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Bacterial acrylamidase

Mini Review: Classification of Proteins Antibiotics

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ABSTRACT

The proposed classification was exclusively on the basis of biosynthetic gene clusters encoding for only antibiotic proteins. Biosynthetic gene clusters (BGCs) are organized groups of genes within the genome of prokaryotes which are involved in the production of specialized bioactive compound. These biosynthetic gene clusters contain all the genes encoding for the production of enzymes that catalysed the formation of antibiotic proteins, these include ribosomal peptides which are synthesized by the ribosome (RP), non-ribosomal peptides synthetase (NRPS).The antibiotic proteins produced by the members of the domain archaea are mainly archaeocins which are synthesized by the ribosomal pathways. Archaea have been overlooked and therefore under investigatigated for antibiotic proteins production, because only 15 achaeocins were described and characterized from haloarchaea and sulfolobus archaea, while there are many potentially untapped archaeocins in the archaeal environment, however, today there is an increase in the number of research on archaea due to the availability of molecular techniques such as 16S ribosomal RNA gene sequencing and metagenomic sequencing which revealed that they are found in not only the extreme environment but also the non-extreme (common) environment. Bacteriocins are protein toxins that inhibit the growth of similar or closely related bacterial strains at a certain concentration.Bacteriocins with their properties such as thermal tolerance and wide pH activity are now becoming promising alternatives to conventional antibiotics. Research into their production, mechanisms of action, and spectrum of activity can position them as valuable and safe antibiotic agents. Expanding research on Archaea and Bacteria using molecular techniques such as next-generation sequencing, CRISPR-Cas9 gene editing and genome mining resources (antiSMASH) can enhance the exploration and discovery of novel antibiotics and their BGCs.

INTRODUCTION

Various types of antibiotic classification exist on many bases including sources, biological properties, molecular structures, mode of action, spectrum of activity, route of administration, etc [1]. However, due to the diversity of antibiotics and the emergence of new compounds with therapeutic potentials, the classification is becoming complex, and the previous classification cannot accommodate and cover the major and minor classes of antibiotics [2]. Antibiotics were first defined as chemical compounds produced by microorganisms (bacteria and fungi) that inhibit or destroy other microorganisms [3,4]. In this review, a classification of proteins antibiotics was developed on the basis of biosynthetic pathways (**Fig. 1**). The antibiotic-producing ability of microorganisms is critically determined by biosynthetic gene clusters within their genome [5]. Biosynthetic gene clusters (BGCs) are organized groups of genes within the genome of prokaryotes (Bacteria and Archaea) that are involved in the production of specialized bioactive compounds including antibiotic proteins [5-6].

Biosynthetic gene clusters are the genetic building blocks of bacteria and archaea which help in the coordination of some activities such as metabolism, signalling process, and

environmental adaptation. Gene clusters contain all of the genes required for a particular function [7]. Recent studies revealed that the majority of antibiotics were produced by soil microorganisms such as *Bacillus* sp., *Streptomyces* sp., *Penicillium* sp., and *Cephalosporium* sp. [8]. Drug resistance by bacteria has now limited the application of some of the available antibiotics, this leads to the need for more research interest that involves the isolation of novel antibiotic compounds and molecular analysis of biosynthetic gene clusters encoding for antibiotic proteins from microorganisms that can be used in combating multidrug-resistant pathogens [2,9].

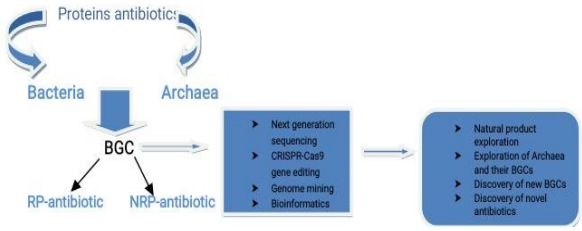

Fig. 1. Classification of antibiotics and avenues for improvement and modification.

Ribosomal Peptides Antibiotics

Ribosomal peptides (RPs) antibiotics are short amino acid sequences (usually 100 amino acids) produced on the ribosome of bacteria which undergo extensive post-translational modification into mature compounds [2]. Most of these ribosomally-synthesized peptides are referred to as bacteriocins or lantibiotics when they contain unusual amino acids such as thioether lanthionine (Lan), methyl-lanthionine (MeLan) and dehydrated amino acids which undergo posttranslational modification into mature peptides [2,10].

