

# Development and Research Progress of Anti-Drug Resistant Bacteria Drugs

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**Abstract:** Bacterial resistance has become increasingly serious because of the widespread use and abuse of antibiotics. In particular, the emergence of multidrug-resistant bacteria has posed a serious threat to human public health and attracted the attention of the World Health Organization (WHO) and the governments of various countries. Therefore, the establishment of measures against bacterial resistance and the discovery of new antibacterial drugs are increasingly urgent to better contain the emergence of bacterial resistance and provide a reference for the development of new antibacterial drugs. In this review, we discuss some antibiotic drugs that have been approved for clinical use and a partial summary of the meaningful research results of anti-drug resistant bacterial drugs in different fields, including the antibiotic drugs approved by the FDA from 2015 to 2020, the potential drugs against drug-resistant bacteria, the new molecules synthesized by chemical modification, combination therapy, drug repurposing, immunotherapy and other therapies.

**Keywords:** multidrug-resistant bacteria, antimicrobial resistance, novel antibiotics, antibiotics, antibiotic discovery

## Introduction

The golden age of antibiotics was ushered in by the accidental discovery of penicillin in 1929.<sup>1</sup> About 70% of the antimicrobials used in human medicine today were obtained during the golden age of antibiotic discovery, and most of which were isolated from Actinomycetes.<sup>2</sup> As one of the most important medical discoveries in the 20th century, antibiotics have revolutionized medical practice with their ability to treat infections caused by pathogenic microorganisms, which has saved countless lives and made important contributions to the prevention and treatment of human infectious diseases.<sup>3</sup> However, since the 1970s, the research and development of antimicrobials has focused more on the modification or optimization of known compounds in laboratory conditions; obtaining antibiotics with development value from microbial metabolites by pure culture method has been difficult; and fewer antibiotics can be used in clinical trials.<sup>4</sup> Data display that 270 antibiotics have been approved by the US Food and Drug Administration (FDA) for clinical use from 1928 to early 1970s.<sup>5</sup> Although infectious diseases caused by bacteria, viruses, parasites, or fungi are the second leading cause of death in the world, only 27 antibiotics out of the 1090 FDA-approved drugs were commercialized between 2000 and 2020.<sup>6</sup> While the development of antibiotics is becoming increasingly difficult, the resistance of bacteria to antibiotics is increasing year by year.<sup>7</sup>

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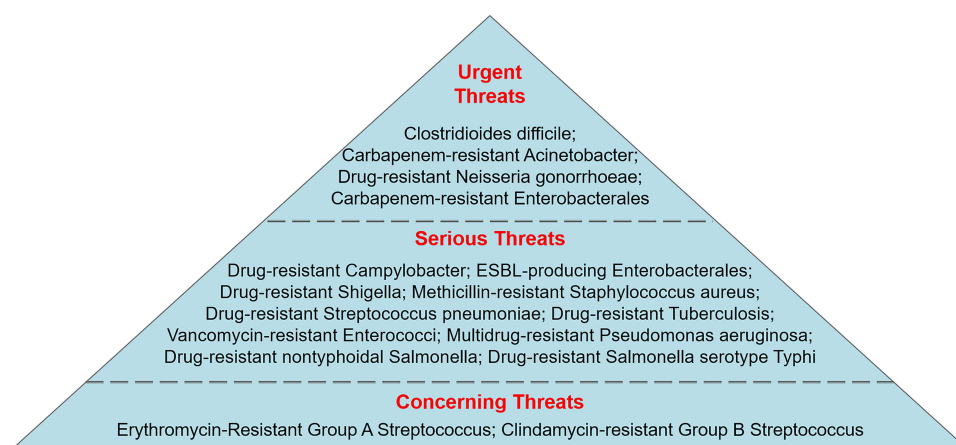
Seven of the 17 Sustainable Development Goals of the United Nations 2030 Agenda are related to antimicrobial resistance (AMR). Drug-resistant diseases kill at least 700,000 people globally each year, and this figure could rise to 10 million a year by 2050.<sup>8</sup> Without sustained efforts to curb AMR, some 2.4 million people in high-income countries could die from drug-resistant diseases between 2015 and 2050, and the cumulative global economic losses could amount to about \$100 trillion a year.<sup>9</sup> At least 2.8 million people in the US become infected with drug-resistant diseases each year, and more than 35,000 die from these diseases.<sup>10</sup> Around 33,000 people die in Europe each year from infections with various drug-resistant bacteria, and the burden of these infections is equivalent to that of influenza, tuberculosis, and acquired immunodeficiency syndrome combined.<sup>11</sup> The severity of AMR is particularly acute in low- and middle-income countries because of inadequate surveillance, limited antimicrobial supplies, and inadequate laboratory capacity.<sup>12,13</sup>

At present, the serious lack of new antibiotics and increased antibiotic resistance coexist.<sup>14</sup> Only eight of the 51 newly developed antibiotics could be classified as innovative drugs to treat antibiotic resistance, and most of which are modifications of existing drugs.<sup>15</sup> Most antibiotics in use today are natural or derived from natural antimicrobial drugs.<sup>16,17</sup> The rapid development of drug resistance may render many promising antibacterial drugs useless.<sup>18–20</sup> The lack of effective antimicrobial agents has greatly weakened our ability to effectively control infection. Thus, new treatment strategies for infectious diseases are urgently needed.<sup>21,22</sup>

## Major Drug-Resistant Bacteria

Despite various strategies adopted in clinical practice, mortality due to antibiotic-resistant bacteria has remarkably increased worldwide. “ESKAPE” pathogens, namely, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp., are the most common opportunistic pathogens in nosocomial infection.<sup>23</sup> The acronym “ESKAPE” is close to ESCAPE and vividly reflects the ability of these microorganisms to “escape” the bacterial killing of antibiotics, as well as their insensitivity to conventional antimicrobial therapy.<sup>24</sup> According to the bacteria and fungi listed in the Centers for Disease Control and Prevention’s 2019 Antibiotic Resistance Threat Report, drug-resistant microbial species are classified into urgent, serious, and concerning threats according to their severity.<sup>25</sup> The urgent, serious and concerning threats of drug-resistant bacteria are shown in Figure 1.

Methicillin-resistant *S. aureus* (MRSA) has severe multidrug resistance to aminoglycosides,<sup>26</sup> fluoroquinolones,<sup>27</sup> tetracycline,<sup>28</sup> macrolides, and other antimicrobial drugs.<sup>29,30</sup> Vancomycin-resistant *Enterococcus* (VRE) was first discovered in a clinical isolate in 1986. Vancomycin-resistant *S. aureus* (VRSA) isolates, which pose serious threat to healthcare, were discovered in 2002 because of the transmission of *vanA* resistance genes. VRE-induced nosocomial complicated urinary tract infections (cUTIs) has been reported and can lead to bacteremia (blood infection) and even death.<sup>31</sup> As Gram-negative bacteria (GNB), *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* constitute a special threat because of their double-membrane



**Figure 1** Centre for Disease prevention and Control (CDC) classification on antibiotic-resistant bacteria that cause public threat.

