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PROBIOTICS AGAINST PATHOGENIC BACTERIA AND CANCER

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Abstract

This review focuses on the role of probiotics as alternative prevention and treatment of cancer. In this regard, we discuss the alternative cancer biotherapeutic drugs including live or dead probiotics and their metabolites, such as short chain fatty acids, inhibitory compounds of protein, polysaccharide, nucleic acid and ferrichrome *in vitro, in vivo* and clinical studies. We also summarize the available data on the relationship between the development of cervical, breast and colorectal cancers, and microbiome, as well as data about the potential of probiotics as an alternative approach to cancer prevention and treatment. **Material and Methods.** A literature search was conducted using the Pubmed and eLibrary databases. Of 140 publications, the review included 57 studies. **Results.** The microbiome plays a crucial role in maintaining cellular and genetic stability within the body. It acts as a defense mechanism against infectious agents and various pathological processes including, cancers. The microbiome employs several strategies to neutralize carcinogenic agents. Preliminary clinical trials have yielded promising results, suggesting that probiotics may contribute to cancer prevention and enhance both the safety and efficacy of cancer treatment. However, further research is needed to confirm this suggestion. Current anticancer drugs often have significant drawbacks, including negative impact on patients’ quality of life, development of drug resistance, and high cost. **Conclusion.** The effectiveness of probiotic therapies appears to be influenced by several factors, such as the specific bacterial or fungal strain used, the dosage administered, and the duration of treatment. The review emphasizes the need for further rigorous clinical trials to validate the significant role of probiotics in cancer prevention and treatment. While existing research indicates promising results from probiotic treatments primarily in controlled settings, more extensive studies are required to assess both short-and long-term effects and establish standardized methodologies. This will help minimize potential side effects and find the way for the safe and effective application of probiotics as a medical intervention.

Key words: microbiome, probiotics, breast and colon cancer, gynecological cancers, cancer prevention and treatment.

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ПРОБИОТИКИ ПРОТИВ ПАТОГЕННЫХ БАКТЕРИЙ И РАКА

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Аннотация

Введение. Обзор фокусируется на роли пробиотиков в качестве альтернативных агентов для профилактики и лечения рака. В связи с этим в настоящем обзоре мы обсуждаем альтернативные биотерапевтические препараты для лечения рака, которые применяются в лабораторных условиях, *in vivo* и клинических исследованиях. Эти препараты включают живые или мертвые пробиотики и их метаболиты, в частности, короткоцепочечные жирные кислоты, ингибирующие соединения белка, полисахариды, нуклеиновые кислоты и феррихром. В обзоре представлены имеющиеся данные о взаимосвязи микробиома с развитием рака шейки матки, рака молочной железы и колоректального рака, а также данные о применении пробиотиков для профилактики и лечения рака. **Материал и методы.** Нами был проведен анализ современной литературы с использованием баз данных Pubmed и eLibrary. Из 140 статей на эту тему в обзор были включено 57. **Результаты.** Показано, что микробиом играет важную роль в поддержании клеточной и генетической стабильности в организме. Микробиом действует как защитный барьер от инфекционных агентов и при развитии различных патологических процессов, включая рак. Микробиом использует несколько стратегий для нейтрализации канцерогенных веществ. Предварительные клинические испытания показали, что пробиотики могут быть использованы для профилактики рака и могут влиять на эффективность противоопухолевой терапии. Однако для подтверждения данного предположения необходимы дальнейшие исследования. Современные противоопухолевые препараты часто имеют существенные недостатки, включая негативное влияние на качество жизни пациентов, развитие лекарственной устойчивости и высокую стоимость. **Заключение.** На эффективность пробиотической терапии влияют несколько факторов, таких как конкретный используемый штамм бактерий или грибков, применяемая дозировка, продолжительность лечения. В настоящем обзоре делается вывод о необходимости дальнейших клинических испытаний для подтверждения важной роли пробиотиков для профилактики и лечения рака. Необходимы более масштабные исследования для оценки как краткосрочных, так и долгосрочных эффектов пробиотиков, разработка стандартизированных методик. Применение таких подходов позволит снизить вероятность возникновения побочных эффектов и найти способ безопасного и эффективного применения пробиотиков в клинической практике.

Ключевые слова: микробиом, пробиотики, рак молочной железы, колоректальный рак, гинекологический рак, профилактика и лечение рака.

Introduction

Cancer remains one of the major causes of death worldwide. There is currently no definite cure for cancer. Despite recent advances in the development of anticancer chemotherapy drugs, as well as molecular targeted drugs, their efficiency does not exceed 50 %, therefore it is necessary to find other approaches to improve cancer treatment. Anti-cancer drugs affect the quality of life or promote drug resistance and are expensive enough for widespread use. Therefore, scientists are looking into clinical management of the cancer with high efficiency Multiple clinical strategies including chemotherapy, radiotherapy, and immunotherapy are introduced in practice to manage breast, colon and gynecological cancers. Besides the protective roles of conventional remedial approaches, and non-reversible and deteriorative impacts like healthy cell damage, organ failure, etc., the world scientific community is in a continuous struggle to find some alternative biocompatible and comparatively safe solutions. Among novel treatment modalities of breast cancer as well as other cancer management/treatment options, the role of probiotics has become immensely important [1].

It is well known that the gut microbiota changes or dysbiosis have an essential impact on the initiation and promotion of chronic inflammatory pathways and also have a profound different genetic and epigenetic

alterations leading to dysplasia, clonal expansion, and malignant transformation [2].

Probiotics are living microorganism community that exert potential pathogenic or protective effects, including modulating inflammatory condition and immune responses, affecting HR-HPV oncogene expression and oncoprotein production, regulating oxidative stress and deoxyribonucleic acid (DNA) damage, and inducing metabolic rewiring [3].

