GRADUATION PROJECT

Degree in Dentistry

MICROORGANISMS IN THE ORAL CAVITY

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INDEX

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Abstract: (English)

Introduction: In the gut microbiota the use of probiotics is mostly used for finding an equilibrium in the microbiota preventing or healing diseases as lactose intolerance and inflammatory bowel disease. Faced with the observation that caries and periodontal disease have a big prevalence in the population, different solution has been thought. Aim: The main objective is to explain if the equilibrium of the microbiota can have positive impact and prevent or cure oral disease The secondary objectives are to know if it is possible to do personalize finding of microbiota for patient and so knowing the dental biofilm composition of a patient (healthy microbiota/unhealthy microbiota).

To assess what are the new potential preventive strategies in a therapeutic and diagnostic view for the future and avoid treatment like antibiotics. With the use of studies identify what strains can be used as probiotics. To know if dysbiosis of the oral cavity can be responsible of diseases in others part of the body. Materials and methods: A literature review has been carried out on the PubMed online database, selecting articles in English from 1995-2022. Results: 68 articles were read.32 articles were selected according to the inclusion and exclusion criteria. Finally, 14 articles were strictly used for results. Probiotics and prebiotics show positive evidence in term of prevention for oral disease. Qrsi and targeted peptide shows positive evidence in term of treatment. Finally, a dysbiosis seems linked with other diseases of the body as gut for example.

Conclusion: It has been observed than equilibrium of the microbiota seems a good way for the prevention of oral diseases also than diseases in others part of the body.

Keywords: Dentistry, probiotics, oral cavity, microbiota, core microbiome.

Abstract (Spanish)

Introducción: En la microbiota intestinal el uso de probióticos se utiliza principalmente para encontrar un equilibrio en la microbiota previniendo o sanando enfermedades como la intolerancia a la lactosa y la enfermedad inflamatoria intestinal. Frente a la observación de que las caries y las enfermedades periodontales tienen una gran prevalencia en la población, se ha pensado una solución diferente. Objetivo: El objetivo principal es explicar si el equilibrio del microbiota puede tener un impacto positivo y prevenir o curar la enfermedad oral. Los objetivos secundarios son saber si es posible personalizar el hallazgo de microbiota para el paciente y así conocer la composición de biófilo dental de un paciente (microbiota saludable/ microbiota no saludable)

Evaluar cuál son las nuevas estrategias preventivas potenciales en una visión terapéutica y diagnóstica para el futuro y evitar tratamientos como antibióticos. Gracias a los estudios identificar qué cepas se pueden utilizar como probióticos. Saber si una disbiosis de nuestra cavidad oral puede ser responsable de enfermedades en otras partes de nuestro organismo. Materiales y métodos: Se ha realizado una revisión bibliográfica en la base de datos en línea PubMed, seleccionando artículos en inglés de 1995 a 2022. Resultados: se leyeron 68 artículos. Se seleccionaron 32 artículos según los criterios de inclusión y exclusión. Finalmente, 14 artículos fueron utilizados estrictamente para los resultados. Probióticos y prebióticos muestran evidencia positiva en términos de prevención de la enfermedad oral. Qrsi y péptido dirigido muestra evidencia positiva en términos de tratamiento. Finalmente, una disbiosis parece estar relacionada con otras enfermedades del cuerpo como el intestino, por ejemplo. Conclusión: Se ha observado que el equilibrio del microbiota parece una buena manera de prevenir enfermedades orales y de las otras partes del cuerpo

Palabras clave: Odontología, probióticos, cavidad oral, microbiota, microbioma central.

1 INTRODUCTION

1.1 The study of the oral microbiota

1.1.1 A little introduction about the microbiota

Our body is exposed to a myriad of microorganisms since birth. When the baby is born the newborn leaves their sterile space and contacts the mucosa of their mother and her vaginal flora. The starter points of our immunity.

We call microbiota the total collection of microorganisms within an individual in a specific time and geographic location.

Bacteria live through an equilibrium within their host. The microbiota continues its "development" through the life of the host and their environment as well as behavior. We estimate it at 40,000 bacterial strains which have evolved for more than 1,800 generations so collectively 9.9 million different non-human genes. Research indicates that the whole microbiota mass of a human body is between 1 to 2 kg approximately, the same of a male human adult brain (1).

The Nobel laureate Joshua Lederberg (1925-2008) described for the first time the "*microbiome*" as "the collection of the genomes of the microbes in a particular ecosystem", which he called "animalcules" (2,3).

In 1945, Alexander Goetz was the first scientist to relate term microbiota with bacteria. The term was after used for describing the gingival crevice until 1966, before describing the biggest population of bacteria in the body called the gastrointestinal microbiota (1).

1.1.2 Principals study techniques for the study of the oral microbiota and their disadvantages

Sydney Brenner said, "progress in science results from new technologies, new discoveries and new ideas". In the second part of the 20th centuries, numerous advancements in the field of technologies in the research of the microbiota have been made (2).

1.1.2.1 cultures

The traditional culture has been focused for more than 100 years on the study of isolated units in pure culture and enables the analysis of the genome of a strain of bacterium. Thanks to these studies scientists could identify special bacteria responsible for different oral diseases such as *Streptococcus mutans* responsible for caries**.** Most of the bacteria we study for culture are anaerobic bacteria. They die in contact with oxygen and need a space strictly anaerobic (Hungate roll tube for example) and can be helped by some medium like stool for guts bacteria. Also, we can keep them in a fermenter for a better result. But culture cannot stay a lot of time in an aerobic culture because they will lack nutrients and stop growing. It is also very time consuming and tedious work for little to no results (2).

1.1.2.2 Animals studies

One of the disadvantages we can find is that not all the oral bacteria can be used for traditional cultures. Furthermore, in the time it has been proven we can inoculate specific organisms in animals. Also, some limits can be found, due to the metabolic differences between mice and humans which can change the result wanted. Some recent research has proven that using “free genes” or gnotobiotic mice with a specific inoculate bacteria can be a very interesting option for the research of specific bacteria. A gnotobiotic living organism refers to an organism in which every microorganism before the implantation of the specific bacteria is known. But the biggest problem is the practice of “coprophagy” which can lead to rapid transfer of microbiota and create mistakes and changes as a result. So, we search for other techniques which can detect a bigger spectrum of bacteria and where the “coprophagy” can be discarded (2).

1.1.2.3 metagenomic sequence

Thanks to the pyrosequencing of the DNA 16S which codes for the RNA 16, the 16S ribosomal RNA which is the RNA component of the 30S subunit of the ribosome, it was possible to establish the biodiversity of the oral microbiota. Studies show that due to the bioinformatic and the speed of reading of this computer we can list all the bacteria present in the oral cavity of an individual person. We can also effectuate a metagenomic analysis of an ecosystem to detect the microbiome of an individual person without the need of culture and "shotgun" directly from the organism the DNA sequencing the searcher wants (DNA 16S in our case). But research shows that bacteria with mutations can have changes in their sequencing which can arise challenges for the detection of the "species". So, in different studies we can have changes in the account of the species in the oral microbiota. The identification of species can also pose a long and challenging process for the scientist. Therefore, scientists thought about a "project", one where functional characterization will be required and takes into account the environment of the phenotype (2, 4).

1.1.3 Human Microbiome Project (HMP)

In 2007, the "Human microbiome project" was launched by the "American National institute of health (NIH)" which brings together scientists to identify and characterize the microbiota living in association with humans. They tried to search « fundamental human microbiota » which they then called core microbiome share by comparing patients in good health and therefore created a big data of all this information evolving through time. Finally, specific bad oral health status patients were compared and were established thanks to nine chosen habitats the scientists call taxon (saliva, cheek, gums, palate, tonsils, throat, and tongue soft tissues and supragingival and subgingival dental plaque) for finding similarities. It has been shown that each taxon study is colonized by a characteristic microbiome and that the patient himself is the principal factor as each individual person has their unique microbiota (2,4).

