Challenge in the Discovery of New Drugs: Antimicrobial Peptides against WHO-List of Critical and High-Priority Bacteria

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Abstract: Bacterial resistance has intensified in recent years due to the uncontrolled use of conventional drugs, and new bacterial strains with multiple resistance have been reported. This problem may be solved by using antimicrobial peptides (AMPs), which fulfill their bactericidal activity without developing much bacterial resistance. The rapid interaction between AMPs and the bacterial cell membrane means that the bacteria cannot easily develop resistance mechanisms. In addition, various drugs for clinical use have lost their effect as a conventional treatment; however, the synergistic effect of AMPs with these drugs would help to reactivate and enhance antimicrobial activity. Their efficiency against multi-resistant and extensively resistant bacteria has positioned them as promising molecules to replace or improve conventional drugs. In this review, we examined the importance of antimicrobial peptides and their successful activity against critical and high-priority bacteria published in the WHO list.

Keywords: AMPs; antibacterial activity; critical-priority bacteria; high-priority bacteria; MDR; XDR

1. Introduction

In recent decades, uncontrolled drug use has led to major public health, economic, and environmental problems. As a result, bacteria, as well as other microorganisms, have acquired or developed unfavorable resistance mechanisms toward conventional drugs [1]. The World Health Organization (WHO) has launched a priority list of bacteria that should be studied more rigorously, and all the bacteria on this list are resistant to various drugs [2]. Bacterial resistance is a global public health concern, and it becomes a serious problem when the line of resistance exceeds the inactivation of first-line drugs, which consequently leads to high mortality rates [3]. This problem arises when a bacterium begins to generate defense molecules or acquires resistance plasmids from other bacteria, which is why, in recent years, the use of drugs has been urgently restricted [4]. For this reason, in the search for new drugs, antimicrobial peptides (AMPs) have been highlighted.

AMPs are biomolecules produced as a defense mechanism of living beings, with excellent antibacterial, antifungal, and antiviral properties [5]. They are distinguished by their ability to greatly reduce the bacterial load to low concentrations and to generate a...
minimal response of bacterial resistance due to the rapid action with lipopolysaccharides (LPS) of the cell membrane [6]. This article reviews the growing number of studies that demonstrate the efficacy of antimicrobial peptides against major groups of dangerous bacteria, as potential new substituents for conventional drugs (Figure 1).

Figure 1. Brief description of the interaction between antimicrobial peptides and the bacterial cell wall. PDR: pandrug resistance, XDR: extensive drug resistance, and MDR: multidrug resistance.

2. Why Are AMPs Highlighted in the Development of New Antibiotics?

Innate immunity is the oldest defense system against invading microorganisms. It is the first-line mechanism to virtually protect all multicellular organisms from pathogens. Particularly, a set of biomolecules from the mammalian innate immune system is notably similar to components in other kingdoms, such as plants and insects. In this way, evidence indicates that these molecules—AMPs—could have emerged in common ancestors a long time ago, in the evolutionary processes. Defensins, a classical example of very active AMPs against fungi and bacteria, are found in plants and mammals and have essentially the same tridimensional structure in both organisms [7]. AMPs present a broad structural and functional diversity. Over the last decade, researchers have shed light on AMPs, notably receiving attention for the development of new and natural antibiotic candidates (Figure 2). AMPs are interesting for treating infections, mainly those caused by the so-called and dangerous multidrug-resistant (MDR) bacteria. Nowadays, infections caused by this group of bacteria have reached a pan-drug resistance level, which means resistance to all available conventional antibiotics. Curiously, this scenario was predicted by the penicillin discoverer, Alexander Fleming, who received a Nobel Prize in 1945 and anticipated that the global misuse of antibiotics in several areas could generate a frightening panorama [8].
AMPs share typical features, such as 8 to 50 amino acids, in the primary sequence. A cationic net charge along the structure is often observed, which can induce and facilitate an initial interaction with membrane headgroup components. There is also a predominance of hydrophobic residues, up to 50% of the entire sequence, allowing van der Waals interactions with the membrane lipid tails [9,10]. AMPs can adopt a broad variety of secondary structures: the helical magainin; the protegrin, which forms a \( \beta \)-hairpin due to the presence of a disulfide bond; the disordered indolicidin; and gramicidin, which can be cyclic [11].

AMPs display several mechanisms of action to combat pathogens. These mechanisms depend on physicochemical features such as primary and secondary structures, the number of residues, net charge, and amphipathicity [12]. Overall, they can be classified according to these properties into membrane lytic and nonlytic AMPs. There are four well-established models of membrane lytic peptides in the literature: (i) the carpet model, whereby AMPs bind to an anionic target membrane like a “carpet,” covering the surface. Peptides strongly interact with the lipid head groups throughout the membrane, in a detergent-like disruption process; (ii) the toroidal pore or wormhole model, whereby the AMPs first induce the inner and outer membrane leaflet curvature and, as a consequence, align the pore lumen parallel to the phospholipid orientation, along with the headgroups. A variation of this model is the disordered toroidal pore, performed by magainin analogs and melittin, the pore formation being more stochastic and involving fewer peptide monomers; (iii) the barrel-stave pore or helical bundle model, in which the peptide monomers insert into the membrane, forming a barrel shape and open stables and transmembrane pores, which destabilize the membrane potential and promote ion and biomolecule leakage; (iv) the aggregate channel model comprises a competitive replacement of LPS-associated divalent cations, causing an unstructured aggregation of peptides and lipids, which disrupt the outer and inner membranes. In addition, other lytic membrane models, such as the lipid segregation model, oxidized lipid targeting, changes in membrane potential, and electroporation have been unveiled and described. Regarding the nonmembrane lytic peptide mechanism of action, AMPs mostly target intracellular structures, binding to DNA gyrase and topoisomerase IV, directly affecting transcription/replication. In addition, AMPs can
inhibit protein and cell wall biosynthesis, inactivate enzyme activities in ribosomes, and cause cellular apoptosis [9,11,13].

AMPs can be obtained by chemical synthesis or recombinant production systems. Specifically, the latter typically demands a long and expensive research and development phase, exhibiting some limitations in terms of modifications in the peptide sequence. However, the artificial synthesis of AMPs provides interesting advantages from natural or recombinant obtainment processes. In the solid-phase peptide synthesis (SPPS), amino acids are sequentially added to a solid support, which is considered the most commonly used and mature technology available for AMPs, even for the production of peptides with up to 50 amino acid residues [14]. A detailed approach to the SPPS method is described elsewhere [15]. Interestingly, SPPS offers a precise modification of AMP primary sequences, to modulate their biological activity against different types of pathogens and evaluate structure–activity relationships. Moreover, the design of AMPs via chemical synthesis can incorporate unusual and nonnatural amino acids to study the backbone conformation, dynamics in the membrane, and solution and orientation of peptides [16,17], via spectroscopy techniques [18,19].

Although AMPs are considered a valuable candidate for a new line of antibiotic compounds to tackle bacterial resistance, there are still many challenges to be overcome: (i) poor biostability by proteolytic degradation; (ii) cytotoxicity/high hemolytic activities at concentrations closer to therapeutic dosages; (iii) the lack of efficient delivery systems to the target site for effective release concentrations; and (iv) high manufacturing costs. In this way, the main objective of researchers and biotechnological and pharmaceutical companies is the production of AMPs that are highly selective against pathogenic bacteria, exhibiting higher therapeutic indexes. There are currently several successful AMPs in phase 3 of clinical trials, such as Omiganan, IMX942 (topical application); Surotomycin and Talactoferrin (oral); and Murepavadin and p2TA (intravenous) [11,20]. These AMPs have different targets and mechanisms of action and have aroused high expectations about the development and registration of safer, efficient, and natural antibiotics to combat MDR bacteria and avoid a chaotic future scenario.

3. Critical Bacterial Resistance

The great global concern regarding bacterial resistance to drugs has led the WHO to publish priority lists of bacteria for research and new drugs that may help reduce or control this problem. This list has been separated into critical-priority (CPB), high-priority (HPB), and medium-priority bacteria [21] according to the resistance of the antimicrobials currently used.

