ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2023; 9(1): 330-337

www.oraljournal.com
Received: 04-01-2023
Accepted: 07-02-2023

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The use of oral probiotics in non-surgical periodontal therapy: Literature Review

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DOI: https://doi.org/10.22271/oral.2023.v9.i1e.1702

Abstract
Periodontal disease is a chronic disease that develops through multiple factors. It is directly associated with the accumulation of biofilm. It is characterized by progressive destruction of the supporting tissues of the teeth. Clinically it can be diagnosed through parameters that are gingival inflammation, loss of clinical attachment, increased probing depth, bleeding on probing, and dental mobility. The figures that have been found are around 1.1 billion cases of severe periodontal disease, in 2019. These amounts are equivalent to 15% of the world population. Radio graphically, vertical, horizontal, or both bone loss may be seen. Periodontal therapy is based on five phases: systemic, hygienic, surgical, restorative and maintenance. Currently, adjuvants to periodontal therapy have been found with favorable results. Oral probiotics, the Lactobacillus strain specifically, have been studied in non-surgical periodontal therapy. It has been shown that in patients with gingivitis plus the use of probiotics and periodontal mechanical therapy, patients have a reduction in the previously mentioned clinical parameters. On the other hand, there are also prebiotics that are non-pathogenic bacteria, their function is to improve the health of the host. This is how systemic homeostasis through vitamins and food, proposes a lower risk of developing periodontal disease.

Keywords: Periodontal disease, periodontitis, probiotics, and prebiotics.

Introduction
Periodontal disease is a public health problem due to its high prevalence, resulting in the loss of dental organs, negative effects in terms of chewing and aesthetics [1]. It begins with an uncontrolled inflammatory response that originates from a colonization of pathogenic bacteria in the gingival margin of the oral cavity. This inflammatory response will be triggered by the response of the host's immune system [2].
It affects between 45-50% of adults in its mildest form, reaching around 60% in people >65 years of age [3]. In the most serious forms, they are treated with consultation and treatment depending on the progress of the disease. About 46% of adults over the age of 30 have some sign of inflammation or gum disease [4].
According to the latest figures, this disease is number six, one of the most prevalent in the world [5]. The figures that have been found are around 1.1 billion cases of severe periodontal disease, in 2019. These amounts are equivalent to 15% of the world population [6].
The use of probiotics has been proposed as an adjunct to periodontal therapy due to the origin of the disease based on dental plaque formed by bacteria [7]. Probiotics are defined as living organisms, bacteria that do not have any pathogenic characteristics. They are used as food supplements that, when consumed correctly, have beneficial effects on the balance of health [8]. They are capable of inhibiting the adhesion of pathogens, stimulation and modulation of the immune system [9]. Its way of doing it is by directly interfering with the formation of the biofilm by producing chemicals that prevent the development of other bacteria and activate local immunity [10].
On the other hand, prebiotics are soluble fibers that are fermented by a good micro biota, inducing the secretion of IgA, helping the intestinal barrier and host immunity [11].

Treatment with beta-glucans reduces alveolar bone loss and the expression of IL-10 as an inflammatory mediator [12]. They have the job of cooperating in interactions such as coaggregation, conjugation, and protection against environmental stresses, such as antibiotics [13].

The aim of this study is to conduct a narrative literature review on the use of probiotics as adjuvants in periodontal treatment.

Materials and Methods

A narrative literature review was carried out with the search for the crossing of words "oral probiotics", "oral prebiotics", "periodontitis", "periodontal treatment" in Spanish and English in the Pubmed, Google academic, Scielo, Elsevier databases where original articles, clinical case reports, narrative and systematic literature reviews were included.

Results

Periodontitis

Periodontal disease is a chronic disease that develops through multiple factors. It is directly associated with the accumulation of biofilm. It is characterized by progressive destruction of the supporting tissues of the teeth. These tissues are made up of the periodontal ligament, alveolar bone, gum, and cementum. It is characterized by interacting with certain pathogenic bacteria, the host's immune response and certain environmental factors that influence its progress, such as smoking or smoking [14].

