ABSTRACT

Background: Bacteriocins are proteins groups, produced by gram-positive bacteria having the potential to use as food preservatives and antibacterial agents. Objectives: This review is aim to provide a comprehensive information on bacteriocins and their application. Methodology: Different databases were searched to find relevant information. Results: The protein of bacteriocins is ribosomal synthesized peptides. These proteins are produced by protein synthesis mechanism within a cell with amino acid composition ranging from 30 to 60 amino acids. The peptides have a narrow to wide spectrum of antibacterial activity against gram-positive bacteria, and their antibacterial properties remain intact even when exposed to heat. Bacteriocins proteins can be used in hot environments, such as cooking and food preparation, without losing their effectiveness. Additionally, the producer strain of Bacteriocins can provide a degree of self-protection against its own antibacterial peptide. Other than bacteriocins, specific LAB may generate antimicrobial peptides aiding in the preservation and safety of food due to production of cyclic dipeptides. Nisin is non-toxic, produced by generally recognized as safe (GRAS) bacteria, and quickly eliminated in the digestive system. Bacteriocins does not adversely affect the gut microflora. Conclusion: The bacteriocins can provide immunity for foods, allowing processors to maintain their desired microbial balance even after manufacture is complete.

Keywords: Bacteriocins, Antibacterial, Food safety, Food preservation, Human health, Lactic acid bacteria, Nisin
INTRODUCTION
The bacterial-induced antimicrobial peptides known as bacteriocins can kill or prevent the development of other bacteria. Bacteriocins have historically been used primarily to preserve food, but interest in their potential uses is growing, especially considering the dilemma caused by antibiotic resistance (1). The emergence of disorders involving multiple drug resistance and the tighter restrictions on the use of antibiotics for growth promoters has necessitated the search for alternative methods to control undesirable and potentially resistant microorganisms. Bacteriocins are preferred over chemical preservatives because consumers are concerned with their safety (2). Bacteriocins are generally favored over antibiotics because they can resist high temperatures and abnormal pH conditions. Bacteriocins' benefits make them suitable for many uses. Bacteriocins benefit from the spectrum, stability, bioengineering, diversity, manufacture, and safety (3). The bacteriocins produced by lactic acid bacteria are the most promising for ensuring food safety and promoting human and animal health. A class of Gram-positive, non-sporulating bacteria bacteriocins includes numerous members of food grade. They convert glucose to lactic acid (4).

The best-studied bacteriocin is Nisin, a food preservative by Lactococcus lactis subsp. lactis. It bears the E-number E-234 and has been authorized for use in various food items in more than 50 countries. Pediococcus, Lactococcus, Lactobacillus, and Enterococcus generate lacticin, plantaricin, curvacin, sakacin, and enterocin, among other bacteriocins. Manufacturers have approved pediocin and lacticin for use in food (5).

Bacteriocins may be bacteriostatic, bactericidal, sensitive to proteases, and inactivated by trypsin and pepsin after intake. Eukaryotic cells are not the target of bacteriocins. They hardly affect the gut microbes in this regard. Even though they do not stay in the environment or the body, target strains are less likely to encounter destroyed bacteriocin fragments, which might result in bacteriocin resistance (6). Bacteriocins have the potential to replace antibiotics as natural food preservatives. The current review discusses the uses of bacteriocins in humans and their application in ensuring the quality and safety of food.

Antimicrobial factors
Lactic acid bacteria (LAB) are used in fermentation with the objective to maintain the nutritional content of much food stuff since a long time. The common example of lactic acid bacteria are Lactobacillus, Lactococcus, Leuconostoc, and Pediococcus (7). A starter culture's primary responsibility is to produce lactic acid for efficient fermentation process. Lactic acid bacteria provide proteolytic enzymes during fermentation and the ripening of cheese varieties (8). The common aromatic compounds are diacetyl and acetaldehyde developed from citrate and lactose by mesophilic and thermophilic starter cultures respectively. Lactic acid is the main metabolic byproduct of LAB. The organic acid and its pH lowering may prevent many dangerous bacteria (9). The undissociated molecule affects pH immediately and may collapse susceptible bacteria's electrochemical proton gradient, causing bacteriostasis and death (6).

