Review Article

APPLIED FOOD BIOTECHNOLOGY, 2022, 9 (2):127-143
Journal homepage: www.journals.sbmu.ac.ir/afb

pISSN: 2345-5357
eISSN: 2423-4214

OPEN ACCESS

The Overview of Natural by-Products of Beneficial Lactic Acid Bacteria as Promising Antimicrobial Agents

Joanna Ivy Irorita Fugaban[1], Wilhelm Heinrich Holzapfel[2], Svetoslav Dimitrov Todorov[1*]

1- ProBacLab, Department of Advanced Convergence, Handong Global University, Pohang, Gyeongbuk 37554, Republic of Korea
2- Human Effective Microbes, Department of Advanced Convergence, Handong Global University, Pohang, Gyeongbuk 37554, Republic of Korea

Abstract

Background and Objective: Aside from ability of lactic acid bacteria to conduct fermentation process, by transforming the raw materials into the final food products, they play an essential role in preservation and also production of distinct food flavors through biotransformation of organic acids and compounds. Functionality of lactic acid bacteria has been associated with their ability to produce a wide array of antimicrobial compounds which acts as a gatekeeper for the integrity of food products and safety for the consumers. Bio-preservation properties of lactic acid bacteria is associated to the production of antimicrobial peptides (including bacteriocins), variety of organic acids, diacetyl, reuterin, low molecular organic metabolites, hydrogen peroxide, and carbon dioxide, among many others. Different antimicrobials play an essential role not only in the bio-preservation, based on their antibacterial properties, but can be key factors in the anti-mould and consequently reducing the mycotoxins and/or enhance probiotic properties when lactic acid bacteria were applied as. In this review, we aim to present this in a structured manner with different examples for the application of lactic acid bacteria and their antimicrobials metabolites in bio-preservation and medical sector versus bacterial and molds and as part of the probiotics properties.

Results and Conclusion: Lactic acid bacteria are powerful microbial factories, which are able to conduct different fermentation process, to produce variety of beneficial metabolites not just for food biosafety but also for beneficial properties of probiotics and their health promoting properties.

Conflict of interest: The authors declare no conflict of interest.

Article Information

Article history:
- Received 3 Feb 2022
- Revised 16 Feb2022
- Accepted 22 Feb 2022

Keywords:
- Antifungal
- Antimicrobials
- Bacteriocins
- Lactic acid bacteria
- Probiotic

***Corresponding author:**

Svetoslav Dimitrov Todorov*
ProBacLab, Department of Advanced Convergence, Handong Global University, Pohang, Gyeongbuk 791-708, Republic of Korea ,
Tel: +82-10-3490-3152
E-mail: slavi310570@abv.bg

How to cite this article

Irorita Fugaban JI, Heinrich Holzapfel W, Dimitrov Todorov S. The Overview of Natural by-Products of Beneficial Lactic Acid Bacteria as Promising Antimicrobial Agents Appl Food Biotechnol. 2022; 9 (2): 127-143. http://dx.doi.org/10.22037/afb.v9i2.37544

1. Introduction

The increasing trend for green consumerism has driven industries to find and elucidate functional products for various human applications and consumption. The earnest quest is for products that will fit the category of "sustainable lifestyle" with a primary goal of obtaining beneficial effects for the stakeholders. This led to the exploitation of previously existing technologies that have sustained civilizations in ancient times with the aim of specialized applications.

Fermentation technology has been empirically employed worldwide for thousands of years. The scientific elucidation of the beneficial effects of consuming fermented foods started in the early 1900s when Ilya Metchnikoff and his collaborator, Stamen Grigorov, promoted the consumption of yogurt-fermented milk by "Bulgarian bacillus"– as it seemed to contribute to life longevity. The modernization of fermentation technology has dramatically impacted the consumption of fermented food products globally. The technical and microbiological optimization has been of great advantage particularly for the commercial bulk production of fermented products under specified conditions, with minimal cost, reduction of risk, and efficient control of consistent physicochemical properties [1-3]. Consumption of fermented goods provides an avenue of delivering the auxiliary benefit of various functional and beneficial microbes aimed to improve the health and quality of life of consumers [3]. Although industrially designed fermentation processes have provided safe and uniform final products, the consumption of artisanal fermented foods is still widely favored by the majority, particularly those that are strongly linked to traditions [2]. For example, artisanal Korean traditional fermented foods have been associated with various health benefits and have also been identified as sources of beneficial strains [4]. The majority of the identified beneficial strains associated with these food products are lactic acid bacteria (LAB); they have snatched the keen interest of research on their probiotic properties. In addition, members of this group have also served as sources of metabolites with the potential of combating and controlling food contamination on the small-scale and local production of fermented goods. Furthermore, numerous strains have been shown to produce various antimicrobial by-products [2,5-7]. These have the potential of exploitation as sources of naturally occurring potent antimicrobials and/or biocontrol agents for addressing the continuous rise of antimicrobial-resistant pathogens [8].

LAB are commonly found in foods such as fermented meats, dairy products, fruits, vegetables, on insects, as well as mucosal surfaces of the respiratory tract, intestinal or genital tracts of humans and other animals. Although these organisms are commonly known for their probiotic properties and potential, some species particularly those that belong to *Enterococcus* can be pathogenic. Some of these cause human infections such as urinary tract infection and endocarditis [8]. Also, LAB are known to be naturally resistant to antibiotics, which enables them to successfully colonize the intestinal mucosa. Generally, LAB require a nutrient-rich environment to establish a niche, Furthermore, additional supplements such as amino acids, vitamins, peptides, and salts are required for their growth [9-11].

2. Functional Properties of Lactic Acid Bacteria

Although LAB are prominently known for their probiotic properties, various associated functional properties of these organisms play a key role in their continuous exploitation and applications in the food production, feed production, and pharmaceutical industries. Some of the current applications of these organisms and their metabolic products involve their capacity for antibacterial [12-17], antifungal, antiviral, anti-*Mycobacterium*, anti-biofilm [14,18], immunomodulatory properties particularly the gut-associated immune system [3,19], and as cell factories for alcohol sugars, enzymes, vitamins, and bioactive peptides [19-25] (Figure 1).

3. Antibacterial properties of Lactic Acid Bacteria

The applications of LAB in the food manufacturing industries do not limit their involvement in the fermentation process but also in their capacity to produce a wide range of antimicrobial substances [26]. Multiple studies have focused on the uses of by-products produced by LAB to inhibit the growth of food-borne pathogens and nosocomial obtained pathogens, especially with the continuous emergence of multi-drug resistant mutants [18,27,28].

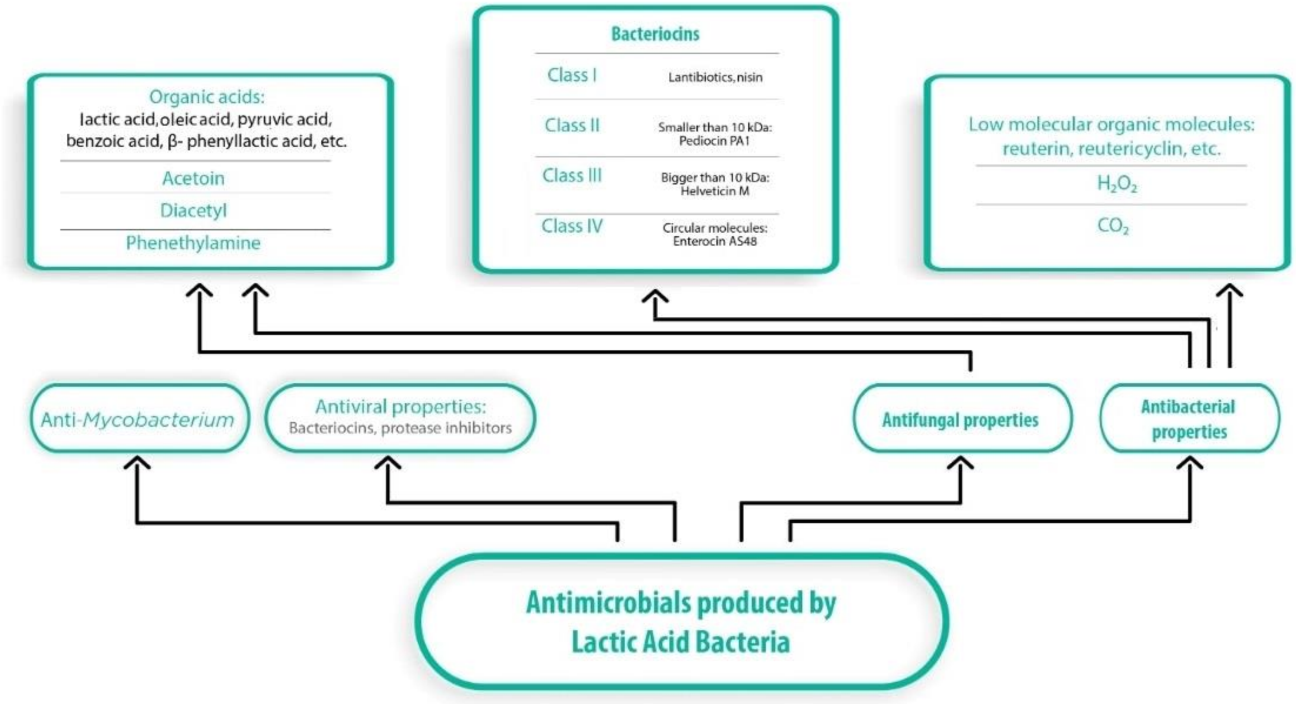

Figure 1. Antimicrobials produced by Lactic Acid Bacteria, their applications and variety

3.1. Organic Acids

Concomitantly with low pH is the accumulation of organic acids that are produced at the end of fermentation. Production of relatively large amounts of lactic acid from hexoses during homolactic and heterolactic fermentation. Whereas the production of acetic acid alongside the lactic acid occurs on heterofermentative LAB. The ability of these weak acids to inhibit contaminant microorganisms is attributed to the dissociation of the acid at a certain pH. As explained by Chikindas et al. [29], acids with the highest pKa values have higher dissociated ions in a specific pH that interacts with the target organism. Comparatively, it was observed that acetic acid had higher antimicrobial activity due to its higher pKa values [30].

Benzoic acid can be produced by some LAB and contribute to their antimicrobial properties. The food industry already explored the application of benzoic acid, specifically its salts in the preservation process for control of molds, yeasts, and some bacteria by moderating anaerobic fermentation of glucose through phosphor-fructokinase decrease by 95% [31]. Benzoic acid has been well employed by the pharmaceutical industry as a key component of treatment for fungal skin diseases such as tinea, ringworm, and athlete’s foot. Moreover, benzoic acid is a general component of some topical antiseptics and inhalant decongestants with a long history of use: as an expectorant, analgesic, and antipyretic [32].

The production of β-phenyllactic acid has been attracting scientific attention for the last few decades related to its strong antimicrobial properties, highlighting its effectiveness against some molds [33]. Moreover, Lavermicocca et al. [34] evaluated application of β-phenyllactic produced by *Lactobacillus plantarum* against different representatives of *Aspergillus*, *Penicillium*, and *Fusarium*.

3.2. Hydrogen Peroxide

LAB, through the action of flavoprotein-containing oxidases, NADH oxidases, and superoxide dismutase, can produce hydrogen peroxide when oxygen molecules are available. Hydrogen peroxide acts as a strong oxidizing agent on the bacteria cell, targeting cell proteins (those that contain sulfhydryl) and membrane lipids. Additionally, the oxygen scavenging action of hydrogen peroxide renders the environment anaerobic contributing to the delimitation of organisms that can survive. Furthermore, the inhibitory effects of hydrogen peroxide can be optimized in the presence of thiocyanate and lactoperoxidases, in which, the reaction between these molecules yields a highly toxic substrate such as hypothyocyanite [35,36].