Prevalence

According to data from the 2009-2014 National Health Survey and Nutritional Examination in the United States of America, 42% of the population had periodontitis and 7.8% had severe periodontitis. Therefore, this survey confirms the prevalence of the disease in around 50% of the adult population when measured in people over 30 years of age [2].

In addition to directly affecting people's ability to perform masticatory movements, they affect their nutritional status and quality of life. The literature supports the association with periodontitis and certain systemic diseases [15].

It affects around 50% of the world population, 64% of which are people over 65 years of age [16].

Systemic pathologies such as autoimmune diseases, diabetes mellitus, Alzheimer's disease, inflammatory diseases, and oral cancer have been identified as being of reciprocal importance in periodontal disease [17].

Etiology

It has been recognized that dental plaque induces a process of gingival inflammation that progresses to the destruction of tissues, giving rise to periodontitis [18].

Today, the balance between bacteria and the host plays a crucial role in its development. When there is a dysbiosis that is the bacterial imbalance, pathogens such as *Porphyromonas gingivalis* abound and induce the same [19].

The microorganisms that are considered periodontal pathogens are strictly anaerobic and are the ones that contribute to the onset of periodontal disease, causing pockets. The polymers that form the biofilm matrix are glucans and fructans that are produced by the action of glucosyltransferase and fructosyltransferase, sucrose enzymes [20].

Amyloids are insoluble proteins that support the architecture of the biofilm. One of them is the Fap1. It is a serine-rich protein that repeats with adhesin, influencing biofilm formation. They are in pseudomonas and when they are overexpressed, they induce cell aggregation, increasing the biofilm. Tas A is another protein with the same function. They go through a formation process in which they change planktonically, which is when they are floating freely on the surfaces [21].

The formation of dental plaque is divided into four phases, beginning with adhesion. It starts being reversible and later irreversible. In the reversible phase, its first colonizers are *Streptococci* and *Actinomycetes*. Its adhesion is by means of phosphate-rich proteins such as staterin and α-amylase. The two families mentioned and gram-negative bacteria adhere to staterin. It becomes irreversible when *Fusobacterium nucleatum* adheres to the staterin, making the change to anaerobic bacteria. *Staphylococcus epidermidis* and *Staphylococcus aureus* are the first to form adhesion [22].

The next level is the maturation that occurs when the cells multiply. Its means of communication is through the perception of the bacterial quorum, which is dedicated to the expression of its genes and increases their density. The layers of bacterial cells are adhering, depending on their metabolism, being the anaerobic ones those in deep areas. Finally, it is the dispersal phase where they continue to multiply until they cause damage depending on the host's response [23].

Clinical characteristics of periodontitis

Clinically, it could present gingival inflammation, clinical attachment loss, increased probing depth, bleeding on probing, and dental mobility. Radiographically, vertical or horizontal bone loss or both may be seen [24].

Case definition of periodontitis

It will be defined when the following parameters are clinically observed: a detectable clinical attachment loss greater than or equal to 2 mm in non-adjacent teeth. Another form would be as buccal or oral clinical attachment loss greater than or equal to 3 mm with pockets greater than or equal to 3 mm in 2 or more teeth. The loss of attachment cannot be attributed to external causes not related to periodontitis, such as 1) gingival recession of traumatic origin, 2) caries that extends to the cervical area, 3) presence of attachment loss on the distal face of the second molar associated with malformation position or previous third molar extraction, 4) endodontic lesion draining into the gingival sulcus and 5) vertical fracture of the dental organ [25].

Periodontal disease classification

The most recent classification for periodontal diseases began in 2015, ending in Chicago in 2017. What was done was to add the periodontal health section, speaking only of periodontitis, called chronic and aggressive periodontitis in the previous classification of 1999, they currently classify it in stages and grades [26].

