A REVIEW ON CHALLENGES AND STRATEGIES TO OVERCOME ANTI-MICROBIAL RESISTANCE: A GLOBAL BURDEN

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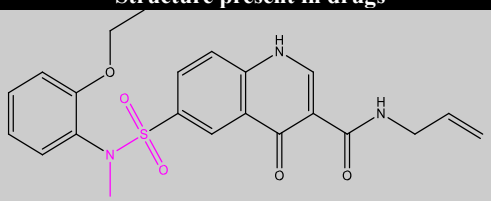
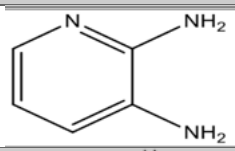
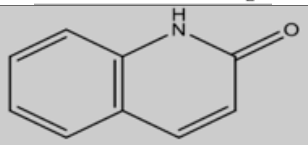
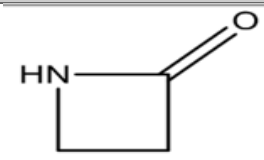
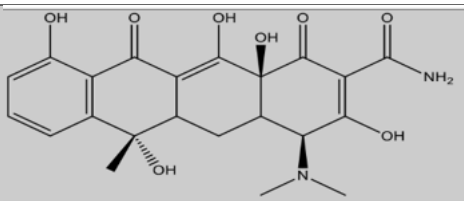
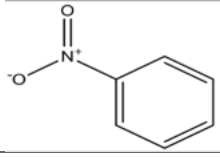
INTRODUCTION-

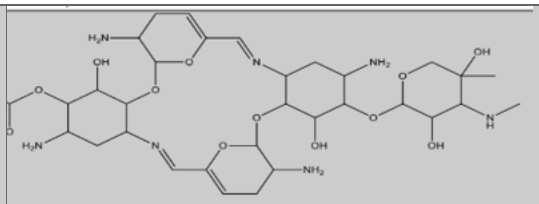
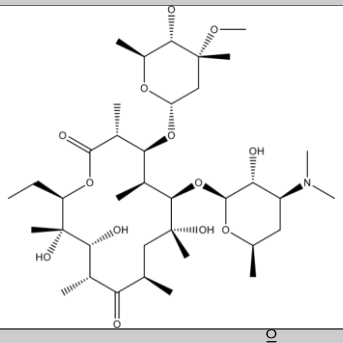
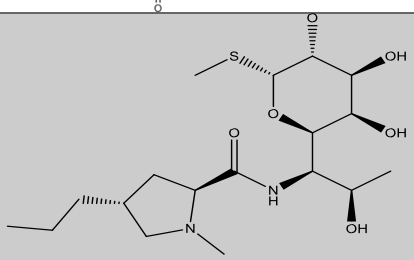
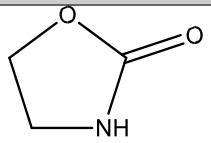
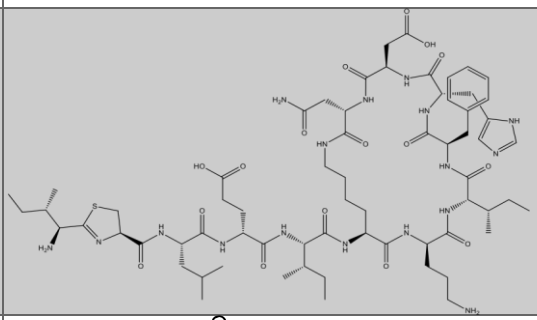
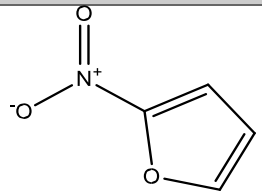
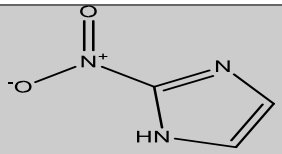
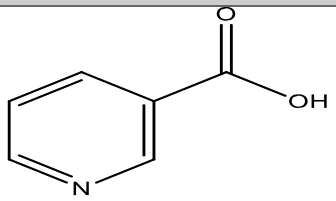
One of the most significant discoveries in therapeutics is anti-microbial agents. Antibiotics are a class of anti-microbial drugs first discovered serendipitously by Dr. Alexander Flemming, a bacteriologist, in 1928 [1]. This accidentally discovered antibiotic, penicillin, is considered a top turning point in medicine. Drugs used to prevent or treat a wide range of infections occurring in humans, animals, and plants are called anti-microbials. According to WHO, the term antimicrobial consists of antibiotics, antivirals, anti-fungals, and anti-parasitics, which can treat or prevent various infectious diseases like tuberculosis, urinary tract infections, pulmonary infections, typhoid, etc. [2] Anti-microbials can be categorized into multiple types. However, a broad classification of anti-microbials is carried out based on chemical structure, mechanism of action, and organism against which it is active.