Colorectal cancer and probiotics therapy

Colorectal cancer (CRC) is a leading cause of human mortality worldwide. As conventional anticancer therapy not always being effective, there is growing interest in innovative "drug-free" cancer treatments or interventions that improve the efficacy of established therapy. CRC is associated with microbiome alterations, a process known as dysbiosis that involves depletion and/or enrichment of particular gut bacterial species and their metabolic functions. Supplementing patient treatment with traditional probiotics (with or without prebiotics), next-generation probiotics (NGP), or postbiotics represents a potentially effective and accessible complementary anticancer strategy by restoring gut microbiota composition and/or by signaling to the host.

In this capacity, restoration of the gut microbiota in cancer patients can stabilize and enhance intestinal barrier function, as well as promote anticarcinogenic, anti-inflammatory, antimutagenic or other important biochemical pathways showing high specificity towards tumor cells. Potential benefits of traditional probiotics, NGP, and postbiotics include modulating gut microbiota composition and function, as well as the host inflammatory response. Their application in CRC prevention is highlighted in this review, where we consider supportive in vitro, animal, and clinical studies. Based on emerging research, NGP and postbiotics hold promise in establishing innovative treatments for CRC by conferring physiological functions via the production of dominant natural products and metabolites that provide new host-microbiota signals to combat CRC. Although favorable results have been reported, further investigations focusing on strain and dose specificity are required to ensure the efficacy and safety of traditional probiotics, NGP, and postbiotics in CRC prevention and treatment [4].

The gut microbiome has an impact on cancer immune surveillance and immunotherapy. Recent studies have shown categorical differences between immunotherapy-sensitive and immunotherapy-resistant cancer patient cohorts. Although probiotics are traditionally being supplemented to promote treatments or sustain therapeutic benefits, the FDA has not approved any for use with immunotherapy. The first step in developing probiotics for immunotherapy is identifying helpful or harmful bacteria down to the strain level. The gut microbiome's heterogeneity before and during treatment is also being investigated to determine microbial strains that are important for immunotherapy. Moreover, dietary fiber intake, prebiotic supplementation and fecal microbiota transplantation (FMT) were found to enhance intratumoral CD8+ T cell to T-reg ratio in the clinics. The possibility of probiotic immunotherapy as a "living adjuvant" to CAR treatment and checkpoint blockade resistance is actively being investigated [5].

Probiotics change the microbial flora by implanting or colonizing some parts of the host's body with a fragment of DT A, which have a beneficial effect on his health [6]. Probiotic bacteria have been shown to manifest antitumor activity throw nonspecific physiological defense and by the initiation the immune response. This review gives the evidence generated in the in vitro and animal models that have explored how probiotics act against cancer development, paying specific attention to the immunomodulatory mechanisms.

Probiotics are defined as living microorganisms that, when administered in adequate quantities, benefit the health of the host. In the review of Sandra A Dos Reis et al. [7], the authors discussed the potential mechanisms of action of probiotics in the prevention of colorectal cancer, in the treatment of precancerous diseases (dysbiosis, adenomas, predisposition to polyposis, etc.)] [7]. In this regard, the composition of the intestinal microbiota is considered as an important risk factor for the development of colorectal cancer and precancerous diseases, and probiotics are able to positively modulate the composition of this microbiota. Studies have shown that regular use of probiotics can prevent the development of colorectal cancer. In this regard, in vitro and experimental studies suggest some potential mechanisms responsible for this anticancer effect. The mechanisms are as follows: modulation of the intestinal microbiota composition; changes in the metabolic activity of the microbiota; binding and degradation of carcinogenic compounds in the intestinal lumen; production of compounds with anticarcinogenic activity; immunomodulation, improvement of the intestinal barrier, changes in the physiology of the host; inhibition of cell proliferation and induction of apoptosis in cancerous and functionally damaged precancerous cells.

Microbiota modulation by probiotics can be considered as a part of a therapeutic regimen for patients with CRC. The interaction between diet, microbiota and host in maintaining homeostasis is an important factor in therapeutic strategies for CRC, and microbiome analysis is a critical component in understanding how these complex interactions affect the development and progression of carcinogenesis.

Probiotics in the inhibition and treatment of cervical cancer

Probiotics are widely used in the treatment of intestinal diseases, but the effect of probiotics on the health of the female reproductive tract is still controversial. Lactobacillus is the most common microorganism in

the vagina associated with the vaginal mucosal barrier. Lactobacilli adhere to the vaginal epithelium and can competitively resist pathogen colonization [8].

We review the progress of research on probiotics represented by Lactobacillus in gynecological diseases such as human papillomavirus (HPV) infection, bacterial vaginosis (BV) and genitourinary syndrome of menopause (GSM) to provide a basis for further identifying the role of probiotics in the treatment of gynecological diseases and women health.

The microbiota in the female genital tract is an intricate assembly of diverse aerobic, anaerobic, and microaerophilic microorganisms, which share the space within the reproductive tract and engage in complex interactions. Microbiome dysbiosis may disrupt the symbiotic relationship between the host and microorganisms and play a pivotal role in the pathogenesis of various diseases, including its involvement in the establishment of human papillomavirus (HPV)-associated cervical cancer (CC). Interventions to restore microbiota homeostasis (e.g., probiotics) and bacterial-vector HPV therapeutic vaccines have been reported to be potentially effective in clearing HPV infection and ameliorating cytological abnormalities. In this review, we place emphasis on elucidating the alterations within the cervical-vaginal microbiota as well as the intratumoral microbiota in the context of high-risk HPV (HR-HPV) infection and its subsequent progression to cervical intraepithelial neoplasia/CC [3]. Furthermore, we pay attention to the mechanisms by which these microbial communities exert potential pathogenic or protective effects, including modulating genital inflammation and immune responses, affecting HR-HPV oncogene expression and oncoprotein production, regulating oxidative stress and deoxyribonucleic acid (DNA) damage, and inducing metabolic rewiring. Lastly, we summarize the latest evidence in human trials regarding the efficacy of probiotics, prebiotics and probiotic-vector HPV therapeutic vaccines. This review aims to foster a deeper understanding of the role of the microbiota in HR-HPV infection-related cervix cancer development, and further provide a theoretical basis for the development of preventive and therapeutic strategies based on microbial modulation [9].

