

Communication

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Communication

Are Probiotics Helpful If There Is a Dysbiotic Microbiome Involved in Oral Squamous Cell Carcinoma?

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Abstract

The oral cavity hosts the second most diverse microbial community. All inflammatory diseases of the oral cavity typically have a polymicrobial origin. Modern epidemiological and metagenomic evidence shows significant associations between potential periodontal pathogens, periodontitis, and oral cancer. Notably, *Fusobacterium nucleatum* and *Porphyromonas gingivalis* have been shown to promote carcinogenesis in mechanistic studies. Probiotics aim to modulate the normal inhabitants of a healthy oral biofilm, preventing the elevation of pathogenic microorganisms (pathobiont). Besides competing for attachment sites and host-derived nutrients, these probiotic strains may also produce bacteriocins to combat pathobiont. Importantly, probiotic strains can modulate the host's innate immune mechanisms and produce anti-inflammatory substances. However, the precise mechanisms by which probiotics help re-establishing a healthy oral biofilm remain under explored. There is inconsistency in the findings regarding the ability of probiotics to reverse dysbiotic microbiomes in oral cancer patients, although there are promising individual cases of success. Inter-individual variations are a significant factor contributing to these discrepancies. Since the prognosis for oral diseases depends on the specific microbiota and immune responses of each patient, the outcomes of probiotic therapy will also vary among individuals. Personalized treatment has been successful in traditional oral healthcare, and probiotic therapy should follow this trend, given the undeniable inter individual variation in the oral microbiome. Expanding combination therapies to include various probiotic bacterial strains and species could enhance our ability to address the diverse microbiomes in individuals, with a focus on prevention and control of oral squamous cell carcinomas (OSCC).

Keywords: OSCC; probiotics; periodontitis

The oral cavity is the main entrance to the human body which is second most complex ecosystem of the human the super organism which harbours more than 700 species of bacteria as well as fungi, archaea, viruses, protozoa and bacteriophages [1,2]. It comprises of anatomical components such as the soft tissues (gingival sulcus, attached gingiva, tongue, cheek, lip and soft palate), hard tissues (hard palate and teeth) and the saliva. Each component represents a distinct niche or microhabitat, providing ideal conditions in terms of nutrient availability, pH, attachment ligands, oxygen availability, and immune elements, which govern the composition of microbial communities in different microhabitats. There is cooperation and synergism among commensals, but competition and antagonism among commensals and opportunistic pathogens [2]. In healthy conditions, opportunistic pathogens and pathobiont are kept under control by the majority of commensals and the host's immune system.

The advent and improvement of omics technologies have corrected the misconceptions of inflammatory oral diseases with a polymicrobial origin. These oral diseases are now viewed as an

imbalance or shift in the homeostasis of the oral microbiome, with an increasing number of species and functions associated with the disease [3].

Numerous epidemiological studies have investigated the relationship between the oral microbiome and oral cancer. Findings from metagenomic studies have revealed a strong association between microbial dysbiosis and oral cancer [4]. Additionally, evidence from omics studies has shown the potential for polymicrobial synergy and dysbiosis of periodontopathogens in the tumor microenvironment of oral squamous cell carcinoma [5]. However, there is a notable lack of epidemiological and laboratory evidence confirming that a single species or consortium of oral microbes directly initiates oral carcinogenesis. Nonetheless, laboratory studies (both in vivo and in vitro) have demonstrated mechanisms through which two significant periodontal pathogens, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, promote oral carcinogenesis in both direct and indirect mechanisms [2]. Therefore, it is essential to treat periodontal diseases in oral cancer patients and get their periodontal disease status improved in order ensure better prognosis.

Traditional oral treatments primarily focus on dietary modifications, oral hygiene advice, and professional fluoride applications to control dental caries, often supplemented with mechanical plaque removal and antibacterial agents for periodontal issues [3]. However, these conventional approaches frequently fall short in restoring a healthy sustainable, oral biofilm. This is largely due to the resilience of the oral microbiome, which tends to rebound rapidly after treatment, combined with the difficulty in effectively reaching and penetrating dysbiotic dental plaque [3]. Hence, in order to truly combat polymicrobial diseases, we must focus on reestablishing a balanced oral microbiome in a sustainable manner and proactively address the risk factors that lead to microbial dysbiosis. This is why innovative strategies aimed at specifically and effectively modulating the oral microbiota among individuals deemed essential. Embracing novel approaches is pivotal for achieving lasting oral health and preventing future complications. Hence, moving beyond conventional methods and investing in targeted, customized solutions tailored to individuals that promise a healthier future for our oral ecosystems has become a cause for concern [3].

