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Colloids and Surfaces B: Biointerfaces 211 (2022) 112303

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Multidrug resistance crisis during COVID-19 pandemic: Role of anti-microbial peptides as next-generation therapeutics

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ARTICLE INFO

Keywords:
Multidrug-resistance
Pandemic
Pathogens
Novel therapies
Anti-microbial peptides

ABSTRACT

The decreasing effectiveness of conventional drugs due to multidrug-resistance is a major challenge for the scientific community, necessitating development of novel antimicrobial agents. In the present era of coronavirus 2 (COVID-19) pandemic, patients are being widely exposed to antimicrobial drugs and hence the problem of multidrug-resistance shall be aggravated in the days to come. Consequently, revisiting the phenomena of multidrug resistance leading to formulation of effective antimicrobial agents is the need of the hour. As a result, this review sheds light on the looming crisis of multidrug resistance in wake of the COVID-19 pandemic. It highlights the problem, significance and approaches for tackling microbial resistance with special emphasis on anti-microbial peptides as next-generation therapeutics against multidrug resistance associated diseases. Anti-microbial peptides exhibit exceptional mechanism of action enabling rapid killing of microbes at low concentration, antibiofilm activity, immunomodulatory properties along with a low tendency for resistance development providing them an edge over conventional antibiotics. The review is unique as it discusses the mode of action, pharmacodynamic properties and application of antimicrobial peptides in areas ranging from therapeutics to agriculture.

1. Introduction

The virulent pandemic caused by SAR-CoV-2 (severe acute respiratory syndrome coronavirus 2) has created an extensive stress on health and economies worldwide. As of now, more than 169,118,995 COVID-19 cases and 3519,175 deaths have been confirmed [1], [2]. The recent detection of SARS-CoV-2 variants - UK's B.1.1.7, South Africa's B.1.351, Brazil's B.1.1.28, Double Mutant Strain B.1.617 are of great concern because of their tendency to transmit easily and mutate rampantly which causes these strains to become immunologically resistant to neutralization by most monoclonal antibodies [3]. Since antibiotics such as macrolides, cephalosporins, fluoroquinolones, and penicillin have been prescribed to a large number of COVID–19 patients to treat secondary bacterial infections, the possibility of antimicrobial resistance and its associated fatalities cannot be ruled out in the near future [4,5]. It has been reported that in Wuhan, amongst 191 COVID-19 hospitalized patients, 95% were treated with antibiotics and 21% were medicated with antivirals [6]. As a result, multidrug resistance (MDR) among microorganisms to conventional antimicrobial agents is one of the most perilous crises that mankind is about to witness. Pan American Health Organization (PAHO), a branch of WHO has reported that the prescription-based and self administration of ineffective antimicrobial drugs during COVID-19 pandemic has led to an incline in drug resistant infections [7]. In a recent study, Karruli et al. has reported the coexistence of SARS-CoV-2 and MDR infections in the patients and also stated the vulnerability of these patients towards MDR [8]. Pandemics are not a new phenomenon; they have posed a threat to human life since the dawn of time [9]. Table 1 summarises the modern era pandemics recorded in human history including Spanish Flu, Asian Flu, Hong Kong Flu, Plague pandemic, Cholera pandemic, SARS, Ebola and Zika [10–13]. Pandemic associated crises have caused adverse effects on health, economies and even national securities worldwide. During the ongoing pandemic, besides SARS-CoV-2 infection itself, increased cases of MDR inflicted collateral damage to the healthcare system [7,8]. Therefore, MDR is of utmost importance from a medical perspective and researchers across the globe are working on the future roadmap to handle multidrug

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https://doi.org/10.1016/j.colsurfb.2021.112303
Received 26 August 2021; Received in revised form 3 December 2021; Accepted 16 December 2021
Available online 20 December 2021

Table 1
Modern Flu Pandemics [25,262728].

S. No.	Pandemic	Year	Catastrophe
1	Black Death	14th century	75,000,000 deaths
2	Cholera	18th century	Every year 1,300,000 to 4,000,000 people are infected around the world, killing 21,000 to 143,000 people
3	Third plague pandemic	19th century	12,000,000 – 15,000,000 deaths
4	Spanish Influenza	1918–1920	500,000,000 people were affected
5	Asian Influenza	1957–1958	2,000,000 deaths globally
6	Hong Kong Influenza	1968–1969	1,000,000 death worldwide
7	Russian Influenza A (H1N1)	1977	–
8	HIV/AIDS pandemic	First detected in 1981 and it was a pandemic by late 20th century	Approximately 35,000,000 deaths
9	Severe Acute Respiratory Syndrome (SARS)	2002	8422 cases and 916 fatalities
10	Swine Flu pandemic (H1N1 Influenza)	2009–2010	151,700 to 575,400 deaths
11	Ebola epidemic	2014–2016	28,600 reported cases and 11,325 deaths
12	Covid-19 Pandemic	2019–present day	169,118,995 reported cases and 3,519,175 deaths

resistance. MDR is defined as acquired nonsusceptibility or resistance developed by the pathogens against known antimicrobial drugs. It is one of the major causes of antibiotic failure and a genuine concern in antimicrobial therapy. There are numerous mechanisms that microbes use to develop resistance to antimicrobial drugs such as enzymatic modification of the drug, prevention of drug penetration or accumulation and modification of the antimicrobial target [14,15]. Unregulated application of antimicrobial drugs, unhygienic conditions, hospital acquired infections and inefficient measures in prevention of infections are mainly responsible for the rise of MDR globally [16]. Since the current pandemic is significantly threatening the antimicrobial stewardship activities resulting into various multidrug resistant strains, it requires immediate attention in order to control the rise in antibiotic resistance [17]. As the incidence of infections caused by MDR bacteria has increased in clinical settings, requirement for novel antimicrobial formulations has intensified drastically. Several previous studies have reported the use of different strategies for the treatment of MDR induced diseases such as encapsulation of liposomes [18], nanoparticle based drug delivery [19], combination of allosteric and orthosteric drug strategy to overcome kinase drug resistance (phase II clinical trials) [20] and use of antimicrobial peptides (AMPs) as effective therapeutics against MDR [21,22]. AMPs, also known as host defence peptides (HDPs), have lately emerged as a promising treatment option for inhibiting growth of MDR organisms [21]. AMPs are amphipathic molecules present as innate immune system in all living organisms. They serve as primary defence towards pathogenic incursion by modulating immunological functions, activating and mobilising immune cells thereby initiating angiogenesis and inflammatory processes that contribute to healing [23]. AMPs exhibit exceptional mechanism of action enabling rapid killing of microbes, antibiofilm activity, immunomodulatory properties along with a low tendency for resistance development which provides them with an edge over conventional antibiotics [24]. Also, extensive research into genesis, structure-function features and synthesis processes has enhanced the applicability of AMPs as therapeutic agents [21]. This review will focus on current strategies being used to overcome the menace caused by MDR organisms with emphasis on AMPs as novel alternatives to conventional antimicrobial therapies. We will also address the applications of AMPs against resistant microorganisms.

2. Multidrug resistance

In the past few years, occurrence of microbial infections has significantly increased worldwide. Since the discovery of penicillin in 1928, antimicrobial agents have been used extensively to treat various microorganism induced infections [29]. However, inadequate diagnosis of infection, unregulated prescriptions leading to drug overuse along with poorly regulated use of antibiotics in agriculture and animal-derived products resulted in antibiotic resistance amongst various microbial strains [30]. According to the Center for Disease Control and Prevention (CDC), antibiotic-resistant diseases affect more than two million people in the United States annually adding upto 20 billion dollar as a direct burden in healthcare costs [31]. Annually 7,00,000 deaths have been reported worldwide due to the infections associated with MDR and further projections of these numbers are also worse as 10 million deaths per year are estimated by 2050 [32]. These projections are expected to vary as these are dependent upon the evolution of microbial organisms and effectiveness of various antibiotics. As a result of the increased appearance of antibiotic resistance, a variety of issues have arisen, including high morbidity and mortality rates, as well as an expensive healthcare system [33]. This resulted in the replacement of conventional ineffective drugs by novel drugs. Various effective antimicrobial drugs are being developed and marketed rapidly and many others are in clinical trials. These scientific findings have a short life and are often challenged by rapid progression of MDR species, which has the ability to develop resistance at an alarming rate making it challenging for the scientific community to stay abreast. MDR is defined as resistance shown by microorganisms to various antimicrobial drugs (viz. antibiotics) despite earlier sensitivity to them [33–35]. Almost all the pathogenic microorganisms such as bacteria, fungi, viruses, and parasites have developed high degree of resistance towards different antibiotics and hence, are called "super bugs" [33].

