Review Article

A Review of Lactic Acid Bacteria and their Bacteriocins: Classification, Biosynthesis, and Mechanism against Oral Pathogens

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ABSTRACT

Lactic acid bacteria produce substances such as bacteriocins which inhibit the growth of pathogens. Their application holds promises in protecting the human body against pathogens provided that the strains used are suitable and appropriate. Oral pathogens affect the local and even the systemic health of an individual. Dental caries, gingivitis and periodontitis are the most common diseases related to these pathogens, but they are also associated with worsening systemic diseases such as diabetes, cardiovascular disease and bacterial pneumonia. Another concern is that they are developing a resistance against antibiotics. The aim of this paper is to review the characteristics and capabilities of bacteriocin-producing lactic acid bacteria isolates to control oral pathogens. A narrative approach was used to classify the biosynthesis and application of the antimicrobial producing LAB in the oral cavities. A total of 6,028 articles from Google Scholar, PubMed and Mendeley were gathered and screened based on the criteria of this paper. The final articles included were 17. Through analysis of the gathered data, this review suggests that LAB can potentially inhibit oral pathogens and therefore maintain homeostasis of the oral flora. Since LAB are now relevant for their emerging applications in the prevention of infection and amelioration, further studies on the effect against oral pathogens are needed.

Key words: Antimicrobial Property, Bacteriocin, Biosynthesis, Classification, Lactic Acid Bacteria, Oral Pathogens.

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INTRODUCTION

Lactic acid bacteria (LAB) are known to be a group of gram-positive, catalase-negative, anaerobic and facultative aerobic, fastidious microorganisms that consist of both cocci and bacilliformis in which it can be used as a probiotic and is also characterized by the growth of bacteriocins.[1] The bacteriocins produced by these LAB have the capability to target specific pathogens with the advantage of not making an impact for commensal microbiota which is a concern for antibiotics. These bacteriocin-producing LAB are shown to have health promoting activities such as modulating immune response, reduction of inflammation in the bowel, and inhibition of pathogenic organisms such as the colonizer of oral microbiota.[2] Unbalanced oral microbiota could make opportunistic bacteria to cause dental caries and periodontal diseases which are the most prevalent microbial-mediated oral disease worldwide which may result in some severe illnesses such as intestinal disease and disruption of host immune system.[3,4] Dental plaque, which is composed of estimately 700 bacterial species, is the main etiological agent for the formation of these oral diseases. Oral care is necessary to prevent the said concerns in which antibacterial substances are needed; and bacteriocin was

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proven to be one. Studies on the antibacterial activity of bacteriocins continuous to progress leading to its promising feature as an essential alternative in promoting oral health care or prevention of oral diseases.[5,6] Even if bacteriocins have wide range of studies about its antibacterial activity, further and in-depth understanding of its classifications, mechanisms, and biosynthesis will help to the thorough understanding of its inhibitory activity against oral pathogens.

OBJECTIVE

The objective of this narrative review is to present a scientific overview that evaluates lactic acid bacteria as well as the bacteriocins it produced regarding their mechanisms and biosynthesis that may explain their antagonistic effects against oral pathogens. Therefore, this review will focus on the classifications of lactic acid bacteria specifically, bacteriocin-producing LAB, and their inhibiting potential to some oral pathogens.

METHODOLOGY

Search strategy

The library databases used in this study are Mendeley, Pubmed, and Google Scholar. Combinations of "Lactic Acid Bacteria" OR "Classification" OR "Bacteriocins" OR "Oral pathogens" AND "Oral pathogens health" are the keywords used to find relevant articles regarding Lactic Acid Bacteria and their bacteriocins against oral pathogens.

Eligibility criteria

Articles included were related to bacteriocin-producing Lactic Acid Bacteria and their antimicrobial activities are specific to oral pathogens. Data indicating the classes of bacteriocin, its effectiveness against oral pathogens, biosynthesis and mechanism against oral pathogens were also included. Additional eligible related articles and review papers that are relevant on the researchers' narrative review retrieved from the reference lists were analyzed and included. The eligibility of the selected articles were determined by the following exclusion criteria used to screen articles including full text not available, antimicrobial properties of bacteriocins are specific for pathogens that are in different parts of the human body, bacteriocin produced cannot kill oral pathogens, and studies that are not written in English.

Selection strategy

The eligibility of all the articles for inclusion were analyzed independently by four reviewers. All discrepancies and disagreements were settled with the assistance of the research adviser. Articles were double-checked and assessed.

Data Extraction

Information from eligible journals were extracted such as the author's name, year of publication, title, and its characteristics. The important parts of the articles, such as the abstract and discussion were analyzed to further retrieve and extract essential data. The following information of the eligible articles included are listed in Table 1.

RESULTS

The initial search retrieved are 6,028 articles. The articles retained after the removal of the duplicates were 2,344. Titles and abstract were screened, which led to 40 articles. These were further evaluated for their eligibility. Additional 5 articles from reference screening were added upon the assessment of the 12 articles remaining. Thus, the final articles included in this review paper were 17. The selection process of this study is illustrated in Figure 1.