In the last decades, special focus was given to the application of LAB as probiotics (beneficial organisms), including their role in the healthy functional properties of the vagina. LAB, particularly *Lactobacillus* spp., has a health-promoting role in the cervicovaginal environment where production of hydrogen peroxide (H_2O_2) by some vaginal lactobacilli plays a critical factor in the *in vivo* vaginal microbiota antimicrobial properties [37]. A combination of different antimicrobial factors, including lactic acid, H_2O_2, antimicrobial peptides, etc, can play an important role in the antimicrobial properties of protective vaginal *Lactobacillus* spp. [37].

3.3. Carbon dioxide

The production of carbon dioxide is primarily associated with heterofermentation of hexoses, but some metabolic pathways also produce this molecule as a by-product. Accumulation of CO_2 in the system curates an anaerobic environment that primarily limits the range of possible contaminating organisms. Due to this mechanism, carbon dioxide has been long applied for vacuum or modified air packing in the food and beverage industries [38,39].

Carbon dioxide has been well-studied for its dual physiological role in microorganisms’ life. It can both stimulate and inhibit cell development depending on the specificity of oxygen/CO_2 requirement of bacterial cells. The inhibitory action of CO_2 has been intensively exploited by the food industry to improve the hygiene parameters of both liquid and solid food products and protect them from bacterial spoilage [40]. Moreover, Blickstad et al. [41] reported on the effect of carbon dioxide on the microflora of pork and suggested that the increase of the partial pressure of CO_2 supplemented to packaging atmosphere can play the role and extend the shelf life of the stored meat products.

3.4. Diacetyl

Production of diacetyl is dependent on the citric acid metabolism, wherein some LAB including *Streptococcus, Leuconostoc, Pediococcus,* and some *Lactobacillus* species can produce this molecule that showed strong inhibitory properties against *Bacillus* spp. The antimicrobial activity of diacetyl is more effective against Gram-negative bacteria. This activity is associated with the ability of these molecules to interact with the arginine-binding proteins of the target cells, affecting the protein utilization of the target organisms [42-44]. The antimicrobial properties of certain compounds can be influenced by different environmental factors, has been shown that can be antagonized by glucose, acetate, and Tween 80 [44]. However, the beneficial properties of diacetyl was much more related to his organoleptic properties and role in the formation of the aromatic specificity of dairy products [44], as flavor related to a butter already around 1929 by van Neil et al. (presented in Jay et al. [44]). Moreover, some of the first reports on antibacterial properties for diacetyl date from 1936 [44], and even traditional medicine in Finland was suggested for the treatment of tuberculosis. Some research projects described the effect of diacetyl against *Mycobacterium* (*M.*) *tuber-*

culosis or killing effect against *Corynebacterium diphtheriae, Enterobacter aerogens, Escherichia coli, Klebsiella pneumoniae, Mycobacterium phlei, Neisseria gonorrhea, Staphylococcus* (*St.*) *aureus* (summarized by Jay *et al.* [44]). Even if diacetyl was never received an industrial antimicrobial application as a pharmaceutical component, his role in the complex antimicrobial properties in the food industry and artisanal food productions is a well-acknowledged fact and plays an essential role in the control of different foodborne pathogens in preparation and bio-conservation of fermented food products. Kang and Fung [45] demonstrated the role of diacetyl for control of *E. coli* O157:H7 and *Salmonella* Typhimurium in meet fermented products; Langa et al. [46] suggested a combination of reuterin and diacetyl for control of *E. coli* O157:H7, *Salmonella* Enteritidis, and *Listeria* (*L.*) *monocytogenes* in dairy products.

3.5. Low molecular weight antimicrobials

The low pH environment established during fermentation allows optimal conditions for low molecular weight antimicrobial substances produced by LAB. Reuterin, which was found to be a broad-spectrum antibiotic, and reutericyclin, which acts as proton ionophore, are both molecules produced by *Lactobacillus reuteri.* Another metabolite called pyroglutamic acid or PCA which is typically produced by *Lactobacillus casei* and *Streptococcus bovis.* It was mentioned that PCA has the same mechanism of action as organic acids, but PCA has demonstrated higher antibacterial activity compared to lactic acid in the same concentration [47,48].

Asare et al. [49] pointed out that reuterin needs to be regarded as a broad-spectrum antimicrobial system (consisting of 3-hydroxypropionaldehyde (3-HPA), 3-HPA hydrate, 3-HPA dimer, and acrolein), where acrolein is the main component associated with its antimicrobial activity. *Lactobacillus reuteri* is the main producer of reuterin via the anaerobic metabolism of glycerol. Antimicrobial effectiveness of acrolein/reuterin was described versus *Campylobacter jejuni* and *Campylobacter coli* at low MIC dosses (1.5 and 3.0 µM acrolein, respectively) and was suggested as bio-preservatives for meat products [49].

Arques et al. [50] suggested the application of reuterin which can either be used as an independent antimicrobial agent or in combination with nisin for control of different food-borne Gram-positive and Gram-negative pathogens in dairy products. Authors pointed out that it only requires at least 8 AU ml^{-1} of reuterin to be bacteriostatic activity against *L. monocytogenes*, and moderate bactericidal against *St. aureus,* however, strong bactericidal activity was recorded versus *E. coli* O157:H7, *Salmonella choleraesuis* subsp. *choleraesuis*, *Yersinia enterocolitica*, *Aeromonas hydrophila* subsp. *hydrophila* and *Campylobacter jejuni*, all of them are well-known food-borne pathogens. Moreover, potential synergistic effect on inhibition of *L. monocytogenes* and cumulative effect on *St. aureus* was detected when reuterin (8 AU ml^{-1}) was applied in combination with nisin (100 AU ml^{-1}) [50].

3.6. Bacteriocins from LAB

Aside from the major products of homolactic and heterolactic fermentation, other antimicrobial substances such as bacteriocins are also produced. Bacteriocins, defined as small peptides that act as bactericidal molecules against closely related bacteria, produced by LAB have been considered food-grade or safe for applications. The continuous discoveries for novel bactericidal and naturally produced antimicrobials, especially with the continuous rise of multi-drug resistant pathogens, have been the center of interest as the need for the new era of antimicrobials is rapidly increasing. Exploiting LAB as sources of these antimicrobials has been of great interest, which is highly attributed to their GRAS (generally recognized as safe) status [51]. The discovering of new generation of antibiotics is considered to be exponentially behind as compared to the rise of emerging “super-bugs”. Nisin, which is the solely commercialized bacteriocin up to date, has been in the market for decades but the follow-up for newly commercialized bacteriocins is yet to be established. But the characterization of bacteriocins isolated from LAB was observed to be increasing. Some of the notable bacteriocins have been isolated from species belonging to *Enterococcus, Lactobacillus, Lactococcus,* and *Pediococcus* [12,15,52,53].

Bacteriocins are biologically active peptides or protein complexes produced by LAB (and other microorganisms) which act as bactericidal agents against closely related organisms [29]. These antimicrobial proteins are generally classified into three groups namely: Class I or the lantibiotics, Class II or the non-lanthionine containing bacteriocins, and Class III or the large heat-labile proteins [54,55]. Bacteriocins produced by LAB are promising in food-preservation industries especially against *Bacillus cereus* [56], *L. monocytogenes* [14,57,58], and *St. aureus* [18,27] which are common food contaminants and spoilage organisms.

The biological role of bacteriocins initially was associated with their killing property against closely related bacterial species [29]. Their application was extensively explored as a potent bio-preservative for the reduction and killing of different spoilage and food-borne pathogens, including *L. monocytogenes*, *Clostridium* spp., and *Staphylococcus* spp. [29]. Several research projects were evaluating the role of bacteriocins in the reduction of the above-mentioned organisms in different food-associated matrices, showing the role of the bacteriocins as individual inhibitory/killing agents or in combination with other antimicrobials, exploring the cumulative or synergetic mode of actions [59]. However, in the last two decades, several reports suggested that bacteriocins from LAB have much broader spectrum of activity, especially against some fungal, yeast, Gram-negative, *Mycobacterium* spp., or even viruses [59]. Such as reports are adding a positive hope that some bacteriocins can be applied in the different, including pharmaceutical applications. Extensive modifications bio-engendered on existing bacteriocins are used as tools for the optimization of the their activity [29], or exploring the combination of the bacteriocins with other antimicrobials metabolites [29,59] are only two of the different research approaches in extending the applications of bacteriocins.

But there is still a question of whether bacteriocins are just simple killers or they have a more complex role in the microbial universe. According to the Chikindas et al. [29] bacteriocins can play a much more diverse role and can serve as quorum sensing molecules, involved in intracellular communications. Maybe in the next decades, there will be more reports on the role of bacteriocins as well.

4. Applications of bacteriocins

4.1. Bacteriocins for food bio-preservation

The potential of LAB in food production has long been exploited due to its ability to impart desirable sensory and technological characteristics to fermented foods, in addition to the ability to inhibit the multiplication of contaminating microorganisms and pathogens [59,60]. A wide range of bioactive metabolites with antimicrobial activities is produced by this group including lactic acid, hydrogen peroxide, diacetyl, and other organic acids [29]. Aside from these by-products resulting from their metabolism, some species are also capable of synthesizing proteinaceous antimicrobial compounds called bacteriocins [15,60,61].

Bacteriocins are ribosomal synthesized antimicrobial peptides that have antagonistic activity against pathogens and niche competitors, especially those which are phylogenetically related to the producer strains [12,29,59,62,63]. Some bacteriocins are also active against certain Gram-negative bacteria, *Escherichia coli* and *Salmonella typhimurium* [59] and even *Campylobacter jejuni*, one of the leading causative agents of gastric ulcers in the world [64]. Some studies have shown significant reductions in the counts of pathogens and deteriorating microorganisms through the use of bacteriocins in different food matrices (Table 1).

4.2. Bacteriocins in the medical field

Although bacteriocins have been widely studied and employed as biocontrol agents in the food industry, their antimicrobial potential, on the other hand, pans out more than this scope. One of the known applications of bacteriocins in the medical field includes their potential as an alternative to conventional antibiotics as shown in Table 2, highlighting their application against drug-resistant pathogens. Additionally, some bacteriocins are also elucidated to be active against some viruses, but their mechanisms for this application are yet to be demonstrated in a detailed manner. Some of the proposed and well-studied mechanisms for this specific application include viral aggregation, block specific reactions, or on the receptor sites [76].

The continuous rise of 'super bugs' or multidrug-resistant pathogens between enterococci has been continually threatening the efficacy of the existing conventional antibiotics. Although representatives of this group are considered as natural members of the human and animal microbiota that localized in the gastrointestinal tract. And this made the problem even more relevant to have effective antimicrobials with effect on pathogens, but not on commensal enterococci.