Various prebiotics, probiotics, and other non-medical medications have been reported to display therapeutic effects in cervical disorders. Numerous studies have reported an association between human papillomavirus infection and subsequent cervical dysplasia, as well as declines in Lactobacillus species. A continuum of microbiota composition is observed from the vagina to the upper parts of the FGT, but there is no evidence to suggest that manipulation of the vaginal microbiota can help change the composition of other compartments of the FGT [8].

Therefore, recommending probiotics, prebiotics, or other over-the-counter supplements for gynecologic cancer prevention requires larger, well-designed studies [8]. Probiotics are products containing a sufficient number of living microorganisms that change the microbial flora by implanting or colonizing some parts of the host's body with a fragment of DT A, which have a beneficial effect on his health [6].

Lactobacilli have been proposed as vaginal probiotics due to their properties, such as acidification of the vaginal environment, participation in the stabilization of the vaginal bacterial flora, the ability to adhere to vaginal epithelial cells and disease prevention. Several reports have shown that probiotic bacteria such as Lactobacillus casei *Lactobacillus plantarum*, *Lactobacillus rhamnosus GG* and *Lactobacillus acidophilus*, exert their antitumor effect by activating NK cells and maturing dendritic cells [10]. Various mechanisms by which lactic acid bacteria exhibit anticancer activity include [11]: the production of antitumor metabolites (such as short-chain fatty acids, lactic acid and bacteriocins); regulation of cell differentiation, inhibition of cancer cell migration and regulation of the immune system.

Moreover, the cell-free supernatants of lactic acid bacteria contain secretory compounds, such as bacteriocins, which are biologically active proteins and are known as antimicrobial peptides that disrupt cell wall synthesis and ultimately cause cell death. In addition, exopolysaccharides produced by heat-treated bacteria can inhibit cancer cells, significantly inhibiting the growth of pathogenic bacteria [12].

Lactobacillus is the most common microorganism in the vagina associated with the vaginal mucosal barrier. Lactobacilli adhere to the vaginal epithelium and can competitively resist pathogen colonization. Factors produced by lactobacilli, such as bacteriocin and hydrogen peroxide (H_2O_2), can inhibit the growth of pathogens and maintain a low pH level in the vagina. Probiotics play an important role in maintaining the stability of the vaginal microenvironment, enhancing immune defenses and blocking the progression of cervical cancer [8].

Currently, there are some investigations on probiotic effect against HPV associated cervix cancer. The effect of prebiotics on HPV clearance was investigated in four recent studies, three of which showed an increased rate of clearance of HPV infection following treatment. Five studies investigated the rates of cytological and colposcopic clearance of abnormalities, and all showed positive results following prebiotic treatment. In the study of Di Pierro and colleagues, none of the 35 participants had an L crispatus-dominant vaginal microbiota at baseline, but after 3 months of treatment with the L crispatus M247 probiotic, 33 (94 %) of 35 participants had switched to a L crispatus-dominant vaginal microbiota, as shown using Illumina MiSeq. Of the five studies investigating probiotics in cervical disease, only one showed increased rates of HPV clearance following treatment with *L. rhamnosus*, and four reported increased rates of clearance of cytological abnormalities. The duration of administration ranged

Table 1/Таблица 1

Antitumor effects of probiotic lactobacilli (conventional probiotics and lactobacilli)

Противоопухолевые эффекты пробиотиков lactobacilli (конвенциональные пробиотики и lactobacilli)