DISCUSSION

Lactic Acid Bacteria- Classification, Distribution and Sources

Lactic acid bacteria (LAB) are substantial microorganisms that can be found in any environment rich mostly in carbohydrates, including plants, and fermented foods. It can also be found in mucosal surfaces of humans and animals. Lactic acid bacteria are part of the normal microbiota or microflora in which they are in a large number of different bacterial species and strains.[7]

The group of the Lactic acid Bacteria are classified in the phylum *Firmicutes,* class *Bacilli,* and order *Latobacillales*. The typical genera of these LAB are *Lactobacillus, Carnobacterium, Lactococcus, Streptococcus, Vagococcus, Enterococcus, Leuconostoc, Pediococcus, Tetragonococcus, Oenococcus, Aerococcus* and *Weissella.* For the classification of these LAB; morphology, growth at different temperatures, mode of glucose fermentation, configuration of the lactic acid produced, acid or alkaline tolerance and ability to

Table 1: Characteristics of the Studies Included.

Study	Bacteriocin/ LAB	Oral Pathogen Inhibited	Mechanism Suggested
Alvarez-Sieiro *et al*.	Zoocin A, Antilisterial Abp118	*Streptococci* and *Listeria monocytogenes*	Antimicrobial activity against other *streptococci*. Inhibits the pathogen *L. monocytogenes*
Arweiler NB., and Netuschil L.	Oral Microbiota	All colonizer of the oral pathogens	Protection against colonization of extrinsic bacteria
Çaglar *et al*.	*Bifidobecterium bifidum, B. breve, B. lactis, B. lactis HN019, B. longum, B. longum SBT-2928, B. longum BB53, B.* sp, *L. acidophilus, Lactobacillus acidophilus, L. acidophilus 7, L. acidophilus Lat 11/83, L. acidophilus NCFB 1748, L. acidophilus SBT-2062, L. bulgaricus, L. casei DN-114 001, L. casei Shirota*	*Streptococcus mutans*, *streptococci* caries pathogen, *Streptococcus oralis* OMZ607, *Veillonella dispar* OMZ493, *Actinomyces naeslundii* and *Streptococcus sabrinus.*	Combat infections by using harmless bacteria to displace pathogenic microorganisms
Gomez A., and Nelson KE.	viridin B, *lantibiotics*	*S. mutans*	Using cloning, fingerprinting, and high throughput sequencing technologies to reveal micro ecosystem may harbor over 800 to 1000 different oral bacterial taxa
Klaenhammer, T.R	*Nisin, Lacticin 481, Lactocin S, Carnocin, Diplococcin*	*Staphylococcus aureus* and *Listeria monocytogenes*	Shown to have bactericidal activity against a wide range of Gram-positive bacteria such as *Staphylococcus aureus* and *Listeria monocytogenes*
López-Cuellar, M. *et al*.	*ESL5, Salivaricin, nisin A, mersacidin, lacticin 3147* and *leucocin*	*Streptococcus mutans* and *Candida albicans*	Bacteriocin produced by *Streptococcus salivarius K12* which prevents colonisation of bacteria such as *Streptococcus mutans* and *Candida albicans* in the oral cavity.
Negash, A. W. *et al*.	ESL5, *plantarun* ACA-DC 269	*Streptococcus oralis.*	Produces bacteriocins solely against *Streptococcus oralis.*
Parada, J. *et al*.	*Paracasei, plantaricin* 35d, *thermophylin, Yersinia pseudotuberculosis, Yersinia enterocolitica, Bacteriocins* ST28MS and ST26MS, *L. plantarum* and *L. lactis*	Enteropathogenic *Eschericia coli*	Plantaricin 35d shows bacteriocin activity against Gram-negative bacteria Paracasei shows inhibition activity against *Eschericia coli*
Perez, R. *et al*.	*Enterococcus faecium* NKR-5-3, *Streptococcus uberis, Enterococcus faecium* T8, *Lactococcus lactic* QU 4.	*Staphylococcus aureus* and *Enterococcus faecalis*	Shows inhibition activity against Gram-positive human and animal pathogens, including MDR pathogens such as methicillin-*resistant Staphylococcus aureus* (MRSA) strain and vancomycin-resistant *Enterococcus faecalis* (VRE) strain
Quinto, E. J. *et al*.	*Plantarum* LPL-1, *mesenteroides* strain 406, *pentosaceus* 147, *infantarius* subs	*Lactbacillus acidophilus L. plantarum spp L. casei, L. acidophili*	Aid in developing novel oral vectors for mucosal delivery strategies, constituting attractive alternatives to attenuated pathogens.

Continued...

Table 1: Cont'd.