Table 1. Some examples of the use of bacteriocins in the control of pathogenic and deteriorating

Bacteriocin	Producer	Target	Applied to	Reduction log CFU.g^{-1}	Reference
Nisin	*Lactococcus lactis*	*Brochotrix thermosphacta*	pork meat	3.5	[65]
Nisin	*Lactococcus lactis*	*Listeria monocytogenes*	fermented milk	6.0	[66, 67]
Pediocin AcH/PA1	*Lactobacillus plantarum*		milk	2.0	[68]
Enterocin	*Enterococcus faecium*	*Staphylococcus aureus*	milk	2.0	[69]
Enterocin	*Enterococcus faecalis*		sausages	5.3	[70]
Nisin Z	*Lactococcus lactis* subsp. *lactis*		cheese Afuega'l Pitu	2.0	[71]
Divercin V41	*Carnobacterium divergens* V41	*Listeria monocytogenes*	smoked salmon	4.0	[72]
Enterocin CRL35	*Enterococcus mundtii* CRL35		cheese	5.0	[73]
Curvacin MBSa2	*Lactobacillus curvatus* MBSa2		salami	2.0	[74]
Sakacin P/Q	*Lactobacillus sakei* subsp. *sakei* 2a		cheese spread	5.0	[75]
Curvacin NPAC1	*Lactobacillus curvatus* UFV-NPAC1		calabrese, fresh sausage	1.0	[60]

Table 2. Main applications of bacteriocins as therapeutic agents, some examples

Area of application	Bacteriocin	Activity	Reference
VRE and MRSA	Nisin	*Enterococcus* lysis	[99]
	Nisin	Anti MRSA	[100]
	Lacticin 3147	Anti MRSA and VRE	[101]
Clostridium difficile colitis	Mutacin 1140	Anti MRSA and VRE	[102]
	Nisin	Anti *Helicobacter pylori*	[103]
	Mutacin B-Ny266	Anti *Helicobacter pylori*	[103]
Gynecology	Nisin	Anti *Gardnerella vaginalis*	[104]
	Subtilosin	Anti *Gardnerella vaginalis*	[105]
Contraceptive	Nisin	Spermicidal	[106]
	Lacticin 3147	Spermicidal	[107]
Dental care	Lacticin 3147	Anti *Streptococcus mutans*	[108]
	Nisin	Treatment of gingivitis	[109]
	Staphylococcin 1580	Anti-caries	[110]
Skin care	*Lactococcus* sp. HY-499	Anti *Propionibacterium acnes, Staphylococcus aureus, Pseudomonas*	[111]
	Enterocin ESL5	Anti *Propionibacterium acnes*	[45]
	Enterocin AS-48	Treatment and prevention of mastitis	[112]
	Nisin	Treatment and prevention of mastitis	[113]
	Lacticin 3147	Treatment and prevention of mastitis	[114]
Tuberculose	Nisin	Anti *Mycobacterium*	[115]
	Lacticin 3147	Anti *Mycobacterium*	[116]
	BacST194BZ	Anti *Mycobacterium*	[117]
Antiviral	Enterocin CRL35	Anti-herpes simplex virus (HSV-1 and HSV-2)	[76, 118]
	Lactococcus lactis subsp. *lactis* and *Enterococcus durans*	Anti-herpes simplex virus (HSV-1 and PV-1)	[119]
	Enterococcus mundtii ST4V	Anti-herpes simplex virus (HSV-1 and HSV-2), anti-polio virus (PV), and anti-measles virus (MV)	[118]
	Lactobacillus delbrueckii	Anti influentsa virus	[120]
Antifungal	BacTN635	Anti *Candida*	[121]
	Nisin	Anti *Candida*	[122]
pharmaceutical	Enterocin EJ97	Anti VRE	[123]
	Enterocin K1	Anti VRE	[123]
	Garvicin KS	Anti VRE	[124]
	Nisin	Anti VRE	[125]

Recently, the World Health Organization (WHO) have issued an increase in the priority on the constant climb of cases of vancomycin-resistant enterococci-associated infections obtained nosocomial [77,78].

The existence of VRE was first noted in the1980s, and the numbers of this pathogen, strains alike, have been constantly increasing while the discovery of antibiotics has been falling behind. The development of these “super bugs” or the new era pathogens has been exacerbated by the suitable conditions that allow them to thrive and survive in various environments [78,79]. These enable them to influence the increasing colonization amplified by the selective pressure of extensive treatment with anti-anaerobic antibiotics, specifically vancomycin, which remove colonization resistance and provide a vacant niche for the VRE to proliferate and successfully invade the GIT [78]. This then facilitates possible systemic infection. Some enterococci are known to be innately resistant to many classes of antibiotics, but when they acquire additional resistance through, for example, mobile genetic elements, they become increasingly difficult to destroy [79,80]. Several factors can be involved in the virulence of VRE, including enterococcal surface protein, aggregation substance, gelatinase, and collagen adhesion molecule; these are generally linked with their ability to colonize different tissues [81-83]. Thus, the pressing need for new classes of antibiotics or alternative antimicrobials that can be used either with antibiotics or independently against resistant pathogens such as small antimicrobial peptides or bacteriocins [59,84].

VRE can be associated with presence of different resistance phenotypes including van A, B, C, D, E, and G and generally was accepted that *van*A and *van*B resistances is associated with plasmid located genetic material. However, the distinction between the two (*van*A and *van*B) includes specific co-resistance to teicoplanin as associated only with vanA phenotypes, related to the associated modifications in the N-acetylmuramic acid [85,86]. However, vanB phenotype which is normally associated with its high resistance to vancomycin (MIC more than 250 mg l^{-1}) is usually as well located on a plasmid DNA and has increased threat regarding the possible transfer of resistance genes. Regarding the *van*C and *van*D resistance-associated genes, they are chromosomally located and generally low possibility transferrable and manifested by low resistance to vancomycin (16-32 mg l^{-1}) [87-89]. Additionally, vancomycin resistance genes *van*E and *van*G are both characterized as non-transferrable genes and also associated with resistance to low concentrations of vancomycin [90].

The development of new antimicrobials, including new antibiotics, is an essential pharmaceutical quest; however, there is a growing need for a new type of antimicrobials, targeting pathogenic bacterial species by different mechanisms to control the ever-developing resistance. Antimicrobial peptides, including bacteriocins, often to achieve an advantage over competing bacteria in certain ecological niches [59]. Additionally, aside from the antibacterial activities of these small peptides, these molecules also have an auxiliary function of serving as a molecule for intracellular communications [29]. Bacteriocins can be produced by different bacterial species, including both Gram-positive and Gram-negative species [29,55,63,78]. New bacteriocins are frequently described in the literature, however, discovering their mechanisms of action has traditionally been more challenging [78]. Recent advances in receptor identification via, for example, genome sequencing of resistant mutants have significantly increased the ability to elucidate bacteriocin mechanisms and we need to agree that the knowledge of bacteriocins' mode of action, the way they exert their antibacterial effect is essential to apply further bacteriocins to *in vivo* treatment of infection and evaluate them as potent pharmaceutical antibacterial tools [91]. The advantages of these small peptides with the conventional antimicrobials include having both broad or narrow spectra, multiple target receptors and mechanisms of action, highly potent, and selective targets particularly those that are bioengineered [29,84,92]. Most bacteriocins are membrane-active peptides, targeting specific components, often proteins, in target cells, but in addition, some can be interrupting replication, translation processes, or interfere with protein synthesis and intracellular enzymatic activities. Additionally, bacteriocins generally do not target the same cell components as antibiotics, and therefore, often have potent activity against antibiotic-resistant strains, and more important perspective in antibiotic-resistance problems [29,59,78,84]. More bacteriocins need to be further assessed *in vivo* to promote bacteriocins as relevant treatment options. Although the use of bacteriocins as *in vivo* treatment is still limited, for now, the use of bacteriocins as additives in food has been recognized, especially with nisin [52,53].

Moreover, combined application of bacteriocins and antibiotics and/or other antimicrobial metabolites are considered as well as promising treatment options, especially against antibiotic-resistant bacterial pathogens. Recently Hayes et al. [93] reported that erythromycin and nisin can have a synergistic effect against strains of group B streptococcus; Nisin also exhibits synergistic with polymyxin B against *Acinetobacter baumannii* infections, which are serious nosocomial infections in medical practice [94]. Furthermore, several combinations of nisin and antibiotics are effective against Salmonella, including experiments, both *in vitro* and *in vivo* in a murine model [95]. On the other hand, Chi and Holo [96] described synergy interactions between garvicin KS (bacteriocin) and farnesol or polymyxin B against a range of bacteria, indicating that nisin is not the only bacteriocin that has synergy with the traditional antibiotics. Hanchi et al. [97] investigated synergy between durancin 61A and several traditional antibiotics, such as vancomycin and tetracycline. Durancin/vancomycin was favorably synergistic against *St. aureus*, another critical antibiotic-resistant pathogen. The synergy of antibiotics, bacteriocins, and other novel antimicrobials was described in a mini-review by Wolska et al. [98], describing how combinatorial therapy has implications for many fields such as the food industry, agriculture, and medicine. Moreover, different examples of synergetic effects between bacteriocins and antibiotics in control of *L. monocytogenes* were reviewed by Todorov et al. [59]. Despite these examples, there are relatively few studies in this important area, as in other aspects of clinical bacteriocin research, which it is necessary to deal with to fully use bacteriocins and their potential.

Thus, further understanding and characterization of the underlying functional mechanisms should be investigated to fill in the knowledge gaps on the benefits of beneficial microbes obtained from these artisanal foods.

5. Antifungal properties of Lactic Acid Bacteria

Lactic acid bacteria produce a wide range of fermentation end products that are found to have antifungal properties. Some of these compounds include organic acids that are primary metabolites of fermentation, but other molecules that are attributed to be antimicrobial also exhibited antifungal properties. Aside from the major metabolites produced during homofermentative and heterofermentative sugar fermentation, some of the notable antifungal substances include hydrogen peroxide, formic acid, propionic acid, derivatives of lactic acid, acetoin, and diacetyl [29]. The application of LAB as biocontrol for both yeasts and molds has been demonstrated in various test organisms and systems [34,126-130].

The negative effect of the yeast and molds on the food industry is reflected in the loss of the food commodities due to spoilage and/or to the contaminations with different mycotoxins produced by molds [131]. Fungal growth and consequent mycotoxin release in food commodities and feed products can have a serious consequence on human health which might even, in acute cases, lead to death.

Fungal plant-associated pathogens cause spoilage of up to 30 % of crop products worldwide, and are directly responsible for toxic contamination of about one-quarter of raw materials produced by agriculture worldwide [131].

Sevgi and Tsveteslava [132] suggested that the annual economic loss caused by spoilage of bread by fungi is around more than 200 million Euros only in Western Europe. The role of the LAB in the prevention of moulds can be associated with the production of active compounds such as fatty acids, organic acids, hydrogen peroxide, peptides, bacteriocins, and low molecular antimicrobial organic molecules, including reuterin and can represent potential bio preservatives for replacing the conventional chemical antifungal preservatives with activity against spoilage, and toxigenic compounds in food [133,134]. Moreover, it was suggested that 25% of Europe’s diet and 60% of the diet of many developing countries is composed of fermented foods, and LAB or *Bacillus* spp. play an essential role in the fermentation process [135,136]. Thus, showing the potential role of the LAB and *Bacillus* spp. as effective factors in the control and prevention of yeast and mould growth in the food processing industry.

Antifungal properties of LAB were employed by the food production practices based on empiric knowledge and the role of the starter cultures for conducting fermentation processes and providing the production of safe commodities with extended shelf life [137]. From industrial application and mass production of fermented food products, involvement of LAB with antifungal properties in the preparation of some fermented foods has been demonstrated and as consequence was able to reduce chemical preservative usage in the food. Axel et al. [138] pointed out that the use of sourdough fermented with specific strains of antifungal LAB resulted in the reduction of chemical preservatives typically applied in bakery products [138]. Moreover, *in situ* addition of antifungal metabolites producing LAB into food and feed was proven to delay fungal growth, and to extend the shelf life. Some examples for previous can be bio-preservation processes of fruits and vegetables, sour cream and semi-hard cheese, quinoa, and rice bread [138-140]. Bioactive components normally involved in these processes are different organic acids (lactic acid, formic acid, acetic acid, caproic acid, and phenyl-lactic acid), and/or other metabolites produced by LAB (carbon dioxide, hydroxyl fatty acids, hydrogen peroxide, diacetyl, ethanol, reuterin, cyclic dipeptides, protein compounds, reutericyclin, proteinaceous, acetoin) and volatile compounds like diacetyl are naturally antimicrobial and antifungal metabolites produced by LAB [132,140].

6. Anti-viral properties of Lactic Acid Bacteria

Research in the development of the antiviral drugs is related to follow the specificity of virus lifecycle and possibility to interfere on key stage of replication processes. Normally viruses hijack the host cells’ biosynthetic machinery with the aim to replicate themselves. Replication processes include the need for specific proteases, enzymes having a key role in the viral life cycle. The critical issue is first to determine which protease(s) are from essential priority, which of them needs to be targeted and then which inhibitor/s will be able to interfere with virus replication, however, at the same time exhibiting little or no toxicity for the host. These general principles have already been explored in the development of pharmaceutical preparations for control of a wide variety of viruses [59] with variable levels of success.

