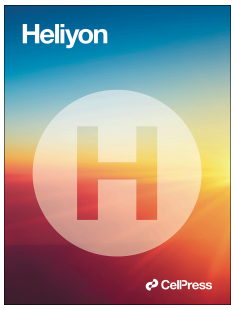

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PII: S2405-8440(24)13085-X

DOI: https://doi.org/10.1016/j.heliyon.2024.e37054

Reference: HLY 37054

To appear in: *HELIYON*

Received Date: 14 August 2023

Revised Date: 22 August 2024

Accepted Date: 27 August 2024

Please cite this article as: Emerging Lactic Acid Bacteria Bacteriocins as Anti-cancer and Anti-tumor Agents for Human Health, *HELIYON*, https://doi.org/10.1016/j.heliyon.2024.e37054.

Emerging Lactic Acid Bacteria Bacteriocins as Anticancer and Tumors Agents for Human Health and Food

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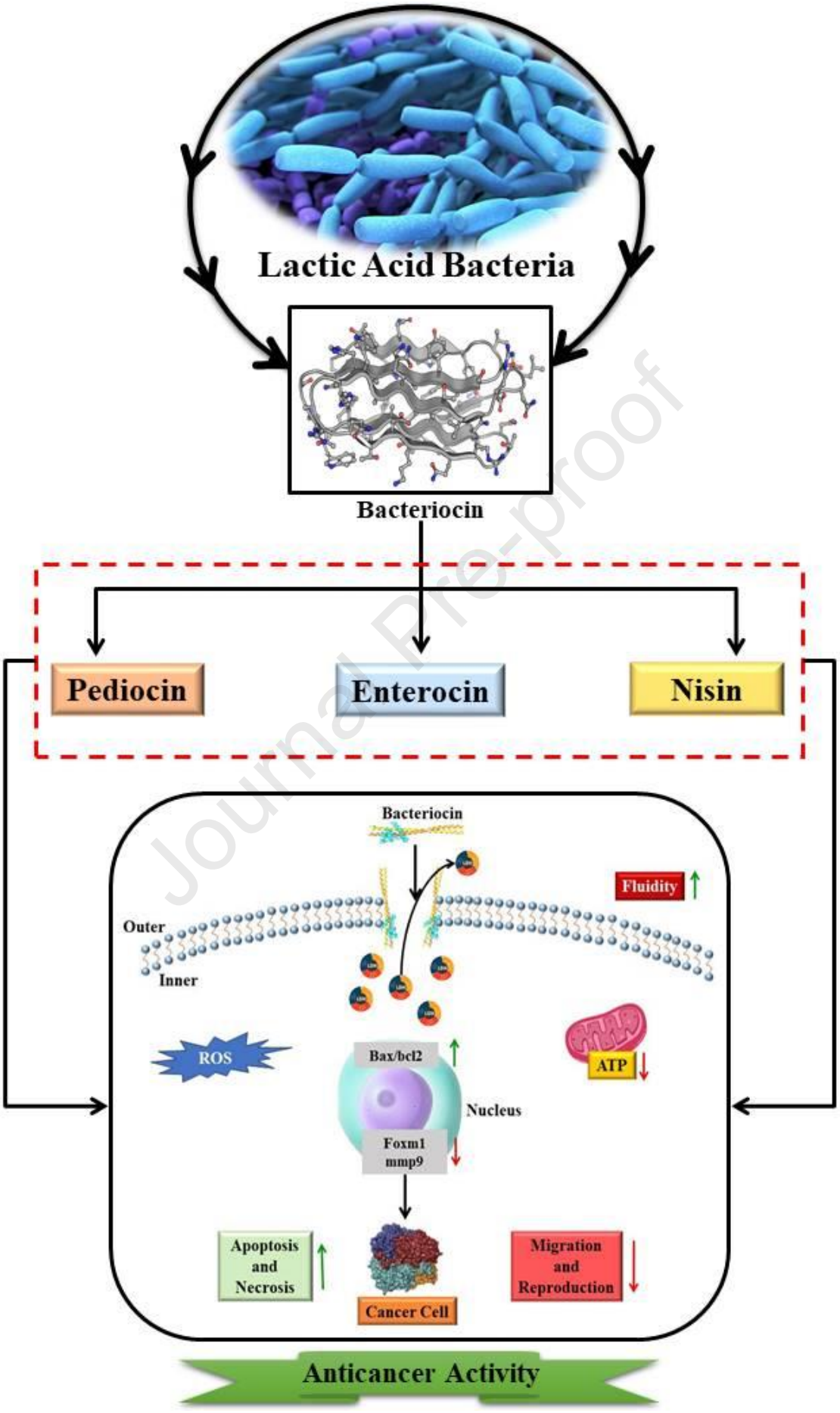
AKN, STGA, DKV, DB, RMS, AKS, ST and ARP have conceptualized, interpreted, corrected, and compiled literature and technically sound final versions of the manuscript; AKN and STGA have compiled the tables for manuscripts; DKV, AKN, ARP, RMS, AKS, GLU, DB, WAHA, MLC and SS have read the manuscript and provided suggestions and corrections. PPS and CAN have provided technical suggestions and corrections for the final submission of the manuscript. All authors critically reviewed and approved the final version of the manuscript for submission.

Graphical Abstract



Emerging Lactic Acid Bacteria Bacteriocins as Anti-cancer and Anti-tumor Agents for Human Health

Abstract

Modern cancer diagnostics and treatment options have greatly improved survival rates; the illness remains a major cause of mortality worldwide. Current treatments for cancer, such as chemotherapy, are not cancer-specific and may cause harm to healthy cells; therefore, it is imperative that new drugs for cancer be developed that are both safe and effective. It has been found that lactic acid bacteria (LAB) have the potential to produce bacteriocins, which could potentially offer a promising alternative for cancer treatment. They have been shown in several studies to be effective against cancer cells while having no effect on healthy cells. More research is needed to fully understand the potential of LAB bacteriocins as anti-cancer medicines, to find the appropriate dose and delivery route, and to conduct clinical trials to evaluate the effectiveness and safety of the products in human patients, as is suggested by this work. Furthermore, LAB bacteriocins may evolve into a significant new class of anti-cancer drugs and food products. Patients with cancer may have a safe and effective alternative treatment option in the form of anti-cancer foods and drugs. Therefore, the aim of this study is to provide an in-depth analysis of the recent breakthroughs and potential future technical advancements of significant bacteriocins that are produced by LAB, how these bacteriocins function, and how these bacteriocins may be utilized as an anti-cancer agent. In addition, the current analysis emphasizes the significant constraints and boundaries that bacteriocins face when they are used as an anti-cancer factor.

Keywords: Bacteriocin; Lactic acid bacteria; Cancer cells; mode of action; anti-cancer;

1. Introduction

Cancer is one of the top causes of sickness and mortality throughout the world **[1, 2]**. It is one of the non-communicable diseases that cause this. Recent evidence released by the World Health Organization (WHO) suggests that cancer is the second leading cause of death in the world, having been responsible for the passing of 10 million people in the year 2020 **[2, 3]**. The harsh repercussions of cancer treatments have a significant psychological and financial impact on nations that are afflicted by the disease. This is in addition to the growing death rates caused by the disease **[1]**. In the meantime, the disciplines of biotechnology and medical sciences are consistently making substantial improvements, leading to a better knowledge of a variety of human diseases. This, in turn, has led to improved treatment options. Understanding the difference between a tumor and cancer is crucial as they represent separate medical conditions **[4, 5]**. The first condition, the tumor is characterized by the development of an abnormal growth or mass in the tissue, which may be referred to as a lesion, lump, or neoplasm. On the other hand, cancer is characterized by the uncontrolled proliferation and spread of aberrant cells. Cancer cells are aberrant cells that avoid the regular processes that govern their growth. This allows cancer cells to proliferate unchecked. In a healthy cell, the equilibrium between the process of cell renewal and the process of cell death is normally maintained and the generation of new cells is carefully controlled to maintain a constant number of cells of a certain kind **[6, 7]**. However, due to genetic defects that are either inherited or produced by environmental stimuli, cells stop responding to the typical processes that regulate their proliferation. This results in the production of cell clones that multiply uncontrolled and may evolve into tumors or other forms of cancer. Cancer cells exhibit six significant alterations in their cellular physiology. These alterations include a limitless replicative capacity, self-sufficient growth signals, susceptibility to growth-

inhibitory signals, resistance to programmed cell death, prolonged angiogenesis, and the capability to metastasize **[8].**

Chemotherapy, surgery, and radiation are all methods that can be used to treat cancer, but chemotherapy is the one that is utilized the most **[9]**. Due to their inability to selectively target cancer cells, traditional chemotherapy treatments that target rapidly proliferating cells have the potential to cause damage to healthy cells and organs **[10]**. In addition, cancer cells frequently acquire resistance to chemotherapy as a result of a number of different factors. These factors include increased expression of drug-detoxifying enzymes and drug transporters in addition to improved DNA repair mechanisms in the cellular machinery that is responsible for apoptosis **[11]**. Surgery and radiation treatment are both effective ways of treating cancers that are confined, but they are not effective against tumor cells that have spread throughout the body. In situations like these, chemotherapy continues to be the most successful beneficial choice **[12]**. As a consequence of this, there is a huge demand for cancer cell-specific targeted treatments that may either be utilized as a stand-alone treatment or as an adjuvant to lower the therapeutic dosages of current anti-cancer drugs **[13]**. Because of the growing interest in bioactive peptide treatments, researchers are investigating the potential of bacteriocins as novel therapeutic agents for the treatment of cancer. Bacteriocins are predominantly generated by lactic acid bacteria (LAB), which are the focus of the current investigation. Different bacterial strains have the ability to produce a range of metabolites, including antimicrobial peptides called ribosomally produced bacteriocins. These metabolites help the bacteria fend off competition from other invading bacteria and allow them to thrive in specific environments [**14**]. Bacteriocins are peptides produced by specific bacteria that are non-immunogenic and biodegradable. They have been extensively studied by researchers [**14, 15, 16**]. These peptides are typically harmless to

mammals and are used as natural preservatives in food, such as milk and meat products [**14**]. This is due to their specificity towards microbes of the same or similar species. Historically, there was a prevailing belief that bacteriocins could only impede the growth of closely related strains or species. However, recent advancements in research have revealed that they possess a broad spectrum of antimicrobial effects. Furthermore, recent studies have demonstrated the ability of bacteriocins to inhibit the growth of various cancer cell lines [17]. Bacteriocins are responsible for the harmful effects that are caused by viruses or parasites; as a result, under certain conditions, they are also capable of targeting the eukaryotic cells that are found in the host **[14]**.

