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Bacteriocins: Production, different strategies of purification and applications

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ABSTRACT

Food safety and quality are the major concern for food processing industries. In today's world, people are getting more conscious about food safety parameters. In this regard, bacteriocin plays a major role in ensuring the safety and quality of food products. From those, LAB bacteriocins are of great interest due to their GRAS status. They are widely used in food preservation, agriculture and pharmaceutical industries. They have also been incorporated into food packaging material due to their both antibacterial and antifungal properties. In this review, we highlighted the possible ways to produce and purify bacteriocin and also the potential application to be used as a natural preservative.

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INTRODUCTION

In the world, approximately 1.3 billion tonnes of food gets wasted every year, which is about one-third of the total food production for human consumption. Globally fruits and vegetables accumulate the highest wastage rate among any of the food article followed by cereals, meat and dairy products. In Europe and North America per capita, food loss is about 95-115 kg/year whereas, in South-Eastern Asia and sub- Saharan Africa, per capita food loss is 6-11 kg/year. The stages of the food supply chain where food get wasted is shown in Figure 1. In approx total US $ 680 billion get wasted because of food loss in industrialized countries and US $ 310 billion in developing countries (F.A.O., 2019). By 2030, global food demand is about to reach to 35%. This demand can only be covered by increasing the production of food or by reducing food waste. Such demand has opened up new avenues for the use of bio preservatives evolved from plants, animals or microbial sources. Bacteriocins grant one possible solution to be used as natural preservatives. These are small antimicrobial peptides ribosomally synthesized extracellularly released compounds produced by bacterial species that have antagonistic activity to the producer strain (Jack *et al.*, 1995).

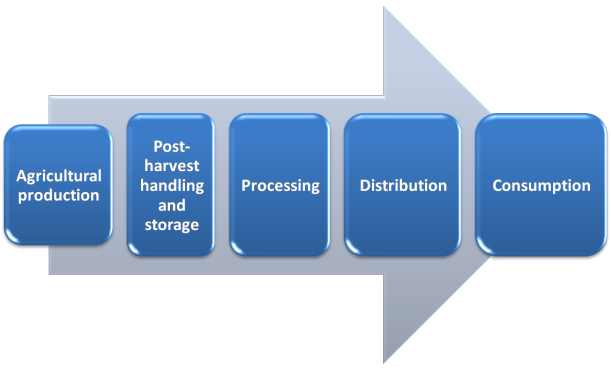

Figure 1: Stages of the food supply chain

These antimicrobial peptides produced by various gram-positive and gram-negative bacteria and those

which are produced by lactic acid bacteria have great potential to be used in food industries for many reasons i.e. they acquired GRAS (generally recognized as safe) status by U.S. FDA and also inhibits a large range of food spoiling and foodborne pathogens (Hansen, 2002). They are diverse from conformist antibiotics, as bacteriocins are the primary product of log-phase, whereas antibiotics are secondary metabolites (Table 1) (Cleveland *et al.*, 2001)

Table 1: Difference between bacteriocins and antibiotics.

Characteristics	Bacteriocin	Antibiotics
Activity	Reduced Spectrum	Variable spectrum
Synthesis	Ribosomally synthesized	Secondary Metabolites
Interactive Requirement	Non-specific targets	Specific targets
Immunity to host cell	Yes	No
Toxicity	Unknown	Yes
Mode of action	Pore formation in membrane	Intracellular targets/cell membrane

Bacteriocins have varying of the inhibitory spectrum and this characteristic permit their use in food safety and spoilage (Knoll *et al.*, 2008). If they are produced by one bacteria are inhibitory to other bacteria of the same species, then they are classified as a narrow spectrum, and if bacteriocins showed inhibition activity against bacteria of another genera, then they are known as broad-spectrum bacteriocins (Juturu and J.C, 2018) . The discovery of nisin accordingly opened a dynamic area in bacteriocin research and flagstone the way for identification of novel bacteriocin to be used as food preservatives. The joint Food and Agriculture Organization and the World Health Organization had internationally accepted nisin as a natural food preservative in 1969 (WHO, 1969). In 2001-2004 bacteriocins were the part of $ 22 billion global food additive with an annual growth rate of approximately 2.4% per annum and in 2007 it had reached about $ 24 billion. Incorporation of bacteriocin in packaging film for inhibition of pathogenic microorganisms to control food spoilage is also an area of active research.

