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Chandrani Goswami
Department of Veterinary Public Health, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

Himasri Das
Department of Veterinary Microbiology, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

Sophia Makdoh Gogoi
Department of Veterinary Microbiology, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

Nayanmoni Konwar
Department of Veterinary Microbiology, College of Veterinary Sciences and Animal Husbandry, Aizawl, Selesih, Central Agricultural University, Mizoram, India

Durlav Prasad Bora
Department of Veterinary Microbiology, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

Razibuddin Ahmed Hazarika
Department of Veterinary Public Health, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

Corresponding Author
Himasri Das
Department of Veterinary Microbiology, College of Veterinary Science, Khanapara, Guwahati, Assam Agricultural University, Assam, India

A comprehensive review on bacteriocin: Potential applications and nano based delivery systems

Chandrani Goswami, Himasri Das, Sophia Makdoh Gogoi, Nayanmoni Konwar, Durlav Prasad Bora and Razibuddin Ahmed Hazarika

Abstract
Bacteriocins are ribosomally synthesised group of antimicrobial peptides synthesised by almost all groups of bacteria and demonstrates bactericidal or bacteriostatic activity, usually against members of closely related species and different strains of similar species. Bacteriocin has gained much attention worldwide over the last decade especially for their advantages in regards to physical stability and non-toxicity. Various bacteriocins have been reported to act as promising food preservatives or in the health industry as antimicrobial agents or bio-controlling agents and as so as for fight against antimicrobial drug resistance. They are also being exploited for their anticancer properties as a new tool in fighting cancer. Bacteriocins also plays a major role in food industry by safeguarding public health and food safety as they found their utility in chemical free preservation, enhancing shelf-life, and as well as inhibition of food-borne pathogenic microorganisms from farm till food-processing stages. Nanotechnology has proven to be effective drug delivery system and so as so as to avoid any existing limitation of bacteriocins. With the increasing bacterial resistance, the evolution of nanotechnology has proven to be an effective upgrade of traditional drug delivery systems. The incorporation of bacteriocins into nanoparticles and site-directed delivery to areas of infection may soon become an effective method of treatment.

Keywords: bacteriocins, antimicrobial peptides, nanotechnology, delivery system, therapeutics

Introduction
Bacteriocins are ribosomally synthesised group of antimicrobial peptides synthesised by almost all groups of bacteria and demonstrates bactericidal or bacteriostatic activity, usually against members of closely related species and different strains of similar species (Castellano *et al*., 2012; El-Gendy *et al*., 2012) [1, 2]. Gratia in the year 1925 discovered the first ever bacteriocin from *Escherichia coli* (Gratia, 2000) [3]. Bacteriocin-producing bacteria have been recognised from a wide group of bacterial strains, they possess a competitive survival advantage over other prokaryotes in the biological niche (Preciado *et al*., 2016) [4]. Multidrug and even pan drug resistant strains of both gram-positive and gram-negative bacteria have been frequently encountered in hospital settings against the most influential antibiotics. The most dangerous being methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococci* (VRE) which continues to increase the morbidity and mortality rates (Simons *et al*., 2020) [5]. Many bacteriocins from bacteria showed antimicrobial efficacy against human as well as animal microbial pathogens including MRSA and VRE without showing toxicity (Xia *et al*., 2013) [16] (Calfee, 2012) [7] and thus helping to fill some gaps in the medical sector. Emergence of multi drug resistant drug which has become one of the major global health-concern and the need of hour requires investigation and screening of natural novel compounds like bacteriocins with potent killing mechanisms in order to assist and replace the existing antibiotics and against which bacteria won't develop resistance easily. Various bacteriocins have also been reported to act as promising food preservatives (Papagianni, 2003) [8] or in the health industry as antimicrobial agents or bio-controlling agents (Van Heel *et al*., 2011; van Staden *et al*., 2012) [9, 10]. They are also being exploited for their anticancer properties as a new tool in fighting cancer (Riaz *et al*., 2020) [11]. However, in spite of many potential applications of bacteriocins, nisin is the only bacteriocin to get the generally recognized as safe (GRAS) status by the Food and Drug Administration and is presently used as a food preservative in various countries (Delves-Broughton, 1996) [12]. Researches are still under process to enhance the efficacy of bacteriocin and so as to avoid any existing limitation, the use of nanotechnology is a novel approach to maximize the output of these peptides

(Fahim *et al*., 2016) [13]. This review aims to discuss the potential applications of bacteriocins in the field of antimicrobial therapeutics including classification and mode of action along with utilisation of nanotechnology in enhancing the antimicrobial efficacy of bacteriocins

Bacteriocin Classification

Several approaches have been taken to classify bacteriocins. The first bacteriocin classification system was proposed by Klaen hammer in 1993 (Zou *et al*., 2018; Klaenhammer, 1993) [14, 15]. Bacteriocins were initially classified into four classes (Rea *et al*., 2011) [16]. However, the fourth class of bacteriocins, consisting of large complexes with carbohydrate or lipid moieties, has been aborted and were named as bacteriolysins (Güllüce *et al*., 2013) [17]. Thus, bacteriocins are classified mainly into three classes (Liu *et al*., 2014) [8].

