Review Paper:

A review on bacteriocin nanoconjugate for effective delivery system

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Abstract

There are certain restrictions that create limitations on the function of bacteriocins like efficacy, sensitivity to proteolytic enzymes and target delivery. These problems are overcome by the interaction of bacteriocins with nanoparticles. Nanoparticles are ultra-fine materials used as a potential drug delivery system that protects bacteriocins from degradation and enhances their antimicrobial activity and stability. It also improves bacteriocins physicochemical properties and specifies target delivery to prevent undesirable interactions.

This interaction has emerged as a promising source that expands the bacteriocin uses in the field of medicines and food safety. Several established nanotechnological approaches are used for the interaction of bacteriocins with organic and inorganic nanoparticles. This review enlightens the hurdles regarding bacteriocin utility and clearing these limitations by the use of different nanotechnological practices like incorporation, encapsulation andconjugation and also the production of bacteriocin via internalization of nanoparticles into antimicrobial peptides producing bacteria.

Keywords: Bacteriocins, Nanoparticles, Drug delivery system, Antimicrobial activity, Interaction of bacteriocins, Nanotechnological.

Introduction

Bacteriocins are a ribosomally synthesized heterogeneous group of peptides exhibiting antibacterial activity against different bacteria. It involves peptides of different molecular weight, amino acid sequences, modified or unmodified and action mechanism. They are recognized as a bio preservative, alternative to various chemical preservatives and have promising application in the field of food technology. In the biomedical sector, it plays a role as a potential drug candidate, which is used to treat pathogenic bacteria to maintain human health and used in cancer therapy.

Despite of its advantages, bacteriocins have some limitations to their applications including the phenomenon of bacteriocin resistance, dosage quantity according to specific pathogenic bacteria, poor yielding by ineffective purification methods, loss of activity, low bioavailability, undesirable interactions, low permeability across barriers, sensitive to digestive enzymes, high cost of commercial production, poor integration andsometimes observed to eliminate only narrow-spectrum bacteria[4,9,43].

The most efficient strategy to overcome these problems is through the use of nanotechnology as nanoparticles itself have antimicrobial properties[18]. Nano techniques protect bacteriocin from undesirable *in vivo* and *ex-situ* interactions by delivering the peptide to specific tissue and infected sites, therefore reducing the high dosage requirements. Nanomaterials have proven to be promising redesigns of the traditional drug delivery system because of their bacterial resistance properties[4,54]. Interaction of bioactive compounds with nanostructures opens up doors to many prospects and opportunities to improve and maximise antimicrobial activity and other properties of bacterial peptides, also solve problems regarding their limitations like bioavailability, undesirable interactions andlow permeability across barriers[34,53.]

The research on nanoparticles has been reaching noticeable importance in biology, food, medicine andelectronics fields, because of their high surface to volume ratios and quantum confinement, their unique size and shape-dependent physical, chemical andbiological properties. All these characteristics of nanoparticles make them suitable for various biomedical applications in drug targeting, drug delivery, cell imaging, labelling experiments, cancer therapy, biofilm inhibition andbiosensors[42]. As a potential antimicrobial agent and targeted drug delivery system, it improves the uptake of poorly soluble drugs and delivers to the targeted site of disease and protects antimicrobial peptides from degrading proteolytic enzymes[9,46].

The nanoparticle is a medium to enhance the inhibitory action of bacteriocins and binds with the bacterial cell surface that unsettles essential cell functions and various structural changes leading to cell death[53]. Nanoparticles target various cellular pathways by affecting the protein and enzyme activation gene expression, cell membrane permeability andoxidative stress. It becomes difficult for the bacteria to resist nanoparticles because of its repetitive use[44]. Nanoparticles have increased applications as ingredients in the food industry due to their particular physicochemical properties and functional attributes and used to develop as a particle-based system for a variety of purposes.