Effects/Эффекты	Mechanisms/Механизмы	Bacteria/ Бактерия	Reference/ Ссылка
Inducing apoptosis and inhibiting oncogenic signaling/ Индукция апоптоза и ингибиция онкогенных сигналов	Increasing expression of Caspase-3 and decreasing expression of Bcl-2, the prevention of colorectal cancer/ Увеличение экспрессии каспазы-3 и снижение экспрессии белка Bcl-2, предсказание эффективности терапии при колоректальном раке.	*Lactobacillus delbrueckii*	[7]
Inducing apoptosis and inhibiting oncogenic signaling/ Индукция апоптоза и ингибиция онкогенных сигналов	Upregulating the expression of apoptotic genes BAX, BAD, Caspase-3, Caspase-8 and Caspase-9 and downregulating the expression of the BCl-2 gene. Anticancer potential against cervix cancer (HeLa) cell line/ Up-регуляция экспрессии апоптотических генов *BAX, BAD*, каспаза-3, каспаза-8, каспаза-9. Down-регуляция экспрессии гена BCL-2	*Lactobacillus casei SR1, SR2, paracasei SR4*	[24]
Inducing apoptosis and arresting cancer cell cycle/ Индукция апоптоза и остановка цикла опухолевых клеток	Downregulating cell-cycle related genes and regulating human papillomavirus oncogenes. Inhibitory effect on cervical cancer cells/ Down-регуляция генов-регуляторов клеточного цикла и регулирование онкогенов вируса папилломы человека	*Lactobacillus jensenii* (supernatants)/ *Lactobacillus jensenii* (супернатант)	[25]
Inducing apoptosis and inhibiting proliferation/ Индукция апоптоза и ингибирование пролиферации	Enhancing Natural Killer cells activity and dendritic cells maturation/ Усиление активности естественных клеток-киллеров и созревания дендритных клеток	*Lactobacillus plantarum BF-LP284* (heat-killed)/ *Lactobacillus plantarum BF-LP284* (уничтожается при нагревании)	[26]
Inducing apoptosis and reducing cancer cells proliferation/ Индукция апоптоза и ингибирование пролиферации	Suppressing activity of Nuclear Factor-κB (NF- κB)/ Супрессорная активность NF-kB	*Pediococcus pentosaceus GS4*	[27]
Activating immune system/ Активация иммунной системы	Stimulating Natural Killer cells activation and dendritic cells maturation (Anticancer effects of the microbiome and its products)/ Стимулирование активации естественных клеток-киллеров и созревания дендритных клеток (Противоопухолевые эффекты микробиома и его продуктов)	*Lactobacillus rhamnosus GG*	[10]
Activating immune system/ Активация иммунной системы	Enhances antigen-specific IgA secretion. Inducing Interleukin (IL)-12 and follicular helper T cells secretion/ Усиливает секрецию антигенспецифического иммунноглобулина А (IgA). Стимулирует секрецию интерлейкина 12 (IL-12) и фолликулярных хелперных Т-клеток	*Lactobacillus casei Paracasei MCC1849* (orally administered heat-killed)/ *Lactobacillus casei Paracasei MCC1849* (при пероральном приеме уничтожается при нагревании)	[28]
Modulating immune system/ Модулирование иммунной системы	Decreasing the production of TNF-α and increasing the IL-10 production cervical tumor cells (HeLa)/ Снижение выработки TNF-α и увеличение выработки IL-10 опухолевыми клетками шейки матки (HeLa)	*Exopolysaccharides (EPSs) of Lactobacillus gasseri*/ *Экзополисахариды (EPSs) Lactobacillus gasseri*	[29]
Inhibiting cancer cells migration/ Ингибирование миграции опухолевых клеток	Upregulating expression of E-cadherin/ Up-регуляция экспрессии Е-кадхерина	*Lactobacillus delbrueckii*	[30]
Inhibiting proliferation and migration of cancer cells/ Ингибирование пролиферации и миграции опухолевых клеток	Activating Phosphatase and tensin homolog (*PTEN*) and inhibiting AKT pathways/ Активация гомолога фосфотазы и тензи (*PTEN*) и ингибирование AKT сигнального пути	*Pseudomonas aeruginosa mannose-sensitive hemagglutinin* (PAMSHA)/ Гемагглютинин, чувствительный к маннозе *Pseudomonas aeruginosa* (PAMSHA)	[31]

End of Table 1/Окончание таблицы 1

Antimicrobial effect on carcinogenic bacteria *Salmonella Typhimurium and Enterohaemorrhagic Escherichia coli*/ Антимикробный эффект в отношении канцерогенных бактерий *Salmonella Typhimurium* и *Enterohaemorrhagic Escherichia coli*	Increasing the production of conjugated linoleic acids (CLAs)/ Увеличение продукции конъюгированных линолевых кислот (CLAs)	*Lactobacillus casei ATCC 334* (LC-WT)	[32]
Modulating immune system/ Модулирование иммунной системы	Decreasing the production of TNF-α and increasing the IL-10 production/ Снижение продукции TNF-α и увеличение продукции IL-10	*Lactobacillus gasseri* (anaerobe)/ *Lactobacillus gasseri* (анаэробы)	[29]
Inhibiting oncogenic signaling. Antiviral activity/ Ингибирование онкогенных сигналов. Антивирусная активность.	Suppressing *E6* and *E7* oncogene expression/ Подавление экспрессии онкогенов *E6* и *E7*	Bifidobacterium adolescentis SPM1005-A	[33]
Inhibit cervical cancer cell migration in vitro and reduce tumor burden/ Ингибирование миграции опухолевых клеток при раке шейки матки и редукция опухолевой массы	Upregulation of E-cadherin/ Up-регуляция Е-кадхерина	*Lactobacilli spp* (*in vitro*)	[30]
Cytotoxicity effects on cancer cells/ Цитотоксические эффекты на опухолевые клетки	–	*Lactobacillus plantarum* (postbiotic metabolites)/ *Lactobacillus plantarum* (постбиотические метаболиты)	[34]

Note: created by the authors.

Примечание: таблица составлена авторами.

from 3 to 12 months or, in one study, until the high-risk HPV DNA test yielded negative results. One of the five studies reported the use of a placebo agent. The size of the study cohorts ranged from 35 to 160 women. It were unable to identify any studies investigating the use of prebiotics or probiotics for the prevention of endometrial, epithelial ovarian, vulval, or vaginal malignancy [8].

Lactobacilli have been considered as vaginal probiotics due to their properties, such as acidification of the vaginal environment, participation in the stabilization of the vaginal bacterial flora, the ability to adhere to vaginal epithelial cells and disease prevention [10, 11].

Moreover, the cell-free supernatants of lactic acid bacteria contain secretory compounds such as bacteriocins, which are known as antimicrobial peptides that disrupt cell wall synthesis and ultimately cause cell death. In addition, exopolysaccharides produced by heat-treated bacteria can inhibit cancer cells, significantly inhibiting the growth of pathogenic bacteria [13].