Study	Bacteriocin/ LAB	Oral Pathogen Inhibited	Mechanism Suggested
Yang *et al.*	Nisin A, Nisin U, Nisin Z, Mersacidin, Labyrinthopeptin A2, subtilosin A.	*Staphylococcus salivarius Lactobacillus salivarius* subsp *Lactobacillus casei*	Class I peptides are post-translationally modified bacteriocins or lantibiotics with less than 28 amino acids small membrane-active peptides (<5 kDa), linear or globular peptides which contain lanthionine, β-methyl lanthionine, and dehydrated amino acids.
Zacharof and Lovitt	*Lactacin F, L. johnsonii* spp., *Lactocin 705, L. casei* spp., *Lactoccin G, L. lactis* spp., *Lactococcin MN, Lactococcus lactis* var *cremoris, Nisin, Lactococcus lactis* spp., *Leucocin H, Leuconostoc* spp., *Plantaricin EF, Plantaricin W, Plantaricin JK, Plantaricin S*	*L. plantarum* spp., *Lactobacillus casei*	Fragments of nisin have been used to identify the regions that are involved in membrane interaction
Sampaio-Maia, B. *et al*.	*Methanobrevibacter oralis, Methanobacterium curvum/ congolese and Methanosarcina mazeii*	*Trichomonas tenax Streptococcus spp., Veillonella spp., P. gingivalis, A. actinomycetemcomitans, T. denticola, F. nucleatum, T. forsythia, and Neisseria spp*	Plays a role in increasing energy uptake by the human large intestine in obese persons
Savadogo, A. *et al*.	Nisin, Pediocin A, Pediocin AcH, Leucocin, Helveticin J, Carnobacteriocn	*Lactbacillus acidophilus* and *Enterococcus faecalis*	Thermostability and detaining of activity at a wide pH values and resistance of some proteases enzymes.
Sookkhee, S. *et al*.	*JCM 1229, plantaricin 423*	*Candida albicans* ATCC 13803 and *C. albicans* DTMU 2	Oral lactobacillus isolates were proven to be satisfactory antimicrobial producers which have the capacity to combat a few oral pathogens.
Todorov, S	Plantaricin 423 (108), plantaricin ST31 (88)	*Staphylococcus* spp. and *Listeria monocytogenes*	Inhibition activity against *L. monocytogenes*
Todorov and Dicks	ST151BR, *plantaricin* 35d, *bacteriocin* AS-48, KCA2386, Nisin, actis	*Lactobacillus casei, Lactobacillus sakei, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli* and *Acinetobacter baumanii.*	Two bacteriocins, ST28MS and ST26MS, produced by *Lactobacillus plantarum* isolated from molasses, inhibited the growth of *Lactobacillus casei, Lactobacillus sakei, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli* and *Acinetobacter baumanii.*

grow at high salt concentrations are considered. There are tools in the identification of these lactic acid bacteria, in which, PCR-based fingerprinting techniques, 16S rRNA gene sequencing and soluble protein patterns have the most promising routine.[7,8]

Bacteriocins Produced by Lactic Acid Bacteria

Bacteriocins are classified as a group of small, complex, proteinaceous peptides that are synthesized ribosomally as primary metabolites. They are usually produced or secreted by some bacteria, such as lactic acid bacteria, which actively kill other closely related micro-organ-

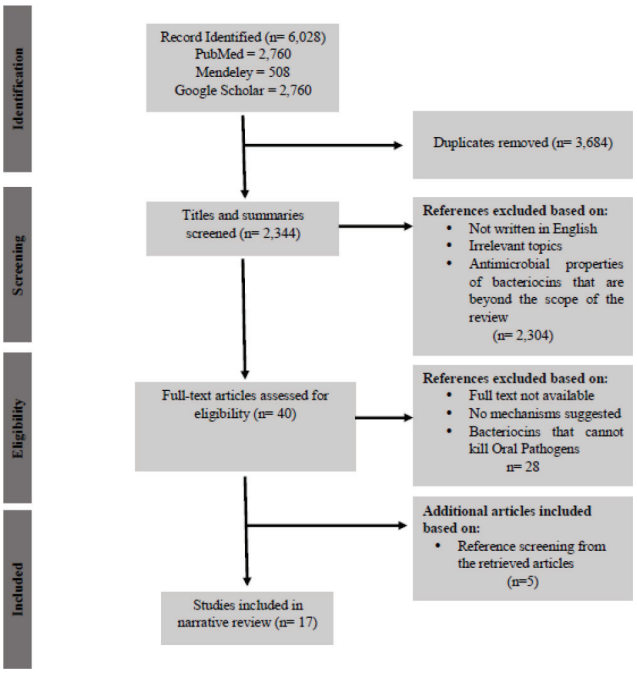

Figure 1: Flow diagram of the study selection process for including articles in the study.

isms or competitively inhibit their growth in order for them to acquire advantage for the same nutrient pool or ecological niche.[9,10]

Generally, bacteriocins are cationic peptides which are hydrophobic (non-polar) in nature and range from about 30-60 of amino acids.[10,11] Different scientific studies in which bacteriocins are characterized provided information that these amphiphilic substances are capable to remain actively stable at pH values that range from 2.0 and 12.0 even after an incubation of 2 hr. At a temperature of 100°C for 90 min or at 121°C after 20 min, the antagonistic properties of bacteriocins remain stable and their thermotolerance is potentially related to its small peptide molecular structure with the absence of tertiary structure wherein the cytoplasmic membrane of their target organism is the site where bacteriocins act up to damage the proton motive force.[10-13]