Antimicrobial packaging film prevents the growth of pathogenic microorganisms on food surface by direct contact of film with the food surface, e.g. Cheese slice. That is why; the antimicrobial film must be in contact with the food surface so that bacteriocin can diffuse to that surface and inhibits the growth of food spoiling pathogens. Although a bulk of research has been carried out in the area of bacteriocins on their isolation, characterization, purification and mode of action over last few decades but only a few of them have been commercialized include nisin, pediocin PA-1 and carnocyclin A (Field *et al.*, 2018). In this review, we have discussed various strategies for the production and purification of bacteriocins and also their application in various industries.

Production of bacteriocins

Bacteriocin production is generally a growth associated process and follows primary metabolite kinetics (Leroy and Vuyst, 1999) that usually occurs during the growth phase of producing organisms and the bacterial activity reduced at the end of bacterial growth due to protease degradation (Vuyst and Vandamme, 1994; Parente *et al.*, 1994). Although the amount of bacteriocin production is proportional to the amount of biomass, it is significantly affected by the changes in media composition and culture conditions, i.e. change in pH and temperature (Kim *et al.*, 2006). The presence of sodium chloride in the growth medium usually decreases the bacteriocin production (Verluyten *et al.*, 2004). (Mandal *et al.*, 2008) optimized the growth condition for bacteriocin production of *Pediococcus acidilactici* by growing the strain in different media like MRS, TGE, TGE+ Tween 80 (0.05%), TGE+ buffer (containing 0.02% sodium citrate, sodium acetate and dipotassium hydrogen phosphate) and TGE+ Tween 80+ buffer at various pH 2-12. The optimum media and growth conditions were found to be in TGE+ Tween 80+ buffer (pH 6.8) for 24 hours at 37ºC, and the bacteriocin activity was maximum at stationary phase. The medium, i.e. TGE+ Tween 80+ buffer have more buffering components that controlled the pH, which showed higher bacteriocin production as compared to TGE+ Tween 80. Also, Tween 80 helps in releasing the bacteriocin molecules form producer strain's cell wall into the growth medium (Keren *et al.*, 2004). (Naz and Rasool, 2013) subjected the producer strain *Pseudomonas aeruginosa* SA188 to different culture conditions for higher bacteriocin production. The producer strain was grown in nutrient broth (NB), Trypticase soya broth (TSB), Brain heart infusion broth (BHI), Lactose broth (LB) and pseudo agar base (PAB), for different incubation temperature (4, 10, 29, 37 and 40) and incubation period (5, 10, 15, 20, 24, 36, 48 and 72 hours). pH ranges from 2 to 14 was used. The maximum bacteriocin production was found in brain heart infusion broth,

i.e. 640 AU/ml. In the enriched media, carbon and nitrogen carries significance for maximum bacteriocin production (Mataragas *et al.*, 2004). Glucose is the main source of carbon besides lactose, raffinose and galactose (Vamanu and Vamanu, 2010). There are few statistical experimental design techniques to optimize the culture conditions for maximum bacteriocin production, i.e. Plackett-Burman design, Response surface methodology and central composite design. In 2014, Hwanhlem et al. used the PBD statistical experimental design to optimize the bacteriocin production by producer strain *Enterococcus faecalis* KT2W2G in flask cultures. In this design, lactose and temperature were two main factors whose effects on bacteriocin activity were further determined by using the central composite design (CCD). The optimal composition of lactose and temperature were found 14.85 g/l and 25.59ºC, respectively. The bacteriocin activity was increased by 8 fold in 18-hour fermentation. (Meng *et al.*, 2012) use response surface methodology to optimize the culture conditions for *Lactococcus lactis* subsp *lactis* LLC518. Chopra et al., 2015 optimize the media composition and environmental conditions of producer strain *Bacillus sonorensin* MT93, bacteriocin sonorensin, by using Plackett-Burman design and response surface methodology. PB design was used to identify the important variables of culture medium that affects sonorensin production, then the central composite rotatable design was used to optimize the major variables selected by PB design. From PB design yeast extract, beef extract and peptone were found to be the most effective variables for sonorensin production. Fermentation parameters, i.e. pH, temperature and rate of agitation, were also optimized at flask level by using CCRD. *B sonorensin* MT93 showed 23680 AU/ml, i.e. 15 fold higher activity by using optimized culture conditions than using initial growth medium. One more study conducted for maximum bacteriocin production from *Enterococcus faecium* MC13 by optimizing the fermentation medium using one-variable-at-a-time (OVAT) for preliminary screening of nutrients and then they were further optimized by response surface methodology. The bacteriocin activity was increased by 3 fold in the optimized medium and less expensive than commercial MRS media (Kanmani *et al.*, 2011). These studies revealed that the optimization of culture conditions for the enhancement of bacteriocin production brings significance in research and cost-efficacy as well.