The integration of nanoparticles and natural antimicrobial compounds provides a possible application by inhibiting

food borne and multidrug resistance pathogens to battle against infectious diseases and also proved to be more potent in possibly lower doses due to the broad antibacterial spectrum[3]. There are various methods used for nanoparticle synthesis; most of them are hazardous for the environment. Eco-friendly green synthesis of nanoparticles is also gaining a lot of attention in various fields by using various bacteria, yeasts, fungi andplants[47].

Several approaches have been used to integrate bacteriocin with nanoparticles including 1) production of bacteriocin via internalization of nanoparticles into antimicrobial peptides producing bacteria[25], 2) conjugation of bacteriocins with organic and inorganic nanoparticles, 3) encapsulation of bacteriocin in nanoliposomes[18] and4) incorporation with polymeric nanofibers[12].

The internalization of bacteriocin into nanoparticles has been approached by several methods like nanoprecipitation[10] and synthesis of bacteriocins by treating the bacteriocin producing microbes with nanoparticles[25]. Bacteriocin loaded nanoparticles are also prepared by using ionic interaction[24] and hot, high-pressure homogenization[36]. Various types of bacteriocins formulation using nanotechnological approaches are listed in table 1.

Methods of nanoconjugate formation with bacteriocins

Conjugation of bacteriocins with organic and inorganic nanoparticles: In recent years, metallic nanoparticles (gold, silver, palladium, copper andzinc) and organic materials (chitosan, carrageenan andalginate) are served as potential nanocarriers for antimicrobial peptides. Chitosan is an organic substrate produced by the deacetylation of chitin (second most abundant natural biopolymer on earth isolated from crustacean shells)[33] consisting of copolymers of glucosamine and N-acetyl-glucosamine[22] that serves both structural and storage functions in food, biomedical andenvironmental areas[19.]

It is a naturally occurring cationic biopolymer with characteristics of antimicrobial, biocompatible, biodegradable, non-toxic andbio adhesion[1]. Due to its colloidal size and distinct characteristics, it has the ability to deliver antimicrobial agents and drugs to their target destination[51].

A report by Namasivayam et al[32] by the use of ionic gelation method, chitosan nanoparticles were incorporated into bacteriocins. Chitosan and bacteriocin cultures were suspended into 1% acetic acid followed by stirring and drop wise addition of sodium triphosphate (TPP).

Table 1
Bacteriocins formulation using nanotechnological approaches[4,18]

Bacteriocin	Nanotechnological approaches	Fabrication method
Nisin	Phosphatidylcholine nanoliposomes	Reversed-phase and hydration film methods
Nisin, Nisin A	Phosphatidylcholine nanoliposomes	Thin-film hydration method
Nisin	Solid lipid nanoparticles (SLN)	High pressure homogenization
Pediocin	Phosphatidylcholine nanoliposomes	Thin-film hydration method with bath-type sonicator
Plantaricin 423	Nanofiber scaffolds	Electrospining process
Plantaricin 423 and bacteriocin ST4SA	Nanofibers electrospining	Electrospining
Antimicrobial peptide P34	Nanoliposomes	Thin-film hydration method
Nisin	Chitosan /carageenan nanocapsules	Ionic complexation method
Nisin	Tri polymeric nanoformulation prepared from chitosan, sodium alginate and pluronic F68	Ionotropic pre-gelationmethod followedby polycationic crosslinking
Nisin	Nanofibers	Electrospinning process
Enterocin	Silver nanoparticles	Silver particles capped with bacteriocins
Nisin	Carbohydrate-based nanoparticles	Bacteriocin-stabilizing carbohydrate emulsion

After centrifugation, chitosan-bacteriocin conjugates are settled as pellets and used for lyophilization. Entrapment efficiency (%) =

$$\frac{\text{Total bacteriocin - Bacteriocin in supernatant}}{\text{Total bacteriocin}} \text{ X } 100$$

In vitro release of bacteriocins from nanoparticles studied by continuous dialysis bag method and minimum inhibitory concentration (MIC) of the nanoformulation against the *Listeria monocytogenes*, was determined by a turbidimetric method. Nanoformulation with bacteriocins is characterized to determine particle size by Scanning electron microscopy (SEM) and Transmission electron microscope (TEM)[32]. In another study, to protect and deliver nisin has been done by using food-grade biopolymers for encapsulating. Chitosan-based microcapsules can be prepared by methods like emulsion-precipitation, crosslinking, emulsion-precipitation, precipitation- coacervation.