In its latest updates, between 2015 and 2017, the FDA approved the use of avibactam, bezlotoxumab, ceftazidime, delafloxacin, malacidin, obiltoxaximab, ozinoxacin, teixobactin, vabomere, and vaborbactam [22], and in 2018–2019, cefiderocol, cilastatin, relebactam, eravacycline, imipenem, lefamulin, omadacycline, rifamycin, plazomicin, pretomanid, sarecycline [23]. The mechanisms of action and antimicrobial activity of the new drugs are described in Table 1, published by the FDA between 2017 and 2021.
| Drug               | Approval Date | FDA-Approved Application                                                                 | Mechanism of Action                                                                                                                                                                                                 | Antibacterial Activity                                                                                                                                                                                                 |
|--------------------|---------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cefiderocol        | 14 November 2019 | To treat patients with complicated urinary tract infections who have limited or no alternative treatment options | - Cephalosporin with activity against Gram-negative aerobic bacteria.  
- Functions as a siderophore and binds to extracellular free ferric iron.  
- Passive diffusion via porin channels.  
- Actively transported across the outer cell membrane of bacteria into the periplasmic space using a siderophore iron uptake mechanism.  
- Cefiderocol exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins (PBPs). | Gram-negative: *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Citrobacter freundii* complex, *Citrobacter koseri*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Serratia marcescens*, *Stenotrophomonas maltophilia*. |
| imipenem, cilastatin, and relebactam | 16 July 2019 | To treat complicated urinary tract and complicated intra-abdominal infections | - Imipenem is a penem antibacterial drug, cilastatin sodium is a renal dehydropeptidase inhibitor, and relebactam is a beta lactamase inhibitor.  
- Cilastatin limits the renal metabolism of imipenem and does not have antibacterial activity. The bactericidal activity of imipenem results from the binding to PBPs 2 and 1B in Enterobacteriaceae and *Pseudomonas aeruginosa* and the subsequent inhibition of PBPs.  
- Inhibition of PBPs leads to the disruption of bacterial cell wall synthesis. Imipenem is stable in the presence of some beta lactamases.  
- Relebactam has no intrinsic antibacterial activity, and it protects imipenem from degradation by certain serine beta lactamases such as Sulhydryl Variable (SHV), *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Fusobacterium nucleatum*, *Parabacteroides distasonis*, *Enterococcus faecalis*, *Methicillin-susceptible Staphylococcus aureus*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Citrobacter koseri*, *Enterobacter asburiae*, etc. | Complicated Urinary Tract Infections and Complicated Intra-abdominal Infections. Some important bacteria: *Citrobacter freundii*, *Klebsiella aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Fusobacterium nucleatum*, *Parabacteroides distasonis*, *Enterococcus faecalis*, *Methicillin-susceptible Staphylococcus aureus*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Citrobacter koseri*, *Enterobacter asburiae*, etc. |
| lefamulin           | 19 August 2019 | To treat adults with community-acquired bacterial pneumonia | - Systemic pleuromutilin antibacterial.  
- Inhibits bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and van der Waals forces) with the A- and P-sites of the peptidyl transferase center (PTC) in domain V of the 23s rRNA of the 50S subunit. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents the correct positioning of tRNA. | *S. pneumoniae*, *H. Influenzae*, and *M. pneumoniae* (including macrolide-resistant strains), and bacteriostatic against *S. aureus*, and *S. pyogenes* at clinically relevant concentrations |
| pretomanid         | 14 August 2019 | For treatment-resistant forms of tuberculosis that affect the lungs | - Nitroimidazooxazone antimycobacterial drug.  
- Inhibiting mycolic acid biosynthesis, thereby blocking cell wall production. | Mutations in five *M. tuberculosis* genes (dhn, fgd1, fbiA, fbiB, and fbiC) have been associated with pretomanid resistance. |
| Drug     | Approval Date | FDA-Approved Application                                                                 | Mechanism of Action                                                                                               | Antibacterial Activity                                                                                                                                 |
|---------|---------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| omadacycline | 2 October 2018 | To treat community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections | - Aminomethylcycline antibacterial (tetracycline class of antibacterial drugs).  
- The drug binds to the 30S ribosomal subunit and blocks protein synthesis.  
- Active in vitro against Gram-positive bacteria expressing tetracycline resistance active efflux pumps (tetK and tet L) and ribosomal protection proteins (tet M).  
In general, omadacycline is considered bacteriostatic; however, omadacycline has demonstrated bactericidal activity against some isolates of *S. pneumoniae* and *H. influenzae*. | Gram-positive bacteria that carried ribosomal protection genes (tet M) and efflux genes (tet K and tet L), and in *Enterobacteriaceae* that carried the tetB efflux gene. Some *S. aureus*, *S. pneumoniae*, and *H. influenzae* strains carrying macrolide resistance genes (erm A, B, and/or C), or ciprofloxacin resistance genes (gyrA and parC) and beta-lactamase-positive *H. influenzae*. |
| eravacycline | 27 August 2018 | To treat complicated intra-abdominal infections in patients 18 years of age and older     | - Fluorocycline antibacterial (tetracycline class of antibacterial drugs).  
- This drug disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit, thus preventing the incorporation of amino acid residues into elongating peptide chains. | In general, is bacteriostatic against Gram-positive bacteria (e.g., *Staphylococcus aureus* and *Enterococcus faecalis*); however, in vitro bactericidal activity has been demonstrated against certain strains of *Escherichia coli* and *K. pneumoniae*. |
| plazomicin | 25 June 2018  | To treat adults with complicated urinary tract infections                                | - Aminoglycoside that acts by binding to the bacterial 30S ribosomal subunit, thereby inhibiting protein synthesis. | Enterobacteriaceae in the presence of certain beta-lactamases, including extended-spectrum beta-lactamases (TEM, SHV, CTX-M, AmpC), serine carbapenemases (KPC-2, KPC-3), and oxacillinase (OXA-48). Bacteria producing metallo-beta-lactamases often co-express 16S rRNA methyltransferase, conferring resistance to plazomicin. |
| secnidazole | 15 September 2017 | To treat bacterial vaginosis                                                             | - 5-nitroimidazole antimicrobial.  
- 5-nitroimidazoles enter the bacterial cell as an inactive prodrug where the nitro group is reduced by bacterial enzymes to radical anions. It is believed that these radical anions interfere with the bacterial DNA synthesis of susceptible isolates. | *Bacteroides* spp., *Gardnerella vaginalis*, *Prevotella* spp., *Mobiluncus* spp., *Megasphaera*-like type I/II |
### Table 1. Cont.

| Drug                  | Approval Date | FDA-Approved Application                          | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Antibacterial Activity                                                                                     |
|-----------------------|---------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| meropenem and vaborbactam | 29 August 2017 | To treat adults with complicated urinary tract infections | - The meropenem is a penem antibacterial drug.  
- The bactericidal action of meropenem results from the inhibition of cell wall synthesis. Meropenem penetrates the cell wall of most Gram-positive and Gram-negative bacteria to bind PBP targets. Meropenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by Gram-negative and Gram-positive bacteria, with the exception of carbapenem hydrolyzing beta-lactamases. The vaborbactam is a nonsuicidal beta-lactamase inhibitor that protects meropenem from degradation by certain serine beta-lactamases such as *Klebsiella pneumoniae* carbapenemase (KPC). Vaborbactam does not have any antibacterial activity. Vaborbactam does not decrease the activity of meropenem against meropenem-susceptible organisms. | Gram-negative bacteria: *Enterobacter cloacae* species complex, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Providencia* spp., *Pseudomonas aeruginosa*, *Serratia marcescens*. |
| delafloxacin           | 19 June 2017   | To treat patients with acute bacterial skin infections | - Fluoroquinolone class of antibacterial drugs and is anionic in nature.  
- Inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes, which are required for bacterial DNA replication, transcription, repair, and recombination.                                                                                                                                                                                                                                                                                                                                                         | Gram-positive bacteria  
*Staphylococcus aureus* (including methicillin-resistant and methicillin-sensitive strains), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Enterococcus faecalis*, *Streptococcus dysgalactiae*.  
Gram-negative bacteria  
*E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, *P. aeruginosa*, *Enterobacter aerogenes*, *Haemophilus parainfluenzae*, *Klebsiella oxytoca*, *Proteus mirabilis*. |

For a better understanding of the bacterial resistance of this priority list of bacteria, the classification of conventional drugs used worldwide is shown in Table 2 (where the new drugs mentioned above are not listed).
Table 2. Classification of antimicrobial agents according to the Food and Drug Administration (FDA) [25].

