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Lactobacilli for the Treatment of Oral Diseases

Anja Hoffmann and Rolf Daniels*

Department of Pharmaceutical Technology, Eberhard Karls University, Tuebingen, Germany

***Corresponding author:** Rolf Daniels, Department of Pharmaceutical Technology, Auf der Morgenstelle 8, 72076 Tuebingen, Germany, Tel: +49 (0) 7071 2972462; E-mail: rolf.daniels@uni-tuebingen.de

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Abstract

Probiotics are defined as live microorganisms that beneficially affect the host. Probiotic bacteria have been used therapeutically for years to target gastrointestinal disease by rebalancing the complex microflora. Besides the gastrointestinal tract also the oral cavity is highly colonized by bacteria and many different bacterial species are part of the microbiota in the mouth, as it offers ideal conditions for bacteria with a stable temperature, moist surface with a relatively stable pH and regular supply of nutrients. By disturbing the balance of microorganisms in the oral cavity or by extensive accumulation of plaque, the ratio of pathogenic organisms can increase and lead to oral health problems. Probiotic bacteria, like *lactobacilli*, are a promising treatment strategy for oral diseases with a microbiological aetiology. Those include plaqueassociated diseases like dental caries, which is an infectious disease with microbial processes eroding and destroying the hard dental tissue or inflammation of periodontal tissue, namely gingivitis and the more severe periodontitis. Moreover, endodontic infections, and even fungal, viral and acute bacterial infections could be treated by a probiotic therapy. The interest of probiotics in the field of oral health is growing, although it is still in its infancy. The present review adresses criteria for the selection of probiotic *lactobacilli* strains. It encompasses existing evidence on the use of *lactobacilli* for caries, halitosis and candidiasis, as well as for periodontal disease like Gingivitis and periodontitis.

Keywords: Probiotics; Oral health; Caries; Periodontitis; Gingivitis

Introduction

The word probiotics comes from the Greek words "pro" and "bios", meaning 'for life'. The term probiotics was first mentioned by Lilley and Stillwell in 1965 and was defined as the opposite of antibiotics [1]. "Organisms and substances which contribute to intestinal microbial balance" was a later definition from Parker [2]. Although this definition is still used today, this interpretation included also antibiotics, which is not commonly used today. An advancement was the interpretation from Fuller in 1989, because the importance of living cells was emphasised and the word "substances" was eliminated to avoid confusion. "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance" [3]. Ever since, the definition has been reworked several times and it was for instance broadened by Vrese and Schrezenmeir, who included other target location than the gut [4]. An often cited definition is the one in the WHO/FAO report from 2006, wherein probiotics were defined as: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [5].

Probiotics are mainly used in dairy products, but they are increasingly becoming available as dietary supplements and pharmaceutical preparations. A large variety of microorganisms are classified as probiotics at present. Holzapfel [6] listed strains used as probiotics. Lactic acid bacteria are of most importance in food and nutrition, especially *lactobacilli* and the genus Bifidobacterium, whereas non-lactic acid bacteria are mainly used in pharmaceutical preparations. Different *Lactobacillus* species are also found in the oral cavity and in the saliva, the most common of which are: *L. fermentum*, *L. rhamnosus*, *L. salivarius*, *L. casei*, *L. acidophilus* and *L. plantarum* [7-9]. Three of these species are used in dairy products, but yet it is not clear, if they are detected due to frequent consumption of dairy products leading to temporary colonisation, or if the oral environment is the natural habitat [10].

If probiotics are taken orally, they are considered to be safe. A theoretical concern is that these viable bacteria move into the bloodstream and cause systemic infections. Lactobacillus rhamnosus GG (LGG) became available in Finland in 1990. Salimen et al. analysed blood samples in the period between 1990-2000 and did not find an increase related to the increasing probiotic use of LGG-containing commercial dairy products [11]. One case has been published that was caused by probiotic *lactobacilli*. A *L. rhamnosus* GG strain was isolated from a liver abscess in 19994. Some cases of Endocarditis [12] or *L. rhamnosus* GG leading to bacteraemia [13] are described, but it is estimated, that only 0.05%-0.4% of these cases are due to *lactobacilli* and bifidobacterial [14]. These *lactobacilli* and bifidobacteria are thought to be part of the commensal microbiota, instead of administered probiotics. Most cases of probiotic bacteraemia responded well to appropriate antibiotic therapy. Common risk factors to *Lactobacillus* bacteraemia are immunosuppression, prior hospitalisation and previous antibiotic treatment [15]. Even in HIV-infected patients, the use of the probiotic *L. rhamnosus* GG was well tolerated and no adverse effects, like bacteraemic outbreaks, were observed [10]. The consumption of 1×10^{10} CFU/day was safe and well tolerated in a HIV-positive population [16]. Antibiotic resistance of *lactobacilli* can be another safety issue. Probiotics should not carry transmissible antibiotic resistance genes [17]. *Lactobacilli* are naturally resistant to some antibiotics, as shown by Charteris [18], but this resistance is usually not of a transmissible type. Non-transmissible antibiotic resistance is usually of no safety concern. Lactobacillus plantarum CCUG 43738 displayed atypical phenotypic resistance to tetracycline and minocycline, from a plasmid-located tet (S) gene. This