Certain antimicrobial peptides and/or other metabolites produced by LAB were also evaluated as potential candidates for the control of some viruses. Nisin, the bacteriocins produced by *Lactococcus lactis* is maybe the most extensively studied and commercially utilized of all the bacteriocins and was approved both by EFSA and the FDA [137]. In the last two decades, the research interest for the application of bacteriocins and other antimicrobial metabolites produced by LAB was focused as well on the control of viruses. The mechanisms of the reported antiviral activities of bacteriocins are still being clarified, including proposed that can be associated with inhibition of some proteases involved in viral replication [76,119]. Antimicrobial peptides, including bacteriocins from different strains of LAB, including *Lactobacillus*, *Lactococcus*, and *Enterococcus* spp., have already been shown to exhibit activity against various viruses including poliovirus, the herpes virus (HSV-1 and HSV-2), measles virus, Newcastle disease virus, coliphage HAS and HIV-1 [76,119]. Wachsman et al. [76] have investigated and proposed mechanisms showing the interaction of an enterocin produced by *E. mundtii* CRL35 and herpes virus in terms of the blocking of replication of the viral gamma protein (glycoprotein D) during the process of virus invasion. Moreover, Serkedjieva et al. [120] reported that a *Lactobacillus delbrueckii* bacteriocin had virus-inhibitory activity. Other examples are some bacteriocins produced by LAB isolated from traditional fermented food products with moderate antiviral activity against various viruses including herpes virus [76,119]. However, it is needed to be underline that similar to the proteinase inhibitors, bacteriocins are not directly involved in the killing of the virus themselves, but rather interfere with viral replications via inhibiting some enzymes, associated and critical in the virus life cycle [76]. The entire processes are still not well understood and it has been suggested that different mechanisms are involved in these interactions (between virus and bacteriocin), and this can be relevant topic for intensive research.

7. Anti-Mycobacterium properties of Lactic Acid Bacteria

Mycobacterium tuberculosis is considered one of the most robust, antibiotic-resistant organisms, and maybe the oldest infectious agent known to humans [141]. Even with the development and application of different antibiotics, tuberculosis is still a serious medical problem. With the introduction of the BCG vaccine and an increasing quality of life in the last 70 years, tuberculosis was considered a controllable disease. However, due to increasing antibiotic resistance and the emergence of mutants of *M. tuberculosis* treatment of that disease is considered a serious medical problem. The antibiotics suggested for the treatment of tuberculosis are very strong drugs, associated with unpleasant side effects for the patient. LAB can be considered as one of the promising tools in this resurgent crusade against *M. tuberculosis,* since already traditional medicine has recommended some LAB fermented products containing metabolites inhibitory to the growth of *M. tuberculosis* [142].

As part of the different metabolites with potential activity *versus M. tuberculosis*, bacteriocins have been suggested as possible tools in these processes [141]. Carroll and O'Mahony [141] suggested that lipid II can be possible involve in these processes of inhibition even if this lipid is modified in *Mycobacterium* spp. In order to increase the killing effect of bacteriocins, some modifications (with modifications to amino-acids 21 and 22) to the structure of nisin have been generated with an aim of for development of effective biotechnologically modified/engineered bacteriocins with activity against *Mycobacterium* spp. [116]. Moreover, Todorov et al. [59] reported on the potential of some bacteriocins produced by *Lb. plantarum* ST202Ch and ST216Ch, *En. faecium* ST211Ch, and *Lb. sakei* ST153Ch and ST154Ch as anti-mycobacterial agents. Taking one step further, we can speculate that some LAB associated bacteriocin, applied as probiotics can have a potential role in decreasing *M. tuberculosis* infection, especially in countries with high infection rates [59].

However, we still need to find an answer to the question about the mode of action of bacteriocins *versus M. tuberculosis*. We can consider bacteriocins as promising pharmaceutical agents for control of not only Gram-positive pathogens but some Gram-negative bacterial representatives, fungal, viral, yeast, *Mycobacterium* spp. related infectious organisms. Under the proposed concept, we can consider that bacteriocins can be applied as singly as therapeutic agents or in combination with already existing conventional antibiotics and explore their synergetic effects.

8. Probiotic Properties

Probiotics are defined as live microorganisms applied to improve health. Such beneficial microorganisms have unintentionally been patronized by consumers for centuries by the fermented foods as part of the diet. The use and consumption of LAB probiotics have been associated with direct and indirect-mechanism-based to confer health benefits, particularly with their immunomodulatory functionalities [143]. Some of which include the application against irritable bowel syndrome [144,145], diabetes [146], lowering effect on blood cholesterol [147], and even against mental-health-associated disorders [148]. But aside from this, the application of probiotics can also be exploited for their antagonistic activities against pathogens as suggested by Kim et al. [149].

LAB have been employed as starter cultures in the production of different food products from the beginning of human civilization and still plays a principal role in the production of a diversity of fermented foods involving milk, vegetables, meats, sourdough by inducing rapid acidification of the raw material and conduction biotransformation processes [150,151]. Moreover, LAB possesses an essential preservative and detoxifying role, enhancing food safety [150]. From the perspective of 21 century, when consumed regularly, LAB fermented food can provide health benefits to humans and other animals, by improving the defense mechanisms of the consumers against pathogenic bacteria [152]. This is only one of the potential benefits of LAB as probiotics, which received considerable attention over the past few years. LAB may play an essential role in the biotransformation of different compounds in the GIT, where can be actively involved in the production of bioavailable macromolecules, such as vitamins and short-chain fatty acids [153,154]. Moreover, immune modulation, involvement in the processes of anticarcinogenic and antitumor activity, reduction of cholesterol, reducing the allergenicity of lactose, normalization of stool transit, hepatic encephalopathy, and treatment of peptic ulcers are several health benefits and safety of probiotics LAB. Furthermore, some modes of action of probiotic LAB are associated with adhesion to mucus and epithelial cells, production of antimicrobial compounds, and immune stimulation [155,156].

9. Conclusion

Although LAB are known for their functional properties in the fermentation system, where various metabolites produced during this process contribute to the safety and integrity of the fermented food products and plays an essential role in the formation of the organoleptic properties. However, the antimicrobial properties of LAB are one of the principal foci in several research projects. Different antimicrobial metabolites produced by LAB play an essential role principally to ensure the safety of the fermented food products; however, several of them can be associated with further beneficial effects for the consumers as well. The specificity of antimicrobial metabolites produced by LAB with activity against AMR strains, including VRE and MRSA has a key role not only in ensuring food safety but already showing potential for clinical applications in human and veterinary practices. Multifunctional properties of LAB with probiotic potential and strong antimicrobial properties need to be considered as next the level not only in preventions but as well in active therapeutical practices.

10. Authors Contributions

Conceptualization, S.D.T.; writing-original draft preparation, J.I.I.F. and S.D.T.; writing-review and editing, S.D.T and W.H.H.

11. Acknowledgement

To Cecilia Alejandra Vazquez Bucheli for designing the figure.

12. Conflict of Interest

The authors report no conflicts of interest.

References

1. Bell V, Ferrao J, Fernandes T. Nutritional guidelines and fermented food frameworks. Foods 2017; 6(8): 65. https://doi.org/10.3390/foods6080065

2. Tamang JP, Tamang B, Schillinger U, Guigas C, Holzapfel WH. Functional properties of lactic acid bacteria isolated from ethnic fermented vegetables of the Himalayas. Int J Food Microbiol. 2009; 135(1): 28-33. https://doi.org/10.1016/j.ijfoodmicro.2009.07.016

3. Voidarou C, Antoniadou M, Rozos G, Tzora A, Skoufos I, Varzakas T, Lagios A, Bezirtzoglou E. Fermentative foods: Microbiology, biochemistry, potential human health benefits and public health issues. Foods 2021; 10(1): 69. https://doi.org/10.3390/foods10010069

4. Patra JK, Das G, Paramithiotis S, Shin H-S. Kimchi and other widely consumed traditional fermented foods of Korea: A review. Front Microbiol. 2016; 28: 7:1-15. https://doi.org/10.3389/fmicb.2016.01493

5. Angmo K, Kumari A, Savitri A, Bhalla TC. Probiotic characterization of lactic acid bacteria isolated from fermented foods and beverage of Ladakh. LWT Food Sci Technol. 2016; 66: 428-435. https://doi.org/10.1016/j.lwt.2015.10.057

6. Jeong D-W, Kim H-R, Jung G, Han S, Kim C-T, Lee J-H. Bacterial community migration in the ripening of doenjang, a traditional Korean fermented soybean food. J Microbiol Biotechnol. 2014; 24(5): 648-660. https://doi.org/10.4014/jmb.1401.01009

7. Todorov SD, Botes M, Guigas C, Schillinger U, Wiid I, Wachsman MB, Holzapfel H, Dicks LMT. Boza, a natural source of probiotic lactic acid bacteria. J Appl Microbiol, 2008; 104(2): 465-477. https://doi.org/10.1111/j.1365-2672.2007.03558.x

8. Thakur M, Kumar V. Expanding antimicrobial resistance and shrinking antibiotic arsenal: Phytochemicals-A ray of hope. MGM J Med Sci. 2019; 6: 191-193 https://doi.org/10.4103/mgmj.mgmj_22_20

9. Stiles ME, Holzapfel WH. Lactic acid bacteria of foods and their current taxonomy. Int J Food Microbiol. 1997; 36(1): 1-29. https://doi.org/10.1016/s0168-1605(96)01233-0

10. Holzapfel WH. Culture media for non-sporulating Gram-positive food spoilage bacteria. Int J Food Microbiol. 1992; 17(2): 113-133. https://doi.org/10.1016/0168-1605(92)90110-O

11. Nazzaro F, Fratianni F, Nicolaus B, Poli A, Orlando P. The prebiotic source influences the growth, biochemical features and survival under simulated gastrointestinal conditions of the probiotic *Lactobacillus acidophilus*. Anaerobe 2012; 18(3): 280-285. https://doi.org/10.1016/j.anaerobe.2012.03.002

12. Aymerich T, Garriga M, Ylla J, Vallier J, Monfort JM, Hugas M. Application of enterocins as biopreservatives against *Listeria innocua* in Meat Products. J Food Protect. 2000; 63(6): 721-726. https://doi.org/10.4315/0362-028x-63.6.721

13. Bottazzi V. Bacteriocins of lactic acid bacteria: Microbiology, genetics and applications. Trends Food Sci Technol. 1994; 5(8): 274-175. https://doi.org/10.4014/mbl.2001.01004

14. Camargo AC, de Paula OAL, Todorov SD, Nero LA. *In vitro* evaluation of bacteriocins activity against *Listeria monocytogenes* biofilm formation. Appl Biochem Biotechnol. 2016; 178(6): 1239-1251. https://doi.org/10.1007/s12010-015-1941-3

15. Deegan LH, Cotter PD, Hill C, Ross P. Bacteriocins: Biological tools for bio-preservation and shelf-life extension. Int Dairy J. 2006; 16(9): 1058-1071. https://doi.org/10.1016/j.idairyj.2005.10.026

16. Alemzadeh I, Afarin M, Dehghan A, Alizadeh Sani M, Teimouri M, Seilani F, Abbasi P, Vaziri AS. Clinical uses and survival study of free and encapsulated probiotic bacteria in fruit Juices: A review. Appl Food Biotechnol. 2021;8(3): 161-180. https://doi.org/10.22037/afb.v8i3.33749

17. Golshahi M, Pirnia MM, Jafari P, Ebrahimi E, Tafvizi F, Dameshghian M, Tajabadi Ebrahimi M. Characterization of effective native lactic acid bacteria as potential oral probiotics on growth inhibition of *Streptococcus mutans*. Appl Food Biotechnol. 2021; 8(3): 201-212. https://doi.org/10.22037/afb.v8i3.33704