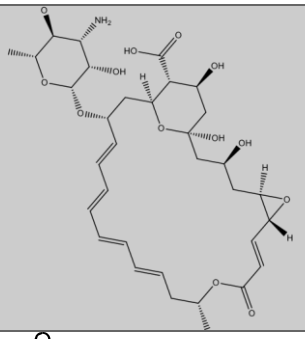
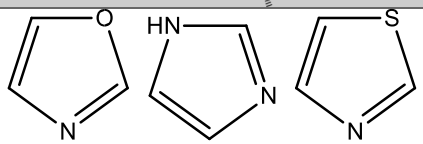
Classification of Anti-microbials

The arrival of anti-microbials changed physicians, medicinal chemists, and researchers' perception of the drug because of their powerful action on diseases that were earlier considered a ticking bomb. Anti-microbial drugs are designed to produce a bacteriostatic or bactericidal effect against the targeted pathogen by producing little or no consequence on the receiver. Drug acts on a component of the microorganism (e.g., bacterial cell wall) or metabolic processes (e.g., folate synthesis) which is missing in the host or has a high affinity for specific microbial biomolecules (e.g., trimethoprim for bacterial dihydrofolate reductase). Antibiotics are substances formed by microorganisms or synthesized in the lab, which suppress the development of pathogens or kill other microorganisms at very minute concentrations [3]. Anti-microbial Classification:

Based on the chemical structure

Chemical moiety	Drugs	Structure present in drugs	Uses
Sulfonamide (1935)	Sulfadiazine Sulfones-Dapsone Paraaminosalicylic acid		UTI IBD For Burns Active against grampositive and negative
Diaminopyrimidine	Trimethoprim Pyrimethamine		Prevention and treatment of toxoplasmosis and malaria
Quinolones	Nalidixic acid fluroquinolones		Active against both Gram-positive and Gram- negative bacteria primary agents for treating urinary tract infections (UTIs) and infections of the digestive tract and respiratory system
Beta-lactam	Penicillins Cephalosporins Monobactams Carbapenems		Respiratory tract infections skin infection, resistant bacteria meningitis intra-abdominal and gynecologic diseases, septicemia
Tetracycline	Chlortetracycline Doxycycline Moinocycline Methacycline		Acne Gonorrhea Chlamydia Infections Spread by ticks and mites Antiviral
Nitrobenzene	Chloramphenicol		Conjunctivitis Superficial optic infections