acquired antibiotic resistance is undesirable for potential probiotics [19]. There are additional reports of acquired antibiotic resistance [20,21]. The transferal of antimicrobial resistance genes between probiotics and closely related opportunistic bacteria may take place [10]. More studies are needed, because the development of resistance to antibiotic drugs is a global issue. The US Food and Drug Administration (FDA) designation 'Generally Recognized as Safe' (GRAS) has been applied to several Lactobacillus strains [22] being a strong indication for safety in human consumption.

Lactobacilli for Oral Health

Strain selection

The selection of appropriate probiotic strains is a key issue. In contrast to the often used dietary *lactobacilli*, indigenous bacteria offer an advantage, because they are well adjusted to the human oral ecology. Consequently, the use of orally derived probiotics is recommended. Furthermore, the binding of LAB to mucus might be necessary to show positive effects, if administered to the oral cavity. Carbohydrate-protein interactions probably play a key role in the adhesion of these proteins to mucin-bound oligosaccharides [23]. Presently, most reports on mucus binding of probiotics are in the gastrointestinal field, because this is the main field of application. Several adhesion promoting proteins in Lactobacillus spp. are described and summarised by Van Tassell et al. [23] and by Vélez et al. [24]. The most studied mucus-targeting bacterial adhesin is mucus-binding protein (MUB), which is produced by *L. reuteri* [25]. An adhesion-promoting protein that mediated *L. fermentum* 104R binding to both small intestinal porcine mucus and porcine gastric mucin is described by Royas et al. [26]. Moreover, some *Lactobacillus* strains adhere to Caco-2 cell cultures, which was observed by Tuomola and Salimen [27]. A mucus adhesion promoting protein, MapA, mediates the adhesion of *L. reuteri* to human intestinal epithelial cells [28]. In *L. plantarum* WCFS1 a lectin-like mannose-specific adhesin that interacts with the host intestinal tract has also been described [29]. It is expected, that bacteria, intended as oral probiotics, should adhere to and colonise surfaces of the oral cavity [30]. Yli-Knuuttila et al. investigated whether *L. rhamnosus* GG could be detected in the oral cavity after discontinuation of administration of a probiotic product. This strain could only temporally be detected, but did not colonise the oral cavity. The authors concluded, that colonisation with this strain is improbable, but possible in some cases [30]. In a clinical study, the application of a chewable tablet of *L. reuteri* ATCC 55730 (10^8 CFU/tablet) for 2 weeks did not lead to permanent colonisation of the oral cavity [31]. The consumption of probiotic yoghurt-containing *lactobacilli* did also not lead to their installation in the oral cavity [32]. In contrast, salivary *Lactobacillus* counts increased after consumption of a product containing seven different Lactobacillus strains [33]. *L. plantarum* 299v (Lp299v) and *L. paracasei* showed survival in saliva for 24 h. The *L. paracasei* strain bound well to a surface mimicking human dental enamel, because over 20% of the added bacteria were bound but, for Lp299v the binding was poor with below 5% [34]. Lactobacillus GG, incorporated into yoghurt, was consumed twice a day for 7 d. After discontinuation of consumption, the bacterium was recovered in saliva samples, and after 2 weeks the strain was still present in 8 out of 9 subjects [35].

A final aspect to consider is lactic acid production by *lactobacilli*, because this process has been implicated in enamel demineralisation and dental caries in the mouth. The ability to produce acid varies significantly between strains and if they belong to the homofermentative or heterofermentative group [36]. Some strains, such as *L. plantarum* 299v can not only ferment carbohydrates (e.g., glucose and fructose) but also sugar alcohols (e.g., mannitol or sorbitol) leading to a decrease in pH *in-vitro*. In contrast Keller and Twetman found no evidence for an increased plaque acidity for *L. plantarum* 299 v with fructose or xylitol [37]. Strains with low metabolic activity are favourable, for example *L. paracasei* [38].