The preparation of chitosan-nisin microcapsules was optimized by the response surface methodology (RSM). RSM is a statistical method to obtain certain data, multivariate quadratic regression equation to fit a function of factors, a response between the values, making out the optimal process parameters analysis through the regression equation[17]. Chitosan (0.1%- 0.5%, W/V) was dissolved in 1% acetic acid. Stock powder of nisin was diluted in 1% acetic acid (with the ratio of chitosan: nisin= 1:1, 3: 1, 5:1, W/W) to prepare stock solution of nisin. To prepare CS-nisin particles, precipitant salt solution (sodium sulfate or trisodium citrate dihydrate) and Tween 80 (1.5%, V/V) was added to CS solution. Centrifuge and freeze dry to collect CS-nisin particles. Inhibitory effect of free chitosan, free nisin and chitosan-nisin microcapsules was detected against *B. subtilis*.

The antimicrobial activity of chitosan combined with nisin was better than that of free chitosan and nisin[22]. Another report signifies the inhibitory activity of the free nisin and the nisin loaded with chitosan/alginate against *Staphylococcus aureus* ATCC 19117 and *Listeria monocytogenes* ATCC 25923[55]. The promising result was highlighted in another study performed by Maresca et al[27] using vibrating technology with high efficiency to develop nisin microcapsules with alginate matrix. Antimicrobial activity of these microcapsules was tested against *Brochothrix thermosphacta* 7R1 at different conditions of pH and temperature. The best antimicrobial performance of microcapsules was shown at pH 6.0 in stirring conditions.

The metal ion acts as a free radical that disrupts the cellular membrane and shows broad-range inhibitory spectrum against pathogens and because of its size and positive charges that allow the large surface area of positively charged nanoparticles binding to the negatively charged pathogen surface[26,40]. The gold nanoparticles show inhibitory properties by attaching to the membrane of the cell that creates damage by causing gaps and pits, structural changes and reduces the activity of respiratory chain enzymes[20]. These nanoparticles are non-toxic compared to other metallic nanoparticles of silver and platinum[5].

The combined effects of antibacterial activity of gold nanoparticles with bacteriocin produced by *Lactobacillus plantarum* strain ATM11 and alone and nisin along with nanoparticles and alone were tested by using an agar well diffusion method against food spoiling organisms such as *Bacillus cereus*, *Escherchia coli*, *Staphylococcus aureus* and*Micrococcus luteus*.

Silver bioconjugate is characterized by using nanoparticle tracking analysis, X-ray diffraction, zeta potential measurement, UV-Vis spectroscopy and transmission electron microscopy.[48] In another report, gold nanoparticle solution with nisin was mixed and incubated at room temperature with constant shaking and centrifuged. The restrictive activity of gold nanoparticles was observed against various pathogenic strains of *S. aureus* and *E. faecalis* by using agar well diffusion assay, minimum bactericidal concentration assay and minimum inhibitory concentration[35].

Silver nanoparticles can enter into the bacterial cell because of their small size and interact with the phosphorous and sulfur-containing molecules leading to cell death by attacking the respiratory chain and cell division. Bacteriocin-capped silver nanoparticles are treated against several food pathogens[29.] In another research, bacteriocin-capped silver nanoparticles were developed by mixing sodium borohydride with silver nitrate and enterocin. Change in the color of the solution from colorless to yellow was observed, which indicates the formation of enterocin-capped silver nanoparticles (En-SNPs), later on, confirmed by FTIR spectroscopy.