**Notes:** Data from: U.S. Department of Health and Human Services; Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States; 2019. Available from: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>. Accessed March 2, 2021.<sup>205</sup>

coating, which inhibits the access of antibiotics to their target; therefore, the infections caused by these bacteria cannot be cured even by a lethal dose of antibiotics.<sup>32</sup> Thus, MDR-GNB occupies an important position in nosocomial infections.<sup>33,34</sup> MDR *A. baumannii* and *P. aeruginosa* are the leading causes of nosocomial infections worldwide and are currently the key priority pathogens of the WHO in terms of drug resistance, AMR surveillance, and the discovery of new antibiotics.<sup>35</sup> The current resistance rates of Enterobacterales to third-generation cephalosporins are above 10%, and the resistance rates of Enterobacterales, *K. pneumoniae*, *P. aeruginosa*, and intensity care unit-acquired *A. baumannii* to carbapenems are 2%–7%, >25%, 20%–40%, and 40%–70%, respectively.<sup>36</sup> In addition, linezolid was sold in 2000, and reports of resistance to linezolid appeared in just 1 year.<sup>37</sup> Therefore, the research and development of new antibiotic drugs that can effectively deal with the infection of these resistant bacteria are urgently needed.

## Progress in Research and Development of Drugs Against Drug-Resistant Bacteria

### Antibiotic Drugs Approved for Marketing by FDA from 2015 to 2021

The following antibacterial drugs were approved for marketing by FDA from 2015 to 2020. Ceftazidime/avibactam was approved in 2015. Obiltoxaximab and bezlotoxumab were approved in 2016. Delafloxacin, meropenem/vaborbactam, and ozenoxacin were approved in 2017. Plazomicin, eravacycline, sarecycline, omadacycline, and rifamycin were approved in 2018. Imipenem/cilastatin/relebactam, pretomanid, lefamulin, and cefiderocol were approved in 2019. No FDA-approved drugs targeting resistant bacteria hit the market in 2020. Oritavancin was approved by the FDA in April 29, 2021.

Ceftazidime/avibactam is a combination of the third-generation cephalosporin, ceftazidime, and the beta-lactamase inhibitor, avibactam. Ceftazidime inhibits peptidoglycan synthesis by inhibiting penicillin-binding proteins (PBPs), which results in cell wall instability and cell death. Avibactam is a synthetic, non-beta-lactamase inhibitor that inhibits the activity of class A and C beta-lactamases and some class D beta-lactamases.<sup>38</sup> Avibactam protects ceftazidime from breakdown by the beta-lactamases produced by these drug-resistant GNB

but does not inhibit subclass B1 beta-lactamases, such as New Delhi metallo-beta-lactamase (MBL), Verona integron-encoded MBL, and Imipenemase.<sup>39</sup> Ceftazidime/avibactam is used to treat complicated intra-abdominal infections (cIAI) and cUTI caused by susceptible GNB. The adaptive bacteria, including MDR *P. aeruginosa*, carbapenem-resistant GNB, and extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E), are widespread. The most frequently encountered adverse reactions include hypersensitivity, diarrhea, and central nervous system reactions (such as seizures), which occur most often in patients with renal damage.<sup>40</sup> According to clinical trials, the effect of Ceftazidime/avibactam is better than that of carbapenems.<sup>41</sup> The combination therapy of ceftazidime/avibactam and metronidazole is recommended for cIAI.<sup>42</sup> Although the combination has been available clinically for only a few years, cases of resistance to Ceftazidime/avibactam have already been reported.<sup>43</sup>

The new inhaled anthrax treatment, obiltoxaximab, is a monoclonal antibody against the protective antigen of *Bacillus anthracis* and is designed to neutralize the toxin produced by *B. anthracis* to prevent the bacterium from binding to the cellular receptor.<sup>44</sup> Obiltoxaximab alone or in combination with antibiotics remarkably improved the survival rate of rabbits who inhaled a challenge dose of *B. anthracis* spores without interfering with immune development.<sup>45</sup> The most frequently reported side effects of obiltoxaximab include headache, itching, upper respiratory tract infection, cough, stuffy nose, and hives, as well as bruising, swelling, and pain at the injection site. The label of obiltoxaximab carries a black box warning that the drug may cause allergic reactions, including anaphylactic shock.<sup>46</sup>

Bezlotoxumab is a human monoclonal IgG1 antibody against *Clostridioides difficile* toxin B30. Bezlotoxumab works by preventing the B toxin from binding to colon cells and thus prevent the development of *C. difficile* infection. Bezlotoxumab can reduce the proinflammatory reaction in vitro and reduce the damage to the colon explant tissue by neutralizing toxin B. It has no direct antibacterial activity against *C. difficile* and has low immunogenicity and good tolerability.<sup>47</sup> However, it causes an unexplained increased risk of heart failure in patients with underlying congestive heart failure. Therefore, the bezlotoxumab adaptation population need to be further improved.<sup>48</sup>

Delafloxacin, as a dual-targeted fluoroquinolone compound, was first approved by FDA on June 19, 2017 for clinical use in the treatment of acute bacterial skin and

skin structure infections (ABSSSI). Delafloxacin can form a ternary complex with DNA and topoisomerase IV or DNA cyclotron to inhibit the formation of bacterial DNA superhelix and disrupt the DNA replication process.<sup>49</sup> Delafloxacin protects against Gram-positive bacteria (GPB, such as MRSA) and GNB (including quinolone-resistant *E. coli*, *P. aeruginosa*, and *K. pneumoniae*) and is more active against MRSA than other fluoroquinolones.<sup>50</sup> Its bactericidal ability under acidic environment is also more prominent than most approved zwitterionic fluoroquinolone drugs. Delafloxacin is well tolerated with a termination rate of only 0.9% because of side effects in a Phase 3 clinical trial. The common adverse reactions are gastrointestinal disorders, including nausea, diarrhea and vomiting. It did not cause QT prolongation and phototoxicity and has no adverse effects on liver function, renal function, or glucose utilization.<sup>51</sup>

Meropenem/vaborbactam is composed of the broad-spectrum carbapenem, meropenem, and the beta-lactamase inhibitor, vaborbactam. Meropenem acts on PBPs and causes bacterial lysis by inhibiting cell wall biosynthesis. Vaborbactam is a new type of beta-lactamase inhibitor. It does not have any antibacterial activity but can protect meropenem from degradation by certain serine beta-lactamases without reducing meropenem activity. Meropenem/vaborbactam has a broad-spectrum inhibitory activity against the members of the beta-lactamase family, and almost all (99%) *K. pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae has in vitro activity.<sup>52</sup> Vaborbactam has a strong inhibitory activity against type A and C beta-lactamases but not against type B and D beta-lactamases.<sup>53</sup> In August 2017, the FDA approved Meropenem/vaborbactam for the treatment of adult patients with cUTIs, including pyelonephritis caused by certain bacteria. This drug has good efficacy against GNB, especially bacteria with beta-lactam antibiotic resistance, and has good safety and tolerability.<sup>54</sup> The most common adverse effects of Meropenem/vaborbactam are headache, phlebitis or infusion site reactions, and diarrhea. Rare and serious adverse reactions include anaphylaxis and epilepsy.<sup>55</sup>

Ozenoxacin is a dual inhibitor of DNA helicase and topoisomerase IV and belongs to the non-fluoroquinolone class of drugs. Ozenoxacin was approved by the FDA in December 2017 for the treatment of impetigo caused by *S. aureus* or *Streptococcus pyogenes* in pediatric patients and adults older than 2 months of age.<sup>56</sup> The drug kills bacteria by inhibiting bacterial DNA replicases, DNA

cyclotron A, and topoisomerase IV. Ozenoxacin has excellent activity against *S. aureus* (including methicillin-resistant isolates) and *S. pyogenes*. Adverse reactions include rosacea or seborrheic dermatitis.<sup>57</sup>