Class I bacteriocins (composed of 19–50 amino acids) are extensively post-translationally modified results in the formation of unusual amino acids, such as lanthionine, methyllanthionine, dehydrobutyrine, dehydroalanine, and labionin. They target the skeleton of the cell wall of pathogens, particularly Gram-positive bacteria and also are heat-stable (González-Martínez, 2003). Class I is further subdivided into Lantibiotics (Class Ia), these peptides are positively-charged elongated bacteriocins that kill bacteria by pore formation. The prototype antibiotic nisin is a member of this group (Le Lay *et al*., 2016) [20], few other bacteriocins of this class includes lanthionine and/or beta-methyllanthionine. Labyrintopeptins (Class Ib), bacteriocins, includes lacticin 481, cytolysin and salivaricin, which are characteristically globular, inflexible, with a negative charge or with no net charge. They inhibit various catalytic enzymes required to complete the life-supporting processes of susceptible bacteria (Deegan *et al*., 2006) [21] and Sactibiotics (Class Ic), bacteriocins that contain cysteine sulphur to α-carbon linkages (Mathur *et al*., 2015) [22].

Class II contains small (less than 10 kDa) in size and they exhibited moderate (100 °C) to high (121 °C) heat stability, non- lantibiotics or non-modified peptides, with isoelectric points (pIs) varying from 8.3 to 10.0. Subclass IIa were comprised of Listeria-active peptides that contain a specific N-terminal sequence (Tyr-Gly-Asn-Gly-Val-Xaa-Cys-), the representative bacteriocins of this group are leucocin A, acidocin A (Radaic *et al*., 2020) [23], mesentericin, pediocin PA-1 and sakacin P (Venema *et al*., 1997) [24]. Class IIb bacteriocins (two-peptide bacteriocins) require at least two different peptides for activity e.g. thermophilin 13, lactococcin G and lactacin F. When associated together, they are reported to show a synergistic effect and the level of bacterial susceptibility changes with that of individual peptides (Nissen-Meyer *et al*., 2009; Perez *et al*., 2018; Perez *et al*., 2014) [25-27]. Class IIc (circular bacteriocins), these are small, heat-stable peptides that are carried by leader peptides. They contain about 58 and 70 amino acids. Their circularised structure conferred by covalent binding between the first and last residues, helps them to be heat resistant (some retain their activity after treatment at 121 °C for 15 min), adopt to pH variation, and untouched by proteolytic digestion (Martínez *et al*., 2016) [28]. Finally, class IId (unmodified, linear, non-pediocin-like bacteriocins) (Oppegård *et al*., 2007; Belguesmia *et al*., 2011) [30] is made out by all bacteriocins that cannot be included in any of the first three classes includes lineal peptides, such as lactococcin A, bacteriocins that do not have a dedicated export system but use the general secretory mechanism of the cell; e.g. lactococcin 972 (Martínez *et al*., 1999) [31] and leaderless bacteriocins, such as lacticin Q, which, significantly, has a formylated methionine as its first residue (Fujita *et al*., 2007) [32].

Class III bacteriocins generally contain large (> 30 kDa) heat-labile peptides and little is known about them e.g. colicin produced by *E. coli*, classified as heat-labile lytic bacteriocins and heat-labile non-lytic bacteriocins (Joerger and Klaenhammer, 1986; Vaughan, *et al*., 1992) [33, 34]. Another bacteriocin of this category, dysgalacticin works by either interfering with either glucose transport or metabolism by binding to the phosphoenolpyruvate-dependent glucose and mannose phosphotransferase transport system (Joerger and Klaenhammer, 1986; Vaughan *et al*., 1992) [33, 34].

Mechanism of Action

Different mechanisms of action have been proposed that differ from those of antibiotics. These mechanisms can be generally divided into those that function primarily at the cell envelope and those that are active primarily within the cell, affecting gene expression and protein production (Cotter *et al*., 2013) [35]. The interaction of many bacteriocins to the plasma membrane depends on their physicochemical and structural properties (Ahmad *et al*., 2017) [36]. Upon interaction with the negatively charged cell envelope, pore-forming positively charged bacteriocins, when in larger concentration in the μM range insert into the plasma membrane. Lipid II which is the key intermediate in the peptidoglycan biosynthesis machinery within the bacterial cell envelope or the membrane components of mannose Phosphotransferase System (Man-PTS) may act as receptors or docking molecules to promote pore formation. Lipid II inhibits the synthesis of peptidoglycan upon binding to the cell wall precursor, which may be combined with pore formation or not. Hydrolysis of the peptidoglycan is accomplished by activation of endogenous autolysins (Martínez *et al*., 2016) [28]. Nisin and several lantibiotics, in addition to some class II bacteriocins, target lipid II (Bierbaum and Sahl, 2009; Martin and Breukink, 2007) [37, 38] causing inhibition of peptidoglycan synthesis, and for some this is the sole mechanism of action. As a docking molecule, lipid II can be used by other lantibiotics to facilitate the formation of pores in the cell membrane, resulting in a loss of membrane potential and, thereby, cell death (Bierbaum and Sahl, 2009; Martin and Breukink, 2007) [37, 38].

Class II (Non-lantibiotics), such as pediocin-like and the one-peptide non-pediocin-like bacteriocins (class IIa and class IId), binds to Man-PTS, these bacteriocins getting into the target cell membrane causes an irreversible opening of an intrinsic channel, which leads to the diffusion of ions through the membrane, causing target cell death (Nissen-Meyer *et al*., 2009; Diep *et al*., 2007; Nes *et al*., 2013) [25, 39, 40]. Class IIb (two-peptide unmodified bacteriocins) works by permeabilising the membrane of sensitive bacteria forming pores. Circular bacteriocins (class IIc) have a positive net charge, they interact directly with the negatively charged bacterial membrane without requiring any receptor molecules leading to pore formation in the cell membrane, causing ions efflux and the dissipation of the membrane potential, leading to cell death (Van Belkum *et al*., 2011; Perez *et al*., 2018) [41, 26].