World Health Organisation (WHO) has listed this situation of MDR microorganisms as one of the leading adverse effects on human health [36]. Some of the most common MDR microorganisms as per WHO studies have been summarised alongwith the diseases associated with them in Table 2 and also discussed further in the review. *Staphylococcus aureus, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumanni and Enterobacter species (ESKAPE* pathogens*)*, are accountable for majority of the infections worldwide and have shown high rates of drug resistance and there are several instances of their association with life-threatening diseases [37,38]. There are certain other MDR microorganisms such as *Escherichia coli* [39–41], *Streptococcus pneumonia* [42–47], *Mycobacterium tuberculosis* [48], *Cryptococcus neoformans,* Human immunodeficiency virus (HIV), Influenza virus, Hepatitis B virus (HBV), *Plasmodia spp., Leishmania* spp., *Trichomonasvaginalis,* etc. which are resistant to the drugs like cephalosporin, macrolides, rifampicin, isoniazid, fluoroquinolone, fluconazole, antiretroviral drugs, adamantane derivatives, neuraminidase inhibitors, lamivudine, chloroquine, artemisinin, atovaquone, pentavalentantimonials, miltefosine, paromomycin, amphotericin B, and nitroimidazoles, respectively [49]. Resistance caused by these microorganisms towards traditional treatment regimen leads to the development of numerous diseases such as urinary tract infection, blood infection, pneumonia, meningitis, otitis, tuberculosis, meningoencephalitis, AIDS, influenza, hepatitis B, malaria, leishmaniasis, and trichomoniasis [33].

2.1. Classifications of MDR

Despite administering adequate doses of drugs over a substantial period of time, the survival of disease-causing organisms indicates the development of drug resistance in them. Survival of these microbes

Table 2
Common MDR microorganisms and diseases associated with them. Reprinted with permission from Copyright © 2014 Jyoti Tanwar et al. [33].

Name of microorganisms	Associated diseases	Drug resistance
Staphylococcus aureus	Systemic, skin, bone, and lung infections	Penicillin, Methicillin, and Vancomycin
Escherichia coli	Systemic infection and urinary tract infections (UTI)	Cephalosporins, fluoroquinolones, penicillin, erythromycin, amoxicillin
Klebsiella pneumoniae	Systemic infection, UTI, pneumonia, abdominal infection, pyogenic liver abscess, and meningitis	Cephalosporins carbapenems, aminoglycoside, quinolones, tetracycline, and colistin
Streptococcus pneumoniae	Pneumonia, otitis, and meningitis	B-lactams, fluoroquinolones, macrolides, lincomycin, tetracyclines, and trimethoprim-sulfamethoxazole
Mycobacterium tuberculosis	Tuberculosis (TB)	Rifampicin, isoniazid, and fluoroquinolone
Cryptococcus neoformans	Cryptococcal meningitis	Fluconazole, Flucytosine
HIV	AIDS	Antiretroviral drugs
Influenza virus	Respiratory infections	Adamantane derivatives and neuraminidase inhibitors
HBV	Hepatitis B (Liver infection which can lead from cirrhosis to liver cancer)	Lamivudine, nucleos(t)ide analogues (NUCs)
Plasmodia spp.	Malaria	Chloroquine, artemisinin, and atovaquone
Leishmania spp.	Leishmaniasis	Pentavalentantimonials, Diamidine, Miltefosine, Paromomycin, Amphotericin B, Ketoconazole, Allopurinol
Entamoeba	Amoebiasis	Metronidazole, Trifluoromethionine
Trichomonasvaginalis	Trichomoniasis	Nitroimidazoles, Trifluoromethionine

might not only be dependent upon their resistance to certain drugs but might also be due to poor drug bioavailability, rapid drug metabolism and poor immunity of the host body [50,51]. However, persistence of microorganisms after significant conventional treatments throws light on different categories of resistance such as primary, secondary, or clinical resistance [33].

2.2. Primary resistance

Resistance in organisms to one or more drugs without having prior exposure to the particular drug of interest is called primary resistance [52]. Primary drug resistance can be caused by altered drug metabolism or drug target modification [53]. Drug metabolism mainly involves the absorption, excretion and detoxification. Absorption is mainly dependent upon the chemical nature of the drug and the receptors or transporters responsible for its uptake. Therefore, any alteration in these receptors or transporters can lead to the development of the resistance. Also, various membrane transporters which enhance the efflux of the drug, are responsible for the development of the resistance. Further, drug inactivation by altering the metabolic processing and alterations in the drug targets such as modifications in the binding site can complement the resistance [54]. For example, in studies conducted by Khalilzadeh et al. and Song et al., clinical isolates of *M. tuberculosis* showed primary resistance towards rifampicin, isoniazid, streptomycin, and ethambutol [55,56]. Rifampicin and isoniazid resistance is associated with mutations in the *rpoB* gene of the RNA polymerase and *katG*, *inhA*, *ahpC*, *kasA* genes, respectively [48,57].

2.3. Secondary resistance

Secondary resistance in the organisms is acquired only after prior exposure to the drug of interest. It is also known as 'acquired resistance'. However, this type of resistance can be further classified as intrinsic and extensive resistance. **Intrinsic resistance**, also known as MDR is referred to as the resistance of microorganisms to certain common first-line drugs. For instance, MDR-TB (*M. tuberculosis*) is resistant to the two first line drugs, rifampicin and isoniazid. Whereas, **extensive resistance**, also known as extensive drug resistance (XDR) is referred as resistance developed by microorganisms against not only first-line drugs but also second-line drugs. For example, XDR-TB is resistant to fluoroquinolone and injectable second-line drugs such as amikacin, capreomycin, etc. along with the first-line drugs [52,55,58]. Fluoroquinolone resistance in *M. tuberculosis* is associated with the chromosomal mutation in *gyrA* and *gyrB* genes [48].

2.4. Clinical resistance

This can be defined as the resistance of organisms to the clinically approved doses of the drug that is associated with failure of therapy or reappearance of infections due to impaired host immune function, such as, neutropenia. These microorganisms can be effectively inhibited with drug concentrations which are much higher than the therapeutically safer doses or with combination therapies [33]. For example, *A. baumanni* is resistant to meropenem and *S. aureus* is resistant to vancomycin [59–61]. The most common cause of resistance to meropenem in *A. baumanni* is overexpression of chromosomal *AmpC* gene [62] however, vancomycin resistance to *S. aureus* is mediated by a *vanA* gene cluster, carried on the mobile genetic element Tn*1546* acquired from vancomycin-resistant *enterococcus* [63,64].

2.5. Mechanism of MDR

Although various novel drugs have been introduced widely, MDR among infectious pathogens is growing rapidly and noticeably, especially in patients that are under prolonged exposure to therapeutics [52]. In general, antimicrobial drugs act on the microorganisms either by competing with the substrates of enzymes involved in cell wall synthesis or by inhibiting their metabolic pathways such as nucleotide or protein synthesis [33]. Microbes have developed different strategies to survive the drug exposure by counteracting the efficacy of drugs. The four basic biochemical mechanisms by which microorganisms develop resistance to antibiotics are modification of the target, inactivation or destruction of antibiotics by enzymes, decreased antibiotic uptake through decreased membrane permeability and antibiotic efflux via efflux transporter **(**Fig. 1**)** [14,65].

Modifications of targets are induced by certain changes in metabolic pathways which overexpress target enzymes, resulting into target bypass and generate alternate target molecules and interfere with the synthesis of proteins [33]. Target modifications are typically affected by spontaneous mutation of the chromosomal bacterial gene. For example, RNA polymerase and DNA gyrase mutations lead to resistance towards rifamycin and quinolones, respectively. In certain instances, certain type of genetic exchange (conjugation, transduction, or transformation) from other organism might lead to the development of resistance. For examples, acquisition of the *mecA* genes encoding methicillin resistance in *S. aureus* and the various van genes encoding glycopeptide resistance in *enterococci* [66].

