreatic cancer mouse models, reducing the risk of metastasis (Chen et al., 2020).

Kefir water, the grain-free supernatant, had antimetastatic and antiangiogenic effects when used in the treatment of murine breast cancer cells due to its ability to induce upregulation of tissue inhibitors of MMPs (TIMPs) (Zamberi et al., 2016). Postbiotics of *Lact. casei* and *Lact. rhamnosus* GG in the form of cell-free supernatants increased levels of the tight junction

protein ZO-1 as well as decreased levels of matrix metalloproteinase-9 (MMP-9). This resulted in a reduced incidence of colon cancer, and hence reduced metastatic effects (Mohd Fuad et al., 2022).

Disruption of the basement membrane is the first step in metastasis and can be inhibited by suppressing the VEGF-MMP2/9 signaling pathway. The cell-free supernatant postbiotic of *Lact. plantarum* YYC-3 suppressed the vascular endothelial growth factor (VEGF)-MMP2/9 signaling pathway, preventing metastasis of colon cancer cells. This is because VEGF is a signaling protein that significantly promotes the growth of blood vessels and matrix metalloproteinases (MMPs) adversely affect the extracellular matrix. Thus, postbiotic treatment was able to suppress the (VEGF)-MMP2/9 signaling pathway, helping to reduce the risk of colon cancer cells metastasis (Mohd Fuad et al., 2022). These findings demonstrate the antimetastatic abilities of probiotics and postbiotics against a variety of cancer cells.

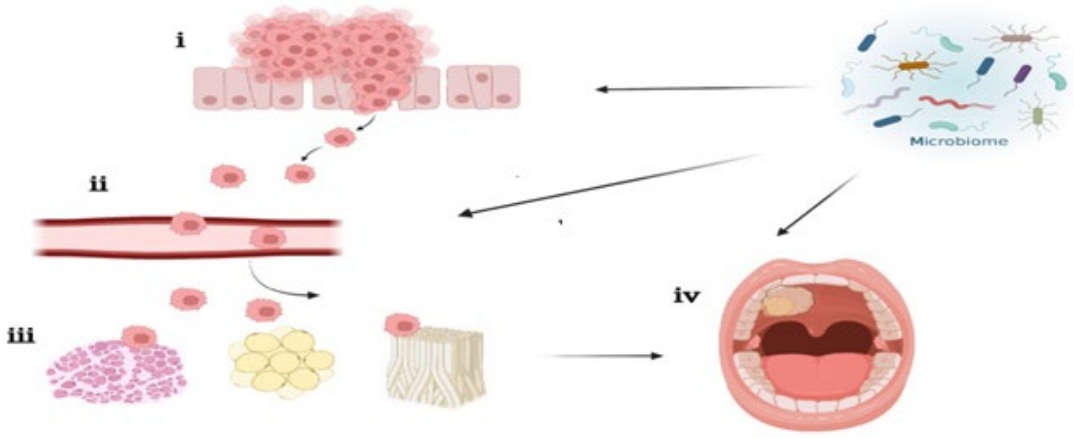

Figure 3. Mechanism of Metastasis in Oral Cancer Sample *(i) Infiltration of cancer cells through the basement membrane is shown, and their colonization as (ii) after intravasation into the surrounding vasculature or lymphatic system (iii) into secondary tissue and (iv) as secondary tumors is schematically illustrated in Figure-3 (Mohd Fuad et al., 2022).

Conclusion

According to recent research, postbiotics can be considered as an adjunctive treatment for cancer prevention and cancer treatment, and may also help reduce side effects caused by treatment methods. There are studies on postbiotics that generally focus on strain specificity. Research is also needed to determine the effectiveness and safety of postbiotics in the prevention and treatment of cancer, indicating appropriate doses of use. Additionally, postbiotic research has generally been conducted on experimental animals. More human studies are needed to examine the effects of postbiotics on cancer in detail. For these reasons, more studies are needed to evaluate the effects of postbiotics on cancer and metastatic cancer. Overall, these new treatments for cancer are worth exploring due to their broad potential.

Conflict of Interest

The authors declare that they have no conflicting interests.

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