Periodontal disease

Three main factors considered for plaque-related periodontal inflammation are: a susceptible host, which is hard to address; second the presence of pathogenic species and the reduction or even absence of 'beneficial bacteria'. Today, periodontal therapies aim to reduce the bacterial threat and are based on mechanical subgingival debridement plus improvement of oral hygiene [39]. The subgingival microbiota then shifts towards a less pathogenic composition, meaning a higher proportion of Gram-positive aerobic species and fewer periodontopathogens [40]. Unfortunately, this shift is only temporary. The use of antibiotics or antiseptics for a certain time does not improve the long-term effect of periodontal therapy [41]. The use of probiotics in this field offers the possibility to restore the reduced numbers of beneficial bacteria to prevent and treat plaque-related periodontal disease. On the one hand the inhibition of specific pathogens is a possible mechanism and on the other hand the host response could be affected by probiotics.

To date, the following effects have been shown for probiotics in the field of periodontal disease. *L. salivarius* tablets reduced 5 periodontopathic bacteria in subgingival plaque after 4 weeks and the levels tended to be lower up to 8 weeks compared with placebo [42]. In a clinical trial with *L. reuteri* containing tablets the number of periodontal pathogens in the subgingival microbiota was reduced, but no significant clinical impact could be shown [43]. A *Lactobacillus* microbiota inhibited growth of *S. mutans*, *P. gingivalis* and *P. intermedia* [44]. Furthermore, antimicrobial effects against *P. gingivalis* have been described [45,46]. Co-aggregation activity of probiotic strains with oral pathogens (Porphyromonas endodontalis, *T. forsythia*, *Eubacterium saphenum*, *Filifactor alocis* or *P. gingivalis*) can be another mode of action [44,45,47]. Competition with peridontopathogens for the uptake of nutrients could also improve oral health [48]. Some strains produce biosurfactants, which are able to prevent the adhesion of pathogens [49]. *L. salivarius* TI 2711 administered as tablets did not significantly change the total number of bacteria in the saliva, or the number of mutans-streptococci and *lactobacilli*. Only for black-pigmented anaerobic rods, which include most periodontopathic bacteria, a significant decrease was found [50]. A promising strain is also *L. reuteri Prodentis*, because not only antimicrobial, but also inflammatory, effects were found along with inhibition of plaque formation [51]. The reduction of pro-inflammatory cytokines (TNF-α, IL-8) in gingival crevicular fluid can be regarded proof of concept for the application of *Lactobacillus reuteri* in a chewing gum. The modulating effect of short-term intake of probiotics on the oral immune response is dose dependent [52]. An anti-inflammatory effect of *Lactobacillus brevis*, administered as lozenge to patients with chronic periodontitis, was shown by a significant decrease in the amount of nitrite/nitrate, prostaglandin E2 and matrix metalloproteinase in saliva [53]. Different microbial species show anti-inflammatory activity [46]. Although an anti-inflammatory effect of probiotic milk drink containing *L. casei* Shirota was shown in a clinical trial, increased plaque accumulation occurred, which is

probably linked to the high sugar content [54]. The same product increased the plaque index and papilla bleeding index compared to baseline, whereas the amount of matrix metalloproteinase-3 was reduced [55]. By using a probiotic treatment (*L. reuteri*) also clinical effects were found, like a significant reduction in the gingival index and plaque scores [56]. Smokers showed a significantly greater improvement in plaque scores in a clinical trial using freeze-dried probiotic tablets of *L. salivarius* [57]. Even heat-killed *L. plantarum* decreased the depth of periodontal pockets in a randomised, double-blind, placebo-controlled clinical trial [58].

Caries

Dental caries is on the one hand associated with *S. mutans*, but also with *lactobacilli*. Indeed, *L. plantarum* and *L. paracasei* are among the species found in adult and childhood caries [59]. Various *Lactobacillus* spp. have numerical importance in carious dentine [60] and are often found in caries lesions [61]. *L. salivarius* LS 1952R induced dental caries in rats [62]. In an *in-vitro* model the combination of LGG and *S. mutans* was more cariogenic than monospecies biofilms of *S. mutans*. Therefore, LGG did not reduce the caries activity, but contributed to the caries process [63]. Another finding in this direction is that after restoration of caries, *S. mutans* and *lactobacilli* are reduced in saliva [64]. By now the role of *lactobacilli* in caries is not absolutely sure. It has been observed, that *lactobacilli* from caries-free people exert more effective inhibition of mutans-streptococci than *lactobacilli* isolated from caries-active subjects *in-vitro* [65]. *L. plantarum* 299 v and other *Lactobacillus* strains coaggregate *in-vitro* with selected oral streptococci. Coaggregation is an important factor in the development of biofilms and dental plaque [66].