Cell wall plays a major role in the survival of microorganisms and antibiotics inhibit the synthesis of the cell wall by interacting with the peptidoglycan layer in the bacteria or disrupting the synthesis of ergosterol in the fungi, thereby preventing their cell growth and division [67]. These microbes undergo chromosomal modifications or extra-chromosomal DNA exchange by transformation or conjugation which leads to changes in the makeup of cell membrane resulting in poor

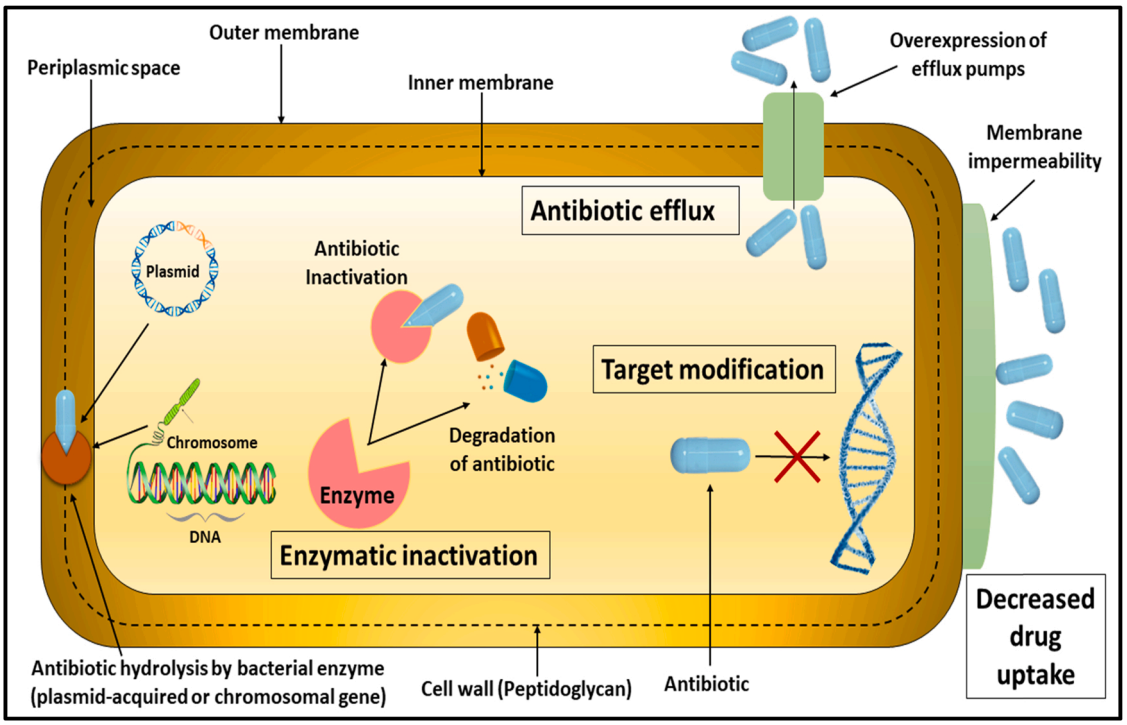

Fig. 1. Diagrammatic representation of mechanisms of bacterial multidrug resistance.

permeability and drug penetration into the cell [34,52,68,69]. Alterations in cell membranes also contribute to the loss of active target sites for the binding of drugs [67]. Mutations in the encoding of genes for the target induce molecular changes and maintain cellular function which eventually makes it less susceptible to inhibition [70].

Another prominent resistance mechanism is associated with the emergence of bacterial enzyme superfamilies owing to the diversity of gene encoding [71]. There are certain bacterial enzymes that can inactivate or destroy the antibiotics by hydrolysing their ester or amide bonds, e.g., β-lactam antibotics inactivated by β-lactamases. Chemical transformation of antibiotics by phosphorylation, acetylation, glycosylation, adenylation and hydroxylation has also become increasingly evident reason of MDR [34,69,72]. The resistant strains of various microbial pathogens acquire the ability to oxidize or reduce the antimicrobial properties in order to prevent their interaction against the targets [33]. Antibiotics typically target microbial DNA polymerase having reverse transcriptase activity to inhibit the replication of microbes. The interaction of drug with enzyme is affected by the mutant strains that are resistant to drugs and undergo mutations in the reverse transcriptase of polymerase gene. Some conformational modifications or altered substrate binding to the viral polymerase can result in drug resistance against the enzyme [73]. Microorganisms like *Plasmodium* species and *Toxoplasma gondii* undergo point mutations which eventually result in altered drug targets and homeostasis of calcium in endoplasmic reticulum and remove drugs from the cells [74,75].

However, the predominant MDR mechanism is still the drug resistance regulated by drug efflux pumps [76,77]. MDR is also caused by transport or removal of drugs from the cell due to overexpression of genes that encode ATP-binding cassette transporter membrane proteins, also known as multidrug efflux pumps [69,72,78]. For example, in *Leishmania* and *Entamoeba* species membranes, overexpression of P-glycoprotein affects the drug permeability and fluidity which results in an ATP-dependent antimicrobial efflux [79,80]. Besides microorganisms, MDR is also developed by cancer cells limiting the use of prolonged chemotherapies. Resistance to chemotherapies may occur either at the initial stage or during the course of treatment. The mechanism of MDR in cancer cells accounts to the overexpression of certain multidrug resistant proteins that result into apoptosis inhibition, DNA repair mechanisms, alteration in drug targets and modification in the composition of cell membrane. This further promotes an increase in drug efflux which prevents absorption of drugs into the cells [81,82].

2.6. *Strategies to overcome MDR*

While various types of antibiotics and experimental designs have been studied, the outcomes have been consistent throughout, strongly indicating an extensive correlation between tolerance and evolution of resistance towards antibiotics. Henceforth, substantial efforts are made to establish strategies that can eradicate the persistent microbial cells which could potentially lead to resistance evolution [83]. The most common approaches to combat MDR pathogens are drug repurposing and repositioning (viz. anti-inflammatory, anti-psychotics, anti-cancerous drugs, etc.), combination therapies, anti-virulence compounds, new molecules and antimicrobial peptides which will be further discussed in this review (Fig. 2).

2.6.1. *Drug repurposing against resistant pathogens*

As the synthesis of new antibiotics is limited and generally ineffective, MDR pathogens are evidently increasing with time. Hence, new strategies need to be developed to strengthen the fight against infectious diseases. Therefore, non-antibiotic drugs are being preferred. This strategy is referred to as drug repurposing and repositioning. It has been reported that pathogens rarely developed resistance when drug repurposing strategies were used against MDR. It can be due to the fact that active molecule attacks a different target other than the antibiotic target. For example, anti-inflammatory drugs inhibit cyclooxygenase (COX), anti-psychotic drugs inhibit dopaminergic, noradrenergic, cholinergic and histaminergic neurotransmission etc. which will further be discussed in this section [84,85].

2.6.1.1. Anti-inflammatory drugs. Anti-inflammatory drugs exert their therapeutic activities by reducing inflammation, pain and fever by inhibiting COX, the prostaglandin-forming enzyme. Vijayashree et al. reported an *in-silico* study on antibacterial activity of anti-inflammatory

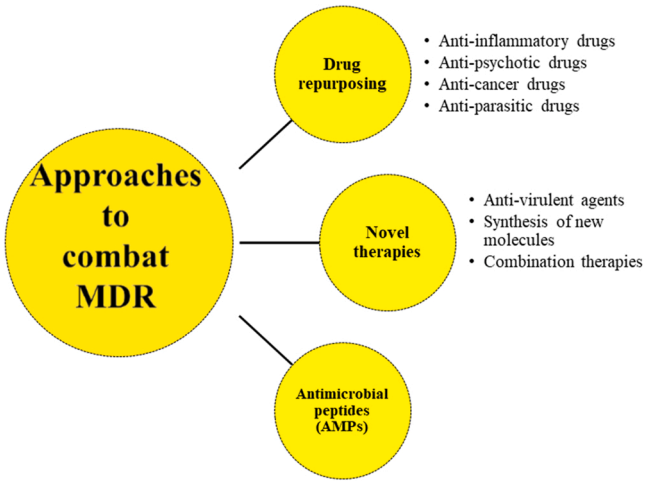

Fig. 2. Anti-infectious strategies explored aiming to combat resistant and persistent microorganisms.

cum anti-pyretic drugs viz. ibuprofen and acetaminophen on *Treponema denticola, Porphyromonas gingivalis*, and *Tannerella forsythia* as these pathogens are associated with periodontal disease-related inflammatory conditions [86]. As per the *in-silico* studies these drugs were found to interact with bacterial cytoplasmic proteins involved in virulence, cellular processes, and metabolism. Considering the bioinformatics prediction, the authors reported several epitopes in the virulent proteins which can be evaluated during in-vitro studies.

