Review Paper:

Bacteriocins- Convincible component of antimicrobial film for food packaging: A Review

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Abstract

The global population is growing, and food waste from spoilage and contamination is a serious problem. Modern packaging systems are crucial nowadays to address these problems and maximize the profitability of the food industry by extending the shelf life and storage of food products. Among these, active packaging is attracting greater attention as it prevents microbial attack and extends the storability of the products. Bacteriocins and proteinaceous toxins from bacteria, can be integrated into the food packaging materials.

Though they have not been widely used in the food packaging sector, they have previously been acclaimed as a potential alternative to chemical preservation techniques. This review encompasses a wide range of bacteriocins used in food packaging to prevent microbial contamination. More importantly, the difficulties encountered in the industry and the latest measures to remediate them are discussed in detail.

Keywords: Bacteriocins, anti-microbials, food packaging, contamination, active packaging, preservation.

Introduction

Food spoilage accounts for almost 110 billion USD worldwide every year in productivity lost and medical bills. One in every ten people dies from consuming contaminated food every year, which accounts for 600 million lives. These grim statistics illustrate the need for effective, efficient, and safe food packaging solutions. Moreover, consumers have become more aware of the flaws and ill effects of conventionally mass-produced synthetic packaging, pushing the industry to develop new methods of packaging food. Modern food packaging has become highly specialized such as active, smart, and intelligent packaging. Continuous monitoring of packaged food by gauging the microbial content or inherent ripeness of the food product is smart packaging. Physicochemical properties like pH, color, moisture content, tamper, gas release, and chemical composition can be checked with the help of indicators[40].

As a result, the packaging material may include certain mineral components and even lab-on-a-chip type sensors. Intelligent packaging consists of indicators, data carriers like bar codes, and sensors that help quantify the presence of analytes in food products[16]. Active packaging gets a step further by actively seeking to remediate the issue of food spoilage by prolonging the shelf life of foods by denoting that the packaging material must display some form of anti-microbial properties.

Recently, nano-sized materials like silver, copper, and titanium have been used and incorporated into the packaging material with the intent of preventing microbial spoilage[40]. The need for bioactive packaging stemmed from the perceived and proven health concerns regarding the use of such materials in packaging. Environmental concerns have similarly influenced the requirements for biodegradable packaging as solution[32]. Bioactive packaging is a subset of active packaging. Bioactive packaging includes bio-based additives to enhance the shelf life as well as to fortify the nutritional content of the overall food product which is the niche part. Most bioactive additives such as phytochemical constituents, vitamins, and other natural polymers are used to achieve the requirement of antimicrobial properties in food packaging[41].

Bacteriocins

Bacteriocins are antimicrobial proteins produced by both Gram-positive and Gram-negative strains of bacteria. They mimic antibiotics in their mechanism of action although differ in the aspect of targeting only the bacterial strain that produced them along with its closely related species[9]. They were first discovered in 1925 by Gratia who was working on highly specific antibiotics. The label "bacteriocine" was first used in 1952 when it was revealed that various bacterial species produced such peptides with anti-microbial activity. Bacteriocins are classified under two broad groups, those produced by Gram-positive bacteria and others produced by Gram-negative bacteria as shown in the fig. 1.

The first category can be further distinguished into four classes. Class I peptides contain atypical amino acids and are linear (Type A) or globular (Type B) in structure and show variance in protein charge. Class II bacteriocins are produced by ABC- transport proteins and are below 10 kDa in molecular weight. Unlike class I peptides, they are not post-translation modified and do not contain atypical amino acids. Based on structure, they are subdivided into five types.

Class IIA bacteriocins are known for their conserved sequences at the C-terminal and differentiated N-terminals. They show great potential in the food preservative industry as a result of their anti-listeria activity.

Class IIB can be classified as dipeptides that target *Enterococcus* species. They target them by forming pores in the bacterial membrane which create ionic leakage. Class IIC refers to the cyclical peptides which display a broad range of antimicrobial activity like Bacteriocin AS-48. Class IID consists of enterocins and lactococcins. They are not as well-defined as the other subclasses. The newest addition to the class II bacteriocin family is IIE which is composed of around 3-4 peptides and has shown good activity against *Listeria monocytogenes*. The third class consists of those with molecular weight above 30 kDa. They are further classified based on their mode of antimicrobial activity.