1.1.4: Stable Isotope probing (SIP): a new advance in study technique of the microbiota

Today the stable isotope probing seems to be the best technique for the detection of different bacteria in each taxon in vivo. This technique brings together new different techniques and shows a great efficiency. Thanks to this technique, mixed microbial communities can be incubated with heavy stable isotopes (C (13), N (15) and 0 (18)), and can therefore study directly the DNA, the RNA, and proteins.

Scientists use the Raman micro spectroscopy (use of vibration) or/and the ion mass spectrophotometry to check if the isotopes have been integrated in the metabolism of the microbes. It was then able to detect the active microbes from those that have not integrated. SIP is used in tandem with the T-RFLP technique: a technique that measures the height of a distinct coding fragment and its fluorescence thanks to an x and y axis following this order, it behaves like a "bacteria fingerprint".

Scientists describe this technique longer and more challenging compared to the sequential one. It is also very expensive; some isotopes can spread between different communities' species which can give biased results. Today, researchers work on the heavy water isotope (D20) that can be cheaper and show very encouraging results. But for now, the "heavy water" technique with SIP can only be done artificially in laboratories, and as a result, may not completely show the real activity observed in vivo (2).

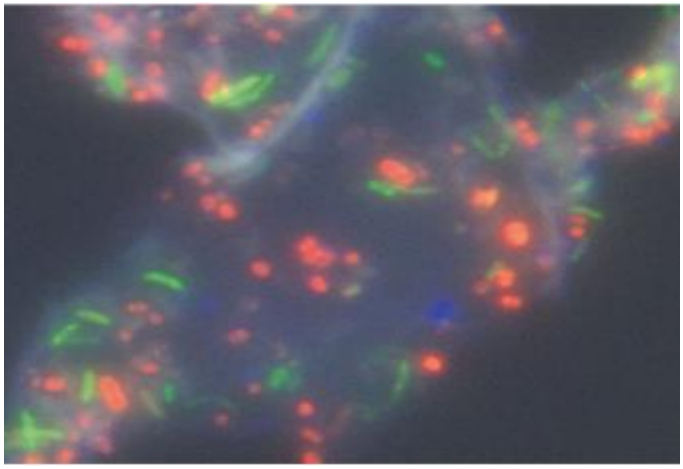

Figure 1: Fluorescent in situ hybridization in a fecal sample that allow us to have a direct visualization of bacterial environmental sample we can observe in a taxon (2).

1.2 General information about the oral microbiota

1.2.1 Core microbiome

Over 700 bacterial species can be found in the oral microbiota as research shows we all have a unique microbiome (4). Scientists state that fifty percent of them are not cultured yet and remain a mystery as a digital fingerprint for each human. (4,5)

The microbiome can be very variable from one person to another, but some scientific advance speaks about the possibility of a core microbiome. A microbiome can be different due to its composition but similar in each patient by the function they convey. Studies shows that the biological function of a microbiome is interchangeable in each person but because of lifestyle, environment and genetics, each person has a different susceptibility of becoming "ill" (6).

1.2.2 The habitat of bacteria in the oral cavity

The oral microbiota is in the buccal cavity delimited by the palate, the tongue, the cheeks, the lips and the pharynx (Fig 2(4)).

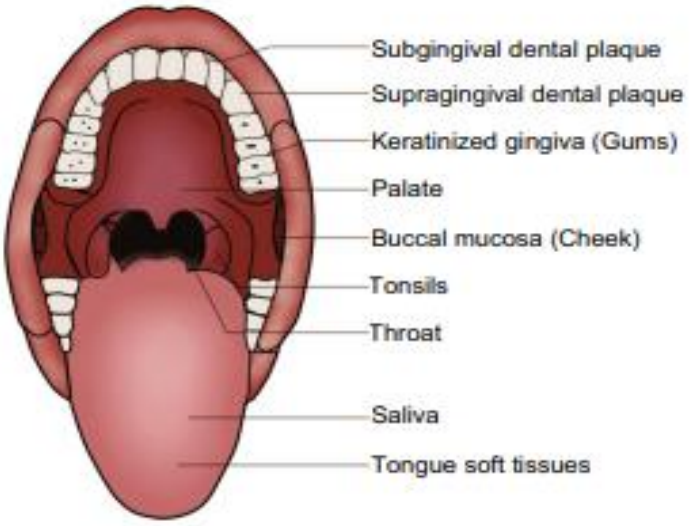

Figure 2: limits of the oral cavity (4)

The bacterial composition can change depending on the habitat and the environmental properties as well as the available nutrients on the site (table 1 (5)).

Table 1: environmental properties of the microflora of the oral cavity (5).

Property	Comments
High species diversity	The oral microflora, and especially dental plaque, consists of a diverse number of microbial species, some of which are present only in low numbers
Surface attachment/coaggregation (coadhesion)	Oral microorganisms attach firmly to surfaces and to each other and, therefore, have to be dispersed without loss of viability
Obligate anaerobes	Many oral bacteria lose their viability if exposed to air for prolonged periods
Fastidious nutrition/unculturable	Some bacteria are difficult to grow in pure culture and may require specific cofactors etc. for growth
	Some groups (e.g. certain spirochaetes; TM7 group) cannot as yet be cultured in the laboratory
Slow growth	The slow growth of some organisms makes enumeration time consuming (e.g. they may require 14–21 days incubation)
Identification	The classification of many oral microorganisms still remains unresolved or confused; simple criteria for identification are not always available (particularly for some obligate anaerobes)

Studies show that bacteria can adopt two life modes:

The planktonic state where bacteria float in the saliva: Bacteria cannot multiplicate in the saliva. This is known due to saliva not having the proper resident microbiota as it is eliminated in the stomach mostly and so does not have a pathogenic power.

A state of biofilm where they adhered on a surface: Two types of surfaces exist called shredding and non-shredding surface (like natural teeth and other dental artificial materials surfaces). Studies show that the tongue is the most stable part that supports the biggest bacterial population in the shredding group. 1/3 of all the bacterial population has been found in this anatomic part. The shredded part is easier to have a biofilm on their surface and is therefore less likely to have a disease thanks to it desquamate faculty.

The dental biofilm studies mention two major types, “the fissure biofilms” dominated by facultative species which are mostly responsible for caries and as a result, endodontic problems. Also, the “Supragingival biofilm” contains, related to its maturation and

thickness, a mix of facultative and anaerobic bacteria's which can cause gingivitis followed by periodontitis with invasion of subgingival habitat (5).

After the biofilm phase happens, bacteria can move and change its habitat in the oral cavity, which is called "dispersion" (7).

Environmental properties are specific to each nest and will determine what organisms will colonize it. Scientists speak about a characteristic and specific microbiota for each habitat (3).

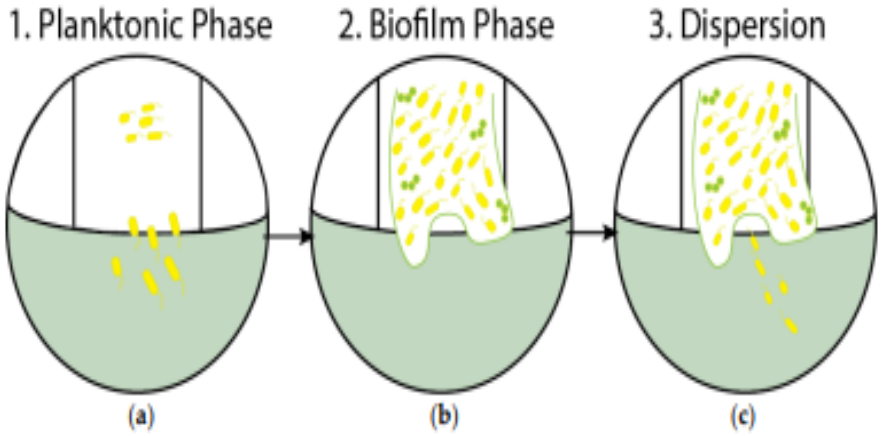

Figure 3 of the Biofilm life cycle:

(a) Stage 1: Planktonic and free-floating bacteria contact a surface randomly or by chemical attraction through saliva.