Therefore, as was pointed out in the previous paragraph, bacteriocins generated by lactic acid bacteria are an essential component of human biology for maintaining good health. Therefore, the purpose of this study is to provide an in-depth analysis of the recent breakthroughs and potential future technical advancements of significant bacteriocins that are produced by lactic acid bacteria, how these bacteriocins function, and how these bacteriocins may be utilized as an anti-cancer agent. When bacteriocins are used as an anti-cancer factor, they are subject to a number of key limits and limitations, which are brought to light in the present review.

2. Classification of the LAB-produced bacteriocins and their mechanism of action

LAB is a group of gram-positive bacteria that can be differentiated from one another using a wide range of morphological, microscopic, and biochemical tests **[14]**. The structure of the cell, the properties of glucose fermentation, the ability to utilize sugar, and the temperature ranges that are optimal for growth are all investigated in these tests **[18]**. Because of this, *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Lactococcus* make comprise the core group of four genera. The recent use of molecular biological techniques has resulted in a rise in the number of genera, some

examples of bacteria are as follows: *Aerococcus*, *Alloiococcus*, *Carnobacterium*, *Dolosigranulum*, *Enterococcus*, *Lactosphaera*, *Melissococcus*, *Oenococcus*, *Sporolactobacillus*, *Tetragenococcus*, *Vagococcus*, and *Weissella* **[19]**. It is important to note that the genus Lactobacillus has been reclassified and divided into approximately 25 new genera since the year 2020 [**20**]. These new genera include the following: *Lactobacillus*, *Acetilactobacillus*, *Agrilactobacillus*, *Amylolactobacillus*, *Apilactobacillus*, *Bombilactobacillus*, *Companilactobacillus*, *Dellaglioa*, *Fructilactobacillus*, *Furfurilactobacillus*, *Holzapfelia*, *Lacticaseibacillus*, *Latilactobacillus*, *Lactiplantibacillus*, *Lapidilactobacillus*, *Lentilactobacillus*, *Levilactobacillus*, *Ligilactobacillus*, *Limosilactobacillus*, *Liquorilactobacillus*, *Loigolactobacilus*, *Paralactobacillus*, *Paucilactobacillus*, *Schleiferilactobacillus*, and *Secundilactobacillus* **[20]**.

LABs can produce a variety of chemicals, some of which can prevent the growth of microorganisms **[14, 15]**. A few examples of these include lactic acid, acetic acid, and propanoic acid. Other examples are hydrogen peroxide, flavor compounds like acetoin and diacetyl, ethanol, and bacteriocins. Bacteriocins, in particular, have been used as natural preservatives in foods due to their capacity to inhibit the growth of microorganisms that are potentially hazardous to the health of humans. They do not alter the quality or safety of the food in any way and can be consumed without any concerns. Numerous species of LAB have been categorized by a variety of databases **[14, 15]**. These LAB species differ from one another in terms of their characteristics, structures, mechanisms of action, physicochemical attributes, activity range, and target cell wall receptors **[21]**.

Bacteriocins, which are produced by gram-positive bacteria such as LAB, have been categorized into five distinct groups as depicted in **Figure-1**, according to the genetic and

physicochemical characteristics that differentiate them from one another **[14, 15]**. These characteristics include the presence of modified amino acids after DNA translation, resistance to high temperatures, stability against proteolytic enzymes, the occurrence of SS-bonds (which mean two sulfur atoms bonded together, for example, disulfide bonds), and the effectiveness of antimicrobial activity. Class I bacteriocins, which are also known as "lantibiotics," have distinctive amino acids such as lanthionine, β-methyl lanthionine, and dehydroalanine as part of their fundamental structure. These amino acids help the bacteriocins kill bacteria. The antibacterial properties of the bacteriocins, as well as the stability of the peptides, are influenced by these particular amino acids that are formed by post-translational modifications of DNA. Approximately thirty percent of the class I bacteriocins that have been identified were produced by LABs. These bacteriocins include nisin, lacticin, and mersacidin **[22]**. Class II bacteriocins are peptides that can remain stable at high temperatures. They are known as pediocin-like bacteriocins due to their capacity to interact with the membranes of bacterial cells. These bacteriocins have a low molecular weight and vary from 2 to 10 kDa; moreover, they are composed of those amino acids that include sulfur. Bacteriocins such as Pediocin PA-1, Pentocin 31, Enterocin P, Sakacin G, and Enterocin A are all examples of bacteriocins that belong to this class **[23]**. When compared to class I and class II bacteriocins, class III bacteriocins are peptides that have a higher molecular weight (more than 10 kDa) and are more sensitive to heat. Bacteriolysins and non-lytics are the two subcategories that are further subdivided within this larger group of bacteriocins. Bacteriolysins are peptides that inhibit the growth of bacterial cells by destroying the cell walls of the bacterium. This results in the death of the cells. Lysostaphin, a peptide with a molecular weight of 27 kDa that degrades the cell walls of a variety of *Staphylococcus* species, is considered to be the original bacteriolysin. On the other hand, non-

lytic bacteriocins inhibit the target cells by affecting on the potential of the plasma membrane **[24]**. Class IV bacteriocins are peptides that contain lipid and carbohydrate moieties integrated into their peptide structures. This incorporation of lipid and carbohydrate moieties results in the synthesis of glycoproteins and lipoproteins. The characteristics of the bacteriocins can be altered depending on the makeup of these moieties. Lactocin 27 and leuconocin S are examples of prototype bacteriocins belonging to this class. Both of these bacteriocins are known to cause damage to the cell walls of bacteria. However, due to the properties of their structure, they are vulnerable to the impacts of enzymes that are involved in glycolysis or lipolysis **[25]**. Because of the circular nature of their structures, class V bacteriocins are characterized by a superior resistance to the effects of a wide variety of stresses. This is in contrast to the majority of bacteriocins, which have linear structures. Cleavage of the leader chain peptide is the first step in the biosynthesis of circular bacteriocins. This step is followed by circularization and then departure from the producing cell. The prototype bacteriocins that belong to class V are known as enterocin AS-48, pumilarin, lactocyclicin Q, and plantaricyclin A **[26]**.

3. Relationship between food and bacteriocins

Lactic acid bacteria play a crucial role in the natural fermentation process of different food products, particularly in the case of fermented milks [**14, 27]**. The release of bacteriocins by lactic acid bacteria occurs within the food matrices as they undergo growth. The presence of bacteriocins can naturally improve the shelf life of a particular food product by inhibiting the growth of spoilage organisms. This natural antimicrobial substance acts as a food preservative, helping to maintain the quality of the food [**14, 15**]. Therefore, when consuming such food, one can also derive health benefits from the specific bacteriocin found in a particular fermented food product. In cases where natural fermentation and production of bacteriocins cannot be achieved

in food products, purified bacteriocin can be added externally as a food preservative [**14, 28**]. Foods such as fermented milks are widely recognized for their ability to effectively deliver bacteriocins, which are natural therapeutic agents [**14, 27**]. These bacteriocins can be used alone or in combination with other drugs, making them a promising option for various applications.

To summarize, the application of bacteriocins in the food industry provides several valuable benefits. These antibacterial products have a low toxicity level and can be easily broken down by digestive enzymes. Their widespread adoption will mark a significant advancement in the food industry, as they are projected to decrease reliance on chemical substances and minimize the need for intense heat treatment methods. This approach will also be highly valuable in developing products that are both economical and environmental friendly, while still meeting consumer expectations.

4. Biofunctional mechanism of the lactic acid bacteria-produced bacteriocins

The vast majority of bacteriocins that have anti-cancer capabilities are cationic and amphiphilic and bacteria that have been cultured in a variety of growth mediums are the most common source of these bacteriocins **[14, 15, 29]**. When they come into contact with the negatively charged cell wall, these cationic peptides, which are also referred to as “membrane-active peptides,” engage in some sort of interaction with it. Since cancer cells have a higher concentration of negatively charged molecules on their surface, it is thought that the process of killing cancer cells happens by a lytic attack on the cell membrane **[30, 31]**. This hypothesis is supported by the observation that cancer cells have a thinner cell membrane.

Many different types of bacteria produce a range of substances, including antimicrobial peptides called ribosomally-produced bacteriocins. These metabolites help the bacteria defend against other invading bacteria and thrive in specific environments [**14**]. Bacteriocins are

peptides produced by a specific bacterial species. They are non-immunogenic and biodegradable [**14**, **15**, **16**]. These peptides are normally non-toxic to mammals and are utilized as natural preservatives in food such as milk and meat products **[14, 15, 29]**. This is because they are targeted against microbes of the same or similar species. In the past, it was believed that bacteriocins could only inhibit the growth of genetically related strains or species; however, current research has demonstrated that they have a wide range of antimicrobial effects. In addition to this, researchers have shown that bacteriocins can stop the proliferation of many cancer cell lines **[17]**.