Betamethasone is a well-known glucocorticoid anti-inflammatory steroid but it has certain immunosuppressive effects in sepsis patients which makes its usage extremely controversial [87]. Though the usage of these drugs in sepsis patients seemed futile, Emgard and co-workers reported the efficacy of topical betamethasone for the treatment of external otitis caused by *Candida albicans* and *P. aeruginosa* [88]. It was observed that it triggered transcription and translation of proteins (lipocortin and vasocortin) in the nucleus which inhibited the production of inflammatory mediators such as leukotrienes, prostaglandins and histamine [89]. Similar to the periodontal disease, these studies could be explained in light of the fact that inflammation is a principal factor in the development of external otitis. However, despite its efficacy against bacterial strains, anti-inflammatory drugs have certain downsides which cannot be ignored. These drugs tend to cause digestive problems which can lead to stomach ulcers. The risk of developing an ulcer ranges from 1% to 18% depending on the risk factors associated with an individual. Over exposure to these drugs can also lead to kidney failure. Besides, anti-inflammatory drugs also act as blood thinners, hence they are limited to the people who are not undergoing blood-thinning therapies.

2.6.1.2. Anti-psychotic drugs. Antipsychotics, also known as tranquilizers and neuroleptics, are a type of drugs commonly used for the treatment of psychosis such as delusions, hallucinations, or anxiety, particularly in individuals suffering from schizophrenia and bipolar disorders [90,91]. They are also used to treat people with depression and Alzheimer's disease [92–95]. These drugs exert their therapeutic activity by blocking the neurotransmitters. However, a decade ago, Leiberman and Higgins reported a study to treat intracellular infection caused by *Listeria monocytogenes* by using anti-psychotic drugs viz. thioridazine (used to treat schizophrenia) and bepridil (calcium channel blocker). These drugs were administered in a dose-dependent manner by considerably decreasing the ability of L. *monocytogenes* to escape from in-vitro vacuoles. It is a promising approach to strengthen the application of drug repurposing. Such calcium channel blockers present a potential strategy to treat the brain damage as well as to counter bacterial pathogenic diseases. Furthermore, it has also been reported that thioridazine has antimicrobial activity against other bacterial species, such as *S. aureus* [96] and *M. tuberculosis* [97]. However, use of thioridazine is banned because it binds to the histamine receptors resulting into severe cardiac arrhythmia in some patients [98].

Andersson et al. reported another psychotic drug, 'trifluoperazine' with antibacterial efficacy [99]. This antipsychotic drug has boosted the endurance of *Yersinia pestis* infected macrophages in-vitro and also prevented the death of infected mice in-vivo. But, the minimum inhibitory concentration (MIC) values of trifluoperazine to enter into the plasma were too high and the drug could not inhibit the growth of *Yersinia pestis* cells. It has also shown significant results by increasing the survival rate when tested against *Salmonella enterica* and *Clostridium difficile* infected murine models, however, its antibacterial activities against the pathogens are yet to be defined.

2.6.1.3. Anti-cancerous drugs. Anticancer drugs, or antineoplastic drugs, are a class of drugs which have potential effects in treating diseases that are malignant or cancerous. However, to treat persistent pathogens, use of anti-cancerous agents may seem surprising.

Recently, Cheng et al. reported three anti-cancerous drugs viz. 5-fluorouracil, 6-thioguanine, and pifithrin-μ which potentially inhibited the growth of MDR *A. baumanni* [100]. Among the drugs, 5-fluorouracil and 6-thioguanine appeared to be the most potential ones in the treatment of MDR *A. baumannii*, as the inhibitory concentration and MIC values were lower than that of the standard plasma medicines, signifying potential use without major risk factors. Another study was reported by Hijazi et al. claiming antimicrobial activity of metal gallium against MDR ESKAPE pathogens [101]. Gallium is the second most used metal in cancer treatment. It is an iron mimetic metal and hence, interrupts ferric redox reactions or pathways which inhibit bacterial growth. This research suggests that the bacterial sensitivity to Gallium varies among different species and different strains of same species. The concentration of iron and nutrients in the medium had also influenced the bacterial sensitivity to this particular metal. Gallium activity was also evaluated in phase 2 trials in patients diagnosed with cystic fibrosis lung infections caused by *P. aeruginosa* [102]. It potentially enhanced the pulmonary capacity without hindering the human enzyme (superoxide dismutase and aconitase) activity which suggested safety and efficacy for infections in human. However, Chowdhury et al. also reported an anti-cancerous drug, cisplatin [cis-diamminodichloroplatinum(II)], which forms cross-links of intra-strand DNA and thus disrupts MDR cells of *E. coli, P. aeruginosa,* and *S. aureus* through a growth-independent mechanism [103]. Cisplatin crosslinks DNA mainly in the same DNA strand with crosslinks of intra-strand in AG sequences, between purines in adjacent guanines, and in GNG sequences (N be any nucleotide). Thus, the efficacy of cisplatin towards the resistant bacterial cells might be due to this potent crosslinking activity. Farha et al. reported that hormonal modulators used as anti-cancerous drugs also help to counter the resistant microbes. For example, clomiphene, selective estrogen receptor modulator, usually used to treat breast cancer has displayed in-vitro activity against *S. aureus*, with an MIC value of 8 mg/L. It inhibited the activity of undecaprenyl diphosphate synthase, an enzyme responsible for the synthesis of peptidoglycan and teichoic *S. aureus* cell wall [104].

Despite the potential benefits of repurposing anti-cancer drugs as antibacterial, the side effects of anticancer antibiotics should not be ignored. These drugs, as compared to other antibiotics are highly toxic and have severe side-effects such as immunosuppression, hair loss and blood cell damage. They also exhibit certain antimetabolite and alkylating agent-like toxicity causing severe damage to heart and lungs [105], [106].

2.6.1.4. Anti-parasitic drugs. Anti-parasitic drugs, also known as anthelminthic drugs expel parasites from the host body by either stunning or killing them and without causing major damage to the host. They

are also known as vermifuges or vermicides. A class of anti-parasitic drugs, salicylanilides dissociates uncouple oxidative phosphorylation from electron transport, inhibiting the production of ATP, thus impairing parasite motility. Rajamuthiah et al. reported the efficacy of niclosamide, a salicylanilides, in damaging the bacterial membrane of MDR isolates of *S. aureus* [107]. Antibacterial efficacy of niclosamide against *P. aeruginosa, K. pneumonia* and *A. baumanni* has also been reported. It works by blocking quorum sensing and virulence genes in *P. aeruginosa* and also raises the negative charges present on the cell walls of *K. pneumonia* and *A. baumannii*. This increase in charge on cell walls results in synergistic interaction with cationic colistin and re-sensitizes these microbes to this drug [108,109]. Another study was reported by Gooyit and Janda suggesting that rafoxanide and closantel (salicylanilide family) had shown significant bactericidal activity during logarithmic and stationary phases of *C. difficile* [110]. Omansen et al. reported in-vitro efficacy of avermectin, another anti-parasitic drug, against *M. tuberculosis* and *M. ulcerans,* with the suggested MIC in the ranges of 1–8 mg/L and 4–8 mg/L, respectively [111]. A decade ago, Zhang et al. reported that ivermectin boosted the survival of mice injected with lethal doses of lipopolysaccharide (LPS), potentially decreasing the overall tumor necrosis factor α (TNF- α), IL-1b, and IL-6 levels [112]. Ivermectin also decreased endotoxemia and inflammation associated by blocking the nuclear factor kappa-light-chain-enhancer of the activated B-cell pathway. Although these drugs have shown antimicrobial efficacy against certain MDR strains, usage of these drugs are contradictory. At high dose, these drugs can cause central nervous system signs such as lethargy, ataxia, mydriasis, tremors, leading to death. Besides, anti-parasitic drugs are off limits for the patients with cirrhosis, ocular cysticercosis, and pregnancy as these have also shown teratogenic effects. It also caused renal insufficiency, a condition in which the kidneys are unable to remove waste and balance fluids [113,114].

2.6.2. Novel therapies

2.6.2.1. Anti-virulent agents. Anti-virulence is the concept where virulence factors are blocked. Bacteria have a range of virulence factors such as adhesins which bind to host cells and form colonies, or toxins which alter the transduction of signals in the host cells. These factors trigger certain diseases in the host. Therapeutic anti-virulence approaches deal with these virulence factors, thereby restricting bacterial pathogenesis without affecting bacterial growth [115].