Plazomicin is a new generation of aminoglycoside antibiotics that can inhibit the 30S subunits of bacterial ribosomes and then kill bacteria. Plazomicin is made by chemical modification on the basis of sisomicin, which avoids being damaged by the aminoglycoside-modifying enzyme (AME) and thus inactive.<sup>58</sup> Plazomicin was approved by the FDA in June 2018 for the treatment of adult patients with cUTIs (including pyelonephritis) caused by certain Enterobacterales infections with very limited or no treatment options. The application was submitted to the European Medicines Agency (EMA) for review in June 2018. Plazomicin has antimicrobial activity against MDR Enterobacterales, *P. aeruginosa*, *S. aureus* (including MRSA), ESBL-E, carbapenem-resistant Enterobacterales (CRE), polyclistin-resistant Enterobacterales, and AME-producing bacteria.<sup>59,60</sup> Adverse reactions include nephrotoxicity (the incidence of nephrotoxicity is lower than that of colistin), diarrhea, hypertension, headache, nausea, vomiting, and hypotension.<sup>61</sup>

Eravacycline is a fully synthetic fluorocycline antibiotic that is a part of a novel tetracycline broad-spectrum antibiotic with C-7 and C-9 modifications to the D-ring of the tetracycline core. Similar to other tetracyclines, eravacycline inhibits bacterial protein synthesis by binding to the 30S subunit of the ribosome.<sup>62</sup> Eravacycline has broad-spectrum antimicrobial activity against GNB, GPB, and anaerobic microorganisms, as well as against MDR bacteria, including MRSA, VRE, CRE, and *Acinetobacter* spp. that produce ESBL.<sup>63,64</sup> The most common adverse reactions are infusion site reactions (7.7%), nausea (6.5%), vomiting (3.7%), and diarrhea (2.3%).<sup>65</sup>

Sarecycline is a tetracycline-derived oral antibiotic designed specifically for acne. It was approved by the FDA in 2018 for the treatment of inflammatory conditions associated with moderate to severe non-nodular acne.<sup>66</sup> Sarecycline has strong anti-inflammatory activity against GPB, such as *Cutibacterium acnes*, and has minimal anti-inflammatory activity against aerobic GNB.<sup>67</sup> It has a low resistance rate in tetracycline-resistant *S. aureus*, as well as erythromycin-resistant and clindamycin-resistant bacteria. In clinical trials, adverse events were found in vulvovaginal mycosis (0.8%) and vulvovaginal candidiasis (0.6%) in

less than 1% of female subjects; thus, the adverse events were small.<sup>68</sup>

Omadacycline is a novel tetracycline antimicrobial agent for the empirical treatment of community-acquired bacterial infections. The C9 and C7 sites of the D ring of the tetracycline core are chemically modified to stabilize the exhaust pump and ribosomal protective protein mechanism of tetracycline resistance.<sup>69</sup> Similar to other tetracyclines, omadacycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Omadacycline provides a promising treatment plan for ABSSSI and community-acquired bacterial pneumonia (CABP). Moreover, omadacycline has a broad spectrum of activity against aerobic and anaerobic GPB and GNB; atypical bacteria; and antibiotic-resistant organisms, such as MRSA, methicillin-sensitive *S. aureus* (MSSA), and penicillin-resistant and MDR *Streptococcus pneumoniae* and VRE, but it has no activity against *P. aeruginosa*, *Proteus* spp., and *Providencia* spp.<sup>70</sup> In clinical trials, the most common adverse reactions (incidence  $\geq 2\%$ ) were nausea, vomiting, infusion site reaction, increased alanine transaminase, increased aspartate transaminase, increased  $\gamma$ -glutamyltransferase, hypertension, headache, diarrhea, insomnia, and constipation.<sup>71</sup>

Rifamycin inhibits bacterial DNA-dependent RNA polymerase by inhibiting RNA synthesis.<sup>72</sup> It was approved by the FDA in November 2018 for the treatment of non-invasive *E. coli* strains that cause traveler's diarrhea. In clinical trials, adverse reactions were constipation (3.5%), headache (3.3%), abdominal pain (0.5%), and fever (0.3%), and 1% of patients discontinued treatment.<sup>73,74</sup>

Imipenem/cilastatin/relebactam is a combination of imipenem, cilastatin, and relebactam. Imipenem/cilastatin is a combination antibiotic product that has been in use for decades under the brand names Primaxin and Tienam. Relebactam is a novel beta-lactamase inhibitor that protects Imipenem from degradation by certain serine beta-lactamases. Gram-negative strains resistant to imipenem became more sensitive to imipenem when combined with relebactam. In July 2019, the FDA approved Imipenem/cilastatin/relebactam to treat cUTIs and cIAI caused by designated sensitive GPB for patients aged 18 years of age and older who have limited or no other treatment options.<sup>75</sup> In addition, it was approved in 2020 for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in adult patients caused by a variety of specific microorganisms, such as *Enterobacter cloacae*, *E. coli*,

*K. pneumoniae*, *Clostridium perfringens*, *P. aeruginosa*. The common adverse reactions of Imipenem/cilastatin/relebactam include nausea, diarrhea, and headache.<sup>76,77</sup>

The novel compound, pretomanid, which is a part of a three-drug, six-month, all-oral regimen, bedaquiline–pretomanid–linezolid (BPAL), kills actively replicating *Mycobacterium tuberculosis* by blocking cell wall production under anaerobic conditions. Pretomanid is also active against non-replicating *M. tuberculosis* and acts as a respiratory poison to inhibit protein synthesis.<sup>78</sup> It is used for the treatment of patients with extensively drug-resistant (XDR) tuberculosis (TB) or MDR-TB (collectively referred to as “highly drug-resistant TB”) who are drug intolerant or unresponsive. Treatment options and prognosis for people with highly drug-resistant TB are poor. Data from the pivotal Phase III NIX-TB trial showed that 90% of patients achieved negative sputum culture status 6 months after the completion of treatment with short-course fully oral BPAL. In the clinical trials of the BPAL program, peripheral neuropathy and anemia were the recognized adverse reactions.<sup>79–81</sup>

Cefiderocol is an injectable siderophore cephalosporin discovered and being developed by Shionogi & Co., Ltd., Japan, and it has a unique mechanism of penetrating the cell membrane of GNB by entering the bacterial periplasmic space as a result of its siderophore-like property.<sup>82</sup> Cefiderocol can inhibit the biosynthesis of bacterial cell walls and has strong bactericidal effect against all GNB, including carbapenem-resistant Gram-negative non-fermenting *A. baumannii*, *P. aeruginosa*, and refractory CRE. Cefiderocol has pioneered in the field of serious diseases, where mortality rates are high and medical needs are not met. FDA approved cefiderocol intravenous Injection and the Committee for Medicinal Products for Human Use of the EMA has also granted cefiderocol with accelerated assessment status.<sup>83–85</sup> The common adverse reactions of cefiderocol include gastrointestinal disorders, hypertension, infusion site pain, and diarrhea.<sup>82</sup>