Bacteriocins can exert their effect on the lipid II that is present on cell walls, and the mechanism in which they do so might vary greatly depending on the type of bacteriocin that is being used **[16, 32]**. Targeting the permease mannose phosphotransferase system, undecaprenyl pyrophosphate phosphatase, maltose ABC transporter, or zinc-dependent membrane-bound proteases are some examples of what they can do **[33]**. Studies have demonstrated that the expression level of the mannose-specific phosphotransferase system in bacteriocin is relatively low [**16**]. Bacteria that have become resistant to bacteriocins may alter the structure of their teichoic acid, which lowers the negative surface charge of the bacterial cell wall **[34]**. Teichoic acid is a polymer that is rich in phosphates and is anionic; polyglycerol phosphate links it to the membrane in the form of a glycolipid anchor so that it may be accessed there. In addition to being constituted of polyribitol phosphate, the core of the teichoic acid molecule can also be made up of a variety of polyols, such as mannitol, erythritol, or arabitol. The formation of a D-alanyl ester bond requires the usage of D-alanine, which may be substituted for the ribitol-phosphate in the backbone structure of teichoic acid. When it goes through the process of D-alanylation, teichoic acid carries a positive charge that neutralizes the anionic polymer. In its

natural state, teichoic acid leaves the cell wall with a negative charge because of the charge it carries when it exits the cell. Some bacterial species change anionic phospholipids with L-lysine to generate lysylphosphatidylglycerol, which is a basic phospholipid. This process is very similar to the D-alanylation process that teichoic acids go through to become virulence factors. Because of this, the cytoplasmic membrane now possesses a net positive charge, which can serve to defend it against bacteriocins such as the lipopeptide daptomycin **[16, 33, 34]**.

5. Anti-cancer activity of the lactic acid bacteria-produced bacteriocins against dfferent cancer cells

Bacteriocins have been found to have the power to destroy some cancer cells and prevent other cancer cells from infiltrating the body [**30, 31, 35, 36**]. As a result, there has been a growing interest in the research community on the anti-cancer characteristics of bacteriocins **[30, 35, 36, 37, 38]**. Inducing cell death, disrupting the cell cycle, limiting cell migration, destroying cell membrane structure, inhibiting angiogenesis, and influencing the immune system are some of the anti-cancer mechanisms of bacteriocins that have been recognized so far **[5, 9, 25, 29, 39]**.

Bacteriocins are produced by ribosomes in an inactive prepeptide form, which includes a signal sequence of amino acid residues at the *N*-terminus of the peptide [**14, 29, 40**]. Furthermore, a thorough and detailed discussion of the production of bacteriocin and its mechanism is presented in the following manner, as shown in **Figure-2**. An extra length of amino acid residues is present on the *N*-terminus of the peptide, and this stretch is referred to as a signal sequence. Bacteriocins are generated by ribosomes in their inactive prepeptide state. Immediately following the completion of translation (**Figure-2**), the prepeptide is subjected to posttranslational alterations [**40, 41**]. These changes include the production of changed amino acid residues within the prepeptide. The subsequent step involves the movement of the

prepeptide across the cytoplasmic membrane and into the extracellular space of the creature. After that, the prepeptide is cleaved by a proteolytic enzyme, which results in the removal of the *N*-terminal signal peptide (**Figure-2**). There are three significant functions that the *N*-terminal signal sequence performs. To begin, the signal sequence, which is also referred to as a transit peptide, serves as a signal that operates as an actual signal suggesting that such peptides are to be secreted to the outside of the living cells [**14, 29, 40**]. Second, because the prepeptide form is completely inactive, it guarantees that the bacteriocins will not become active until after they have been released first. Last but not least, the signal sequence imparts a particular shape to the prepeptide by means of its interaction with the *C*-terminal region, which is a region that will eventually become bacteriocin. The enzymes that are responsible for the synthesis of changed amino acid residues need to have this particular structure in order to recognize the prepeptide since it is necessary for their function. There is a single gene cluster that contains all of the genes that are involved in the production of active bacteriocins. These genes include those that code for the bacteriocin prepeptide, the modification enzyme, their transport apparatus, the protease that is necessary for the removal of the signal peptide, immunity, regulation, and many more [**14, 29, 40, 41**].

Bacteriocins have the ability to enhance the fluidity of cell membranes and create ion channels on the membranes of cancer cells (**Figure-3**). This, in turn, leads to an increased release of LDH. The presence of bacteriocins triggers the buildup of intracellular reactive oxygen species, resulting in an increase in the apoptotic index (bax/bcl2) [**42**]. Additionally, it suppresses the expression of FOXM1 and MMP9, hindering mitochondrial energy metabolism and glycolysis (**Figure-3**). As a result, the energy supply is reduced, leading to apoptosis and necrosis. Moreover, bacteriocins also impede the migration and proliferation of cancers,

ultimately promoting apoptosis and necrosis [**42**]. **Figure-3** depicts these cancer-fighting mechanisms of bacteriocins clearly and concisely. LABs can produce a diverse range of antimicrobial peptides known as bacteriocins. These bacteriocins have been extensively studied for their ability to inhibit the growth of pathogenic bacteria. Recent research has revealed that specific bacteriocins produced by LAB have the ability to hinder and decelerate the proliferation of cancer cells using different mechanisms **[5, 43, 44]**. One way bacteriocins can hinder the growth of cancer cells is by triggering apoptosis, a process of programmed cell death **[5]**. Studies have shown that certain bacteriocins, like nisin and pediocin, can trigger apoptosis in cancer cells. This process involves activating different signaling pathways that ultimately result in cell death **[6, 43]**. Another way that bacteriocins can hinder the growth of cancer cells is by interfering with the cell membrane, an important component for cancer cell function **[5, 32]**. Studies have demonstrated that certain bacteriocins, like lacticin 3147 and enterocin AS-48, can interfere with the cell membrane of cancer cells, ultimately causing their demise **[41, 44]**. Bacteriocins can also potentially hinder angiogenesis, the crucial process of forming new blood vessels that are necessary for tumor growth and metastasis. Some bacteriocins, like lactocin 27 and enterocin CRL35, have been identified to hinder angiogenesis by interfering with the signaling pathways responsible for blood vessel formation **[28]**. Furthermore, LAB-produced bacteriocins have been observed to influence the immune system, a vital component in the growth of cancer **[1, 13]**. Studies have shown that certain compounds, like pediocin and nisin, can have a positive effect on the immune system. These compounds have been found to activate immune cells like natural killer cells and macrophages, which can aid in the elimination of cancer cells **[16, 39, 45]**.

A wide variety of cancer cells can have the apoptotic process that leads to cell death, known as apoptosis, activated by nisin and other bacteriocins **[6, 43, 44]**. Following treatment with bacteriocin at various doses, cancer cells exhibited an increase in their apoptotic index, the cell cycle stopped, and the expression of genes that are involved in cell migration and proliferation was stifled **[45]**. In addition, bacteriocin can cause damage to cell membranes, which can result in the release of L-lactate dehydrogenase (EC 1.1.1.27). It can also enhance the production of reactive oxygen species, and impede anaerobic glycolysis and mitochondrial respiration, which ultimately causes cancer cells to exhaust their energy reserves. Bacteriocin, an interesting anti-cancer agent, can be together with other anti-cancer drugs to significantly increase the effectiveness of such treatments against cancer *in vivo* **[6, 30, 37]**. It has been suggested that increasing the level of cardiolipin can enhance the possibility of bacteriocin binding to the mitochondrial membrane. This might make it possible to focus cytotoxicity of certain cancer cells while minimizing damage to healthy cells **[14, 32, 38, 46]**. An anionic lipid called cardiolipin is one of the factors that contribute to the negative charge of the mitochondrial membrane **[32]**.

Research has shown that some bacteriocins, such as lacticin 3147 and enterocin AS-48, can cause the cell membrane of cancer cells to become disrupted, which ultimately results in the death of the cancer cells **[16, 30]**. Bacteriocins also can impede angiogenesis, which is the process of new blood vessel production and is crucial for the growth of tumors as well as their ability to spread to other parts of the body. Researchers have proven that lactocin 27 and enterocin CRL35 can prevent angiogenesis by causing disruptions in the signaling pathways that are necessary for the development of blood vessels **[30, 31]**. In addition to the mechanisms described above, it has also been shown that the bacteriocins produced by LAB can affect the

immune system, which is one of the most important factors in the progression of cancer. It has been demonstrated that some bacteriocins, such as pediocin and nisin, can boost the immune system. This is accomplished by activating a variety of immune cells, such as natural killer cells and macrophages, both of which can aid in the destruction of cancer cells **[16,** 17**, 30, 31]**.