En-SNPs were dialyzed through a membrane to remove unbound enterocin and free silver. Tests against *B. cereus* and *L. monocytogenes* showed minimum inhibitory concentrations. En-SNPs were characterized by different physicochemical techniques such as zeta potential, dynamic light scattering (DLS), UV-Vis spectroscopy, infrared spectroscopy and circular dichroism (CD). The morphology of nanoparticles was observed using an atomic force microscope (AFM) and scanning electron microscopy (SEM)[41].

In a recent study, silver bioconjugate was prepared by the conjugation of nisin with nanoparticles. In a recent study, silver bioconjugate was prepared by the conjugation of nisin with nanoparticles. The stock solution of silver nanoparticles was mixed with nisin solution in a dropwise manner, then kept overnight and centrifuged. Unbound nisin molecules were washed out by distilled water. Agar powder and polysorbate 80 were added to form the silver nanoparticles-

bioconjugated film. *In vitro* inhibitory activity of silver and silver-bioconjugate was tested against *P. fluorescens, L. monocytogenes, S. aureus, A. niger andF. moniliforme*. It was observed that the growth inhibition activity of silver-bioconjugate was more than silver nanoparticles and nisin[34].

Encapsulation of bacteriocin in nanoliposomes: Encapsulation in nanoparticles proposes a potential way to protect antimicrobial molecules and also enhances their efficacy and stability[28]. Nanoparticles as a solid colloidal particle contain the active substances and these combinations of both are named nanospheres and nanovesicles (or nanocapsules)[38]. In nanovesicles, the antimicrobial peptide can be dispersed in the core or embedded in the wall. Nanospheres have a matrix-type structure where the drug may be absorbed or entrapped in their surface[9]. Various methods are observed for the encapsulation of peptides in nanostructures including emulsification-polymerization, a combination of sonication, solvent evaporation, salting out, layer-by-layer technology, interfacial polymerization, surface-functionalized particles andcoacervation[50]. Nanovesicle encapsulation protects antimicrobial peptide against degradation or interaction with undesirable compounds resulting in its enhanced therapeutic activity and improved stability[9].

Lipid-based nanoparticles are used in food industries because of their ability to encapsulate both hydrophilic and lipophilic compounds, targetability and adaptability with most of the food products without any undesirable effects[39]; its nanoencapsulation systems include solid lipid nanoparticles, nano-emulsions, nanostructured lipid carriers, nano-liposomes and lipid-based nano-micelles[52]. Liposomes are spherical colloidal structures composed of single or multiple phospholipid bilayer membranes having an internal aqueous pool with a size ranging from nanometer to micrometer[9,18] and employed in the entrapment, transport and release of water-soluble, lipid-soluble and amphiphilic materials due to the presence of both aqueous and lipid phases[30.]

Production of nano-liposomes requires more energy than the formation of liposomes. Nano-liposomes are produced by several methods like microfluidization, sonication andextrusion[6]. There are two methods used to encapsulate antimicrobial molecules into lipid nanovesicles - thin-film hydration method and the reversed-phase method[9]. In the thin-film hydration method, the hydration of preformed lipid film with an aqueous buffer containing the antimicrobial molecules is done. Peptide encapsulated in heterogeneous multilamellar vesicles further processed (energy input, heating, membrane extrusion and sonication), resulting in small unilamellar vesicles of uniform size[23].

Reverse phase method is performed by mixing the lipid solution with an antimicrobial peptide aqueous solution to form water in oil emulsion, further, sonication is done to yield homogeneous opalescent dispersion of reverse micelles, it results in a highly viscous organogel after evaporation and reverted to nanovesicles by adding ultrapure water. After exposition to Maillard reaction, bacteriocin like substance P34 encapsulated in phosphatidylcholine nanovesicles which showed higher residual activity compared to the free peptide.