Several studies have been published that hint towards an anti-caries effect of *lactobacilli*. *L. casei* ATCC 11578 is able to prevent and even decolonise the adhesion of *S. mutans* to saliva-coated hydroxyapatite by modifying the protein composition of the salivary pellicle [67]. In a clinical study using *L. paracasei* GMNL-33 a significant reduction of salivary *S. mutans* was detected after 4 weeks [68]. *L. paracasei* showed maximum interference activity against *S. mutans in-vitro*, as reported by Simark-Mattsson et al. [65]. Lozenges containing *L. brevis* CD2 taken by school children with a high caries risk, resulted in a reduction in plaque acidogenicity, salivary mutans-streptococci and bleeding on probing [69]. *L. reuteri* significantly inhibited the growth of *S. mutans*, if applied as yoghurt [70], via straws and tablets [71,72] or as chewing gum [73]. A combination of *L. sporogens*, *L. bifidum*, *L. bulgaricus*, *L. thermophilus*, *L. acidophilus*, *L. casei* and *L. rhamnosus* either as capsule or as liquid form was tested. The counts of *lactobacilli* in the saliva increased significantly, but *S. mutans* was not significantly influenced. Unfortunately, no follow-up was performed after the trial [33]. *Lactobacilli* (including *L. plantarum* 299v, *L. paracasei*, *L. reuteri*, *L. acidophilus* and *L. rhamnosus*) showed co-aggregation with mutans-streptococci *in-vitro* and inhibited the clinical mutans-streptococci [74]. In a randomised, double-blind, placebo-controlled intervention study in 594 children, milk containing LGG reduced dental caries and the counts of mutans-streptococci after 7 months. Consequently, the risk of caries was significantly reduced [75]. In another double-blind, placebo-controlled trial of milk supplemented with fluoride and/or *L. rhamnosus* the effect on primary root caries lesions was investigated. The use of milk only supplemented with *lactobacilli* showed a positive effect, as well as the fluoride, but the beneficial effect was strongest by combining both [76].

Halitosis

There is currently limited evidence to support the use of *lactobacilli* in halitosis. After taking *L. salivarius* WB21 and xylitol in tablet form daily, the scores of an organoleptic test and bleeding on probing significantly decreased after 4 weeks [77]. In a randomised double-blind, placebo-controlled cross-over trail with 25 adults a probiotic chewing gum with *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 5289 or placebo was used. After a treatment duration of 14 days the organoleptic scores were significantly lower in the group with probiotic chewing gum [78].

Candidiasis

For candidiasis there is also little evidence available. In a randomised, double-blind, placebo-controlled study the consumption of probiotic cheese (*L. rhamnosus* GG plus *Propionibacterium freudenreichii susp. Shermanii* JS) led to reduced *C. albicans* counts [79]. However, in a 3 week intervention for which subjects ate 5 × 15 g cheese per day containing LGG and *L. rhamnosus* LC 705, no significant difference in the effect between the probiotic and control cheese on salivary Candida counts was found [80]. The administration of *L. casei* and *Bifidobacterium breve* for 20 d significantly reduced Candida prevalence and the level of anti-Candida immunoglobulin A [81]. Lozenges with *L. reuteri Prodentis* are available on the market and reduce the prevalence of oral Candida in fragile elderly people [82]. Finally, *L. plantarum* and *L. paracasei* showed some co-aggregation with *C. albicans* [83].

Discussion

The cited studies are often limited due to small sample size, lack of appropriate randomisation, blinding, duration of intervention plus follow-up and study set-up. Even fewer studies make inter-group comparison with true placebo or a negative control. The tested population is very heterogeneous and the probiotic doses applied differ up to 2 log scales. Furthermore, the vehicles used to administer the probiotics also clearly differ and might influence the outcome of the study. Typical means of probiotic administration are yoghurt, cheese [79], lozenges and tablets [72], capsules or liquids [33]. Besides, it is expected to be difficult to induce a microbiological shift or a clinical probiotic effect in a matured oral microbiological environment. The probiotics will have difficulties in colonising the mouth. A pre-treatment, to reduce the levels of indigenous microbiota, might be useful and necessary. The authors of a meta-analysis concluded, that the evidence supporting the use of probiotics to prevent or treat caries and periodontal disease is insufficient at present. In spite of the lack of evidence, they also state, that no adverse effects were reported, so there is no strong argument against using such a treatment [84].

Conclusion

Probiotic effects are strain-specific and cannot be transferred to other subspecies, or even other strains without any tests. Therefore, clear nomenclature of the evaluated strains is crucial for allociation of effects and for the judgement of efficiency. Overall, *lactobacilli* seem to be a promising way forward regarding restoration of periodontal health, especially in gingivitis, but better designed clinical trials in larger populations are needed. Moreover, combining different probiotic strains could lead to synergistic effects. This research field is in a very early state and enormous efforts are necessary to advance this promising strategy. An application in caries is questionable, as long as

the impact of *lactobacilli* on the cause and progression of the disease is not clarified.

Conflict of Interest

Anja Hoffmann reports Personal fees from Symrise AG and Rolf Daniels reports Grants from Symrise AG, both outside the submitted work. In addition, Rolf Daniels and Anja Hoffmann have a patent EP 15 184849.6 pending.

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