https://doi.org/10.15407/microbiolj86.06.074

L.A. SAFRONOVA[1*], Y.V. PYLYPIUK[2], I.O. SKOROCHOD[1], Z.M. POLOVA[3]

[1] Zabolotny Institute of Microbiology and Virology, NAS of Ukraine,
154 Akademika Zabolotnogo Str., Kyiv, 03143, Ukraine
[2] Poltava State Medical University,
23 Shevchenko Str., Poltava, 36011, Ukraine
[3] Bogomolets National Medical University,
22 Yevhena Chykalenka Str., Kyiv, 01004, Ukraine

*Author for correspondence; e-mail: safronova_larisa@ukr.net

PROBIOTICS AND THEIR POTENTIAL FOR THE PREVENTION AND TREATMENT OF INFECTIONS

The study of the properties of probiotic microorganisms is currently a relevant area in microbiology, biotechnology and medicine, which expands our knowledge of the evolution of their relationship with the human body and its microbiome, and also opens up new prospects for the practical use of active probiotic strains to maintain health and prevent and treat various pathological conditions. The review provides data on the known biological effects of probiotics, characterized mechanisms of the body's relationship with probiotic microorganisms, and highlighted their role in improving immunological status. Particular attention is paid to the possibilities of practical use of probiotic microorganisms, particularly strains of the genus Bacillus, for the treatment of infectious diseases. The results of studies confirming the effectiveness of probiotic strains against pathogenic microorganisms are presented.

Keywords: *probiotic microorganisms, microbiome, biological effects, Bacillus, biologically active metabolites, infectious diseases, antibiotic resistance, methicillin-resistant Staphylococcus aureus.*

Probiotics are among the effective and safe products for revitalization of the human body, which are now widely used in clinical practice. As defined by the World Health Organization (WHO) (2001), probiotics are «living microorganisms that, when used in adequate doses, promote the health of the host» (Health and nutritional properties of probiotics in food including

Citation: Safronova L.A., Pylypiuk Y.V., Skorochod I.O., Polova Z.M. Probiotics and their Potential for the Prevention and Treatment of Infections. *Microbiological journal.* 2024 (6). P. 74—91. https://doi.org/10.15407/microbiolj86.06.074

powder milk with live lactic acid bacteria. FAO, WHO, Argentina; 2001) and are included in compositions of certain fermented food products, tablets, powders, and liquid drops.

At the beginning of the twentieth century, the concept of probiotics was proposed by Nobel laureate I.I. Mechnikov, who created the first analogs of modern probiotics based on lactic acid bacteria with high antagonistic activity against purulent gut microbiota. First of all, the ability to inhibit the development of pathogenic microorganisms is primarily associated with the health-promoting preventive and therapeutic functions of probiotics. In addition, they have immunomodulatory properties that can stimulate the proliferation and differentiation of epithelial cells and help strengthen the intestinal barrier (Aponte et al., 2020; Javanshir et al., 2021).

Over the past 20 years, interest in probiotics has been growing rapidly, due to the increasing amount of scientific evidence of their benefits to human health. (Liu et al., 2018; Skoufou et al., 2024). The results of many clinical trials have shown that probiotics can be useful in the treatment and prevention of various diseases and health problems. Advantages of their use include the protective effect of probiotics on the digestive tract, metabolism, antioxidant, anti-inflammatory, antimicrobial, anti-tumor, and psychobiotic properties (Fu et al., 2023; Ross, 2023). Health-friendly microorganisms can compete with pathogens and modulate the intestinal microbiota, as well as provide immunomodulatory effects, anti-obesity, anti-diabetes, and anti-cancer. In addition, recent studies have shown that probiotics can neutralize COVID-19 infections. Thus, probiotics have become an alternative to several drugs, including antibiotics (Mohseni et al., 2018; Das et al., 2022).

The probiotics market is currently growing exponentially and is estimated to reach $85.4 billion by 2027 (http://www.marketsandmarkets.com/PressReleases/probiotics.asp).

The most common species of microorganisms used in probiotic research and development include *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Enterococcus*, *Streptococcus,* and *Saccharomyces.* Most of them are considered as commensal gut microbiota (Aponte et al., 2020).

The accumulation of evidence of the therapeutic and prophylactic efficacy of probiotics demonstrates the growing importance of discovering new probiotic strains with reliable functionalities that have great potential for commercialization worldwide as functional foods and therapeutic agents.

The mechanisms responsible for the various probiotic effects. The beneficial effect of probiotics is determined by the strain characteristics of their components. Some of them are able to modify the microbiome composition and influence its functions (Ciorba, 2012; Yang et al., 2022), while others can prevent metabolic disorders by normalizing cholesterol levels, increasing insulin sensitivity, improving tolerance to lactose and other food compounds, etc. (de Preter et al., 2011; Jones et al., 2013, 2014), as well as improving human sensory and motor functions (Ciorba, 2012; Pracash et al., 2011; Ross, 2023).