18. Kranjec C, Ovchinnikov KV, Gronseth T, Ebineshan K, Srikantam A, Diep DB. A bacteriocin-based antimicrobial formulation to effectively disrupt the cell viability of methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms. NPJ Biofilms Microbiom. 2020; 6(1): 58. https://doi.org/10.1038/s41522-020-00166-4

19. Bajic SS, Dokic J, Dinic M, Tomic S, Popovic N, Brdaric E, Golic N, Tolinacki M. GABA potentiate the immunoregulatory effects of *Lactobacillus brevis* BGZLS10-17 via ATG5-dependent autophagy *in vitro*. Sci Rep. 2020; 10(1): 1347. https://doi.org/10.1038/s41598-020-58177-2

20. Cano-Garrido O, Seras-Franzoso J, Garcia-Fruitos E. Lactic acid bacteria: reviewing the potential of a promising delivery live vector for biomedical purposes. Microb Cell Fact. 2015; 14(1): 1-12. https://doi.org/10.1186/s12934-015-0313-6

21. LeBlanc J-G, del Carmen S, Miyoshi A, Azevedo V, Sesma F, Langella P, Bermidez-Humaran LG, Watterlot L, Perdigon G, de Moreno de LeBlanc A. Use of superoxide dismutase and catalase producing lactic acid bacteria in TNBS induced Crohn's disease in mice. J Biotechnol. 2011; 151(3): 287-293. https://doi.org/10.1016/j.jbiotec.2010.11.008

22. Li P, Gu Q, Wang Y, Yu Y, Yang L, Chen JV. Novel vitamin B12-producing *Enterococcus* spp. and preliminary *in vitro* evaluation of probiotic potentials. Appl Microbiol Biotechnol. 2017; 101(15): 6155-6164. https://doi.org/10.1007/s00253-017-8373-7

23. Vrancken G, De Vuyst L, Van der Meulen R, Huys G, Vandamme P, Daniel H-M. Yeast species composition differs between artisan bakery and spontaneous laboratory sourdoughs. FEMS Yeast Res. 2010; 10(4): 471-481. https://doi.org/10.1111/j.1567-1364.2010.00621.x

24. Do T-B-T, Nguyen T-A, Vandamme P. Isolation, screening, identification and optimization of culture parameters to produce γ-aminobutyric acid by *Lactiplantibacillus pentosus* R13, an isolate from ruoc (fermented shrimp paste). Appl Food Biotechnol. 2022; 10(1): 1-8.

https://doi.org/10.22037/afb.v9i1.36103

25. Salleh F, Lani MN, Kamaruding NA, Tuan Chilek TZ, Ismail N. Lactic acid bacteria producing sorbic acid and benzoic acid compounds from fermented durian flesh (Tempoyak) and their antibacterial activities against foodborne pathogenic bacteria. Appl Food Biotechnol. 2021; 8(2): 121-132. https://doi.org/10.22037/afb.v8i2.32749

26. Vandamme P, De Bruyne K, Pot B. Lactic Acid Bacteria: Biodiversity and Taxonomy. In: Lactic Acid Bacteria: Biodiversity and Taxonomy. Hozlapfel, W.H. and Wood, B.J.B. (Eds.). 2014. pp.31-44.

27. Inoue Y, Hagi A, Nii T, Tsubotani Y, Nakata H, Iwata K. Novel antiseptic compound OPB-2045G shows potent bactericidal activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* both *in vitro* and *in vivo*: a pilot study in animals. J Med Microbiol. 2015; 64(1): 32-36. https://doi.org/10.1099/jmm.0.080861-0

28. De Vuyst L, Foulquie Moreno MR, Revets H. Screening for enterocins and detection of hemolysin and vancomycin resistance in enterococci of different origins. Int J Food Microbiol. 2003; 84(3): 299-318. https://doi.org/10.1016/s0168-1605(02)00425-7

29. Chikindas ML, Weeks R, Drider D, Chistyakov VA, Dicks LM. Functions and emerging applications of bacteriocins. Curr Opin Biotechnol. 2018; 49: 23-28. https://doi.org/10.1016/j.copbio.2017.07.011

30. Desniar, Rusmana I, Suwanto A, Mubarik NR. Organic acid produced by lactic acid bacteria from bekasam as food biopreservatives. IOP Conf Ser: Earth Environ Sci. 2020; 414: 1-8. https://doi.org/10.1088/1755-1315/414/1/012003

31. Pastrorova I, de Koster CG, Boom JJ. Analytic study of free and ester bound benzoic and cinnamic acids of gum benzoin resins by GC-MS HPLC-frit FAB-MS. Phytochem Anal. 1997; 8: 63-73. https://doi.org/10.1002/(SICI)1099-1565(199703)8:2<63::AID-PCA337>3.0.CO;2-Y

32. Caroline KF, Esar SY, Soewandi A, Wihadmadyatami H, Widharna RM, Tamayanti WD, Kasih E, Tjahjono Y. Evaluation of analgesic and antiplatelet activity of 2-((3 (chloromethyl)benzoyl)oxy)benzoic acid. Prostaglandins Other Lipid Mediat. 2016; 145: 1-8. https://doi.org/10.1016/j.prostaglandins.2019.106364

33. Fugaban JII, Bucheli JEV, Park YJ, Suh DH, Jung ES, Franco BDGM, Ivanova IV, Holzapfel WH, Todorov SD. Antimicrobial properties of *Pediococcus acidilactici* and *Pediococcus pentosaceus* isolated from silage. J Appl Microbiol. 2022; 132(1): 311-330. https://doi.org/10.1111/jam.1520

34. Lavermicocca P, Valerio F, Visconti A. Antifungal activity of phenyllactic acid against molds isolated from bakery products. Appl Environ Microbiol. 2003; 69(1): 634-640. https://doi.org/10.1128/AEM.69.1.634-640.2003

35. Batdorj B, Trinetta V, Dalgalarrondo M, Prevost H, Dousset X, Ivanova I, Haertle T, Chobert J-M. Isolation, taxonomic identification and hydrogen peroxide production by *Lactobacillus delbrueckii* subsp. *lactis* T31, isolated from Mongolian yoghurt: inhibitory activity on food-borne pathogens. J Appl Microbiol. 2007; 103(3): 584-593. https://doi.org/10.1111/j.1365-2672.2007.03279.x

36. Ito A, Sato Y, Kudo S, Sato S, Nakajima H, Toba T. The screening of hydrogen peroxide-producing lactic acid bacteria and their application to inactivating psychrotrophic food-borne pathogens. Curr Microbiol. 2003; 47: 0231-0236. https://doi.org/10.1007/s00284-002-3993-1

37. Tachedjian G, O'Hanlon DE, Ravel J. The implausible "*in vivo*" role of hydrogen peroxide as an antimicrobial factor produced by vaginal microbiota. Microbiome 2018; 6: 1-5. https://doi.org/10.1186/s40168-018-0418-3

38. Adeniyi BA, Adetoye A, Ayeni FA. Antibacterial activities of lactic acid bacteria isolated from cow faeces against potential enteric pathogens. Afr Health Sci. 2015; 15(3): 888–895. https://doi.org/10.4314/ahs.v15i3.24

39. Maragkoudakis PA, Mountzouris KC, Psyrras D, Cremonese S, Fischer J, Cantor MD, Tsakalidou E. Functional properties of novel protective lactic acid bacteria and application in raw chicken meat against *Listeria monocytogenes* and *Salmonella enteritidis*. Int J Food Microbiol. 2009; 130(3): 219-226. https://doi.org/10.1016/j.ijfoodmicro.2009.01.027

40. Debs-Louka E, Louka N, Abraham G, Chabot V, Allaf K. Effect of compressed carbon dioxide on microbial cell viability. Appl Environ Microbiol. 1999; 65(2): 626-631. https://doi.org/10.1128/AEM.65.2.626-631.1999

41. Blickstad E, Enfors S-O, Molin G. Effect of hyperbaric carbon dioxide pressure on the microbial flora of pork stored at 4 or 14 °C. J Appl Bacteriol. 1981; 50: 493-504. https://doi.org/10.1111/j.1365-2672.1981.tb04252.x

42. Albayrak ÇB, Duran M. Isolation and characterization of aroma producing lactic acid bacteria from artisanal white cheese

for multifunctional properties. LWT Food Sci Technol. 2021; 150: 112053. https://doi.org/10.1016/j.lwt.2021.112053 33

43. El-Gendy SM, Abdel-Galil H, Shahin Y, Hegazi FZ. Acetoin and diacetyl production by homo- and heterofermentative lactic acid bacteria. J Food Prot. 1983; 46(5): 420-425. https://doi.org/10.4315/0362-028X-46.5.420

44. Jay JM. Antimicrobial properties of diacetyl. Appl Environ Microbiol. 1982; 44(3): 525-532.

45. Kang BS, Seo J-G, Lee G-S, Kim J-H, Kim SY, Han YW, Kang H, Kim HO, Rhee JH, Chung M-J, Park YM. Antimicrobial activity of enterocins from *Enterococcus faecali*s SL-5 against *Propionibacterium acnes*, the causative agent in acne vulgaris, and its therapeutic effect. J Microbiol. 2009; 47(1): 101-109. https://doi.org/10.1007/s12275-008-0179-y

46. Langa S, Martin-Cabrejas I, Montiel R, Landete JM, Medina M, Arques JL. Combined antimicrobial activity of reuterin and diacetyl against foodborne pathogens. J Dairy Sci. 2014; 97(10): 6116-6121. https://doi.org/10.3168/jds.2014-8306

47. Cleusix V, Lacroix C, Vollenweider S, Duboux M, Le Blay G. Inhibitory activity spectrum of reuterin produced by *Lactobacillus reuteri* against intestinal bacteria. BMC Microbiol. 2007; 7(1): 1-9. https://doi.org/10.1186/1471-2180-7-101

48. Holtzel A, Ganzle MG, Nicholson GJ, Hammes WP, Jung G. The first low molecular weight antibiotic from lactic acid bacteria: Reutericyclin, a new tetramic acid. Angew Chem Int Ed Engl. 2000; 39(15): 2766-2768.