Lactic acid bacteria are widely studied microorganisms that have the capacity to produce bacteriocins. Bacteriocins from LAB strains enable them to compete against closely related bacteria through their antagonistic feature and provide them defense against their own toxins reliant on the expression of a specific immunity protein found in the operons of bacteriocins. They typically take action by making pore formation or by inhibiting the gene expression as well as the production of protein within the cells of their target organisms.[10,14,15] Bacteriocin-producing LAB creates interest in different studies due to their extensive benefits and applications. Nisin, which is a type of Class I bacteriocin found in LAB proven to present various application to bio preservation in the food system and has been approved by the Food and Drug Administration (FDA), Joint Food and Agriculture Organization/ World Health Organization Expert Committee on Food Additives (JECFA), European legislation as generally recognized as safe (GRAS).[16] In addition, bacteriocins of LAB are viewed as a key probiotic trait essential in exerting significant health benefits when administered adequately and the potential of bacteriocin as an alternative to antibiotics also continuously studied, in addition related literatures present promising ability against oral pathogens, specifically *Streptococcus salivarius* K12 colonises which are oral cavity producing both salivaricin A and B that have an antagonistic effect to the biofilm formation resulting to oral malodour from *Streptococcus mutans*.[9,17,18]

Classification of Bacteriocins from Lactic Acid Bacteria (LAB)

Initially, bacteriocins were divided structurally and chemically into four different classes established by Klaenhammer in 1993, wherein Class IV were considered as complex bacteriocins having large peptides combined with one or more chemical moieties (carbohydrates or lipids) which are vital for activity. Eventually, through the continuous study in the biochemical and genetic characteristics of bacteriocins, Cleveland *et al.* (2001), later on approved by other recent researchers, discovered that Class IV bacteriocins are just an artifact from the partial purification. That idea resulted in the removal of the fourth class and just named as bacteriolysins made up of both leuconocin S and lactocin 27.[19,20] Thus, the established classes were revised and bacteriocins are now classified into three major classes based on both of their biochemical and genetic characteristics. Though there is no definite classification scheme that is adopted universally, the majority of these bacteriocins are classified based on the type of cell wall of its producer organisms, primary structures, molecular sizes, genetic origin, biochemical properties, and their mode of action.

Class I Bacteriocins

Class I bacteriocins are named as lantibiotics which include all peptides that go through enzymatic modification during biosynthesis and typically consist of 19-50 amino acids residues found in their molecular structure. They are considered as heat-stable peptides acting on membrane structures and only possess very low weight of < 5 kDa.[16,17,20] Lantibiotics are ribosomally synthe-

sized and extensively modified after translation to reach their mature form, forming both lanthionine (Lan) and methyllanthionine (MeLan). These events take place in a two-step process: Initially, Serine as well as threonine, which are both gene-encoded, undergo enzymatic dehydration resulting to the formation of dehydroalanine and dehydrobutyrine, respectively.[13,21] Lactocin and nisin are well studied bacteriocins that represent class I. This group is subdivided into class Ia (lantibiotics), class Ib named as labyrinthopeptins, lastly, class Ic known as sanctibiotics.[10-20]

Class II Bacteriocins

Bacteriocins in this class are composed of 37-58 amino acids and considered as small (< 10 kDa) thermostable, hydrophobic peptides that have an amphiphilic helical form. Unlike the previous class, they do not undergo extensive post-translational modification. The structural conformation of the bacteriocin in this class is vital to permeabilize the membrane of their target cells which also leads to depolarization of membrane or cell death. This class is also divided into four subclasses. First is the class IIa; pediocin-like bacteriocins are the most dominant in this class.[17] Class IIb are the two-peptides unmodified bacteriocins. Class IIc are the circular bacteriocins. Lastly, class IId are the linear, unmodified, non-pediocin-like bacteriocins, example of this is bactofencin A.[20]

The antibacterial activity of bacteriocins is thought to be mediated induction of membrane permeability of the target cell membrane. Where the induction causes basal membranes to release, then the change of permeability of the inner and outer membranes will accommodate this release process through formation of ion-selective pores, leading to dissipation of the proton-motive force and depletion of intracellular ATP. In detail, the mode of action begins when N-terminal b-sheet-like domain mediates binding of the class IIa bacteriocin to the target cell surface through electrostatic interactions.[22] Lastly modification of pediocin box will occur to alter and modify the antimicrobial activity of the peptide, also its interaction with liposomes,[23] resulting to rapidly deplete the ATP of bacterias, however membrane-permeabilizing mode of action varies on the model of Class II Bacteriocins such as bavaricin MN,[24] enterocin P,[25] and the like.