In the section on gingivitis and gingival conditions, they reaffirm that bleeding on probing should be the first parameter to determine it. They accepted the condition that a patient with gingivitis can return to a state of gingival health, however a patient with periodontitis remains on maintenance therapy for life. Added that gingival inflammation may not be induced by plaque and other conditions [27].

In the classification of previous periodontitis, published in 1999, it is classified by age and degrees of progression. In the updated classification they were based on stages and grades of the disease. As can be seen in Table 1, periodontitis can be classified into 4 stages, which include variables such as: level

of clinical insertion, amount and percentage of bone loss, probing depth, presence and extent of bone defects, involvement of furcations, dental mobility and loss of teeth due to periodontitis [28].

Table 1: Description of the stages of the new 2017 periodontal disease classification. Source: Papanou *et al*. (25).

Periodontitis Stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1-2 mm	3-4 mm	>5 mm or equal	>5 mm or equal
	Radiographic bone Loss	Coronal Third <15%	Coronal third 15% al 33%	Expanding to the middle or apical third of the root.	Expanding to the middle or apical third of the root.
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of <4 or equal teeth	Tooth loss due to periodontitis of >5 or equal teeth
Complexity	Local	Maximum probing depth < 4 or equal. Mostly horizontal bone loss	Maximum probing depth <5 or equal. Mostly horizontal bone loss	In addition to stage II complexity: Probing depth equal or > 6 mm. Vertical bone loss of > 3 mm or equal Furcation involvement class II or III Moderate ridge defect	In addition to stage II complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree >2 or equal Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (< 30% of teeth involved), generalized, or molar/incisor pattern			

The grades used to classify periodontal disease can be seen in Table II in three levels, of which grade A is the lowest risk, grade B has little or low risk, and grade C has a high risk of progression. In this part, they are based more than anything on the systemic state of the patient, her general health, the number of cigarettes per day, and metabolic diseases such as diabetes mellitus [29].

Table 2: Description of the grades of the new classification of periodontal disease 2017 Source: Papanou *et al*. [25]

Periodontitis Grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Logitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	< 2 mm over 5 years	➢ 2 mm or equal over 5 years
	Indirect evidence of progression	% of bone loss/age	<0.25	0.25 a 1.0	> 1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarretes/day	Smoker >10 or equal cigarretes/day
		Diabetes	Normoglycemic/no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c >7.0% in patients with diabetes

This new classification focused on factors that influence the development of periodontal disease. Specifically it includes systemic diseases and conditions that may affect periodontal tissues. Said 2017 classification also includes mucogingival conditions, occlusal forces and finally classified the disease in dental implants [30].

Local and systemic risk factors

Periodontal disease is characterized by being polymicrobial or composed of multiple microorganisms. It can occur at the same time as other diseases, but this is directly related to the host's immune defense status so that it may be susceptible to it. It is activated by the host's immune response primarily for protective purposes and induces tissue destruction, synthesis of cytokines, inflammatory mediators, and proteinases [31].

Risk factors may be associated with smoking, reduction in polymorph nuclear leukocytes or immunosuppression, genetic polymorphisms related to cytokine production, and accumulation of biofilm bacteria [32].

Obesity is one of the systemic risk factors for periodontal disease. This is because in its presence, more diseases develop, such as type II diabetes mellitus, hypertension, arteriosclerosis, cardiovascular diseases, among others [33].

Periodontal diagnosis

Periodontal treatment is divided into five phases. This is because one goes hand in hand with the other, the most recommended is to carry out each of the phases at a step

through which there is already clear evidence that you can continue to the next phase following the protocols that the patient needs. Starts with periodontal evaluation [34].

This diagnostic phase is based on a complete periodontal examination. Based on the taking of clinical parameters, radiographs and photographs, a correct diagnosis and prognosis can be given to the patient. Education is evaluated because based on that, clinical pathologies or disease progression are observed. Gives information to the specialist, how to communicate, instructions but above all the understanding of the patient [35].

