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Effect of probiotics and prebiotics on oral mucosa – a mini review

Wpływ probiotyków i prebiotyków na błonę śluzową jamy ustnej – mini przegląd

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Abstract

Introduction and Objective. As the field of medicine continues to evolve dynamically, the spotlight increasingly falls on probiotics – beneficial living microorganisms, and prebiotics – substances impervious to digestive enzymes. The aim of this review is to present current knowledge about probiotics and prebiotics and their impact on the oral mucosa based on scientific publications of online databases, including PubMed and Google Scholar.

Brief description of the state of knowledge. The findings highlight probiotics' efficacy in reducing periodontitis-related bacteria and Candida, which is responsible for oral candidiasis. Probiotics have been further demonstrated to effectively lessen the severity of gingivitis, reduce plaque accumulation in moderate to severe gingivitis cases, and significantly decrease the levels of inflammatory cytokines: Interleukin 8 (IL-8) and tumour necrosis factor alpha (TNF-alpha). The potential of probiotics in diminishing sulfur compound derivatives also indicates their usefulness in halitosis prevention and treatment. In addition, *in vitro* and animal model studies also underscore their possible role in hindering the progression of oral cancer. Prebiotics are known to promote the growth of beneficial microorganisms and enhance the effectiveness of probiotics. This synergistic effect is intended to re-establish microbiome balance in patients, a goal unattainable through traditional treatment methods.

Conclusion. Probiotics and prebiotics are pivotal in impacting oral mucosa health by managing specific pathogens.

Key words

probiotics, prebiotics, oral mucosa, oral health, microbiome

Streszczenie

Wprowadzenie i cel pracy. Wraz z dynamicznym rozwojem medycyny coraz częściej w centrum uwagi znajdują się probiotyki – pożyteczne żywe mikroorganizmy – oraz prebiotyki – substancje oporne na działanie enzymów trawiennych. Celem pracy jest przedstawienie aktualnej wiedzy na temat probiotyków i prebiotyków oraz ich wpływu na błonę śluzową jamy ustnej na podstawie publikacji naukowych pochodzących z baz danych, m.in. PubMed i Google Scholar.

Opis stanu wiedzy. Badania podkreślają skuteczność probiotyków w ograniczaniu rozwoju bakterii związanych z zapaleniem przyzębia i grzybów z rodzaju Candida, które wywołują kandydozę jamy ustnej. Ponadto wykazano, że probiotyki skutecznie zmniejszają nasilenie zapalenia dziąseł, gromadzenie się płytki nazębnej w przypadkach umiarkowanego do ciężkiego zapalenia dziąseł i znacząco obniżają poziom cytokin zapalnych: interleukiny 8 (IL-8) i czynnika martwicy nowotworów alfa (TNF-alfa). Potencjał probiotyków w zmniejszaniu zawartości pochodnych związków siarki wskazuje również na ich przydatność w zapobieganiu i leczeniu nieprzyjemnego oddechu. Badania *in vitro* i na modelach zwierzęcych podkreślają ich możliwą rolę w hamowaniu rozwoju nowotworów jamy ustnej. Z kolei prebiotyki sprzyjają rozwojowi pożytecznych mikroorganizmów, zwiększając skuteczność probiotyków. Efektem ich wspólnego działania jest przywrócenie równowagi mikrobiomu jamy ustnej, czego nie można osiągnąć tradycyjnymi metodami leczenia.

Podsumowanie. Probiotyki i prebiotyki odgrywają kluczową rolę w utrzymywaniu zdrowia jamy ustnej, wpływając na zdrowie błony śluzowej jamy ustnej poprzez zwalczanie określonych patogenów oraz stymulowanie wzrostu mikroorganizmów korzystnych dla zdrowia naszego organizmu.