Pan et al. reported a chemical substance named BF8 [(Z)−4-bromo-5-(bromomomethylene)− 3-methylfuran-2(5 H)-one] which potentially reduced the persistence of *E. coli* and significantly defeated its antibiotic resistance [116]. BF8 disrupts biofilms of *E. coli* making associated cells highly responsive to ofloxacin. In another study an antimicrobial agent, ADEP4 (acyldepsipeptide antibiotic) was reported that potentially activated ClpP protease and significantly lead to the bacterial cell death by degrading about 400 proteins [117]. Furthermore, ADEP4 has also been reported to be effective against planktonic and biofilm states of the resistant cells. When ADEP4 was combined with rifampicin, it inhibited the growth of *S. aureus* biofilms in-vitro as well as in-vivo in a chronic infection murine model. Starkey and co-workers reported a chemical compound named M64 (phenoxy substituted benzamide ring), which significantly reduced the development of antibiotic resistant *P. aeruginosa* persistent cells [118]. M64 blocks the formation of both MvfR-dependent pro-persistence and pro-acute signalling molecules. It binds the transcriptional regulator for global virulence quorum sensing and inhibits the MvfR regulon in MDR isolates. It is also found to be active against the infections in murine models caused by *P. aeruginosa* without interfering with bacterial growth.

While the apparent benefits of developing a highly selective antimicrobial agent against pathogens, successful clinical use of such agents is still a major challenge as their usage depends on rapid and reliable diagnosis of the infecting strain and/or whether it expresses the virulence factor targeted. Administration of anti-virulent drugs is also time dependent as in-vivo expression of virulence gene is a function of time and space. Thus, it is crucial to recognize and target the pathogenesis bottlenecks. Moreover, most anti-virulence agents may not be as "broad-spectrum" as any of the currently used antibiotics [119].

2.6.2.2. New molecules. As traditional antibiotics are not efficacious in the treatment of microorganism-caused infections, novel antimicrobial agents are highly in demand. Recently, Kim et al. reported two synthetic retinoids, CD437 and CD1530 which significantly inhibited the growth and persistence of methicillin resistant *S. aureus* by disrupting their lipid bilayers [120]. These retinoids are anchored by carboxylic acid and phenolic groups present on their surfaces to the bacterial membrane bilayer by binding firmly to the hydrophilic lipid heads. The retinoids thus penetrate the bilayers and gets incorporated in the lipid molecules in the outer membrane, causing significant disruptions and permeabilizations in the bacterial membranes. Besides that, both the compounds showed synergistic interactions with gentamicin, and significant activity against clinical strains of *S. aureus* and *E. faecium*. Yet, the matter of concern to use these compounds as therapeutics is their potential cytotoxicity [121]. Teratogenicity is the most detrimental consequence of systemic retinoids. Besides, when applied topically, skin irritation, erythema and peeling are observed. Acute retinoid toxicity has resulted in dry lips, cheilitis, ophthalmic and nasal mucosa, overall skin dryness and pruritus, peeling of palms and soles, and fingertip fissuring. Higher doses of these agents may lead to Telogen effluvium. However, chronic retinoid toxicity is more adverse as they affect the organs. Long-term exposure to these compounds can lead to hypercalcemia and osteoporosis. Hypothyroidism hypertriglyceridemia, renal dysfunction, liver damage leading to fibrosis and hepatic stellate cell activation were also seen in patients [122].

2.6.2.3. Combination therapies. MDR-related diseases have now become a global problem and are worsened by the dearth of new groups of antibiotics. Thus, recent advances in drug combination therapies for treating MDR phenotype are of great interest. Such strategies include combinations of two or more antibiotics, or combinations of antibiotics with non-antibiotic adjuvant molecules that either specifically target resistance mechanisms or indirectly hinders resistance by depriving the bacterial signalling pathways.

Antibiotic – antibiotic combination therapies are very common and critical in certain medical areas, hence, must be taken into account during the process of developing drugs. For example, drug combinations have efficiently played it roles in treating cancer patients [123], HIV infected patients [124] and also malaria treatments [125]. These combination therapies are also effective in the bacterial infection treatments such as tuberculosis (TB) caused by *M. tuberculosis*, combining up to four typical drugs i.e. combination of isoniazid, rifampicin, ethambutol and pyrazinamide inhibiting targets in different pathways [126]. Combined therapies also inhibit different targets in same pathway, for example, combination of sulfamethoxazole and trimethoprim. Brennan-Krohn et al. explored the combination of colistin with linezolid, rifampin, or azithromycin against colistin-resistant *Enterobacteriaceae.* These combination therapies have synergies with colistin-resistant strains, as colistin permeabilizes the bacterial cell membrane even in MDR strains [127].

Whereas, **antibiotic – non-antibiotic combinations** are alternatives to two or more antibiotic combinations in order to treat MDR pathogenic infections. A non-antibiotic when combined with an antibiotic, enhances the activity of the antibiotic by blocking the resistance mechanism of pathogens. Resistance to antibiotics can be either because of inactivation of antibiotics or removal of antibiotics from the microbial cells, or modification of the target so that the antibiotic doesn't effectively bind to it. A typical example of such combination is Augmentin, a combination of amoxicillin (a β- lactam antibiotic) and clavulanic acid

(a β–lactamase inhibitor). Clavulanic acid prevents β – lactamase activity in-vivo and enables amoxicillin to restrict biosynthesis in the cell wall. Consequently, this combination has facilitated the continuous amoxicillin usage to combat various infections caused by microbes with β-lactam resistance [128]. Clavulanic acid, however, failed to effectively inhibit many β-lactamases such as carbapenem hydrolyzing oxacillinases and metallo-β-lactamases, for example, New Delhi metallo-β-lactamase (NDM-1) [129]. The malonate derivative, ME1071 and cocktail inhibitor, BAL30376 are promising agents in restoration of the efficacy of β-lactam antibiotics against metallo-β-lactamases producing bacterial strains. BAL30376 is a combination of clavulanic acid, siderophore monobactam (BAL19764), and a bridged monobactam (BAL29880) which prevents class C β-lactamases and has exhibited strong in-vitro activity against metallo-β-lactamases [130]. However, interference with the pathways that are responsible for bacterial response to antibiotics and activating resistance mechanism is an alternative to directly inhibiting enzymes or proteins. In response to external stimuli, bacterial two-component systems control the gene expression, regulating a range of bacterial activities including antibiotic resistance. These regulatory systems enable bacteria to sense and react to environmental changes around them and are triggered by a range of factors like nutrient level, pH and antibiotic presence [131].

Despite many benefits of combination therapies, there are certain drawbacks that cannot be overlooked. Administration of multiple drugs apparently increases the risk of adverse drug reactions. Incompatible pharmacokinetics, nephrotoxicity, coagulopathy, diarrhoea, epilepsy, and hypersensitivity reactions are well-known complications of antimicrobial combinations which limit the use of such therapies [132,133].

Both drug repurposing strategies and novel therapies show toxic effects on different organs such as kidney, heart, lungs, liver, CNS, bones, etc. making cytotoxicity as one of the major drawbacks of these strategies [105,106]. In addition to cytotoxicity, several other limitations associated with these strategies are immunosuppression, time dependency, teratogenicity caused by anti-cancer drugs, anti-virulent drugs, anti-parasitic drugs and systemic retinoids, respectively [113, 119,122]. One of major complications observed in combinations therapies is incompatible pharmacokinetics. Two different therapeutic agents might act inversely on the body leading different absorption, bioavailability, distribution, metabolism, and excretion rates [134,135]. Considering these downsides of the aforementioned strategies and lack of efficacy of conventional antimicrobial drugs, novel antimicrobial agents are highly in demand. Also, the growth of microbial biofilms induces severe chronic infections, dental plaque and form antimicrobial resistant environments. Therefore, there is a progressive effort to conquer or curb these challenges, through novel compounds. All these downsides of existing therapies have led the researchers to look for new classes of antimicrobials to combat the drug resistance. In search of a promising lead compound against MDR, AMPs have emerged as the attractive ones. AMPs have emerged as the most appealing molecules in the quest for new anti-MDR drugs. AMPs have gained considerable attention as a novel class of antimicrobial medications because of their minimal resistance potential, wide antibacterial efficacy, and capacity to influence the host immune response. [136,137]. Though clinical translation of AMPs as prospective therapeutic agents against MDR has been impeded by certain structural and functional restrictions, recent developments in computational approaches in synergism with exhaustive experimentation has opened new opportunities for application of AMPs as novel therapeutics against various pathogen induced infection [138].