Purification of bacteriocin

Purification of bacteriocin is an essential step for their characterization. A general understanding of bacteriocin from its production to the final step of characterization is depicted in Figure 2. As the crude extract of bacteriocin contain many undesirable compounds of fermentation broth which have to be purify to used them as a bio preservative. Because of their heterogeneous nature, a purification technique varies for each bacteriocin.

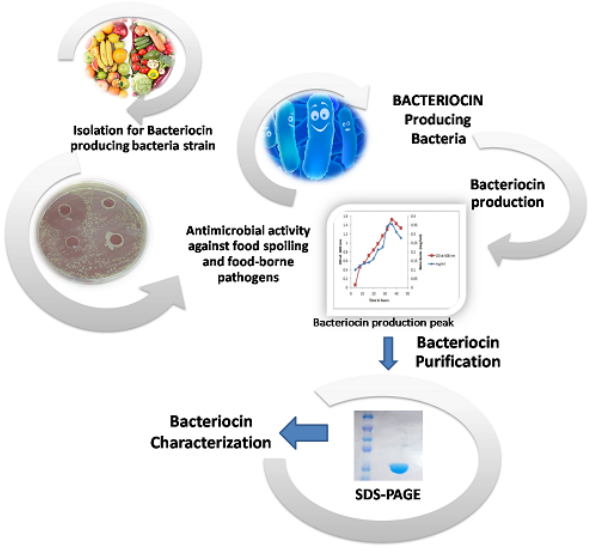

Figure 2: Bacteriocin layout from its production to characterization.

From the last few decades to till date, these techniques are being modified in order to reduce the time and cost. There are three major strategies for the complete purification of bacteriocin, these are, conventional multi-step method, simple three-step method and single-step bed adsorption. (Piva *et al.*, 1994) purified pediocin A by dialysis followed by butanol extraction that results in 3.9% yield and 7834 purification fold. As most of the bacteriocins are low molecular weight, cationic and hydrophobic in nature, so the most successful purification process was initially developed by (Nissen-Meyer *et al.*, 1992) for lactococcin G. Bacteriocins are produced in small amount, therefore, the activity will be lost at every step. (Yang *et al.*, 1992) developed a novel method for their purification in minimal steps which exploits their cationic nature. In this method, the bacteriocin was produced in a nutrient medium, followed by heating at 70ºC to kill the cells. This results in the adsorption of bacteriocin to heat-killed cells which are removed from the medium and resupended in saline buffer. This results in desorption of cationic bacteriocins that dialysed followed by lyophilization. RP-HPLC was performed to purify them to homogeneity. This method was suitable for nisin, pediocin ACH and leuconocin Lcm1 which recover about 90% of bacteriocin but only 44% was recovered in case of sakacin A which indicates that this procedure may not be