Bacteriolysins will dissolve the bacterial cell wall causing cellular death whilst non-lytic antimicrobial peptides act on intracellular targets. Class IV bacteriocins require and include a carbohydrate moiety in their structure for full activity. Gram-negative bacteria produce two types of bacteriocins: Colicins secreted by E. coli and Microcins that target enteric bacteria[24]. To ensure that only the recent advancements in bacteriocin implementation were discussed, manuscripts published from 2015 to 2021 were selected for this descriptive review. Fig. 2 represents a timeline illustrating the historical progression in the field of bacteriocins[3,28,43].

General applications of Bacteriocins in food industries: The most popular application of bacteriocins is their use as a bio preservative in dairy products, meat, eggs, and vegetables. As of today, the only FDA-approved bacteriocin used as a preservative is nisin used in over 48 countries. Bacteriocins that promote growth or disease resistance can be applied to a plant or a plant seed to help with its growth as shown by a patent for the use of bacteriocins for plant growth[8].

There are numerous clinical applications too. Nisin, subtilosin, fermenticin, and lacticin 3147 have shown spermicidal properties by decreasing or altering the motility of human sperm, which shows the potential of bacteriocins as spermicides[46].

Research in cancer therapy shows that Bacteriocins inhibit tumor cells. Given bacteriocin's status as safe to use, they could be a candidate for an anti-tumor drug[54]. Bacteriocins increase membrane permeability leading to induced cell death of cancer cells[26]. Several bacteriocins have been shown to exhibit antiviral properties, for instance, against HSV-1 and HSV-2.

It has been established that bacteriocins derived from the *Enterococcus* species show marked activity against viruses from the Herpesviridae family. However, the mechanism of such activity remains archaic[46].