Bacteriocins of many different types, including pyocins, nisin, azurin, colicin, pediocin, microcin, enterocin, and plantaricins, have been shown to have antineoplastic activities against cancer cell lines **[14, 30, 36, 38, 47, 48]**. Bacteriocins like these can block endothelial cells from migrating and moving around by directly interacting with the protein p53, or they can restrict the proliferation of endothelial cells by themselves **[45, 49]**. Overexpression of many growth factors can be found in tumor cells, including vascular endothelial growth factor and fibroblast growth factor **[50]**. There is evidence that the interaction of bacteriocins with the cell membrane is the mechanism that explains the anti-cancer activity of these molecules **[51]**. This is because the cell membranes of normal tissue cells and cancer cells are quite different from one another. On the other hand, normal tissue cells do not have cancer. Phospholipids, for instance, can be found on both the inside and exterior surfaces of human cells, and they exhibit asymmetry with each other **[37]**. Because of the high levels of anionic phosphatidylserine, *O*-glycosylated mucins, sialylated gangliosides, and heparin sulfates that are present in cancer cells, these cells almost always have a negative charge. On the other hand, typical human cells are asymmetric, with zwitterionic phospholipids covering the outer surface and amino-phospholipids such as phosphatidylserine and phosphatidylethanolamine covering the interior surface **[35]**. The presence of a negative charge on glycosaminoglycan sulfate residues makes it possible for LAB bacteriocins to bind directly to those residues. This helps prevent damage to the plasma membranes of eukaryotic cells like HT-29 and HeLa cells. On the other hand, positively charged cationic bacteriocins are

far more successful in binding to the negatively charged cell membrane of cancer cells than they are to the neutrally charged membrane of normal cells **[52]**.

Ultimately, the bacteriocins produced in the LAB possess the capability to impede and decelerate the proliferation of cancer cells by means of diverse mechanisms, including triggering apoptosis, interfering with the cell membrane, restraining angiogenesis, and regulating the immune system **[1, 13, 24]**. Additional investigation is required to thoroughly examine the possibilities of bacteriocins in the advancement of innovative cancer treatments.

6. Lactic acid bacteria-produced bacteriocins as potential anti-cancer agents

6.1. Anti-cancer effect of Nisin

Nisin is a bacteriocin that was produced by LAB and has recently received a lot of interest in both the industrial sector and the scientific community **[53, 54, 55]**. *Lactococcus lactis* is the bacteria responsible for its production **[56]**, and it is classified as a lantibiotic group of class I, type A (**Figure-1**). Nisin is composed of 34 different amino acids and has a molecular weight of 3.5 kDa. It is cationic and hydrophobic, and it possesses five internal ring structures that are disulfide bridged and contain carboxyl and amino end groups. Lanthionine, dehydroalanine, and β-methyllanthionine are three of the rare amino acids that might be found in nisin **[54, 56].** In 2006, it was discovered that nisin had the ability to inhibit the growth of two types of human adenocarcinomas, specifically those found in the colon and colorectal areas. This revelation shed light on the potential anti-cancer properties of nisin **[55]**. This finding indicates that nisin may possess anti-cancer capabilities. Further research that was conducted in 2012 indicated that treatment with nisin decreased the viability of human breast tumor cells (MCF-7 cells) and human liver hepatocellular carcinoma cancer cells (HepG2 cells) **[57]**. It was eventually discovered that Nisin was able to kill SW480 colon cancer cells **[45]**.

Numerous investigations have been conducted to examine the mechanism by which nisin A kills cancer cells. These studies have uncovered a variety of cellular consequences, including damage to epithelial integrity and cell polarization. The stimulation of apoptosis has been shown to be associated with the death of cells (**Table-1**). Nisin increases the expression of cytochrome C transcripts as well as the proapoptotic cation transporter regulator and apoptotic mediator glutathione-specific γ-glutamylcyclotransferase1 (*CHAC1* gene), which causes tumor cells to induce apoptosis. The stimulation of apoptosis employing the *CHAC1* gene might lead to an increase in the influx of calcium ions and the promotion of cell cycle arrest **[58, 59]**, which could ultimately result in a reduction in cell growth (**Figure-4**). An oversimplified diagram is showing the action mechanism of nisin in the fight against cancer cells in **Figure-4**.

Nisin types A and Z have been found to produce apoptosis in animal models of head and neck squamous cell carcinoma both *in vitro* and *in vivo*. This apoptosis was induced in the mouse models by both types of this nisin **[53, 69, 71]**. In addition, research has shown that both types of nisin inhibit angiogenic sprouting and hasten the death of endothelial cells. In yet another study, it was shown that Nisin Z affects several mitochondrial pathways in A375 melanoma cell lines, which ultimately results in the death of the cells due to oxidative stress **[59]**. Finally, to assess whether or not it is more effective than chemotherapy on its own, the combination of nisin with a chemotherapeutic drug has been the subject of at least two separate research investigations. According to Preet and co-workers who worked on this project, using doxorubicin on its own to cure skin cancer in mice is not nearly as successful as using it in combination with nisin **[71]**. The researchers, Rana and co-workers conducted a study to explore the potential of a specific nanoconstruct in fighting cancer [**69**]. This nanoconstruct consisted of oligomeric chitosan-coated silver nanoparticles, which were loaded with bacteriocin nisin and 5-florouracil (5-

FU/nisin-CHI-AgNPs). The study focused on its effectiveness against DMBA/TPA-induced murine skin cancer. Nisin was found to boost the anti-cancer effects of 5-fluorouracil in both *in vitro* and *in vivo* study conditions **[69]**. Combination treatment reduces the rate of cell division, speeds up the process of apoptosis, and stops the formation of new blood vessels.

By integrating bacteriocins with nanoscale drug delivery systems (nano-DDS), we can address certain drawbacks of bacteriocins, such as susceptibility to degradation by proteases, resistance mechanisms, and inefficient intracellular delivery. According to a study conducted by a team of researchers, they found that solid lipid nanoparticles loaded with nisin, when compared to free nisin, have a significant impact on inhibiting the growth of *Treponema denticola*, an oral pathogen [**72**]. It is widely recognized that nisin, being a natural antimicrobial peptide, is extensively utilized in the food industry due to its remarkable capability to inhibit a wide range of Gram-positive bacteria [**14, 21, 43, 50, 54, 63**]. The increased effectiveness of embedded nisin, as opposed to free nisin, can be attributed to various factors that are discussed as follows. The heightened effectiveness of embedded nisin in comparison to free nisin can be attributed to its improved stability, precise delivery, protection against inactivation, extended interaction with bacterial cells, and potential synergistic effects with other antimicrobial agents [**14, 70**]. The numerous benefits of embedded nisin make it a highly effective and dependable choice for antimicrobial applications across a range of industries, such as food preservation and biomedical uses [**14, 34, 50, 63, 70, 71**].

Additionally, these nanoparticles were able to disrupt oral biofilms and reduce the viability of oral squamous cell carcinoma cells (OSCC). In addition, when OSCC cells were exposed to SLN-Nisin, noticeable morphological changes were observed under scanning electron microscopy (SEM) **[72]**. These changes were not observed in cells treated with empty

nanoparticles or free nisin. The results suggest that nano-DDS have the potential to enhance the properties of bacteriocin, making them a promising tool.

6.2. Anti-cancer effect of Pediocin

Pediocin is a molecule that is positively charged and has a low molecular weight, with a range that goes from 2.7 to 17 kDa **[23]**. Produced by specific species of *Pediococcus*, it characteristics a hydrophilic *N*-terminal region that contains the pediocin box (YGNGV) motif and a hydrophobic or amphiphilic *C*-terminal variable section **[23]**. These LABs are frequently found in fermented foods like pickles and sauerkraut, for example **[23, 49]**. Pediocin can prevent the growth of a wide variety of bacterial cells and works on the formation of pores in the cytoplasmic membrane. It does this by preventing the targeted cells' ability to absorb amino acids from phospholipids found in the cytoplasmic membrane. Pediocin is distinguished by a number of characteristics, including resistance to proteolytic enzymes, thermostability, and the capacity to maintain its action throughout a wide pH range. Pediocin is an effective antibiotic that can stop the growth of bacteria that cause food to go spoiled as well as hazardous microorganisms like *Listeria monocytogenes* and *Salmonella enterica*, which are the pathogens that lead to foodborne diseases **[49]**.

Although the precise mechanism of action of pediocin has not been fully elucidated, it is believed that it involves the instability of the cell membranes of bacteria, which leads to the release of intracellular components such as proteins and DNA. These released components can then be utilized by the immune system to identify and eliminate cancer cells once they have been recognized. In addition, research conducted in the laboratory has shown that pediocin is capable of inducing apoptosis, also known as programmed cell death, in cancer cells that are grown *in vitro* **[39]**. In recent years, there has been a rising interest in researching the idea of employing

pediocin as an anti-cancer agent. This interest has been fueled by the discovery that pediocin inhibits the growth of cancer cells. In the context of laboratory examinations, many investigations have demonstrated that pediocin can inhibit the growth of different kinds of cancer cells, including breast cancer cells and melanoma cells, amongst others **[36]**. In addition, oral or intravenous administration of pediocin in animal models has been shown to reduce the growth of tumors, as a result of the research that was conducted before the clinical trials. In addition to its possible use as an anti-cancer agent, pediocin has also been tested to see whether or not it is effective in treating other diseases, such as HIV/AIDS and malaria. The results of preliminary investigations show that it may have therapeutic promise against various disorders **[47]**; however, further study must be conducted before any conclusions can be formed. The survival rate of cells treated with 25 µg/mL of rec-pediocin and native pediocin CP2 was 5.5% and 1.2%, respectively, for both the HepG2 line and the MCF-7 line **[72]**. The sensitivity of the HeLa cells to rec-pediocin was significantly lower than that of the other lines investigated in that study.

In general, the potential of pediocin as an anti-cancer medication is quite promising, as it has been demonstrated to limit the development of cancer cells in laboratory trials as well as in organisms. This suggests that it may one day be used to treat cancer. Further investigation into the method through which pediocin kills cancer cells might shed light on its mode of action, which in turn can facilitate the development of innovative treatments for cancer patients. The findings of the experiments that were carried out to evaluate the efficacy of pediocin as an anti-cancer agent are presented in **Table-2**.