Aminoglycosides	Streptomycin Knanamycin Amikacin Tobramycin Neomycin		For infections Caused by Aerobic gram-negative bacilli Endocarditis Sepsis Complicated intraabdominal infections
Macrolide	Azithromycin Clarithromycin Erythromycin		For gram-positive bacteria Pneumonia Sinusitis Pharyngitis Tonsillitis
Lincosamide	Lincomycin Pirlimycin Clindamycin		Septicemia bone and joint infections Treatment of severe infections due to susceptible strains of streptococci, pneumococci, and staphylococci.
Oxazolidinone	Linezolid		bacterial pneumonia skin and skin structure infections vancomycinresistant enterococcal (VRE) infections
Polypeptide	Actinomycin Bacitracin Colistin Polymyxin B		For treatment of dermatological infections, infection of hair and scalp. Systemic infections caused by susceptible strains of multidrug-resistant organisms such as Pseudomonas aeruginosa
Nitrofuran	Furazolidone (FZD) Nitrofurazone (NFZ) Furaltadone (FTD) Nitrofurantoin (NFT)		Treating and prophylaxis of urinary tract infections such as cystitis
Nitroimidazole	Benzimidazole Azomycin Metronidazole Ornidazole Tinidazole		Treating anaerobic bacterial infections like trichomoniasis, giardiasis, amebiasis, and bacterial vaginosis
Nicotinic acid derivative	Isoniazide Pyrazinamide Ethionamide Nicotinamide		Anti-tubercular drugs

Polyene derivative	Filipin Amphotericin B, Nystatin Natamycin		Invasive fungal infections superficial mycotic infections of the eye
Azole derivative	Ketoconazole Miconazole Clotrimazole Itraconazole Fluconazole		Anti-fungal

Based on the mechanism of action

1. **Inhibit cell wall synthesis**: Penicillins, Cephalosporins, Cycloserine, Vancomycin, and Bacitracin.
2. **Cause leakage from cell membranes**: Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes—Amphotericin B, Nystatin, Hamycin
3. **Inhibit protein synthesis**: Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.
4. **Cause misreading of m-RNA code and affect permeability**: Aminoglycosides—Streptomycin, Gentamicin, etc.

Based on the type of organisms against which it is primarily active-

1. **Anti-bacterial**: a type of anti-microbial substance against active bacteria. Examples of antibacterial drugs are Penicillin, Aminoglycosides, Erythromycin, Fluoroquinolones, etc.
2. **Anti-fungal**: An anti-fungal agent is a drug that selectively inhibits the fungal pathogens from minimal host minimal toxicity to the host. Griseofulvin, Amphotericin B, Ketoconazole, etc.
3. **Antiviral**: Acyclovir, Amantadine, Zidovudine, etc
4. **Antiprotozoal**: Chloroquine, Pyrimethamine, Metronidazole, Diloxanide,

Anti-microbial resistance-

Anti-microbial resistance (AMR) is a global public health danger that needs to be addressed. According to WHO, 700,000 people die yearly from drug-resistant diseases, including 230,000 from multidrug-resistant tuberculosis. AMR resistance occurs when a bacteriostatic or microbicidal effect of a drug is no longer effective against pathogenic species such as viruses, fungi, bacteria, and parasites [4]. Anti-microbial resistance (AMR) is considered a fast-evolving global pandemic, and according to data, it is suggested that by 2050 more than 10 million deaths per annum will be caused by AMR. The prediction of deaths is thought to be caused by various life-threatening nosocomial pathogens, which are often termed ESKAPE pathogens *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp* [5]. According to reports published by the Centers for disease control and Prevention (CDC), anti-microbial threats can be classified into four categories, as mentioned in the table below.

THREAT	SPECIES
Urgent	Carbapenem-resistant *Acinetobacter* *Candida auris* *Clostridioides difficile* Carbapenem-resistant *Enterobacterales* Drug-resistant *Neisseria gonorrhoeae*
Serious	Drug-resistant *Campylobacter* Drug-resistant *Candida*
	ESBL-producing *Enterobacterales* Vancomycin-resistant *Enterococci* (VRE) Multidrug-resistant *Pseudomonas aeruginosa* Drug-resistant nontyphoidal *Salmonella*

	Drug-resistant *Salmonella* serotype *Typhi* Drug-resistant *Shigella* Methicillin-resistant *Staphylococcus aureus* (MRSA) Drug-resistant *Streptococcus pneumoniae* Drug-resistant Tuberculosis
Concerning	Erythromycin-Resistant Group A *Streptococcus* Clindamycin-resistant Group B *Streptococcus*
Watchlist	Azole-resistant *Aspergillus fumigatus* Drug-resistant *Mycoplasma genitalium* Drug-resistant *Bordetella pertussis*

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Anti-microbial resistance cases-

Due to the increase in resistance daily, the need for designing newer antibiotics is also increasing. The extent of resistance can be categorized as extensive drug resistance (XDR), multidrug resistance (MDR), pan-drug resistance (PDR), difficult-to-treat resistance (DTR), and modified DTR [6]. The five extents most commonly found are MDR, XDR, and PDR. Close monitoring of the resistance species is required to tackle the menace of anti-microbial resistance.