49. Asare PT, Zurfluh K, Greppi A, Lynch D, Schwab C, Stephan R. Lacroix C. Reuterin demonstrates potent antimicrobial activity against a broad panel of human and poultry meat *Campylobacter* spp. isolates. Microorganisms 2020; 8(1): 1-12. https://doi.org/10.3390/microorganisms8010078

50. Arques JL, Fernandez J, Gaya P, Nunez M, Rodrıiguez E,Medina M. ntimicrobial activity of reuterin in combination with nisin against food-borne pathogens. Int J Food Microbiol. 2004; 95(2): 225-229. https://doi.org/10.1016/j.ijfoodmicro.2004.03.009

51. Broberg A, Jacobsson K, Strom K, Schnurer J. Metabolite profiles of lactic acid bacteria in grass silage. Appl Environ Mictobiol. 2007; 73(17): 5547-5552. https://doi.org/10.1128/AEM.02939-06

52. Ellis J-C, Ross RP, Hill C. Nisin Z and lacticin 3147 improve efficacy of antibiotics against clinically significant bacteria. Future Microbiol. 2019; 14(18): 1573-1587. https://doi.org/10.2217/fmb-2019-0153

53. Furtado DN, Favaro L, Nero LA, de Melo Franco BDG, Todorov SD. Nisin production by *Enterococcus hirae* DF105Mi isolated from Brazilian goat milk. Probiotics Antimicrob Prot. 2019; 11(4): 1391-1402. https://doi.org/10.1007/s12602-019-09553-6

54. 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. Microb Pathogen. 2019; 128: 171-177. https://doi.org/10.1016/j.micpath.2019.01.002

55. Rea MC, Ross RP, Cotter PD, Hill C. Classification of Bacteriocins from Gram-Positive Bacteria. In: Drider D, Rebuffat S. (Eds.) Prokaryotic Antimicrobial Peptides: From Genes to Applications. New York, NY, USA, Springer. 2011: 29-53. https://doi.org/10.1007/978-1-4419-7692-5_3

56. Munoz A, Maqueda M, Galvez A, Martinez-Bueno M, Rodriguez A, Valdivia E. Biocontrol of psychrotrophic enterotoxigenic *Bacillus cereus* in a nonfat hard cheese by an enterococcal strain-producing enterocin AS-48. J Food Prot. 2004; 67(7): 1517–1521. https://doi.org/ 10.4315/0362-028x-67.7.1517

57. Achemchem F, Abrini J, Martinez-Bueno M, Valdivia E, Maqueda, M. Control of *Listeria monocytogenes* in goat's milk and goat's jben by the bacteriocinogenic *Enterococcus faecium* F58 strain. J Food Prot. 2006; 69(10): 2370-2376. https://doi.org/10.4315/0362-028x-69.10.2370

58. Todorov SD, Dicks LMT. Bacteriocin production by *Pediococcus pentosaceus* isolated from marula (*Scerocarya birrea*). Int J Food Microbiol. 2009; 132(2-3): 117-126. https://doi.org/10.1016/j.ijfoodmicro.2009.04.010

59. Todorov SD, Franco BDGM, Tagg JR. Bacteriocins of gram-positive bacteria having activity spectra extending beyond closely-related species. Benef Microbes, 2019; 10(3): 315-328. https://doi.org/10.3920/BM2018.0126

60. De Castilho NPA, Colombo M, Oliveira LL, Todorov SD, Nero LA. *Lactobacillus curvatus* UFV-NPAC1 and other lactic acid bacteria isolated from calabresa, a fermented meat product, present high bacteriocinogenic activity against *Listeria monocytogenes*. BMC Microbiol. 2019; 19(1): 1-13. https://doi.org/10.1186/s12866-019-1436-4

61. Galvez A, Abriouel H, Lopez RL, Ben Omar N. Bacteriocin-based strategies for food biopreservation. Int J Food Microbiol. 2007; 120(1-2): 51-70. https://doi.org/10.1016/j.ijfoodmicro.2007.06.001

62. Dal Bello B, Cocolin L, Zeppa G, Field D, Cotter PD, Hill C. Technological characterization of bacteriocin producing *Lactococcus lactis* strains employed to control *Listeria monocytogenes* in Cottage cheese. Int J Food Microbiol. 2012; 153(1): 58-65. https://doi.org/10.1016/j.ijfoodmicro.2011.10.016

63. Gong HS, Meng XC, Wang H. Plantaricin MG active against Gram-negative bacteria produced by *Lactobacillus plantarum* KLDS1.0391 isolated from "Jiaoke", a traditional fermented cream from China. Food Control. 2010; 21(1): 89-96. https://doi.org/10.1016/j.foodcont.2009.04.005

64. Stern NJ, Svetoch EA, Eruslanov BV, Kovalev YN, Volodina LI, Perelygin VV, Mitsevich EV, Mitsevitch IP, Levchuk VP. Paenibacillus polymyxa purified bacteriocin to control Campylobacter jejuni in chickens. J Food Protect. 2005; 68(7): 1450-1453. https://doi.org/10.4315/0362-028x-68.7.1450

65. Nattress FM, Yost CK, Baker LP. Evaluation of the ability of lysozyme and nisin to control meat spoilage bacteria. Int J Food Microbiol. 2001; 70(1): 111–119. https://doi.org/10.1016/s0168-1605(01)00531-1

66. Mitra S, Mukhopadhyay BC, Biswas SR. Potential application of the nisin Z preparation of *Lactococcus lactis* W8 in

preservation of milk. Lett Appl Microbiol. 2011; 53(1): 98-105. https://doi.org/10.1111/j.1472-765X.2011.03075.x

67. Delves-Broughton J. Nisin and its uses as a food preservative. Food Technol. 1990; 44(11): 100–117.

68. Loessner M, Guenther S, Steffan S, Scherer S. A pediocin-producing *Lactobacillus plantarum* strain inhibits *Listeria monocytogenes* in a multispecies cheese surface microbial ripening consortium. Appl Environ Microbiol. 2003; 69(3): 1854-1857. https://doi.org/10.1128/AEM.69.3.1854-1857.2003

69. Elotmani F, Revol-Junelles A-M, Assobhei O, Millière J-B. Characterization of anti-*Listeria monocytogenes* bacteriocins from *Enterococcus faecalis*, *Enterococcus faecium*, and *Lactococcus lactis* strains isolated from raib, a Moroccan traditional fermented milk. Curr Microbiol. 2002; 44(1): 10-17. https://doi.org/10.1007/s00284-001-0067-8

70. Ananou S, Maqueda M, Martínez-Bueno M, Galvez A, Valdivia E. Control of *Staphylococcus aureus* in sausages by enterocin AS-48. Meat Sci. 2005; 71(3): 549-556. https://doi.org/10.1016/j.meatsci.2005.04.039

71. Rilla N, Martinez B, Rodrigues A. Inhibition of a methicillin-resistant *Staphylococcus aureus* strain in Afuega'l Pitu cheese by the Nisin Z-producing strain *Lactococcus lactis* subsp. *lactis* IPLA 729. J Food Protect. 2004; 67(5): 928–933. https://doi.org/10.4315/0362-028x-67.5.928

72. Vaz-Velho M, Todorov S, Ribeiro J, Gibbs P. Evaluation of *Carnobacterium divergens* V41 and supernatant V41 abilities for reducing *Listeria innocua* 2030c numbers during processing and storage of cold-smoked salmon trout. Food Control. 2005; 16(6): 540-548. https://doi.org/10.1016/j.foodcont.2004.05.012

73. Pingitore EV, Todorov SD, Sesma F, Franco BDGM. Application of bacteriocinogenic *Enterococcus mundtii* CRL35 and *Enterococcus faecium* ST88Ch in the control of *Listeria monocytogenes* in fresh Minas cheese. Food Microbiol. 2012; 32(1): 38-47. https://doi.org/10.1016/j.fm.2012.04.005

74. Barbosa MS, Todorov SD, Ivanova I, Chobert JM, Haertle T, Franco BDGM. Improving safety of salami by application of bacteriocins produced by an autochthonous *Lactobacillus curvatus* isolate. Food Microbiol. 2014; 46: 254-262. https://doi.org/10.1016/j.fm.2014.08.004

75. Martinez RCR, Staliano CD, Vieira ADS, Villarreal MLM, Todorov SD, Saad SMI, Franco BDGM. Bacteriocin production and inhibition of *Listeria monocytogenes* by *Lactobacillus sakei* subsp. *sakei* 2a in a potentially synbiotic cheese spread. Food Microbiol. 2015; 48(1): 143-152. https://doi.org/10.1016/j.fm.2014.12.010

76. Wachsman MB, Castilla V, de Ruiz Holgado AP, de Torres RA, Sesma F, Coto CE. Enterocin CRL35 inhibits late stages of HSV-1 and HSV-2 replication *in vitro*. Antiviral Res. 2003; 58(1): 17-24. https://doi.org/10.1016/s0166-3542(02)00099-2

77. Remschmidt C, Schroder C, Behnke M, Gastmeier P, Geffers C, Kramer TS. Continuous increase of vancomycin resistance in enterococci causing nosocomial infections in Germany 10 years of surveillance. Antimicrob Resist Infect Control 2018; 7: 1-7. https://doi.org/10.1186/s13756-018-0353-x

78. Reinseth IS, Ovchinnikov KV, Tønnesen HH, Carlsen H, Diep DB. The increasing issue of vancomycin resistant enterococci and the bacteriocin solution. Probiotics Antimicro Prot. 2020; 12(3): 1203-1217. https://doi.org/10.1007/s12602-019-09618-6

79. Ahmed MO, Baptiste KE. Vancomycin-resistant enterococci: A review of antimicrobial resistance mechanisms and perspectives of human and animal health. Microb Drug Res. 2018; 24(5): 590-606. https://doi.org/10.1089/mdr.2017.0147

80. Leavis HL, Willems RJL, van Wamel WJB, Schuren FH, Caspers MPM, Bonten MJM. Insertion sequence-driven diversification creates a globally dispersed emerging multiresistant subspecies of *E. faecium*. Plos Pathog. 2007; 3(1): 75-96. https://doi.org/10.1371/journal.ppat.0030007

81. Coque TM, Patterson JE, Steckelberg JM, Murray BE. Incidence of hemolysin, gelatinase, and aggregation substance among enterococci isolated from patients with endocarditis and other infections and from feces of hospitalized and community-based persons. J Infect Dis. 1995; 171(5): 1223-1129. https://doi.org/10.1093/infdis/171.5.1223

82. Del Re B, Sgorbati B, Miglioli M, Palenzona D. Adhesion, autoaggregation and hydrophobicity of 13 strains of *Bifidobacterium longum*. Lett Appl Microbiol. 2000; 31(6): 438-442. https://doi.org/10.1046/j.1365-2672.2000.00845.x

83. Franz CMAP, Holzapfel WH, Stiles ME. Enterococci at the crossroads of food safety? Int J Food Microbiol. 1999; 47(1): 1-24. https://doi.org/10.1016/s0168-1605(99)00007-0

84. Steckbeck JD, Deslouches B, Montelaro RC. Antimicrobial peptides: new drugs for bad bugs? Expert Opin Bio Therapy. 2014; 14(1): 11–14. https://doi.org/10.1517/14712598.2013.844227

85. Coombs GW, Pearson JC, Daley DA, Le T, Robinson OJ, Gottlieb T, Howden BP, Johnson PDR, Bennett CM, Stinear TP, Turnidge JD. Molecular epidemiology of enterococcal bacteremia in Australia. J Clin Microbiol. 2014; 52(3): 897-905. https://doi.org/10.1128/JCM.03286-13

86. Faron ML, Ledeboer NA, Buchan BW. Resistance mechanisms, epidemiology, and approaches to screening for vancomycin-resistant *Enterococcus* in the health care setting. J Clin Microbiol. 2016; 54(10): 2436–2447. https://doi.org/10.1128/JCM.00211-16

87. Courvalin P. Vancomycin resistance in Gram-positive cocci. Clin Infect Dis. 2006; 42: S25-S34. https://doi.org/10.1086/491711

88. Leavis HL, Willems RJL, Wamel WJB, Schuren FH, Caspers MPM, Bonten MJM. Insertion sequence-driven diversification creates a globally dispersed emerging multiresistant subspecies of *E. faecium*. Plos Path. 2007; 3(1): 75-96. https://doi.org/10.1371/journal.ppat.0030007

89. Tendolkar PM, Baghdayan AS, Gilmore MS, Shankar N. Enterococcal surface protein, esp, enhances biofilm

formation by *Enterococcus faecalis*. Infect Immun. 2004; 72(10): 6032–6039. https://doi.org/10.1128/IAI.72.10.6032-6039.2004

90. Du F, Lv X, Duan D, Wang L, Huang J. Characterization of a linezolid- and vancomycin-resistant *Streptococcus suis* isolate that harbors *optr*A and *van*G operons. Front Microbiol. 2019; 10: 1-12. https://doi.org/10.3389/fmicb.2019.02026

91. Diep DB, Skaugen M, Salehian Z, Holo H, Nes IF. Common mechanisms of target cell recognition and immunity for class II bacteriocins. PNAS 2007; 104(7): 2384-2389. https://doi.org/10.1073/pnas.0608775104

92. O'Sullivan L, Ross RP, Hill C. Potential of bacteriocin-producing lactic acid bacteria for improvements in food safety and quality. Biochimie 2002; 84(5-6): 593-604. https://doi.org/10.1016/s0300-9084(02)01457-8

93. Hayes K, Cotter L, O'Halloran F. *In vitro* synergistic activity of erythromycin and nisin against clinical Group B *Streptococcus* isolates. J Appl Microbiol. 2019; 127(5): 1381-1390. https://doi.org/10.1111/jam.14400

94. Thomas VM, Brown RM, Ashcraft DS, Pankey GA. Synergistic effect between nisin and polymyxin B against pandrug-resistant and extensively drug-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents. 2019; 53(5): 663-668. https://doi.org/10.1016/j.ijantimicag.2019.03.009

95. Singh K, Kallali B, Kumar A, Thaker V. Probiotics: A review. Asian Pac J Trop Biomed. 2011; 12: S287-S290. https://doi.org/10.1016/S2221-1691(11)60174-3

96. Chi H, Holo H. Synergistic antimicrobial activity between the broad spectrum bacteriocin garvicin KS and nisin, farnesol and polymyxin B against Gram-positive and Gram-negative bacteria. Curr Microbiol. 2018; 75(3): 272–277. https://doi.org/10.1007/s00284-017-1375-y

97. Hanchi H, Hammami R, Gingras H, Kourda R, Bergeron MG, Ben Hamida J, Ouellette M, Fliss I. Inhibition of MRSA and of *Clostridium difficile* by durancin 61A: synergy with bacteriocins and antibiotics. Future Microbiol. 2017; 12: 205-212. https://doi.org/10.2217/fmb-2016-0113

98. Wolska KI, Grzes K, Kurek A. Synergy between novel antimicrobials and conventional antibiotics or bacteriocins. Pol J Microbiol. 2012; 61(2): 95-104.