The mechanisms of action of probiotics include inhibition of pathogen adhesion; enhancement of mucosal barrier function; modulation of the innate and adaptive immune system (including induction of tolerogenic dendritic cells and regulatory T-cells); release of bioactive metabolites; regulation of the intestinal microbiota and central nervous system (Liu et al., 2018; Wang et al., 2021).

Probiotic mechanisms involved in microbiome reorganization include coaggregation, production of surfactants, biosynthesis of bacteriocins and hydrogen peroxide, competitive pressure, modification of nutrient composition, etc. (Reid et al., 2011; Teame et al., 2020). In particular, aggregation of probiotic strains with pathogenic strains can interfere with

pathogenesis, and biosynthesis of surfactants can prevent pathogens from adhering to the host tissue surface.

Metabolomic studies have shown that the effect of probiotics on numerous metabolic processes is associated with the synthesis of short-chain fatty acids (SCFA), metabolism of amino and bile acids, and plasma lipoproteins (Martin et al., 2008; Mirzaei et al., 2022). SCFAs can inhibit the development of opportunistic bacteria with proteolytic metabolism, which results in suppression of purulent processes and the formation of ammonia, aromatic amines, sulfides, and endogenous cancerogens.

There is a growing body of evidence demonstrating the critical importance of regular probiotic intake for maintaining gut microbiome homeostasis, health, and quality of life. Some probiotics can prevent the development of serious diseases, reduce the possibility of postoperative infectious complications (Gill et al., 2006) and allergies (Guarner et al., 2006), help treat metabolic disorders (diabetes type II), improve cognitive abilities and mood, and have an antidepressant effect (Marin et al., 2017; Owen et al., 2014; Sepp et al., 2014).

All the biological effects of probiotics are aimed at restoring the composition and functions of a healthy human microbiome, primarily the intestinal microbiome. Probiotics have a wide range of widely recognized and undeniable advantages over antibiotics (e.g., recolonization of surfaces depleted of commensal bacteria after antibiotic treatment, ability to prevent the growth of pathogenic microorganisms), as well as a wider range of off-target, long-term additional benefits (e.g., anticancerogenic effects, immune system modulation, mitigation of side effects of medications or invasive therapies, etc.) (Mirzaei et al., 2022b). Probiotics are generally considered safe and are administered in doses of several billion microbial cells. Although monitoring and ongoing supervision, as well as precautions, are mandatory, the advantage of probiotics is that they have no (or limited) side effects associated with overdose.

A number of studies have demonstrated significant interest in probiotics aimed at treating infectious diseases. This is due to the fact that in recent decades, a new problem has emerged in the world, which is that antibiotics that were developed to fight infectious diseases are becoming less effective due to antimicrobial resistance of pathogenic strains of microorganisms (Peri et al., 2019). Therefore, there is an urgent need for new types of interventional and preventive methods to reduce the burden of infectious diseases. The positive effect of probiotics is observed in the treatment of infectious diseases of the gastrointestinal tract, urogenital and upper respiratory tract infections, oral and skin infections (Meroni, 2021; Wiegers et al., 2022).

Urinary tract infections. Urogenital infections are one of the most common all over the world (Skerk & Marcotić, 2010; Yang et al., 2022). It is estimated that one billion women worldwide suffer from nonsexually transmitted urogenital tract infections each year, including bacterial vaginosis, yeast vaginitis, and urinary tract infection (UTI). Although most patients can be treated with antimicrobial therapy, recurrence rates are high and associated with adverse events (Reid et al., 2003).

The genitourinary system is the confluence of the urinary tract and the reproductive system. Since both systems are open to the environment, they are susceptible to infections. Some infections are brought in from the outside, while others arise from an imbalance in the microbiota of the urogenital tract. UTIs are usually caused by bacteria that live in the colon and rectum. When the bacteria enter the urethra, they multiply and spread to the bladder. *E. coli* is the most common microorganism responsible for UTIs, accounting for 80—85 % of the total number of isolates, with *Staphylococcus saprophyticus* causing 5—10 % of cases (Ci-

cinelli et al., 2012; Flores-Mireles et al., 2015). Other bacterial agents causing UTIs are *Klebsiella, Proteus, S. aureus, Enterococcus, Enterobacter* spp., etc. Complications caused by UTIs are bladder infection (cystitis), urethral and ureteral infection (urethritis), and kidney infection (pyelonephritis) (Giudice et al., 2016; John et al., 2016). Recent studies have emphasized the importance of a healthy and balanced vaginal microbiome dominated by *lactobacilli* not only to prevent sexually transmitted diseases and premature birth (Hanson et al., 2016) but also to maintain women's quality of life (Marrelli et al., 2012).

Changes in the vaginal microbiome are a significant risk factor for the development of diseases of the female reproductive tract. *Lactobacillus* spp. are the dominant bacteria in the human vagina and play a major role in maintaining homeostasis, preventing colonization or overgrowth of pathogens (Miller et al., 2016). *Lactobacilli* produce metabolites, including organic acids, hydrogen peroxide, bacteriocins, and biosurfactants, which contribute to the antimicrobial effects (Amabebe & Anumba, 2018).