Bacteriolysins (class IIIa bacteriocins) contribute to cell wall hydrolysis, causing cell lysis (Sun *et al*., 2018; Simmonds *et al*., 1996) [42, 43]. Non bacteriolytic bacteriocins (class IIIb)

exert their action by disrupting the glucose uptake by cells and hence disturbing the membrane potential. Another mechanism is inhibiting the biosynthesis of DNA and proteins of target bacteria (Meade *et al*., 2020; Müller and Radler, 1993; Swe *et al*., 2009) [44-46]. The class III bacteriocin lysostaphin kills Gram-positive *Staphylococcus aureus* through cell wall lysis (Gründling and Schneewind, 2006) [47]. Colicin A exhibits DNA nuclease activity e.g. colicin E2 and can also inhibit biosynthesis of proteins e.g. colicins E3, E5 (Ahmad *et al*., 2017) [36]. Moreover, Gram-negative bacteria like *Yesinia* spp. and *Escherichia coli* are sensitive to a high molecular weight bacteriocin (pesticin) by the mechanism of cell wall degradation through breaking the glycosidic bonds of the cell wall (Ahmad *et al*., 2017) [36]

Bacteriocins Resistance

Bacteriocins are considered encouraging alternatives due to their stability, low toxicity, frequently excellent potency and high specificity. For any antimicrobial under study, it is important to consider the potential emergence of resistant pathogens with respect to clinical applications. Many bacteriocins interact electrostatically with the cell membrane and introduce permeabilisation through interaction with receptor or docking molecules (O'Connor *et al*., 2020) [48]. Bacteriocin resistance in pathogens may be innate, which is intrinsically observed in particular genera/species, or acquired, commonly observed with susceptible strains (Collins *et al*., 2012) [49]. It can also be associated with the pathogenic organisms' ability to produce degradation enzymes or the presence of immunity proteins, while acquired resistance occurs due to horizontal gene transfer or gene mutations that alter the cell membrane, binding receptors or transport systems (de Freire Bastos *et al*., 2015; Dicks *et al*., 2018) [50, 51]. Studies revealed resistance to bacteriocins that have intracellular targets could arise through mutations in the genes encoding the bacteriocin targets (Cotter *et al*., 2013) [35]. Another mechanism called immune mimicry is indicated which is used to describe resistance that occurs in non-bacteriocin-producing strains which possess bacteriocin immunity genes, or immunity as a consequence of producing a closely related bacteriocin (Draper *et al*., 2009). Remarkably, antibiotic and bacteriocin resistance are independent and, consequently, no cross-resistance has been recorded so far (Martínez *et al*., 2016) [28].

Knowledge of a bacteriocins' mode of action (Cotter *et al*., 2013) [35] and how it acquires resistance facilitate the development of methodologies to minimise resistance occurrence (Draper *et al*., 2015) [53]. Strategies successfully used to reduce resistance include combining bacteriocins with other bacteriocins with different modes of action (Dicks *et al*., 2018; Algburi *et al*., 2017; Hols, Ledesma-García *et al*., 2019) [51, 54, 55], other antimicrobials (Perales-Adán *et al*., 2018; Mathur *et al*., 2017) [56, 57], or phages or, generating peptides with increased antimicrobial resistance through bioengineering (Field *et al*., 2019) [58]. These hurdle technology approaches have the added advantages of broadening the antimicrobial spectra while reducing costs and toxicity (Mathur *et al*., 2017) [57]. Pharmacokinetics and pharmacodynamics of drugs are key factors to consider for any *in vivo* therapeutics (Mathur *et al*., 2017) [57].

Potential Applications of Bacteriocins

Food preservative applications of bacteriocins

Bacteriocins with promising potential have gained much interest due to their application in the food industry as natural bio preservatives (Zacharof and Lovitt, 2012) [59]. They can be directly added as purified or partially purified components or incorporated into food during cultivation with the help of bacteriocin-producing bacterial strains (Snyder and Worobo, 2014) [60]. Bacteriocins are reported to be effective against food spoilage microorganism, have minimal effect on human microbiota are resistance to heat, pH and food associated enzymes and are found to be stable in the food substrate in which they are incorporated with no alteration of the organoleptic properties of food, being tasteless, odorless, and colorless; no toxicity to eukaryotic cells and simplicity to scale-up production. (Johnson *et al*., 2018) [61] (Martínez *et al*., 2016) [28]. Nisin is a broad-spectrum Class I lantibiotic, produced by *Lactococcus lactis subsp*. lactis, Nisin was the first antimicrobial agent in reaching the category of food-safe additive in 1969 and most studied bacteriocin and has received the Generally Regarded as Safe (GRAS) designation by the FDA (Cotter *et al*., 2005) [62]. Enterocin AS-48 and enterocin RM6 have been studied for their food preservatives and sanitation efficiency against food pathogens, *Listeria monocytogenes* (Espitia *et al*., 2013) (Barbosa *et al*., 2013). Gassericin A, food preservative from *Lactobacillus gasseri* LA39, reported to be stable for 3 months (4 °C), 2 months (37 °C), 5 hours (60 °C) and 30 minutes (100 °C) (Ahmad *et al*., 2017) [36].