| Group         | Sub-Group                      | Classification             | Main Drugs                                      |
|---------------|--------------------------------|-----------------------------|-------------------------------------------------|
| **ß-Lactamic**|                                | natural penicillins or benzinpenicillins | crystalline penicillin                          |
|               |                                | penicillin G procaine       | penicillin G procaine                           |
|               |                                | benzathine penicillin G     | benzathine penicillin G                         |
|               |                                | penicillin V                | penicillin V                                    |
| Penicillins   | aminopenicillins               | ampicillin                  | ampicillin                                      |
|               |                                | amoxicillin                 | amoxicillin                                     |
|               | penicillins resistant to penicillinases | oxacillin                | oxacillin                                       |
|               | Broad-spectrum penicillins     | carboxypenicillins          | carboxypenicillins (carbenicillin and ticarcillin) |
|               |                                | ureido-penicillins (mezlocillin, piperacillin, and azlocillin) | ureido-penicillins (mezlocillin, piperacillin, and azlocillin) |
| Antimicrobial agents | 1st generation | cephalothin               | cephalothin                                     |
|               | cefazolin                    | cephalaxin                 | cephalaxin                                      |
|               | cepadroxil                   | cefoxitin                  | cefoxitin                                       |
| Cephalosporins| 2nd generation               | cefuroxime                 | cefuroxime                                      |
|               | cefaclor                     | cefotaxime                 | cefotaxime                                      |
|               | ceftriaxone                  | ceftazidine                | ceftazidine                                     |
|               | 4th generation               | cefepime                   | cefepime                                        |
|               | Imipenem                     | meropenem                  | meropenem                                       |
| Carbapenems   |                                | ertapenem                  | ertapenem                                       |
|               | doripenem                    | biapenem                   | biapenem                                        |
|               | tebipenem                    |                            | tebipenem                                       |
| Monobactams   |                                | aztreonem                  | aztreonem                                       |
| Quinolones    |                                | levofoxacin                | levofoxacin                                      |
|               | gatifloxacin                 | moxifloxacin               | moxifloxacin                                     |
|               | gemifloxacin                 | vancomycin                 | vancomycin                                       |
| Glycopeptides |                                | teicoplanin                | teicoplanin                                      |
|               | branchplanin                 |                            | branchplanin                                     |
| Oxazolidinones|                                |                            | linezolid                                        |
Table 2. Cont.

| Group          | Sub-Group | Classification | Main Drugs         |
|----------------|-----------|----------------|--------------------|
| Aminoglycosides-| -         | -              | streptomycin       |
|                | -         | -              | gentamicin         |
|                | -         | -              | tobramycin         |
|                | -         | -              | amikacin           |
|                | -         | -              | netilmicin         |
|                | -         | -              | paromomycin        |
|                | -         | -              | spectinomycin      |
| Macrolides     | -         | -              | azithromycin       |
|                | -         | -              | clarithromycin     |
|                | -         | -              | erythromycin       |
|                | -         | -              | spiramycin         |
|                | -         | -              | myocamycin         |
|                | -         | -              | roxithromycin      |
| Lincosamines   | -         | -              | lincomycin         |
| Nitroimidazole | -         | -              | metronidazole      |
| Chloramphenicol| -         | -              | chloramphenicol    |
| Streptogramins | -         | -              | quinupristin       |
|                | -         | -              | dalfopristin       |
| Sulfonamides   | -         | -              | sulfanilamide      |
|                | -         | -              | sulfisoxazole      |
|                | -         | -              | sulfacetamide      |
|                | -         | -              | para-aminobenzoic acid |
|                | -         | -              | sulfadiazine and sulfamethoxazole |
| Tetracyclines  | -         | -              | tetracyclines      |
| New Antimicrobials | -       | Glycyclines    | colistin (polymyxin E) |
|                | -         | -              | tigecycline        |
|                | -         | Polymyxins     | polymyxin B        |
|                | -         | -              | daptomycin         |

The bacterial resistance to beta-lactam and quinolone drugs is highlighted on the CPB list, leading to strong interest in developing new drugs and pharmaceutical combinations [26]. Beta-Lactam drugs are a broad class of antibiotics consisting of a β-lactam ring and a broad spectrum, which act as inhibitors of cell wall formation, preventing peptidoglycan biosynthesis [27]. All antibiotics of this class (except for tabtoxinine-β-lactam, which inhibits glutamine synthetase) bind to penicillin-binding proteins (PBPs), a type of transpeptidase responsible for the synthesis of the bacterial cell wall [28]. Resistance to carbapenems is the main concern of the WHO [26]. Carbapenem drugs (β-lactam group) are used in the treatment of highly uncontrollable multidrug-resistant (MDR) bacterial diseases. Their action also allows the blocking of cell wall formation by interrupting peptidoglycan transpeptidation in the cell wall [29]. Over the years, several drugs of this subgroup have been discovered and approved, such as imipenem (1985), meropenem (1993), panipenem/betamipron (1993), ertapenem (2001), doripenem (2007), biapenem
(2001), and tebipenem (2015). Despite being excellent bacterial inhibitors, many bacterial strains have developed resistance [30].

The first report of bacterial resistance to β-lactams was on penicillins (1940) through hydrolysis reaction, efflux pumps, and alterations of the target, producing, in many cases, certain enzymes known as β-lactamases, which inactivate the action of these drugs (hydrolyzing β-lactam bonds) [27]. Other studies prioritize AMP-drug activity (synergic effect) to enhance the action of carbapenems, as recently reported, using meropenem-vaborbactam to kill high-risk bacteria with resistance to carbapenems. Vaborbactam is a boron-based inhibitor that inactivates the action of Klebsiella pneumoniae carbapenemase (KPC), which does not have antibacterial activity when used unimolecularly [31], Imipenem-cilastatin [32], and Imipenem-cilastatin-relebactam [32,33]. The combined activity or synergistic effect has had positive results in recent years, and its mechanisms still need to be studied in depth.

Resistance to fluoroquinolones was also highlighted out on this list because different drugs, such as ciprofloxacin, were used to treat infectious diseases such as Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria gonorrhoeae, and Enterobacteria. Due to their uncontrolled use and/or the discontinuation of treatment, new mutations were reported worldwide [34–36]. The action of fluoroquinolones occurs by the accumulation of -OH radicals, chromosomal fragmentation, and an increase in reactive oxygen species. However, similar to carbapenems, quinolone-resistant bacteria also present resistance mechanisms such as efflux pumps and enzymes, diverting the drug target, reducing drug accumulation, and/or generating defense plasmids [37]. AMP-drug activity was also reported to have a synergistic effect between Melimine, Protamine, and Mel4, together with ciprofloxacin and cefepime, which resulted in the elimination of all MDR bacteria with lower minimal inhibition concentration (MIC) values, thus enhancing the use of these two drugs, which, by themselves, lose their action against MDR bacteria [38].

Other drug resistances shown in the WHO list involve glycopeptides, which are frequently used against enterococci, streptococci, and MDR staphylococci. Among them, vancomycin and teicoplanin, derived from Actinobacteria, are included on the HPB list [39]. These drugs act by binding to the peptidoglycan ends of the cell membrane (binding between the D-Ala-D-Ala dipeptide and Lipid II precursor); this reduces the activity of transglycosylases and transpeptidases, thus blocking bacterial replication caused by a metabolic imbalance, until cell death [40]. Telavancin, Dalbavancin, and Oritavancin were the last drugs approved and FDA-incorporated as treatments, as reported until 2018 [39]. However, bacterial resistance in this group of drugs occurs mainly to vancomycins, when these bacteria replace the production of D-Ala-D-Ala by D-Ala-X, X being a D-Lac (vanA, vanB, and vanC) or D-Ser, which removes one of the five bonds formed by vancomycin, and, therefore, they lose their affinity and effectiveness [39]. This effect improved when a conjugate of vancomycin with cationic AMP, known as FU002, was used. This conjugate made it possible to drastically decrease the MIC values in several Staphylococcus aureus methicillin-resistant (MRSA) strains, increasing its effect 1000 times and achieving a profile of controlled biodistribution [41]. For an in-depth review of glycopeptide-resistant bacteria, see Blaskovich et al. [39].