Several ribosomal peptide antibiotics have been described from bacteria and archaea, however, the majority of them were produced by gram-positive bacteria [11]. The chemical structure and function of ribosomal peptides depend on the activities of some enzymes that mediate the modification of these peptides into mature compounds [2]. The antimicrobial activities of ribosomal peptide antibiotics have been reported by previous research and reviews [2,12,13]. In addition to the bacteriocins, other antibiotic peptides which are also ribosomally-synthesized include; quorum-quenching and cell wall degrading enzymes [2,4].

Bacteriocins

Bacteriocins are multifunctional protein substances that are produced in the bacterial ribosomes [2,10]. In addition, bacteriocins are protein toxins that inhibit the growth of similar or closely related bacterial strains at a certain concentration. Bacteriocins can be described as narrow-spectrum when they inhibit bacteria belonging to the same species, however, they are generally described as broad-spectrum if they inhibit bacterium from another genus [14]. Previous literature revealed that 99% of bacteria are able to produce bacteriocin for self-defence, competition, and succession in their environment, colicin was the first reported bacteriocin from *Escherichia coli in* 1925, while nisin was produced by Lactic acid bacteria and it was the only FDA approved bacteriocin to be used for only food and pharmaceutical application due to its antibacterial potential [15]. Bacterial cells that produce bacteriocins are not inhibited by it, this is due to the action of some specific immunity proteins produced by the producer strain. [2,16]. Bacteriocins are nowadays considered valuable and safe antibacterial proteins with some properties that render them alternative to conventional antibiotics, i.e., tolerant of thermal stress and activity at a wide pH range [14,16 17].

Classification of Bacteriocins

Bacteriocins of Gram-negative Bacteria

Bacteriocins from Gram-negative bacteria are categorized into two main classes which include; colicins which are high molecular mass proteins (30-80kDa) and Microcins which are low molecular mass proteins (1-10kDa), colicins and microcins are mainly produced by members of *Enterobacteriaceae* [14,18]. **Table 1**, shows some of the bacteriocins produced by Gram-negative bacteria.

Bacteriocins of Gram-positive bacteria

Bacteriocins of gram-positive bacteria were categorized into class-I, class-II, and class-III, based on physicochemical and structural properties. Class I bacteriocins are also called lantibiotics, they are small (<5 kDa), heat stable, and post-translationally modified peptides [2,14,15,17]. Furthermore, lantibiotics are classified into two based on their charges, Type-A lantibiotic which is positively charged proteins with 2-4kDa, examples include; nisin and lacticin 3147. The other sub-class I lantibiotic is type -B lantibiotics, which are peptides of 2-3kDa without net charge, Examples of type B lantibiotics include mersacidin,cinnamycin, duramycin B and C. [15-19]. Similarly, lantibiotics were also classified on the basis of their biosynthetic pathways, according to this classification, class I lantibiotics are peptides modified by two enzymes, LanB (dehydratase) and LanC (cyclase). However, class II lantibiotics are peptides that are modified by only LanM enzymes with dehydratase and cyclase activity [11,15-16]. Class III lantibiotics were modified by Lan KC enzymes, while class IV lantibiotics were modified by LanL enzymes [17-19].To date there are many lantibiotics with therapeutic applications, however, nisin was the only approved and fully exploited lantibiotic, many in-*vivo* and in-*vitro* studies revealed the antimicrobial potency of many lantibiotics against drug-resistant pathogens, some lantibiotics such as nisin Z has been reported to be effective against cancer cells [17,20]. Class II bacteriocins are small (<10 kDa) linear and non-modified peptides, which are also heat tolerant and positively charged, the biosynthetic pathways involve the addition of Dha or Dhb on the cysteine residue, which can lead to the formation of lanthionine and methyllanthionine bridges [2,16].

There are four sub-classes of class-II bacteriocins, these include pediocin-like, two peptides, circular and nonpediocin-like linear. While class-III bacteriocins are large molecular weight (>30 kDa) heat-labile proteins, studies on the biosynthesis mechanisms of class III bacteriocin show that its always associated with phospholipase activity, examples of class III bacteriocins include; megacins from *B.megaterium*, klebicin from *K. Pneumonia*, helveticin I from *L. Helveticus* and enterolysin from *Enterococcus faecalis* [10,14]. Furthermore, Class III bacteriocins are subdivided into two classes, group A bacteriocins which cause lysis of the cell wall of bacteria (Enterolysin A), and group B bacteriocins which are non-lytic proteins (Helveticin and caseicin) [18]. The mode of action of bacteriocins has not been understood yet, but class II bacteriocins such as subtilin exhibit antibacterial activity by inhibiting cell wall synthesis of the target bacteria through binding with lipid II, similarly, Class III bacteriocins cause cell wall hydrolysis which may result in cell wall inhibition, other group of ribosomally-synthesized antibiotics that inhibit cell wall synthesis include; colicin and microcin [2,10]. Gram-positive bacteria that produced bacteriocins were listed in **Table 1**.