(b) Stage 2: Cells aggregate and form microcolonies on the surface; nascent biofilm is formed.

(c) Stage 3: Dispersion phase, virulent bacteria disperse and colonize other surfaces (7).

1.3 The dental plaque or dental biofilm

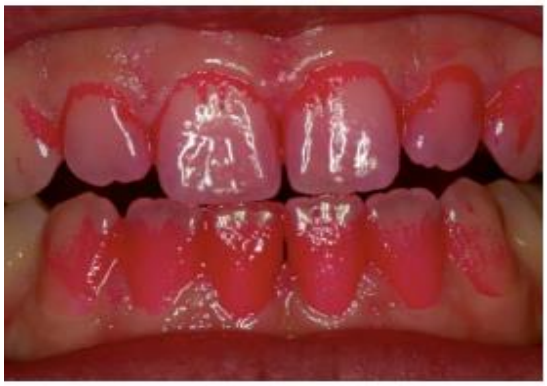

Figure 4: Dental biofilm show thanks to a plaque revelator solution (5).

The dental plaque is a polymicrobial biofilm on the dental surface in a polymer extracellular matrix composed of microbiota and saliva. Listgarten in 1999 described it as a "*bacterial aggregates, usually existing as closely associated communities, that adhere to assorted natural or artificial surfaces, usually in aqueous environment that contains a sufficient concentration of nutrients to sustain the metabolic needs of the microbiota"*. They can accumulate on different dental materials in the mouth like dentures or implants. This dental plaque can after cause inflammation and periodontal issues. (7) Studies stay that sugar is the most known "fuel" for the creation of dental plaque as it acidifies the pH and damages the remineralization tissue and enhances the arrival of opportunistic pathogens. (8) Also, for subgingival plaque, the main source of nutrients is from the gingival crevice fluid (CGF). The microbiota in the biofilm interacts not independently but dependently from the others as a community in synergy. Due to this, it can implicate the communities to other infections associated with the biofilm (5,8).

1.3.1. Dental plaque composition

The dental plaque composition is separated into two main groups: gram negative and positive and is then divided into subgroups such as cocci and rods which are mainly found in the human microbiota. *Streptococcus spp*, *Neisseria* and *actinomyces* are the main bacteria's found in dental plaque.

Gram-positive	Gram-negative
Cocci:	Cocci:
Streptococcus	*Neisseria*
Peptostreptococcus	*Veillonella*
Rods:	Rods:
Actinomyces	*'Bacteroides'*[a]
Bifidobacterium	*Campylobacter*
Corynebacterium	*Eikenella*
Eubacterium	*Fusobacterium*
Lactobacillus	*Haemophilus*
Propionibacterium	*Leptotrichia*
Rothia	*Prevotella*
	Porphyromonas
	Selenomonas
	Treponema

Table 2: General bacteria found in human dental plaque (9).

The predominant bacteria found in fissures and gingival crevices is *streptococcus* and in interproximal surfaces we can find mostly *actinomyces* (9).

Bacterium	Percentage viable count (range)		
	Fissures	Approximal surfaces	Gingival crevice
Streptococcus	8–86	<1–70	2–73
Actinomyces	0–46	4–81	10–63
Other obligately anaerobic Gram-positive rods	0–21	0–6	0–37
Neisseria	0[a]	0–44	0–2
Veillonella	0–44	0–59	0–5
Obligately anaerobic Gram-negative rods	0[a]	0–66	8–20

Table 3: percentage viable count of bacteria found at three distinct anatomical sites on the tooth surface (9).

The most present bacteria in the dental plaque leading to caries is the *streptococcus mutans* which is a subgroup of *streptococcus spp. Actinobacillus*

actinomycetemcomitants and porphyromona gingivalis are the leading cause of periodontal disease (10).

Caries	Periodontal diseases
Streptococcus mutans	*Actinobacillus actinomycetemcomitans*
Streptococcus sobrinus	*Fusobacterium nucleatum*
Lactobacillus spp	'*Bacteroides forsythus*'
(*Actinomyces* spp)[a]	*Campylobacter rectus*
	Porphyromonas gingivalis
	Prevotella intermedia
	Eikenella corrodens
	Eubacterium spp
	Treponema spp

[a]Possibly implicated in root surface caries

Table 4: predominant plaque bacteria implicated in caries and periodontal diseases (9).

1.3.2 The matrix

The matrix is constituted of bacterial and salivary polymer. It is like a scaffolding that acts on the stability, and protects the biofilm structure, as well as retaining the nutrients for the microbiota. Thanks to the circulation system of saliva, the biofilm can create the phase of dispersion by giving nutrients and evacuate dead cells and other waste. They can also reduce the access of medicines on the microbiota and can therefore protect them from all "attack" (5, 8).

Studies mention extracellular DNA in the biofilm of the matrix. Studies explain that they can play an important role in the adhesion in cariogenic biofilm with a liaison DNA-glucan and hence become a source of phosphate and ions through the time (8).

1.3.3. Biofilm bacteria formation (Socransky complexes)

"Socransky and Haffajee" did an analysis on periodontal patients and healthy patients. Thanks to "molecular biology technique" on 13 000 plaques samples, they grouped the bacterial "inhabitant" depending on their colour complexes as well as other factors (the complexes of socransky). The yellow complex was mainly *streptococci,* the earliest bacteria colonizers in accordance with past studies.

The orange complex was grouped with different species, the most important colonizer was the *Fusobacterium nucleatum.* Studies described it as a bacterium with an ability to congregate with other bacteria.

The red complex was mostly comprising of *P.gingivalis, Tannerella forsythus and Treponema denticola*. All are highly associated to periodontal disease.

Studies show that the red and the yellow complexes were linked thanks to the orange complex, and so the *Fusobacterium nucletum* is the most important bacteria for the coaggregation and biofilm formation (5,10,11).

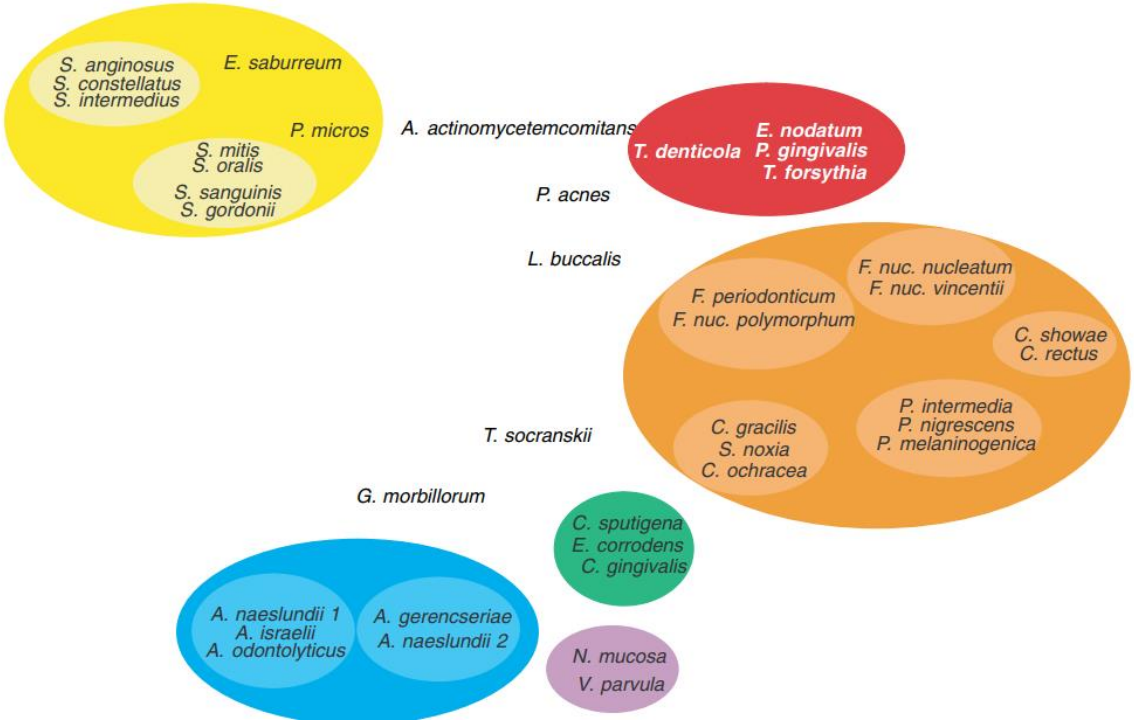

Figure 5: Diagram of the different species between microbial complexes in supragingival biofilm samples. The studies explain that diagram has been based on the results of nine clusters and two community ordination with the help of 187 subjects (11).