Engineering bacteria for the treatment of cervical cancer

Currently, there is convincing evidence confirming the interest in the use of lactic acid bacteria (ICD), in particular, strains of lactococci and lactobacilli, as well as bifidobacteria, for the development of new living vectors for the purposes of protecting human and animal health. ICD is a gram-positive bacteria that has been used for thousands of years to produce fermented foods. In addition, numerous studies have shown that genetically modified lactic acid bacteria and bifidobacteria can induce a systemic and mucosal immune response against certain antigens when administered through the mucous membrane. Therefore, they are good candidates for developing new strategies for delivery through the mucous membrane and are an attractive alternative to vaccines based on attenuated pathogenic bacteria, the use of which poses a health risk. The development of molecular biology, obtaining genome-wide sequences of many bacteria-representatives of the microbiota (bacterial genome sequences) and the development of new methods of genetic modification of bacteria and mammalian cells have expanded the possibilities of using bacteria to treat cancer [14]. Genetically engineered bacteria have demonstrated good potential for the diagnosis and treatment of a wide range of diseases. The researchers plan that the engineered bacteria will be cost-effective, minimally invasive, safe and more effective than conventional treatments [15]. In a study by Zitvogel et al. [10], engineered bacteria were able to enhance

Table 2/Таблица 2

Antitumor effects of probiotic bacteria of the transient microflora (Bacillus spp)
Противоопухолевые эффекты пробиотических бактерий транзиторной микрофлоры (Bacillus spp)

Effects/Эффекты	Mechanisms/Механизмы	Bacteria/commercial foreign drugs/ Бактерия, коммерческие зарубежные препараты	Reference/ Ссылка
Immunomodulatory and antimicrobial properties. Growth inhibition of the chancellor-associated strain of *Helicobacter pylori*/ Обладает иммуномодулирующими и антимикробными свойствами. Подавление роста штамма *Helicobacter pylori,* ассоциированного с раком	Increased interferon production, mitogenic T cell proliferation, and mitogen-induced lymphokine production in *ex vivo* and *in vivo* models/ Повышенная выработка интерферона, митогенная пролиферация Т-клеток и индуцированная митогеном выработка лимфокинов в моделях *ex vivo* и *in vivo*	*Bacillus clausii* Domuvar (BioProgress SpA., Italy); Enterogermina (Flora-Balance, USA); Lactopure (Pharmed Medicare, India); Lactospore (Sabinsa Corp., USA); Neolactoflorene (Newpharma S.r.l., Italy); Sustenex (Ganeden Biotech Inc., USA)/*Bacillus clausii* Домувар (BioProgress SpA., Италия); Энтерогермина (Flora-Balance, США); Лактопур (Pharmed Medicare, Индия); Лактоспора (Sabinsa Corp., США); Неолактофлорен (Newpharma S. r.l., Италия); Сустенекс (Ganeden Biotech Inc., США)	[35, 36]
Antimicrobial action against a wide range of intestinal opportunistic bacteria with carcinogenic potential/ Антимикробное действие против широкого спектра кишечных условно-патогенных бактерий, обладающих канцерогенным потенциалом	Production of coagulants, bacteriocins/ Производство коагулянтов, бактериоцинов	*Bacillus coagulans*, spore-forming lactic acid-producing bacteria//Lactopure/Pharmed Medicare (India), Neolactoflorene/Newpharm S.r.l. (Italy) and Sustenex/Ganeden Biotech Inc. (USA)/*Bacillus coagulans*, спорообразующие бактерии, продуцирующие молочную кислоту//Lactopure/ Pharmed Medicare (Индия), Neolactoflorene/Newpharm S.r.l. (Италия) и Sustenex/Ganeden Biotech Inc. (США)	[37]
Antimicrobial effect by reducing the pH of the microenvironment/ Антимикробный эффект за счет снижения pH микросреды	Lactic acid production/ Производство молочной кислоты	Bacillus coagulans	[38]
Bactericidal and bacteriolytic effects against cancer-associated opportunistic bacteria (*Listeria spp.*)/ Бактерицидное и бактериолитическое действие против условно-патогенных бактерий, ассоциированных с раком (*Listeria spp.*)	Production of a new anti-listerial bacteriocin (coagulin)/ Производство нового противоопухолевого бактериоцина (коагулина)	*Bacillus coagulans I4*	[39]
Inhibition of cancer cell growth/ Ингибирование роста опухолевых клеток	Production of cytotoxic enterotoxins/ Продукция цитотоксических энтеротоксинов	*B. cereus*//Bactisubtil (Marion Merrell Dow Laboratories, France; Hoechst, France; Aventis Pharma, France; Cassella-Med, Germany); Biovicerin (Geyer Medicamentos S.A. Porto Alegre, Brazil); Subtyl (Mekophar, Vietnam)/*B. cereus*//Бактисубтил (Marion Merrell Dow Laboratories, Франция; Hoechst, Франция; Aventis Pharma, Франция; Cassella-Med, Германия); Биовицерин (Geyer Medicamentos S.A., Порту-Алегри, Бразилия); Субтил (Мекофар, Вьетнам)	[40]
Enhances cognitive functions and glucose homeostasis in diabetic rats with experimental Alzheimer's type dementia/ Улучшает когнитивные функции и гомеостаз глюкозы у крыс с диабетом и экспериментальной деменцией по типу болезни Альцгеймера	Regulation of glucose homeostasis and accumulation of b-amyloid in the hippocampus of the brain/ Регуляция гомеостаза и накопление β-амилоида в гиппокампе головного мозга	*Bacillus licheniformis* (in combination with other probiotics: с *B.subtilis*/Biosporin (Biopharma, Ukraine; Gas (Russia); MegaSporeBiotic (Microbiome Labs, USA)/Лихениформис (в комбинации с другими пробиотиками: с *B.subtilis*/Биоспорин («Биофарма», Украина; «Газ», Россия); МегаСпореБиотик («Лаборатории микробиома», США)	[41]