6.3. Anti-cancer effect of Enterocin

Enterocin is a bacteriocin that is produced by *Enterococcus faecium* **[76]**. *Enterococcus* species are capable of producing enterocins, which are efficient against *L. monocytogenes* **[28, 41]**. *L.*

436 *monocytogenes* is a pathogenic bacteria that can cause serious foodborne diseases. It has been
437 demonstrated that several forms of enterocins, such as Enterocin CCM4231, Enterocin CRL35,
438 and Enterocin AS-48, can decrease the number of *L. monocytogenes* cells that are present in
439 dairy products **[27, 28, 77]**. Additionally, enterocins A and B demonstrate anti-*Listerial*
440 capabilities in minced pork, and enterococci can be utilized as starting cultures in the production
441 of cheese to inhibit the growth of *L. monocytogenes* **[78]**. Enterocin AS-48 was the first circular
442 enterocin to be identified, and it is classified as a member of class Ib. Its structure is made up of
443 a hydrophilic component at the *N*-terminal that contains methionine and a hydrophobic variable
444 section at the *C*-terminal that contains tryptophan. It is a short peptide that consists of 70 amino
445 acid residues and does not have any disulfide bridges within its structure. The molecule
446 possesses a compact hydrophobic core that is surrounded by five α-helices that are organized in a
447 spherical configuration. These features contribute to the molecule's resistance to high pH, heat,
448 and denaturing chemicals. Because of its durability, enterocin AS-48 has achieved widespread
449 application in food processing technology. In a nutshell, studies have shown that enterocins can
450 inhibit the growth of the pathogen *L. monocytogenes* in a variety of food products. Thus, it can
451 be concluded that Enterocin AS-48, which stands out among enterocins because of its one-of-a-
452 kind structure and exceptional stability, is currently utilized for significant applications in the
453 food processing industry **[41, 77]**.

454 Researchers have explored the possibility of enterocin as a cancer treatment due to its
455 notable capacity to block the growth of several cancer cell lines **[44, 76]**. Cesa-Luna and
456 coworkers have carried out research to determine whether or not enterocin has the potential to
457 act as an anti-cancer agent **[30]**. According to the findings of the researchers, enterocin was
458 successful in preventing the proliferation of several distinct human cancer cell lines, including

459 those originating from the breast, colon, and prostate. In addition, researchers noticed that
460 enterocin was able to inhibit the development of tumors *in vivo* and trigger apoptosis, all of
461 which point to the possibility of enterocin as a viable therapeutic approach for the treatment of
462 cancer. The study also investigated the molecular targets of enterocin and identified potential
463 mechanisms of action involving pro-inflammatory cytokines, transcription factors, and signal
464 transduction pathways. These findings offered important new perspectives on the potential of
465 enterocin as an innovative and powerful cancer-fighting agent **[30]**. In another study, Ankaiah
466 and colleagues investigated the impact of enterocins on the growth and development of cancer
467 cells **[44]**. The purpose of this study was to see if the researchers could prevent the proliferation
468 of cancer cells. To accomplish this, the researchers examined the effects of enterocins on human
469 tumor cell lines, including breast, lung, and colon cancer cells. Researchers revealed that the
470 growth of the tumor cell lines was affected by enterocins in a manner that was proportional to the
471 concentration of the enterocin present **[44]**. This indicates that a larger concentration of enterocin
472 results in a greater growth-inhibiting impact. Researchers concluded that enterocins, due to their
473 capacity to suppress the proliferation of tumor cells, had the potential to be employed as a
474 therapeutic agent in the fight against cancer. This research reveals recent developments on the
475 potential of enterocins as anti-cancer agents and demonstrates the need for more investigation
476 into this subject matter. Recently, Sharma and co-workers investigated both the safety and
477 efficacy of enterocin as an anti-cancer agent **[76]**. They used the HeLa (cervical cancer) and
478 MCF-7 (breast cancer) cell lines in their research to examine the efficacy of enterocin as an anti-
479 cancer agent. The findings of the research indicated that enterocin possessed substantial anti-
480 cancer effects in both of the cell lines used in the study, with an IC_{50} value of 6.22 μg/mL for
481 HeLa and 8.35 μg/mL for MCF-7, respectively. In addition, the research demonstrated that

enterocin had a very low toxicity level in normal human fibroblast cells, which suggests that it might be utilized as an anti-cancer agent without risk **[76]**. Based on these findings, enterocin appears to be a promising candidate for usage as an anti-cancer agent in the future since it is free of potential side effects while still being very effective. Confirming the efficacy of enterocin as an anti-cancer agent and determining whether or not it has the potential to be used in other cancer treatments is the subject of further in-depth investigation and study. In general, it is becoming increasingly apparent that enterocin has the potential to be an innovative, effective, and secure therapeutic agent against cancer. Research conducted *in vitro* as well as *in vivo* has shown that it inhibits the growth of cancers. This research has also led to the discovery of polyphenolic and phenethylated enterocin derivatives that have significant anti-cancer activity. In addition, clinical trials are currently being conducted to investigate whether or not enterocin has the potential to be turned into a possible therapeutic candidate for the treatment of cancer.

6.4. Anti-cancer effects of Plantaricin

In a study conducted by De Giani and colleagues, they investigated a compound found in *Lactiplantibacillus plantarum* PBS067 that has properties similar to bacteriocin. This compound showed antimicrobial activity and was tested on both normal and cancerogenic human intestinal cells, revealing its potential effects [***79***]. The isolated Plantaricin P1053 exhibited significant effects on both normal and cancerous epithelial intestinal cell lines. It was found to enhance the viability of healthy cells while reducing the proliferation of cancer cells [***79***]. The heat resistance of Plantaricin DM5, derived from *L. plantarum* DM5, was demonstrated at a temperature of 121 °C for 15 minutes. Although it was susceptible to proteolytic enzymes, it exhibited stability within a pH range of 2.0-10.0. Additionally, it retained its activity even when exposed to surfactants and detergents. The study conducted by **Das and Goyal [80]** demonstrated the non-

toxic and biocompatible properties of plantaricin DM5, which was derived from the probiotic *L. plantarum* C11. The effects of this compound were observed on human embryonic kidney 293 (HEK 293) and human cervical cancer (HeLa) cell lines. In a study conducted by **Sand et al. [51]**, it was found that plantaricin A derived from *L. plantarum* C11 exhibited a membrane-permeabilizing antimicrobial effect. This cationic peptide demonstrated promising properties in the field of antimicrobial research.

6.5. Anti-cancer effects of other lactic acid bacterial bacteriocins

In recent years, several bacteriocins produced by LAB have been investigated for their ability to inhibit cancer cells or cancer cell lines (**Table-3**), both *in vitro* and *in vivo* [**36, 50, 72, 74**]. Some of the most important findings from the studies that were carried out to evaluate the effectiveness of additional bacteriocins derived from LAB as an anti-cancer agent against a variety of cancer cell lines are given in **Table-3**. About 37% of bacteriocin research has been directed toward the treatment of diseases such as cancer, systemic infections, stomatology, cosmetics, and contraception. In comparison, 29% of bacteriocin research has been directed toward the preservation of food, 25% has been directed toward the study of bio-nanomaterials, and 9% has been directed toward the treatment of animals **[81]**. In addition to this, there has been a rise in the number of patents for bacteriocins **[14]**. Although research has been conducted on a number of additional bacteriocins that are generated from LAB, bacteriocins such as nisin, pediocin, and enterocin are the ones that are most frequently utilized for the treatment of cancer cells and cancer cell lines (**Table-1** and **Table-**2).

6.6. Anti-cancer effects of bacteriocins from genetically modified organisms

There is a limited amount of research available on the cytotoxic effects of bacteriocins derived from genetically modified organisms. A study conducted by **Kumar et al. [91]** examined the

cytotoxic effects of pediocin CP2, which is produced by *P. acidilactici* CP2 MTCC5101, and its recombinant version, a synthetic fusion protein cloned in *E. coli* BL21(DE3)-*ped*A. The researchers tested these substances against various human cancer cell lines, including HepG2, HeLa, and MCF7. Recombinant pediocin and native pediocin both showed the ability to inhibit HepG2 and MCF7 cells in a dose-dependent manner. However, it seems that HeLa cells were more resistant to the effects of these pediocins. The results of the DNA fragmentation method revealed that the recombinant pediocin induced apoptosis of the cancer cells after 48 hours of incubation, as reported by Kumar and co-workers **[91]**.

As part of a previous study, researchers successfully used a technique involving the cloning of recombinant Pediocin PA-1 in a yeast called *Pichia pastoris* **[92]**. They also observed that the native pediocin produced by *P. acidilactici* PAC1.0 had a similar inhibitory effect on the growth of two different cell lines: DLD-1, a human colon adenocarcinoma, and A-549, a human lung carcinoma **[92]**. Interestingly, the regular pediocin PA-1 exhibited a cytotoxic effect even at extremely low concentrations of 1.6 μM. On the other hand, the recombinant pediocin did not show any effectiveness at this concentration.

In a recent study, two bacteriocins called rhamnosin and lysostaphin were produced in high quantities in *E. coli* **[83]**. These bacteriocins were derived from probiotic bacteria *Lacticaseibacillus rhamnosus* and *Staphylococcus simulans*, respectively. The purification process involved immobilized-Ni^{2+} affinity chromatography. The researchers then examined the anti-cancer properties of these bacteriocins against CCA cell lines. It was discovered that both bacteriocins were able to effectively hinder the growth of CCA cell lines in a manner that depended on the dosage. Additionally, they were found to be less harmful to a normal cholangiocyte cell line **[83]**.