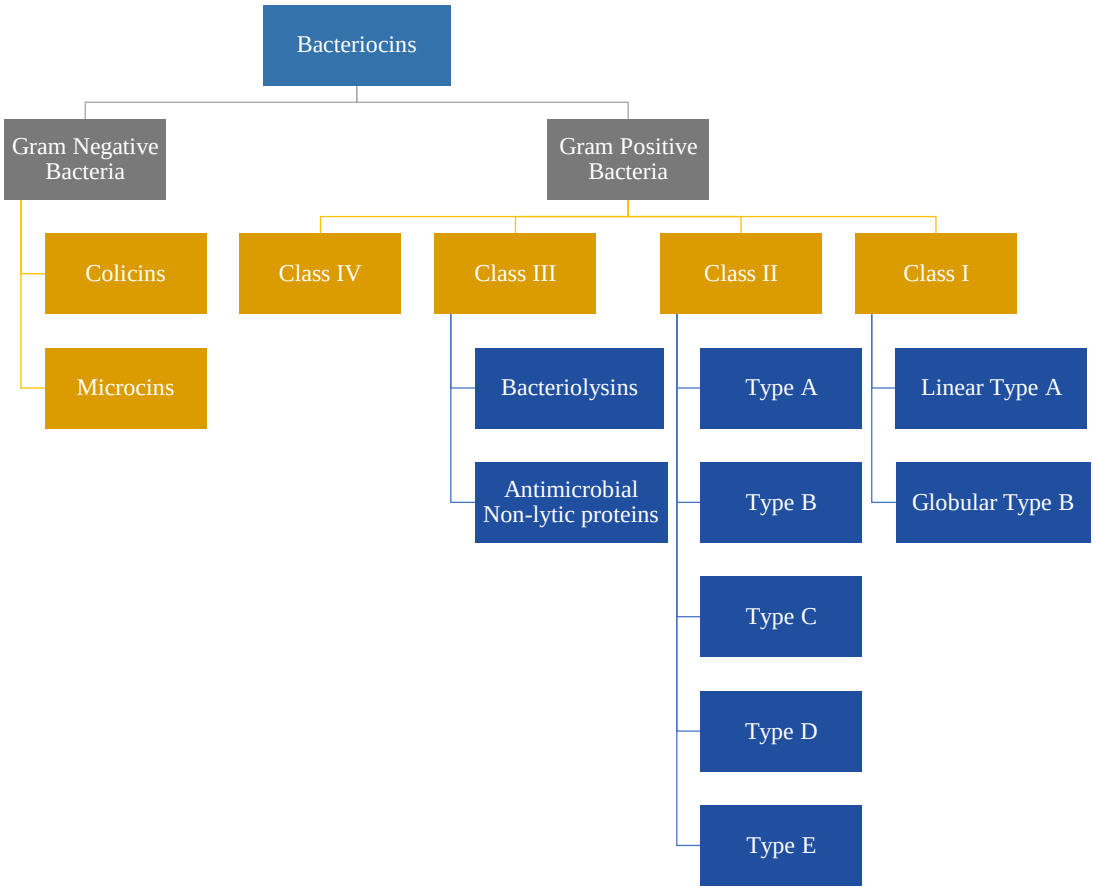

Fig. 1: Demarcations between the various types of bacteriocins

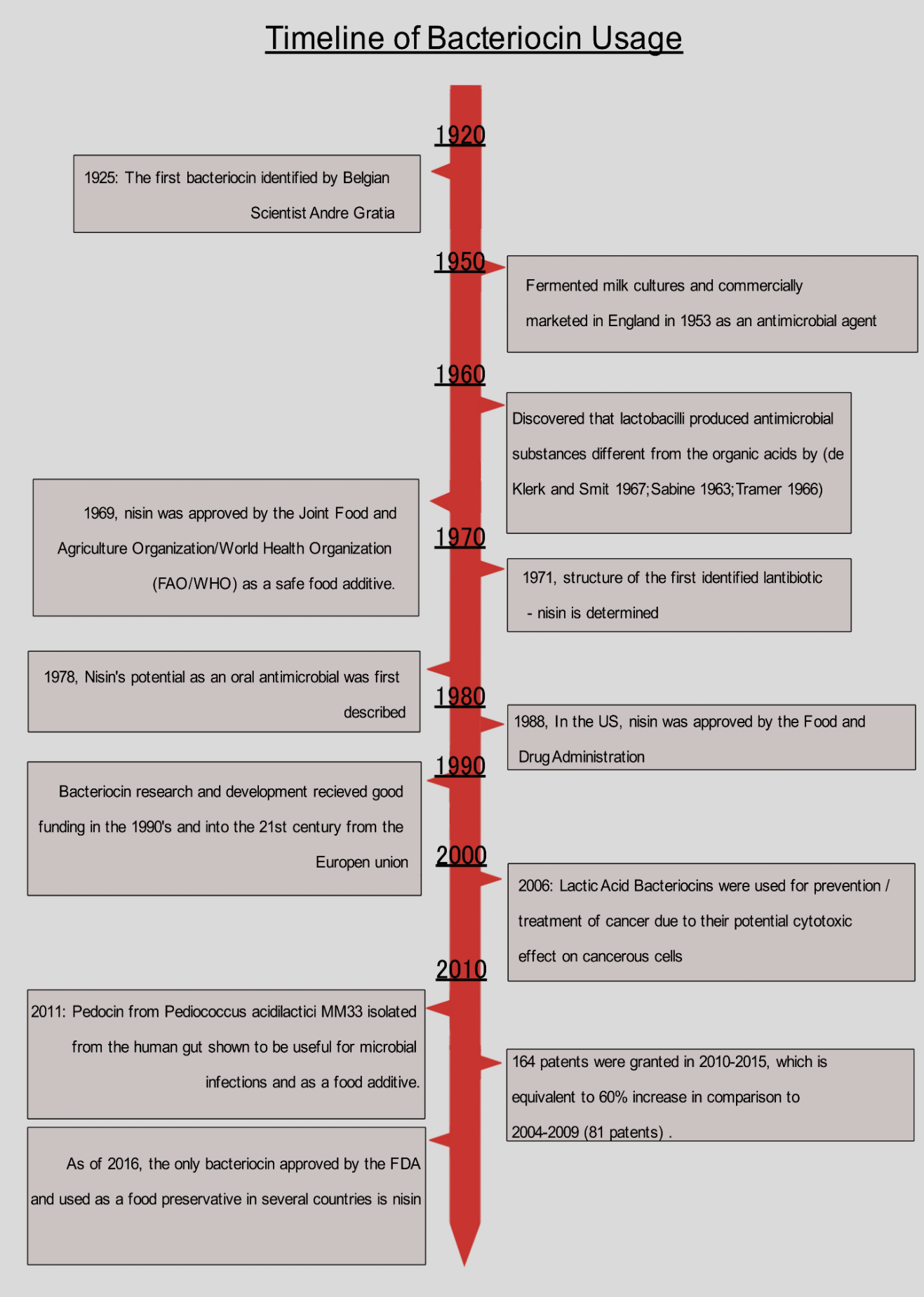

Fig. 2: A timeline illustrating the historical progression in the field of bacteriocins

In skin care, Bacteriocin-based lotions have been shown to reduce inflammatory lesions as in the case of the action of ESL5 bacteriocin on lesions caused by *P. acnes*[23]. Studies by Zoumpopoulou et al[57] illustrate that certain bacteriocins, namely *L. plantarum ACA-DC 269*, *L. fermentum ACA-DC 179*, and *S. macedonicus ACA-DC 198* can be used to target pathogenic oral bacteria. It could be useful to further investigate as it could lead to formulation of effective antimicrobials. Bacteriocins are employed even in veterinary circles. Antibiotic methods of treating mastitis increase the risk of antibiotic resistance[35]. Numerous studies have demonstrated that nisin can be used as an alternative to conventional antibiotics to bypass the effects of antibiotic resistance[34].