Class III Bacteriocins

Class III are heat-labile bacteriocins consisting of large molecular weights of > 30 kDa which are produced by Gram-positive and Gram-negative bacteria. They are unmodified bacteriocins and known as antimicrobial proteins that present bacteriolytic or non-lytic mechanisms of action.[16] Among all the classes of bacteriocin, class III bacteriocins have a unique mode of action where their protein structure plays a huge part in the complexity of this class. This class is further subdivided into two subgroups which are class IIIa and class IIIb bacteriocins. Examples of this are colicin produced by *E. coli*, helviticin M which is known to be effective against gram-positive and even gram-negative bacteria, helviticin J and enterolysin A.[20,26]

In addition, Class III bacteriocins are usually composed of different domains. Such domains dictate the capability of each variety of domain, for instance, *Enterolyn A* consist of N-terminal endopeptidase domain and a C-terminal substrate recognition domain similarly to *zoocin A*.[27,28] Mode of action takes place when *zoocin A* which is characterized LAB bacteriolysins acts to reveals the antimicrobial activity against other streptococci by splitting the peptidoglycan cross-links of the target cell wall, afterward the z*if* gene which is nearby *zoo A*, encodes an immunity protein which adds L-alanine into the peptidoglycan cross-bridges, thus decreasing the ability of zoocin A to degrade the peptidoglycan layer.[29] Other domains such as *Millericin B* a murein hydrolase depends on the expression of gene encoding *millericin B pre-cursor,), immunity protein (MilF), and transporter protein (MilT)*,[30] in addition, other domains act on their varying components.

Biosynthesis and Production of Bacteriocin-producing LAB

Production of bacteriocins depends on the microbial strain and culture conditions. Bacteriocins are ribosomally synthesized peptides, which are initially biologically inactive, and subsequently changed to attain an active state.[10] N-terminal leaders were recently synthesized into newly-synthesized bacteriocins. Bacteriocins are formed by the bacteriocin gene cluster, which then gets modified by amino acids that are coded by the bacteriocin gene cluster until they are exported out of the cell.[31] Any modifications involve intermolecular addition of cysteins to the amino acids after dehydration of serine and threonine residues followed by intermolecular addition of lathionines or methyllanthionines, produced by the dehydration of serine and threonine residues.[32] Bacteriocin expression is regulated by external induction factors, which are typically secreted by the producer strain, or it can be constitutive, while bacteriocin biosynthesis is influenced by environmental factors like temperature and pH.[33]

Bacteriocin-producing strains produce complex immunity proteins to protect themselves from the harmful effects of their own bacteriocin. The genes that code for these proteins are genetically similar to those that code for bacteriocin structural and processing genes.[34] Most certainly, the immunity gene and the structural bacteriocin gene are on the same operon. For LAB, the Lan I (multicomponent ABC transporter) and Lan EFG (multicomponent ABC transporter) systems have been identified. The Lan I protein, in particular, protects producer cells by pushing back bacteriocin molecules that have inserted into the membrane, preventing pore formation and keeping the bacteriocin concentration in the membrane under control.[31]

Oral Pathogens and Health Effects

It is known that microbiota is a normal part of the human body. Like in the skin, oral microbiota protects its own habitat from colonization against extrinsic bacteria. This in return protects the human host. When this becomes out of balance, either weak immune system or overloaded bacteria, local and even the systemic health is at risk. Oral cavity is the main entrance for the respiratory and gastrointestinal system, that is why infection here may affect the systemic health. These oral pathogens have a high adherence mechanism in which they colonize the oral cavity. Poor oral health causes oral microorganisms to enter the bloodstream or even the lymphatic system, which may lead to metastatic injury.[35]

At birth, oral cavities are dominated by *Streptococcus* spp. and Fusobacterium. *Streptococcus* metabolic product on dietary oligosaccharides (breastmilk or formula) may possibly pave the way for other oral commensals to grow. From the first month to adulthood, microbes in the mouth become diverse. Lactic acid bacteria (such as *Lactobacillus crispatus*, *Lactobacillus gasseri*, and *Streptococcus*), *Escherichia coli*, *Staphylococcus*, and *Pseudomonas* are commonly found in the oral cavity at first month even before the tooth eruption. *Tenericutes, Fusobacteria, Synergistetes*, SR1 and TM7 will dominate further in life. *Veillonella, Fusobacterium, Prevotella, Neisseria, Rothia, S. mutans* and *Treponema* will also emerge in which they are potentially cariogenic microbiomes.[36] More diversity for these microbes contributes to a healthier community, while a decrease in diversity is associated with disease.[37]

Habitat of these microbes includes the saliva which is being continuously swallowed, whereas majority is found in the tongue. Concurrently, natural teeth and artificial hard surfaces such as the lips, palate, and cheek each support distinct microbes through their intrinsic biological properties.[38]

The ability of these microbes to produce acid will result in the metabolism of carbohydrates, further leading a drop in pH, hence the formation of dental caries. *Bifidobacterium, Propionibacterium, Scardovia, Actinomyces gerencseriae, Actinomyces israelii,* and *Actinomyces naeslundii* are responsible for this formation. In endodontic infections, phyla Firmicutes, Actinobacteria, Fusobacteria, Bacteroidetes, Proteobacteria, Actinobacteria, Synergistes and Spirochaetes are held responsible. For periodontal diseases, bacteria such as *Actinomyces* spp. produces toxins which in return induces inflammatory response (gingival tissue) and increased crevicular fluid flow providing an essential environment for the growth of anaerobic bacteria. Oral microbiomes are also associated with oral, gastrointestinal, pancreatic, and postmenopasual breast cancer. These microbiomes are also responsible for worsening systemic diseases such as cardiovascular disease and diabetes.[37]

Antibiotics are widely used in treating dental related issues such as dental caries which leads to public health troubles because of the development of the resistant pathogens. Learning their appropriate uses and including the application of probiotics are helpful strategies to avoid the increasing development of resistant pathogens.

