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REVIEW ARTICLE

# The Diversity of Bacteriocin and Its Antiviral Potential: An Overview

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## ABSTRACT

*The viral resistances to the known antiviral agent have raised the need for developing alternatives antiviral agents.one of the promising alternatives are bacteriocins. Bacteriocin are natural peptides ribosomal synthesized by gram negative and gram positive bacteria. Bacteriocins are secreted as a method for the producer to compete in the environment. Bacteriocin gene cluster can be found on plasmid or chromosome. Bacteriocins have presented wide range of activity against bacteria, fungi, virus and cancer cells and have a high margin of safety which encouraged its use in food and pharmaceutical applications. Nisin is one example of bacteriocins approved by FDA for use as food preservative. Bacteriocin nature variation is one of its unique qualities. Bacteriocin varies in physical, chemical, molecular and genetic nature. This variation have been studied and recoded over the years. In this review we discuss and summarized the diversity of bacteriocins and their different mechanism of actions against virus.*

## INTRODUCTION

The current pandemic[1] and the continuous resistance of antiviral agents have raised the need for antiviral agents[2] meanwhile bacteriocins have been suggested as an alternative antiviral agents [3]. Bacteriocins are ribosomal synthesized peptides produced by gram negative and gram positive bacteria [4]. It is considered a golden weaponry arsenal against different pathogen [5] because of its high safety margin[6] and the diversity of its structures and characters[7]. The first bacteriocin was discovered in the year 1925 by Gratia from *Escherichia coli* and later named as colicin[8]. Since then large number of bacteriocins have been identified from a diverse group of bacterial strains. bacteriocins were also successfully applied in the food industry as bio preservative[9] e.g., Nisin which have been approved by FDA[10]. Moreover several applications have been reported for bacteriocins such as antimicrobial[11]and anticancer[12] which encouraged the attempts to use bacteriocins in pharmaceutical industry [13]. In this review we discuss the diversity of bacteriocins and their different mechanism of actions against virus.

**Bacteriocin from Gram positive bacteria**
**Lantibiotics:**

Lantibiotics are <5kda peptidesthat can endure heat and PH [14] .They are called Lantibiotics because it have lanthionine ,metyl-lanthionine and unsaturated amino acids residue which form rings[15]. Lantibiotics have been classified as class I of gram positive bacteria and can be sub-categorized to class Ia and class Ib. Class Ia is flexible elongated structure that acts by binding of N-terminal to lipid II which inhibits peptidoglycan and C-terminal form pores in the cell membrane .On the other hand class b are negative charge inflexible globular structures that act by inhibiting cell enzymes[16].

**Non -lantibiotics: Class II, III and IV.**

Class II are small heat stable that is not post transitionally modified except for disulfide bond[17]. This class have four sub classes IIa, IIb, IIc and IId. Class IIa is a linear Pediocin like bacteriocin with a distinct amino acid sequence that is active against *Listeria monocytogenes*. Class IIb is two peptides that act together for activity class IIC contains cysteine and are called thiolbiotics and cystibiotics and lastly class IId contain the class II bacteriocin that doesn't belong to the other three sub classes[18]. The class II are cationic that act on target microorganisms by permeabilization of the membrane[19]. Class III are heat sensitive >30kda protein and class IV have a lipid or/and carbohydrate part [20].

**Bacteriocins from gram negative bacteria.**
**Microcins:**

Microcins are < 10 kda peptides that can endure drastic PH and temperature also protease enzyme[21].They are entitled as microcins due to its distinct low

molecular weight [22] Microcins have been grouped to class I which are post-transitionally modified and have < 5 kda molecular weight and class II which are seldom modified post-transitionally with molecular weight between 5 and 10 Kda[23]. Microcins have been found to exert its activity against target microorganism by either pore formation in cell membrane[24] or inhibiting enzymes such as DNA gyrase [25].

**Colicins:**

Colicins are >10kda high molecular weight protein and heat sensitive produced by *E.coli* as an sos reaction which is a DNA repair system that allows DNA replication to bypass errors in the DNA induced by the environment[26]. Colicins have been grouped to group A which require Tol protein to cross the cell outer membrane[27] and group B which requires TonB protein to cross the cell outer membrane[28].