Table 1 illustrates some of the inherent advantages of bacteriocins like their nature as a safe-to-use additive in food preservation along with a high degree of thermal stability. The majority of bacteriocin peptides used are stable in the neutral range of pH which is common to most food products. Unlike certain bioactive ingredients, bacteriocins from the lactic acid bacteria family (LAB) have yet to display any signs of adverse effects on test subjects. Despite these redeeming qualities, their use in commercial packaging and preservation is limited at best.

Inherent challenges posed by bacteriocins

Ever since it was first discovered in milk in 1928, and first commercially produced in the 1950's, nisin remains the sole FDA-approved bacteriocin used in the food processing industry[56]. Several obstacles hinder the widespread commercial use of bacteriocins and other such antimicrobial peptides. First, their commercial production is expensive. Large-scale manufacturing of bacteriocins requires a protein purification stage which is more expensive than antibiotic manufacturing.

Additionally, proteolytic degradation of peptides causes loss of activity, these compounds also undergo various physical and chemical changes during the various food processing stages[7]. The majority of bacteriocins possess narrow spectrum activity and those that show a wide range, are not as abundant[36] as nisin.

Due to its limited range of activity, it is unable to protect food from a variety of microorganisms. Finally, there is also the threat of bacteriocin-resistant strains emerging. Despite peptides being ubiquitous, only a few instances of resistance have been observed[4]. There is evidence that a similar phenomenon is occurring among bacteriocins. *L. monocytogenes* has shown resistance to nisin, leucocin A, pedocin and mesenterocin[27].

Advances in bacteriocin modification against proteolytic degradation: Proteolytic degradation of a peptide often depends upon its amino acid sequence. Previous methods were based on chemical modification of the amino acid sequence.

Table 1
Properties of Bacteriocins used in Food Packaging

Class	Name	Source	Targets	Food product	Heat resistance	pH tolerance	Safety status
I	Nisin[19,35,55]	*L. lactis spp*	*L. monocytogenes, C. botulinum*	Fruit beverages, meat and dairy products	Relatively stable when PEGylated at 160 ℃	Below 8	GRAS by FDA
I	Lacticin 3147 A1[30,47]	*L. lactis DPC3147*	*L. monocytogenes, B. subtilis*	Dairy products	80 ℃for 20 mins	Around 7	Tested safe till 18 mg/kg dose in rats
II A	Enterocin A[1,35,39]	*Enterococcus faecium MMRA*	*L. monocytogenes*	Meat products	80 ℃ for 15 mins	Around 4	Safe to use
II	Aureocin A70[35]	*S. aureus*	*L. monocytogenes*	Milk	16 weeks at 4 ℃	Around 7	No adverse effects noticed
II A	Bacteriocin CAMT2[1]	*B. amyloliquefaciens*	*L. monocytogenes*	Raw Meat products	100 ℃	2-10	No adverse effects noticed
II A	Pediocin PA-1[30,35]	*Pediococcus spp.*	*S. aureus, E. coli and Pseudomonas*	Dried, fermented meats	121 ℃ for 20 mins	2-10	No adverse effects noticed
II A	Leucocin A[18,35]	*Leuconostoc gelidum*	*Lactic acid bacteria, L. monocytogenes*	Meat products	100 ℃ for 20 mins	2-5	No adverse effects noticed
III	Enterocin AS-48[6,33]	*Enterococcus faecalis S-48*	*S. aureus, L. monocytogenes*	Dairy products	65 ℃ for 5 mins	4-9	Tested safe up to a concentration of 200 µg/ml

Studies done by Arias et al[2] demonstrate the structural activity of these antimicrobial peptides, their results indicate that the activity of bacteriocins increased with the inclusion of arginine and its derivatives whilst Lysine concurrently decreased the activity of the whole peptide. Moreover, they indicate that a reduction in side-chain length for lysine shows an increased stability towards proteolytic degradation[2]. Backbone cyclization has shown promising results in this aspect of development. Adding a disulphide bond between the two cysteines or an amide bond between the N and C terminals confers stability against the protease degradation of bacteriocins.