Lactic acid bacteria also produce trace quantities of acetic and propionic acids. They are antimicrobial in fermented foods and have a synergistic antibacterial effect with lactic acid. Alcohol, formic acid, fatty acids, hydrogen peroxide, diacetyl, reuterin, and reutericyclin are all products of lactic acid bacteria (10). Diacetyl and acetaldehyde not only provide cultured dairy products flavor, but they also have an antibacterial function. Escherichia coli may have its cell division inhibited by acetaldehyde, and diacetyl inhibits yeasts and both Gram positive and Gram-negative bacteria (11). Due to its strong aroma and the relatively high levels needed for preservation, the latter cannot be used as a food preservative. Many LAB that lacks the enzyme catalase produce hydrogen peroxide, like Lactobacillus spp. Microbes, including Staphylococcus aureus and Pseudomonas spp., are inhibited by H₂O₂.

Additionally, the lactoperoxidase system (a natural antibacterial system in milk) may produce the thiocyanate ion (SCN) and the antagonistic radical hypo thiocyanate by reacting with hydrogen peroxide (12). This method inhibits microorganisms in fresh and processed dairy products and extends cottage cheese and new milk shelf life. H₂O₂ generated by LAB is oxidizing; therefore, free radicals
may cause rancidity of lipids and oils and discoloration responses, limiting food preservation ability (13).

Reuterins, also known as b-hydroxy propionaldehyde, is an inhibiting substance produced by Lactobacillus reuteri when grown in anaerobic circumstances with glycerol. Reuterin has an inhibitory effect against an extensive range of microorganisms, including yeasts, fungi, protozoa, and both Gram-positive and Gram-negative bacteria. Reuterin inhibits species of Staphylococcus, Listeria, Clostridium, Salmonella, Candida, Shigella, and Trypanosoma, as well as other pathogens important to public health (14).

Other than bacteriocins, specific LAB may generate antimicrobial peptides that may aid in the preservation and safety of food. Because they produce cyclic dipeptides, Lactobacillus plantarum strains have antifungal activity are derived from grass silage and sourdough (15). The bacteriocins are a different class of inhibitory compounds that will be the subject of this review paper. Numerous bacterial species generate these antimicrobial peptides, but those produced by LAB members are of particular interest to the food industry since they can be employed as food preservatives because they have GRAS (generally recognized as safe) classification (16).

**Bacteriocins**

Bacteriocins are bioactive peptides produced on the ribosome and excreted extracellularly; they kill or inhibit the growth of other bacteria. Many of these heat-stable peptides are active at nanomolar concentrations and may have a restricted or broad target spectrum. Bacteriocin formation aids the viability of the producing cells since, in every instance, the producing cell displays specific immunity to the effect of its bacteriocin. A postponed antagonism experiment, in which clusters of the suspected producer are topped with a microbial lawn of a cell line, allows for the easy identification of such producing strains (17).

Further incubation revealed inhibitory zones in the delicate grass. Initially in 1953, the bacteriocin was used to produce antimicrobials of E. coli protein called colicins. In most cases, but not all, they are thought to disrupt the proton-motive force and kill off their targets by creating holes in the lipid bilayers of the bacterial cytoplasmic membrane (18).

Although five primary categories of LAB bacteriocins are reported, the system used here classifies all bacteriocins into two groups: class I bacteriocins, which contain the amino acid lanthionine and have a broad host range, and class II bacteriocins, which do not contain lanthionine and include the shaped LAB bacteriocins (class II) (19).

Other atypical residues in lantibiotics may be the consequence of posttranslational modification. The bacteriocins that don't include lanthionine are short (10 kDa), heat-stable peptides, but unlike lantibiotics, they don't undergo considerable posttranslational transformation (20) The bigger, heat-labile murein hydrolases used to be grouped in class III; however, it has been proposed that they be renamed bacteriolysis to reflect their unique properties better (21).