Likewise, AMPs have shown strong performance against bacteria resistant to macrolides such as clarithromycin. This resistance is generally caused by mutations alleged to Helicobacter pylori, which is installed in the gastric mucosa and is the main cause of stomach cancer in the world [42]. This macrolide binds to the 50S subunit, inhibiting protein synthesis and, consequently, its replication. Resistance to macrolides is produced by the genetic alteration of rRNA 23S and the production of efflux pumps, which hinders the action mainly of clarithromycin [43]. AMP T4 was described as a promising peptide because it acts independently of the type of resistance, evaluated against H. pylori MDR and showing better results than the drugs usually used [44].
In summary, the application and design of new AMP or AMP homologs are necessary to meet the demand for new drugs against resistant bacteria. Various studies of AMPs against these MDR, extensively drug-resistant (XDR), and pan-drug resistant (PDR) bacteria were reviewed and classified according to their location on the WHO-list (CPB and HPB).

4. AMP Applications in Critical-Priority Bacteria

The CPB list groups Acinetobacter baumannii and Pseudomonas aeruginosa, carbapenem-resistants, Enterobacteriaceae (Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., Serratia spp., Proteus spp., Providencia spp., and Morganella spp.), carbapenem-resistant (CRE), third-generation cephalosporin-resistant, and Mycobacterium tuberculosis [21].

All the bacteria on this list show severe antimicrobial resistance, and most reported cases are found in patients admitted to intensive care units (ICUs). Acinetobacteria sp. are a special group of microorganisms present in the ICU that easily acquire resistance to antibiotics during the treatment of patients hospitalized for other diseases. In particular, A. baumannii causes pneumonia and dermal and urethral infections [45]. This large-negative bacterium, in the form of a coccobacillus, belongs to the group of opportunistic bacteria and the reservoir of resistance genes that is more difficult to control [46]. Due to these parameters, carbapenems were the most efficient treatment against these bacteria until the last decade, when new bacterial strains with resistance to carbapenems were reported, which was even more worrying [29].

A. baumannii can generate resistance by enzymatic or nonenzymatic routes. It was observed in recent years that the alteration of PBPs would be involved in a mechanism of resistance to β-lactam drugs and, consequently, to carbapenems [47,48]. In addition, the ratio of the decrease in the size of the outer membrane proteins (OMP), known in A. baumannii as CarO proteins, would be the main way to identify their nonenzymatic resistance. Another means would be the presence of active expulsion or efflux pumps, which are the main source of bacterial resistance in all MDR bacteria [29]. Commonly used drugs for this type of MDR bacteria are colistin sulfate, tobramycin, levofloxacin, kanamycin, and carbenicillin disodium [49]. Different successful studies were carried out to eliminate this bacterium with AMPs, as listed in Table 2.

P. aeruginosa causes lung inflammation due to the release of IL-6 and TNF-α induced by their LPS, which are associated with cystic fibrosis and chronic obstructive pulmonary disease [49]. They are difficult bacteria to treat, and like A. baumannii, many of those with MDR or XDR are biofilm-forming, which prevents the action of most drugs [50]. In the same way, combined studies of AMP-drugs have been carried out to improve their bactericidal activity, and even AMPs have been considered new biomolecules with antibiofilm action, which allows the promotion of the development of new drugs for this list of potentially infectious bacteria [51,52].

Enterobacteriaceae have become a family of problematic bacteria due to the ease of resistance and the production of extended-spectrum β-lactamas and carbapenemases (KPC and others), which induce carbapenem-resistant Enterobacteriaceae (CRE) infections [53,54]. Klebsiella pneumoniae MDR is a highly complex bacterium to treat and, due to its persistence, the mortality rate in humans continues to increase. The use of polymyxin (polypeptides approved by the FDA) has been intensified to combat many MDRs, as this peptide helps to improve the action of obsolete drugs during treatment [54]. A study revealed that there are certain amino acid conformations of peptides that could efficiently fight this type of MDR/XDR/PDR bacteria by modifying the conformation of this capsule, although there is an unknown information barrier to explain this event that must be explored [55]. An in-depth study of CRE was reported by Suay-García et al. [54].

Mycobacterium tuberculosis is a bacterium that causes a high mortality rate worldwide. It has distinct defense mechanisms, in comparison with other bacteria, due to its capsule composition of peptidoglycans. It is also capable of remaining in the latency phase for many years with no symptoms of infection [56]. Thus, many studies against this bacterium have been carried out at the genetic-molecular and biochemical levels to reach new therapeutic
objectives and control it, as conventional antibiotics are not effective enough, require a long time, and cause unpleasant adverse effects [57]. A study reported that the regulation between the relationship of cortisol and dehydroepiandrosterone in the human body could be related to the human immune response to tuberculosis, and this relationship could increase or decrease the production of innate AMPs, such as cathelicidin LL-37, and human β-defensin 2 and 3, to combat this bacterium [58]. The use of AMPs against tuberculosis or the regulation of their innate production is an attractive option that has created great expectations.

In a recent study, Abraham et al. [56] synthesized a 21-residue peptide called B1CTcu5, which was originally isolated from the cutaneous secretion of Clinotarsus curtipes, a frog of Indian origin. The brevinin-1 family of AMP has shown promising results in the search for a new agent against tuberculosis. It was able to selectively kill intracellular bacteria without causing damage to macrophages and had an overall hydrophobicity of 65%. The hydrophobic nature of the peptide may act as a driving force to move from an aqueous environment to a hydrophobic one and increase its affinity for the acyl lipid chains of the membrane. The hydrophobic interaction between amphipathic AMP and the cell membrane forms a specific peptide–lipid complex, which can produce changes in the bacterial membrane, such as thinning, pore formation, altered curvature, and localized alterations. The AMP can translocate across the membrane and diffuse into the cytoplasm, possibly interacting with intracellular targets. According to Orme et al. [59], potential compounds should have <10 µg/mL MIC values. Most therapeutic drugs are effective below 1 µg/mL. Table 3 shows AMPs designed to have great antimicrobial activity against CPB. The analysis was based on a systematic review in the ScienceDirect database and Google scholar search engine in 2019–2021.

Table 3. Several reviews (2019 to 2021) of antimicrobial peptides applied against WHO-list (CPB).

| AMPs          | Peptide Sequence | MIC (µg/mL) | System | Natural Source | PDR/MDR/XDR Bacteria | Ref. |
|---------------|------------------|-------------|--------|----------------|----------------------|------|
| ZY4 peptide   | VCKRWKKKWKGRKKKCV | 2.0–4.5     | In vitro/In vivo | Snake venom of Bungarus fasciatus | P. aeruginosa (CICC21625, CMCC10104, C1, C2, C3, and C5) | [49] |
|               | In the sequence, disulfide bond (C-C) is formed by the Cystein. | 4.6–9.4     | | | A. baumannii (22933, CN40, 18C116, 18C132, 18C135, and 18C136) | |
| Zp3           | GIIAGIIIKIKK     | 4 µM        | In vitro/In vivo | NR           | A. baumannii ATCC 19606 | [60] |
| WWW Symmetric peptides | XRWWWWWX (XRW), XWWWWWX (XWRW), XRRWWWRX (XRRW) | 2–>128 µM | In vitro/In vivo | NR           | E. coli ATCC 25922, P. aeruginosa ATCC 27853/9027, Acinetobacter baumannii ATCC 19606, K. pneumoniae ATCC 700603, E. coli ML-35 ATCC 43837, E. coli 780/804, P. aeruginosa 50/73, A. baumannii 9931/97830 | [61] |
|               | X = G, I, L, W, F, V, A | | | | | |
| NR            | HKEMPFPK, TTMPLW, YYQKPV, and AVYPQQR | 1.5–5 mg/ mL | In vitro | Casein prediction | A. baumannii ATCC 19606, E. coli O157 NCTC 12900, P. aeruginosa PAO1 | [62] |
| B1CTcu5       | LIAGLAANFPLQQLCKARKC | 12.5 | In vitro | Clinotarsus curtipes | A. baumannii MDR | [56] |
| Ctx(Ile21)-Ha | GWLDVAKKIGKAASVAKSFI | 64 µM | In vitro | Hypsiboa albobopunctatus | A. baumannii MDR | [5] |
Table 3. Cont.