The lipid layer enhances the antimicrobial activity, provides protection and controls the release of nisin. Phosphatidylcholine nanovesicles were loaded with bacteriocin-like substances from *Bacillus licheniformis* P40 restrict *Listeria monocytogenes*[47.] In brain heart infusion (BHI) agar, the nisin-loaded nano-liposome significantly shows enhanced antibacterial activity in comparison with free nisin against two main foodborne pathogens *Staphylococcus aureus* and *Listeria monocytogenes*[56].

In another study, nisin was encapsulated into phosphatidylcholine showing strong inhibitory activity against *Listeria monocytogenes*[8]. Solid lipid nanoparticles (SLNs) are consisting of a phospholipid coat and a triglyceride core. Phospholipid coat has a high melting point which is responsible for keeping them in a solid-state at different temperatures[37]. SLNs have advantages of incorporating drugs for controlled drug release, the low cytotoxicity due to its composition of physiological compounds and the possibility for loading both lipophilic and hydrophilic drugs into the solid matrix.

In a study, the production of nisin-loaded solid lipid nanoparticles was done by hot high-pressure homogenization. *In vitro* release of nisin from SLNs was observed throughout the 25 days. The increase in pH of buffer (from 2.0 to 7.4) and the salt concentration (up to 0.5 M sodium chloride) decreased the release rate. Nisin loaded SLNs show inhibitory activity for up to15 days against *Lactobacillus plantarum* TISTR 850 and up to 20 days against *Listeria monocytogenes* DMST 2871, whether free nisin only for one and three days[31].

An experiment was done by Prombutara et al[36] on solid lipid nanoparticles; nisin powder with different concentration (0.5%, 1.0%, 2.0% and 3.0% (w/w)) was solubilized in different melted solid lipid at 80^{o}C. The lipid phase of the solid lipid was melted down and assorted with the aqueous surfactant solution containing 2.5% or 5.0% (w/v) poloxamer 188 and 0.125% (w/v) sodium deoxycholate, resulting in a pre-emulsion. Homogenization at melting and recrystallization at cooling temperature was done[36].

Incorporation with polymeric nanofibers: Nanofibers are biopolymer-based encapsulation systems, treated in a specific manner to form filaments of nanometers in diameter. Electrospinning is the easiest and cost-effective method to produce large amounts of nanofibers with the requirement of a high voltage supplier, a capillary tube, a feeding pump and a collecting screen of metal[6]. Potential uses of electrospun nanoparticles are in biomedical

applications for development of tissue engineering scaffolds, drug delivery system for antimicrobial peptides for use as wound dressings and enhance the immobilization of hydrophilic and charged macromolecules[9]. Nanofibers have high encapsulation efficiency, large surface area and providing high stability for sensitive compounds[16].

In the process of electrospinning, a combination of polymers and the bacteriocin is dissolved in a solvent and injected into a capillary tip. A high voltage is applied on solution of polymer and bacteriocin and starts deformation through surface tension because of inducing surface charge of liquid solution. When the applied current exceeds the charge of the solution, a Taylor cone forms and the bacteriocin-loaded polymer propels from the tip[4]. Polymers nanofibers are collected in nano- to micro-meter diameters by a metal screen collector loaded with bacteriocin.

In a recent study, encapsulated plantaricin 423 was shown efficacy for up to 6 days against a common nosocomial infection, *Enterococcus faecium* HKLHS, following wound dressing[21]. Another study acknowledged that nanofibers prevent the interaction of nisin with other food components so that its antimicrobial activity enhanced against *L. mesenteroides*[45].

Other methods to prepare nisin nanoparticles: A recent study focused on the preparation of nisin nanoparticles by the nanoprecipitation method. Nisin was dissolved in a hydrochloric acid aqueous solution, distilled water was added dropwise to solution and stirred. Nisin nanoparticles were prepared, freeze-dried and examined for the proper temperature and pH in the antibacterial activity.