7. Restrictions/limitations of bacteriocins as an anti-cancer factor

Bacteriocins have shown promise as anti-cancer agents; nevertheless, their application is restricted for several reasons. First, their activity spectrum is limited, and they may not be effective against all cancer cell types, limiting their utility as a broad-spectrum anti-cancer agent. Second, they may have low *in vivo* bioavailability and stability, reducing their efficacy as an anti-cancer agent. Rapid elimination from the body may also diminish their therapeutic importance. Third, the use of bacteriocins as an anti-cancer drug may give rise to safety concerns. Bacteriocins have the potential to be harmful to healthy cells and tissues, which can result in unfavorable side effects such as cytotoxicity or the alteration of metabolic activities **[93, 94]**. Furthermore, the relatively short half-lives of these bacterial peptides present a significant obstacle in the process of formulating cancer-curing drugs. The high expense of mass production, a lack of resistance to proteolytic cleavage, poor distribution to cancer cells, and a lack of well-designed clinical studies are some of the other difficulties **[95, 96]**. Therefore, it is very necessary to confirm these findings *in vivo* before bacteriocins may be utilized as an anti-cancer agent. It is required to perform further study in this field to confirm the methods and genetically modify the naturally existing bacteriocins to overcome the constraints that were highlighted before. To thoroughly investigate the possibility of bacteriocins serving as a treatment for cancer, it is necessary to address these constraints and do further research in this area.

8. Conclusions, recommendations and future prospects

Bacteriocins produced by LAB have a number of benefits that set them apart from other types of anti-cancer drugs. They are regarded as safe and are well tolerated by the human body. They also have a low level of toxicity and are highly selective for the cells that cause cancer. In addition to

this, there is the possibility that they might be able to enter cancer cells and cause cell death. Bacteriocins are a great choice for further study and clinical investigations due to their little harm to normal cells and enhanced selectivity for various types of cancer cells. This makes them an excellent prospect for further investigation. To further understand the processes of interaction between bacteriocins and cell surface receptors to establish concrete results, consequences, and outcomes, further research is necessary.

Despite the fact that research on LAB bacteriocins as anti-cancer agents is still in its infancy, the findings that have been revealed so far are encouraging. Several studies have suggested that LAB bacteriocins could be able to inhibit the development of cancer cells both *in vitro* and in animal models of the disease. In addition, it has been demonstrated that the use of LAB bacteriocins in conjunction with other anti-cancer drugs can increase the overall effectiveness of the treatment. In furtherance of this, it is essential to have a full understanding of the effectiveness of bacteriocins in different cell lines when tested *in vivo*. Chemical alterations, such as the replacement of amino acids, cyclization, and the exchange of alkaline amino acids, can be performed on bacteriocins to lengthen their half-lives and improve their stability. Furthermore, it has been demonstrated that some bacteriocins have a synergistic effect when coupled with other traditional anti-cancer drugs for the purpose of acting as chemotherapeutic agents. It has been concluded, on an overall basis, that LAB bacteriocins, as well as bacteriocins in general, have the potential to be used as anti-cancer therapies; this, however, is contingent upon a substantial extensive study that needs more to be carried out in this field.

It is necessary to do more studies to fully understand the potential of LAB bacteriocins as anti-cancer agents. This should involve studies to determine the optimal dose and delivery method, as well as clinical trials to evaluate the products' efficacy and safety in human subjects,

as well as further research. In the event that more research on the topic is carried out, LAB bacteriocins have the potential to develop into a substantial new class of anti-cancer drugs. Cancer patients would therefore have access to a second treatment option that is not only effective but also risk-free as a result of this development.

Ethical approval

Not required

Ethics statement

Not applicable

Data availability

No data was used for the research described in the article. No data associated with this study has been deposited into a publicly available repository.

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List of Tables

Table-1: Several significant findings emerged from the trials that evaluated the effectiveness of Nisin, either on its own or in combination with other compounds, as a potential anti-cancer treatment for various types of cancer cells.

Nisin type	**Bacterial source**	**Cancer cell type**	**Anti-cancer activity and remarks**	**References**
Nisin	-	Colorectal cancer cells	Colorectal cancer was effectively suppressed by reducing the Bcl-2/Bax ratio and increasing the activity of caspase-3.	**[61]**
Nisin A	-	MCF-7 breast cancer cell line	Nisin demonstrated significant and specific cytotoxicity against the MCF-7 cell line, with an IC_{50} value of 11.68 μg/mL.	**[62]**
Nisin Z	-	Melanoma cancer	The utilization of nisin in a nano-formulation resulted in a significant reduction of CD31 expression, which is an important factor in angiogenesis, within tumor tissues.	**[59]**
Nisin ZP	-	Non-small cell lung cancer	The results of the *in vitro* cytotoxicity studies demonstrated the significant inhibition of lung cancer cells with KRAS mutation, regardless of p53 tumor protein expression. This effect was observed in both A549 cells, which overexpress p53, and H1299 cells,	**[63[**

			which have non-functional p53. Additionally, nisin ZP was found to be effective against EGFR mutations in H1975 cells.	
Nisin	-	Myelogenous leukemia cell line (K562)	Genes and proteins associated with cell survival were decreased, while genes and proteins related to cell death were increased. Nisin exhibited a significant anti-cancer effect on K562 cells by modulating the expression of Bcl-2 and Bax genes, primarily through the intrinsic pathway involving mitochondria.	**[64]**
Nisin	-	Colorectal cancer	During the in vitro experiment, there was a notable increase in the mRNA expression level of bax, bax/bcl2 ratios, caspase 3, and caspase 9. On the other hand, there was no notable rise in the mRNA expression level of caspases 6 and 8 following 24-hour and 48-hour incubation.	**[65]**
Nisin	-	Gastric cancer	After analyzing cancer cells, it was shown that Nisin had the highest level of apoptosis.	**[66]**
Nisin A	*Lactococcus lactis* subsp. *lactis*	Head and neck squamous cell carcinoma (HNSCC) cells	Apoptosis was induced in head and neck squamous cell carcinoma cells by means of a route that was dependent on calpain.	**[53]**

Nisin A	*Lactococcus lactis* subsp. *lactis*	Colon cancer cells (SW480 cells)	There was a significant anti-proliferative impact as well as an increase in the apoptotic index (the ratio of bax to bcl-2) at both the mRNA and protein levels.	**[45]**
Nisin A	*Lactococcus lactis* subsp. *lactis*	Human liver cancer (HepG2 cell line)	In hepatocellular carcinoma cells, this resulted in a suppression of both cell growth and the expression of mRNA and protein encoding PI3K and AKT.	**[67]**
Nisin Z	*Lactococcus lactis* subsp. *lactis*	Head and neck cancer	Both the size of the tumor and the number of cancer cells with characteristics that promote apoptosis had decreased.	**[68]**
Nisin A	*Lactococcus lactis* subsp. *lactis*	Liver cancer cell lines (HuH-7, and SNU182)	TWIST1 expression was observed to be decreased following nisin treatment when compared to untreated SNU182 and HuH-7 cell lines. This finding was made in regard to the examination of the expression of EMT transcription factors ZEB1, SNAI1, and TWIST1 in relation to nisin treatment.	**[58]**
Nisin	*Lactococcus lactis* subsp. *lactis*	Murine skin cancer	Shown a statistically significant reduction in both the mean volume of tumors (68.34%) and the mean burden of tumors (82.39%). In addition to this, it repaired the histoarchitecture of the skin and enhanced the oxidant/antioxidant condition.	**[69]**

Nisin	*Lactococcus lactis* subsp. *lactis*	Breast cancer and liver hepatocellular carcinoma; MCF-7 (human breast adenocarcinoma cell line), HepG2 (human hepatoma cells)	When the nisin concentration was increased to 140 mM, the cell viability of both cell lines dropped to less than 20%. The decrease in cell viability of cancer cell lines was demonstrated to be dependent on the dosage. Observations were made of cell shrinkage, vacuolization of cytoplasm, condensation, and lateralization of nucleus at concentrations above IC_{50}.	**[57]**
Nisin Z	*Lactococcus lactis* subsp. *lactis*	Colon and breast cancer cells (HT-29)	HT-29 cancer cells were shown to be more susceptible to the cytotoxic effects of the treatment than MCF-7 cancer cells.	**[70]**
Nisin ZP	*Lactococcus lactis* subsp. *lactis*	Lung cancer (A549 and H1299)	In non-small cell lung cancer, caused apoptosis and a halt in the cell cycle in the G0/G1 phase regardless of whether or not the tumor protein p53 was present.	**[50]**
Nisin-loaded solid lipid nanoparticles (SLN-Nisin)	*Lactococcus lactis* subsp. *lactis*	Oral squamous cell carcinoma cell (OSCC)	Significant changes in morphology were seen in OSCC cells that were challenged with SLN-Nisin. These changes were found in comparison to the empty-nanoparticle or free nisin. These modifications indicate that SLN-Nisin likely affects cell viability by increasing pore development.	**[70]**

- Not reported

Table-2: Some key findings from the trials conducted to assess the efficiency of pediocin as an anti-cancer agent.

Pediocin type	**Bacterial source**	**Type of cancer cell line**	**Pediocin activity**	**References**
Pediocin SR6	*Pediococcus pentosaceus* SR6	T47D	Inhibits growth	[**48**]
Pediocin PA-1	*Pediococcus acidilactici*	HeLa	Strongly inhibits growth	**[73]**
Pediocin CP2	*Pediococcus acidilactici* MTCC 5101	MCF-7	Inhibits growth	**[72]**
Pediocin K2a2-3	*Pediococcus acidilactici* K2a2-3	HT2a	Inhibits growth	**[74]**
Pediocin PA-1	*Pediococcus acidilactici* PAC1.0	A549	Weakly inhibits growth	**[75]**

Table-3: Some significant findings emerged from the trials that evaluated the effectiveness of different bacteriocins as a potential anti-cancer treatment for various types of cancer cells.