| AMPs                        | Peptide Sequence          | MIC (µg/mL) | System       | Natural Source          | PDR/MDR/XDR Bacteria                                                                 | Ref.   |
|-----------------------------|---------------------------|-------------|--------------|-------------------------|-----------------------------------------------------------------------------------|--------|
| CDP-B11 peptide            | VRNSQSCRRNKGICV           | 25          | In vitro     | Cow                     | A. baumannii # 0035                                                               | [63]   |
|                             | PIRCPGSMRQI GTCL           | 100         |              |                         | E. coli # 0061                                                                    |        |
|                             | GAQVKCCRRK                 | 200         |              |                         | E. coli # 0346, P. aeruginosa # 0054 y K. pneumoniae # 0347                      |        |
| P10 + conventional antibiotics | LAREYKKIVEKLR              | 4–32        | LL-37 derivative |                         | A. baumannii XDR 1, XDR 2, XDR 3, XDR 4, XDR 5, ATCC 19606.                      | [64]   |
| K11                         | KWKSFIKKLTKFKHSAKKF        | NR          | In silico/In vitro | Cecropin A1, melittin, and magainin                          | A. baumannii, P. aeruginosa, and K. pneumoniae                                  | [65]   |
| Magainin 2 (Mag2) (molecule and homologues) | GIKKFHSAKKFGKAVGE IMNS    | 12.5        | In vitro     | African clawed frog    | P. aeruginosa                                                                     | [66]   |
|                             | GIKKFLXSXKFKVFXK           | 3125        |              |                         |                                                                                  |        |
|                             | SSIKKSSLKSAXKFVKAFF        | 1.56        |              |                         |                                                                                  |        |
|                             | GI KKSSLKSXXKFKVKAFF       | 0.78        |              |                         |                                                                                  |        |
|                             | GIKKFLSXXKFKVKAFF          | 0.78        |              |                         |                                                                                  |        |
|                             | GIKKFLXSXXKFKVKAFF         | 3125        |              |                         |                                                                                  |        |
|                             | GIKKFLR8LKSXKSVKAPFK       | 1.56        |              |                         |                                                                                  |        |
|                             | GIKKFLR8AKKFVSFK           | 3125        |              |                         |                                                                                  |        |
|                             | GIKKFLR8KKSXKFKAS5K        | 3125        |              |                         |                                                                                  |        |
| Phe-Lys-Phe tripeptide      | FKF                        | 45.4 µM     | In vitro     | NR                      |                                                                                  | [67]   |
|                             |                           | 34.0 µM     |              |                         |                                                                                  |        |
| CEC4                        | GWLKKIGKKIERVQNTRD ATIAQIGVAOQAAN-VAAFLKK  | 4           | In vitro     | NR                      | 200 biofilm-forming strains MDR and XDR of P. aeruginosa (clinic isolates)       | [68,69]|
| BSI-9 analogs               | K-Nal-KK-Bip-O2Oc-Nal-Ks   | 1–32        | In vitro     | Cyclic peptide          |                                                                                  | [70]   |
|                             |                           | 2–32        |              |                         |                                                                                  |        |
|                             |                           | 32–>64      |              |                         |                                                                                  |        |
| AMPs          | Peptide Sequence                  | MIC (µg/mL) | System     | Natural Source                          | PDR/MDR/XDR Bacteria                  | Ref.         |
|--------------|-----------------------------------|-------------|------------|-----------------------------------------|---------------------------------------|-------------|
| TC19         | LRCMCIKWWSGKHPK                   | 3.75 µM     | In vitro   | Thrombocidin-1-human peptide-derived   | E. coli ESBL                          | [73]        |
|              |                                   |             | In vivo    |                                         | A. baumannii LUH15100 and S. aureus   |             |
|              |                                   |             |            |                                         | JAR060131                             |             |
|              |                                   |             | 8 and 1 µM |                                         | E. coli W3110                          |             |
|              |                                   |             | 2 µM       |                                         | A. baumannii 5075                     |             |
|              |                                   |             | 2 and 1 µM |                                         | A. baumannii 17978                    |             |
| PepC/        | ILIACLGLKLLRYRRYY/WWWA[Dab]YGL[Y] | >128 and 2 µM | In vivo/   | NR                                      | K. pneumoniae MKP103                   | [55]        |
| PepW         | [Dab]LL[Dab]Y[Dab][Dab]WY          |             | In vitro   |                                         | K. pneumoniae ATCC 1705                |             |
|              |                                   |             |            |                                         | K. pneumoniae clinical isolate 1433   |             |
|              |                                   |             |            |                                         | K. pneumoniae ATCC 13883 (K3 serotype)|             |
|              |                                   |             |            |                                         | K. pneumoniae ATCC 43816 (K2 serotype)|             |
|              |                                   |             | 64 and 2 µM|                                         | K. pneumoniae ATCC 10031               |             |
| Human β-defensin 2 | HBD2/L-HBD2                      | 0.25–0.5 µM | In vitro   | Human Pyorubin-producing P. aeruginosa strain | A. baumannii ATCC 19606               | [74]        |
| Human β-defensin 3 | HBD3                          | 1 µM        | In vitro   |                                         | P. aeruginosa (ATCC 19660)            |             |
| Tridecaptin M + rifampicin | Gdab*G*S*W*S*Dab*Dab*I*Q*I*S–D-aminoacids* | 16          | In vitro   | Paenibacillus sp. M152                  | A. baumannii ATCC 25922               | [75]        |
|              |                                   |             |            |                                         |                                      |             |
| Tilapia Piscidin 4 (TP4) | FIHHIIGGLFSAGKAI HRLIRRRRR | 3125        | In vivo/   | Nile Tilapia (Orochromis niloticus)     | K. pneumoniae (ATCC 10031)            | [76]        |
|              |                                   |             | In vitro   |                                         | A. baumannii (Icu53)                  |             |
|              |                                   |             |            |                                         | A. baumannii (Sk44)                   |             |
|              |                                   |             |            |                                         | K. pneumoniae (NDM-1)                 |             |
|              |                                   |             |            |                                         |                                      |             |
| Oncocin      | VDKPPYLPPRPRP PRRYNR              | 8 µM        | In vitro   | Oncopelthus fasciatus (milkweed bug)   | E. coli ATCC 25922                    |             |
|              |                                   |             |            |                                         | K. pneumoniae ATCC 10031              |             |
| MDAP-2       | SRDSRPVQPRV/QPP PPDKQKPSYDTPPRRGGKTMYA | 512 µM | In vitro   | Musca domestica larvae                  | E. coli ATCC 25922                    | [77]        |
|              |                                   |             |            |                                         | K. pneumoniae ATCC 10031              |             |
|              |                                   |             |            |                                         | K. pneumoniae CMCC 46117              |             |
|              |                                   |             |            |                                         | E. coli ATCC 25922 (ASbmA)            |             |
|              |                                   |             |            |                                         | E. coli ATCC 25922 (ASbmA)            |             |
| OM19R (MDAP-2 + Oncocin) | VDKPPYLPPRP PRRPGGR | 256 µM | In vitro   | hybrid                                  | E. coli ATCC 25922                    |             |
|              |                                   |             |            |                                         | K. pneumoniae ATCC 10031              |             |
|              |                                   |             |            |                                         | K. pneumoniae CMCC 46117              |             |
|              |                                   |             |            |                                         | E. coli ATCC 25922 (ASbmA)            |             |
| AMPs                        | Peptide Sequence         | MIC (µg/mL) | System          | Natural Source                                      | Bacteria                                      | Ref. |
|-----------------------------|--------------------------|-------------|-----------------|-----------------------------------------------------|-----------------------------------------------|------|
| Piscidin 3 (g6498.t1)       | CIMGKHLRLNWGAKAIYNGAKAGWTEFK | 45          | In vivo/In vitro | Oreochromis niloticus                                | P. aeruginosa                                  | [78] |
| Piscidin 1 homologues       | I9A-piscidin-1           | 3.1         | In vitro        | Clinical strain of colistin-resistant A. baumannii   |                                               | [79] |
|                             | I16A-piscidin-1          |             |                 |                                                     |                                               |      |
|                             | I9K-piscidin-1           |             |                 |                                                     |                                               |      |
|                             | I16K-piscidin-1          |             |                 |                                                     |                                               |      |
| EcDBS1R6                    | PMKKLFKLLARIAKVIPvW      | 3 µM        | In vitro/In silico | K. pneumoniae ATCC 13883                              | P. aeruginosa ATCC 27853                        | [80] |
|                             |                         | 6.25 µM     |                 |                                                     |                                               |      |
|                             |                         | 3 µM        |                 |                                                     |                                               |      |
|                             |                         | 3 µM        |                 |                                                     |                                               |      |
| Iztli peptide 1 (IP-1)      | KFLNRFWHWLQKPGQPMY      | 8 µg/100 µL | In vitro        | M. tuberculosi H37Rv (ATCC 27294)                    |                                               | [81] |
|                             |                         |             |                 |                                                     |                                               |      |
| Buforin II + monocarboxylic acid derivate | TRSSRAGLOPFPVGRVHRLLRK | 1 µM        | In vitro        | E. coli (MG 1655)                                   |                                               | [82] |
|                             |                         | 2 µM        |                 |                                                     |                                               |      |
|                             |                         | 0.5 µM      |                 |                                                     |                                               |      |
|                             |                         | 4 µM        |                 |                                                     |                                               |      |
|                             |                         | 32          |                 |                                                     |                                               |      |
|                             |                         | 256         |                 |                                                     |                                               |      |
|                             |                         | 256         |                 |                                                     |                                               |      |
|                             |                         | 64          |                 |                                                     |                                               |      |
|                             |                         | 32          |                 |                                                     |                                               |      |
|                             |                         | 32          |                 |                                                     |                                               |      |
|                             |                         | 0.7–3 µM    |                 |                                                     |                                               |      |
|                             |                         |             |                 |                                                     |                                               |      |
| SET-M33 protease resistant  | (KKIRVRLSA)4K2KβA-OH    |             | In vivo/In vitro | A. baumannii (3 strains MDR/XDR)                     |                                               | [84] |
|                             |                         |             |                 |                                                     |                                               |      |
|                             |                         | 3–6 µM      |                 |                                                     |                                               |      |
|                             |                         |             |                 |                                                     |                                               |      |
| DP7                         | VQWRIRVAVIRK            | 16–32       | In vivo/In vitro/In silico |                                               | P. aeruginosa (MDR various strains)          | [85] |
| DP7 + vancomycin or azithromycin |                     | NR          |                 |                                                     |                                               |      |
| DP-C and DP-C Dimer         | [(KLAKLAK)*2-L-C] *D-amino acids (right-handed) | 16–32 | In vitro/In silico |                                               | P. aeruginosa                                 | [86] |
|                             |                         | 4–8         |                 |                                                     | A. baumannii                                  |      |
|                             |                         | 4–16        |                 |                                                     |                                               |      |
|                             |                         | 16–128      |                 |                                                     |                                               |      |
### Table 3. Cont.