Nisin Z, one of the His27Asn variant of nisin A, have a greater solubility at higher pH and hence finds its applicability in food industry and is also commercially available as, for example, Nisin Z1P ultrapure nisin. By utilising food grade techniques, nisin variants can be bioengineered and thus nisin can be custom designed for specific applications by increasing production, increasing potency against specific targets or enhancing antimicrobial spectrum of inhibition thereby increasing its commercial potential as a food preservative (Field *et al*., 2018) [65].

Hospital-acquired infections

Bacteriocins are playing pivotal role in hospital settings where Multi-Drug Resistant pathogens is most noticeable and many nosocomial infections due to such MDR strains are becoming a worldwide threat to human health. Emergence of antimicrobial resistance against commonly used antibiotics has become a serious issue which requires feasible alternative to antibiotic for the safeguard of human health. Many bacteriocin are being successfully used as probiotic in place of antibiotic and thus boosting our immunity system (Riaz *et al*., 2020) [11]. Bacteriocins have very high specificity unlike antibiotics, and can inhibit pathogens without causing deleterious imbalances to the host microbiota (O'Connor *et al*., 2020) [48]. The main disease-causing pathogens in hospital settings are *Staphylococcus aureus, Enterococci, Pneumococci, Acinetobacter baumannii, Citrobacter freundii, Escherichia coli, Klebsiella pneumoniae and Proteus* spp. (Ghodhbane *et al*., 2015; Michalet *et al*., 2007) [66, 67]. Reports suggests Nisin and lacticin 3147 shows efficacy against various pathogens in the liver, spleen and kidneys and similarly also found to be effective against Methicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant enterococci (VRE) (Piper *et al*., 2009) [68].

Respiratory tract infections

Major pathogens of respiratory tract include *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,*

Enterobacteriaceae, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Neisseria meningitidis*, *Pasteurella multocida* and *Mycobacterium tuberculosis* which cause infections such as pneumonia, otitis, rhinitis and tuberculosis. Many reports are suggestive of control of many by bacteriocins (Mandell *et al*., 2007; Pascual *et al*., 2008; Ghobrial *et al*., 2009; Knoetze *et al*., 2008) [69-72]. Two of the potent lantibiotics produced by *Streptococcus* salivarius K12 are salivaricin types A and B, both of which are used to treat infections of the upper respiratory tract caused by streptococcal organisms (Balakrishnan *et al*., 2000) [73].

Anti-tuberculous activity of bacteriocins

Lactoferrin is an iron-binding glycoprotein present in mucosal secretions and neutrophilic granules and considered to be important factor for innate immunity and possess ability to alter host reactions in *M. tuberculosis* infection (Actor *et al*., 2009) [74]. Lactoferrin alone did not alter the growth of *M. tuberculosis* in either macrophages or broth culture, but enhanced *IFN-γ* mediated killing of the *M. tuberculosis* through the macrophages. Hence, lactoferrin suggests potential to be used for the treatment of tuberculosis and be helpful to minimise immune-mediated tissue damage in infectious diseases (Welsh *et al*., 2011) [75]. Bacteriocin isolated from *Lactobacillus salivarius*, *Streptococcus cricetus* and *Enterococcus faecalis*, have shown more antimycobacterial activity in comparison to equal concentrations of rifampicin in an *in vitro* model. These bacteriocins didn't showed ant toxicity at a concentration of 0.1 mg/L for mouse macrophages with activity of >90 MIC (Sosunov *et al*., 2007) [76]. Lantibiotics evidently possess sufficient potential for future therapies treating tuberculosis (Sivaraj *et al*., 2018) [77].

Antiviral activity of bacteriocins

Many bacteriocins has shown antiviral activity against murine norovirus S99 (MNV), influenza A Virus A/WSN/33 (H1N1), Newcastle disease virus, Montana and feline herpes virus KS 285 (Lange-Starke *et al*., 2014) [79]. The safety and efficacy of a subtilosin-based nanofibre formulation have also been evaluated against herpes simplex virus type 1 (Torres *et al*., 2013) [80]. Some bacteriocins, such as subtilosin A from Bacillus subtilis, were reported as having anti-viral (Quintana *et al*., 2014) [81].

Antifungal activity of bacteriocins

The application of bacteriocins for the control of fungal growth may at first thought appear an ambitious and perhaps illogical idea. However, if achievable this strategy could certainly have widespread practical application. Is the targeting of such taxonomically-distant microbes a reasonable expectation for conventional proteinaceous bacteriocin molecules or are the occasionally-reported observations of anti-fungal activities by bacteria attributable to the activity of non-bacteriocin inhibitory molecules (Todorov, *et al*., 2019) [82]. The cyclic dipeptides cyclo (L-Phe-L-Pro) and cyclo (L-Phe-trans-4-OH-L-Pro) produced by *L. plantarum* MiLAB 393 were identified as potential antifungal agents by Ström *et al*. (Ström, *et al*., 2002) [83]. These small peptides cannot of course be considered to be 'true' bacteriocins. Various cyclic dipeptides have previously been shown to have both antibacterial and antifungal activities (Graz *et al*., 1999) [84] and it is likely that these substances, previously only reported from strains of *L. plantarum* (Lindgren and Dobrogosz, 1990) [85], are also produced by other LAB, such as *P. pentosaceus* and *L. sakei* (Magnusson *et al*., 2003) [86].