Case I- Extensively drug resistance (XDR)

Strains that are difficult to damage or kill by at least one agent in all but two or fewer anti-microbial categories are known as XDR strains [7]. Methicillin-resistant Staphylococcus aureus (MRSA) strain of gram-positive bacteria of coccus shape. It is currently resistant to most antibiotics, including beta-lactams, macrolide, oxazolidinone, aminoglycosides, tetracycline, sulphonamides, and chloramphenicol [8]. Further genetic alterations in MRSA make it even more resistant to antibiotics. Other species which are considered to acquire XDR are enterococcus species [9]. Not many cases are reported. Few known cases, such as Carbapenem-Resistant Enterobacteriaceae (CRE) and Vancomycin-Resistant Enterococci (VRE), are known.

β-lactam antibiotics show bacteriostatic action on S. aureus by inhibiting cell wall synthesis. They covalently bind to the transpeptidase domain of penicillin-binding proteins (PBPs), which crosslink the polypeptide chains of the peptidoglycan layer that surrounds the bacterial cytoplasm, which plays a crucial role in the survival of bacteria [10]. 95% of the S.aureus strain have now acquired the mecA gene, which is responsible for synthesizing a novel peptidoglycan transpeptidase, penicillin-binding protein 2a (PBP2a), due to which the affinity of the beta-lactam towards S.aureus has decreased significantly thereby gaining resistance towards methicillin and penicillin [11]. This resistant bacteria is known as MRSA. To treat MRSA-related infections on which methicillin and penicillin could no longer be used, vancomycin or daptomycin was suggested as first-line treatment [12]. Vancomycin binds to the D-alanyl-D-alanine, a peptide precursor, thus successfully inhibiting transpeptidation reactions. But again, evolution in bacteria is a significant threat [13]. Staphylococcus is also finding a way to deceive by acquiring resistance against vancomycin. The mechanism of developing resistance to vancomycin is not known accurately. One of the possible mechanisms is due to cell-wall thickening. Another explanation of this phenomenon is in vitro experiments and mouse skin transfers of a vanA gene cluster from Enterococci to S. aureus in the laboratory [14]. It was observed that colonies of Staphylococci would undergo horizontal gene transfer at infection sites with Enterococci [15]. However, no knowledge of any van gene clusters in experimental Staphylococci isolates is known, and a mechanism of this nature is not yet observed. Recent research has shown single amino acid substitution in RNA polymerase, which can cause resistance to the oxazolidinone and other ribosome-targeting antibiotics in S. aureus [8].

Case II- Multidrug resistance (MDR)

Strains that are difficult to damage or kill by at least one agent in 3 or more anti-microbial categories are known as MDR strains [16]. Multidrug resistance is found in *Mycobacterium tuberculosis* which is responsible for MDT-TB [17]. Because of this resistance, the bacteria have developed a way to survive and decrease the affinity of the two most potent anti-tubercular drugs:

Isoniazid and rifampicin [18].

Isoniazid and rifampicin are the first-line drugs for treating tuberculosis (TB) [19]. A mycobacterium attack on the lungs and other parts of the body, such as the kidney, spine, and brain, generally causes TB. Isoniazid is bacteriostatic and bactericidal depending on the rate of growth of Mycobacterium [20]. It is a prodrug and is activated by KatG [21]. Mycolic acid synthesis is crucial for Mycobacterium to become less susceptible to

antibiotics and circumvent the immune system [22]. INH inhibits this mycolic acid synthesis and stops or inhibits bacteria growth. Rifampicin exerts bacteriostatic action by binding to the beta subunit of DNA-dependent RNA polymerase enzyme and inhibiting the synthesis transcription and translation [23].