1.3.4 Dental biofilm formation

3 phases exist:

The first phase is called the “aforementioned pellicle” which is like a conditioning film, and Buescher and Van der Mei describe it as a “linking film”.

The second phase is called accumulation of bacterial adhesion and bacterial growth, also called “*quorum sensing*”. (4,5) It is a chemical process where bacteria communicate between each other. Due to this, then can send extracellular signals and adhere and multiplicate as synchronized and organized groups (12).

The third and last phase is called existence: it is when the biofilm reaches a balance between its growth and the erosion of the surfaces it is in contact with, for example the inflammation of periodontal ligaments (4,5).

1.4 Dental biofilm and its link with health

Bacteria live in symbiosis with the host. The relationship is mutually beneficial between members of microbial communities, all community (quorum sensing) and their host. Dental and periodontal health can be considered as a steady state in which the bacterial population coexists with the host and no irreparable damage does not occur in the host tissues (1-3).

The biofilm associated with health includes the *Streptococcus spp., Leptotrichia, Eikenella, Granulicatella, Actinomyces, Fusobacterium, Corynebacterium, Rothia, Porphyromonas, Prevotella, Haemophilus, Treponema, Neisseria, Capnocytophaga, Lactobacterium, Veillonella, Peptostreptococcus, Gamella, Staphylococcus, Eubacteria, and Propionibacterium***.**

Biofilm bacteria maintain a healthy environment with a neutral pH active balance between slow acid production rates and alkaline generation. These conditions help to manage the occurrence of periodontal and dental disease and “stabilize” the health of the mouth. This need for biodiversity for health could suggest that each species has a specific role necessary to maintain balance and homeostasis in the oral cavity. An ecological balance and a diverse microbiota that practices commensalism (symbiosis) with itself and mutualism (interaction between organisms of two different species with its host seem to be the key points of oral health) (3).

Studies also show that in some cases, a large number of bacteria is a result of a possible prevention for oral diseases due to their mechanisms.

1.5 Therapeutic and preventive strategy for maintain the oral microbiota equilibrium.

The prevalence of caries, periodontal and others Bucco dental diseases is a challenge. Their elevated cost has motivated research for other types of treatment and prevention.

1.5.1 The 3 mains concepts

1.5.1.1: The oral homeostasis

Thanks to past research, it has been demonstrated that carries and periodontal disease are caused by a little number of organisms. Subsequently, the health administration focused its watch on this target and so eradicate it with antimicrobial agent for example with prevention, therapeutical and diagnostical strategy on this specific's targets. Recent discoveries show that this group of diseases are associated to oral microbial dysbiosis which are variable depending on the individual. As said before, a lot of studies are focused on bacteria responsible of oral diseases who are caused by bacteria but lately studies are more interested on ones associated with health. Approaches in future should recognize this multifactorial microbial etiology and can therefore be more focussed on new approaches based on the restoration of the microbial ecological balance in the oral cavity (13,14,15).

1.5.1.2 Biofilm control

Today, the prevention is mainly organized on the disorganization of the dental biofilm by mechanical and chemical means as the use of toothbrush or mouthwash (chlorhexidine after a periodontal treatment) for the health maintenance of patients.
As the biofilm is responsible of oral disease, scientists explain that the biofilm should not be eradicated completely. Indeed, Bacteria may bear beneficial factors necessary for our health. Bacteria thanks to numerous competitive interactions can avoid colonization of non-beneficial bacteria (13).
It is therefore necessary to monitor this composition and functions interfering with its formation, structure, and development (5).

1.5.1.3 Personalized dentistry

Today, gut disease implicates that the microbiota is customized for each patient. Thanks to probiotics, diseases are treated or prevented such as irritate and inflammatory bowel syndrome. Today, using the probiotics with a personalized support as prevention and treatment is a good option for the future of dentistry.

1.5.2: Probiotic and prebiotic

The different epithelium and mucosa of the human body in contact with the outside and the inside environment have a unique and characteristic microbial community specific depending of the surface and different for each individual.

They are relatively stable over time under normal circumstances. However characteristic changes can occur in the composition of the microbiota when an individual is sick as "inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), atopic and allergic, periodontitis, infectious diseases, metabolic syndrome, and cancer".

Surprisingly, dysbiosis has been also observed in psychiatric disorders such as autism and depression.

As we know, several diseases are associated with a dysbiosis of the microbiota in the human body. In most cases scientists are unclear on dysbiosis as they do not know if the dysbiosis is the cause or the result of a disease. They thought of a rational approach for therapeutical or preventive prophylaxis which consist of manipulate the microbiome with the administration of either living bacteria underrepresented in the sicked individual, substances aimed to increase the bacteria population or a combination of both (probiotics and prebiotics) (16).

1.5.2.1: Probiotic

In 1965 Lilly and Stillwell described for the first time the term “probiotic” as an “unidentified factor produced by one ciliate (*Colpidium campylum*) that promoted growth of another (*Tetrahymena pyriformis*)”.

Today the World Health Organization and the Food and Agriculture Organization of the United Nations probiotics defined the term as *“live microorganisms which when administered in adequate amounts confer a health benefit on the host”*.

Probiotics are sold as naturally fermented or non-fermented food, powder, tablets, etc. Probiotic bacteria are marketed and administered as naturally fermented or non-fermented food products in various matrices, food supplement powders, tablets etc. These products can contain single strains or a mixture of different probiotics bacteria (17).

Today probiotics are mostly used for intestinal disease caused by bacterial dysbiosis. Technically we should succeed at healing oral diseases with the same system. Our challenge is to define the good probiotic species we can use to handle that task (13,17). Studies show that the ideal probiotic stem in dental health should present these properties:

-Not pathogenic

-Not toxic

-Absence of genes expression that can be the cause of resistance with antibiotics

-The probiotic doesn’t colonize permanently it is there to enhance the immunity of the host

-Must be alive and from human origin

When we have to treat a patient the probiotic given is usually combined with prebiotics (18).

1.5.2.2 Prebiotic

In 1995, Gibson and Roberfroid defined the word prebiotic as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health” (19).

The fermentation of the prebiotic by the probiotics bacteria induces specifical changes in the activity and the composition in the activity of the microbiota with beneficial changes on the health of the host.

We can use them as food supplements as they act in symbiosis. They influence the host by promoting the growth of probiotic bacteria within the bacteria (20).

Studies show that ideal prebiotics:

- It must be resistant in the media that it is present in.

-It must be fermented by oral bacteria microbiota of the media.

-It must stimulate the growth and/or activity of oral bacteria associated with the characteristic we want to selectively stimulate (19).

2 OBJECTIVES

2.1 Principal objective

The principal objective is to explain if the equilibrium of the microbiota can have positive impact and prevent or cure oral diseases.

2.2 Secondary objective

To know if it is possible to do personalize findings of microbiota for patients and to know the dental biofilm composition of a patient (healthy microbiota/unhealthy microbiota)
To assess what are the new potential preventive strategies in a therapeutic and diagnostic view for the future and avoid treatment like antibiotics.
To identify what strains can be used as probiotics due to recent studies.
To know if a dysbiosis of our oral cavity can be responsible for diseases in others part of our organism.