The morphology of nisin nanoparticles was determined by transmission electron microscopy (TEM). Inhibitory activity of the free nisin and the nisin nanoparticles was examined against the growth of gram-positive bacteria *S. aureus*. As a result, nisin nanoparticles showed higher antibacterial spectrum than free nisin[10].

In another study, nisin nanoparticles were developed using a double emulsification method followed by solvent evaporation for vaginal candidiasis treatment. The emulsion was prepared by dripping aqueous solution of nisin onto a dichloromethane poly-e-caprolactone solution under magnetic stirring, 100% amplitude of ultrasound probe sonication and ice bath. The primary emulsion was transferred onto polyvinyl alcohol aqueous solution.

After sonication and solvent rotary evaporation under reduced pressure, the nisin-nanoparticles suspension was obtained, then centrifuged to collect nanoparticles and washed three times for the removal of non-encapsulated material. The supernatant was preserved for nisin loading efficiency assay, while pellets having nanoparticles were dispersed into purified water. Blank nanoparticles were prepared without nisin under the same conditions[13].

$$\text{Process Yield \%} = \frac{\text{Mass of nanoparticles after lyophilisation (mg)} \times 100}{\text{Mass of nisin (mg)} + \text{Mass of poly-ε-caprolactone (mg)}}$$

Production of bacteriocin via internalization of nanoparticles into antimicrobial peptides producing bacteria: Recently another study was done that describes bacteriocin production by the internalization of nanoparticles into probiotics. Pediocin, a bacteriocin, was produced by the internalization of phthalyl dextran nanoparticles into probiotics, *Pediococcus acidilactici* KCTC 21,088. Production of pediocin was done by using Bradford assays, RT-PCR and pediocin activity assays. Produced pediocin with the enhanced antimicrobial property was tested against the *Listeria monocytogenes*, a gram-positive pathogen and*Salmonella gallinarum*, a gram-negative pathogen, *Escherichia coli* K88, *Escherichia coli* O157: H7[25].

Purification of nanoparticles-bacteriocin conjugates: Unbound metal and bacteriocins are removed by the dialysis of suspension into water[43]. Chitosan nanoparticles - bacteriocin was dispersed in water and moved into dialysis bag to dialyze against physiological saline, then regulated by a thermostat at 37°C and mechanically stirred at 75rpm. After some intervals, portion of the dialysis medium was taken for quantitation of flutamide and was syringe filtered and spectrometrically read at 291nm[32]. The chitosan- nisin particles were added into 0.02 M phosphate buffer and stirred and then, ultrasound and maintained under shaking at 150 rpm for 20min at room temperature. After a while, the supernatant was filtered with a membrane[22]. Centrifugation at 2,500 g for 10 min at 4C was done to separate the nisin loaded nanoparticles from free polymers[55].

The prepared enterocin-silver nanoparticles were transferred to dialysis through a 10-kDa membrane overnight to remove unbound enterocin and free silver[41]. The prepared small unicellular vesicles were allowed to stand at room temperature and centrifuged at 1000 *g* for 15 min to remove foreign particles followed by extrusion through polycarbonate membrane with 100 nm pore diameter. The nisin-loaded liposomes were collected by centrifuging 1500 *g* for 1 h at 25 ◦C[56]. By the use of electrospinning, process nano-fibers loaded with nisin are produced and collected in a metal collecting screen[6]. After solvent rotary evaporation, the nisin-nanoparticles suspension was obtained under reduced pressure and centrifuged at 20,000 rpm for 1h, then washed three times to remove non-encapsulated material[13].

Applications of bacteriocin based nanoparticles: The integration of nanoparticles and bacteriocin solves the problems belonging to the limitations of bacteriocins and has attracted much attention for their applications in the food, biomedical and environmental fields. This integration is useful for effective and targeted delivery, protection from degradation, rise in the antimicrobial activity, improving drug potency and physicochemical properties[18].