The decrease in the presence of lactobacilli in the microbiome of women and vaginal infections have raised the question of whether artificial administration of lactobacilli can reduce the rate of infection (Hanson et al., 2016). Considering that resistance to commonly used antibiotics (e.g., trimethoprim/sulfamethoxazole) is increasing among uropathogens. Preventive therapy for UTIs is currently almost entirely dependent on the use of antibiotics. Modern therapy involves the long-term use of low doses of antibiotics, which involves the active destruction of bacteria that enter the bladder. The increasing antibiotic resistance of strains of microorganisms that cause urogenital infections is stimulating the search for alternative treatments. Probiotic therapy with lactobacilli has been considered for the development of a non-chemotherapeutic remedy to restore and maintain a healthy genitourinary tract, and there is evidence that certain strains can be effective when administered directly into the vagina or when migrating from the rectum after oral administration. The strains *Lactobacillus rhamnosus* and *Lactobacillus fermentum* (the species *L. fermentum* and *L. rhamnosus,* recently taxonomically reclassified as *Limosilactobacillus fermentum* and *Lacticaseibacillus rhamnosus*, respectively: https://site.unibo.it/subcommittee-lactobacillus-bifidobacterium/en) have been shown to be highly effective in this case (Tatullo et al., 2012).

L. fermentum L23 and *L. ramnosus* L60 are probiotics that produce bacteriocins. They showed antimicrobial activity against all 207 strains of bacteria isolated from patients with urogenital infection, and this activity was higher than that of antibiotics used for these diseases. A synergistic effect was obtained in 68.6 % of tests (Ruiz et al., 2009).

It is considered that vulvovaginal candidiasis may also be associated with an imbalance of the vaginal microbiome, in particular with a decrease in the local colonization by *Lactobacillus*, which is promoted by antibiotic therapy using spermicides, oral contraceptives, and the presence of diabetes (Ceccarani et al., 2019). Oral or vaginal use of *L. acidophilus*, *L. rhamnosus,* and *L. fermentum* can prevent candida colonization or recurrence of candidiasis (De Gregorio et al., 2019; Reid et al., 2009).

A repeated intake of probiotics may be important not only for women predisposed to recurrent urogenital infections but also for all healthy women to prevent severe infections and superinfection of the vaginal mucosa. In fact, the urogenital environment often changes, and the number of lactobacilli decreases, which increases the risk of local acute infection (Reid et al., 2001; Yang et al., 2022). Probiotics have shown the ability to protect against UTIs and maintain the vaginal microbiome in proper bal-

ance. Studies in this area have shown that daily administration of *L. rhamnosus* and *L. fermentum* can improve the condition of the vaginal microbiota.

Oral administration of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 in clinically healthy women for 60 days did not cause side effects and restored the bacterial flora that is typical for asymptomatic vaginosis to normal colonizing microflora in 37 % of patients against 13 % with placebo. The probiotics remained in the vagina for up to 60 days, and their concentration decreased significantly after 90 days. The concentration of fungi and coliform bacteria decreased significantly after 28 days (Reid et al., 2003).

There are reports on the use of probiotics for the prevention of urinary tract infections that are common in people with spinal cord injury. Probiotics attract special attention because of the decreased effectiveness of treatment of patients with UTIs associated with the appearance of multidrug-resistant strains of microorganisms, which is a threat to the prevention and treatment of any infections (Toh et al., 2017, 2020).

In patients with urogenital infection after spinal cord injury, the inflammatory process in the bladder was suppressed by oral administration of probiotic strains *L. ramnosus* GR-1 and *L. reuteri*, which reduced the levels of local proinflammatory cytokines, especially IL-6, IL-8, and TNF-alpha (Anukam et al., 2009).

Recently, it has been shown that other types of probiotics can also have a positive effect on vaginal infections. For example, *Pediococcus pentosaceus* SB83 has been reported to be used as a vaginal probiotic to prevent *Listeria monocytogenes* colonization in pregnant women (Borges et al., 2013). The use of the probiotic strain *B. coagulans* UniqueIS-2 together with antibiotic therapy in the treatment of patients with bacterial vaginosis led to a decrease in the frequency of disease recurrence and the disappearance of concomitant clinical symptoms (Ratna Sudha et al., 2012).

The probiotic strains *B. subtilis* KATMIRA 1933 and *B. amyloliquefaciens* B-1895 and their natural metabolites, such as subtilin and subtilosin, demonstrated antimicrobial activity against biofilms of the clinical strain *Proteus mirabilis*, which is one of the etiologic agents of urinary tract infections (Algburi et al., 2020).

These data confirmed the effectiveness of probiotics in improving and maintaining the health of the genitourinary system. However, further research on the composition, function, and dynamics of the urogenital microbiome in women and clinical trials with large sample sizes and standardized strains, doses, routes, and outcome measures are needed.

Probiotics in the fight against methicillin-resistant *Staphylococcus aureus*. Recently, Barzegari et al. (2020) evidenced the possibility of applying probiotics and their derivatives against pathogenic biofilms and the need for *in vivo* studies to determine the best antibiofilm activity associated with strain features. Further research will help to expand knowledge about the mechanisms by which probiotics and their metabolites can be properly used to treat biofilm infections in humans.