suitable for all bacteriocins. One more simple procedure was developed by (Venema *et al.*, 1997) for lactococcin B that requires minimal steps. In this method, the bacteriocin was precipitated by adding precooled ethanol (4ºC) to the CFS. Recently this method was used for sakacin C2 (Gao et al., 2010) and pediocin SA131 (Lee *et al.*, 2010). A different technique was developed by (Pingitore *et al.*, 2009) to purify salivaricin 1328 produced by *Lactobacillus salivarius* 1328. They produce the bacteriocin in a chemically-defined medium which was devoid from any contaminating peptides, so a single step ultrafiltration was sufficient for its purification. Ammonium sulfate precipitation is the most commonly used method for initial volume reduction and concentration of bacteriocins. Other methods like amberlite resin (XAD 16), ultrafiltration and lyophilization are also be used for initial volume reduction. Bacteriocins are produced in very small quantities in a large volume of culture medium, so initial volume reduction is a necessary step for their purification. However, this step is not very discriminatory because proteins and peptides are also get concentrated along with bacteriocin. Therefore further purification steps are mandatory to purify bacteriocin to homogeneity. For the final purification step most commonly used techniques include hydrophobic interaction chromatography, gel-filtration chromatography, Reverse-phase High-Pressure Liquid Chromatography (RP-HPLC) etc. In these techniques, RP-HPLC is usually the final step to purify bacteriocins to homogeneity (Saavedra and Sesma, 2011). After these purification steps, the purity of bacteriocin is confirmed by SDS-PAGE as a result of single active band in the gel confirms that the bacteriocins have been purified to homogeneity and then the primary structure is determined by using mass spectrometry, N-terminal sequencing etc. As most of the studies reported that purification of bacteriocin is a very critical and complex process, so its being necessary to simplify the process by using some efficient purification method that results in high yield of bacteriocin. (Wong *et al.*, 2017) first time purified bacteriocin-like inhibitory substance from *Pediococcus acidilactici* Kp10 by using surfactant precipitation with Bis(2-ethylexyl) sulfosuccinate sodium salt (AOT) that results into a satisfactory recovery of BLIS from its complex fermentation broth, i.e. 83.3% recovery activity and 53.8 purification fold. It is very simple, rapid and cost-effective method. (Garsa *et al.*, 2014) reported that extraction (solid/liquid) and centrifugation steps results in low purification fold than chromatography steps. A recent study by (Du *et al.*, 2018) involved the purification of plantaricin GZ1-27, produced form *Lactobacillus Plantarum* GZ1-27, by using three-step process including ammonium sulfate precipitation, gel filtration chromatography and RP-HPLC. Following ammonium sulfate precipitation to specificity was increased from 246.59 to 262.44 IU/mg with a protein concentration of 102.50 mg/ml form 41.77 mg/ml. After purification by Sephadex G-50 and HPLC, the specific activity was increased to 2601.24 IU/mg by 10 fold purification with protein content 3.21 mg/ml. MALDI-TOF/MS was then used for sequence analysis of plantaricin GZ1-27. Similar purification method was used for bacteriocin plantaricin ZJ008 (Zhu *et al.*, 2014), garvicin A (Maldonado-Barraga *et al.*, 2013), plantaricin 163 (Hu *et al.*, 2013) and enterocin 7A and 7B (Lohans *et al.*, 2013). In another study by (Alexey *et al.*, 2017), a bacteriocin-like inhibitory substance produced by *Enterococcus faecium* was purified by the two-step purification process. At the first stage, desalting was achieved by size exclusion chromatography, and then the separation of active fractions was achieved by RP-HPLC. To confirm the purity of peptide SDS-PAGE was performed. (Kaur and Tiwari, 2018) purified a bacteriocin LB44 produced from *Pediococcus pentosaceus* LB44 by using activity-guided chromatography methods. Ammonium sulfate precipitation was used for initial volume reduction, and desalting was done by 2 KDa cut-off dialysis membrane. Then gel-filtration chromatography was performed to separate the proteins and remove salts from protein sample to achieve the active fraction, which was further applied to RP-HPLC, showed a single peak confirming the homogeneity of purified peptide. RP-HPLC is the most commonly used and reliable technique to test the purity of bacteriocins (Pal and Ramana, 2010). Enterocin LD3 and T1 also purified with the same purification process (Gupta *et al.*, 2016). The third method single-step bed adsorption was achieved by (Cheigh *et al.*, 2004) for purification of nisin Z by applying the culture broth on an expanded-bed ion-exchange chromatography and eluted the fraction using 0.15 M NaCl that results in 90% yield and 31-fold purification. This method reduces the number of purification steps used in the conventional method, thus increasing the productivity and operation conditions like high flow rate and processing volume.