Bacteriocin type	**Bacterial source**	**Molecular weight (kDa)**	**Cancer cell lines**	**References**
-	*Enterococcus Faecalis*	27	MCF-7, WRL68	**[82]**
Rhamnosin	*Lacticaseibacillus rhamnosus* (probiotic)	ND	CCA (Cholangiocarcinoma)	**[83]**
Lysostaphin	*Staphylococcus simulans*	ND	CCA (Cholangiocarcinoma)	**[83]**
Bac10307	*Lactobacillus acidophilus*	4.2	HepG2	**[84]**
Nisin	*Lactococcus lactis*	3.5	NHDF cells	**[85]**
-	*Pediococcus pentosaceus*	ND	T47D	**[73]**
-	*Lactobacillus*	-	HCT–116, PC–3 and HepG–2	**[86]**
Colicin E1 and enterocin A	*Enterococcus faecalis*	ND	AGS gastric cancer cell lines	**[87]**
Enterocin	*Enterococcus faecium* 12a	65	various human cancer cell lines (HeLa, HCT-15, A549, MG-63, and normal human PBMCs)	**[76]**
-	*Lactococcus lactis*	ND	MCF-7, CCL-119	**[88]**

Enterocin LNS18	*Enterococcus thailandicus*	ND	HepG2	**[46]**
Bovicin HC5	*Streptococcus bovis* HC5	2.4	MCF-7, HepG2	**[57]**
Plantaricin A	*Lactiplantibacillus plantarum* C11	ND	GH4, Reh, Jurkat, PC12, N2A	**[51]**
Plantaricin DM5	*Lactiplantibacillus plantarum* DM5	15.20	HeLa	**[80]**
m2163 peptide	*Lacticaseibacillus casei*	2.70	SW480	**[43]**
m2386 peptide	*Lacticaseibacillus casei*	2.70	SW480	**[43]**
KL15 peptide	*Lacticaseibacillus casei*	1.90	SW480, CaCo-2	**[89]**
Plantaricin P1053	*Lactiplantibacillus plantarum* PBS067	1.05	E705	**[79]**
Lacticin	*Lactobacillus delbrueckii*	13.00	HeLa, MCF-7, HT1080, H1299, HEK293T,	**[90]**

ND: Not Detected; - Not reported

List of Figures

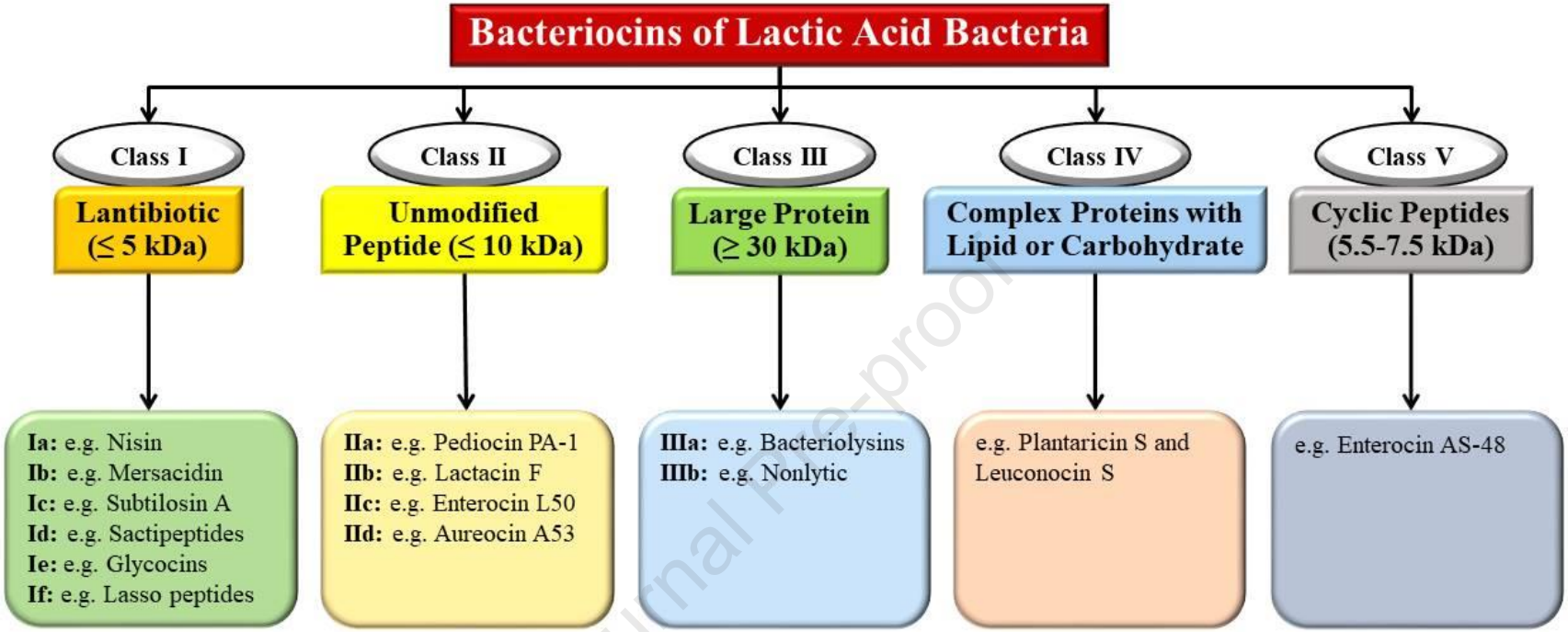

Figure-1: A schematic illustration of the classification of bacteriocins produced by lactic acid bacteria.

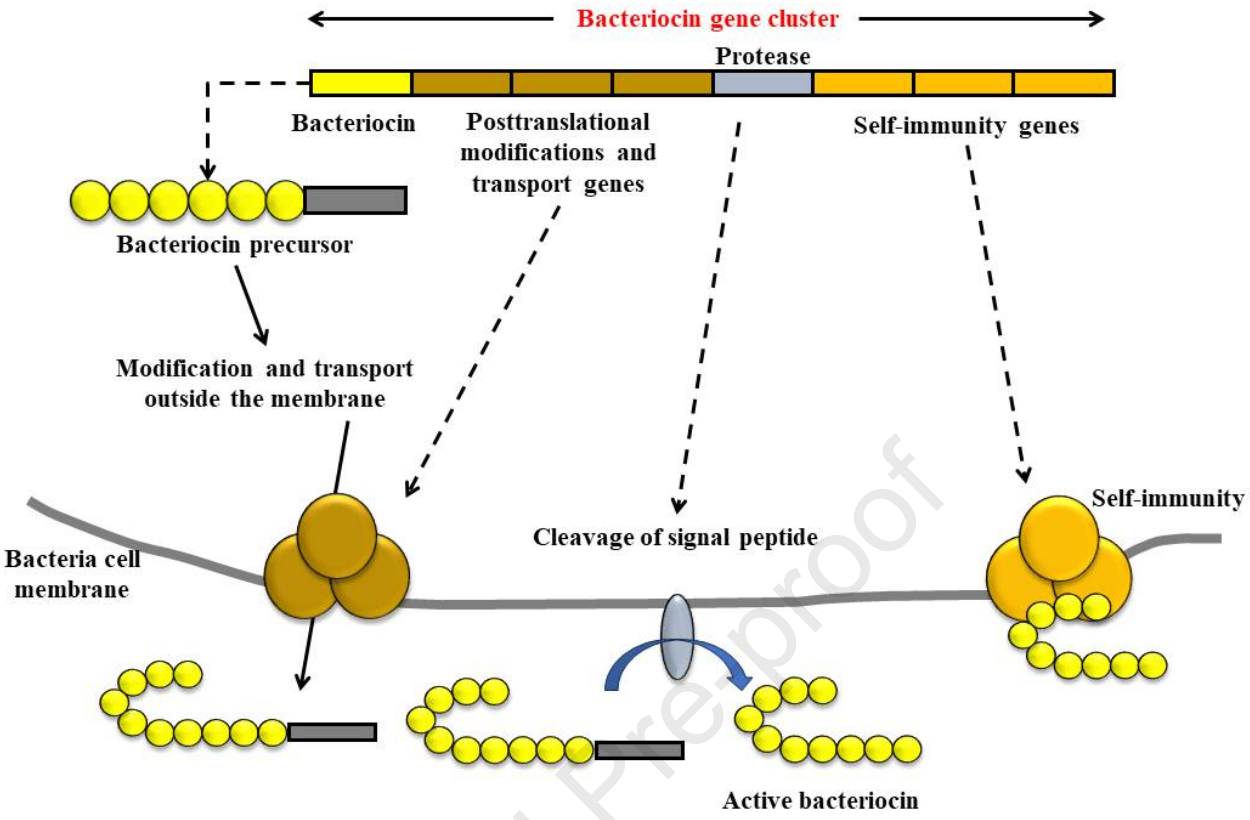

Figure-2: Schematic presentation on the production of bacteriocin and its mechanism **[14, 29, 40, 41]**. Following translation, the prepeptide goes through posttranslational modifications, resulting in the formation of altered amino acid residues within the prepeptide. After that, the prepeptide is moved across the cytoplasmic membrane to the exterior of the cell. A proteolytic enzyme subsequently cleaves the prepeptide to eliminate the *N*-terminal signal peptide. The *N*-terminal signal sequence serves three crucial functions. Initially, the signal sequence, also known as a transit peptide, functions as a genuine indicator that these peptides are intended for secretion to the extracellular environment. Furthermore, the prepeptide form remains inactive, guaranteeing that the bacteriocins are only activated once they have been secreted. Ultimately, through its interaction with the *C*-terminal region, the signal sequence imparts a distinct conformation to the prepeptide, which is a precursor to a bacteriocin. The precise arrangement is necessary for the enzymes to identify the prepeptide and produce altered amino acid residues. The genes responsible for producing active bacteriocins, including those that encode the bacteriocin prepeptide, modification enzyme, transport machinery, protease for signal peptide removal, immunity, regulation, and more, are all located together in a single gene cluster.