In this phase, a systemic evaluation of the patient should be carried out. If there is a disease, the state of the disease must be known, the control it has and the risk factors because the treatment plan will be given based on this. This plan could be made up of non-surgical therapy, periodontal reevaluation, surgical periodontal therapy, and maintenance periodontal therapy [36].

Non-surgical periodontal therapy

This first phase is based on scaling and root planning of teeth affected by periodontal disease. Therapy includes manual and ultrasonic instrumentation which removes supragingival and sub gingival calculus with maintenance of supragingival biofilm control reinforcement [37].

It is affirmed that there is a successful treatment when there is absence of bleeding, decrease or absence of periodontal pockets and a gain in clinical attachment. This treatment could result in a reduction of the pocket due to the recession that occurs after the treatment and the gain of clinical insertion. When lower and inactive pocket depth levels are obtained after treatment, the treatment is considered successful [38].

Factors that must be taken into account for the success of non-surgical treatment are the associated factors that the patient may present, such as the severity of the disease and, in case he is a smoker, it will have negative consequences for the treatment [39].

Non-surgical periodontal therapy will be considered successful when probing depths less than 5 mm are obtained [37]. The goal is to return the tissues to an inflammation-free state to restore periodontal health. This therapy also results in decreased pain, bleeding gums and halitosis according to what patients report [40].

Periodontal reevaluation

The reduction of periodontal pockets and stopping the progression of the disease is the main objective of periodontal treatment. The reevaluation is one of the most important parts in the periodontal evaluation of a patient since many times the instrumentation does not become completely effective due to different factors [41].

Residual periodontal pockets or bleeding on probing greater than 10% of the sites can be caused by pockets that are active, or because total calculus removal was not achieved due to the amount of sub gingival calculus present, or the depth of said pockets; the deeper, the less effective in calculus removal in root planning. Both systemic and oral health needs of the patient are reviewed. An accurate periodontal review is carried out to make decisions about the possibilities of carrying out surgical periodontal therapy [42].

Surgical periodontal therapy

Residual periodontal pockets larger than 5 mm are very commonly associated with increased risk of periodontal disease progression and tooth loss. The European Federation of Periodontics, declared that 6 mm is the minimum depth that a periodontal pocket must have to decide to perform periodontal surgery in the area [43].

Periodontal access surgery is recommended in the presence of bleeding or exudate and residual calculus detected in periodontal pockets. This is done with the aim of having greater visibility to the root surface and alveolar bone to achieve adequate calculus removal [44].

Multi-rooted teeth tend to have greater bone destruction, both horizontally and vertically, which causes furcation areas to become involved with the progression of periodontal disease, also called furcation's. The prognosis of these pieces will depend on the levels of clinical insertion that they present, therefore they are one of the factors that must be taken into account when performing surgery in these areas due to their higher prevalence [45].

Periodontal maintenance

When patients are diagnosed with periodontal disease, it remains latent. It has been studied that those patients who carry out regular periodontal maintenance through intervals experience less loss of clinical attachment and dental organs than patients who do not receive supportive periodontal therapy. As soon as they fully master the biofilm removal technique, they can enter this program [46].

The Merin classification classifies patients into three classes. Class A, patients with excellent results who were maintained for more than a year with good hygiene and minimal stone accumulation. Class B, good results for 1 year but inconsistent or poor hygiene, heavy calculus formation, systemically compromised, some remaining pockets, some teeth with less than 50% bone support, smoker, among others. Class C presents poor and inconsistent oral hygiene, heavy calculus formation, systemic diseases that make it prone to periodontal disease, remaining pockets, most teeth with less than 50% bone support, bleeding on probing, among others [47].

Depending on the classification, it is how the patient will be assigned the frequency of their periodontal maintenance appointments. Class A every six months to a year. Class B every three to four months. Class C every month or maximum every three months [48].