Applications of bacteriocins

Over the past few decades, several physical and chemical treatments have been used to increase the shelf life of food products. Nowadays, consumers are anxious about the possible detrimental health effects due to the presence of chemical additives in food, that increase the demand of minimally pro-

cessed food with no chemical preservatives. Most of the food processing industries are focusing on biopreservation. This increases the demand for natural preservatives, i.e. bacteriocins. Due to target specificity bacteriocins from class, I and class IIa are the most acceptable and likely to be used in food preservation (Weerapong *et al.*, 2016). Nisin produced from *Lactococcus lactis* is the only approved bacteriocin by U.S. FDA which is commercially available as Nisaplin® and used as a preservative in around 45 countries all over the world (Settanni and Corsett, 2008). Nisin is the first antimicrobial peptide produced by LAB (Rogers, 1928). Earlier at the time of discovery, producing strains were identified as *Streptococcus lactis* and later on, they classified as *Lactococcus lactis* (Schleifer *et al.*, 1985). Another bacteriocin pediocin PA-1 produced from *Pediococcus acidilactici* is also commercially available as Alta® 2341 that inhibits the growth of listeria monocytogenes in meat products (Field *et al.*, 2018). The bacteriocins have many fascinating properties that make them applicable in food preservation (Chen and Hoover, 2003).

- Their GRAS status
- Inactivated by digestive proteases
- Non-Toxic to eukaryotic cell
- Active over a broad range of pH and temperature
- Synthesized on the ribosome and undergo post-translational modifications

Large numbers of bacteriocins have been tested as a preservative in a wide range of food products which include fruits, vegetables, seafood, dairy and meat products (Khan *et al.*, 2010) and they have various applications in different industries like dairy, meat, fruits and vegetables, livestock and also in pharmaceuticals.

Dairy industry

The dairy industry is a dynamic global business which plays an important role in the sustainability of the economies of many countries. Dairy product global market is estimated to flourish at a significant CAGR by 2027. Novel products with better quality and improved nutritional values are been introduced by major players to capture this increasing demand of the market. Bacteriocins have wide applications in the dairy industry, especially during the fermentation of the product. Nisin has been approved as a food additive (E234) in the European Union according to directive 95/2/EC in the following products: semolina and tapioca puddings (3mg/kg), ripened and processed cheese (12.5 mg/kg) (EFSA, 2006). Nisin containing camembert and semi hard cheese with prolonged shelf-life were made using *Lactococcus lactis*. Plantaricin C is a broad spectrum bacteriocin produced by *Lactococcus Plantarum,* isolated from ripening cheese. The use of bacteriocin producing bacteria as a starter culture for in situ biosynthesis during milk fermentation becomes an effective alternative strategy to incorporate bacteriocin in dairy food. Lacticin 3147 producing strain *Lactococcus lactis* DPC 3147 used as a protective culture in chedder cheese which reduce the number of *Listeria monocytogenes* to <10 cfu/g within 5 days at 4ºC (Chen and Hoover, 2003). Other LAB strains such as L. Plantarum WHE92 used as an adjunct to the starter culture reduced *Listeria monocytogenes*, *Listeria innocua* and *Escherichia coli* O157: H7 counts in cheese as a consequence of the production of plantaricin. Danisco developed a freeze-dried culture of *Pediococcus acidilactici* (marketed as CHOOZIT Flav 43) for use as a bacteriocin-producer adjunct in chedder and semi-hard cheese.