99. Brumfitt W, Salton MRJ, Hamilton-Miller JMT. Nisin, alone and combined with peptidoglycan-modulating antibiotics: Activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. J Antimicrob Chem. 2002; 50(5): 731-734. https://doi.org/10.1093/jac/dkf190

100. Arnusch CJ, Pieters RJ. Breukink E. Enhanced membrane pore formation through high-affinity targeted antimicrobial peptides. Plos One. 2012; 7(6): 1-5. https://doi.org/10.1371/journal.pone.0039768

101. Piper C, Draper LA, Cotter PD, Ross RP, Hill C. A comparison of the activities of lacticin 3147 and nisin against drug-resistant *Staphylococcus aureus* and *Enterococcus* species. J Antimicrob Chem. 2009; 64(3): 546-551. https://doi.org/10.1093/jac/dkp221

102. Kers, JA, Sharp RE, Defusco AW, Park JH, Xu J, Pulse ME, Weiss WJ, Handfield M. Mutacin 1140 lantibiotic variants are efficacious against *Clostridium difficile* infection. Front Microbiol. 2018; **9:** 415. https://doi.org/10.3389/fmicb.2018.00415

103. Kim T-S, Hur J-W, Yu M-A, Cheigh C-I, Kim K-N, Hwang J-K, Pyun Y-R. Antagonism of *Helicobacter pylori* by bacteriocins of lactic acid bacteria. J Food Prot. 2003; 66(1): 3-12. https://doi.org/10.4315/0362-028x-66.1.3

104. Sutyak KE, Wirawan RE, Aroutcheva AA, Chikindas ML. Isolation of the *Bacillus subtilis* antimicrobial peptide subtilosin from the dairy product-derived *Bacillus amyloliquefaciens*. J Appl Microbiol. 2008; 104(4): 1067-1074. https://doi.org/10.1111/j.1365-2672.2007.03626.x

105. Aroutcheva A, Gariti D, Simon M, Shott S, Faro J, Simoes JA, Gurguis A, Faro S. Defense factors of vaginal lactobacilli. Am J Obstet Gynecol. 2001; 185(2): 375-379. https://doi.org/10.1067/mob.2001.115867

106. Silkin L, Hamza S, Kaufman S, Cobb SL, Vederas JC. Spermicidal bacteriocins: lacticin 3147 and subtilosin A. Bioorg Med Chem Lett. 2008; 18(10): 3103-3106. https://doi.org/10.1016/j.bmcl.2007.11.024

107. Reddy KVR, Aranha C, Gupta SM, Yedery RD. Evaluation of antimicrobial peptide nisin as a safe vaginal contraceptive agent in rabbits: *in vitro* and *in vivo* studies. Reproduction 2004; 128(1): 117-126. https://doi.org/10.1530/rep.1.00028

108. Hillman JD. Genetically modified *Streptococcus mutans* for the prevention of dental caries. Antonie Van Leeuwenhoek 2002; 82(1): 361-366.

109. Howell TH, Fiorellini JP, Blackburn P, Projan SJ, de la Harpe J, Williams RC. The effect of a mouthrinse based on nisin, a bacteriocin, on developing plaque and gingivitis in beagle dogs. J Clin Periodontol. 1993; 20(5): 335-359. https://doi.org/10.1111/j.1600-051x.1993.tb00369.x

110. Fitzgerald RJ, Morhart RE, Marquez C, Adams BO. Inhibition of caries in hamsters treated with staphylococcin 1580. Infect Immun. 1986; 54(2): 288-290. https://doi.org/10.1128/iai.54.2.288-290.1986

111. Oh S, Kim S-H, Ko Y, Sim J-H, Kim KS, Lee S-H, Park S, Kim YJ. Effect of bacteriocin produced by *Lactococcus* sp. HY 449 on skin-inflammatory bacteria. Food Chem Toxicol. 2006; 44(8): 1184-1190. https://doi.org/10.1016/j.fct.2005.08.008

112. Davidse EK, Balla E, Holzapfel WH, Muller CJC, Cloete SWP, Dicks LMT. Peptide AS-48 (*Enetrococcus faecalis*) for prevention and treatment of mastitis in dairy cows. Online J Vet Res. 2004; 8: 22-32.

113. Broadbent JR, Chou YC, Gillies K, Kondo JK. Nisin inhibits several Gram-positive, mastitis-causing pathogens. J Dairy Sci. 1989; 72(12): 3342-3345. https://doi.org/10.3168/jds.S0022-0302(89)79496-0

114. Sobrino-Lopez A, Martin-Belloso O. Use of nisin and other bacteriocins for preservation of dairy products. Int Dairy J. 2008; 18(4): 329-343.

https://doi.org/10.1016/j.idairyj.2007.11.009

115. Montville TJ, Chung H-J, Chikindas ML, Chen Y. Nisin A depletes intracellular ATP and acts in bactericidal manner against *Mycobacterium smegmatis*. Lett Appl Microbiol. 1999; 28(3): 189-193. https://doi.org/10.1046/j.1365-2672.1999.00511.x

116. Carroll J, Field D, O'Connor PM, Cotter PD, Coffey A, Hill C, Ross RP, O'Mahony J. The gene encoded antimicrobial peptides, a template for the design of novel anti-mycobacterial drugs. Bioengin Bugs. 2010; 1(6): 408-412. https://doi.org/10.4161/bbug.1.6.13642

117. Todorov SD, Wachsman MB, Knoetze H, Meincken M, Dicks LMT. An antibacterial and antiviral peptide produced by *Enterococcus mundtii* ST4V isolated from soy beans. Int J Antimicrob Agents, 2005; 25(6): 508-513. https://doi.org/10.1016/j.ijantimicag.2005.02.005

118. Minahk CJ, Dupuy F, Morero RD. Enhancement of antibiotic activity by sub-lethal concentrations of enterocin CRL35. J Antimicrob Chem. 2004; 53(2): 240-246. https://doi.org/10.1093/jac/dkh079

119. Cavicchioli VQ, de Carvalho OV, de Paiva JC, Todorov SD, Junior AS, Nero LA. Inhibition of Herpes simplex virus 1 and Poliovirus (PV 1-1) by bacteriocins from *Lactococcus lactis* subsp. *lactis* and *Enterococcus durans* strains isolated from goat milk. Int J Antimicrob Agents. 2018; 51(1): 33-37. https://doi.org/10.1016/j.ijantimicag.2017.04.020

120. Serkedjieva J, Danova S, Ivanova I. Antiinfluenza virus activity of a bacteriocin produced by *Lactobacillus delbrueckii*. Appl Biochem Biotechnol. 2000; 88: 285–298. https://doi.org/10.1385/abab:88:1-3:285

121. Smaoui S, Elleuch L, Bejar W, Karray-Rebai I, Ayadi I, Jaouadi B, Mathieu F, Chouayekh H, Bejar S, Mellouli L. Inhibition of fungi and Gram-negative bacteria by bacteriocin BacTN635 produced by *Lactobacillus plantarum* sp. TN635. Appl Biochem Biotechnol. 2010; 162: 1132-1146. https://doi.org/10.1007/s12010-009-8821-7

122. Le Lay C, Akerey B, Fliss I, Subirade M, Rouabhia M. Nisin Z inhibits the growth of *Candida albicans* and its transition from blastospore to hyphal form. J Appl Microbiol. 2008; 105(5): 1630–1639. https://doi.org/10.1111/j.1365-2672.2008.03908.x

123. Lopez RL, Garcia MT, Abriouel H, Omar NB, Grande MJ, Martinez-Canamero M, Galvez A. Semi-preparative scale purification of enterococcal bacteriocin enterocin EJ97, and evaluation of substrates for its production. J Ind Microbiol Biotechnol. 2007; 34(12): 779-785. https://doi.org/10.1007/s10295-007-0254-0

124. Lindenstrauss AG, Pavlovic M, Bringmann A, Behr J, Ehrmann MA, Vogel RF. Comparison of genotypic and phenotypic cluster analyses of virulence determinants and possible role of CRISPR elements toward their incidence in *Enterococcus faecalis* and *Enterococcus faecium*. System Appl Microbiol. 2011; 34(8): 553-560. https://doi.org/10.1016/j.syapm.2011.05.002

125. Kamboj M, Cohen N, Gilhuley K, Babady N, Seo S, Sepkowitz K. Emergence of daptomycin-resistant VRE: Experience of a single institution. Infect Control Hosp Epidemiol. 2011; 32(4): 391-394. https://doi.org/10.1086/659152

126. Magnusson J, Schnürer J. *Lactobacillus coryniformis* subsp. *coryniformis* strain Si3 produces a broad-spectrum proteinaceous antifungal compound. Appl Environ Microbiol. 2001; 67(1): 1-5. https://doi.org/10.1128/AEM.67.1.1-5.2001

127. Strom K, Sjogren J, Broberg A, Schnurer J. *Lactobacillus plantarum* MiLAB 393 produces the antifungal cyclic dipeptides cyclo(L-Phe-L-Pro) and cyclo(L-Phe-trans-4-OH-L-Pro) and 3-phenyllactic acid. Appl Environ Microbiol. 2002; 68(9): 4322-4327. https://doi.org/10.1128/AEM.68.9.4322-4327.2002

128. Ahmadova A, Todorov SD, Hadji-Sfaxi I, Choiset Y, Rabesona H, Messaoudi S, Kuliyev A, Franco BDGM, Chobet J.-M, Haertle T. Antimicrobial and antifungal activities of *Lactobacillus curvatus* strain isolated from homemade Azerbaijani cheese. Anaerobe 2013: 20: 42-49. https://doi.org/10.1016/j.anaerobe.2013.01.003

129. Bartkiene E, Bartkevics V, Lele V, Pugajeva I, Zavistanaviciute P, Zadeike D, Juodeikiene G. Application of antifungal lactobacilli in combination with coatings based on apple processing by-products as a bio-preservative in wheat bread production. J Food Sci Technol. 2019; 56(6): 2989-3000. https://doi.org/10.1007/s13197-019-03775-w

130. Zoghi A, Massoud R, Todorov SD, Chikindas ML, Popov I, Smith S, Khosravi-Darani K. Role of the lactobacilli in food bio-decontamination: friends with benefits. Enzyme Microb Technol. 2021;150 (2021): 1-12. https://doi.org/10.1016/j.enzmictec.2021.109861