Biofilm formation is one of the main strategies of antibacterial resistance. Accordingly, preventing and attenuating biofilm formation has become a new approach to fighting resistant infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major bacterial pathogens causing chronic infections, mainly due to its ability to form biofilms. In recent years, there has been a tendency to increase the number of publications on biofilm-forming probiotics against MRSA (Srivastava et al., 2017; Chamignon et al., 2020).

A biofilm is a «sessile» community of bacteria, highly adapted to adverse environmental conditions, embedded in a self-produced extracellular polymeric matrix, which is attached to the substrate and consists of extracellular DNA (eDNA), proteins, and polysaccharides. Bio-

films are associated with more than 65% of all bacterial infections (Dufour et al., 2010; Mirzaei et al., 2020b). In the 1970s, Bill Costerton discovered a link between the cause of persistent infection and the accumulation of bacteria in patients with cystic fibrosis, which led to the introduction of the term «community growth pattern», the so-called biofilm (Vestby et al., 2020; Høiby, 2017).

The stages of biofilm formation include attachment of planktonic bacteria to the surface or to each other, formation of microcolloids and extracellular polymeric substances, maturation of microcolloids and extracellular polymeric substances, maturation of biofilm, dispersion of biofilm, formation of biofilm, and dispersion of bacteria integrated into the biofilm (Tolker-Nielsen, 2015).

In some cases, the biofilm formed by probiotic bacteria is potentially active against the development of infections caused by pathogenic bacteria (Carducci et al., 2011). On the other hand, biofilm formed by pathogenic bacteria can cause chronic infection in humans (Mirzaei & Ranjbar, 2022), demonstrating resistance to the immune system and antibiotics (Vestby et al., 2020).

S. aureus is one of the most important biofilm-forming pathogens with a wide range of complications and life-threatening infections (Mirzaei et al., 2020a). In this regard, MRSA is one of the most resistant strains that is transmitted both in healthcare facilities and in the community, leading to skin and soft tissue infections, as well as bone infections, joint infections, bacteremia, and endocarditis (Joshi et al., 2018).

Antibiotic resistance of *S. aureus* has become a serious public health problem, and MRSA strains are one of the most common causes of hospital-acquired infections worldwide (Mirzaei et al., 2020b; Shanehbandi et al., 2014).

Even with the ongoing development of new antibiotics, active surveillance efforts, and advances in infection prevention, MRSA remains an important pathogen with consistently high mortality (Turner et al., 2019). The WHO recently published a list of priority pathogens, including MRSA that urgently need new antibiotics (Antimicrobial Resistance: Global Reporton Surveillance, WHO, 2014).

Obviously, with the appearance of biofilm-forming multidrug-resistant (MDR) strains of *S. aureus*, the need for more effective therapeutic approaches has become urgent (Chung & Toh, 2014). Several main strategies have been developed to prevent biofilm formation at certain stages of its development, such as inhibition of bacterial adhesion, destruction of preformed biofilm, and the use of quorum sensing inhibitors. However, these approaches are not highly effective, and given the growing resistance of MR-MRSA strains and their tendency to form biofilms, it has been suggested that their eradication should not depend on these strategies alone (Kumar et al., 2017; Barzegari et al., 2020).

Probiotic strains can act as an adjunct to antibiotic therapy by reducing adverse effects, improving antibiotic function, and enhancing mucosal immunity and play an important role in the prevention or treatment of gastrointestinal infections in humans (Reid, 2006; Liu et al., 2018). Probiotics also play a protective role by directly competing with pathogens through signal interference (Piewngam et al., 2018).

Metabolites of probiotic strains, such as lactic acid, hydrogen peroxide, and bacteriocins, have been shown to be effective against bacterial pathogen growth, adhesion, and biofilm formation (Reid, 2006). Furthermore, since MRSA cannot be easily eliminated by antibiotics, probiotics and their derivatives to prevent and eliminate pathogenic biofilms are more rational (Barzegari et al., 2020). In this regard, the use of probiotic strains, such as lactic acid bacteria, has been recognized as one of the effective methods of biofilm control (Kimelman & Shemesh, 2019; Aw & Fukuda, 2019).

Effective antibiofilm agents are needed to inhibit and damage biofilm pathogens. Probiotics can prevent the colonization and biofilm formation of pathogens at the site of infection and compete with them for nutrients (Kos et al., 2003). In the study by Braïek et al. (2019), two strains of *Enterococcus lactis* Q1 and 4CP3 were used as probiotics to inhibit the biofilm formation of MRSA. The cell-free supernatant (CFS) with a synergistic binary combination of *E. lactis* Q1 and 4CP3 showed a high antibiofilm effect.

Two other studies in Spain and France (Al Atya et al., 2016; Gómez et al., 2013) evaluated the antibiotic film effect of *E. faecalis*. The first study found that enterocins DD28 and DD93 improved the inactivation of planktonic and non-planktonic staphylococci and reduced biofilm formation when combined with a specific biocide. Gómez et al. (2013) found that AS-48 enterocins purified from *E. faecalis* culture supernatants were able to synergistically interact with two antibiotics, erythromycin and kanamycin, used to treat MRSA.