3 MATERIALS AND METHODES

3.1 Research

To respond to the objectives, I researched articles on the data bases PubMed, Medline, on google directly and through the website Crai Uem.

Data base	Terms used	Filter and limits
-PubMed and Medline (by the website CRAI UEM through Bing and google)	-biofilm -oral microbiota -dental plaque -Core microbiome -study of the oral microbiota -dentisani - quorum sensing -probiotics -microorganisms in the oral cavity -socransky -Haffajee -rhamnosus -targeted,antimicrobial treatment -Alex Mira	Years of publication: 1995 to 2022 Article types: Metanalysis, multicentric study, review, in vivo, in vitro studies and systemic review Language: English

Table 5: Combination of terms used for database.

3.2 Parameters of exclusion and inclusion

Inclusion criteria	Exclusion criteria
Articles related to the oral microbiota subject	studies inferior of 2009 for results
Studies and cases about the oral microbiota	Subject without relevance to the subject
Modifications and update on the oral microbiota	Articles that are not related to the subject chosen

Table 6: inclusion and exclusion criteria of the study

4 RESULTS

4.1 Flowchart

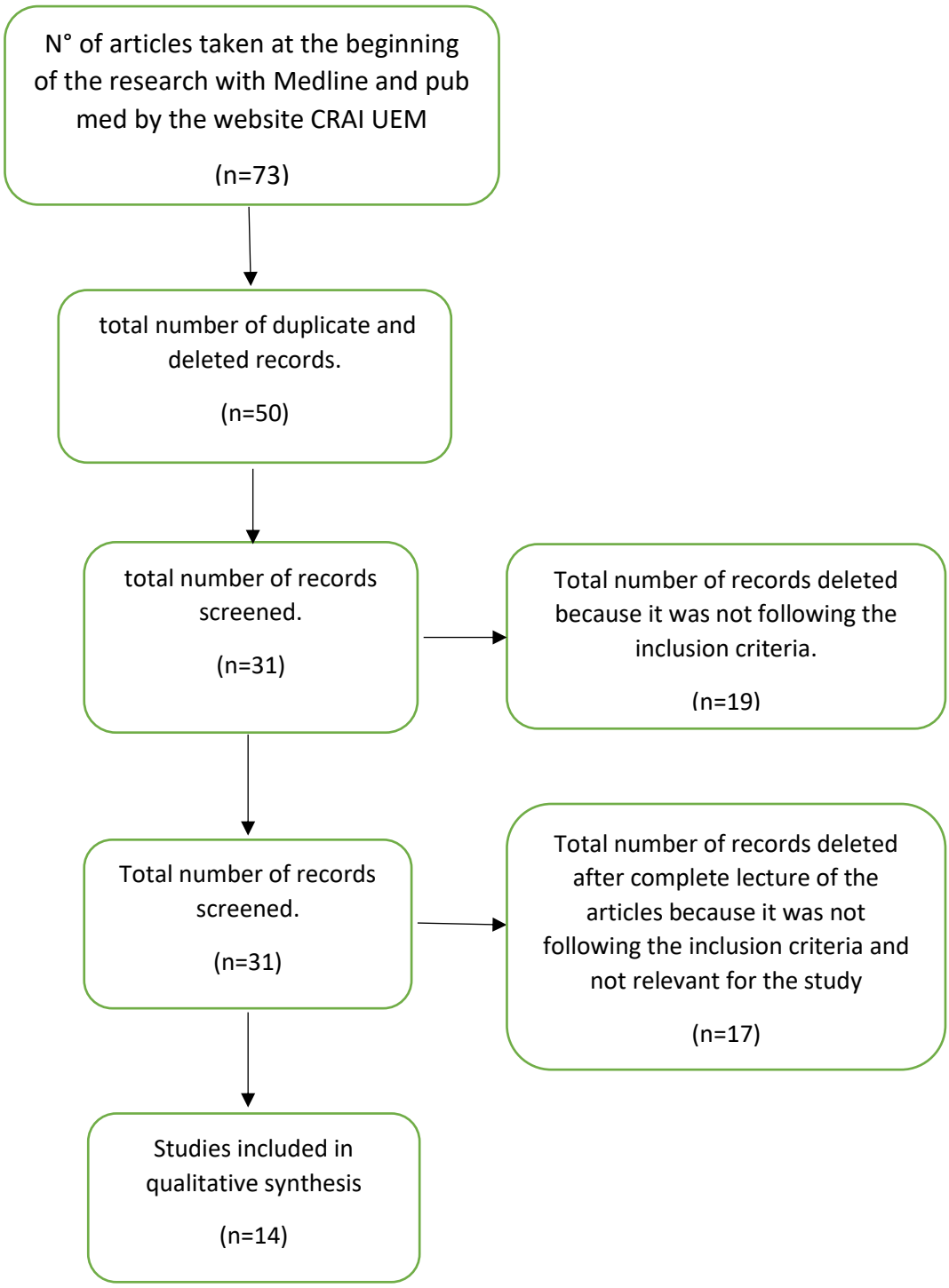

Figure 6: Flow chart of the TFG (trabajo fin de grado)

First, we selected 62 articles. After analyzing all the articles, I selected 32 articles for all the review. Finally, after further analysis for the results part I included 14 articles in accordance with our inclusion and exclusion criteria for writing the results.

Autor and year of publication	**Type of study**	**Technique used**	**result**
Neua, Eric E. Allenb,c, and Kaustuv Roy (2021) (6).	meta-analysis	Compare different studies about the micobiome and found that the best way to find the perfect "core microbiome" for patients in the future for the "Human microbiome project".	-75,4% of the studies about taxons are focused on the "occurrence" of microbial taxa. -4% are focused strictly on the relative abundance of the microbiome - 11,6% of the studies use relative abundance and occurrence as a guideline. -18% does not have any guideline for the study. -67% of the study are followed in one site. -22,3% are using temporal data. -50% of the studies are not using Out's clustered (finding similarity between bacteria thanks to sequencing of bacteria) at 99-100%.
Alexander T Arantxa López-López, Anny Camelo-Castillo , María D. Ferrer, Áurea Simon-Soro and Alex Mira (2017) (13).	Meta analyzes in vitro	Streptococcus dentisani in 300 ml of brain hearth infusion broth in 5 g/l of L-arginine monohydrochloride 98% (AlfaAesar)	The probiotic substrate inhibit the growth of S. mutans, S. sobrinus, or Prevotella intermedia also than fusobacterium nucleatum. Experiments performed suggest a peptide origin of the inhibition and so

			caused by bacteriocin from the *dentisani.* In presence of arginine the *dentisani* can buffer in pH close to 6-6,5 thanks to its production of ammonia in the media.
S. Twetman and M.K. Keller (2012) (18).	Meta analyzes of clinical trials	Lactobacillus rhamnosus-LB21 with or without fluor in milk	The probiotic with fluor (69%) has a better prevention and control on the root caries in elderly patient than fluor (61%) or the probiotic alone (52%). The probiotic shows a better prevention of root caries compared to controlled patients. (No negative side effects or potential risks were reported) Instead, children show not significant results as we suspect a bad following of protocols by the parents.
P. Hasslöf, L. Granqvist C. Stecksén-Blicks, S. Twetman (2022) (21).	Randomized control trial	Lactobacillus reuteri in goplet	The results on children are not significant, we suspect a problem of brushing their teeth by the parents and not a good following of protocols. Nevertheless, control patients show caries more extensive as we see 4 extraction vs 2 respectively in control and in L*. Reuteri* patients.