Given the success of this approach in trials on the eradication of *Pseudomonas aeruginosa* with the aid of D-enantiomers of antimicrobial peptides, synthesizing D-enantiomer versions of the current crop of peptides is a prospective remedy[11]. This might be due to the relative abundance of L-peptides in nature as opposed to D-peptides. Experimentation on modification efficacy illustrates that the modifications made at sites 2-4 residues away from the cleavage site hinder protease cleavage the most. Tests by Werner et al[53] have gauged D-alpha residue modification to be the most protective followed by C-alpha methyl alpha residue modification and N-methyl alpha modification.

Nanotechnology-based formulations and applications lead the foray with advancements like nanoliposomal encapsulation, chitosan nanoparticles, and polymeric nanofibres. They have been proven to increase both the stability and spectrum of activity of bacteriocins upon application. Phytoglycogen-encapsulated nisin has been tested against *L. monocytogenes* with positive results whilst solid lipid nanoparticles of nisin show a marked increase in active life against *L. monocytogenes* and *S. aureus*[12]. Fluorination is not a suitable method of stabilizing the peptides, as it depends upon numerous factors such as protease cleavage site, nature of the adjacent group, location of substitution concerning the enzymatic cleavage site, and inherent hydrophobicity of respective bacteriocin. Once these factors are further illuminated, fluorination can be considered as a solid measure against protease degradation[52].

Advances in bacteriocin target spectrum and potency improvement

Bacteriocin development concerning spectrum improvement and increased potency have witnessed numerous approaches to remediation. From mutagenesis to nanotechnology and combinatorial implementation to the isolation of new strains, there have been several breakthroughs in the field. Site saturation mutagenesis of nisin A is one such example that yielded several nisin variants which displayed enhanced antimicrobial activity towards strains like *E. coli*, *Salmonella enterica* along with other Gram-positive and negative species. The serine to glycine substitution at the 29th amino acid demonstrated by Field et al[13] yielded three S29 variants. Similar experiments by Sun et al[48] demonstrated that site-specific mutagenesis in the 29th position of Pediocin PA-1 yielded enhanced anti-microbial activity in the resulting mutants.

According to conventional reasoning, combining several bacteriocins will result in a more comprehensive strategy for food preservation since each bacteriocin has a distinct mode of action and targets a range of pathogenic microorganisms. By co-expressing leucocin C and nisin Z, Fu et al[14] were able to successfully protect pasteurized milk from *Listeria monocytogenes*[14]. Combinatorial research with the bacteriocins nisin, pediocin 34, and enterocin FH99 demonstrated that the antibacterial impact increased noticeably when the bacteriocins were used together[25]. Nanotechnology has been implemented in the pursuit of improved potency with relative success. Recently, avicin was observed displaying greater anti-bacterial activity when paired with layered double hydroxide nanoparticles against *Lactobacillus sakei LMGT 2313*[12].

Similar studies conducted on button mushrooms demonstrated the beneficial effects of pairing nano-silica, nisin and chitosan in anti-microbial food packaging thus illustrating the possible improvements towards increasing potency and spectrum of action in bacteriocins[42]. New broad-spectrum bacteriocins are being isolated and identified with positive implications for food preservation. For example, a broad-spectrum novel bacteriocin BM1122 was isolated from *Lactobacillus crustorum MN047* by Lu et al[29] in 2020. It displayed antimicrobial activity in a wide range of pH and temperature[29]. Another broad-spectrum bacteriocin was discovered in yak yogurt "LP 21-2" which displayed broad-spectrum anti-microbial activity against *S. aureus, S. typhi,* and even *S. cerevisiae* when tested[37].

Advances in reducing production costs and increasing efficiency

As bacteriocin-producing LAB needs complex nutrition to grow properly, the cost increases as does the difficulty of purification[21]. Medium optimization is necessary as large-scale production of bacteriocins usually employs complex, expensive media. One of the hardest issues to overcome is the feasibility of scaling up production for industrial use[15]. There have been various efforts to produce media for bacteriocin growth from cheaper sources. One example is the work done by Metsoviti et al[31] who showed that adequate amounts of bacteriocins can be produced by using waste molasses as a source of carbon.