Słowa kluczowe

probiotyki, prebiotyki, błona śluzowa jamy ustnej, zdrowie jamy ustnej, mikrobiom

INTRODUCTION

The oral cavity is one of the most complex microbial environments in the human body, inhabited by hundreds of different species of bacteria [1]. Over the last decade,

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rapid development in the knowledge about probiotics and prebiotics has been seen. The balance of the oral microbiome is important for overall human health, affecting not only teeth and periodontium, but also the entire human organism. As indicated in many studies, the imbalance can lead to various oral diseases, such as tooth caries, periodontal diseases, or oral candidiasis. Nowadays, more and more clinical studies confirm the beneficial effect of probiotics and prebiotics on the oral mucosa. According to the International Scientific Association for Probiotics and Prebiotics, probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [2], whereas a prebiotic a substrate that is selectively utilized by host microorganisms conferring a health benefit [3]. Typical examples of prebiotics are such natural dietary ingredients as starch, dietary fibre or food additives (dietary supplements) of a health-promoting nature. Unlike a probiotic, a prebiotic does not contain any microorganisms, only stimulating substances. Non-digestible food ingredients resistant to the action of digestive enzymes in the gastrointestinal tract and have a beneficial effect on the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon, improve the health of the host.

The combination of a probiotic and a prebiotic in one preparation is called a symbiotic [4]. Probiotics, on the other hand, play a key role in oral care due to growing concerns about antibiotic resistance. Different strains of bacteria have different effects on oral health, making an individual assessment essential. They offer many benefits, including maintaining a healthy bacterial balance, boosting local immunity, defending against oral infections and preventing bad breath [5]. *Lactobacillus* and *Bifidobacterium* are the main probiotic genera, with specific strains such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* [6]. The *Lactobacillus* genus includes *Lactobacillus acidophilus, Lactobacillus johnsonii, Lactobacillus rhamnosus, Lactobacillus gasseri* and *Lactobacillus reuteri*. Similarly, the strains of *Bifidobacterium* contain *Bifidobacterium bifidum, Bifidobacterium longum* and *Bifidobacterium infantis* [7]. These types of bacteria are considered part of the normal human microflora. Other species commonly isolated from saliva samples include *Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus* and *Lactobacillus salivarius*. Probiotics have a beneficial effect on reducing the number of bacteria involved in periodontitis, and *Candida* species causing oral candidiasis. They are used in the prevention and treatment of halitosis and influence the development of oral cancer.

OBJECTIVE

The aim of this review is to present current knowledge about probiotics and prebiotics and their impact on the oral mucosa, based on existing literature, including the Pubmed and Google Scholar databases. The key words used in the databases searched were: probiotics, prebiotics, probiotics and periodontal disease, probiotics and oral candidiasis, probiotics and halitosis, probiotics and oral cancer, prebiotics and periodontal disease, prebiotics and oral candidiasis, prebiotics and halitosis, prebiotics and oral cancer. The effects of different probiotics on the oral mucosa are presented in Table 1.

The impact of probiotics and prebiotics on periodontal health. Periodontal disease, a complex inflammatory condition triggered by dental biofilm, affects the gums and supporting tissues, often leading to bone resorption and tooth loss [8]. It has become a significant public health concern, ranking second after dental caries in