In scientific literature, antibiotics and bacteriocins are often interchanged. But bacteriocins are distinct from antibiotics in their manufacture, method of action, antibacterial spectrum, and toxicity. Also, bacteria that develop antibiotic resistance often do not build cross-resistance to bacteriocins (22). This difference is crucial because it allows the use of bacteriocins in food. Therefore, "biological food preservatives" have been offered as a phrase, or bacteriocins have been described as "innate immunity in food". Unlike antibiotics, bacteriocins have yet found a place in clinical practice despite receiving much attention in recent years (23). Humans had benefited from the accidental development of bacteriocins in foodstuff 8000 years. The purposeful usage of bacteriocins as preservatives was publicly suggested in 1951. During Cheese production, Lactic acid bacteria along with their inherent characteristics also produce bacteriocins, which might alter the cheese microflora distribution and inhibit the growth of adventitious spoilage/pathogenic bacteria (24). Since LAB bacteriocins are so effective at this, there has been a resurgence of interest in their usage, particularly considering raising public awareness of the potential dangers of conventional preservatives and the subsequent desire for minimally processed, high-quality, unadulterated options (25).

After its first release in England in 1953, Nisin quickly gained approval for usage in more than 48 other nations worldwide. Food and
Agriculture Organization, Expert Committee on Food Additives and the World Health Organization has declared Nisin as safe in 1969. This bacteriocin, designated as E234 on the European Union's food additives list, first gained approval from the USFDA in 1988 for pasteurized and processed cheese (26). Its efficacy as a preservative has prompted studies to discover complementary bacteriocins from GRAS species that either have a broader spectrum of action than Nisin or show more potent activity in conditions where Nisin is ineffective (23).

Since many bacteriocins have been shown to have antibacterial activity against a wide variety of pathogenic/food spoilage bacteria. Bacteriocins and bacteriocin-producing lactic acid bacteria are pose a significant role in improving the quality, safety, and authenticity of both fermented and nonfermented food products (27). However, a thorough discussion of the archetype of these compounds, Nisin, may be the most compelling way to show the potential use of these compounds (28).

**Nisin**

Gram-positive bacteria such as staphylococci, listeria, micrococi, streptococci, lactobacilli, and many spore-forming species of Clostridium and Bacillus are inhibited by nisin. Gram-negative bacteria, yeasts, and fungi are unaffected by routine usage. Due to its nature as a lantibiotic (29), Nisin is subject to extensive posttranslational modification. If added to sensitive cells, Nisin may kill them within a minute. Recent research has demonstrated that Nisin influences cell wall production and membrane integrity, suggesting that it has many modes of action. Peptidoglycan production is blocked due to its interaction with lipid II ("docking" molecule), an intermediary in peptidoglycan assembly (30).

After Nisin is inserted into the membrane and a pore is formed, low-molecular-weight chemicals rapidly and specifically effluxes, depolarizing the membrane. Liposomes without an electrical charge are unable to enter membranes (31). The current thinking is that now the membrane-associated nisin proteins combine to produce amphiphilic holes, which are then used by the small-molecule compounds to escape (32). When a cell's ability to generate energy for the synthesis of macromolecules like proteins and nucleic acids is compromised, the cell quickly dies (33). Nisin is generally ineffective against Gram-negative cells, but chelating chemicals have been shown to make them vulnerable by compromising the outer sheath by allowing the bacteriocin to enter into cytoplasm (34).

Formally, nisin was considered as an antibiotic, but it is incapable to combat Gram-negative bacteria. Its susceptibility to stomach proteases, and disintegration at physiological pH. Contrarily, nisin is non-toxic, produced by GRAS bacteria, and quickly eliminated in the digestive system (28). Thus, it does not adversely affect the gut microflora. These characteristics make it a suitable food preservative. Nisin resistance has not been shown to have any detrimental effects on antibiotic therapies and is not employed in clinical settings (35).

Due to its physicochemical features, the retention, solubility, and activity of Nisin are improved at low pH. Mainly, it is used to stop spores from spreading in processed cheese varieties. It prevents Clostridium botulinum types A, B, and E from growing (36). However, proteolytic forms are more resistant, and specific spore-forming species, such as Bacillus stearothermophilus, are more susceptible than others (37). Nisin sensitivity rises with decreasing pH, increasing temperature, prolonged heat shock, and reduced spore load. Notably, it kills spores instead of only preventing their growth (38).

**Uses of nisin**

The brand name for nisin is nisaplin. Nisaplin is a powdered, very stable formulation containing 2.5% nisin. The remainder comprises milk and milk solids. Here are just a handful of the various ways Nisin has been used in the food sector.