Another study tried replacing expensive components in MRS medium (peptone, Y.E, dextrose) with cheaper alternatives (red lentil, molasses, and baker's yeast). The medium with these cheaper alternatives was found to be useful for the production of bacteriocins[51]. For low-cost nisin production, Kaktcham et al[22] isolated LAB from freshwater fish and showed that fish processing by-products supplemented with molasses work as a medium for the production of nisin. Another factor is centrifugation, which at the industrial scale, bottlenecks the purification process of

nisin Z, and hence various protocols have been devised for large-scale bacteriocin purification, skipping the centrifugation step[15].

By using the hydrophobic and cationic behavior of bacteriocins, they can be isolated through a process called expanded bed absorption[5]. This process is faster and reduces many purification steps which increase productivity which in turn reduces operating costs and thus, is ideal for large-scale purification processes. Another interesting study was done by Jawan et al[21] to improve medium composition for the production of Bacteriocin Inhibitory Substances (BLIS) by modeling the medium optimization process using Response Surface Methodology (RSM) and Artificial Neural Network (ANN).

Lactococcus lactis GH1 produces BLIS which has antibacterial action against *Listeria monocytogenes*. The study found that BLIS production was 1.4 times higher in optimized media than in nonoptimized and ANN and RSM were concluded to be effective and adaptable approaches for modeling complicated bioprocesses.

Advances against bacteriocin resistance

All of the observed instances of bacteriocin resistance came from *in vitro* studies. The potential extent of *in vivo* resistance development is unknown at this time[17]. According to research by Inglis et al,[20] the environment that bacteria are exposed to will determine whether they develop resistance. In bacteria exhibiting resistance, changes to cell surface receptors or intracellular targets have been observed[49]. Bacteriocin degradation can also cause resistance; certain bacteria, such as Bacillus spp., produce an enzyme called nisinase which degrades nisin. The mechanisms of acquisition of bacteriocin resistance are complex and even among the same species, different mechanisms have been observed[10]. The chances of resistance developing could be reduced as bacteriocins usually act fast[7].

A possible way of dealing with the risk of resistance arising is to pair bacteriocins with other antimicrobials like in the study done which showed that to inhibit the growth of *L. monocytogenes* that grow on meat products, a mixture of nisin and thyme essential oil is effective[45]. Irradiation is another method to improve bacteriocin efficiency as shown in the studies where the susceptibility of *L. monocytogenes* to irradiation was increased by encapsulated nisin, oregano, and cinnamon essential oil[49].

Bacteriocins can be designed to become more efficient and improve their functions with bioengineering as unlike antibiotics. Amino acids in their structure can be mutated to better target pathogens[27]. Also, unlike other antimicrobials which generally inhibit enzymes, bacteriocins cause cell apoptosis by targeting the membranes of the cells, thus it can be said that the evolution of cross-resistance to antimicrobials that have different modes of action is unlikely[50]. Even so, to use bacteriocin products in a clinical environment, caution must be exercised no matter how unlikely resistance is.

Conclusion

Despite being first identified nearly one hundred years ago, nisin remains the only bacteriocin widely used worldwide. Bacteriocins have shown ubiquitous use in various industries for their preservative and antimicrobial properties, yet they are severely underutilized today. While bacteriocins do face certain problems that hinder their large-scale application, they are not obstacles that the food sector cannot mitigate. The consumers of today wish for less processed foods, and chemical preservatives and opt for more natural options. Bacteriocins can fill this market niche. Their use as an additive in bio packaging could be particularly useful.

With great strides in biotechnology and advances in nanotechnology, many of the stability and efficiency-related issues can be addressed. Bacteriocins hold great potential in the future of preservation and food packaging. Interestingly, incorporating bacteriocins into food packaging materials can assist in improving food safety and expanding the lifespan of perishable foods. Bacteriocins could be used in food packaging depending on many aspects including compatibility with packaging materials to maintain their durability and efficiency. They should not disrupt the packaging's integrity or interact negatively with it. To ensure their efficacy, bacteriocins must be released from the packing material under controlled conditions.

The release mechanism must be created to deliver a gradual release of bacteriocins that is both regulated and sustained. They can target particular bacterial strains or species with their targeted antibacterial effects. The choice of bacteriocins should be based on the specific food products and the pathogens or spoilage microorganisms which are of concern. It should be subjected to regulatory approvals and safety assessments to evaluate the safety and efficacy of new food packaging technologies before their commercial usage. A new generation of bio packaging might emerge when this field attracts investors and is effectively promoted by consumers.

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