The known mutation due to which the potency of anti-tubercular drugs is decreasing is targetbased, namely rpoB, inhA, gyrA/B, atpE drug activation based- katG and efflux pump Rv0678.
[24, 25, 26, 27]

FACTORS ACCELERATING AMR –

MUTATION	GENE	EFFECT OF MUTATION
Target based	rpoB	Results in modification of beta subunit of RNA polymerase by a mutation in D441V, S456Q, R454Q, H451P inducing binding hindrances in rifampicin. [28,29]
	inhA	Alteration in S94A or overexpression results in resistance towards isoniazid and ethambutol. [29]
	gyrA/B	Mutation in the gyrase A subunit (G88C, A90V, D94G) and gyrase B subunit (less prominent)(G512R, D94G) is responsible for the development of resistance against fluoroquinolones. [30]
	atpE	ATP synthase subunit C (AtpE) catalyzes the production of ATP from ADP important for cell survival. L49P is responsible for resistance against Bedaquiline. [31]
Drug activation based	katG	S315T, S315I alterations are responsible for high INH resistance because this gene expresses catalaseperoxidase, which is essential for converting INH prodrug. [32]

Anti-microbial resistance (AMR) is considered one of the most vicious public health concerns globally, as it ranks among the top ten global public health concerns [33]. Different drivers are responsible for the acceleration of resistance. According to WHO main drivers of anti-microbial resistance includes misuse or overuse (due to over-prescription of antibiotics or Patients not finishing the entire antibiotic course); lack of access to clean water, sanitation, and hygiene (WASH) for both humans and animals; low-grade infection and disease prevention and control in healthcare facilities and farms; poor access to quality, affordable medicines, vaccines, and diagnostics; lack of awareness and knowledge, Poor hygiene and sanitation. Another factor that profoundly affects anti-microbial resistance is the limitation of developing new drugs. Furthermore, antibiotics' pharmacokinetics and pharmacodynamics properties need to be studied to increase the binding affinity of a ligand to the receptor and the potency.

Misuse and Overuse of Antibiotics

All clinically relevant bacteria adopt various resistance mechanisms as a survival strategy. The intake of antibiotics can cause resistance to an illness in which an antibiotic plays no role in curing or prevention, such as viral infections, common cold, flu, etc., or by not completing the antibiotic course [34]. This is known as antibiotic abuse which disrupts the average balance of friendly bacteria, such as lactobacillus, in the body and harmful bacteria [35]. Hence administration of antibiotics unnecessarily could result in abuse or misuse. Developing accessibility and equity is a significant concern due to poverty and inadequate enforcement of regulatory policies on prescribed drugs. To make drugs available in rural areas with poor health facilities, antibiotics are commonly sold over the counter with poor quality. Rapid accessibility of drugs creates a patient to undergo self-treatment for diseases that generally require no antibiotic treatment [36].

Additionally, over-prescription plays a crucial role in developing resistance because physicians write unnecessary prescriptions for prolonged courses of antibiotics to get financial incentives [37]. Incentives are not the only factor due to which overprescribing is being carried out. Rather expectations of patients by healthcare providers also contribute equally. Self-medication, using antibiotics according to patient experience and knowledge, also leads to the progression of AMR [38]. When a fast recovery is seen with the use of antibiotics for common ailments such as flu,

gastro-intestinal tract diseases, fever, tonsillitis, etc., patients start considering antibiotics as a 'magic pill' [39] and use them to self-treat themselves to heal quickly after having an encounter with same illness again. This results in resistance toward a drug they have been self-medicating themselves with. This practice is not recommended as it can increase the severity of the infection and unwanted interactions of drug molecules and worsen the adverse effects.