Inhibitory activity of peptides produced by *L. plantarum* strain LR/14 against *A. niger*, *Rhizopus stolonifer*, *Mucor racemosus and Penicillium chrysogenum* was reported (Gupta and Srivastava, 2014) [87]. The peptides were able to inhibit both spore germination and hyphal growth; however, the former stage exhibited heightened, dose-dependent susceptibility. Strains of several Pediococcus species have also been found to produce substances able to control the growth of mycotoxinogenic fungi (Mandal *et al*., 2007; Rouse *et al*., 2008) [88, 89]. In the study by Mandal *et al*. (Mandal *et al*., 2007) [88] a strain identified as *Pediococcus acidilactici* LAB 5, isolated from vacuum-packed fermented meat, exhibited varying degrees of antifungal activity against *Aspergillus fumigatus*, *A. parasiticus*, *Fusarium oxysporum* and *Penicillium* sp.

Anti-cancerous activity of bacteriocins

Anticancer activity of bacteriocins can be attributed to the interaction with targeted membrane. Bacteriocins being positively charged (cation) bind effectively with negatively charged cell membrane of cancer cells compared to neutral charged normal cell membranes (Hoskin and Ramamoorthy, 2008; Martín *et al*., 2015) [90, 91]. Presence of large number of microvilli in the cancerous cells membranes (Chaudhary and Munshi, 1995) [92] assist the anticancer activity of bacteriocins by binding more efficiently to the same in opposition to normal cells' (Chan *et al*., 1998) [93]. Few of the bacteriocins have been put forwarded as potential candidate for cancer chemotherapy (Baumal *et al*., 1982; Farkas-Himsley and Yu, 1985) [94, 95] or to help in the diagnosis of some types of cancer (Kaur and Kaur, 2015) [96] (Loiseau *et al*., 2016) [97]. Compared to normal cells, Pediocin PA-1, nisin and plantaricin A are reported to show relatively increased cytotoxicity toward cancerous cells. Bacteriocins, hence due to this selective toxicity makes them very promising candidates for further research and trials (Kaur and Kaur, 2015) [96].

Bacteriocins in veterinary medicine

Mastitis, an intramammary bacterial infection caused by *Staphylococcus aureus*, *Streptococcus uberis* and *Streptococcus dysgalactiae* is common in dairy animals against which a nisin-based udder disinfectant and an intramammary infusion product containing nisin viz Wipe OutR dairy wipes (Immucell, Portland, ME) and Mast OutR (Immucell) respectively has been approved by FDA recently (Hernández-González *et al*., 2021) [98]. Lacticin 3147 produced by *Lactococcus lactis* DPC3147, lantibiotic having high inhibitory potential, has been evaluated against many mastitis-causing microorganisms as a dry cow therapy in teat seal formulations (Dicks *et al*., 2018) [51]. In poultry, likewise antimicrobial property of bacteriocins has been studied to control and inhibit pathogenic microorganisms. In broiler chickens, Plantaricin from *Lactobacillus plantarum* F1was put forwarded as a viable replacement of antibiotics against colibacillosis (Ogunbanwo *et al*., 2004) [99]. Combination of partially purified enterocin CLE34 and Plantaricin CLP29 have wide antibacterial activity against *Salmonella pullorum* and *E. coli* (Wang *et al*., 2012) [100]. Increment of body weight have been observed in broilers when they were fed a combination of bacteriocins divercin AS7 and nisin as an additive in the diet (Józefiak *et al*., 2013) [101]. Studies

reported use of colistin (polymyxin E) in piglets against Enterotoxigenic E. coli causing diarrhea has led to the development of a resistant strain (Bin *et al*., 2018) [102] (Aguirre *et al*., 2020) [103]. A synergistic effect against colistin-resistant *E. coli* strains isolated from pigs was observed when a combination of nisin or enterocin DD14 along with colistin was used, the reason being the interaction of colistin with Lipopolysaccharide which allows the entry of bacteriocins causing loss of membrane stability to damage the cell wall (Al Atya *et al*., 2016) [104]. Nisin was also reported to prevent the formation of dento-bacterial plaque and gingivitis in dogs, similar to action of chlorhexidine (Howell *et al*., 1993; Cunha *et al*., 2018) [105, 106]. Incorporation of enterocin M in the feed of horses reduced Gram-negative bacteria such as coliforms, Campylobacter, and Clostridium spp. with no physiological parameter being altered (Lauková *et al*., 2018) [107]. Nisin when added to the feed and water of weaned rabbits found to have reduced harmful intestinal microorganism, also increase in both weight was observed and the meat quality remained unchanged (Lauková *et al*., 2014; Pogány Simonová *et al*., 2019) [108, 109]. Bacteriocins have an immense potential in veterinary medicine and can be further more investigated to exploit their use as a substitute for antibiotics and represent a strong new antimicrobial. These findings highlight the immense potential of bacteriocins in veterinary medicine as an excellent antibacterial alternative against potentially pathogenic agents that prevent could bacterial resistance as well as improved growth performance (Schofs *et al*., 2020; Preciado *et al*., 2016) [110, 4].

Other applications of Bacteriocins

Along with the mentioned above, various other studies are also under process to exploit more potentials of bacteriocins. Along with many others some includes their effectivity to treat skin diseases**.** Bacteriocins from *Enterococcus hirae* DCH5 and *Lactococcus* subsp. QU12 has successfully showed efficacy *invitro* been examined vitro against staphylococci, enterococci, lactobacilli and *Listeria monocytogenes* (Sánchez *et al*., 2007; Sawa *et al*., 2009; Wu *et al*., 2005) [111-113]. Immunomodulatory effect of bacteriocins are also under study, efficaciousness depends upon the concentration of bacteriocin used which in turns adds to the bactericidal effect, thereby increasing host safeguard, especially during the period of infections (Hernández-González *et al*., 2021) [98].