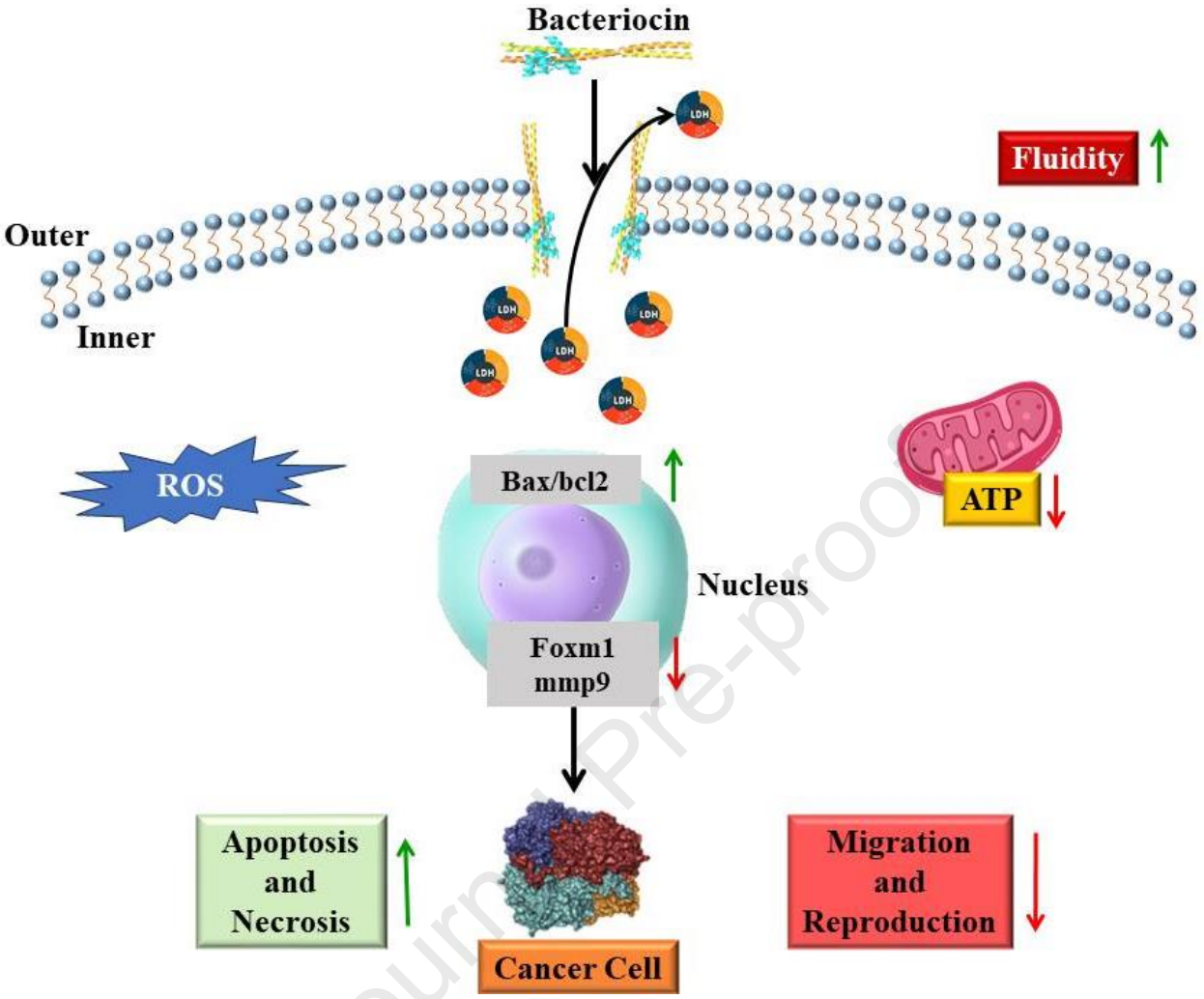

Figure-3: Schematic presentation on various mechanisms to inhibit and limit the growth of cancer cells, while antibiotics employ specific molecules and mechanisms to effectively combat cancers. **[6, 42, 43, 44]**. [***Abbreviations***: ROS: reactive oxygen species; ATP: Adenosine triphosphate]

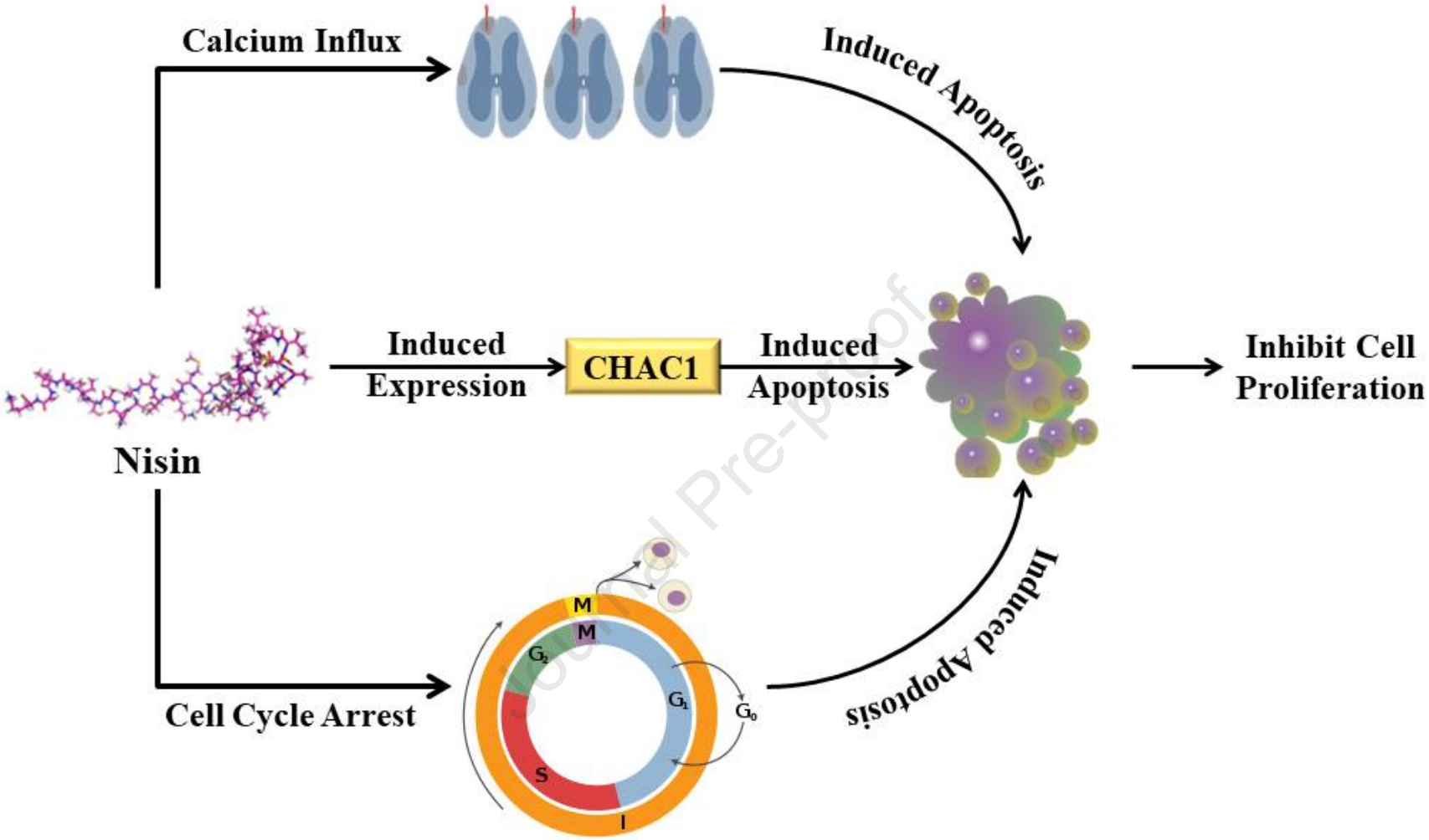

Figure-4: Schematic depiction of the mechanism of action of nisin in relation to the suppression of cancer cells [**60**]. Exploring the intricate workings of nisin's impact on cancer cell lines involves delving into the molecular mechanisms at play. These mechanisms encompass the influx of calcium molecules, the expression of the apoptosis-mediator *CHAC1* cation transport regulator, and the induction of cell cycle arrest.

Highlights:

- Important lactic acid bacteria-produced bacteriocins have been focussed.
- Safe bacteriocins are identified as an alternative to existing cancer treatments.
- Cationic and amphiphilic bacteriocins have shown anti-cancer activities.
- Cationic bacteriocin reacts with anionic cell membranes to prevent cancer growth.
- Lacking in *in vivo* anti-cancer analysis, bacteriocins have been suggested for future study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.