Table 1. Classification of bacteriocins and archaeocins.

Bacteriocin	Producing bacteria	Class	Properties	Molecular weight (kDa)	Ref.
Gram Positive bacteria					
Nisin A/Z	*Lactococcus lactis*	Class I(lantibiotics),subclass:	Small, modified, heat-stable peptides	3.4	[11]
Subtilin	*Bacillus subtilis*	Class I (lantibiotics)	Small, modified, heat-stable peptides	3.3	[14]
Lacticin 418	*Lactococcus lactis*	Class I (lantibiotics)	Small, linear, and non-modified peptide	2.9	[12]
Plantaricin C	*Lactobacillus plantarum LL441*	Class I (lantibiotics)	Small, globular, and modified peptide	2.9	[18]
Mersacidin	*Bacillus* sp.	Class I (lantibiotics	Small, globular, and modified peptide	1.8	[11]
Subtilosin A	*Bacillus subtilis*	Class I (lantibiotics) subclass:sactipeptides	Small, modified, and heat-stable peptides	3.4	[16]
Thurincin H	*Bacillus thuringiensisSF361*	Class I (lantibiotics) subclass:sactipeptides	Small, modified, and heat-stable peptides	3.1	[11]
Glycocin F	*Lactobacillus plantarum*	Class I (lantibiotic) subclass:glycocins	Small, modified, and heat-stable peptides	4.0	[16]
Sublancin 168	*Bacillus subtilis*	Class I (lantibiotic) subclass:glycocins	Small, modified, and heat-stable peptides	3.7	[2]
Leucocin	*Leuconostoc geldium UAL187*	Class II, subclass: pedicin-like peptides	Unmodified, heat-stable non-lanthionine peptides	ND	[2]
Lactacin F	*Lactobacillus acidophilus*	Class II, subclass: Two peptides	Unmodified, heat-stable non-lanthionine peptides	6.3	[14]
Enterocin B	*Enterococcus faecium T136*	Class II, subclass: circular	Unmodified peptides, heat stable, and non-lanthionine.	ND	[14]
Lysostaphin	*Staphylococcus simulans*	Class III, subclass: bacteriolytic	Large proteins, heat-sensitive hydrophilic peptides.	27	[18]
Helveticin J	*Lactobacillus helteticus 481*	Class III, subclass:non-bacteriolytic	Large proteins, heat-sensitive hydrophilic peptides.	37	[18]
Gram-negative bacteria					
Colicin B	*Escherichia coli*	Colicin, subclass: B	High molecular mass proteins.	54.9	[14]
Colicin A	*Escherichia coli*	Colicin, subclass: A	High molecular mass proteins.	63.0	[14]
Colicin E	*Escherichia coli*	Colicin, subclass: E	High molecular mass proteins.	59.6	[16]
Pyocin S1	*Pseudomonans aeruginosa*	Colicin, subclass: Pyocins	High molecular weight soluble protein.	65.5	[16]
Microcin	*Enterobacteriaceae*	Microcins	Low molecular weight proteins	ND	[14]
Microcin M	*Escherichia coli*	Microcin, subclass: M	Low molecular weight protein	7.3	[16]
Salmocin E2	*Salmonella enteritica*	Colicin, subclass:Salmocin	High molecular weight protein.	52.8	[11]
Archaeocin					
Halocin S8 (halS8)	*Haloarchaeon strain S8a*	Microhalocin	Broad spectrum	3.6	[21]
Halocin *HalR1*	*Halobacterium salinarum GN101*	Microhalocin	Broad spectrum	3.8	[21]
Halocin C8 (*HalC8*)	*Halobacterium* sp.*AS7092*	Microhalocin	Broad spectrum	6.3	[22]
Halocin A4 (*HalU1*)	*Haloarchaeon strain TuA4*	Microhalocin	Low molecular weight broad spectrum	5.0	[22]
Halocin H6 (*HalH6*)	*Haloferax gibbonsii Ma2.39*	Microhalocin	Stable at 90C	3.2	[21]
Halocin Sech7a	*Haloferax erranei AY823953*	Microhalocin	Heat labile at temp. <80C	10.7	[22]
Halocin SH10	*Natrinema* sp.*BTSH10*	Microhalocin	ND	ND	[22]
Halocin H4	*Haloferax mediterranei R4*	Protein halocin	Stable at temp <60, narrow spectrum	39.6	[21]
Halocin H1	*Haloferax mediterranei Xai3*	Protein halocin	Stable at temp. <50, broad spectrum	31.0	[22]