Table 2/Таблица 2

Antioxidant and anti-inflammatory properties, influence on the physical barrier function of the intestine, induction of improvement of the composition of the intestinal microbiota with a higher ratio of beneficial bacteria and a lower content of opportunistic bacteria/ Обладает антиоксидантными и противовоспалительными свойствами, влияет на физическую барьерную функцию кишечника, способствует улучшению состава кишечной микробиоты с более высоким содержанием полезных бактерий и более низким содержанием условно-патогенных бактерий.	Increased synthesis of superoxide dismutase and glutathione peroxidase enzymes; decreased serum IL-1 levels ($P < 0.05$); increased intestinal morphological integrity (villi height, crypt depth, dense compounds (ZO-1, claudine-1 and occludin) and functional lipase activity in the intestine/ Увеличение синтеза ферментов супероксиддисмутазы и глутатионпероксидазы; снижение уровня IL-1 в сыворотке крови ($P < 0,05$); повышение морфологической целостности кишечника (высота ворсинок, глубина крипт, наличие плотных соединений (ZO-1, клаудин-1 и окклюдин) и функциональной активности липазы в кишечнике	*B. licheniformis DSM5749*	[42]
Antimicrobial properties against *S. aureus KCM 32359*, *Clostridium perfringens ATCC3624* and *H. pylori* associated with carcinogenesis/ Антимикробные свойства в отношении *S. aureus KCM 32359*, *Clostridium perfringens ATCC 3624* и *H. pylori*, ассоциированных с канцерогенезом	Production of polyfermentsin SCD (bacteriocin)/ Продукция полиферментицина SCD (бактериоцин)	*Bacillus polyfermenticus SCD*//Bispan, Binex Co., Ltd.)/*Bacillus polyfermenticus SCD*//Биспан, Binex Co., Ltd.)	[43]
Antitumor effect/ Противоопухолевый эффект	Inhibits the expression of ErbB2 ErbB3 in colorectal cancer tumor cell cultures (HT-29, DLD 1, and Caco-2)/ Ингибирование экспрессии ErbB2 ErbB3 в культуре клеток при колоректальном раке HT-29, DLD 1 и Caco-2	*B. polyfermenticus SCD*//Bispan (Binex Co. Ltd., South Korea/*B. polyfermenticus SCD*//Биспан (Binex Co. Ltd., Южная Корея)	[44]
Inhibition of cancer cell growth/ Ингибирование роста опухолевых клеток	–	Bacillus polyfermenticus KU3	[45]
Antimicrobial, antiviral and antitumor properties, regulation of the microbiome composition of broiler chickens/ Антимикробные, противовирусные и противоопухолевые свойства, регуляция состава микробиома цыплят-бройлеров	–	*Bacillus subtilis DSM 32315*//Biocult (Protein Health Care), Biosporin (Biofarma, Ukraine).; Garars (Russia), Lactan Plus (Instituto Biochimico Italiana SpA, Italy), Bibactil (Tendifar Corporation, Vietnam), Biosubtil (IVAC, Vietnam), Bidisubtilis (Bidifar Binh Dinh Pharmaceutical Company, Vietnam) and Biobaby (Ildong Pharmaceutical Co. Ltd., Korea)/*Bacillus subtilis DSM 32315*//Биокульт (Protein Health Care), Биоспорин (Биофарма, Украина); Гаррард (Россия), Лактан Плюс (Институт биохимии Итальяно СпА, Италия), Бибактил (Корпорация Тендифар, Вьетнам), Биосубтил (IVAC, Вьетнам), Бидисубтилис (фармацевтическая компания Бидифар Бинь Динь, Вьетнам) и Biobaby (Ildong Pharmaceutical Co. Ltd., Корея).	[46, 47]
Inhibits the adhesion of *Salmonella enteritidis, Listeria monocytogenes* and *E. coli* to HT-29 cells/ Ингибирование адгезии *Salmonella enteritidis, Listeria monocytogenes* и *E. coli* к HT-29 клеткам	–	B. subtilis P223 inhibits the adhesion of Salmonella enteritidis, Listeria monocytogenes and E. coli to HT-29 cells/B. subtilis P223 ингибирует адгезию *Salmonella enteritidis, Listeria monocytogenes* и *E. coli* к клеткам HT-29	[48]
Inhibition of growth of conditionally pathogenic bacteria, including *H.pylori*/ Подавление роста условно-патогенных бактерий, включая *H. pylori*	Secretion of antibiotics amicumacin A and neamicumacin/ Секреция антибиотиков амикумацина А и неамикумацина	*Bacillus subtilis 3 (B.subtilis 2335/105 Subalin recipient)*/Bacillus subtilis 3 (реципиент субалина *B.subtilis 2335/105*)	[49]