Lefamulin, an intravenous and oral formulation, was approved by the FDA in August 2019 for the treatment of adult CABP. It represents an important new, short-term, empirical monotherapy regimen.<sup>86</sup> Lefamulin, a first-of-its-kind, system-administered semisynthetic pleuromutilin antibiotic that acts differently from other approved antibiotics. It can inhibit bacterial protein synthesis and thus inhibit bacterial growth by binding to the peptidyl transferase center of the 50S subunit of the bacterial ribosome.<sup>87</sup> Lefamulin has a targeted in vitro activity

spectrum against the most common pathogenic Gram-positive, Gram-negative, and atypical pathogens associated with CABP. Lefamulin also exerts activity against *S. aureus*, MRSA, and vancomycin-resistant *E. faecium*.<sup>88</sup> The adverse effects of lefamulin include prolonged QT interval (increases the risk of kidney failure or liver dysfunction in patients), infusion reactions, diarrhea, nausea, hypokalemia, insomnia, and headaches.<sup>89</sup>

Ceftolozane/tazobactam is a combination of ceftolozane, a novel cephalosporin antibiotic, and tazobactam, a beta-lactamase inhibitor. It was approved by the FDA in 2014 for the treatment of adult patients with cIAI and cUTI and was approved by the FDA in 2019 for the treatment of adult patients with HABP and VABP caused by certain susceptible GNB. Ceftolozane had a strong inhibitory effect on PBP. Compared with ceftazidime, imipenem, and ciprofloxacin, ceftolozane has demonstrated an 8–16-fold reduction in minimum inhibitory concentration against *P. aeruginosa*.<sup>90</sup> The efficacy of ceftolozane is limited by ESBLs and AMPC beta-lactamase.<sup>91</sup> Therefore, tazobactam was added to ceftolozane to overcome this barrier and increase the in vitro activity against drug-resistant strains, such as beta-lactamase- and ESBL-producing strains (eg, *E. coli*, *K. pneumoniae*, and *Proteus novelis*); their combination also has certain inhibitory effects against AmpC inhibitory Enterobacterales and *Citrobacter* strains. Ceftolozane/tazobactam also has higher in vitro activity against Enterobacterales than existing cephalosporins but is still readily hydrolyzed by MBL and KPC enzymes.<sup>92–94</sup> Ceftolozane/tazobactam has good in vitro activity against most Enterobacterales, including pathogens that produce ESBL, and has remarkable efficacy against *P. aeruginosa*.<sup>95</sup>

In addition, the FDA approved the anti-MRSA antibiotics dalbavancin and oritavancin in May and August 2014, respectively.<sup>96</sup> Dalbavancin is a novel semi-synthetic glycopeptide antibiotic and a derivative of the equivalent A40926. Dalbavancin has the same mechanism as vancomycin and teicoplanin, that is, it inhibits the biosynthesis of the cell wall of GPB. It is widely used for the treatment of skin and soft tissue infections.<sup>97</sup> In vivo and in vitro studies have shown that dalbavancin has antimicrobial activity against GPB, including MRSA, MSSA, coagulase-negative staphylococci (CoNS), and *Streptococcus*.<sup>98</sup> Dalbavancin is the first antibiotic approved by the FDA for the treatment of GPB (including MRSA) infection. It is used to treat ABSSSI caused by GPB (including MRSA). Oritavancin, an antibiotic for the treatment of GPB (including MRSA) infection, has been

approved for the treatment of adult patients with ABSSSI caused by sensitive GPB (including MRSA).<sup>99,100</sup>

The US FDA approved oritavancin on March 12, 2021 for the treatment of ABSSSI caused by susceptible isolates of GPM, including MRSA.<sup>101</sup> Oritavancin is a single-dose long-acting lipopeptides antibiotic made in a 1200 mg vial in combination with 0.9% sodium chloride injection and 5% glucose sterile water for rapid bactericidal activity. Oritavancin is to be infused within 1 hour (ie, a single, 1-hour, 1200 mg infusion provides a full course of ABSSSI treatment).<sup>102</sup> Oritavancin has three bactericidal mechanisms: transpeptidase inhibition, transglycosylation inhibition, and cell membrane destruction. The efficacy and safety of oritavancin were demonstrated in the SOLO clinical trial of another oritavancin product. The experimental results showed that oritavancin was comparable to oritavancin in efficacy and safety. The common adverse reactions of oritavancin products are nausea, vomiting, diarrhea and other gastrointestinal symptoms, and headaches. The adverse reactions of oritavancin are manifested as hypersensitivity, pruritus, and chills.<sup>103</sup>

## Potential Drugs Against Drug-Resistant Bacteria

Odilorhabdins (ODLs) are a novel ribosome targeted antibiotic produced by the nematode symbiotic bacterium, *Xenorhabdus nematophila*. ODL's overall mechanism of action is to interfere with protein synthesis, and the pattern it works depends on the concentration of the drug.<sup>104</sup> Notably, its binding site is different from other inhibitors that target the 30S ribosomal subunit, and the mutations that render the mitochondrial ribosome susceptible to aminoglycosides are not expected to affect the binding or action of ODLs.<sup>105</sup> ODLs exhibit excellent broad-spectrum antimicrobial activity against a broad range of GNB and GPB (*K. pneumoniae*, *E. coli*, *Enterobacter aerogenes*, *E. cloacae*, *Proteus mirabilis*, *S. aureus*, and *Enterococcus faecalis*), including drug-resistant strains that are difficult to treat, such as carbapenemase-producing Enterobacterales. Moreover, ODLs were able to cure bacterial infections in animal models but did not exhibit bactericidal activity against cytotoxic in mammalian HepG2 and HK-2 cells. Their ability to cure bacterial infections in animal models and the novelty of their binding site made ODLs a promising candidate for new drug development.<sup>106,107</sup>

Teixobactin, a depsipeptide antibiotic derived from poorly cultivated soil microorganisms, is composed of 11 amino acids; this unique molecular structure confers its remarkable bacteriostatic activity.<sup>108,109</sup> Its unique and novel antimicrobial mechanism is to bind to the conserved sequences of peptidoglycan precursor lipid II and teixobactin precursor lipid III on the bacterial cell wall such that the bacterial cell wall cannot synthesize toxins. It is capable of killing a variety of drug-resistant pathogenic bacteria.<sup>110</sup> Teixobactin has a remarkable inhibitory activity against most GPB in vitro.<sup>111</sup> It also has strong inhibitory activity against *M. tuberculosis* with long treatment cycles and high clinical costs. Teixobactin has profound inhibitory activity for a variety of MDR bacteria, such as MRSA and VRE. Teixobactin is not effective against most GNB but exhibits good activity against *E. coli* asmb1, which has a defective outer membrane permeability barrier. In vitro toxicology experimental studies showed that teixobactin has no substantial toxic side effects.<sup>112</sup> Thus, teixobactin is considered the “star antibiotic”.<sup>113,114</sup> At present, the total chemical synthesis of teixobactin has been completed, and remarkable progress has also been made in the chemical synthesis of teixobactin analogs, which further drives the development of novel antibacterial drugs against drug-resistant strains.<sup>115</sup>