Nanoformulated Bacteriocins

Nanotechnological techniques and Bacteriocin delivery system

In accordance to the Science and Technology Committee of the House of Lords of the United Kingdom, nanotechnology is the transformation of functional materials and structures into nanoscale sizes (with diameters from 1 to <1000 nm) (Klaessig *et al*., 2011) [114]. Drugs are loaded onto nanomaterials to improve pharmacokinetics by altering physical characteristics, such as solubility, half-life and bioavailability (L. Zhang *et al*., 2010) [115]. This is a completely novel technology that has several applications in various fields of science, due to the unique properties of synthesized nanoparticles (Chou *et al*., 2011) [116]. The amalgamation of nanotechnology and biotechnology opens a paradigm of vast set of opportunities and future perspectives to resolve the concerns with regards to wide biological products. Bacteriocins are one of the many entity whose benefit can be extracted most by such innovative combination.

For instance, nanoencapsulation of bacteriocins intended for use as bio-preservatives could protect them from degradation by proteolytic enzymes, in addition to rescuing them from undesirable interactions with other food components, and hence, increasing their stability for longer periods (Brandelli, 2012) [117]. Furthermore, some recent studies have shown that encapsulation of bacteriocins in nanoparticles has enhanced the activity of these peptides against food-spoiling microorganisms and multidrug-resistant bacteria (Arthur *et al*., 2014; Mossallam *et al*., 2014) [118, 119]. In addition, the use of nanotechnology-based materials and/or methods has, in most cases, shown a positive impact on bacteriocin yield, thus facilitating their commercial production (Zacharof *et al*., 2013) [120]. Through this amalgamation, efficient delivery, targeting, protection from degradation, as well as improved drug activity and physicochemical properties, can be achieved (Farokhzad and Langer, 2009) [121].

Nanomaterials can be developed to deliver the payload to specific target tissue or infected sites, thus reducing the amount of antimicrobial required for effective treatment. With the increasing bacterial resistance, the evolution of nanotechnology has proven to be an effective upgrade of traditional drug delivery systems. Bacteriocins incorporated nanoparticles and infection targeted site-directed delivery may soon become an effective method of treatment. Bacteriocins in a concentrated form such as nanoparticle encapsulation delivery system, would enhance their effectivity and minimize possible side effects (Zimina *et al*., 2020) [122].

Encapsulation of bacteriocin in liposomes

Liposomes are biocompatible and non-toxic spherical vesicles constituting single or multiple phospholipid bilayer membranes (Gómez-Hens and Manuel Fernández-Romero, 2005) [123]. They are non-toxic and biodegradable agents are capable of encapsulating both hydrophobic and hydrophilic compounds. Nano-sized liposomes, size varying from micrometers to nanometers, called nano-liposomes are emerging as promising vehicles for the encapsulation and delivery of several bioactive components like that of therapeutic bacteriocins to specific target cells along with other food additives, enzymes and vitamins (Akbarzadeh *et al*., 2013) [124].

Encapsulation by liposomes protects the encapsulated compounds from environmental and physicochemical alterations (Mozafari *et al*., 2008) [125]. A technique called thin film hydration method is used to encapsulate bacteriocins in liposomes. In this technique, the chemically synthesized lipid film is hydrated at a higher temperature than the phase transition temperature of lipids with bacteriocin containing aqueous buffer leading to production of manifold population of multilamellar vesicles of about >400 nm in size where bacteriocins are encapsulated, which are then further processed by sonication or heating or membrane extrusion into homogeneous, small unilamellar vesicles of about 20–80 nm in size (Chandrakasan *et al*., 2019) [126].

A study reported, nanoliposomes co-encapsulated with nisin and garlic extracts showed enhanced broad spectrum activity against various food-spoiling pathogens *viz L. monocytogenes*, *Salmonella enteritidis*, *E. coli*, and *S. aureus*. (Pinilla and Brandelli, 2016) [127]. In another investigation, prominent inhibitory activity against *Listeria monocytogenes*

was displayed when nisin was encapsulation into phosphatidylcholine, incorporated into biopolymer-based films of gelatin or cellulose indicating it to be a promising active packaging material (Boelter and Brandelli, 2016) [128]. Moreover, no hemolytic activity on human red blood cells was seen upon use of encapsulated bacteriocin-like substances, thus signifying their safety as food preservatives (Teixeira *et al*., 2008) [129].

Liposome encapsulation delivery systems have several other advantages such as improved stability, degradation protection, reduced doses in therapeutic applications and enhanced antibacterial activity in terms of the time taken to exercise the antimicrobial action and the activity spectrum. While nano-encapsulation of bacteriocins give numerous advantages, studies also indicated adverse effect on the antimicrobial role of bacteriocins (da Silva Malheiros *et al*., 2010) [130]. Nevertheless, with appropriate selection of phospholipid bacteriocin, this adverse effect can be prevented by preventing unhealthy interactions between bacteriocins and liposomes. An appropriate phospholipid bacteriocin combinations, the avoidance of adverse liposome–bacteriocin interactions, and utmost purity of starting materials are the key to the productive implementation of bacteriocins encapsulated liposome (Pinilla and Brandelli, 2016) [127].