Table 1. Different probiotics and their effects on the oral mucosa

Probiotic	Action on oral mucosa
Bacillus subtilis	Demonstrates antifungal properties, helping to protect against oral fungal infections
Bifidobacterium bifidum	Supports a healthy oral microbiota, promoting overall oral health
Bifidobacterium infantis	Contributes to oral health by maintaining a healthy microbiota balance
Bifidobacterium lactis HN019	Possesses antibacterial and immunological properties; inhibits periodontal pathogens and modulates the immune response, reducing inflammation
Bifidobacterium longum	Maintains oral health by supporting the balance of beneficial bacteria in the mouth
Lactobacillus acidophilus	Supports oral health by maintaining a healthy balance of bacteria in the mouth
Lactobacillus brevis	Antifungal activity against *Candida albicans* affects mRNA expression of cancer-related pathways, potentially inhibiting oral cancer progression
Lactobacillus casei	Produces lactic acid and antifungal peptides which lower fungal viability by disrupting their cell membranes
Lactobacillus gasseri	Aids in maintaining oral health by supporting the balance of oral microbiota
Lactobacillus johnsonii	Contributes to a healthy oral microbiota, promoting overall oral health
Lactobacillus paracasei	Demonstrates antifungal properties, inhibiting the growth of *Candida albicans*, a common oral pathogen
Lactobacillus plantarum	Antifungal activity against *Candida albicans* affects mRNA expression of cancer-related pathways, potentially inhibiting oral cancer progression
Lactobacillus reuteri	Used in periodontal disease treatment; reduces pathogenic bacteria, decreases inflammation, and improves clinical periodontal parameters
Lactobacillus rhamnosus	Exhibits antifungal activity by producing lactic acid and antifungal peptides, which inhibit fungal growth
Lactobacillus salivarius	Helps treat halitosis and prevent oral cancer; inhibits the up-regulation of COX-2, an enzyme linked to cancer progression
Lactobacillus salivarius G60	Helps treat halitosis and prevent oral cancer; inhibits the up-regulation of COX-2, an enzyme linked to cancer progression
Streptococcus salivarius K12	Inhibits the adhesion of *Candida albicans*, helping to prevent oral candidiasis; also beneficial in treating halitosis

oral cavity diseases. During the last three decades, its prevalence has increased by almost 10% [9]. Key bacteria linked to periodontitis include *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, and Treponema denticola* [10]. In pursuit of effective management, the genera *Lactobacillus* and *Bifidobacterium* have been explored as adjuncts. Notably, *Lactobacillus reuteri*, a probiotic strain, has shown remarkable promise [11]. Consumption of *Lactobacillus reuteri* containing probiotics produces significant benefits, improving parameters such as bleeding on probing (BoP), gingival index (GI), plaque index (PI), attachment level, and pocket depth [12]. This probiotic exhibits antibacterial and immuno-inflammatory properties, reducing metalloproteinase-8 (MMP-8) levels in gingival cervical fluid and inhibiting the growth of pathogenic microorganisms. *Lactobacillus reuteri* consists of two strains: DSM 17938, which acts as an antibiotic-producing reuterin, inducing oxidative stress in pathogens, and ATCC PTA 5289, with anti-inflammatory characteristics, producing tumour necrosis factor alpha, (TNF-α), Interleukin 8 (IL-8), and Interleukin 1beta (IL-1beta) [13]. Additionally, *Bifidobacterium lactis HN019* is shown to be an effective probiotic for non-surgical periodontal treatment. Its anti-microbial and immunological properties are instrumental [12]. *Bifidobacteria* competitively inhibit periodontopathogens, possibly by outcompeting them for nutrients and growth factors. Furthermore, they create acidic conditions hostile to key periodontopathogens. *Bifidobacteria* also reduce plaque mass by inhibiting interspecies bacterial coaggregation, disrupting biofilm formation [11]. Beyond their anti-microbial action, bifidobacterial probiotics exhibit immunomodulatory effects, regulating inflammatory mediators and bone remodelling, and play a key role in chronic periodontal diseases. Systemic or topical use of bifidobacterial probiotics promotes the expression of anti-inflammatory cytokines like interleukin-10 (IL-10) while curbing pro-inflammatory cytokine production.

These findings underscore the potential of specific probiotic strains to mitigate periodontal diseases through multifaceted mechanisms, launching a new era of periodontal care [14]. It can also be concluded that nitrate can be an ecological factor stimulating health associated with oral genera, with the potential to decrease periodontitis by stimulating eubiosis and reduce dysbiosis in the oral cavity. In addition, two weeks consumption of nitrate-rich lettuce juice improved gingival health in a recent clinical study [15]. The authors demonstrated that the mean Gingival Index in patients with chronic gingivitis after 14 days of lettuce juice drinking three times a day was significantly lower than in the placebo group (0.3 vs. 0.5) [11].