Note: ND-not determined

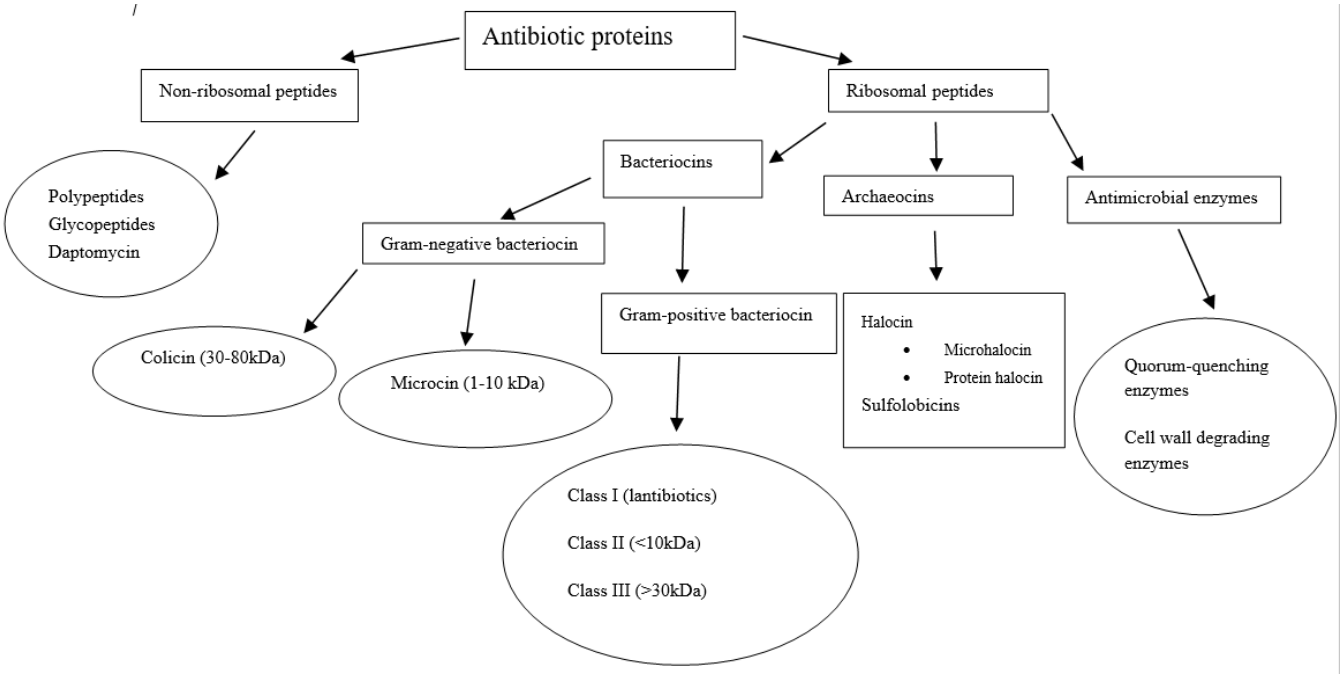

Fig. 2. Classification of proteins antibiotics.

Archaeocin

Archaeocins are a class of ribosomally-synthesized antibiotics that are derived from Archaea, they are bacteriocin-like antimicrobial proteins produced by the domain Archaea [21]. Today there are only 15 achaeocins described between haloarchaea and sulfolobus archaea, however, there are many potentially untapped archaeocins in the archaeal environment, because, they are overlooked and subsequently under-investigated. The first achaeocins described were halocins produced by halophilic archaea, while the archaeocins produced by Sulfolobus are sulfolobicins which are a novel class of antimicrobial proteins [22]. Halocins are classified into two main classes based on their size, microhalocin (peptides) and protein halocin (**Fig. 2**).