3. Anti-microbial peptides (AMPs)

AMPs are polypeptides having short string of amino acids and have broad spectrum applications against microbes along with the modulation of immune system acting as the first line of defence in case of a pathogenic invasion. They are naturally produced by a wide range of living organisms such as bacteria, fungi, animals, plants, humans, etc. while others are designed using peptidomimetic techniques and chemically synthesized in the laboratory [139]. When compared to other strategies to combat MDR, these molecules are found to be safer with least cytotoxicity. These peptides show simple structure-activity relationship, thermal stability and good AMP solubility [140,141]. There various AMPs which have shown significant antimicrobial efficacy against several MDR strains (Table 3) [21]. However, AMPs have different antimicrobial mechanisms from traditional antibiotics, which make less susceptible to develop resistance. AMPs have a greater ratio of cationic amino acids; they are cationic in nature and interact with negatively charged bacterial cell membrane by neutralizing the charge. Further, they penetrate the cell membrane resulting into bacterial death [137]. In last 5 years, there are many reports that have shown the effectiveness of AMPs against MDR pathogens, while parallel efforts have also been made to synthesize AMPs with enhanced therapeutic potential and minimal side effects [142–150].

3.1. Resistance evolution of AMPs

Antibiotic resistance is a growing problem as pathogens have developed resistance against multiple conventional antibiotics. AMPs have been proposed as a promising class of new antimicrobials because they are less susceptible to bacterial resistance. Mode of action and pharmacodynamic properties of AMPs which differ considerably from conventional antibiotics might be the possible cause for resistance evolution. Pharmacodynamics are based on time-kill kinetics curves between drug doses and bacterial growth or death rates. AMPs have much greater steepness of pharmacodynamic curves as compared to that of antibiotics [151]. The AMPs are more effective as the time-kill assay suggests much stronger maximum killing effect of AMPs than that of antibiotics [152,153]. AMPs thus exhibit a narrower mutation selection window than antibiotics, hence resistance is less likely to develop [153–155].

Another major characteristic effecting resistance mechanism is DNA recombination. Recombination, along with gene duplication and amplification [156], plays a major role in antimicrobial-resistance development [157]. Several traditional antibiotics increase mutation rates of bacteria leading to increase in recombination rate [158,159], however, the AMPs that have been tested so far have no effect since it does not cause the recombination of bacterial DNA [160]. Rodríguez-Rojas et al. have a panel of cationic AMPs along with a recombination-stimulating antibiotic, ciproflaxacin as a positive control agaisnt *E. coli* MG1655. They have also tested human serum against the becterial isolates as complement dependent bactericidal activity of human serum is an important host defence mechanism against bacterial infections. It was reported in their results that none of the AMPs have shown increase recombiation frequency, whereas, ciprofloxacin has shown almost 10-fold increase in recombination frequency as compare to control (non-treated bacteria). Thus, it can be considered that bacterial resistance development against AMPs has a lower probability than against antibiotics [153].

Besides, another mechanism of successful antimicrobial agents is to attack nonprotein molecules. Lipid II is one of the best studied nonprotein targets. It is a membranous cell wall precursor found in bacteria but absent in the human host [161,162]. AMPs are less susceptible to bacterial resistance development because unlike conventional antibiotics, AMPs are specifically targeted against lipid II instead of enzymes in the cell wall biosynthetic pathways [21]. Lipid II is a potential target for antimicrobials because it is easily accessible on the exterior side of the bacterial cell membrane. Lack of resistance development through mutations is associated with targeting lipids implicated in crucial bacterial mechanisms [163]. Lipid II being a nonprotein target, it may not be modified by mutation easily. Therefore, MDR strains doesn't readily develop resistance against lipid II-binding AMPs [162].

Considering the relatively low rate of resistance emergence of AMPs,

Table 3
AMPs with potent activity against MDR pathogens [21].

Peptides	Sequence	Clinical Trial Phase	Source	Activity
Human LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	Preclinical	Human leucocytes	Acts on cell membrane by pore formation and has immunomodulation activities
SAAP-148	LKRVWKRVFKLLKRYWRQLKKPVR	Preclinical	LL-37 derivative	Membrane permeabilization and wound healing activity
Cathelicidin-BF	KFFRKLKKSVKKRAKEFFKKPRVIGVSIPF	Preclinical	Snake venom	Antifungal, antibacterial and low hemolytic activity against various strains including MDR pathogens
D-OH-CATH30	KFFKKLKNSVKKRAKKFFKKPRVIGVSIPF	Preclinical	Snake venom	Shows activity against gram-positive and gram-negative strains, with low hemolytic activity and in-vivo toxicity
Ci-MAM-A24	WRSLGRTLLRLSHALKPLARRSGW-NH_2	Preclinical	*Ciona intestinalis*	Antibacterial activity through pore formation against MRSA, VRE, and MDR *P. aeruginosa*
S-thanatin	GSKKPVPIIYCNRRSGKCQRM	Preclinical	Thanatin derivative	Exhibits bactericidal effects with low hemolytic activity and reduced sepsis
AA139	GFCWYVCARRNGARVCYRRCN	Preclinical	Analog of arenicin-3 with β-hairpin structure	Antimicrobial activity against MDR gram-negative pathogens
SET-M33	KKIRVRLSA)$_4$K$_2$KβA-OH	Preclinical	Synthetic tetra-branched peptide	Shows significant antibacterial activity against MDR strains.
EC-hepcidin3	APAKCTPYCYPTHDGVFCGVRCDFQ	Preclinical	Marine fish	Antimicrobial activity against *S. aureus* and *Pseudomonas* spp.
Tachyplesin-1	KWCFRVCYRG ICYRRCR	II	Horseshoe crab	Exhibits antibacterial activity against gram-negative and gram-positive strains but shows high cytotoxicity
Indolicidin	ILPWKWPWWPWRR	III	Bovine leucocytes	Exhibits bactericidal activity through pore formation
Omiganan	ILRWPWWPWRRK-NH_2	III	Indolicidin derivative	Has significant therapeutic efficacy against acne and catheter related infections.
Pexiganan	GIGKFLKKAKKFGKAFVKILKK-NH_2	III	Magainin analog	Exhibits potent antimicrobial activity to treat bacterial infections and diabetic foot ulcers.

they serve as a potential base for the formulation of peptide-based therapeutic agents.

3.2. Mode of action of AMPs

The mechanism of AMP depends on its physicochemical properties such as amino acid sequence, charge, amphipathic nature, and structure [164]. The understanding of mode of action of AMPs is inevitable as it is essential for the improvements of AMP based therapeutics. The mode of action can be broadly classified into two categories: direct killing and immune modulation (Fig. 3). The mechanisms for direct killing of action can further classified into membrane targeting and non-membrane targeting.

3.2.1. Membrane targeting

The membrane targeting AMPs can have two types of interactions: receptor based or non-receptor based. Interaction of AMPs with the bacterial membrane components plays the major role in its function. The outer surface gram-positive bacteria contain teichoic acid and gram-negative bacteria contain lipopolysaccharide, each possessing negative charge on the surface, allows electrostatic attraction with the cationic AMPs [77]. The AMPs accumulate at a surface and self-assemble after the electrostatic and hydrophobic interactions on the bacterial membrane [99,166]. AMPs further disrupt the bacterial membranes by inducing structural changes, which can be classified as membrane pore forming and non-pore forming mechanisms. The membrane pore forming mechanisms include barrel-stave model and toroidal pore model while non-pore mechanisms include carpet-like model and detergent-like model (Fig. 4) [77,167]. According to the barrel-stave

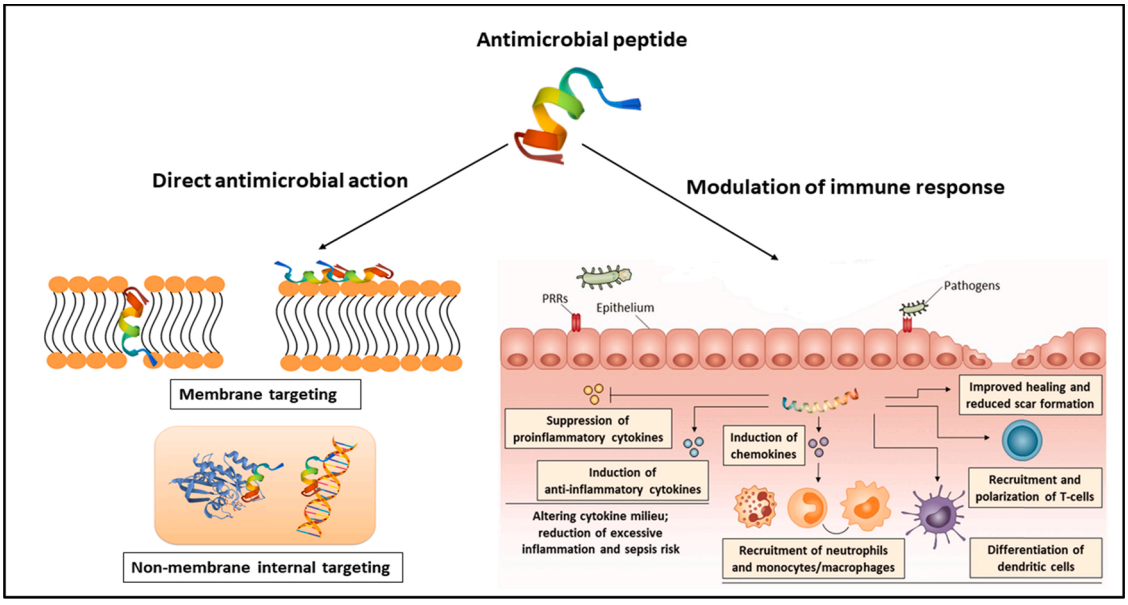

Fig. 3. Schematic representation of mechanisms of action of antimicrobial peptides.
Figure is modified from [21,165].