The impact of probiotics and prebiotics on oral candidiasis. Oral candidiasis is an opportunistic fungal infection that can affect the oral mucosa. *Candida albicans*, the causative organism, is a highly versatile organism and is well adapted to its human host. Changes in the host microenvironment can promote the transition from commensalism to pathogenesis [16]. Mycelial growth of *Candida albicans* is often observed in mucosal infections (Tab. 1) and is thought to contribute to pathogenesis through biofilm formation [17]. During the search for an effective probiotic strain, attention was drawn to an existing strain, *Streptococcus salivarius K12*. Substituting the bacteria responsible for bad breath with competitive bacteria, such as *Streptococcus salivarius K12,* could offer an efficient approach to reduce the intensity of halitosis. *Streptococcus salivarius K12* may play a protective role against oral candidiasis by inhibiting adhesion [18, 19]. Furthermore, other strains have been proven to be beneficial in inhibiting *Candida albicans*. Also, hydrogen peroxide produced by this strain has a strong oxidative effect that damages the fungal molecular structure [20]. *Lactobacillus* has antifungal activity and operates through two main mechanisms. Firstly, its strains generate lactic acid which permeates the membrane of target fungi, lowering their cytoplasmic pH, and resulting in loss of viability. Secondly, they produce various antifungal peptides, which can disrupt fungal membranes or deactivate intracellular molecules upon internalization. However, the specific inhibitory mechanisms of antifungal peptides of *Lactobacillus casei* and *Lactobacillus rhamnosus* have not been elucidated [21].

Lactobacillus pentosus, Lactobacillus acidophilus, Bacillus subtilis, Lactobacillus brevis, produce more than 40 biosurfactants that also have antifungal properties. They have been shown to have anti-adhesive and antimicrobial activity which has been demonstrated on *Candida albicans*, *Candida tropicalis* and *Candida krusei*. In addition, they protect the integrity of the mucosa [22, 23]. What is more, another study showed that a synbiotic combination of *Lactobacillus rhamnosus* and *Pediococcus acidilactici* with inulin-type fructans showed growth and biofilm inhibition against *Candida albicans*. These synbiotic formulations may represent a promising alternative to the use of antifungal drugs [24, 25]. Similar studies demonstrated inhibition of *Candida albicans* occurring at concentrations of 12.5, 25, and 50% of the *Lactobacillus paracasei* supernatant, and at a concentration of 50% of the *Lactobacillus plantarum* supernatant [25].

The impact of probiotics and prebiotics on halitosis. Halitosis is a common pathology that affects the mental and social aspects of the patient and reduces their quality of life. It can be long-term or intermittent, which makes it difficult to obtain epidemiological data on oral pathology [26]. In fact, there is little evidence of the long-term efficacy of any method of treating bad breath, although brushing the tongue currently appears to be the best option, probiotics are emerging as a research-based therapeutic alternative [27]. Clinical studies have shown that probiotics and prebiotics can prevent and treat oral infections such as bad breath and periodontitis [28]. To show the clinical use of probiotics, a study was carried out in 32 patients who were divided into a study group who received subgingival probiotics and a mouthwash also enriched with probiotics, while a control group received a placebo. After a period of three months, malodorous breath was assessed and found to have largely disappeared in the study group [29]. To validate the use of probiotics in the care of patients' breath, a study was conducted in patients with halitosis using two strains of probiotic lactic acid bacteria, such as *Lactobacillus reuteri* or a placebo. The final measure was the concentration of sulfur compounds measured with a Halimeter. The results suggest that probiotic chewing gum can affect bacteria that produce odours in patients with halitosis [30]. Mousquer et al. conducted a study on the effects of *Lactobacillus salivarius G60* combined with inulin to test the efficacy of this combination in the treatment of halitosis. Treatment

with *Lactobacillus salivarius G60* in combination with or without inulin was shown to significantly reduce Halimeter scores and improve breath quality in patients with halitosis [31]. Although a lot of research remains to be done in this area, the use of probiotics with a suitable composition can have a positive effect on the comfort of halitosis patients.

The combination of prebiotics and probiotics provide synergistic effects on the oral health and therefore prevent halitosis. In principle, prebiotics stimulate the growth of probiotics in a selective manner, which depends on dose and strain. Prebiotics act during fermentation, storage or passage through the gut as a selective growth substrate for the probiotic strain. Luminal and systemic aspects of the host defence system may also be altered by prebiotics [32].