| AMPs                  | Peptide Sequence                  | MIC (µg/mL) | System     | Natural Source                  | PDR/MDR/XDR Bacteria                                      | Ref.          |
|-----------------------|-----------------------------------|-------------|------------|--------------------------------|----------------------------------------------------------|--------------|
| **Ω76 peptide**       | FLKAIKKFGKEFKKIGAKLKL             | 16          | In vivo/In vitro | Mag derivative             | carbenem and tigecycline-resistant A. baumannii          | [87]         |
|                       |                                   |             | 128        |                                   | K. pneumoniae                                              |              |
|                       |                                   |             | 4          |                                   | E. coli                                                   |              |
| NuriPep 1653          | VRGLAPKKSLWPF GGPFKSPFN            | 12          | In vitro   | PS4 nutrient reservoir protein of Pisum sativum | A. baumannii-resistant (ColRAB) PDR                       | [88]         |
|                       |                                   |             | 400        |                                   | A. baumannii susceptible (colSAB)                        |              |
|                       |                                   |             | 100        |                                   | K. pneumoniae 50183                                        |              |
|                       |                                   |             | 8          |                                   | E. coli ATCC 25922                                         |              |
| Tachyplesin III       | KWCFRVCYRGICYRKCR                  | 10 mg/kg    | In vivo    | β-sheet AMP                      | P. aeruginosa ATCC 27853                                 | [89]         |
| Melittin              | NR                                | 16          | In vivo/In vitro | NR                  | A. baumannii (XDR and MDR strains, clinic isolates)     | [90]         |
| Progrerin-1           | RGGRLCYCRRRFCCVGCVR                | 4–8         | In vitro   | β-sheet peptides (cathelicidin family) | A. baumannii (XDR and MDR strains from surgical wounds) | [91]         |
| Aurein 1.2            | GLFDIJKIAESF-NH2                   | 16          |            |                                |                                                          |              |
| CAMEL                 | KWKFLFKKIGAVLKL-NH2                | 2           |            |                                |                                                          |              |
| Citropin 1.1          | GLFDVIKKVASVIGGL-NH2               | 16          |            |                                |                                                          |              |
| LL-37                 | LLGDFERRSSKEGIGKEFSKRIV QRIKDFLRNILVPRTES | 4     | In vitro   |                                |                                                          |              |
| Omigangan             | ILRWPPPWWRRK-NH2                   | 32          |            |                                |                                                          |              |
| r-Omigangan           | KRRWPWWPWRRI-NH2                   | 16          |            |                                |                                                          |              |
| Pexiganan             | GIGKFLKAKKFGKAFVKILKK-NH2          | 2           |            |                                |                                                          |              |
| Temporin A            | FLPLIGRLSGIL-NH2                   | 128         |            |                                |                                                          |              |
| Bac5(1–17) native/ Bac5-derivatives | wt, 258, 272, 278, 281, and 291 peptides | 1–16        | In vitro   | NR                              |                                                          | [92]         |
|                       |                                   |             | 1–2        |                                |                                                          |              |
|                       |                                   |             | 16–>64     |                                |                                                          |              |
|                       |                                   |             | 8–>64      |                                |                                                          |              |
| SA4 peptide           | IOWAGOLFOLFO-NH2                   |             |            |                                |                                                          |              |
| SPO peptoid           | nInOnWnAntGnOnLnFnOnLnFnO-NH2      | 50          | In vitro   |                                |                                                          | [94]         |
| AMPs                  | Peptide Sequence            | MIC (µg/mL) | System | Natural Source                  | PDR/MDR/XDR Bacteria                                                                                  | Ref. |
|----------------------|----------------------------|-------------|--------|---------------------------------|--------------------------------------------------------------------------------------------------------|------|
| D87(Lys1–6 Arg-1)    |                            | 0.8         |        |                                 |                                                                                                         |      |
| D84(Lys1–6 Lys-1)     |                            |            |        |                                 |                                                                                                         |      |
| D85(Lys1–6 Orn-1)     |                            | 0.5         |        |                                 |                                                                                                         |      |
| D86(Lys1–6 Dab-1)     |                            | 1.0         |        |                                 |                                                                                                         |      |
| D105(Lys1–6 Dap-1)    |                            | 1–1.2       | In vitro | NR                              | 7 Strains of *A. baumannii* resistant to Polymyxin B and Colistin and 20 Worldwide 2016 and 2017 Isolates resistant to 18 Classical Antibiotics | [95] |
| D101(Lys1Ser26-5 Lys-1) |                            | 0.8–1       |        |                                 |                                                                                                         |      |
| D102(Lys1Ser26-5 Dab-1) |                        | 0.6–0.7     |        |                                 |                                                                                                         |      |
| D85(K13A/K16A)-(Lys1–6 Orn-1) |                  | 1.9–2       |        |                                 |                                                                                                         |      |
| D86(K13A/K16A)-(Lys1–6 Dab-1) |            | 0.9         |        |                                 |                                                                                                         |      |
| D105(K13A/K16A)-(Lys1–6 Dap-1) |                | 1.3–2       |        |                                 |                                                                                                         |      |
| Agelaia-MPI INWLKLGKAIIDAL |                    | 6.25–25 µM |        | Agelaia pullipes pallipes       |                                                                                                         |      |
| Polybia-MPII INWLKLGKMVIDAL |              | 12.5–25 µM |        |                                |                                                                                                         |      |
| Con10 FWSFLVKAASKILPS LIGGGDDNKS S | | 12.5–25 µM | In vitro |                                 | Clinical isolates of MDR *A. baumannii* identified as AB 02, AB 53, and AB 72 | [96] |
| NDBP-5.8 GILGK IVE GKL S LI |                      | >25 µM      |        |                                 |                                                                                                         |      |
| Polydim-I AVAGEKLWLLP HLLKMLLLTPTP |                    |             |        |                                 |                                                                                                         |      |
| ARV-1502 Chex-RPDKPRPTL PRPRPPRPVR |             | 50          | In vivo | Insect                          | *A. baumannii* Strain HUMC1                                                                                         | [97] |
| Bac7(1–35) NR         |                            | 4           | In vitro | NR                              |                                                                                                         |      |
| P5 + meropenem RIVQRIKKWLKKWKLGY |            | 16          | In vitro | NR                              | *P. aeruginosa* M1351                                                                                          | [50] |
| PEP01 to PEP04 GKIMYILT KKS, FGKLRSVWKK, FGKLRSVWKK, and FGKLRVWK KWD | | 62.5–125 µM | In silico | NR                              | *K. pneumoniae* MTCC619                                                                                       | [99] |
| NZX                  |                            | 1.6–3.2 µM  | In vitro | Plectasin derivate              | *M. tuberculosis*                                                                                             | [100]|
5. AMP Applications against High-Priority Bacteria