End of Table 2/Окончание таблицы 2

Antiviral activity against DNA and RNA viruses (influenza virus, herpes virus and equine encephalomyelitis virus)/ Противовирусная активность в отношении ДНК- и РНК-вирусов (вирус гриппа, вирус герпеса и вирус энцефаломиелита лошадей)	–	*Bacillus subtilis 3 in vitro and in vivo models (mice)*/ Bacillus subtilis 3 на моделях *in vitro* и *in vivo* (мыши)	[50]
Antiviral effect/ Антивирусный эффект	Production of peptide P18 with antiviral activity/ Выработка пептида P18, обладающего противовирусной активностью	*Bacillus subtilis 3,* on animal models/*Bacillus subtilis 3,* на животных моделях	[51]
Regulation of hemostasis, reduction of blood clotting/ Регуляция системы гемостаза, снижение свертываемости крови	Production of fibrinizing enzymes/ Производство фибринизирующих ферментов	*B. subtilis Hammo*	[23, 52, 53]
Causes a shift in the intestinal microbiome of broilers towards butyrate-producing bacteria (Ruminococcus, Lachnoclostridium and Anaerostipes, and improves intestinal histomorphology and animal productivity/ Вызывает сдвиг в микробиоме кишечника бройлеров в сторону бактерий, продуцирующих бутират (*Ruminococcus, Lachnoclostridium* и *Anaerostipes*), а также улучшает гистоморфологию кишечника и продуктивность животных	Induction of butyrate in butyrate-producing bacteria and metabolites that help strengthen intestinal barrier function/ Синтез бутирата бактериями и метаболитами, продуцирующими бутират, которые помогают укрепить барьерную функцию кишечника	*Bacillus subtilis 29784*	[54]
Induce the production of interferon IFN in the cells of the mucous membranes/ Индуцируют выработку интерферона IFN в клетках слизистых оболочек	–	*B. subtilis* controversies/споры *B. subtilis*	[55]
Microbiome Editing: an increase in the number of *Christensenellaceae* and *Caulobacteraceae* and a decrease in the concentration of *Vampirovibrio, Escherichia/Shigella* and *Parabacteroides* in broiler chickens/ Редактирование микробиома: увеличение количества *Christensenellaceae* и *Caulobacteraceae* и снижение концентрации *Vampirovibrio, Escherichia/Shigella* и *Parabacteroides* у цыплят-бройлеров	–	Bacillus subtilis DSM 32315	[56]
Immunomodulating and immunostimulating activity restores age-related decrease in immune responses in an experiment on mice/ Иммуномодулирующая и иммуностимулирующая активность восстанавливает возрастное снижение иммунных реакций в эксперименте на мышах	In 22-month-old mice, the production of IFN and IFN type was restored to the levels of these indicators in the blood plasma of 19-week-old mice/ У 22-месячных мышей выработка IFN и IFN-типа восстановилась до уровней этих показателей в плазме крови 19-недельных мышей	*B. subtilis per os*	[57]

Note: created by the authors.

Примечание: таблица составлена авторами.

the anti-cancer effect of 5-fluorouracil (5-FU) on a mouse model [10].

Engineered bacteria have also been used to treat cervical cancer. Komatsu et al. [16] reported that a therapeutic HPV vaccine based on a recombinant strain of *L. casei* producing E7 papillomavirus type16 antigens can induce a mucosal immune response to the E7 antigen due to the production of mucosal immunity by IFNG-producing Th1 cells and can be used for the treatment of grade 2 and 3 cervical intraepithelial neoplasia of the 2nd and 3rd degree (CIN2 and CIN3), which are is a precancerous disease for which there is no conventional therapy [16]. After additional optimization of the expression level of the E7 gene, placebo-controlled randomized clinical trials of the strain for the treatment of patients with HPV16-positive CIN2 were conducted. Only in the GLBL101c group, two patients had complete regression (CR; regression to normal for 16 weeks) and E7-specific Th1 immune responses in the mucosal link were observed. The authors believe that further improvement of the strain with higher immunogenicity is necessary. Considering that IL-12 has been successfully used in immunotherapy and cancer therapy for a long time, a recombinant probiotic secreting the native heterodimeric form of IL-12 was constructed on the basis of the probiotic strain Lactococcus lactis. The biological activity of IL-12 produced by *L. lactis* was confirmed in vitro on mouse spleen cells and in vivo by intranasal administration to mice and as an adjuvant by combining them with *L. lactis* expressing the E7 antigen. To assess the preventive and curative capabilities of recombinant lactococcus, a mouse model was developed in which tumors were induced by subcutaneous cell implantation. The results showed that prophylactic administration of lactococci before injection of tumor cells led to inhibition of tumor development in 50 % of immunized animals. In addition, a significant adjuvant effect of IL-12 co-delivered with the E7 antigen was found; in the absence of an IL-12-producing strain, tumor disappearance was observed in only 25 % of immunized mice. Moreover, mice immunized with LL-E7 and LL-IL12, were able to resist the second exposure (2 months after the first immunization), which indicates the persistence of induced immunity [17]. Therapeutic use of these strains in mice with already implanted tumors led to complete regression of tumors in 35 % of treated animals. These antitumor effects were the result of a cytotoxic response dependent on CD4+ and CD8+ T-lymphocytes. These results in mice represent the first evidence of a preventive and curative effect against cervical cancer by vaccination of the mucous membrane with strains. Probiotics from lactobacilli are the most technologically developed and studied. The thousand-year history of the safe use of these probiotics in the composition of lactic acid food products is the main confirmation of their usefulness and harmlessness to humans. The antitumor properties of lactobacilli in probiotics are presented in Table 1. However, their use as commercial products in various probiotic forms is limited by some factors: loss of viability in the aggressive environment of the gastrointestinal tract when ingested, which requires the development of encapsulated forms and protective coatings; limited shelf life by the requirements of a cold chain; the mechanism of interaction of lactobacilli with epithelial cells has not been fully studied, strains associated adhesion and biofilm formation are observed, which undoubtedly limits the use of lactobacilli as a vector for the delivery of bioactive antitumor molecules, in particular cytokines, interferons, etc., since proper pharmacological dose-dependent control is not provided.