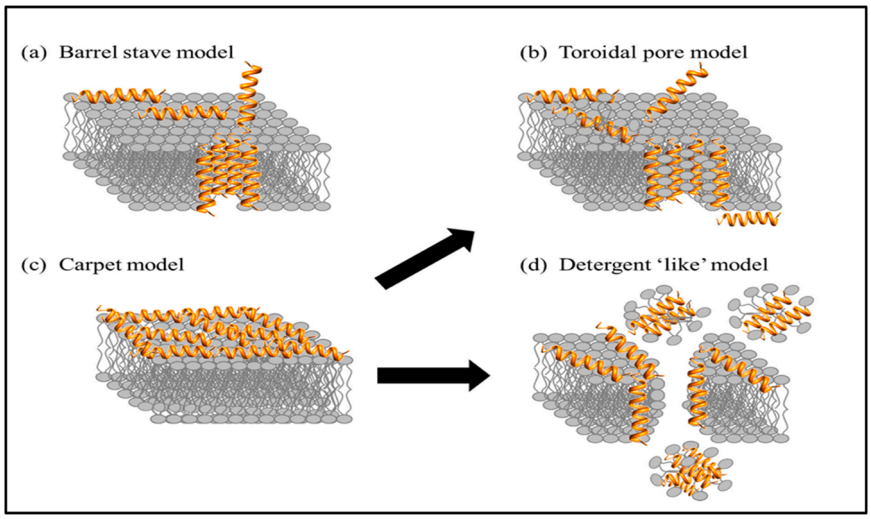

Fig. 4. Mechanism of action of AMPs targeting membrane. Copyright © 2018 Kumar, Kizhakkedathu and Straus. Reprinted with permission from [77].

model, initial interaction of bacterial membrane led to some conformational changes in AMPs which are responsible for the incorporation of hydrophobic segment of AMPs into the hydrophobic core of the membrane. Further, as the concentration of AMPs increase, these tend to polymerize and penetrate deeper in to the bacterial membrane leading to the formation of barrel-stave channels. These channels can act like the membrane ion-transport channels and can transport the AMPs across the concentration gradient [168–170]. Some AMPs such as alamethicin, pardaxin, protegrins and ceratotoxin exert their anti-bacterial activity by forming barrel-stave channels [170–172]. According to toroidal-pore model, AMPs are inserted in to the bacterial membrane and form a transmembrane pore consisting of AMP molecules and lipid head groups. Toroidal-pore formation leads to the structural changes and induce a bend in the curvature of the bacterial membrane [172–174]. These pores are formed by various AMPs such as PGLa, magainin 2, lacticin Q, aurein 2.2, cathelicidin, HPA3 and melittin [172,175,176]. In the carpet-like and deter-like model, AMPs do not induce pore formation inside the membrane. AMPs bind to the membrane surface just like a carpet on the floor and induce some conformational changes leading to the loss of membrane integrity. Further, the membrane disintegrates and micelles are formed which are the characteristics of the detergent-like model [176–178]. These models are followed by various AMPs such as cecropin, indolicidin, aurein 1.2, ovisprin, caerin 1.1 and LL-37 [177, 179–181].

3.2.2. *Non-membrane targeting*

The non-membrane targeting AMPs function either by inhibiting the bacterial cell wall synthesis or by targeting intracellular nucleotides. Unlike conventional antibiotics, AMPs interact with precursor biomolecules viz. lipid II and lipid III, essential for the biosynthesis of cell wall and growth and viability of bacterial pathogens[182,183]. Human β-defensin 3, nisin, subtilin, α-defensin 1, epidermin, mersacidin, cinnamycin and Pep5 are reported to form interactions with precursor molecules involved in the cell wall synthesis [77, 139, 182–186]. These interactions can further induce the pore formation in the lipid bilayer and alterations in the bacterial membrane integrity [182].

AMPs exerting antibacterial activity by the altering the membrane integrity are accumulated intracellularly inside the bacterial cytosol. When AMPs intrude the intracellular environment inside the bacterial cytosol, these molecules can alter the crucial biological processes, such as, synthesis of biological macromolecules like proteins and nucleic acids and maintenance of enzymatic activity, which are required for the survival of bacterial pathogens [170]. Some AMPs such as pyrrhocoricin, apidaecin, Microcin B17 and drosocin alter the activity of various nucleic acid synthesizing enzymes involving DnaK heat shock protein and DNA gyrase [187–190]. Also, some other AMPs such as buforin II, PR-39, human β-defensin 4, human α-defensin 1, indolicidin and tPMP interfere with the synthesis of cytoplasmic proteins and nucleic acids leading to cell death [191–196].

3.2.3. *Modulation of immune response*

The modulation of the immune response is one of the critical features of the mechanism of action of AMPs. Various immunocytes such as macrophages, neutrophils and phagocytes secrete AMPs in response to the infection or entry of any pathogen. This secretion of AMPs lead to the release of pro-inflammatory cytokines in a controlled manner. These cytokines are further responsible for the recruitment of various other immunocytes at the site of infection, inhibition of the production of reactive oxygen species and induction of angiogenesis [197–199]. Cathelicidins and defensins have the ability to bind the chemokine receptors leading to the chemoattractant properties and also, recruitment of various immunocytes [200]. Some AMPs such as human cathelicidin LL-37, Chicken NK-lysin based cNK-2 peptide, alpha-defensins1–3, CCL20 and beta-defensin-2 have been reported to possess immunomodulatory activity [120, 200–204].

4. Application of AMPs against MDR pathogens

AMPs have been widely implicated in the recent developments in therapeutics. Also, it is inevitable to undermine the potential role of AMPs in next generation therapeutics. The antiviral properties of AMPs are under the lens as the effective treatments against COVID 19 are still not available [205]. AMPs against MDR pathogens are being studied extensively in various disciplines for applications having novel relevance. Most widely studied applications are mainly in the areas of therapeutics, food, animal farming, and agriculture (Fig. 5), which will further be discussed in the review.

4.1. *Therapeutics*

Applications of AMPs is expanding at a higher rate in the field of medicines, such as dental, surgical, wound healing and ophthalmology. However, US Food and Drug Administration (FDA) have approved only three AMPs i.e., gramicidin, daptomycin, and colistin [206].

Common dental diseases that occur in human oral cavity are endodontic infections, candidiasis, dental caries (tooth decay), and

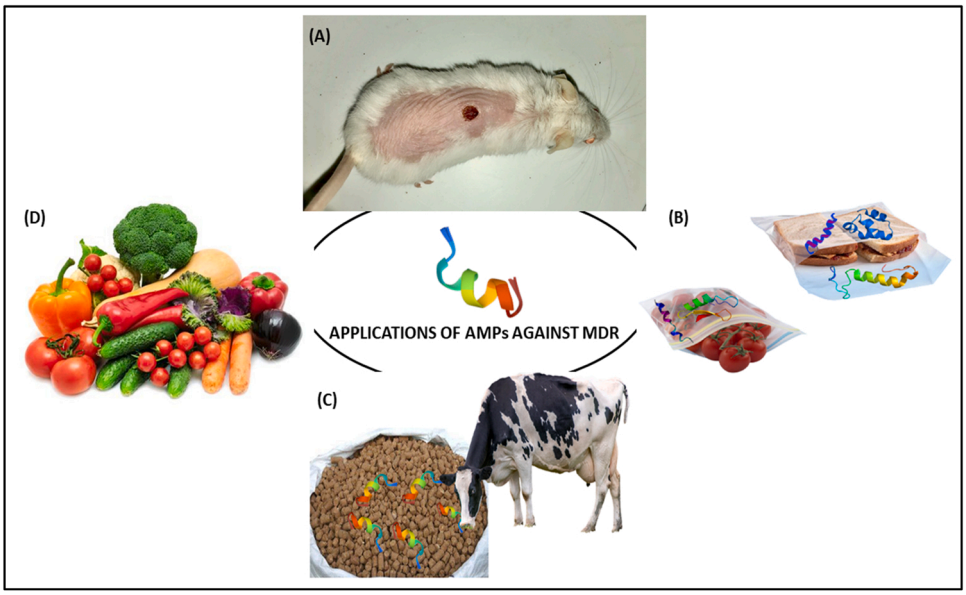

Fig. 5. Applications of AMPs against MDR pathogens in diverse fields as (A) Therapeutic agent to threat wound infection on murine model, (B) Antimicrobial food packaging materials, (C) AMP-based animal growth promoters, and (D) Infection-free healthy agricultural products [224].

periodontal disease. Dental caries is commonly caused by some acidic bacteria like *Straptococcus* sp. [207]. AMPs like ZXR-2 and PAC-113 have shown potent activities against microbes such as *Streptococcus mutans*, *Streptococcus sobrinus*, and *Porphyromonas gingivalis,* and *Candida* sp. causing dental caries and oral candidiasis, respectively [208].