Also, Boopathi et al. (2017) in India investigated the inhibitory effect of *E. durans* and showed that CFS bacteria significantly reduced MRSA biofilm formation (94 ± 0.9 %). Thus, this type of enterococci can be proposed together with other antibiotics for the treatment of MRSA infections and should be given more attention.

Representatives of the genus *Bacillus* are promising species of probiotic bacteria that inhibit biofilm formation. Algburi et al. (2020) showed the inhibitory effect of the combination of cefotaxime with *B. subtilis* and *B. amyloliquefaciens*, as well as CFS strains of bacteria on MSSA and MRSA biofilms. These results confirmed the ability of beneficial bacteria to compete with pathogens for a colonization site or nutrient source. In another study, it was shown that *B. paralicheniformis* strain UBBLi30 could produce the antimicrobial peptide bacitracin with biological activity against a range of Gram-positive bacteria and inhibition of MRSA biofilm (Ahire et al., 2020).

Thus, *Bacillus* species can be effective as probiotics for the treatment of infections caused by *S. aureus*. It should be noted that today there is a need to conduct research on these bacteria and their antibiotic effect on biofilms.

One of the groups of compounds with great potential for therapeutic use is antimicrobial peptides of bacterial origin, lantibiotics, which are characterized by the presence of unusual amino acids including lanthionine and/or methyllanthionine (Cotter et al., 2005; Bierbaum & Sahl, 2009). The most thoroughly studied lantibiotic is nisin, produced by *Lactococcus lactis*. Nisin has antibacterial activity against a wide range of Gram-positive bacteria, including foodborne pathogens such as staphylococci, clostridia, and bacilli (Shin et al., 2016). Field et al. (2016) studied the antibiofilm effect of nisin and found a significant decrease in the metabolic activity of formed biofilms treated with nisin V + chloramphenicol and the combination of nisin I4V + chloramphenicol.

Specific probiotic combinations demonstrate significant benefits for humans every day, and the evidence for antibiofilm activity against various respiratory, genitourinary, wound and tissue pathogens becomes increasingly convincing. This prompts intensive research on the interaction of probiotics and biofilm pathogens and methods of combating infectious biofilms through the so-called «good bacteria» of probiotic strains, emphasizing that there are also «useful» or «good» biofilms. Efforts should be focused on the selection of such promising strains and the study of the mechanisms of their antibiofilm action. Given the uncertain durability of antibiotics, it is extremely important to explore alternative products, and so far, probiotics are one of the most promising of them (Meroni, 2021). The use of probiotics or their metabolites to interrupt interbacterial metabolism during aggregation and prevent the

formation and stabilization of pathogenic biofilms may represent a new milestone in clinical microbiology and an effective alternative to antibiotic therapy.

Probiotics are often taken orally, but their positive effects are not limited by the gastrointestinal tract. The documented changes affecting the urinary tract, oral cavity, and skin microbiota indicate a wide range of their therapeutic effects (Meroni, 2021).

Probiotics in the therapeutic arsenal of dermatologists. The skin is the largest organ of the human body, colonized by a diverse microbiota that works harmoniously to protect it. Skin damage can result from disease, surgery, or burns. However, when damage occurs, the skin microbiota is also disrupted, and pathogens can enter the wound and cause infection. The skin and its microbiota serve as physical barriers to prevent pathogens penetration.

The skin commensals are important for maintaining the function of the epithelial barrier, regulating the host immune system and protecting against the penetration of pathogenic microorganisms. Johnson et al. (2018) have shown in preclinical and clinical studies how changes in the microbiome of various acute and chronic skin wounds affect the regeneration of wound tissue, reviewed healing mechanisms and alternative strategies for treating infected wounds in the face of growing concerns about antibiotic resistance. Commensals, symbionts, and skin pathogens have been found to play an important role in the inflammatory response, highlighting several potential strategies for treating infected non-healing wounds.

The most effective wound care strategy is to prevent infections, promote healing, and prevent excessive scarring. Probiotics based on beneficial microorganisms and their metabolites are one of the possible alternative treatments to fight skin pathogens due to their antimicrobial effectiveness. It has been found that probiotics can promote skin healing by stimulating the production of immune cells and also have an antagonistic effect against pathogens through competitive displacement of pathogens (Fijan et al., 2019). *In vitro* studies have shown effective inhibition of skin or wound pathogens by probiotics based on *L. plantarum, L. casei, L. acidophilus,* and *L. rhamnosus.* In studies on mice, rats, and rabbits, probiotics have demonstrated significant potential to combat wound infections.

Most clinical trials have shown a small or statistically significant reduction in the incidence of surgical site infections, foot ulcer infections, or burn infections in patients taking probiotics (Fijan et al., 2022; El-Ghazely et al., 2016). Some of these studies also showed a statistically significant effect on wound healing for the probiotic groups. Analysis of the results of the studies showed that exogenous and oral probiotics contributed to the reduction of wound infections, especially when used as an adjunct to antibiotic therapy (Argenta et al., 2016; Ong et al., 2019; Onbasetal, 2019).