GNB have a double outer membrane that can block pathogens well, which makes them more difficult to kill than other types of bacteria. In the past 50 years, no new antibiotics against GNB have been approved for marketing. Arylomycin found in ordinary soil is a macrocyclic lipopeptide substance that can inhibit bacterial type I signal peptidase (SPase), which is a key membrane-bound enzyme that can decompose proteins and peptides. The active site of SPase, which is located between the cell membrane and outer membrane of GNB, greatly reduces the activity of arylomycin against GNB.<sup>116</sup> G0775, the new molecule obtained after the structural optimization of arylomycin, is 500 times more active than arylomycin against drug-resistant strains. G0775 has a therapeutic effect on a variety of GNB infections, including MDR bacteria, and has strong in vitro antibacterial activity against ESKAPE pathogenic bacteria. The brand-new mode of action of G0775 is that it forms a covalent bond with lysine (K146) in the target, which enhances its binding force to the target. Moreover, G0775 reaches the target not through the conventional channel protein (porin) to penetrate the outer membrane.<sup>117</sup>

Malacidins are calcium-dependent antibiotics usually encoded in soil microorganisms. Unlike other calcium-dependent antibiotics, malacidins interact with lipid II in a calcium-dependent manner.<sup>118</sup> Although vancomycin also binds to lipid II, malacidin is active against vancomycin intermediates and vancomycin-resistant pathogens.<sup>119</sup> Experiments show that malacidins have strong antibacterial activity against GPB resistant to commonly used clinical antibiotics, including vancomycin-resistant pathogens. In addition, malacidins have no obvious toxicity or hemolytic activity to mammalian cells. Therefore, it is a potential antibiotic for the treatment of drug-resistant bacteria that still needs further research.<sup>120</sup>

Researchers obtained the novel antibiotic, darobactin, a metabolite of luminescent *Bacillus*, from the screening of *Photorhabdus* isolates using the classic screening method in natural product research.<sup>121</sup> Darobactin is a novel peptide formed by the rare closed-loop structure of seven amino acids and is encoded by the silencing operon, synthesized by the ribosome, and produced in very small quantities under laboratory conditions. In addition, a novel antimicrobial mechanism has been proposed, that is, darobactin binds to BamA protein located in the outer membrane of GNB, damages the outer membrane, and induces cell lysis.<sup>122</sup> The compound exhibited good activity against wild-type and resistant Gram-negative pathogens, such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Shigella*, and *Salmonella* in vitro and in infected animal models and showed no cytotoxic effects. Therefore, this compound provides a very promising lead material for the development of new antibiotics.

Halicin is a broad-spectrum bactericidal antibiotic and the first antibiotic to be discovered by artificial intelligence without using any human assumptions. Halicin has inhibitory effect on the growth of *E. coli*, *S. aureus*, *K. pneumoniae*, and *A. baumannii* and has rapid bactericidal effect on *M. tuberculosis* and CRE. In a mouse model, halicin was also effective in treating *C. difficile* and pandrug resistant *A. baumannii* infections but had no antibacterial effect against *P. aeruginosa*. Halicin is antibacterial through a special mechanism; it can interfere with bacteria and prevent them from forming an electrochemical gradient across the membrane. It will cause bacterial death without such gradient.<sup>123</sup> However, the process of reshaping the electrochemical gradient is very complicated, which also prevents the generation of drug resistance to the greatest extent. Halicin was discovered by building a deep neural network model with empirical data from 2335 FDA-

approved drugs and natural molecules with a wide range of biological activity. The resulting model was then applied to predict antimicrobial compounds in drug recovery centers, and halicin was finally identified as a broad-spectrum bactericidal antibiotic. The antimicrobial compounds identified by this method are structurally far different from known antibiotics; this finding emphasizes the utility of deep learning methods. The antibiotic library can be expanded and new ideas can be provided for the development of subsequent antibiotics by discovering antimicrobial molecules with different structures.<sup>124,125</sup>

Pseudouridimycin (PUM), produced by microorganisms in soil samples, is a novel inhibitor antibiotic and the first nucleoside analog inhibitor.<sup>126,127</sup> PUM competes with uridine triphosphate to obtain the RNA polymerase (RNAP) active site and inhibit bacterial RNAP by blocking transcription. Although its antimicrobial mechanism is not new, it is unique in the sense that PUM selectively inhibits bacterial RNAP rather than human RNAP. Moreover, PUM has a different binding site compared with other RNAP inhibitors, such as rifampicin and fidaxomicin, which greatly avoids the occurrence of cross-drug resistance.<sup>128</sup> Studies have shown that PUM has antibacterial activity against GPB, GNB, and even more lethal pathogens (such as *E. coli*, *Acinetobacter* spp., and

*Pseudomonas* spp., especially MDR strains). Its mechanism of action made the development of bacterial resistant very difficult. Therefore, PUM is expected to become a true broad-spectrum antibiotics for clinical application.<sup>129</sup>

Table 1 summarizes the source, activity, against, mechanism of action and highlights of these potential drugs, and the chemical structures summarized in Figure 2.

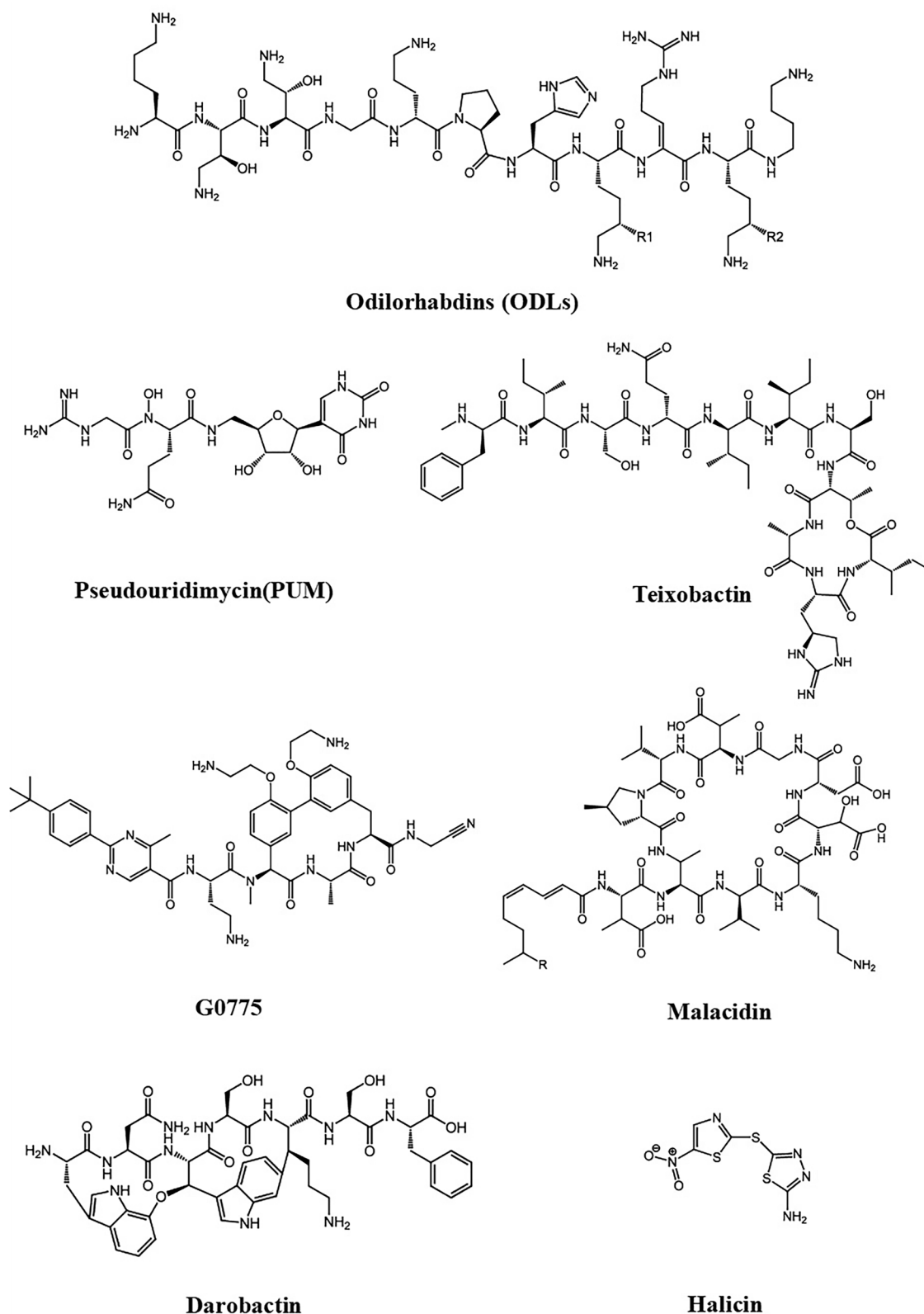
## New Molecules Synthesized by Chemical Modification