Agricultural Use of Antibiotics

Excessive agricultural use of antibiotics in poultry farms or fields is seen as a global threat [40]. According to scientists, resistance may also pass between humans and animals [43]; therefore, unnecessary use of antibiotics needs to be cut down. Approximately 80% of antibiotics are in animals' food in the United States [41]. The addition of antibiotics to drinking water and feeds of animals is carried out as a prophylactic treatment to increase the growth of herds at sub-therapeutic levels and feed efficiency [42]. This method is used as a growth promoter of livestock. Another way by which resistance is developed is due to the use of pesticides. Bacteriostatic and bactericidal properties of pesticides are commonly employed to control weeds, rodents, spiders, insects, nematodes, mollusks, and microorganisms, notably fungi, bacteria, and viruses [44]. Antibioticresistant genes (ARG) and mobile genetic elements (MGE) increase the risk of soil contamination and the presence of antibiotic residues in crops [45, 46].

Bacterial and fungal plant pathogens rarely cause infection in animals and humans. *Burkholderia spp*. changes *Pseudomonas aeruginosa* physiology may lead to infection in immune-compromised people or animals [47]. Mycotoxins produced by numerous plant pathogenic genera, *Fusarium, Aspergillus, and Claviceps,* are harmful to humans and animals [48]. Increasing recognition of contamination of fruits and vegetables with zoonotic pathogens (*Salmonella spp*. and Shiga toxinproducing *Escherichia coli*) could result in passing resistant bacterial strains through the food chain or direct contact [49, 50]. One Health is a concept that explains that the war against antimicrobial resistance could be fought well only by bringing together an interdisciplinary and international team of experts.

Biological Factors

Antibiotic resistance happens spontaneously due to mutation and bacterial evolution [51]. A common mechanism by which bacterial strains acquire resistance is through horizontal gene transfer. Horizontal gene transfer can be carried out by extrachromosomal genetic material 'plasmid,' jumping genes' transposons,' and 'bacteriophages' [52, 53]. This could cause a great variety of resistance genes because of insertion sequences. Transfer of plasmids also transfers resistance among the bacterial species and could lead to the bacterium's evolution [54]. The exchange of genetic factors between bacteria through horizontal gene transfer further accelerates the spread of antibiotic resistance [55].

Environmental

The main driver responsible for making the environment a crucial parameter in AMR is pollution. Pollution caused by industrial polluted surface water, untreated hospital effluent, untreated municipal sewage, etc., and environmental release of fecal bacteria enhance the evolutionary process of resistance by developing new antibiotic resistance genes (ARG) [56]. These ARGs are mobile and can be transferred amongst pathogens in different steps. According to an assessment study conducted in March 2022 on the global health risks of antibiotic resistance genes, it was observed that almost 23.78% of the ARGs pose a health risk, especially those which confer multidrug resistance [57].

COVID-19

Anti-microbial resistance (AMR) continues to substantially affect global Health and the world economy [57]. But it found a way to hide behind COVID-19 for a while. The wrong utilization of antibiotics during the COVID-19 era was responsible for the increase in disastrous effects on AMR management and antibiotic stewardship programs [58].

ESKAPE pathogens, namely *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp*., are the antibiotic-resistant. ESKAPE pathogens tend to cause a large number of infections [59]. The ability of ESKAPE to form biofilm safeguards them against anti-microbial agents [60]. They are responsible for infections occurring in hospitals with high mortality rates. Secondary infection or co-infection in COVID-19 patients in the intensive care unit (ICU) was precisely observed due to the presence of these pathogenic species. All of the ESKAPE pathogens are responsible for coinfection with SARS-CoV-2 [61]. Among all pathogens, *A. baumannii* strains were highly resistant to beta-lactams, fluoroquinolones, and aminoglycosides during the COVID-19 pandemic [62].

The spread of resistance during the pandemic was due to self-medication and overuse of antibiotics,

anti-parasitic, and antiviral drugs [63]. According to studies, the rate of co-infected patients was 6.9% among the 87.7% of patients treated with antibiotics [64]. The cases of AMR are alarmingly cautious, and therefore excessive use of antibiotics should be reduced.