Solid lipid nanoparticles

Solid lipid nanoparticle (SLN) is composed of a solid core of triglyceride with a phospholipid coat of high-melting point, hence maintain a solid state at room and human body temperatures (Puri *et al*., 2009) [131]. In addition to the numerous advantages of liposomes, the solid triglyceride core of SLN makes them powerful tools for largescale production and slow release drug formulation (Feng and Mumper, 2013) [132]. Nisin when incorporated in SLN carriers showed sustained release for about 25 days, depending on the pH and the salt concentration of the buffer solution (Prombutara *et al*., 2012) [133]. Moreover, nisin-loaded SLN have showed activity against *L monocytogenes* DMST 2871 for up to 20 days and *L plantarum* TISTR 850 for up to 15 days, in comparison with free nisin whose activity lasted only for 3 days against the former organism and for 1 day against the latter (Prombutara *et al*., 2012) [133]. These studies suggested that SLN have the potential to protect bacteriocins from degradation, and therefore could be used to prolong their antibacterial activity for a long duration. Though, much studies need to be conducted before taking SLN as a delivery system for bacteriocins as it is still in the early exploratory phases of research. Possible expulsion of the incorporated drug/drug-like agents from the lipid matrix and the low drug-loading capacity are few of the challenges that need to be overcome to fully establish the SLN as a delivery system are the possible expulsion of the incorporated drug/drug-like agents from the lipid matrix and the low drug-loading capacity fna (Jenning *et al*., 2000; Souto *et al*., 2006) [134, 135].

Chitosan

Chitosan is another type of nanoparticle, which is tremendously used with bacteriocins. It is a natural biopolymer which is synthesized by deacetylation of chitin and is biodegradable, biocompatible, non-toxic and bactericidal which makes it an ideal candidate for its use in biomedical applications and food safety. It is one of the most extensively used polysaccharides to produce nanoparticles. Moreover, its antibacterial, antifungal, antiprotozoal and anticancer activity coupled with its ability to deliver drugs to their specific targets is well studied (Sidhu and Nehra, 2019) [136]. The chitosan-bacteriocin conjugation, commonly achieved by ionic gelation method, where chitosan and bacteriocin suspension are mixed and are stirred in 1% acetic acid at room temperature with the addition of sodium tripolyphosphate (TPP) followed by centrifugation and the chitosan incorporated bacteriocins are obtained as pellet which can be lyophilized for further use has been described (Karthick Raja Namasivayam *et al*., 2015) [135]. In contrast with free nisin, higher level of antimicrobial activity was displayed by nisin-loaded chitosan-alginate nanoparticles against *L. monocytogenes* and *S. aureus* (Zohri *et al*., 2013) [138]. Many researchers have used chitosan with bacteriocins to obtain a material showing collaborative antibacterial activity. Synergistic antibacterial activity of chitosan–nanoconjugates loaded with bacteriocins have been described against *Listeria monocytogenes* when compared with those of free bacteriocins (Karthick Raja Namasivayam *et al*., 2015) [137]. Incorporation of biopolymers in place of plastics in food packaging is escalating its safety and biodegradability. Crystalline nanocellulose coated with bacteriocin and reinforced onto starch films enhances the tensile strength of the film by 69% and antibacterial effect by 57% (Bagde and Vigneshwaran, 2019) [139]. This new class of nano-polymer hybrid thus provides a magnitude to fight bacterial pathogens and could therefore be an efficient weapon against food-borne bacterial pathogens (Sharma *et al*., 2012; Chopra *et al*., 2014) [140, 141].

Phytoglycogen nanoparticles

Novel functional nanoconstructs are prepared from phytoglycogen, a polysaccharide material found in plants (Chen *et al*., 2015) [142]. Apart from chitosan that described earlier, phytoglycogen and its derivatives are another carbohydrate based nanoparticle that has been used successfully for encapsulating nisin (Bi *et al*., 2011) [143, 144]. Phytoglycogen and its derivatives were studied as carriers of nisin, and all showed antimicrobial activity against *L. monocytogenes* for longer period than free nisin. Among all phytoglycogen derivatives, 3-amylolysis and octenyl succinate substitutions showed longest activity for about 21 days against common food pathogens in comparison with 7 days in case of the free nisin (Bi *et al*., 2011) [143, 144]. The antibacterial activity of this nanoparticle-stabilized emulsion has been higher than that of the free nisin during 50 days of storage (Bi *et al*., 2011) [143, 144]. These findings signify that there is an enormous scope to explore such nanomaterials as carriers for bacteriocins which could play a great role in public health and food safety.

Metallic Nanoparticles

Presently, the metallic nanoparticles such as zinc, copper, silver, and gold are being thoroughly investigated not only as potential antimicrobials but also for their different prospective biomedical applications (Naskar and Kim, 2020; Naskar *et al*., 2020a; Naskar *et al*., 2020b; Naskar *et al*., 2020c) [145-148]. Such substantial use of these nanoparticles may be accredited to their large surface area of positively charged nanoparticles, which can interact with negatively charged bacterial cell membrane (Seil and Webster, 2012) [149]. Oxidative stress induced by the generated reactive oxygen species, together with the toxicity of the accumulated free metal ions helps to kill the target bacteria (Seil and Webster, 2012) [149]. Silver

and gold are more commonly used and studied nanoparticles, showing synergistic effects in biomedical applications. Many studies indicating antibacterial effects of silver and gold nanoparticles is being reported, making it easier to understand the theory associated with combination of bacteriocins and silver/gold nanoparticles. Many applications of silver nanoparticles are well known such as coating medical devices, wound dressing, coating textile fabrics, to water treatment and filtration (Furno *et al*., 2004; Rujitanaroj *et al*., 2008; Zhang *et al*., 2009; Dankovich and Gray, 2011) [150- 153]. This approach has been demonstrated by Sharma et. al. where they used enterocin- capped silver nanoparticles which showed broad-spectrum inhibition against various food-borne pathogenic bacteria namely *E.coli*, *L.monocytogenes*, and *S.aureus* along with admirable non-toxicity to red blood cells, signifying its biocompatible nature (Sharma *et al*., 2012) [140]. A study also reported increased antimicrobial potential of nisin after conjugation with silver nanoparticles associated with food spoilage against *Listeria monocytogenes*, *S. aureus*, *Pseudomonas fluorescens*, *Aspergillus niger*, and *Fusarium moniliforme* associated with food spoilage (Pandit *et al*., 2017) [154].