Anna K. Szkaradkiewicz, Janina Stopa, Tomasz M. Karpin´ski (2014) (22).	review	Scaling and root planning with *lactobacillus reuteri* with tablets	Probiotic strain of *L. reuteri* induce a significant decrease with chronic periodontitis in proinflammatory cytokine response and improvement of clinical parameters, sulcus bleeding index, periodontal probing, and clinical attachment level (SBI, PPD, CAL)
Niels Høiby, Oana Ciofu , Helle Krogh Johansen , Zhi-jun Song , Claus Moser , Peter Østrup Jensen , Søren Molin , Michael Givskov , Tim Tolker-Nielsen, Thomas Bjarnsholt (2011) (23).	Review	Use of tobramycin with halogenated furanones (quorum sensing inhibitor) from garlic on *P Aureginosa*	The antibiotic alone shows a reduction of the bacteria but not a complete destruction of the bacteria shown on the fluorescent protein tags. Antibiotics and the quorum sensing inhibitors (Qrsi) show complete destruction of the target bacteria.
Egija Zauraa Svante Twetman (2019) (24).	review	Arginine 8% on patients with fluor toothpaste	Prebiotic arginine shows better results compared to fluor as anticaries. Arginine shows a potential to boost fluor toothpaste.
R. Eckert, R. Sullivan, and W. Shi (2012) (25).	review	C16G2 is a Specifically Targeted Antimicrobial Peptides called STAMP designed with antimicrobial specificity for S. mutans with 2 peptide sequences each specific in his own domain. The first peptide is a S. mutans-selective 'targeting domain' derived from a fragment of the S.	The patient after treatment shows a better physiological pH 2 compared to placebo patient 6,6. Less concentration of s mutans in the plaque and in the saliva. Less lactate concentration and less demineralization of the enamel.

		mutans competence stimulating peptide (CSP), named C16, and comprised from amino acids 1 to 16. The second is a “killing domain” derived from a broad-spectrum antimicrobial peptide, named G2, and comprised from amino acids 20 to 35. On patient who rinsed their teeth for 2 minutes.	
Paul Mathias Jansen,Mohamed M. H. Abdelbary, Georg Conrads (2021) (26).	review	Use of three different probiotics *Lactobacillus reuteri* with glycerol 1% *Streptococcus salivarius* *Streptococcus Dentisani* Against bacteria *aggregatibacter actinomycetemcomitans* prevotella intermedia, porphyromona gingivalis and fusobacterium nucleatum).	-The probiotic with lactobacillus reuteri shows the better results but is dependent of glycerol. Also, the study explains the possibility of increase of incidence of caries due to its acidogenic and aciduric component but nothing has been proven in the results. - The mixture of *streptococcus dentisani* with *streptococcus salivarius* inhibit the growth of *aggregatibacter actinomycetemcomitans* and are bactericide against the prevotella intermedia. They also have an effect against *prevotella gingivalis* and *fusobacterium nucleatum* but is not

			efficient as it is with the other targets.
Ferrer MD, López-López A, Nicolescu T, Perez-Vilaplana S, Boix-Amorós A, Dzidic M, et al (2020) (27).	Randomized-double-blind-placebo-controlled clinical study	Gel application with streptococcus dentisani and an adhesive buco dental (2.5 109 cfu/dose) with the help of a dental splint for 5 minutes every 48 h, for 1 month.	-The ecological shift is not strong (the amount of veillonella and prevotella bacteria decrease-healthy shift). -The amount of dentisani increased in the mouth after the treatment (58.3% after the day 30 and 70.8% after the day 45). -The amount of calcium and ammonium are increased in the mouth of the patient. Ammonium, thanks to the metabolization of arginine in ammonium. -The amount of saliva is bigger.
Kristian Havsed, Malin Stensson Henrik Jansson, Miguel Carda-Die´ guez , Anders Pedersen , Jessica Neilands , Gunnel Svensäter and Alex Mira (2021) (28).	Review	Sequencing of the 16S rRNA of bacteria in 20 patients with caries and 20 without caries.	-The study shows the correlation between people with caries and acetic and lactic acid. -It shows correlation between people without caries and succinate, ethanol, isopropanol or Acetone and associate with nitrate. -*Rothia dentocariosa, Corynebacterium matruchotii, Corynebacterium durum* and *Gemella sanguinis* are found in microbiota with absence of caries. -*Prevotella, Leptotrichia buccalis, Abiotrophia*

			defectiva, unassigned Saccharimonadales or Prevotella denticola are found in microbiota with caries with *Abiotrophia* being the more representative. *Streptococcus mutans* is not very representative in 50% of the adolescents with caries and it is slightly little represented or even absent (authors explained the possibility of its absence thanks to the dental prevention). -*Fusobacterium periodonticum, Prevotella melaninogenica, Campylobacter concisus*, and unassigned species of *Veillonella* and *Alloprevotella* have a correlation with high acidity in the mouth following the consumption of sugar. -*Streptococcus salivarius, Fusobacterium nucleatum* and *Campylobacter gracilis* seems to be more found in cases of little acidity following the consumption of sugar.
Adelaida Esteban-Fernández, Maria D. Ferrer, Irene Zorraquín-Peña, Arantxa López-López,	Study in vitro	They used quantitative polymerase chain reactions for determinating the quantity of the oral	*Streptococcus dentisani* modulates cytokine production generating an anti-inflammatory response in HGF-1 cells.

M. Victoria Moreno-Arribas and Alex Mira (2019) (29).		bacterium. *Streptococcus dentisani* in the tongue, saliva, supragingival, and subgingival plaque. Thanks to it, they compare the *streptococcus dentisanii* with two periodontal pathogens which are *porphyromonas gingivalis* and *fusobacterium nucleatum* growth and its attachment to the human gingival fibroblast. -Its anti-inflammatory activity against cytokines has been tested thanks to an in vitro model an enzyme-linked immunosorbent assay (ELISA).	*Streptococcus dentisani* has an anti-microbial capacity, it stops the growth of the two bacteria being studied. -It is an anti-adhesive. It has adherence on fibroblasts in the periodontal ligament of the gingiva and can: compete, displace, and inhibit the adherence to gingival fibroblasts of the bacteria being studied. *Streptococcus dentisani* can modulate the cytokine production in the cell and generate an anti-inflammatory response in in vitro study.
Maria D Ferrer , Salvadora Pérez , Aránzazu López Lopez , José Luis Sanz , Maria Melo , Carmen Llena and Alejandro Mira (2021) (30).	Clinical trial	A sample of 75 volunteers was used. The study measured the presence of caries, plaque and gingival indices were determined. Unstimulated salivary flow, pH, lactate, *Streptococcus mutans* and *Streptococcus dentisani.* -The volunteer's plaque and saliva samples were measured before and after rinsing with a sugar solution. They were separated into two parts. One group had to brush their teeth	-Tooth brushing lowered the amount of lactic acid but not have a significant impact on the amount of *streptococcus mutans,* patient who brush their teeth three times a day showed a lower dmft (Decay-missing-filled index) than patients who brushed their teeth once a day. -The amount of *streptococcus dentisani* increases with the brushing and shows a correlation between dentisani and good oral hygiene.

		three times the other once a day.	*Streptococcus mutans* was more correlated with high amounts of lactic acid and dental plaque after that patient has drunk a sugary solution.
S. Kitamoto, H. Nagao-Kitamoto, R. Hein, T.M. Schmidt, and N. Kamada (2020) (31).	review	Oral Bacteria in the gut which are identified thanks to the "Human Oral Microbiome Database project".	-For patients with inflammatory bowel disease comprising also the Crohn's disease show decrease in the intestinal bacteria and increase in the oral bacteria as *Veillonellaceae, Pasteurellaceae, Enterobacteriaceae, Nisseriaceae, Gemellaceae, and Fusobacteriaceae.* -For patients with colorectal cancer same as the inflammatory bowel, the scientists found an increase in the amount of oral bacteria compared to the normal base of the "Human oral microbiome project" like *Fusobacterium nucleatum, Atopobium*, *Actinomyces*, *Parvimonas micra*, *Peptostreptococcus stomatitis*, *Porphyromonas gingivalis*, and *Sn olobacterium.*

Table 7. Board of Results of 14 different articles

4.2 Probiotics

4.2.1 Lactobacillus rhamnosus

In the study of Twetman and M.K. Keller *lactobacillus rhamnosus* show significant results for root caries in elderly patients when the probiotic is used with fluor compared to fluor alone (18).