**Dairy products**

Processed cheese products, primarily spread, pose a significant threat owing to the influence of C. botulinum and the opportunity for growth and toxin formation. Clostridium sporogenes, butyricum, and tyrobutyricum may also cause processed cheese spoilage. Since their spores can tolerate 85-105 °C for 6-10 minutes, nisin prevents these anaerobic species. In the US, Nisin is used in cheese spreads to suppress C. botulinum development (39). Nisin renders these products moister, lower in sodium chloride and phosphate, and can be...
stored without refrigeration. Food type, spore load, storage time, and temperature range influence nisin dose. Nisin is added to dairy foods to extend its shelf life in the Middle East due to the warm environment, vast distances, and lack of refrigeration. It extends the shelf life of dairy products that cannot be sanitized (40). Nisin suppresses the beginning culture in stirred yogurt postproduction, maintaining taste and avoiding acidification (41).

Canned foods
Some thermophilic spore formers, such as B. stearothermophilus and Clostridium thermosaccharolyticum, can live and even thrive in tinned food when they are kept at high temperatures. Still, this problem may be mitigated by adding Nisin to the canning process. It also permits less intensive heat treatment without endangering food quality (42). It suppresses acid-tolerant spoiling microorganisms like Bacillus macerans and Clostridium pasteurianum in low-pH canned foods like tomatoes. Potato, peas, mushrooms, soup, and cereal pudding cans include it (43).

Meat and fish
Nisin is being explored as a substitute for nitrite in cured meat due to concerns about nitrite's toxicological safety. Food industry thought to explore the other means of preservation. Nisin, however, may be helpful in meat under some circumstance. Sausage is a frequently studied system because it spoils quickly and is typically caused by LAB that bacteriocins may control. Nisin activity has been shown to increase with decreasing fat content, and Nisin, in conjunction with lactic acid, has been shown to inhibit Gram-negative microbes (44).

Nisin inhibits Brochities theosophical (common spoilage organism in chilled raw meats and processed meat products) (32). Smoked fish, exceptionally when unprocessed or just minimally preserved, maybe a breeding ground for the psychrophilic bacterium Listeria monocytogenes (45). The Nisin in smoked salmon is a potent anti literal agent, mainly when the fish is vacuum sealed in a CO₂ (carbon dioxide) environment.

Alcoholic beverages
Nisin may be used to prevent the growth of acid-tolerant spoilage lactic acid bacteria in beer and wine. Common examples of acid-tolerant spoilage lactic acid bacteria are Lactobacillus, Pediococcus, and Leuconostoc. It does not hinder the development or fermentation rate of brewing yeast (29). The flavour of finished product also remains unaffected. It may lengthen the life of beer without requiring as much pasteurization (22). Nisin may also be used to prevent wine from going bad, although this is more difficult since it may kill the beneficial bacteria that cause malolactic fermentations. For this purpose, Nisin may be used in combination with nisin-resistant bacterial starter cultures, like Leuconostoc oenos resistance strains (34). The purpose of combination is to regulate malolactic fermentations. Nisin may be used in place of acid washing in the pitching yeast wash to prevent LAB. It can also help winemakers use less sulfur dioxide when preventing bacterial deterioration (29).

Other applications
Nisin prevents severe nonfermented, low-pH foods such as salad dressings and limits bacteria growth in high-moisture, hot-baked flour products and liquid eggs. It is helpful in the production of soup by inhibiting the development of psychrometric spoiled Bacillus spp., which is resistant to pasteurization (37). For fermentations that rely on Gram-negative bacteria or fungi, such as the generation of single-cell proteins, organic acids, polysaccharides, amino acids, and vitamins, it is also helpful in preventing the development of Gram-positive pollutants (46).

Finally, bacteriocins provide a desirable natural alternative to conventional antibiotics, widely used in veterinary medicine for preventative and curative purposes. Therefore, there is significant interest in using Nisin to treat and prevent cow mastitis, a chronic and expensive inflammation of the udder. Nisin is an active component in two commercially accessible products: a pre- and post-milking dip and cleaning wipes (44).

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MAR contributed to study concept and study design. KA and MYQ contributed in data collection. HT and FI did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.
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