LAB against Oral Pathogens

As mentioned earlier, there are several LAB species that serve as a security for the oral cavity against other harmful pathogens. These bacteria will fight off any foreign pathogen that will try to enter the oral cavity, as a part of their defense mechanism to protect their natural habitat. In a study conducted by Sookkhee, *et al.* (2001), five oral lactobacillus isolates which have antimicrobial properties have the ability to inhibit several oral pathogens. The study found proof that LAB are capable of producing bacteriocins, particularly those from the class II, which are also able to tolerate heat in considerable amounts. Class II bacteriocins such as salivacin 140 from *L. salivarius*, plantaricin 423 from *L. plantarum*, and acidocin J1229 from *L. acidophilus*. Additional LAB isolates that combat oral pathogens were also found in the study, namely *L. rhamnosus* and *L. paracasei* subsp. *paracasei*.[39]

The use of probiotics, particularly from LAB species have been widely used and studied not only for the purpose of maintaining homeostasis of the oral flora but also for combating pathogenic bacteria. Probiotics from microorganisms such as LAB, non-pathogenic *E. coli*, yeasts, and bacilli produce bacteriocins which are used in everyday life.[40] Bacteriocins, as defined

by Yang *et al*., are antimicrobial peptides which are ribosomal-synthesized, functioning to inhibit or kill other strains of bacteria aside from its source.[41] Although there are only a few studies focusing on the microbial phenomenon in the oral environment, Caglar *et al*.[42] presented a few effects of probiotics on oral health, including the hydrolysis of proteins to dipeptides and amino acids by probiotics with lactobacilli to activate the growth of streptococci, which then lowers the pH of the oral cavity to protect against other pathogens. Furthermore, bacteriocins inhibit potentially pathogenic bacteria by entering their cells through conjugation of genetic material, causing the pathogenic bacterial cells to procure immune genes of the bacteriocins.[42]

CONCLUSION AND RECOMMENDATIONS

The authors concluded that there is indirect evidence for co-evolution of competitive interactions between bacterial species that can be found among organisms colonizing the human oral cavity, enabling them to compete against closely related bacteria through their antagonistic feature. In addition, novel application of lactic acid bacteria (LAB) against oral pathogens serves as security for the oral cavity maintaining homeostasis of the oral flora to counter pathogenic bacteria. However, the view of risk against possible oral pathogens lacks studies that focus on the microbial phenomenon in the oral environment. Therefore, the need for more focused research studies must be conducted to include *in vitro* and *in vivo* analysis, and further studies regarding presented effects of LAB on oral health, in order to validate health claims, thus, to ensure the safety and efficacy of LAB and their bacteriocins for clinical applications.

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CONFLICT OF INTEREST

The authors declares that this manuscript have no conflict of interest regarding its publication.

ABBREVIATIONS

ATP: Adenosine triphosphate; **FDA:** Food and Drug Administration; **GRAS:** Generally recognized as safe; **JECFA:** Joint Food and Agriculture Organization/ World Health Organization Expert Committee on Food Additives; **kDa:** Kilodaltons; **LAB:** Lactic acid bacteria; **Lan:** Lanthionine; **MeLan:** Methyllanthionine; **pH:** Potential of hydrogen.