OTB-021(5-methyl-7-(3-nitro-1,2,4-triazol-1-yl)-1,2,4-triazolo[1,5-a]pyrimidine) is a compound that has specific activity against the H37RV strain, which is sensitive to *M. tuberculosis* drugs, but this compound has no activity against other GNB or GPB.<sup>130</sup> OTB-021 isomer showed reverse biological activity, which can inhibit the growth of all ESKAPE pathogens but is inactive against *M. tuberculosis*. The results will help to develop new effective drugs against diseases caused by drug-resistant bacteria.<sup>131</sup>

NAC-3, a new cephalosporin compound, was synthesized using cephalomycin C as the precursor; NAC-3 retained the antibacterial activity of its precursor and possessed improved stability against beta-lactamase with a 7α

**Table 1** Potential Drugs Against Drug-Resistant Bacteria with Their Reported Mechanism

| Name                   | Source                                                  | Activity Against                                                  | Mechanism of Action                                        | Highlights                                                                                                                          |
|------------------------|---------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Odilorhabdins (ODLs)   | From the nematode symbiotic bacterium <i>X. elegans</i> | GNB and GPB, including carbapenemase producing Enterobacteriaceae | Inhibition of protein synthesis                            | <ul style="list-style-type: none"> <li>• A novel binding site;</li> <li>• Drug concentration affects inhibition patterns</li> </ul> |
| Teixobactin            | From poorly cultivated soil microorganisms              | GPB, including MDR strains                                        | Inhibition of cell wall synthesis                          | <ul style="list-style-type: none"> <li>• Novel antimicrobial mechanism;</li> <li>• No significant toxic side effects</li> </ul>     |
| G0775                  | Optimized the structure of arylomycin                   | GNB, including ESKAPE pathogenic bacteria                         | Inhibition of SPase                                        | <ul style="list-style-type: none"> <li>• The way to reach the target is novel</li> </ul>                                            |
| Malacidins             | From the soil microorganisms                            | GPB, including MDR strains                                        | Interaction with lipid II in a calcium-dependent manner    | <ul style="list-style-type: none"> <li>• No cytotoxic effects</li> </ul>                                                            |
| Darobactin             | From the screening of <i>Photobacterium</i> isolates    | GNB, including MDR strains                                        | Damage in the outer membrane                               | <ul style="list-style-type: none"> <li>• Novel antimicrobial mechanism;</li> <li>• No cytotoxic effects</li> </ul>                  |
| Halicin                | From artificial intelligence                            | GPB and GNB, including MDR strains                                | Interruption of the transmembrane electrochemical gradient | <ul style="list-style-type: none"> <li>• Novel antimicrobial mechanism</li> </ul>                                                   |
| Pseudouridimycin (PUM) | From the microorganisms in soil samples                 | GPB and GNB, including MDR strains                                | Inhibition of bacterial RNAP by blocking transcription     | <ul style="list-style-type: none"> <li>• Selectively inhibit bacterial RNAP;</li> <li>• Different binding site</li> </ul>           |



**Figure 2** Potential drugs against drug-resistant bacteria with their chemical structure.

trans methoxy in the beta-lactam ring. In addition, NAC-3 has strong hydrophilicity, which also renders strong antibacterial activity, especially against anaerobic bacteria,

because of its cephalomycin C parent nucleus.<sup>132–135</sup> The antibacterial activity of NAC-3 against GPB, including MRSA, MSSA, methicillin-resistant *Staphylococcus*

*epidermidis*, and methicillin-sensitive *S. epidermidis*, is remarkably better than that of latamoxef and cefepime, but not strong enough against *E. faecalis* and *E. faecium*. Its antimicrobial activity against GNB, including *E. coli* (ESBLs, non-ESBLs), *K. pneumoniae* (ESBLs, non-ESBLs), *A. baumannii*, and *P. aeruginosa*, is low, but it has outstanding anti-MRSA activity, which has important clinical application value. Moreover, NAC-3 has good protective effect on the systemic infections caused by *S. aureus* in vivo, and its therapeutic effect is better than that of the commonly used clinical antibiotics, cefepime and cephalosporin. Hence, it became a new antibiotic candidate for anti-MRSA infection and provided a basis for the further research and development of new cephalosporin compounds.<sup>136</sup>

Serafim et al synthesized a new synthetic 1,3-bis-(aryloxy)propan-2-amine, which has antibacterial activity against GPB, including MRSA. In the future, the continuous optimization of the structure of the compound may also expand the antibacterial spectrum.<sup>137</sup>

Amino acid-conjugated polymers (ACPs) are a new type of molecule developed by chemically linking glycine with polymers. ACPs have high antibacterial activity against MDR *A. baumannii*, have no toxicity to human cells, and does not easily develop drug resistance. Further research on the efficacy of this molecule is needed in animal models.<sup>138</sup> Based on in vitro studies, ACPs have great potential to be developed as future therapeutics.<sup>139</sup> As the hydrophobicity of the amino acid side chain increases, its antibacterial activity and toxicity increase, which could provide new ideas for the subsequent discovery of new antibiotics against drug-resistant bacteria.<sup>140</sup>

## Combination Therapy

Taniborbactam is the first beta-lactamase inhibitor that has direct inhibitory activity on type A, B, C, and D enzymes.<sup>141</sup> The combined application of taniborbactam and the fourth-generation cephalosporin, cefepime, may be used to treat the infections caused by carbapenem-resistant pathogens, such as CRE and *P. aeruginosa*; Gram-negative and Gram-positive susceptible pathogens; and bioterrorist pathogens, such as *Burkholderia* spp.<sup>142</sup>

Synergistic effects between plazomicin and piperacillin/tazobactam or ceftazidime were observed in chessboard studies. These studies suggest that plazomicin has the potential to be used as a monotherapy and combination therapy for the treatment of severe infections caused by MDR Gram-negative Enterobacterales.<sup>143</sup>

In the combination therapy described by Procopio et al, the lectin, casuL, is an antimicrobial membrane agent against some *Staphylococcus* isolates obtained from animals with mastitis. In addition, the synergistic activity of casuL, when used in combination with antibiotics, supports the need for new studies to determine the feasibility of this approach in the treatment of goat and bovine mastitis.<sup>144</sup>