**Classification of bacteriocins**

The diversity of bacteriocins and its producers have hindered its grouping and classifications. Many approaches have been proposed to classify and group bacteriocins [29-30] . One of the most distinct approaches was suggested by Cotter et al [11] which is simple and includes both gram positive and negative bacteria. This approach removed large protein such as colicins to includes peptides only and used post-translationally modified peptides (RiPPs) nomenclature[31]. Cotter et al.[11] classified bacteriocins to Class I (modified post transitionally bacteriocins) and class II (Un modified bacteriocins). Class I was further sub categorized to lantibiotics, proteusins, cyanobactins, thiopeptides ,sactibiotics, bottromycins, glycocins, prenylated, anacyclamide-like cyanobactins, patellamide-like cyanobactins, lasso peptides, linaridins ,linear azole and modified microcins that are not related to the above subgroups and class II was further sub categorized to IIa,IIb,IIc,IId and IIe. Recently Soltani et al[32] suggested an update to this classification by grouping class I as post transnationally modified peptides < 5 KDa with related enzymes embedded in its gene cluster while class II 4-6 KDa unmodified peptides that may or may not have a disulfide bridge. This update signifies class I with higher stability than class II despite the disulfide link. The summery and comparison of Cotter et al [11] and Soltani et al.[32] classification of bacteriocins is presented in (table 1).

**Table 1:Summery and comparison of Cotter et al[11] and Soltani et al[32] classification of bacteriocins.**

| **Class I: post-translationally modified bacteriocins.** | | | | | |
|---|---|---|---|---|---|
| **Cotter et al [11]** | | | **Soltani et al [32]** | | |
| **GROUP** | **properties** | **Examples** | **GROUP** | **properties** | **examples** |
| **Lantibiotics** | Lanthionine bridge | Nisin, actagardine, mersacidin, planosporicin, and mutacin 1140 | **Lantibiotics** | Lanthionine bridge and two peptides lantibiotics | Nisin, actagardine, mersacidin, planosporicin, and mutacin 1140 Two peptides :Lacticin 3147 and Haloduracin |
| **Sactibiotics** | sulphur–α-carbon link | Ruminococcin C, thuricin CD, Subtilosin A. | **Sactibiotics** | sulphur–α-carbon link | Ruminococcin C, thuricin CD, Subtilosin A. |
| **Linaridins** | Linear peptides with dehydrated amino acid | Cypemycin | **Linaridins** | Linear peptides with dehydrated amino acid | Cypemycin |
| **Thiopeptides** | Heterocyclic, pyridine,piperidine, and dihydropyridine | Thiostrepton | **Thiopeptides** | Heterocyclic, pyridine,piperidine, and dihydropyridine | Thiostrepton |
| **Glycocins** | Glycopeptides with S-link | Sublancin 168 | **Glycocins** | Glycopeptides with S-link | Sublancin 168 |
| **Linear azole** | Peptide linear that have heterocyclic oxazole and thiazole | Microcin B17 | **Linear azole** | Peptide linear that have heterocyclic oxazole and thiazole | Microcin B17 |
| **Bottromycins** | Macrocyclic with amidine moiety, decarboxylated thiazole and methylated amino acids | Bottromycin A2 | **Bottromycins** | Macrocyclic with amidine moiety, decarboxylated thiazole and methylated amino acids | Bottromycin A2 |
| **Cyanobactins** | Macrocyclic peptides with heterocycles and | Patellamide A | **Cyanobactins** | Macrocyclic peptides with heterocycles and | Patellamide A |

| | | | | | |
|---|---|---|---|---|---|
| | may or may not have a prenylated amino acid. | | | may or may not have a prenylated amino acid. | |
| **Lasso peptides** | Possess lasso form. | Microcin J25 | **Lasso peptides** | Possess lasso form. | Microcin J25 |
| **MccC7-C51-type bacteriocins** | have aspartic acid with carboxy-terminal | Microcin C7 to C51 | **Nucleotide peptides** | have a nucleotide fragment | Microcin C |
| **Proteusins** | Have several methylation ,hydroxylation and epimerization | Polytheonamide A | **Siderophore peptides** | Possess siderophore type non ribosomal modified linked to C terminal serine containing part | Microcins H47,Microcin E492 |
| | | | **Circular peptides** | Single non modified peptides Cyclized by N to c linkage | Gassericin A , Garvicin ,Enterocin AS-48 |
| **Class II: Non- modified bacteriocins.** | | | | | |
| **Cotter et al [11]** | | | **Soltani et al [32]** | | |
| **GROUP** | **properties** | **examples** | **GROUP** | **properties** | **examples** |
| **Peptides IIa** | Have YGNGV sequence | enterocin CRL35,Pediocin PA-1, carnobacteriocin BM1 | **single Pediocin-like peptides** | Have YGNGV sequence | enterocin CRL35,Pediocin PA-1, carnobacteriocin BM1 |
| **Peptides IIb** | Two peptides are necessary for activity | Lactacin F | **Two-peptides** | Two non-modified or more peptides are necessary for activity | Lactacin F |
| **Peptides IIc** | Peptides in cycle form | Enterocin AS-48 | | | |
| **Peptides IId** | non-pediocin like single peptides | Lactococcin A, Epidermicin NI01, Microcin V | **single Unmodified peptides** | non-pediocin like single peptides | Lactococcin A, Epidermicin NI01, Microcin V |
| **Peptides IIe** | Possess siderophore type non ribosomal modified linked to C terminal serine containing part | Microcin E492 | | | |