This group includes the following bacteria: Enterococcus faecium, vancomycin-resistant; Staphylococcus aureus, methicillin-resistant, vancomycin intermediate, and resistant; Helicobacter pylori, clarithromycin-resistant; Campylobacter, fluoroquinolone-resistant; Salmonella spp., fluoroquinolone-resistant; Neisseria gonorrhoeae, third-generation cephalosporin-resistant, fluoroquinolone-resistant.

5.1. Vancomycin-Resistant Enterococcus Faecium (VRE)

Anoplin (GLLKRIKTLL-NH₂) is a peptide isolated from the venom of the Japanese solitary spider wasp Anoplius samariensis. A study conducted by Munky et al. [101] evaluated the antimicrobial activity of Anoplin and its analogs. The AMP analogs were synthesized by substituting at 2, 3, 5, 6, 8, 9, and 10 amino acid positions. The synthesized analogs were peptides modified at position 5 (Lys⁵ and Trp⁵), position 8 (Lys⁸), positions 5 and 8 together (Lys⁵Lys⁸, Lys⁵Trp⁸, Trp⁵Lys⁸, Phe⁵Lys⁸, and Phe⁵Trp⁸), β-2-naphthylalanine peptides (2Nal², 2Nal³, 2Nal⁶, 2Nal⁸, and 2Nal¹⁰), and β-cyclohexylalanine peptides (Cha², Cha³, Cha⁶, Cha⁹, Cha¹⁰, and Cha²Cha¹⁰). The microdilution broth method was the technique used to determine antimicrobial assay against VRE (700 221), and the MIC values obtained for Anoplin and its 19 analogs varied from 0.8 to 170.6 µM. The positions 5- and 8-modified peptide, Phe⁵Trp⁸, showed the best MIC, 0.8 µM. This excellent activity is related to the increased hydrophobicity of the AMP and, consequently, the better interaction with the lipid membrane of bacteria. This study shows that small changes in peptide structure can alter the antimicrobial activity against certain bacteria.

The novel peptide BF2 was synthesized, purified, characterized, and biologically evaluated against clinical isolates of VRE by Singh et al. [102]. These authors analyzed the BF2 (RWRLLLLKKH) peptide against 2 ATCC strains (ATCC29212 and ATCC51299) and 26 clinical VRE isolates, clinical isolates from blood culture, wound swabs, the right abdomen, a hydrocathered tip, bile, and pus. The peptide showed antimicrobial activity against the standard strains with an MIC of 25 µg/mL and an MIC in the range of 6.25–12.5 µg/mL against the clinical isolates, which shows better activity against these strains. The hemolysis determined the cytotoxicity of BF2 peptide and showed that, up to 5MIC, it was not hemolytic. They also performed a synergistic study between BF2 and the antibiotics (vancomycin, teicoplanin, and linezolid) against ATCC51299 and clinical isolates; and the results showed that vancomycin with BF2 has a synergistic effect with a fractional inhibitory concentration (FIC) index of 0.06–0.25, against ATCC and resistant strains, respectively. Simultaneously, BF2 with teicoplanin showed an FIC of 0.02–0.27 for ATCC and clinical isolates. They observed no effect for the combination BF2/linezolid. An in vivo study was performed on Wistar albino female rats to verify the antimicrobial activity of the BF2 peptide studied by reducing the cell count in the blood of the animals. The inoculation of bacterial cells (VRE) was intravenous. One hour after administration, the animal groups were treated with 12.5 (MIC), 25 (2MIC), and 37.5 mg/kg (3MIC) of the peptide intravenously. After 1 h of treatment, the animals’ blood was collected and plated for quantifying the number of bacterial cells. After a two-day therapy, reductions of 73%, 76%, and 82% were observed for the antimicrobial peptide treatments at MIC, 2MIC, and 3MIC concentrations, respectively, in comparison with the negative control. In contrast, the positive control group, which received linezolid, had the number of colonies reduced by 93%. BF2 is a peptide with good antimicrobial activity against vancomycin-resistant clinical isolates. It is nontoxic and effective in vivo, making it a promising antimicrobial to be studied both alone and in combination with antibiotics.

A cationic peptide composed of 22 amino acids, named Pexiganan or MSI 78, was evaluated in vitro against VRE strains by Flamm et al. [103]. The strains were isolated from diabetic foot infections, and the antimicrobial activity of pexiganan was evaluated by the broth microdilution testing method. The peptide showed good activity against VRE strains, with MIC values of 4 or 8 µg/mL. The results showed that MSI 78 can be used as an antibiotic for VRE strains in diabetic patients.
Delpech et al. [104] evaluated the peptide AP-CECT7121 alone and combined with gentamicin against five clinical isolates of VRE, ampicillin, and tetracycline. The five (DF02–043, DF04–056, DF02–065, DF03–072, and DF03–078)-resistant strains were isolated from mastitic cows. The bactericidal activity was determined by the agar dilution method, and it was observed that the peptide AP-CECT121 was able to kill the isolates, reducing viable cells by more than 4.0log_{10} CFU/mL. However, a synergistic effect could not be observed when combined with gentamicin, as there was only a 0.2 to 0.9 log_{10} CFU/mL reduction in viable cells. Therefore, AP-CEC7121 showed good activity alone and can be considered a candidate to treat bovine mastitis caused by VRE.

To evaluate synergistic effects, Wu et al. [105] performed a check-board study with the antimicrobial peptide P-113 and its derivatives against VRE. The following derivatives were developed with phenylalanine-(Phe-P-113), β-naphthylalanine-(Nal-P-113), β-diphenylalanine-(Dip-P-113), and β-(4,4′-biphenyl)alanine-(Bip-P-113)-substituted histidine-rich antimicrobial peptide P-113 (Ac-AKRHHGYKRKFH-NH2). A clinically isolated strain of VRE (BCRC 15B0132) was purchased from Bioresources Collection & Research Center (BCRC, FIRDI, Hsinchu, Taiwan). The antimicrobial activity assay was determined and vancomycin, P-113, and Phe-P-113 exhibited MIC > 64 µg/mL against E. faecium BCRC 15B0132, while the derivatives Bip-P-113, Dip-P-113, and Nal-P-113 showed an MIC equal to 4 µg/mL. The synergic effect study was performed by combining vancomycin and peptides at the sub-inhibitory concentration (1/4 x MIC). The authors observed that Bip-P-113, Dip-P-113, and Nal-P-113 had a synergistic effect, and the other peptides showed no interaction. To evaluate the mechanism of resensitization of Enterococcus faecium to vancomycin by P-113 and its derivatives, the scientists experimented with BODIPY-labeled vancomycin. They noted that peptides with bulky unnatural amino acids increased vancomycin’s entry into the VRE with the order Bip-P-113 = Nal-P-113 > Dip-P-113 > Phe-P-113 = P-113. This study shows that P-113 derivatives can be used alone or in combination with vancomycin against VRE.

Wang et al. [106] discovered a new peptide, albopeptide, from the soil bacterium Streptomyces albofaciens (NCIMB 10975). After identifying this compound, the researchers synthesized its isomer and confirmed the peptide structure as L-Val-Dha-(E)-Dhb. With the low yield of the natural albopeptide for antibacterial activity against VRE, they used a 50:50 mixture of synthetic and natural peptide material for the experiment. The combination of peptides resulted in a potent activity against VRE K60-39, with a minimum inhibitory concentration (MIC) value of 2.98 ± 0.07 µM.