The drug efflux mechanism and outer membrane permeability barrier of GNB act synergistically to form intrinsic drug resistance.<sup>145</sup> Small molecule adjuvants may be used as a strategy to restore the activity of antibiotics against drug-resistant pathogens.<sup>146</sup> Efflux pump inhibitors (EPIs) block the efflux of antibiotics, but their efficiency in penetrating the outer membrane and resisting efflux is low. Combination with tobramycin carrier can enhance the synergistic effect and effectiveness of EPIs on MDR GNB and inhibit the development of drug resistance. This mechanism provides a strategy for developing more effective adjuvants to address antibiotic resistance in MDR GNB.<sup>147–149</sup> Tobramycin has been approved as an adjuvant beta-lactamase inhibitor for clinical use to prevent the inactivation of beta-lactam antibiotics.<sup>150</sup>

Recent studies have shown that the combination of bacteriophage and antibiotic therapy can provide a new way to treat the infection caused by the MDR strains of *A. baumannii*. *A. baumannii*, which can avoid bacterial killing, produce a sample capsule, and have thick outer layers for self-protection.<sup>151</sup> However, the phage used by the researchers can use the same capsule as an entrance to enter the bacteria and exert bacterial killing. Thus, *A. baumannii* will stop the production of capsule and become resensitized to antibiotics to escape the phage role. Animal experiments have shown that this method has a good therapeutic effect.<sup>152</sup>

## Drug Repurposing

Fosfomycin was discovered early but used less frequently. It currently has a wide range of activities against GNB and GPB, including MDR organisms, such as MRSA, VRE, ESBL-E, and CRE.<sup>153</sup> The broad-spectrum and safety of fosfomycin provide a great prospect for children with MDR organism infection. If fosfomycin is used alone, it may develop rapid drug resistance. However, fosfomycin can have a synergistic effect with other antibiotics in combination therapy, in which cross-resistance is not common; therefore, it needs to be used with caution to maintain the susceptibility of bacteria to fosfomycin.

In recent years, polymyxin B has been re-emphasized as the last resort for the treatment of MDR and XDR GNB infections.<sup>154</sup> Polymyxin plays an important role in the recurrence of GNB infection, especially MDR *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*.<sup>155</sup> The adverse reactions of polymyxin include nephrotoxicity, neurotoxicity, and congenital abnormalities.<sup>156</sup>

Research has revealed a new type of target for the treatment of drug-resistant TB using anti-platelet drugs, which may help the body's immune system fight off drug-resistant TB. Researchers have discovered for the first time in an animal model that platelets may worsen the symptoms of TB.<sup>157</sup> Moreover, the use of antiplatelet drugs may help the body's immune system to resist drug-resistant TB. Therefore, the antiplatelet drug, aspirin, can be used as an affordable drug candidate for TB treatment.<sup>158</sup> In addition, the use of FDA-approved reactive oxygen species (ROS)-reducing drugs prevents antibiotic-induced resistance mutations, but further preclinical trials are still needed to evaluate the effectiveness of such drugs.<sup>159</sup>

## Immunotherapy

The positive effects of antibodies against MDR bacterial infections were discovered in early animal experiments; therefore, antibodies have attracted increasing attention.<sup>160</sup> Researchers have developed antibodies from the blood of healthy individuals that can protect the body against a variety of *K. pneumoniae* subgroups and other bacteria. The chimeric antibody, pagibaximab, has a certain inhibitory effect on MRSA.<sup>161</sup> The monoclonal antibody, bezlotoxumab, against *C. difficile* toxin was approved by the FDA and the EMA in 2017 for the treatment of adult *C. difficile* infections.<sup>162</sup> Immune adjuvants can enhance immunogenicity and antibody titer, change the type of antibody produced, and cause or enhance delayed hypersensitivity. Existing research reports that antibodies play an auxiliary role in the treatment of drug-resistant bacterial infections.<sup>163</sup>

Antimicrobial peptides are a potentially effective therapy. Regardless of whether the bacteria are resistant or not, they kill the bacteria by destroying the bacterial cell membrane.<sup>164</sup> Researchers found that engineered cationic AMPs have a wide range of activities against MDR bacteria.<sup>165</sup> However, their stability is still an important concern.<sup>166</sup> The antibacterial peptide, OH-Cath30, identified in king cobra venom has strong antibacterial activity. In vivo and in vitro studies found that OH-Cath30 and its D-analogs have strong antibacterial activity against almost

all GPB and GNB. It has the highest bactericidal activity against MDR *A. baumannii* and MRSA. OH-Cath30, ciprofloxacin, and levofloxacin have a synergistic effect on drug-resistant *P. aeruginosa*.<sup>167</sup> The overall efficacy of OH-Cath30 and its analogs is higher than that of the nine commonly used antibiotics. Therefore, OH-Cath30 is a promising drug candidate for the treatment of various bacterial infections that are resistant to many conventional antibacterial drugs.<sup>168</sup> A recently reported adjuvant uses Cremophor EL-35 as a surfactant and propylene glycol as a co-surfactant. The adjuvant can increase the specific immune response of serum IgG and related subclasses and increase the survival rate of MRSA-infected mice.<sup>169</sup> Tocotrienols (T3s) is a little-known vitamin E isomer and has been recognized as an immunomodulator. In a mouse model of MRSA-induced wound infection, the use of T3S combined with daptomycin remarkably improved the efficacy of daptomycin.<sup>170</sup> Among natural products, essential oils (EOs) have strong antibacterial ability against GNB and GPB.<sup>171,172</sup> They can directly kill and sensitize bacteria and are often used in the prevention and control of microbial infections.<sup>173–177</sup> In addition, EOs are considered a powerful antibacterial or drug resistance reversal agent against resistant strains led by ESKAPE.<sup>178–180</sup> Moreover, EOs and antibacterial drugs (especially oxacillin against MRSA) show a high synergistic effect at sub-inhibitory concentrations, which lays the foundation for the subsequent development of drugs against drug-resistant bacteria.<sup>181</sup> A cytokine protein called IL-17 is essential to turn on the host's defence against staphylococcal infections. In a mouse model of *S. aureus* skin infection, IL-17 response was mediated by  $\gamma\delta$ T cells, which suggests that the cloned V $\gamma$ 6+V $\delta$ 4+ T cells have a broad and important role in immunity against *S. aureus* or MRSA skin infections.<sup>182</sup> Studies have found that the binding domain of autolyzed protein and lysosome as a peptidoglycan hydrolase can be fused to the fragment crystallizable region of human IgG to form a fully functional homodimer (or "lysi-body") and can be specifically targeted in MRSA.<sup>183,184</sup>

## Other Therapies

The quorum sensing (QS) mechanism enhances the mutual communication and virulence effects of microbial communities and ultimately leads to the emergence of antibiotic resistance.<sup>185</sup> With the increase in resistance to existing antibiotics and antifungal drugs, new strategies rely on inhibiting communication and virulence factors rather

than killing or inhibiting the growth of microorganisms.<sup>186</sup> These compounds are also known as QSI.<sup>187</sup> QSI can be an important antibacterial target for infectious diseases caused by the QS mechanism of GNB and GPB to prevent, inhibition, or treat the infectious diseases caused by resistant bacteria.<sup>188</sup> Indole is a widely existing QS signaling molecule.<sup>189</sup> Bacterial drug resistance mediated by signal molecules is an emerging mechanism that has received much attention in recent years. Researchers reported for the first time that the indole-mediated reversal of the inherent antibiotic resistance of *Lysobacter* spp. is closely related to a new type of BTUD bifunctional transporter.<sup>190</sup> This study also provides a new way to eliminate drug-resistant bacteria.