**Bacteriocins oppose virus:**

The bacteriocins antiviral activity was reported for enterocin CRL35 produced by *Enterococcus faecium CRL35* [33]. It was found that enterocin CRL35 inhibited *Herpes Simplex* (HSV) type 1 and 2 but wasn't virucidal and suggested that enterocin CRL35 acted on viral intracellular multiplication which was further investigated by Wachsman et al [34] whom concluded that enterocin CRL35 acted on glycoprotein synthesis on the viral replication but didn't affect its uptake. Similarly another report showed that enterocin ST4V produced by *Enterococcus mundtii* ST4V inhibited HSV type 1 and 2 by 99.9% [35] while polio virus was inhibited by only 50% and measles virus by 95% ,however Cavicchioli et al [36] reported that *Enterococcus durans Gen12* had antiviral activity against polio virus of 93.7% after adsorption and 27.9% against HSV type 1 before adsorption. Additionally enterocin ST5Ha displayed activity against HSV type 1[37]and enterocin B displayed activity against H3N2, H1N1[38] . Although these report mechanisms are still unknown, it is interestingly to note that most are considered class II bacteriocins. Another mechanism of action was reported by Férir et al [39] for Labyrinthopeptin A1 which is a lantibiotics against HIV and HSV. Labyrinthopeptin A1 inhibits HIV transmission between T-cells by inhibiting entry also by acting on the virus envelope but not the receptor. on the other hand Torres et al [40] suggested that Subtilosin A at a concentration lower than virucidal doesn't act before HSV type 1 and 2 viral protein synthesis which impose that Subtilosin A act on either assembly or the release this was in agreement with Quintana et al [41] findings. The binding of Duramycin to phosphatidylethanolamine in zika virus envelope hindered TIM1 receptor and lowered infection in placental cells and explants[42]. Similar mechanism was observered for Ebola, West Nile and dengue viruses [43]. Hepatitis C virus entry was hindered by Micrococcin P1 also cell to cell transmtion without affecting viral particles secretion[44].Bacteriocins with antiviral activity are compared and summarized in (table 2).

**Table 2: Bacteriocin that have exhibited activity against virus.**

| Bacteriocin | Properties of bacteriocins | Producer microorgansim | Virus active against | Suggested mechanism for antiviral activity | Reference |
|---|---|---|---|---|---|
| **Enterocin CRL35** | ClassII/ pediocin-like bacteriocin | *Enterococcus faecium CRL35* | HSV type 1<br>HSV type 2 | Late stage glycoprotein synthesis on the viral replication | [33,34] |
| **Enterocin B** | Chemically synthesized | *Enterococcus faecium L3* | H3N2<br>H1N1 | Not determined | [38] |
| **Enterocin ST4V** | Non-glycosylated 3950 Da peptide | *Enterococcus mundtii ST4V* | HSV type 1<br>HSV type 2<br>polio virus<br>measles virus | Not determined | [35] |
| **Enterocin ST5H** | ClassII/ pediocin-like bacteriocin | *Enterococcus faecium ST5Ha* | HSV type 1 | Not determined | [37] |
| **Subtilosin A** | Sactibiotics | *Bacillus subtilis KATMIRA 1933* | HSV type 1<br>HSV type 2 | act on assembly or the release | [40,41] |
| **Labyrinthopeptin A1** | lantibiotics | *Actinomadura namibiensis DSM 6313* | HSV type 1<br>HIV | inhibiting entry also by acting on the virus envelope but not the receptor | [39] |
| **Duramycin** | cyclic 19-aa peptide | *Streptomyces cinnamoneus* | Zika virus<br>West Nile virus<br>Dengue virus<br>Ebola virus | inhibit TIM1 receptor | [42,43] |
| **Micrococcin P1** | macrocyclic peptide | *Staphylococcus equorum WS2733* | Hepatitis C virus | Acted on virus cell entry without affecting the secretion of viral particales | [44] |
| **Bacteriocin in cell free supernatant** | Bacteriocin like substance | *Lactobacillus delbrueckii* | Influenza virus<br>H7N7<br>H7N1 | Decreased the Expression of hemag- glutinin ,viral glycoproteins,neuraminidase, and nucleoprotein on the surface of infected cells,and hemagglutinin production and virus yield, | [45] |
| **Semi-purified bacteriocins** | | *Lactococcus lactis GLc03 and GLc05, E. durans GEn09, GEn12, GEn14 and GEn17* | HSV type 1<br>polio virus | Acted after adsorption of polio virus and may have acted on HSV type 1 envelope or affected its binding to the cell receptor | [36] |

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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