Meat industry

The meat industry is one of the largest food processing industries globally. The global processed meat market was around USD 714 billion in 2016 and is expected to increase by USD 1567 billion by 2022, growing at a CAGR of around 14% from 2017 to 2022 (John, 2017). The leading meat producers are Brazil and China, followed by Argentina, India, Indonesia, Mexico, Pakistan and Vietnam (among developing countries). Among the various bacteriocins, Nisin is the only commercially approved additive for processed meat preservation (USFDA, 2000). *Listeria monocytogenes* is a well-known pathogen for food spoilage that convoluted in various foodborne diseases. Fermented sausages and vacuum-packed meat products are extensively eaten products without reheating. For food safety, the presence of *Listeria monocytogenes* in these two products is of great interest. (Aymerich *et al.*, 2000) assayed different meat products like cooked ham, minced pork, meat and chicken breasts, to evaluate the effect of enterocin, a bacteriocin produced from *Enterococcus faecium* CTC492, against *Listeria monocytogenes*. He found the reduction in *Listeria* strain by 7.98 and 9 log cycles in cooked ham and pork respectively when stored for 37 days at 7ºC. (Nieto-Lozano *et al.*, 2006) conducted a study by incubated the sample of Spanish raw meat surface with a bacteriocin produced by *Pediococcus acidilactici* and observed the reduction of *Listeria monocytogenes* by 1, 2 and 3 log cycles after storage for 72 hours at 15ºC and 2.5-3.5 log cycles reduction after storage for 21 days at

4ºC with 1000-5000 AU/ml. It showed great activity against *Listeria monocytogenes* and C*lostridium perfringens*.

Fruits and Vegetables

Due to the health benefits of fresh food, their consumption has greatly increased over the past few decades especially for food of vegetal origin (Olaimat and Holley, 2012; Abadias *et al.*, 2008; Pinela and Ferreira, 2015). The contamination of fruits and vegetables by pathogenic organisms is mainly due to fecal and soil materials from the farm during their growth, harvest, transport and storage (Hsu *et al.*, 2014). Many bacteriocins have been reported to be used for fruits and vegetable preservation, but only nisin and pediocin PA-1 have been approved as a food additive. The fruit products itself have acidic pH that reduces various contaminating bacteria with the heat treatment, but these characteristics are not sufficient to remove thermo acidophilic bacteria like *Clostridium, bacillus, Alicyclobacillus*. Their endospores remain in the soil that causes fruit and vegetable contamination (Carvalho *et al.*, 2007b,a; Bevilacqua *et al.*, 2012; Gouws *et al.*, 2005). *Alicyclobacillusacidoterrestris* is the main cause of contamination in pasteurized fruit juice industry (Wang *et al.*, 2014). For the preservation of fruit products, bacteriocin may incorporate directly in the purified or semi-purified form. One study by (Carvalho *et al.*, 2007b,a) showed that addition of Bovicin HC5, a bacteriocin produced from *Streptococcus bovis* HC5 in mango pulp inhibits *Alicyclobacillus acidoterrestris, Bacillus cereus, and Clostridium tyrobutyricum.* Another bacteriocin pediocin produced from *Pediococcus pentosaceus*, when added in minimally processed papaya showed effective inhibitory activity against mesopilic bacteria and fungi (Narsaiah *et al.*, 2015). LAB bacteriocins play a very important role in the preservation of fermented foods and their microbial safety. (Molinos *et al.*, 2005) observed the reduction in *Listeria monocytogenes* in artificially contaminated alfalfa and soybean sprouts by incorporate the material in AS-48 bacteriocin, a cyclic peptide, solution for 5 minutes. He again observed the extension in shelf-life of Russian salad by inhibiting the growth of *Listeria monocytogenes* and *Salmonella sp.* with bacteriocin AS-48 (Molinos, 2009). Miso (fermented soybean paste) is a very defining seasoning for Japanese and Asian cuisine made up of rice koji fermented by *Aspergillus oryzae* (Yamabe *et al.*, 2007) but *Bacillus* sp. prevents the fermentation of *Aspergilli* and cause the spoilage of food. (Kato *et al.*, 1999) observed the inhibition of *Bacillus subtilis* in fermented soybean by adding nisin. Again in (Kato *et al.*, 2001). observed the growth of *Lactococcus* produced nisin in cooked rice with soybean extract, which prevents the growth of *Bacillus subtilis* in miso. Nisin producing *lactococci* was not affecting the flavors and color of miso and also not inhibiting the growth of *Aspergillus oryzae*, required for koji fermentation. Bacteriocins also plays a very defining role in non-fermented vegetables, i.e. refrigerated pickles, Mungbean sprouts (Reina *et al.*, 2005).