Live microorganisms, when taken in adequate amounts, can significantly enhance the health of the host, earning them the designation of probiotics [6]. Among the most prominent genera utilized in oral medicine for their probiotic qualities are *Lactobacillus*, *Bifidobacterium*, *Weissella*, and *Streptococcus*, along with specific species like *Bacillus subtilis* and the yeast *Saccharomyces cerevisiae* [7]. Over recent decades, the potential of these probiotics for improving oral health has garnered increasing attention, sparking innovative approaches to their application. For probiotics to thrive in their intended environment, it is essential that they are part of the natural flora. This strategic placement enables them to occupy vital ecological niches, effectively blocking less beneficial species from settling in and even pushing out potentially harmful microorganisms, particularly during times of illness or infection [8]. Despite the growing interest in probiotics, we still lack comprehensive insights into their mechanisms for restoring ecological balance. Understanding this could unlock immense benefits for our health and well-being, making research in this area vital.

However, several mechanisms have been disclosed in probiotic functions. Competition with other bacteria for attachment sites, nutrition, and available resources is the main action of probiotics [9]. After adhering to the oral surface or biofilm, they modulate the surrounding environment and the adhesion of other bacteria to oral surfaces. Probiotic species possess surface components that prevent harmful bacteria from adhering to them [8]. While several examples of probiotics inhibiting periodontopathogens growth or reducing cell counts have been described, most of the mechanisms behind these effects are still unknown [7]. Some probiotic strains may emulate mechanism of probiotics [7]. Lipase production with antimicrobial activity has been reported previously [10]. Moreover, it has been revealed that the production of H₂O₂ and acid is active against red complex bacteria [11].

Probiotics play a crucial indirect role in modulating the host's immune response, a phenomenon that has been extensively studied, particularly in the gut. Research has shown that probiotics can alter the balance of pro-inflammatory and anti-inflammatory cytokines secreted by epithelial cells [12].

With the rising popularity of probiotics, studies have increasingly focused on their effects in oral environments. These effects on immune responses include a reduction in the production of inflammatory factors by oral pathogens and an enhancement of the host's defense mechanisms [7]. A common finding in the research on oral probiotics is the decrease in pro-inflammatory factors such as tumor necrosis factor and interleukins (IL-1 β , IL-6, IL-8, IL-17) produced by oral epithelial cells. This reduction in pro-inflammatory factors is often associated with the production of arginine deiminase, which can inhibit nitric oxide (NO) synthesis [13].

Probiotics offer a powerful array of benefits, particularly in their ability to diminish pathogen-induced cytokine production, thereby reducing inflammation and promoting overall health. Remarkably, these beneficial microbes not only suppress harmful cell proliferation and apoptosis [7], but also boost the production of vital anti-inflammatory agents like interleukin 10 (IL-10) [14]. Certain probiotic strains have even been proven to produce β -defensins, the natural antimicrobial peptides that serve as a frontline defense at the epithelial level [15]. Additionally, the use of lactobacilli-based probiotics has been linked to significant increases in hemocyte density, enhancing the immune response. Perhaps one of the most impactful effects of probiotics [16] is their capacity to modulate immune responses through the inhibition of nuclear factor kappa B (NF- κ B) and the regulation of nitric oxide (NO) production in macrophages. By incorporating probiotics into our diets, we harness the potential to fortify our immune systems and promote a balanced, healthy inflammatory response [17].

There are case-control studies and meta-analyses investigating the use of probiotics in promoting oral health, particularly for the prevention and treatment of dental caries and periodontal diseases. Evidence suggests a trend toward higher success rates in managing periodontal disease with probiotics [18]. However, there is ongoing debate regarding their effectiveness, as some meta-analyses indicate that probiotics do not consistently lead to significant improvements in oral health parameters associated with the progression of these diseases [19]. Additionally, the studies demonstrate considerable heterogeneity, including variations in the specific probiotic strains or combinations used, the methods and schedules of probiotic administration, and the dosages applied [7].

There is a heterogeneity found among studies, such as the specific probiotic strains or combination of strains used, the probiotic administration modes and schedules, and the dosage [7]. There are several reasons for the ambiguities. Lack of information on the most effective doses and application modes for oral probiotics may contribute to the variability of outcomes observed [19]. Moreover, inter individual variations in oral microbiome are a major cause of variation. As oral disease prognosis depends on the specific microbiota and immune system of each patient, probiotic therapy outcomes will also vary when administered to different patients. Personalized treatment has been attempted in traditional oral health care with success and probiotic therapy should follow such trends due to undeniable interpersonal variation in the oral microbiome. Expansion of combination therapies by combining various strains and species would enable coverage of interpersonal microbiome with a view to modulation for OSCC prevention and control.

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