REFERENCES

1. Quinto EJ, Jiménez P, Caro I, Tejero J, Mateo J, Girbés T. Probiotic lactic acid bacteria: a review. Food Nutr Sci. 2014;05(18):1765-75. doi: 10.4236/fns.2014.518190.
2. Arena MP, Capozzi V, Russo P, Drider D, Spano G, Fiocco D. Correction to: immunobiosis and probiosis: antimicrobial activity of lactic acid bacteria with a focus on their antiviral and antifungal properties. Appl Microbiol BiotechnolAppl Microbiol Biotechnol. 2018;102(22):9871. doi: 10.1007/s00253-018-9441-3. PMID 30328491.
3. Valm AM. The structure of dental plaque microbial communities in the transition from health to dental caries and periodontal disease. J Mol Biol. 2019;431(16):2957-69. doi: 10.1016/j.jmb.2019.05.016, PMID 31103772.
4. Qi Y, Wu HM, Yang Z, Zhou YF, Jin L, Yang MF, et al. New insights into the role of oral microbiota dysbiosis in the pathogenesis of inflammatory bowel disease. Dig Dis Sci. 2021. doi: 10.1007/s10620-021-06837-2 [advance online publication]. https://doi.org/10.1007/s10620-021-06837-2. PMID 33527328.
5. Zoumpopoulou G, Pepelassi E, Papaioannou W, Georgalaki M, Maragkoudakis PA, Tarantilis PA, Polissiou M, Tsakalidou E, Papadimitriou K. Incidence of bacteriocins produced by food-related lactic acid bacteria active towards oral pathogens. Int J Mol Sci. 2013;14(3):4640-54. doi: 10.3390/ijms14034640, PMID 23443163.
6. Wannun P, Piwat S, Teanpaisan R. Purification, characterization, and optimum conditions of Fermencin SD11, a bacteriocin produced by human orally Lactobacillus fermentum SD11. Appl Biochem Biotechnol. 2016;179(4):572-82. doi: 10.1007/s12010-016-2014-y, PMID 26892008.
7. Florou-Paneri P, Christaki E, Bonos E. Lactic acid bacteria as source of functional ingredients. Lactic acid bacteria - R&D for food, health and livestock purposes. [cited 2021]. doi: 10.5772/47766.
8. Axelsson L. Lactic acid bacteria: classification and physiology. In: Lactic acid bacteria microbiological and functional aspects. 3rd ed: Revised and Expanded (pp. 1–66). CRC Press; 2002.
9. López-Cuellar MdR, Rodríguez-Hernández AI, Chavarría-Hernández N. LAB bacteriocin applications in the last decade. Biotechnol Biotechnol Equip. 2016;30(6):1039-50. doi: 10.1080/13102818.2016.1232605.
10. Mokoena MP. Lactic acid bacteria and their bacteriocins: classification, biosynthesis and applications against uropathogens: A mini-review. Molecules. 2017;22(8). doi: 10.3390/molecules22081255.
11. Savadogo A, Ouattara CAT, Bassole IHN, Traore SA. Bacteriocins and lactic acid bacteria - A minireview. Afr J Biotechnol. 2016;5(9):678-84.
12. Todorov SD, Dicks LMT. Lactobacillus plantarum isolated from molasses produces bacteriocins active against Gram-negative bacteria. Enzyme Microb Technol. 2005;36(2-3):318-26. doi: 10.1016/j.enzmictec.2004.09.009.
13. Parada JL, Caron CR, Medeiros ABP, Soccol CR. Bacteriocins from lactic acid bacteria: purification, properties and use as biopreservatives. Braz Arch Biol Technol. 2007;50(3):512-42. doi: 10.1590/S1516-89132007000300018.
14. Drider D, Rebuffat S. Prokaryotic antimicrobial peptides. Class jIa Bacteriocins: Current Knowledge and Perspectives. 2011:171-95.