Microhalocins are small peptides ranging from 3.6-10 kDa in size, these include HalS8, HalR1,HalC8, HalU1, HalH6, Sech7a, and Sech10. Protein halocin are large proteins that range from 11-35 kDa in size, however, the characterized protein halocin in this class includes HalH1 and HalH4.The most characterized halocin at molecular and/ or genetic level are halocin S8, H4, and C8, the genes coding for S8, H4, and C8 have been identified as *halS8*, *halH4,* and *halC8* respectively, while halocin R1, H6 and H4 were characterized at only protein level [21-22]. However, the archaeocin that are produced by Sulfolobus are called sulfolobicins, which have different properties compared with halocin, studies revealed that sulfolobicin has a narrow spectrum of activity as it only inhibits other members of Sulfolobales. **Table 1** above shows the classification of known archaeocin and their properties [23].

Antibiotics enzymes

There are two major groups of enzymes that are considered antibiotic proteins and are produced through bacterial ribosomal machinery, these include; lytic enzymes and quorum quenching (QQ) enzymes; these enzymes are produced by bacteria such as *Bacillus species* and they exhibit antagonistic activity against both bacteria and fungi [2,10,24]. The lytic enzymes are also known as cell wall degrading enzymes; they include cellulose, protease, glucanase, and chitinase; they are active against fungi by hydrolyzing cellulose, proteins, glucan, and chitin on the fungal cell wall respectively [25]. Hence bacteria that produce these types of enzymes can be used as a biocontrol agent. While the quorum quenching enzymes include lactnase, decarboxylase, deaminase, and acylase, these enzymes exhibit antagonistic activity by blocking quorum sensing (cell-to-cell mechanisms) through hydrolyzing N-acyl-homoserine lactone. Quorum sensing offered a lot of advantages to bacterial populations such as biofilm formation, antibiotic production, virulence factor, sporulation, etc [2,25].

Non-Ribosomal Peptides Antibiotics

These are a class of proteins antibiotics that are produced or synthesized outside the ribosomes, they constitute diverse secondary inhibitory metabolites of microorganisms [26]. They are very diverse with different types of biological properties, hence, they can be used as antitumors, surfactants, pigments, siderophores, antibacterial, antiviral, antifungal, toxins, etc. Non-ribosomal peptides are synthesized by the enzymes called non-ribosomal enzyme synthetase, these are multi-domain enzymes system and are found in prokaryotic and eukaryotic cells [26-27].In addition, non-ribosomal peptides antibiotics are produced by marine and soil-inhabiting microorganisms such as; bacteria, actinomycetes, fungi, and vertebrates.

Previous reports have shown that bacteria are the most potential producers of NRPs antibiotics followed by fungi [2,26]. There are two categories of non-ribosomal peptides antibiotics based on the biosynthetic pathways: the first categories are synthesized either by a multienzyme thiotemplate through sequential addition of amino acid residues (lipopeptides) or by using 2,3-dihydroxybenzoate (DHB)-glycine precursors to produced siderophore (bacillibactin). The second categories of NRPs antibiotics are produced through non-thiotemplate mechanisms as in the case of rhizocticins (anti nematodes) and bacilysin (antibacterial). Non-ribosomal peptide antibiotics include polypeptides, daptomycin, and glycopeptides [2,26-27].

Polypeptides antibiotics

Polypeptide antibiotics are a class of non-ribosomal compounds with antimicrobial and antitumor properties and they are widely been used as alternative anti-infective agents for patients with resistance to conventional antibiotics [28]. Polypeptide antibiotics are very diverse and they are produced by all living organisms as part of natural host defence or self-defence, however, the most important polypeptides with minimal side effects and low toxicity are produced by bacteria [29]. These include; bacitracin, actinomycin-D, colistin, and polymyxin-B. There are many polypeptides that are highly toxic for systemic administration, however, can be administered topically for skin infection. In general, the mechanisms of action of polypeptide antibiotics involve inhibiting the transport of peptidoglycan precursors, this causes an increase in the permeability of the cell envelope, hence causing cell leakage and death [28].

Bacitracin is a polypeptide antibiotic produced by *Bacillus subtilis* and it has been used for only topical application due to its slight toxicity which is not recommended for parental use [17,29]. The mode of action of bacitracin involves inhibition of cell wall synthesis in bacterial cell. Actinomycin-D is a polypeptide antibiotic with antibacterial and anti-tumor activity, actinomycin also known as dactinomycin was isolated from Streptomyces [16,28]. Polymyxins is the first polypeptide antibiotic discovered in 1947 from the bacterium *Paenibacillus polymyxa*. Colistin, also known as polymyxin E, was the first to be used in clinical medicine as an intravenous injection for the treatment of bacterial infection.