In addition to their excellent activity on biofilms, phages also have the advantages of rapid bacteria killing, have low chance of developing drug resistance, and have synergistic activity with other antibiotics and lysine.<sup>191</sup> Phage lysin is also being developed for specific GPB, such as *S. pneumoniae*, *S. aureus*, and *S. pyogenes*, as well as Gram-negative bacilli, such as *P. aeruginosa*, *A. baumannii*, and Enterobacterales.<sup>192</sup> The use of some bacteriophages in combination with antibiotics offers hope that the antibiotics that previously lost their antibacterial effect against drug-resistant bacteria will regain their role in killing these bacteria.<sup>193</sup> Nanoparticles are used as a drug surface coating agent to help the drug to penetrate the outer membrane of GNB and be released; these nanoparticles are called the “Trojan Horse” and greatly reduce the blocking of drugs by biofilms and drug transporters.<sup>194,195</sup> Coagulation factors have the ability to hydrolyze the necessary lipopolysaccharides in bacterial cell membranes, which may be expected to help defend against GNB.<sup>196</sup> Studies have shown that coagulation factors VII, IX, and X may be effective against MDR pathogens.<sup>197,198</sup>

Studies have shown that the water and methanol extracts of *Piper* spp. and *Smilax* spp. can effectively reverse the MDR of bacteria by removing the R-plasmid carried by MDR strains and make the bacteria sensitive to antimicrobial agents. These resources can potentially curb plasmid-mediated MDR.<sup>199</sup>

For the patients who cannot benefit from targeted antibiotic therapy with *C. difficile*, fecal transplantation or microbial replacement therapy will refill the intestines with a variety of microorganisms.<sup>200</sup> These microorganisms may prevent *C. difficile* spores from germinating and spreading diseases through its toxin. Transplantation may

be performed through enema, capsule, and direct infusion. Researchers found that stopping *Salmonella* from producing mucus weakens bacterial communities, which can then be mechanically washed away and are more likely to be killed by antibiotics, disinfectants, or the immune system.<sup>201</sup> The collapsed nature of the dry capsule of GPB was found through the exploration of their cell wall structure.<sup>202,203</sup> This finding overturns the previous related theories about the structure of the outer membrane of bacteria and provides new ideas for the later development of new methods to resist antibiotic resistance.<sup>204</sup>

## Discussion

The development of antibiotics has given humans a weapon against bacteria. However, drug-resistant bacteria have emerged in an endless stream, people gradually lost control of the bacteria that invade the human body, and global incurable crisis reappeared because of the development of drug resistance of pathogens and the abuse of antibiotics by humans. At present, the abuse of antibiotics has not been completely controlled and is still happening in varying degrees in different regions around the world. Therefore, in the face of increasingly tense global health issues that are closely related to the safety of human life, the issue of combating drug-resistant bacteria needs to be formally raised and emphasized again.

From 2015 to 2020, 16 antibiotic drugs, including 5 compound drugs, namely, Ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, pretomanid, and ceftolozane/tazobactam, were approved by the FDA. Among them, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, and ceftolozane/tazobactam are combinations of antibacterial drugs and beta-lactamase inhibitors and have good activity against drug-resistant bacteria, whereas pretomanid has good anti-TB activity.

Moreover, potential drugs against drug-resistant bacteria are also of great importance to the development of antimicrobial drugs for resistant bacteria in the future. ODL, halicin, and PUM are promising as broad-spectrum antibiotics. Among them, the ODL target is novel and has good activity against drug-resistant strains; halicin interferes with the formation of bacterial energy, has inhibitory effect on certain resistant bacteria, but has no bactericidal effect on *P. aeruginosa*; and PUM has a novel target, blocks transcription, and is active against MDR strains. Teixobactin, G0775, and darobactin have novel antibacterial mechanisms. Teixobactin inhibits cell wall synthesis,

has remarkable inhibitory activity against most GPB and a variety of drug-resistant bacteria, but cannot effectively resist GNB. G0775 penetrates the outer membrane in a special way to inhibit bacterial SPase with a new mechanism to kill a variety of GNB, including MDR bacteria. Darobactin destroys the outer membrane of bacteria and shows good activity against wild-type and drug-resistant GNB in vitro and in animal models of infection.

In addition to drugs against drug-resistant bacteria derived from natural products, chemically modified synthetic new molecules have also become an important way for the development of drugs against drug-resistant bacteria. OTB-021 is only sensitive to *M. tuberculosis* and has no effect on Gram-positive or Gram-negative pathogens, but its two isomers are just the opposite. Further NAC-3 has outstanding anti-MRSA activity. The new synthetic 1,3-bis(aryloxy)propan-2-amines have biological activity against GPB. The ACPs developed by chemical linkage have high antibacterial activity against MDR *A. baumannii*.

Combination therapy and the repurposing of old drugs have opened another door to the exploration of drugs and strategies against drug-resistant bacteria and are a promising way to extend the service life of existing antibacterial drugs. Techniques, such as phage therapy, nanotechnology, and fecal transplantation, are gradually being used to overcome the infections caused by resistant bacteria. In addition, phage therapy has rapid killing kinetics, specificity for pathogens, low chance of drug resistance, and synergistic activity with other antibiotics and lysine. At present, nanotechnology is gradually emerging in the treatment of drug-resistant bacterial infections. Fecal transplantation or microbial replacement therapy will help patients who cannot benefit from *C. difficile* targeted antibiotic therapy and prevent *C. difficile* spores from germinating and spreading diseases through its toxin.

## Conclusion

This review comprehensively summarizes the drugs that have been developed against drug-resistant bacteria, the possible potential drugs, and other approaches that can be applied to fight drug-resistant bacteria in addition to antibiotics. Many potential drugs need more experiments to verify their efficacy, and the antibacterial mechanism of most potential drugs is still unclear. FDA-approved drugs against drug-resistant bacteria account for a small proportion of all approved drugs. Researchers search for new drugs or new molecules that can delay or reduce the

emergence of drug-resistant bacteria through the combination of drugs, repurposing old drugs, and library searches and provide different solutions to the serious problem of bacterial resistance. In summary, it is likely that the current crisis of drug-resistant bacteria will not be resolved by a single new product or therapy. And it is believed that, a multidisciplinary research involving experts from various fields will more conducive to resolve the crisis and lay a solid road for the clinical treatment of patients infected with drug-resistant bacteria.

## Acknowledgments

This work was supported by The National Nature Science Foundation of China (grant nos. 81860653 and 82060654); The Science and Technology Foundation of Shaanxi Province [2020JM-550, 2020JM-545, 2020JM-549, and 2021JM-416]; Open Project Foundation of Key Laboratory of noncoding RNA and drugs in Universities of Sichuan Province [FB19-01 and FB20-02]; Open project Shaanxi Engineering and Technological Research Center for Conversation and Utilization of Regional Biological Resources (sxgczx-2019-02); Initial Scientific Research Fund of Yan'an University (YDBK201850 and YDBK2018-43), and Research Program of Yan'an University (YDZ2019-09 and YDZ2020-17).

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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