15. Negash AW, Tsehai BA. Current applications of bacteriocin. Int J Microbiol. 2020;2020:4374891. doi: 10.1155/2020/4374891.
16. Alvarez-Sieiro P, Montalbán-López M, Mu D, Kuipers OP. Bacteriocins of lactic acid bacteria: extending the family. Appl Microbiol Biotechnol. 2016;100(7):2939-51. doi: 10.1007/s00253-016-7343-9, PMID 26860942.
17. Collins FWJ, O'Connor PM, O'Sullivan O, Gómez-Sala B, Rea MC, Hill C, Ross RP. Bacteriocin Gene-Trait matching across the complete Lactobacillus Pan-genome. Sci Rep. 2017;7(1):3481. doi: 10.1038/s41598-017-03339-y, PMID 28615683.
18. Prado FC, Parada JL, Pandey A, Soccol CR. Trends in non-dairy probiotic beverages. Food Res Int. 2008;41(2):111-23. doi: 10.1016/j.foodres.2007.10.010.
19. Klaenhammer TR. Genetics of bacteriocins produced by lactic acid bacteria. FEMS Microbiol Rev. 1993;12(1-3):39-85. doi: 10.1111/j.1574-6976.1993.tb00012.x, PMID 8398217.
20. Kumariya R, Garsa AK, Rajput YS, Sood SK, Akhtar N, Patel S. Bacteriocins: Classification, synthesis, mechanism of action and resistance development in food spoilage causing bacteria. Microbial Pathogenesis. 2019;128:171-7. doi: 10.1016/j.micpath.2019.01.002.
21. Barbosa J, Caetano T, Mösker E, Süssmuth R, Mendo S. Lichenicidin rational site-directed mutagenesis library: A tool to generate bioengineered lantibiotics. Biotechnol Bioeng. 2019;116(11):3053-62. doi: 10.1002/bit.27130, PMID 31350903.
22. Chen Y, Ludescher RD, Montville TJ. Electrostatic interactions, but not the YGNGV consensus motif, govern the binding of pediocin PA-1 and its fragments to phospholipid vesicles. Appl Environ Microbiol. 1997;63(12):4770-7. doi: 10.1128/aem.63.12.4770-4777.1997, PMID 9406395.
23. Fimland G, Pirneskoski J, Kaewsrichan J, Jutila A, Kristiansen PE, Kinnunen PKJ, Nissen-Meyer J. Mutational analysis and membrane-interactions of the beta-sheet-like N-terminal domain of the pediocin-like antimicrobial peptide sakacin P. Biochim Biophys Acta. 2006;1764(6):1132-40. doi: 10.1016/j.bbapap.2006.04.007, PMID 16762606.
24. Kaiser AL, Montville TJ. Purification of the bacteriocin bavaricin MN and characterization of its mode of action against Listeria monocytogenes Scott A cells and lipid vesicles. Appl Environ Microbiol. 1996;62(12):4529-35. doi: 10.1128/aem.62.12.4529-4535.1996, PMID 8953724.
25. Herranz C, Chen Y, Chung HJ, Cintas LM, Hernández PE, Montville TJ, Chikindas ML. Enterocin P selectively dissipates the membrane potential of Enterococcus faecium T136. Appl Environ Microbiol. 2001;67(4):1689-92. doi: 10.1128/AEM.67.4.1689-1692.2001, PMID 11282622.
26. Ibrahim OO. Classification of antimicrobial peptides bacteriocins, and the nature of some bacteriocins with potential applications in food safety and bio-pharmaceuticals. EC Microbiol. 2019;15(7):591-608.
27. Nilsen T, Nes IF, Holo H. Enterolysin A, A cell wall-degrading bacteriocin from *Enterococcus faecalis* LMG 2333. Appl Environ Microbiol. 2003;69(5):2975-84. doi: 10.1128/AEM.69.5.2975-2984.2003, PMID 12732574.
28. Lai AC-Y, Tran S, Simmonds RS. Functional characterization of domains found within a lytic enzyme produced by Streptococcus equi subsp. zooepidemicus. FEMS Microbiol Lett. 2002;215(1):133-8. doi: 10.1111/j.1574-6968.2002.tb11382.x, PMID 12393213.
29. Gargis AS, O'Rourke AL, Sloan GL, Simmonds RS. Prevalence and acquisition of the genes for zoocin A and zoocin A resistance in Streptococcus equi subsp. zooepidemicus. J Mol Evol. 2009;68(5):498-505. doi: 10.1007/s00239-009-9221-x, PMID 19357799.
30. Beukes M, Bierbaum G, Sahl HG, Hastings JW. Purification and partial characterization of a murein hydrolase, millericin B, produced by Streptococcus milleri NMSCC 061. Appl Environ Microbiol. 2000;66(1):23-8. doi: 10.1128/AEM.66.1.23-28.2000, PMID 10618198.
31. Zacharof M, Lovitt R. Bacteriocins produced by lactic acid bacteria a review article. 2012 August [cited 2021]. Available from: https://www.sciencedirect.com/science/article/pii/S2212670812000814?via%3Dihub [cited 14/7/2021].
32. Perez R, Zendo T, Sonomoto K. Novel bacteriocins from lactic acid bacteria (lab): various structures and applications. 2015 August [cited 2021]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4155820/ [cited 14/7/2021].
33. Dimov S, Ivanova P, Harizanova N. Genetics of bacteriocins BIOSYNTHESIS by lactic acid bacteria. Biotechnol Biotechnol Equip. 2005;19(sup2);Suppl 2:4-10. doi: 10.1080/13102818.2005.10817270.
34. Todorov S. Bacteriocins from Lactobacillus plantarum - production, genetic organization and mode of ACTION: produção. Organização genética e modo de ação. 2009 April [cited 2021]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769724/ [cited 14/7/2021].
35. Gendron R, Grenier D, Maheu-Robert L. The oral cavity as a reservoir of bacterial pathogens for focal infections. Microbes Infect. 2000 Jul;2(8):897-906. doi: 10.1016/s1286-4579(00)00391-9, PMID 10962273.
36. Gomez A, Nelson KE. The oral microbiome of children: development, disease, and implications beyond Oral Health. Microb Ecol. 2017 Feb;73(2):492-503. doi: 10.1007/s00248-016-0854-1. PMID 27628595, PMCID PMC5274568.
37. Sampaio-Maia B, Caldas IM, Pereira ML, Pérez-Mongiovi D, Araujo R. The oral microbiome in health and its implication in oral and systemic diseases. Adv Appl Microbiol. 2016;97:171-210. doi: 10.1016/bs.aambs.2016.08.002. PMID 27926431.
38. Arweiler NB, Netuschil L. The oral microbiota. Adv Exp Med Biol. 2016;902:45-60. doi: 10.1007/978-3-319-31248-4_4, PMID 27161350.
39. Sookkhee S, Chulasiri M, Prachyabrued W. Lactic acid bacteria from healthy oral cavity of Thai volunteers: inhibition of oral pathogens. J Appl Microbiol. 2001;90(2):172-9. doi: 10.1046/j.1365-2672.2001.01229.x, PMID 11168719.
40. Dobson A, Cotter PD, Ross RP, Hill C. Bacteriocin production: a probiotic trait? Appl Environ Microbiol. 2012;78(1):1-6. doi: 10.1128/AEM.05576-11, PMID 22038602.
41. Yang SC, Lin CH, Sung CT, Fang JY. Antibacterial activities of bacteriocins: application in foods and pharmaceuticals. Front Microbiol. 2014;5:241. doi: 10.3389/fmicb.2014.00241, PMID 24904554.
42. Çaglar E, Kargul B, Tanboga I. Bacteriotherapy and probiotics' role on oral health. Oral Dis. 2005;11(3):131-7. doi: 10.1111/j.1601-0825.2005.01109.x, PMID 15888102.

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