Colistin (Polymyxin-E) antibiotic is one of the few polypeptides that are used for systemic infections. However, the use of colistin is less common due to the discovery of its toxicity [26,28-29]. Bleomycin is another polypeptide antibiotic with antitumour properties which is derived from *Streptomyces verticillus*, the mechanism of its action includes inhibition of DNA and cell wall synthesis. The efficacy rate of bleomycin in the treatment of cancer is 90% successful but toxicity occurs in 10% of the patient [30].

Daptomycin

Daptomycin is a new class of non-ribosomal antibiotic produced by *Streptomyces roseosporus* which has potent antibacterial activity against gram-positive bacterial pathogens [26,31]. Daptomycin antibiotic is recommended for the treatment of some bacterial infections including; skin infection, bacteremia, meningitis, and urinary tract infection [32]. Daptomycin exhibits a broad spectrum of activity against methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant streptococcus pneumonia, and vancomycin-resistant *enterococci*. However, resistance against daptomycin has been reported from *Staphylococcus aureus, Enterococcus faecium,* and *Enterococcus faecalis* [33]. The structure of daptomycin antibiotic consists of 13 amino acids where 10 of the amino acids are arranged in circular form and the remaining 3 amino acids form a tail where they are attached to the hydroxyl group of L-threonine of the ring, it also contains decanoic acid, a fatty acyl residue on the tail which is attached to the 3 amino acids [31-33].

Glycopeptides

Glycopeptides antibiotics are non-ribosomal polycyclic peptides produced by *Streptomyces orientalis* (Boger 2001). Glycopeptides antibiotics have a broad spectrum of activity against *Enterococci, methicillin-resistant Staphylococcus aureus (MRSA),* and *Clostridium difficile,* therefore, this antibiotic is recommended for the treatment of bacterial infections such as skin infections, lower respiratory tract infection and septicemia [34-35]. Despite the fact that glycopeptides are natural antibiotics there are now semi-synthetic derivatives with improved activity [36]. The structure of glycopeptides is responsible for their spectrum of activity, because of the presence of peptidic backbone, chlorine, and/or sugar in the structure [37]. The natural glycopeptides antibiotics are vancomycin and teicoplanin, however, oritavancin, dalbavancin, and telavancin are semi-synthetic derivatives developed in order to foil antibiotic resistance due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus* [35-37].

Future Opportunities in Antibiotics Discovery

Archaea have been shown to exhibit not only extreme environments, however, research on archaea has also been overlooked, increasing research on archaeal BGCs can uncover novel archaeocins with unique properties. Utilizing advanced molecular techniques can help identify and characterize biosynthetic gene clusters and offer new avenues for antibiotic discovery. Continued development and accessibility of molecular techniques, such as next-generation sequencing and CRISPR-Cas9 gene editing, can enhance the exploration of BGCs across diverse microorganisms.

These tools can facilitate the identification, manipulation, and optimization of BGCs for antibiotic production. Investigating non-extreme environments for microbial diversity and their BGCs can reveal new sources of antibiotic proteins. Understanding the microbial ecosystems in these environments can lead to the discovery of novel BGCs. Expanding the classification and study of BGCs beyond antibiotic proteins to include other bioactive compounds can provide a broader range of therapeutic agents. This holistic approach can enhance the understanding of microbial secondary metabolites and their potential applications. Bacteriocins, with their properties such as thermal tolerance and wide pH activity, represent a promising alternative to conventional antibiotics. Research into their production, mechanisms of action, and spectrum of activity can position them as valuable and safe antibiotic agents.

CONCLUSION

In conclusion, antibiotic proteins represent promising classes of antimicrobial compounds with potential applications in the health care system, however, the diversity of these antibiotic proteins has not been exploited fully because of the existing barrier of research and discovery on Archaea and Bacteria. There are potentially untapped antibiotic compounds in the archaeal environments. Therefore, to break the barrier of antibiotic discovery and expand the classification of antibiotics beyond proteins antibiotics, there are need for expanding research on archaea, advancing molecular techniques such as NGS, and exploring non-extreme environments. Developing bacteriocins into antibiotics is highly encouraged because of their therapeutic properties, which is why they are used as alternatives to antibiotics in the fight against antimicrobial resistance, much is yet to be done in this area because only one bacteriocins were approved to be used in foods by the FDA.

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