131. Sellamani M, Kalagatur NK, Siddaiah C, Mudili V, Krishna K, Natarajan G, Rao Putcha VL. Antifungal and zearalenone inhibitory activity of *Pediococcus pentosaceus* isolated from dairy products on *Fusarium graminearum*. Front Microbiol. 2016; 7: 890. https://doi.org/10.3389/fmicb.2016.00890

132. Sevgi E, Tsveteslava II. Antifungal activity of lactic acid bacteria, isolated from Bulgarian wheat and rye flour. J Life Sci. 2015; 9: 1-6. https://doi.org/10.17265/1934-7391/2015.01.001

133. Cortes-Zavaleta O, Lopez-Malo A, Hernandez-Mendoza A, Garcia H. Antifungal activity of lactobacilli and its relationship with 3-phenyllactic acid production. Int J Food Microbiol. 2014; 173: 30-35. https://doi.org/10.1016/j.ijfoodmicro.2013.12.016

134. Yang E, Chang H. Purification of a new antifungal compound produced by *Lactobacillus plantarum* AF1 isolated from kimchi. Int J Food Microbiol. 2010; 139: 56-63. https://doi.org/10.1016/j.ijfoodmicro.2010.02.012

135. Field D, Ross RP, Hill C. Developing bacteriocins of lactic acid bacteria into next generation biopreservatives. Curr Opin Food Sci. 2018; 20: 1-6. https://doi.org/10.1016/j.cofs.2018.02.004

136. Agata M, Zannini E, Coffey A, Arendt EK. Green preservatives: Combating fungi in the food and feed industry by applying antifungal lactic acid bacteria. Adv Food Nutr Res. 2012; 66: 217-238. https://doi.org/10.1016/B978-0-12-394597-6.00005-7

137. Favaro L, Penna ALB, Todorov SD. Bacteriocinogenic LAB from cheeses-application in biopreservation? Trends Food Sci Technol. 2015; 41(1): 37-48. https://doi.org/10.1016/j.tifs.2014.09.001

138. Axel C, Brosnan B, Zannini E, Furey A, Coffey A, Arendt EK. Antifungal sourdough lactic acid bacteria as biopreservation tool in quinoa and rice bread. Int J Food Microbiol. 2016; 23: 86-94. https://doi.org/10.1016/j.ijfoodmicro.2016.05.006

139. Awah J, Ukwuru M, Alum E, Kingsley T. Bio-preservative potential of lactic acid bacteria metabolites against fungal pathogens. Afr J Microbiol Res. 2018; 12: 913-922. https://doi.org/10.5897/AJMR2018.8954

140. Salas ML, Thierry A, Lemaitre M, Garric G, Harel-Oger M, Chatel M, Le S, Mounier J, Valence F, Coton E. Antifungal activity of lactic acid bacteria combinations in dairy mimicking models and their potential as bioprotective cultures in pilot scale applications. Front Microbiol. 2018; 9: 1-18. https://doi.org/10.3389/fmicb.2018.01787

141. Carroll J, O'Mahony J. Anti-mycobacterial peptides: Made of order with delivery included. Bioengineered Bugs 2011; 2(5): 241-246. https://doi.org/10.4161/bbug.2.5.16229

142. Donaghy J. Lantibiotics as prospective antimycobacterium agents. Bioengineered Bugs 2010; 1 (6): 437-439. https://doi.org/161/bbug.1.6.13855

143. Evivie SE, Huo G-C, Igene JO, Bian X. Some current applications, limitations and future perspectives of lactic acid bacteria as probiotics. Food Nutr Res. 2017; 61(1): 1-16. https://doi.org/10.1080/16546628.2017.1318034

144. Aragon G, Graham DB, Borum M. Doman DB. Probiotic therapy for irritable bowel syndrome. Gastroenterol Hepatol. 2010; 6(1): 39-44.

145. Li B, Liang L, Deng H, Guo J, Shu H, Zhang L. Efficacy and safety of probiotics in irritable bowel syndrome: A systematic review and meta-analysis. Front Pharmacol. 2020; 11: 1-23. https://doi.org/10.3389/fphar.2020.00332

146. Kocsis T, Molnar B, Nemeth D, Hegyi P, Szakacs Z, Balint A, Garami A, Soos A, Marta K, Solymart M. Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials. Sci Rep. 2020; 10(1): 1-14. https://doi.org/10.1038/s41598-020-68440-1

147. Kumar M, Nagpal R, Kumar R, Hemalatha R, Verma V, Kumar A, Chakraborty C, Singh B, Marotta F, Jain S, Yadav H. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases. Exp Diabetes Res. 2012; 2012: 1-14. https://doi.org/10.1155/2012/902917

148. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O'Connor R, Cruz-Pereira JS, Peterson VL, Rea K, Ritz NL, Sherwin E, Spichak S, Teichman EM, van de Wouw M, Ventura-Silva AP, Wallace-Fitzsimons SE, Hyland N, Clarke G, Dinan TG. The microbiota-gut-brain axis. Physiol Rev. 2019; 99(4): 1877-2013. https://doi.org/10.1152/physrev.00018.2018

149. Kim SG, Becattini S, Moody TU, Shliaha PV, Littmann ER, Seok R, Gjonbalaj M, Eaton V, Fontana E, Amoretti L, Wright R, Caballero S, Wang ZX, Jung HJ, Morjaria SM, Leiner IM, Qin W, Ramos RJJF, Cross JR, Narushima S, Honda K, Peled JU, Hendrickson RC, Taur Y, van den Brink MRM, Pamer EG. Microbiota-derived lantibiotic restores resistance against vancomycin-resistant *Enterococcus*. Nature 2019; 572(7771): 665-669. https://doi.org/10.1038/s41586-019-1501-z

150. Beasley S, Tuorila H, Saris PEJ. Fermented soymilk with a monoculture of *Lactococcus lactis*. Int J Food Microbiol. 2003; 81: 159-162. https://doi.org/10.1016/S0168-1605(02)00196-4

151. Garcia C, Rendueles M, Diaz M. Liquid-phase food fermentations with microbial consortia involving lactic acid bacteria. Food Res Int. 2019; 119: 207-220. https://doi.org/10.1016/j.foodres.2019.01.043

152. Azizkhani M, Saris PEJ, Baniasadi M. An *in vitro* assessment of antifungal and antibacterial activity of cow, camel, ewe, and goat milk kefir and probiotic yogurt. J Food Meas Charact. 2020; 1: 1-10. https://doi.org/10.1007/s11694-020-00645-4

153. Pakdaman MN, Udani JK, Molina JP, Shahani M. The effects of the DDS-1 strain of lactobacillus on symptomatic relief for lactose intolerance-a randomized, double-blind, placebo-controlled, crossover clinical trial. Nutr J. 2015; 15: 1-11. https://doi.org/10.1186/s12937-016-0172-y

154. Singh AP, Prabha V, Rishi P. Value addition in the efficacy of conventional antibiotics by nisin against *Salmonella*. Plos One 2013; 8(10): 1-9. https://doi.org/10.1371/journal.pone.0076844

155. Mahmoudi M, Khomeiri M, Saeidi M, Davoodi H. *Lactobacillus* species from Iranian jug cheese: Identification and selection of probiotic based on safety and functional properties. Appl Food Biotechnol. 2021; 8: 47-56. https://doi.org/10.22037/afb.v8i1.29253

156. Mahmoudi M, Khomeiri M, Saeidi M, Kashaninejad M, Davoodi H. Study of potential probiotic properties of lactic acid bacteria isolated from raw and traditional fermented camel milk. J Agr Sci Tech. 2019; 21: 1161-1172. jast.modares.ac.ir/article-23-18423-en.pdf.

Review Article
pISSN: 2345-5357
eISSN: 2423-4214

APPLIED FOOD BIOTECHNOLOGY, 2022, 9 (2): 127-143
Journal homepage: www.journals.sbmu.ac.ir/afb

OPEN ACCESS

بررسی اجمالی فراورده‌های جانبی باکتری‌های لاکتیک اسید مفید به‌عنوان ترکیبات ضدمیکروبی نویدبخش

جوانا ایوی ایروریتا فوگابان[۱]، ویلهلم هاینریش هولزاپفل[۲]، سوتوسلاو دیمیتروف تودوروف[۱*]

۱- لاکتیک اسید باکتری‌های زیست‌یار، گروه همگرایی پیشرفته، دانشگاه جهانی هادونگ، پوهانگ، گیونگبوک ۳۷۵۵۴، جمهوری کره
۲- آزمایشگاه میکروب‌های موثر انسانی، گروه همگرایی پیشرفته، دانشگاه جهانی هاندونگ، پوهانگ، گیونگبوک ۳۷۵۵۴، جمهوری کره

چکیده

سابقه و هدف: صرفنظر از توانایی باکتری‌های لاکتیک اسید در هدایت فرایند تخمیر، با تبدیل مواد اولیه به فراورده غذایی نهایی، نقش ضروری در نگهداری و همچنین تولید طعم‌های متمایز غذایی از طریق تبدیل زیستی ترکیبات و اسیدهای آلی دارند. عملکرد باکتری‌های لاکتیک اسید با توانایی در تولید محدوده گستره‌ای از ترکیبات ضدمیکروبی مرتبط است که به عنوان یک دروازه‌ای برای یکپارچگی محصولات غذایی و ایمنی مصرف‌کنندگان عمل می‌کند. خواص نگهدارندگی زیستی[۱] باکتری‌های لاکتیک اسید به تولید پپتیدهای ضدمیکروبی (شامل باکتریوسین‌ها)، انواع اسیدهای آلی، دی استیل، رویترین، متابولیت‌های آلی با وزن مولکولی پایین، هیدروژن پراکسید، کربن دی‌اکسید، در میان بسیاری دیگر مربوط می‌شود. تفاوت ترکیبات ضدمیکروبی نقش مهمی نه تنها به‌علت خواص ضدباکتریایی در نگهدارندگی زیستی دارد، بلکه هنگام استفاده از باکتری‌های لاکتیک اسید، به‌عنوان ترکیب ضدمیکروبی، می‌تواند عوامل کلیدی در خواص ضدکپک و متعاقب آن کاهش سموم قارچی و/یا افزایش خواص زیست‌یاری شود.
در این مقاله مروری، هدف ارائه ساختاریافته مثال‌های گوناگون از کاربردهای باکتری‌های لاکتیک اسید و متابولیت‌های ضدمیکروبی آنها در نگهدارندگی زیستی و در بخش پزشکی در برابر باکتری‌ها و کپک‌ها، به‌عنوان خواص زیست‌یاری آن می‌باشد.

یافته‌ها و نتیجه‌گیری: باکتری‌های لاکتیک اسید عوامل ضدمیکروبی قدرتمندی می‌باشند که قادرند فرایندهای گوناگون تخمیر را هدایت و انواع متابولیت‌های مفید با کاربرد در ایمنی زیستی مواد غذایی تولید کنند و خواص مفید برای ارتقای سلامت زیست‌یارها را موجب شوند.

تعارض منافع: نویسندگان اعلام می‌کنند که هیچ نوع تعارض منافعی مرتبط با انتشار این مقاله ندارند.

تاریخچه مقاله

دریافت ۳ فوریه ۲۰۲۲
داوری ۱۶ فوریه ۲۰۲۲
پذیرش ۲۲ فوریه ۲۰۲۲

واژگان کلیدی

- باکتریوسین‌ها
- ترکیبات ضدمیکروبی
- باکتری‌های لاکتیک اسید
- ترکیبات ضدقارچی
- زیست‌یارها

***نویسنده مسئول**

سوتوسلاو دیمیتروف تودوروف
لاکتیک اسید باکتری‌های زیست‌یار، گروه همگرایی پیشرفته، دانشگاه جهانی هادونگ، پوهانگ، گیونگبوک ۷۰۸-۷۹۱، جمهوری کره
تلفن: ۳۱۵۲-۳۴۹۰-۱۰-۸۲+
پست الکترونیک:
slavi310570@abv.bg

---

[۱] Bio-preservation