5.2. Clarithromycin-Resistant Helicobacter pylori

Jiang et al. [107] studied the efficacy of the peptide Cbf-K16 (with 30 amino acids), in vitro and in vivo, against clarithromycin- and amoxicillin-resistant H. pylori SS1. An antimicrobial activity assay was carried out in vitro according to the microdilution technique, and the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) obtained were 16 and 32 µg/mL, respectively. Cbf-K16 was also evaluated against H. pylori SS1-infected cells, GES-1 (gastric epithelial cells), and the compound reduced the bacterial count in the supernatant and intracellular samples to 1.9 and 2.9-log_{10} units, respectively, in addition to protecting the epithelial cells. An antimicrobial activity assay in mice infected with drug-resistant H. pylori SS1 was performed with C57BL/6 male mice (4–6 weeks old). The animals received sodium bicarbonate by the intragastric route, and 0.3 mL (1 × 10^9 CFU/mL) of clarithromycin-resistant H. pylori SS1 on three alternate days for infection development. After infection, the mice were divided into different groups: the control group, triple therapy (omeprazole, clarithromycin, and amoxicillin), and peptide Cbf-K16 treatments at different doses (5, 10, and 20 mg/kg). The rats were treated daily for two weeks orally by the intragastric route, and 24 h after the last administration, they were euthanized, their blood was collected, and their stomachs were removed for analysis. Cbf-K16 at a dose of 20 mg/kg reduced the bacterial count in the stomach tissues of the animals to 3.9-log_{10} units, in comparison with the control group. It also reduced the
inflammation of the ulcer and gastric mucosa, as shown in the histological examination. By contrast, the triple therapy could not reduce the bacterial load of the resistant strain and had no action in gastritis. This study showed that Cbf-K16 peptide has in vitro and in vivo activity against a strain of a clinical isolate of Clarithromycin-resistant \textit{H. pylori}.

5.3. Fluoroquinolone-Resistant Salmonella

Szabo et al. \cite{108} studied antimicrobial peptides (AMPs) that carry interaction domains with both the bacterial membrane and intracellular target and exhibit stability in the face of proteolytic degradation. The peptide AE-APO with the sequence (H-Chex-Arg-Pro-AspLys-Pro-Arg-Pro-Tyr-Leu-Pro-Arg-Pro-Arg-Pro-ValArg)$_2$-Dab-NH$_2$ (where Chex is a 1-amino-cyclohexane carboxylic acid and Dab is 2,4-diamino-butyric acid) was analyzed in vitro against a clinical isolate of fluoroquinolone-resistant \textit{Salmonella enterica} serovar \textit{Typhimurium}. The in vitro efficacy was determined by conventional antibacterial growth inhibition assays \cite{109}, and the minimum inhibitory concentration (MIC) was 8-32 mg/L, that is, the peptide showed activity against the fluoroquinolone-resistant strain.

Cationic peptides LS-sarcotoxin and LS-stomoxyn were tested against a panel of 114 clinical MDR Gram-negative bacterial isolates, including fluoroquinolone-resistant \textit{Salmonella enterica}. LS-sarcotoxin and LS-stomoxyn showed MIC$_{50}$ and MIC$_{90}$ values of 4 and 8 mg/L, respectively, against clinical isolate \textit{S. enterica}. The cytotoxicity activity of the peptides was determined by measuring intracellular ATP levels of HepG2 cells, and the authors observed no cytotoxic effect, only an 80% viability at concentrations of 420 and 433 mg/L for LS-sarcotoxin and LS-stomoxyn, respectively. In the hemolytic assay, for both peptides, the minimal hemolytic concentration determined for human erythrocytes was 1024 mg/L, i.e., both showed no evidence of hemolytic activity. The in vivo tolerability assay was performed on healthy male Swiss mice. The animals received a single intravenous dose of 10 mg/kg of the respective peptides (LS-sarcotoxin and LS-stomoxyn). They were evaluated daily for one month and no signs of toxicity were observed for either of the administered compounds. The pharmacokinetic profile of the peptides was determined in this study at 0.08, 0.25, 0.5, 1, 2, 4, 8, and 24 h after administration of the 10 mg/kg dose of the respective compounds. Then, the 10 \( \mu \)L blood sample was collected to quantify the peptide in plasma by tandem mass spectrometry (LC-MS), and the plasma concentrations above the lower limit of quantification (LLOQ) for LS-sarcotoxin and LS-stomoxyn were 1000 and 250 ng/mL, at 5 and 15 min after administration, respectively. The peptides showed good antimicrobial activity against the resistant strain of \textit{S. enterica} and no toxicity, and thus, they can be considered promising new antibiotics. However, they did not exhibit a good pharmacokinetic profile, which needs to be improved before in vivo efficacy assays can be performed \cite{110}.

5.4. \textit{Staphylococcus aureus}

Various AMPs have shown potential against methicillin-resistant, vancomycin-resistant, and intermediate \textit{S. aureus} (MRSA/VRSA/VISA), and most of the peptides against \textit{S. aureus} were isolated from snake venom \cite{111}, bee venom \cite{112}, the skin of reptiles \cite{113}, and even from birds \cite{114}. This is probably one of the most widely studied bacteria in recent decades of AMP applications.

A study that applied the combined action of melittin/mupirocin (4.4 and 14.22 \( \mu \)g/mL) demonstrated the synergistic effect between the AMP-drug during treatment and highlighted its application as anti-biofilm formers against eight strains of MRSA \cite{115}. This AMP is capable of inserting itself into the lipid membrane, forming a toroidal pore, and it also has an anti-VRE potential effect \cite{116}. Likewise, WLBU2 is a promising peptide evaluated with CPB and HPB, which showed activity even in the middle of the biofilm formed. These results allow us to have a base molecule, from which to generate new homologs that reduce its cytotoxicity to take it to the next experimental stage \cite{117}. The previously described Bip-P-113 also showed promising activity against VISA, and thus,
it created expectations about the synergy of peptidomimetics and AMPs [105]. For other high-priority bacterial strains, no AMP studies have been reported yet.

6. Challenges and Perspectives

Many AMPs, as demonstrated, have excellent properties against resistant bacteria. The difficulty in being applied to biological systems lies in the degradation and denaturation caused by biomolecules, such as proteolytic enzymes, and the gastric environment, as peptides and proteins can be hydrolyzed during their transport through the gastrointestinal tract when they are administered mainly orally [118]. This challenge has been deeply investigated through the use of protection and drug delivery technologies, such as micro and nanotechnology, with promising results for the development of new drugs [119,120].

Some AMPs present hemolytic activity, which is considered an important factor to be controlled and evaluated, as human cells could be lysed before the AMPs fulfill their objective [121]. However, some advances indicate that the manipulation of hydrophobicity could be crucial for this type of molecule, and for this reason, more studies of amino acid substitution within the peptide sequence must be carried out [56]. Furthermore, a previous study by our research group indicated that the use of microencapsulation with alginate by ionic gelation could decrease the hemolytic activity without affecting the antimicrobial activity of the Ctx(Ile21) peptide, making it useful as an oral food additive in formulations against MDR bacteria [5]. To the best of our knowledge, this is the first review article including AMPs against bacteria from the WHO priority list.

7. Conclusions

The progress of studies on AMPs against bacteria of critical and high priority according to the WHO has shown that the effectiveness of these peptides is, in certain cases, even better than that of conventional drugs. In addition, the combined use of AMP and drugs has a synergistic effect capable of reactivating the antimicrobial action of many obsolete drugs. The continuous study of AMPs in the pharmaceutical industry has produced promising results to solve the great problem of current bacterial resistance.

Author Contributions: Conceptualization, C.A.R.-B. and P.B.d.S.; investigation, C.A.R.-B., P.B.d.S., M.C.R., R.B.A., L.D.F., J.L.D., E.F.V.; writing—original draft preparation, C.A.R.-B.; writing—review and editing, C.A.R.-B., E.F.V. and F.R.P.; supervision, M.C., E.F.V. and F.R.P.; funding acquisition, F.R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the São Paulo Research Foundation (FAPESP): Research Grant: 2020/13497-4 and Fellowships: 2018/25707-3 and 2020/16573-3. National Council for Scientific and Technological Development (CNPq): Research Grants: 429139/2018-7 and 404181/2019-8. Productivity Research Fellows (PQ CNPq): 303603/2018-6. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: All contributing authors declare no conflict of interest.

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