Similarly, gold and bacteriocins nano-conjugates shows potential antimicrobial activity and reduced toxicity. The use of gold nanoparticles conjugates for other biomedical applications such as the co-delivery of nisin and doxorubicin to treat murine skin cancer (Preet *et al*., 2019) [155]. A study reported, combination of gold nanoparticles with either nisin or a bacteriocin produced by *L. plantarum* ATM11 both showed promising antibacterial effect with comparison with free bacteriocins especially against *M. luteus*, *B.cereus*, *E.coli*, and *S.aureus* indicating usefulness of such combinations in inhibiting common food-spoilage microorganisms and hence prolonging the shelf-life of food products (Thirumurugan *et al*., 2013) [156]. Upon biochemical examinations and histopathological screening tests, nanoconjugate bacteriocin has been reported to be safe and non-toxic (Mossallam *et al*., 2014) [119]. Hence, different nanoconjugates of bacteriocins can be used to increase the antimicrobial array of bacteriocin alone, which can serve as efficient weapon in the fight against food borne pathogens and multi- drug resistant bacteria.

Nanofiber

Nanofibers are extraordinarily fine threads created by electrospinning (Fahim *et al*., 2016) [13]. Nanofibers have gained popularity as carriers for direct distribution and continuous release of many drugs such as of antimicrobials and hemostatic agents for wound healing along with that of bacteriocins. High encapsulation potential, larger surface area, high physical stability, small pores size has made nanofibers potential nanocarriers for target specific drug delivery and sustained release of a variety of drugs (Fahim *et al*., 2016) [13]. In a finding, nisin and silver nanoparticles incorporated into nanofibers has shown broad antimicrobial efficacy against a wide range of Gram-positive and resistant Gram-negative bacteria (Ahire *et al*., 2015) [157]. Nisin released from this nanofiber dressing, maintain its antistreptococcal activity *in vitro* for at least 4 days; remain active for 8 months even after storing of the formulation at 4°C; induce nearly complete wound healing as indicated by the formation of clear fibrotic scar in a group of mice undergoing dressing; significantly reduce *S. aureus* colonization; and as per histological analysis of the treated group, no adverse effects reported by (Heunis *et al*., 2013) [158]. Nanofiber based bacteriocin are also used as antibacterial and antiviral substances. A study reported antiviral activity against Herpes simplex virus type 1 (HSV-1) of subtilosin-loaded poly (vinyl alcohol) (PVOH) nanofiber (Torres *et al*., 2013) [80]. Subtilosin-loaded nanofibers showed potential i*n vitro* activity without exhibiting cytotoxicity (Torres *et al*., 2013) [80] with comparison to modern antiviral treatments regime cytotoxic to nephritic tissue (Ho *et al*., 2000) [159]. Bacteriocin incorporated nanofiber technology may represent a promising novel therapeutic alternative to current drug therapies.

Conclusion And Future Prospects

Bacteriocins are a promising tool that can be exploited for its utilisation in various sector, may it be human or veterinary medicine. The administration of these antimicrobial peptides has proven to show efficacy as anti-tuberculous, antiviral as well as antifungal agents. They have longed been used in food industry as food preservative and so to increase shelf life of food commodities. Bacteriocins have found their utility in domestic animals as they eliminate potentially pathogenic undesirable microorganisms pertaining to reduced toxicity or no toxicity and improves productive parameters in substitution of antibiotics as growth promoters. They have also shown promising efficacy against many dangerous nosocomial diseases known to cause maximum mortality and morbidity. Unquestionably, bacteriocins may play a remarkable role in combating antibiotic-resistant bacterial strains, considering its narrow-target activity, low toxicity, and high stability and specificity. Bacteriocins in combination with antibiotics work synergistically and shows great potency. They also have a role in the immune response as immunomodulators along with their other diverse field of action. Although, they are found to have few side effect, those can be minimised by use of newer techniques like that of nanotechnological approaches. It is well established that incorporation of bacteriocins into nanoparticles and specific delivery to areas of infection may soon become an effective treatment regime. Many instances showed combination of nano-formulation along with free bacteriocins revealed better stability and a broader range of antimicrobial action. Nanotechnological methods provide an interesting option toward the formulation of these antimicrobial peptides at the industry scale level.

Considering the explicit potential of bacteriocins, it is need of the hour to harness the full potential of bacteriocin for the greater good. Exploration of novel bacteriocin producing strains with unique properties and characteristics can open a wide range of application and new prospects. The bacteriocin pharmacokinetics, pharmacodynamics, toxicity, and immunogenicity aspects need to be taken into considering before the products are approved for large scale consumption. Appropriate studies need to be carried out to access their *in vivo* effects, mechanism of action, interaction with the host immune system, and large-scale production costs as well as the emergence of bacteriocin resistance. Other several unexplored drug delivery systems can be the next phase in drug development process.

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