Surgical infections followed by burns, surgery, accidental injury, skin disease, or wound infections are some serious threats to human health [209]. AMPs like PXL150 and D2A21 exhibit significant efficacy as antimicrobial agents for treating such secondary infections [210].

Besides, human eyes are also susceptible to bacterial or fungal infections. Several AMPs are reported to have substantial efficacy against bacterial, viral and protozoan infections on human ocular surface. The AMP OH-CATH30 alone or in combination with levofloxacin, have shown significant antimicrobial efficacy against *P. aeruginosa* induced keratitis in rabbits [211]. Esculentin-1a(1−21)NH_2 have shown bactericidal effects in corneas in a *P. aeruginosa* keratitis murine model [212]. A peptidomimetic named RP444 showed considerable efficacy against *P. aeruginosa* induced keratitis in murine model [213].

Nisin has been found to be effective against biofilm forming pathogens and its role as a constituent of antibacterial coatings in biomedical implants has been highlighted [214]. Fusco et al. has reported the anti-biofilm activity of β-defensins-2 and 3 AMPs against *P. aeruginosa* and *S. aureus* in intestinal epithelial cell line [215]. Also, synergistic effect and anti-biofilm activity of an AMP (Pt5–1c; a derivative of phosvitin) along with oxacillin, vancomycin, streptomycin and azithromycin has been suggested against MDR pathogens such as *S. aureus*, *E. coli* and *K. pneumoniae* [216]. An analog of AMP Jelleine-1 (extracted from the royal jelly of honeybees) has been implicated in the potent inhibition of biofilm formation of MDR pathogen *P. aeruginosa* [217]. Oh et al. has shown the anti-biofilm and anti-inflammatory effects of Lycosin-II (an AMP isolated from spiders) against MDR *S. aureus* and *P. aeruginosa* infections [218]. An analog of PapMA-3 along with vancomycin or erythromycin has demonstrated synergistic anti-biofilm activity against Carbapenem-resistant *Acinetobacter baumannii* infection [219]. Salama et al. has reported the synthesis of an ultra-short AMP (alapropoginine), which has demonstrated synergistic effects along with vancomycin and chloramphenicol against MDR MRSA and *E. coli* respectively [220].

Riool et al. has reported the antimicrobial activity of a derivative of human thrombocidin-1 peptide (TC19) against MRSA and *Acinetobacter baumannii* in a skin wound infection in mice [221]. Gogoi et al. has suggested the topical applications of a short AMP (IRK), which inhibited the growth of *Staphylococcus aureus* and MRSA [222]. Recently, a cell-penetrating AMP (variant of Cecropin A (1−7)-Melittin) has been shown to possess antibacterial activity against MDR *S. Typhimurium* and *S. Enteritidis* strains [223].

4.2. Food

The potential harm caused by food preservatives to the human body calls for alternative natural and safer preservatives. AMPs are found to be promising alternatives to preservatives as they have significant inhibitory effect on bacteria and fungi found on food. AMPs can be easily hydrolysed by the proteases in human body as due to their resistance towards acids, alkalis and high temperature. FDA has approved nisin and polylysine as alternate food preservative [225]. Enterocin AS-48 and CCM4231 are AMPs that are used to preserve cider, fruit and vegetable juices, and, soy milk [226]. Moreover, addition of AMPs in packaging material has greater potential in the food industries. For example, ε-poly-L-lysine added to starch-based biofilms show good inhibitory effects on *Aspergillus parasiticus* and *Penicillium expansum* and nisin being highly surface-active molecule have the potential to preserve the dairy products [227]. Nisin has been reported to inhibit the growth of oral bacteria along with anti-biofilm activity against MDR pathogens such as *Streptococcus mutans*, *Streptococcus sanguinis*, *Streptococcus gordonii*, *Streptococcus mitis, Lactobacillus acidophilus* and *Actinomyces israelii* [228].

4.3. Animal farming

Antibiotics as animal growth promoters are commonly used in animal agriculture all over the globe to prevent or treat infections and accelerate the growth of animals. However, a new antibacterial strategy is the need of the hour because the use of antibiotics in animal feed is banned by European Union since 2006. As growth promoters, AMPs have the ability to boost productivity, immunity and intestinal health, and also, they are potent antimicrobial agents. [229,230]. For example, SIAMPs (Swine intestinal AMPs) are efficacious against infectious bronchitis virus in chicken [231]. AMPs like caerin 1.1, dicentracin and NK-lysine show bactericidal activity on *Nodavirus, Septicaemia haemorrhagic virus, Infectious pancreatic necrosis virus* and *Spring viremia carp virus* [232]. The AMP derived from *B. subtilis* E20 fermented soybean

meal is a potent inhibitor of the *V. parahaemolyticus* and *Vibrio alginolyticus* [233]. Various Nisin variants are recently being employed as constituents of sanitizers to prevent *Staphylococcus* and *Streptococcus* infections in lactating cows [234]. O'Neill et al. has reported the antibacterial activity of AMPs isolated from feline commensal bacterium against Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) induced animal and human skin infections [235].

4.4. Agriculture

For agriculture, bacterial and fungal pathogenic infection leads to a loss of economies, such as, *Aspergillus flavus* induced infection in maize and peanuts, *Penicillium digitatum* induced citrus green molds, *Botrytis cinerea* induced gray mould diseases on strawberries, etc. cause great harm to the growth and post-harvest of agricultural products [236]. Several AMPs have been reported to manage these concerns, for example, PAF26, O3TR/C12O3TR, Ponericin W1, Matoparan-S have shown efficacy against green molds, *Penicillium digitatum*, *Magnaporthe oryzae, Botrytis cinerea, Fusarium graminearum,* and *Aspergillus* sp. [206].

5. Future roadmap and conclusion

In this review, we have discussed the importance, modes of action and applications of AMPs as the potential antimicrobial agents against MDR pathogens. AMPs being cost-effective, more potent and less susceptible to resistance, have emerged as one of most efficacious strategies against microorganisms and can be developed as the next generation of antibiotics to combat MDR. Since most of the existing therapies have been rendered ineffective due to the rapid emergence and spread of resistance, AMPs act as precursor molecules for developing novel antimicrobial agents. Besides these advantages there are several limiting factors associated with the in-vivo use of AMPs such as susceptibility to proteolytic degradation, toxicity, poor bioavailability and expensive production at large scale [21,237]. Currently, considerable effort is being dedicated towards the synthesis of shorter and modified peptides with improved therapeutic efficacy, reduced cytotoxicity and decreased proteolytic digestion [237,238]. Future roadmap ahead should be concerned with the efforts to overcome these obstacles and mass scale studies should be conducted to address these hindrances using various methods including the application of amino acid modifications, testing different formulations, improvement in the expression levels of peptides and addition of fatty acyl chains to short peptides. In conclusion, AMPs are the future of therapeutics as MDR against conventional therapies is continuously growing and several AMP-based drugs are in clinical trials. Also, different strategies should be explored and considered to develop AMPs as better and efficient therapeutics against MDR in future.

CRediT authorship contribution statement

Sheetal Sharma: Resources, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Panchali Barman:** Resources, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Shubhi Joshi:** Writing – review & editing. **Simran Preet:** Conceptualization, Project administration, Supervision. **Avneet Saini:** Conceptualization, Visualization, Project administration, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

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