The impact of probiotics and prebiotics on oral cancers. Oral cancer, which falls under the category of head and neck cancer, ranks as the sixth most prevalent malignant tumour globally. Each year, around 355,000 cases of oral cancer and 93,000 cases of oropharyngeal cancer are identified, constituting approximately 2% and 0.5%, respectively, of all malignant tumours diagnosed worldwide [33]. Oral squamous cell carcinomas (OSCC) is responsible for more than 90% of all oral cancers. Oral cancer can appear at the buccal mucosa, floor of the mouth, tongue and lips. The main risk factors that hugely contribute to oral cancer are excessive alcohol consumption and tobacco smoking. The overall 5-year survival rate is 40% and varies strongly depending on socio-economic circumstances [34].

Recent studies have suggested that probiotics may also possess anti-cancer properties that can prevent oral carcinogenesis [35]. One of the analyses showed that *Lactobacillus salivarius REN* resulted in a 95% reduced risk of developing oral cancer [36]. Also, the ability of probiotics to inhibit the proliferation of oral cancer cells has been reported in several studies [37, 38, 39, 40]. *Lactobacillus salivarius REN* was found to inhibit the up-regulation of Cyclooxygenase-2 (COX-2), an enzyme encoded by the Prostaglandin-Endoperoxide Synthase 2 (PTGS2) [40]. Increased COX-2 expression is commonly seen in many cancers. The product of COX-2 is then converted into Prostaglandin E2 (PGE2) which can stimulate the progression of the cancer. This makes COX-2 inhibition a useful therapy to prevent oral cancer [41]. Furthermore, *Lactobacillus salivarius REN* was also found to inhibit the proliferation of human tongue squamous cell cancer (TCA-8113) [40]. Anti-tumour activity was induced by high doses of *Lactobacillus salivarius REN*. In other words, the anti-tumour activity of *Lactobacillus salivarius REN* against the TCA-8113 cancer cell line was dose dependent.

Another *in vitro* study on the oral cancer KB cell line showed the ability of *Lactobacillus plantarum* probiotic to decrease mitogen-activated protein kinases (MAPK) mRNA expression, a pathway that promotes cancer progression, while increasing the mRNA expression of the phosphatase and tensin homolog deleted on chromosome ten PTEN, a pathway that inhibits cancer progression, within 24 hours of treatment. Co-culture of *Lactobacillus plantarum* with the cancer KB cell line also induces apoptosis, thereby inhibiting cancer progression [42]. No study has evaluated the association between the intake of specific dietary fibres that are classified as prebiotics and the risk of cancer of the upper digestive tract and stomach. In the study, a high intake of galactooligosaccharides was associated with a reduced risk of cancer of the colon and the larynx [43, 44]. The anti-proliferative effects and apoptosis-inducing properties of probiotics in cancer cells is a strong indication that probiotics can be used as a preventive therapy against oral cancer.

CONCLUSIONS

Based on the analyzed literature it can be concluded that both probiotics and prebiotics show beneficial effects on the human organism. The integration of probiotics and prebiotics into oral healthcare holds promise for improving and maintaining oral health. These agents offer a multifaceted approach to managing and preventing various oral conditions, including periodontal disease, oral candidiasis, halitosis, and potentially reducing the risk of oral cancer. Probiotics such as *Lactobacillus reuteri* and *Bifidobacterium lactis HN019* demonstrate effective antibacterial, anti-inflammatory, and immunomodulatory properties. Prebiotics, by selectively stimulating the growth of beneficial bacteria, enhance these effects. The synergistic combination of probiotics and prebiotics presents a powerful tool in oral health management. However, further research and clinical trials are essential to fully understand their mechanisms and optimise their use in clinical practice.

The promising findings of the current studies provide a foundation for future advancements in this field, paving the way for more effective oral healthcare solutions. Furthermore, determining the exact therapeutic dose will be the next step in the field of preventive dentistry.

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