Topical probiotic therapy with *L. plantarum* reduced scarring in rabbits after burn injury and infection (Satish et al., 2017). Venosi et al. (2019) developed a new adapted strategy for the treatment of an infected chronic ischemic wound for topical treatment with a multistrain probiotic.

The efficacy of the antiseptic agent Arederma in the form of a spray with probiotic strains of bacilli (in 1 mL *B. subtilis*> $5{\cdot}10^7$ CFU and *B. megaterium*> $5{\cdot}10^7$ CFU) in the complex treatment of 26 patients with superficial burns due to the reduction of infection of the burn surface and the positive effect of the drug on epithelialization processes were shown (Boyko et al., 2022).

In a study of the antimicrobial effect of seven multistrain and eleven single-strain microbial preparations containing probiotics against 15 clinical wound pathogens, it was shown that multistrain probiotics have a statistically significantly higher antagonistic effect against wound

pathogens than single-strain preparations (Fijan et al., 2022). Individual pathogens were susceptible to different probiotics. Perhaps, an individualized approach, such as a «probiogram,» will become a method for finding the most effective target probiotic strains in the future, without cell supernatants or inactivated cultures of clinical wound pathogens.

The potential use of probiotics in the field of dermatology remains relevant. The use of typical skin microbiota as a basis for a new generation of probiotics with high potential is promising. However, much more research is needed to ensure the regular use of probiotics for the skin.

Human skin's commensal microbiota can directly regulate skin health and disease processes by interacting with numerous cells involved in wound healing mechanisms. These are highly coordinated and complex mechanisms aimed at strengthening the regeneration barrier (Byrd et al., 2018).

Diabetic foot ulcers (DFUs) are a growing concern worldwide, as they pose complications in routine clinical practice, such as diagnosis and treatment. The interaction of bacteria on the skin surface is vital for the pathophysiology of DFU and can control the dynamics of wound healing. In a study of the role of pathogenic bacteria of the genera *Staphylococcus, Streptococcus, Corynebacterium,* and *Pseudomonas* and several anaerobes in the formation of DIC, it was shown that skin commensals, namely *S. epidermidis*, can regulate T-cell functions and induce perforin-2 expression (Lipsky et al., 2012; Patel et al., 2022). Increased expression of perforin-2 by skin cells caused the destruction of *S. aureus* in the cells, facilitating wound healing. There may be cross-interactions between the human commensal microbiome and various cell types involved in skin wound healing, promoting immune response and helping to maintain the barrier function.

The gut can also influence skin health through its immunological and metabolic properties. The exact mechanism underlying the interaction between intestinal and skin microorganisms is still unknown, but it is likely to involve the immune and endocrine systems. The authors emphasize the importance of these pathways in the pathomechanisms of the most common inflammatory conditions, including wound healing in diabetes, and the relevance of studying the effect of probiotics on these processes.

Bacillus probiotics and their antimicrobial properties. Probiotics based on strains of aerobic spore-forming bacteria of the genus *Bacillus*, characterized by high biological activity, are becoming increasingly popular (Elshaghabee et al., 2017; Lu et al., 2022). Representatives of the *Bacillus* genus are characterized by significant antimicrobial and enzymatic activity; positive effect on the immunological status of the host; antioxidant and antimutagenic properties, and increased tolerance and survival in the aggressive environment of the gastrointestinal tract due to the ability to form spores (Sorokulova, 2013). *Bacillus* probiotics are increasingly chosen and used as dietary supplements or live biotherapeutic products (Peng et al., 2019). Currently, more than 40 species of *Bacillus* probiotics are used to treat intestinal and other diseases due to their antibacterial bioactivity and relatively strong stability (Santacroce et al., 2019).

The promising benefits over other probiotic microorganisms are mainly attributed to the activity of structurally diverse metabolites obtained from *Bacillus*, such as antibacterial compounds, short-chain fatty acids, and other small molecules (Zhu et al., 2023). The metabolites produced by *Bacillus* are a key mediator in the interaction with the gut microbiota or the host, such as antimicrobial compounds that directly inhibit pathogen growth and secondary metabolites such as vitamins, which enhance host health.

The continuous growth of multidrug-resistant microbial pathogens is stimulating the identi-

fication and development of new antibacterial compounds more than ever. Recent achievements in genome sequencing have highlighted the genus *Bacillus* as an unexpected source of antibiotic-like compounds (Fickers, 2012).

The ability of these microorganisms to temporarily remain in the intestinal tract of the host after oral intake has been shown to be 10^5 to 10^8 CFU/g in the different parts of the intestine (Sorokulova, 2013). This colonization allows *Bacillus* to continuously use numerous mechanisms to provide protection against infections. Spore-forming strains of *Bacillus* with the ability to survive in the severe environment of the intestinal tract demonstrate a wide range of activities to manipulate host immunity and eliminate invasive pathogens (Lu et al., 2022). A variety of metabolites derived from *Bacillus* can diffuse into the intestinal tract and alter the microbial community, promoting the elimination of intestinal pathogens such as pathogenic *E. coli*, *Salmonella,* or other drug-resistant bacteria (Sumi et al., 2015).