An alternative and supplement to lactic acid bacteria in the arsenal of probiotics are probiotics based on the transient normal microflora of bacteria of the genus Bacillus. They also have a centuries-old history of human use of pickling products, and in some of them, for example, in sauerkraut, the content reaches a therapeutic dose (in 1 g/105–8). The antitumor properties of bacteria of the genus Bacillus and probiotics based on them are presented in Table 2. The absence of adhesive properties, the existence in two physiological forms (vegetative and spore) makes these bacteria an attractive vaccine vector for the delivery of heterologous antigens to the human and animal body, and the use of these bacteria as a pharmacological vector for the delivery of biologically active molecules with antitumor and antiviral effects is also promising. Thus, we have constructed the world's first recombinant probiotic (SUBALIN secreting interferon alpha 2b) based on a recipient probiotic strain that is a part of a Biosporin approved for use in medicine. Antitumor efficacy exceeding the recipient's effects by an order of magnitude, the stability of interferon production in pharmacologically limited terms in volunteers, absolute harmlessness (intraperitoneal administration in doses a hundredfold higher than therapeutic) allowed us to hope for a successful the use of Subalin and its improved forms for the prevention and treatment of cancer in humans [18)].

Microbiome editing strategies with probiotics based on transitor microflora *Bacillus spp.s*

Editing of the human microbiome by probiotic microorganisms is one of the most successfully implemented strategies proposed for the treatment of syndromes of civilization, such as dysbiosis, disorders of the gastrointestinal tract._Probiotics have immunomodulatory properties, antitumor effects and contribute to lowering cholesterol levels. Their function depends on their metabolites, such as bacteriocin, biosurfactant, exopolysaccharide and siderophore, etc. [19]. Recently, the potential effects of psychobiotics on brain cells or emotions have been investigated. These mechanisms are based on the modulation of the intestinal microbiome, which mediates its action through the production of anti-inflammatory cytokines

that affect cognitive functions, causing hyperglycemia. The use of probiotics for many socially significant diseases related to metabolism, tumor, neurodegenerative processes is justified, and the list is constantly expanding. Great hopes are associated with overcoming the antibiotic resistance of pathogens by replacing antibiotics with probiotics with targeted antagonistic properties against pathogens. Based on the results of experimental studies, it is assumed that the effect of probiotics administered orally will not be limited only to the microbiome of the intestinal region, but will be extended to the microenvironment of cells of the urogenital tract, and the tissue microenvironment of immune cells and tumors. The spores of probiotic bacteria are able to be translated through immune barriers, interacting with immune cells and thus providing immunomodulatory and immunoactivating effects [20]. Bimodal probiotic strains of the genus Bacillus make up the microbiota of the human environment and are usually found everywhere in soil, water, a number of non-dairy fermented foods, as well as in the gastrointestinal tract of humans and animals. Some researchers believe that microorganisms Bacillus are a normal component of the human intestinal microflora. And although the number of bacilli existing in the intestine is less than, for example, bifidobacteria, but they regularly in large quantities (107–108 CFU) in fall with food, water, air into the gastrointestinal tract and respiratory tract of healthy people [20]. Probiotic Bacillus spp. are gram-positive bacteria capable of spore formation, which, unlike vegetative cells, have a unique resistance to environmental factors and technological effects during manufacture. Bacillus probiotic spores, as demonstrated by Bernardeau et al. [21], germinate, grow and resporulate in the gastrointestinal tract. The mechanisms of the life cycle and sporulation were studied on an in vitro human stomach model and clinical trials of the properties of probiotic *Bacillus subtilis* [21]. *Bacillus sp.* has a biochemical effect such as antimicrobial and enzymatic activity and other activities (Table 2), thereby contributing to the protection of the gastrointestinal mucosa from conditionally pathogenic and pathogenic microorganisms associated with cancer – pathogens of infections, as well as protection from various toxins and heavy metals [20]. Despite the wide range of beneficial properties for humans, most Bacillus strains belonging to the GRAS safety group are generally recognized as safe (usually considered safe). A number of strains can pose a significant health risk because they carry genes of various toxins, enzymes or antibiotic resistance. The authors note the strictly strain-dependent harmlessness characteristic of this genus, since among the representatives there are strains with increased adhesion to epithelial cells, causing infections and dysbiotic conditions. Therefore, it is emphasized the need for accurate identification of strain affiliation using modern methods of analysis, primarily 16RNA sequencing in combination with MALDI-TOF analysis, as well as determining the presence of toxicity genes in the genome [22]. Promising application of probiotics *Bacillus spp.* can become a biocontrol of microflora in the human body and the immediate human environment [23].

Harmlessness (intraperitoneal administration in doses hundredfold higher than therapeutic ones) allowed us to hope for a successful use of Subalin and its improved forms for the prevention and treatment of cancer in humans.

Conclusion

Advances in omics technologies and new sequencing methods are enabling additional studies of the human microbiome for its use in cancer prevention and treatment.

Preliminary clinical trials have yielded promising results, suggesting that probiotics may contribute to cancer prevention and enhance both the safety and efficacy of cancer treatment.

The need for cancer prevention and therapy already at the stage of dysbiosis, which can directly affect the development, progression and stability of cancer, is becoming more and more obvious. Due to the gut microbiome's heterogeneity, the first step in developing probiotics for immunotherapy is identifying helpful or harmful bacteria down to the strain level. In addition, the use of non-pathogenic bacteria or bacterial products (probiotics) with antitumor properties expands the horizons for the development of new and more effective methods of cancer prevention and treatment.

A wide range of biological activity of bacteria suggests the possibility of creating different forms of medicinal bacilli, for many of them there are already medicines. An important factor for success is the resource base, the use of which, with the use of modern technological capabilities, opens up horizons for the development of this area of drug treatment of malignant neoplasms. The available data suggest that future research protocols should be standardized and include microbiome, virome, and mycobiome interactions, as well as the effects of antibiotics or probiotics on microbiome shifts.

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Conflict of interests

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