4.2.2 Streptococcus Dentisani

The *Streptococcus dentisani* shows effect on bacteria like *S.mutans, S.Sobrinus, Prevotella intermedia* also than *fusobacterium nucleatum* , thanks to arginine it shows buffer capacity (13).

The study of Paul Mathias Jansen and al also demonstrates its effect against *aggregatibacter actinomycetemcomitans.* (26).

The probiotic *dentisani* doesn't induce strong ecological shift in the study, after it's used in gel, it increases its amount in the mouth of the patient (58,3% after 30 days and 70,8% after 45 days). The amount of calcium and ammonium thanks to the metabolization of the arginine because of the probiotic are also increased in the mouth of the patient and a bigger amount of saliva in the oral cavity (27).

Furthermore, this bacterium can modulate the cytokine production in cells and so having an inflammatory response in vitro study shows the anti-adhesive capacity against the different bacteria's responsible for the inflammatory action in periodontal ligaments (29).

Finally, the *streptococcus dentisani* shows a correlation with good oral hygiene and toothbrushing and is seen as the gold standard compared to others technique. Inversely, streptococcus mutans is more related to bad oral hygiene (30).

4.2.3 Lactobacillus reuteri

The probiotic strain of *lactobacillus reuteri* induces a significant decrease with chronic periodontitis in proinflammatory cytokine response and improvement of clinical parameters, sulcus bleeding index, periodontal probing, and clinical attachment level (SBI, PPD, CAL) (22).
Also, the probiotic when combined with glycerol (prebiotic) shows better results against bacteria responsible for caries and periodontal disease compared to the *streptococcus dentisani* gel with glycerol (26).
But when looking at the results on children, caries are not significant, scientist suspect a tooth brushing problem and a bad following of parents (21).

4.3 Prebiotic

4.3.1 Arginine

As prebiotic fluor shows better results compared to arginine as anticaries but when we combine them both they show better anticaries activity compared to fluor alone (24).

As said before in presence of arginine, the *streptococcus dentisani* can metabolize it in ammonium as buffer pH effect (13,27).

4.3.2 Glycerol

Glycerol shows good antibacterial effect when it is used as prebiotic with the *lactobacillus reuteri* (26).

4.4 Quorum sensing inhibitors

The use of tobramycin alone shows a reduction of the bacteria but not a complete destruction of the bacteria shown on the fluorescent protein tags. They also stays alive. The antibiotic and the quorum sensing inhibitors (halogenated furanones from garlic) shows complete destruction of the target bacteria (23).

4.5 Targeted Antimicrobial Peptides

The patient after treatment shows a better physiological pH of 7,2 compared to placebo patients having 6,6. Less concentration of *S. mutans* in the plaque and in the saliva leads to less lactate concentration and less demineralization of the enamel (25).

4.6 New evidence about Bacteria

4.6.1 Bacteria and oral disease

The study shows the correlation between people with caries and acetic and lactic acid.

It shows correlation between people without caries and succinate, ethanol, isopropanol or acetone and associate with nitrate.

Rothia dentocariosa, Corynebacterium matruchotii, Corynebacterium durum and *Gemella sanguinis* are found in microbiota with absence of caries.

But *Prevotella, Leptotrichia buccalis, Abiotrophia defectiva, unassigned Saccharimonadales or Prevotella denticola* are found in microbiota with caries and *Abiotrophia* seems to be the most representative bacteria in this study.

Streptococcus mutans is not very representative in 50% of the adolescents in the study with caries and it is rarely represented or even absent (authors explained the possibility of this absence thanks to the dental prevention).

Fusobacterium periodonticum, Prevotella melaninogenica, Campylobacter concisus, and unassigned species of *Veillonella* and *Alloprevotella* have a correlation with high acidity in the mouth following the consumption of sugar.

Streptococcus salivarius, Fusobacterium nucleatum and *Campylobacter gracilis* seems to be more found in cases of little acidity following the consumption of sugar (28).

4.6.2 Oral bacteria dysbiosis and the relation with disease in the body

4.6.2.1 Inflammatory bowel disease

For patients with inflammatory bowel disease and Crohn's disease show a decrease in the regular intestinal bacteria and an increase in the oral bacteria as *Veillonellaceae, Pasteurellaceae, Enterobacteriaceae, Nisseriaceae, Gemellaceae, and Fusobacteriaceae.*

4.6.2.2 Colorectal cancer

For patients with colorectal cancer same as the inflammatory bowel, the scientists found an increase in the amount of oral bacteria compared to the normal base of the "Human oral microbiome project" like *Fusobacterium nucleatum, Atopobium*, *Actinomyces*, *Parvimonas micra*, *Peptostreptococcus stomatitis*, *Porphyromonas gingivalis*, and *Sn olobacterium* (31).

4.7 "Core microbiome" for the "Human microbiome project"

The study is concentrated on the 16S ribosomal RNA technique and so compares different studies to find the best way for studying the microbiota of an individual. 75,4% of the studies are focused on the "occurrence" of microbial taxa. 4% are focused strictly on the relative abundance of the microbiome. 11,6% of the studies use relative abundance and occurrence as guideline. 18% doesn't have any guideline for the study. 67% of the study are followed in one site. 22,3% are using temporal data. 50% of the studies are not using Out's clustered (finding similarity between bacteria thanks to sequencing of bacteria) at 99-100% (6).

5 DISCUSSION

Our studies show different possibilities for the use of the microbiota as oral therapy.

First as prevention, *Streptococcus Dentisani* and *Lactobacillus Reuteri* seem to be the most effective probiotics to prevent and treat caries and periodontal disease. The *streptococcus dentisani* shows a correlation with good oral hygiene and toothbrushing as it is seen as a gold standard compared to others technique. Inversely, streptococcus mutans is more related to bad oral hygiene (29,30).

One of the main features of the *Streptococcus Dentisani* is its antimicrobial capacity thanks to the spreading of bacteriocine. In addition to its strong bactericidal power against dental caries agent as *Streptococcus mutans*, it has also an effect on the *Fusobacterium Nucleatum*. As we know from studies, the *fusobacterium nucleatum* is responsible for most of the coaggregation of bacteria thanks to the "quorum sensing". Dentisani can avoid this "bridge effect" between early and late colonizers of the dental plaque.

Because of the use of carbohydrates by the patients during the studies, the pH lower than 6 the *Dentisani* shows that the "alkaline arginine deiminase" system (ADS system) acts as a buffering power as it can metabolize arginine in ammonium and, therefore, raises the pH of the oral cavity. It then remineralises dental tissues and provides prevention for any type of erosion (13,27).

However, some of its effects like the enhancement of salivary flow of the oral cavity are still not well understood. The ADS system used by the *dentisani* is not proved yet according to studies. Scientists needs more data about it (27).

Some studies also speak about its periodontal effect and it can modulate the cytokine production in cells and so having an inflammatory response in vitro study shows an anti-adhesive capacity against the different bacteria responsible of inflammatory action in periodontal ligaments. Scientists speaks also about a possibility of competition between the bacteria for the early aggregation on the periodontal ligaments between dentisani and the other bacteria responsible of periodontal diseases. As the *streptococcus dentisani* is an inhabitant of the gingival crevice it could be a "protector" against

“bacterial invader” as *Porphyromona gingivalis* for example. But scientists explain the necessity of more studies on it in vivo (29).

In addition, many studies on *Streptococcus dentisani* shows evidence only in little groups of volunteers in vivo. Studies show that this probiotic is a preventive tools and can maximize a potential beneficial effect on human health (13).

Lactobacillus are used as probiotics for the gut microbiota, studies shows that some of them can be used also as probiotic for the oral cavity. The *lactobacillus rhamnosus* shows significative results on root caries for elderly patients (18).

The *lactobacillus reuteri* induces a significant decrease with chronic periodontitis. Studies show that it can stop the cytokine effect on the periodontal ligaments and so avoid the proinflammatory effect that can occur. They show better results in times on periodontal clinical matters as sulcus bleeding index, periodontal probing, and clinical attachment level (SBI, PPD, CAL). Nevertheless, scientists highlight the possibility that some patients need the use of the probiotic in oral mouth during more time or in more sessions as it can take time to have an effect in some patients (22).