The high antagonistic activity of *Bacillus* bacteria against a wide range of pathogenic and opportunistic microorganisms is directly related to their ability to produce a wide arsenal of antimicrobial substances, including ribosomally and non-ribosomally synthesized lipopeptides, bacteriocins, and other types of peptides (Stein, 2005; Abriouel et al., 2011). Today, about 800 such compounds synthesized by these bacteria are known. Most antibiotics produced by *Bacillus* sp. are non-ribosomal. During their biosynthesis, the formation of a peptide linkage occurs without the participation of ribosomes but with the involvement of multifunctional specific peptide synthetases (Joshi et al., 2012).

The best-known representative of the *Bacillus* genus is *B. subtilis.* Like most of its closest relatives, it is not pathogenic. The US Food and Drug Administration even granted *B. subtilis* GRAS (generally recognized as safe) status. The first known use of *B. subtilis* dates back more than a thousand years, when it was used to produce natto, a Japanese food product made from fermented soybeans. Currently, *B. subtilis* is best-known as a source of beneficial enzymes and other metabolites, as well as an attractive producer of heterologous proteins. Many different enzymes, such as proteases and amylases, originating from *B. subtilis* and related *Bacillus* species are used in industry for a wide range of different applications (Schallmey et al., 2004). It is important to note that *B. subtilis* is capable of producing and secreting large amounts of proteins into the culture medium. Therefore, this organism is widely known as a productive «cell factory» for industrial enzymes and biopharmaceuticals (Westers et al., 2004). *B. subtilis* strains have approximately 4 to 5 % of their genome dedicated to the synthesis of secondary metabolites with the ability to produce more than two dozen structurally diverse antimicrobial compounds (Stein, 2005).

The extracellular metabolites of this species include a variety of low-molecular-weight antimicrobial peptides and bacteriocins, such as surfactin (Kim et al., 2010), bacillisin (Afsharmanesh et al., 2018), and subtilin (Corvey et al., 2003), which have potential importance in biomedicine, nutrition, and agriculture (Stein 2005).

Antimicrobial peptides from *B. subtilis* are promising therapeutic agents due to their broad-spectrum action and rapid killing activity against a variety of pathogens. Due to the growing problems of microbial resistance, irrational use of conventional antibiotics, antimicrobial agents, peptides will play a more significant role in the treatment of bacterial infections (Sumi et al., 2015).

Recent studies have shown that *B. subtilis* uses an interesting strategy to compete with phylogenetically distinct pathogens by increasing antibiotic production when encountering peptidoglycan from pathogens in the same niche (Maan et al., 2022).

The probiotic strain *B. subtilis* 3 is a part of the well-known drug Biosporin, has antagonistic properties against species of the family *Enterobacteriaceae, Staphylococcus* spp., and *Candida* spp**.** It was also found to inhibit *H. pylori*. At least two antibiotics detected by thin-layer chromatography and confirmed by high-performance liquid chromatography analysis were found to be responsible for this antigen of *H. pylori* activity (Pinchuk et al., 2001). One of these compounds was identified as amicumacin A, an antibiotic with anti-inflammatory properties. An additive effect was demonstrated between amikumacin A and a non-amikumacin antibiotic against *H. pylori*. The effect of strain *B. subtilis* 3 against influenza virus *in vitro* and *in vivo* is due to the new peptide P18 produced by the strain. The protective effect of P18 in mice was comparable to that of oseltamivir phosphate (Tamiflu). Further research will evaluate the potential of the P18 peptide as an antiviral compound and a promising candidate for the development of new antiviral vaccines (Starosila et al., 2017).

In Europe, the probiotic preparation Enterogermina based on *B. clausii* (Sanofi-Aventis, France) is widely known (Khatri et al., 2019), which is used for viral diarrhea in children and to reduce the likelihood of side effects of antibiotic therapy. The drug is prescribed for the prevention and treatment of intestinal microflora disorders and as an alternative to conventional antibiotic therapy for infections caused by *S. aureus, C. difficile,* and *E. faecium*. Recently, the analysis of the complete genome of *B. sclausii* identified genes encoding the bacteriocin halidermin, which prevents biofilm formation in *S. aureus* and *S. epidermidis.* This bacteriocin has also been reported to be effective in skin conditions including acne, eczema, folliculitis, and impetigo, where the target organisms are *Propionibacteria, Staphylococci,* and *Streptococci* (Field et al., 2015).

Recently, antibiotics from bacilli have been described such as macrolactin, difficidin (macrolides) and bacillaen (polyene antibiotic) (Fickers, 2012). Macrolactin effectively inhibits even multidrug-resistant strains of bacteria that are insensitive to the action of many other antibiotics (Wu et al., 2021). This substance under the name «7-O-malonyl-macrolactin A» has shown its effectiveness against such pathogens as methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus,* and some other pathogens of the most dangerous hospital infections. Bacillaene in low concentrations has bacteriostatic and bactericidal activity against a wide range of bacteria and fungi. Difficidin is characterized by activity against aerobic and anaerobic bacteria. Many of the difficidin-sensitive human pathogens are resistant to one or more of the antibotics.