Human health

Lantibiotics have potential medical application as they have been studied since 1928 when nisin was first time reported as tubercle *bacilli* inhibitor (Rogers, 1928). *Staphylococcus aureus* is one of the most competently explored bacterial organisms that can cause various nosocomial infections varying from minor skin abscesses to severe life-threatening diseases (Kruszewska *et al.*, 2004). The treatments of these infections are intricate due to multi-antibiotic resistance. A study conducted by (Kruszewska *et al.*, 2004) found that mersacidin, a lantibiotic was an effective antimicrobial peptide that eradicates a nasal human MRSA strain. Nisin A and lacticin 3147 have also been found effective against Methyllin resistance *Staphylococcus aureus* strains (Piper *et al.*, 2009). Lacticin 3147 is a promising bacteriocin for potential use in human health and medicine. It shows great activity over a broad pH range, broad spectrum activity at nanomolar concentration and absence of cytotoxicity towards eukaryotic cells (Piper *et al.*, 2012). A study by Aunpad and Na-Bangchang isolated a bacteriocin producing strain *Bacillus pumilus* was found active against MRSA and VRE (Aunpad and Na-Bangchang, 2007). Nisin F inhibits *Staphylococcus aureus* when administered at a concentration of 8192 AU in non-immuno, and immunosuppressed Wistar rats, without causing any toxic effects to the lungs (Ahmad *et al.*, 2016). Lacticin 3147, located inside macrophages, effectively inhibits *Mycobacterium tuberculosis* H37RV and *Mycobacterium kansasii* (Carroll *et al.*, 2010). Many bacteriocins have been reported to effectively treat skin and soft tissue infections caused by various organisms i.e. *Staphylococcus aureus, Propionibacterium acne, Staphylococcus epidermidis, Bacillus cereus, Bacillus subtilis* etc. (Manosroi *et al.*, 2010; Bowe *et al.*, 2006; Kang *et al.*, 2009; Izquierdo *et al.*, 2009). A bacteriocin hiracin JM79 from *Enterococcus hirae* DCH5 was found active against these skin infection-causing bacteria (Sanchez *et al.*, 2007). Two bacteriocin epidermin produced by *Staphylococcus epidermidis* and gallidermin produced by *Staphylococcus gallinarum* have been reported for effectively treating skin infections (Kellner *et al.*, 1988). Subpeptin JM4B,

a bacteriocin produced from Bacillus subtilis JM4 effectively inhibits Staphylococcus aureus, Enterococcus faecalis, Salmonella, Pseudomonas aeruginosa (Wu, 2005). Bacteriocin like subtilosin A, lacticin 3147, BLISK12 have also been reported to inhibit the growth of various major oral pathogens, i.e. *Porphyromonas gingivalis, Prevotella intermedia* etc. (Hammami *et al.*, 2011; Howell *et al.*, 1993; Tagg, 2014). A bacteriocin mutacin produced from *Streptococcus mutans* VSM43 showed great activity against dental caries. Cancer has become a risk or menace for human health over the past few decades. It is the second leading cause of human death (Center, 2013). Many studies have been reported that bacteriocins can be considered as great anticancer agents due to the presence of a large number of microvilli (Chaudhary and Munshi, 1995) which allow them to more binding of the antimicrobial peptide to the cancer cells. (Joo *et al.*, 2012)conducted a study in which nisin had the efficiency to prevent the growth of cancer cells. Another bacteriocin colicin E1 and A have pore-forming mechanism action that inhibits the growth of fibroblast line MRC5 and tumor cell lines in human (Chumchalova and Smarda, 2003).

CONCLUSION

Bacteriocins are one of the important natural defense mechanism bacteria use to fight with pathogenic microorganisms in the same environment. In recent years a number of technologies have been employed to bolster the potential of bacteriocins in food preservation. The knowledge gained by research carried out in this area will boost our understanding on their global effect in food ecosystem and license more stable approaches for application in food products. A wide variety of bacteriocins are capable in inhibiting the growth the foodborne and food spoiling pathogens have been recently described. The productivity of these compounds is still very low, so various techniques have been used to enhance their production. During the previous decades, many researchers have shifted their focus towards the bacteriocin application in the treatment of antibiotic-resistant disease-causing bacteria and infection. The therapeutic potential of bacteriocins has been enhanced by the use of engineered bacteriocin. This revived era of research in bacteriocin will lead to new application and potential inventions in this field.

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