Probiotics as adjuvants

Over the years, different mouthwashes or rinses have been used, such as chlorhexidine, antibiotics in different presentations, photo modulation, ozone therapies, and different adjuvants to help patients obtain a better result after periodontal therapy. Excellent results have been found regarding the use of probiotics due to the systemic effect that they have shown to have.

The change that is taking place in the micro biomes of the human body has grown in recent years due to its ability to transform and maintain health. Probiotics have been used for intestinal health and over time their potential in relation to oral health has been proven. They are microorganisms commonly derived from *Lactobacillus* or *Bifidobacterium* that have influenced oral health [49].

This is why they have been suggested by many investigations as adjuvants in periodontal treatment. They are living microorganisms that benefit the health of the host. They are potentially effective in prophylactics or for inflammatory diseases. They have presented characteristics such as their ability to balance the micro biome, have the ability to act as

suppressors of pathogens and regulate the expression of immunological genes [50].

In addition to their proven effectiveness in periodontal disease, they have been used as a method of caries prevention. It has been proven that probiotics are effective in the inhibition of Streptococcus mutans, which has been considered throughout many investigations to be the main microorganism associated with the development of caries [49].

Lactobacillus reuteri

The efficacy of probiotics has been identified based on their survival abilities. These can survive in the gastrointestinal tract, have high acid resistance, antibiotic resistance, and the specific ability to excrete clear benefits in the host. Specifically, *L. Reuteri* has multiple beneficial health effects and was isolated around the year 1962 [51].

L. Reuteri can withstand changes in pH since it uses multiple mechanisms to successfully inhibit pathogenic microorganisms, in addition to having been shown to secrete antimicrobial intermediates. It could adhere by many pathways including mucin. It has been shown to reduce the amounts of periodontal pathogens in the sub gingival micro biome without any clinical impact [51].

The efficacy of the *Lactobacillus* strain specifically in scaling and root planning treatment has been extensively investigated. It has been shown that in patients with gingivitis plus the use of probiotics and periodontal mechanical therapy, patients have a reduction in clinical parameters such as decreased bleeding on probing and pocket depths. In addition, they demonstrated regulation of cytokines such as IL-10, IL-1β, IL-8, beta defensins 3, TLR4, and CD4 [52].

Specifically, probiotic supplementation has become an adjunct to periodontal therapy, in addition to its gastrointestinal effect. Its working mechanism is through antimicrobial compounds such as S layer and lipoteichoic acid, with which they can inhibit the growth of pathogenic bacteria. They also inhibit their adhesion and the ability to colonize [53].

L. Reuteri has been extensively studied for its antibacterial and anti-inflammatory effects. It is currently one of the most tested probiotics. It produces a chain called DSM 17938 which produces reuterin that acts as an antibiotic and induces oxidative stress in pathogens. This makes it resistant to proteolytic and lipolytic enzymes. It has another chain ATCC PTA 5289 that specifically presents anti-inflammatory characteristics, which inhibits the production of TNF, IL-8 and IL1 β [54].

This strain can induce the formation of reuterin (3-hydroxypropianaldehyde) which will induce oxidative stress in cells. Other things that have been discovered is its ability to compete with pathogens for epithelial cell adhesion. Also, they interact with TOLL receptors, specifically with TLR2 regulating inflammatory signals against gram positive bacteria [55].

TOLL receptors are responsible for initiating the inflammatory pathways that have the most important job in the immune response. It is directly related to the immune response. Specifically, they are in charge of regulating the inflammatory response, activating the innate or adaptive immunity response towards infectious pathogens [56].

Efficacy of probiotics in relation to periodontitis

Its first step, which is adhesion, has been found to have beneficial effects. The work of the bacterium *F. Nucleatum* in periodontal disease was previously explained. *L. Reuteri* can significantly coaggregate with this bacterium. It directly regulates and decreases the auto aggregation of the bacterial cells of *F. Nucleatum.* Knowing that this bacterium is responsible for the turnover to gram negative bacteria, the probiotic plays a crucial role in stopping it [57].