A high level of antagonism of the probiotic strain *B. amyloliquefaciens* spp. *plantarum* UKM B-5140 against representatives of the genera *Pseudomonas, Staphylococcus, Acinetobacter, Agrobacterium,* and *Clavibacter* can be significantly due to its ability to synthesize the antibiotics surfactin, fenicin, bacillain, macrolactin, and dificidin, as well as the siderophore bacillibactin, whose genes were detected as part of separate operons in the analysis of the full genome by bioinformatics and secondary metabolites by HPLC and MALDI-TOF-MS. The strain is also capable of destroying certain cross-links in the peptidoglycan structure of cell walls of various microorganisms by producing a complex of extracellular bacteriolytic and yeast enzymes (Matseliukh et al., 2015). Of the test cultures studied, *E. coli* and *C. albicans* cells were lysed mostly.

One of the most important ways that probiotic bacteria act against pathogenic microbial species, both from the gut and the respiratory tract, is to modify the microbiota composition in the gastrointestinal tract by creating a more advantageous balance in the microbial population (Gagliardi et al., 2018; Li et al., 2019). The exclusion of pathogenic species often occurs

through two main mechanisms: by producing antimicrobial substances that can kill unwanted bacteria (Caulier et al., 2019; Kimelman & Sheemesh, 2019) and by affecting the gene expression of the pathogenic microorganisms, which leads to inhibition of the ability to colonize the host gastrointestinal tract (Piewngam et al., 2018). By improving the absorption of nutrients, such as certain types of indigestible food fibers, probiotic bacilli can also significantly contribute to the health of the host. *Bacilli* secrete various enzymes for the rapid use of both macronutrients and micronutrients in the environment, which leads to a limited availability of nutritional elements for pathogenic bacteria (Rajasekharan et al., 2021).

Thus, antagonistically active against pathogenic species of microorganisms, probiotics with their ability to modulate the host's immune system and restore the balance of the intestinal microbiota are a promising alternative to antibiotics for the treatment of infectious diseases, including the inhibition of biofilm-forming pathogenic bacteria, in particular staphylococci. The excessive and inappropriate use of antibiotics has led to an increase in bacterial resistance to antimicrobial drugs, which is becoming a growing threat to global health. Therefore, new alternative therapies that are more specific while eliminating harmful side effects to the gut microbiota are crucial. Alternative candidates include bacteriocins, antimicrobial peptides, and probiotics.

Despite the fact that some substances are believed to be responsible for the antimicrobial activity of probiotics, further research should characterize new ones and elucidate their mechanisms of inhibition of pathogenic strains of microorganisms.

Although there is strong evidence for the role of probiotics in counteracting pathogens, research in this area is still in its infancy and requires further discussion. Research is needed to determine the best safe probiotic and dose for specific infections, firstly in animal models and secondly in clinical trials.

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Received 08.02.2024

Л.А. Сафронова[1], Є.В. Пилипюк[2], І.О. Скороход[1], Ж.М. Полова[3]

[1] Інститут мікробіології і вірусології ім. Д.К. Заболотного НАН України,
вул. Академіка Заболотного, 154, Київ, 03143, Україна
[2] Полтавський державний медичний університет,
вул. Шевченка, 23, Полтава, 36011, Україна
[3] Національний медичний університет ім. О.О. Богомольця,
вул. Євгена Чикаленка, 22, Київ, 01004, Україна

ПРОБІОТИКИ ТА ЇХ ПОТЕНЦІАЛ ДЛЯ ПРОФІЛАКТИКИ І ЛІКУВАННЯ ІНФЕКЦІЙ

Вивчення властивостей пробіотичних мікроорганізмів на сьогодні є актуальним напрямком в мікробіології, біотехнології та медицині, що розширює наші знання про еволюцію їх взаємовідносин з організмом людини та його мікробіомом, а також відкриває нові перспективи практичного використання активних пробіотичних штамів для підтримки здоров'я, профілактики та лікування різних патологічних станів. В огляді наведено дані про відомі біологічні ефекти пробіотиків, охарактеризовано механізми взаємовідносин макроорганізму з пробіотичними мікроорганізмами, висвітлено їхню роль у підвищенні імунологічного статусу. Особливу увагу приділено можливостям практичного використання пробіотичних мікроорганізмів, зокрема штамів роду *Bacillus*, для лікування інфекційних захворювань. Наведено результати досліджень, які підтверджують ефективність застосування пробіотичних штамів проти патогенних мікроорганізмів.

Ключові слова: *пробіотичні мікроорганізми, мікробіом, біологічні ефекти, Bacillus, біологічно активні метаболіти, інфекційні захворювання, антибіотикорезистентність, метицилін-резистентний Staphylococcus aureus.*