The *L. reuteri* have also a strong bactericidal effect when it is used with glycerol against caries (26).

Scientists bring to light the possibility of using probiotics and tooth brushing which is considered as the gold standard technique against oral diseases but not proven also the “null hypotheses” of using combination of bacteria as it does not enhance their effects. Studies are also clear about the fact that investigating on the beneficial effect of probiotic is a very important topic but still we need more information as we don’t know all about them. Like for example, the founding of high amount of Streptococcus dentisani in patient with pneumonia hence the need of a “core microbiome” precociously studying (26,30,32).

Articles also highlight the difference of lactate rate between men and women and so the difference of pH between men (more acid) and women. Scientists do not know if it’s intrinsic or extrinsic because of a better hygiene from women patients (30).

Also, results on children caries are not significant, scientists suspect a tooth brushing problem due to a bad following of parents (21).

Finally, scientists highlight this preventive treatment thanks to its economic advantages. As prebiotic Arginine seems perfect for the *Streptococcus dentisani.* Studies emphasise its capacity of strong anticaries effect when it is combined with fluor. Fluor could be also used with the bacteria. Scientists do not show any contraindication for the combination, in contrast, they seem likely to have great preventive effect for oral diseases (24).

Secondary, today as treatment we use mostly antibiotics for infections. But in case of allergies or if we want to avoid any resistance of bacteria against the antibiotics, new measures should be found. As we know, bacteria communicate chemically between them thanks to the quorum sensing and so congregate and for example create dental plaque. Researchers found that some types of seaweed never have been covered by bacteria. They studied them and discovered their composition of halogenate furanone who today could be described as a quorum sensing inhibitor.

The halogenate with tobramycin shows complete destruction of some bacteria culture in vitro. Results show interesting data about the quorum sensing inhibitors, but it has not been tried in humans and the equilibrium of the microbiota could show disequilibrium. But these inhibitors stay a good candidate as they enhance the effects of “weak” antibiotics. These results have led to further development of this inhibitor as pharmaceutical compounds for patient who are subject to “implantation of foreign bodies”. But this treatment stays very invasive. Studies conclude that this treatment should be used in case of chronic biofilms infections (23).

Also, searchers thought about peptides created with antimicrobial for a bacterium. We call them Specifically Targeted Antimicrobial peptides (STAMP). They are in two peptides on acting as a targeted domain and another one acting as a killing domain. Patients after the used of STAMP showed decreased amounts of streptococcus mutans and hence a raised pH and remineralization of the enamel compared to controlled patients.

Scientists explain the necessity to modulate the microbial ecology of dental plaque against dental caries in a pathogen targeted manner. Since indiscriminate antibacterial killing could lead to the disruption of the ecological balance of normal oral flora and result in persistent pathogenesis and possibly unknown clinical consequences (25).

But the *Streptococcus mutans* is not the only cariogenic bacterium. Indeed *Prevotella, Leptotrichia buccalis, Abiotrophia defectiva, unassigned Saccharimonadales or Prevotella denticola* are found in microbiota with caries *Abiotrophia* seems the more representative bacteria in cariogenic patient in the study of Havsed K, Stensson M, Jansson and al. (28).

Since the *mutans* is not the only cariogenic bacterium, a diagnostic device which detects the rate of bacteria can compare with a universal core microbiome which could be the answer to studies. Also, the study created an understanding on how long it takes for the reinvasion of the bacterium in the oral mouth and, which bacterium can cause the elimination of a selective strain. As stated, bacteria act as an equilibrium, however as previously mentioned in studies, if a strain becomes too big, it can trigger a disease as we can see with *Streptococcus dentisani* (25).

Tertiary, as said before, a universal "core microbiome" with the help of the data of the "human microbiome project" enhanced in 2008 looks like the best way for understanding our microbiota and the improvement we can do on the population. Studies explain the necessity of continual taxonomic approach following the time and the space. They also explain the need of a good following of the protocol for detecting the taxon to have a perfect core microbiome as first defined and states the criteria of the core microbiome. Also, then following the method of occurrence and relative abundance at the same time as most of the results, gives to "human microbiome project" are not adequately described.

Secondly following spatial analyses, we can distinguish between local, regional and national as microbiota keep changing with the environment.

Tertiary following temporal analysis as our microbiome is changing all the time.

Fourthly creates sequencing as deep as possible as bacteria can share a big part of the 16 ARNs ribosomal as most of the studies explore only 97% of the sequence. The better way should be to do high quality metagenome, but the price stays today very expensive. As science evolves it could change in the future. This metric analysis is also very interesting as they allow the understanding of the nature of the "core microbiome" and

the ecological and evolutionary process that maintains stable with the association between the host and his microbiota (6,28).

Finally, thanks to our results, the mode of transmission, which is mouth to gut, could be an important bacterial pathway in the gastrointestinal tract.

For patients with inflammatory bowel disease and Crohn's disease show a decrease in the regular intestinal bacteria and an increase in the oral bacteria as *Veillonellaceae, Pasteurellaceae, Enterobacteriaceae, Nisseriaceae, Gemellaceae, and Fusobacteria nucleatum.*

For patients with colorectal cancer same as the inflammatory bowel, the scientists found an increase in the amount of oral bacteria compared to the normal base of the "Human oral microbiome project" like *Fusobacterium nucleatum, Atopobium*, *Actinomyces*, *Parvimonas micra*, *Peptostreptococcus stomatitis*, *Porphyromonas gingivalis*, and *Sn olobacterium.*

The studies demonstrate a possible pathologic link between oral bacteria and extraoral diseases. But scientists need more studies to elucidate this transmigration mechanisms. As they said it should be due to dysbiosis of the oral cavity and so transportation of this pathological bacteria is responsible of oral disease for example *fusobacterium nucleatum* (dental plaque) and *porphyromona gingivalis* (periodontal diseases) (31).

6 Conclusion

The personalization of the microbiota by patient is challenging. A universal “core microbiome” with the help of the data of the “human microbiome project” (HMP) looks like the best way for mapping the microbiota of patients. The necessity of continual taxonomic approach following the time and the space is present, but studies show that mostly scientists are not following well the protocol for detecting the patient’s microbiota. For the HMP a control should be done for reaching this goal.

Today, we know that bacteria can have a positive and a negative effect on the body. Over many years, *Streptococcus mutans* has been the bacteria with the most representative of caries in the mouth but new studies show that *Abiotrophia* may be even more representative in patient of caries. The mapmaking could help to study patients in the future to understand the function of each bacterium.

Scientists thought about different ways to manipulate the oral microbiota as they do today with probiotics, for example with lactobacillus for lactose intolerance. In oral microbiota new bacterium capable of regulating other bacteria responsible for pathology such as *streptococcus mutans* with caries have been found. *Streptococcus dentisani* seems to be the most competent when it is used with arginine and fluor. The use of the bacterium in gel and toothpaste seems a very good preventive possibility for the future. But a correct amount of the bacterium must be used as we know that balance in bacteria equilibrium is very important. Furthermore, the bacteriocin spread by the *Streptoccoccus dentisani* seems very interesting and future work should be directed also towards identifying and correctly characterizing this antimicrobial peptide. Moreover, probiotics are very economic and can be given to everyone.

For treatment and more precise regulation, the STAMP focusses on any bacteria linked to diseases and can be a very interesting solution as it can maybe avoid the use of antibiotics in the future and avoid future resistance. But for that use we must better our understanding on our microbiota and research more data due to the lack of knowledge on this topic.

Finally, a dysbiosis of the oral microbiota seems directly linked with guts diseases as cancer or Cron's and inflammatory bowel disease. As studies show an abnormal number of oral bacteria like *Porphyromona gingivalis.*

Oral equilibrium seems not only important for the oral health of patients but also for their systemic health.

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