It has had good results in tests with periodontitis. To evaluate the success of periodontal treatment, they are based on the probing depth and the reduction is taken as an indicator of success. Studies have shown that the use of oral probiotics has promising results in oral pathologies [58].

The different chains of *L. Reuteri* have demonstrated their ability to decrease probing depth in moderate periodontal pockets (4-6 mm). There are also significant results in the reduction of bleeding on probing. All this at the same time with dental plaque control at home. The best results were seen with oral, paste or pill probiotics [59].

Specifically, a reduction in pathogen microliter copy number of the orange complex has been found. We are talking about a reduction of *P. Intermedia* and *F. Nucleatum*. It is important to emphasize that the positive effect they have against microbiological pathogens has become significant. Specifically, it has been around three months after treatment. Although the periodontal clinical parameters improved significantly during the first three months. In addition to having a change from a pro-inflammatory to an anti-inflammatory response, which leads to an arrest in the continuity of tissue destruction by periodontal disease [32].

It has also been found that they have achieved a suppression of alveolar bone loss through the regulation of IL-10 15 days after taking it. Also, it has reduced the number of osteoclasts and proinflammatory cells, decreasing the levels of cytokines of TNF and IL-beta 30 days after taking it [12].

Prebiotics

Prebiotics are food ingredients that are not digestible. At the time of consumption, they have been found to be beneficial to the host. Its way of working is through the growth of bacteria in the colon. These bacteria are not pathogenic, their function is to improve the health of the host. This is how systemic homeostasis through vitamins and nutrition proposes a lower risk of developing periodontal disease [8].

It has been shown that this type of substrate can induce a change in the biofilm, changing the composition of the multispecies that form it. N-acetyl-D-mannosamine, succinic acid and the di-peptide Met-Pro have been used, which have caused an increase in the species that are beneficial to the oral cavity. Another concomitant effect has been the reduction in the proportion of pathogenic species [13].

Modifying the environment and biochemical conditions will affect the composition of the biofilm, which at the same time will affect the efficacy of the prebiotic compound. It is important that when using them, the interactions of the bacteria are not being affected by other means such as antibiotics. Being in constant turnover, this prevents the work of the prebiotic per se [13].

It has also been found that beta glucan prebiotics have an impact on the reduction of alveolar bone loss and on the reduction of the expression of the inflammatory mediator IL-10. Another compound is the mannan oligosaccharide, which has the same effect, in addition to decreasing the expression of gamma interferon, tumor necrosis factor and IL-1 beta, increasing beta growth factor [12].

Conclusion

Periodontal disease is one of the most common diseases,

according to the WHO, it occurs in about 42% of the population of which 50% are adults. It is directly related to the accumulation of biofilm which develops due to the lack of adequate dental hygiene, among other factors. In addition, it can present with different systemic diseases which are not its etiological factor but increase its complexity. Its treatment is highly studied due to the results that have been obtained in terms of non-surgical and surgical periodontal therapy. With the help of adjuvants such as probiotics, excellent results have been found in their use after non-surgical periodontal therapy. That is why it is verified that its constant use helps to control periodontal disease, in addition to the formation of dental plaque, since it acts by preventing its formation. Probiotics also contribute to the reduction and improvement of periodontal clinical parameters.

Acknowledgments
To CONACYT for the scholarship awarded (Number 1240017).

Author's Contribution
Not available

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
PG Pulido, OE Cantu, NI Rodríguez Franco, JI Rodríguez Pulido, GI Martínez González, GC Palma and GM Sandoval. The use of oral probiotics in non-surgical periodontal therapy: Literature Review. International Journal of Applied Dental Sciences. 2023;9(1):330-337.