In food industries, bacteriocins-nano conjugation is used as bio preservatives that protect from degradation by proteolytic enzymes, resulting in a stable and increased shelf life of food. The development of antimicrobial packaging films is indirect food additive that acts as another line of defense against food contamination, which increases the antimicrobial spectrum of bacteriocins and the shelf life of food without causing any alteration of food components[43]. These films release antimicrobial agents, for surface inactivation, improve food protection and inhibit the growth of *Listeria monocytogenes*, *Listeria innocua* and other foodborne spoilage pathogens for extended periods. Bacteriocins used are nisin, lactocin 705, lactocin AL705 andenterocin 416K1[4].

Live cultures of lactic acid bacteria competitively inhibit the growth of *Saccharomyces cerevisiae* in the gut or vaginal environment and assist in the re-establishment of host microorganisms[14]. In the aquaculture field, prophylactic spraying with bacteriocinogenic dry spray inhibits the growth of *Listeria monocytogenes*[7]. There are some applications of nanoformulation in healthcare industries, drug delivery nanotechnologies improve the pharmacokinetics of bacteriocins by increasing bioavailability, drug potency and enhance inhibitory actions[18]. This integration can act as synergists or alternatives to modern antibiotics that enhance the therapeutic effects of resistant strains. Nanoparticles diffuse through or into the cell membrane to cause leakage, used to treat oral, gastrointestinal and cardiovascular diseases and are the potential alternative for vaginal candidiasis treatment[13].

Nanoformulations show activity against tumor cells, so it can be used in cancer therapy. Bacteriocin-capped nanoparticles reduce overall cell toxicity; reduce red blood cell lysis, the formation of biofilms and dental plaque for prolonged periods[41]. Electrospun nanofibers loaded with bacteriocins are used for novel wound dressing formulations[49]. Bacteriocin coating of medical devices can prevent bacterial colonization and reduce the prevalence of catheter infections.[2] Silver nanoparticles are used in the food industry for the fabrication of food containers, storage bags, refrigerator surfaces and chopping boards[11].

In the clinical field, it is used as an anti-inflammatory agent and wound healer, also used to coat medical instruments to exhibit antimicrobial activity against a range of bacterial species like *Klebsiella pneumoniae*, *Bacillus anthracis*, *Bacillus subtilis*, *Staphylococcus aureus* and *Acinetobacter baylyi*[15].

Conclusion

Bacteriocins are antimicrobial peptides used as antibiotic alternatives or synergists to eliminate multidrug-resistant pathogens. But due to some of its limitations and problems regarding bioavailability, degradability and drug targeting, the exploitation of bacteriocin is moving forward less rapidly.

The development of a novel drug delivery system enhances the efficacy of bacteriocins. Nanoformulations are promising techniques to intensify the utilization of these antimicrobial compounds. Several examples are present that show bacteriocins and nanoparticles integration with enhanced spectrum of inhibitory activities and better stability against degradation in comparison with the free ones. At the industry-scale level, the interaction between nanoparticles and bactericidal peptides provides a compelling possibility by enhancing the antimicrobial activities of bacteriocins against various pathogens.

Future perspectives

A nanotechnological approach used to enhance bacteriocin capabilities has some limitations. There are needs of more examination that are required to elucidate clearly about the nature of conjugation between these peptides and nanoparticles, or their interaction with microorganisms in order to address the bacteriocin limitations. There is an interruption between the *in vitro* and *in vivo* efficacy of bacteriocin. *In vitro* studies explain that some bacteriocins are acutely active against various pathogens and for *in vivo* studies higher concentrations are required. More exploration is required to enhance the use and effectiveness of bacteriocin. Better knowledge about these integrations creates advance in the utilzation of bacteriocins towards various areas like food and healthcare industries.

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