Possible Strategies For Overcoming Anti-Microbial Resistance

Different strategies are required to tackle the prevalence of anti-microbial resistance. Traditional methods are highly time-consuming and require certain modifications to fasten the drug development process. Another disadvantage responsible for delayed developmental process is increased chances of error which by use of artificial intelligence and machine learning might be eliminated. Some of the methods are discussed below-

BASIS	STRATEGY	Application
Siderophore conjugation	-	Cefiderocol
Medicinal chemistry based	Rational based	Linezolid
	Combinatorial chemistry	Bacterial peptidyl-deformylase inhibitor
	Retrobiosynthetic	Griselimycins and telomycins
	Semi-synthetic	Tetracycline derivatives such as doxycycline, minocycline, and rifamycin derivatives- rifampicin and tigecycline
Pharmacological based	Non-essential target inhibitors	Fluoroalanine derivatives
	Anti-microbial peptides	P5 and P9 against MRSA enfuvirtide
	Pathoblockers	LasB inhibitor hydroxamic-acid based, thiols, pentetic acid
Other	Genome mining	the degrading potential of polysaccharides of *Paenibacillus jilinensis*
	Phage therapy	Vibrio cholerae phage in Ganges for cholera

1. Siderophore conjugates

The scarcity of new drugs to combat resistance requires innovative and efficient drug design methods. The Trojan horse technique is an approach to combat rapidly increasing drug resistance [65]. This technique is employed by vectorization of antibiotics which is carried out by designing siderophore-antibiotic complexes (SAC) [66]. Due to resistance, the permeability of the cell membrane acts as a hurdle. This results in poor penetration of anti-microbials, specifically in gramnegative bacteria [67]. SACs are designed to easily penetrate the cell membrane by taking over the iron transport system of bacteria directly into cells, thereby tricking bacteria into suicide [68]. Siderophores are secondary metabolites produced natively, which possess a high affinity towards metal, particularly iron [69]. Linking antibiotics to the siderophore helps to strengthen the diminished activity of existing antibiotics [70]. Five hundred siderophores have been identified and characterized to date. Catecholate, hydroxamate, phenolate, carboxylate, and α-hydroxy carboxylate have been identified as iron-binding motifs which carry out chelation [71]. When iron levels are low in bacterial cells, various metabolic activities halt [72]. During that time, pathogenic use this siderophore for sequestration and transport of iron to carry out necessary activities required for survival [73].

The commercialization of cefiderocol cephalosporin-catecholate by Shionogi & Company Ltd based on the Trojan horse strategy made this technique even more fascinating for overcoming the war with resistance [74]. Various mechanisms can be achieved, but one unique approach for new therapeutics is the inhibition of siderophore biosynthesis as a target. Entities mimicking siderophore and repurposed drugs are also under investigation for designing SAC. Cefiderocol conjugate uses a synthetic chlorine-substituted catecholate group that mimics the siderophore [75]. Since conjugate is cephalosporin based, it also exhibits broad-spectrum action against gramnegative bacteria, namely *Pseudomonas aeruginosa, Burkholderia cepacia, Acinetobacter baumannii, and Enterobacteriaceae* [76].

2. Medicinal Chemistry-based approach-

Medicinal chemistry is a branch of pharmaceutical chemistry that correlates chemistry and pharmacology for in-depth information about the

molecular mechanism of drugs, synthesis, identification, and development of new chemical entities for therapeutic uses.

Rational designing of new molecules using cheminformatics and bioinformatics -

Designing a drug molecule is a tedious process. The rational drug design technique offers great help in creating new molecules with the required features. It helps us to depict how a molecule's structure affects the physicochemical properties of a drug molecule, interpretation of binding affinity with the target, understand the off-target binding, etc. [77]

Bioinformatics and cheminformatics are computing technologies that help to analyze many compound libraries. These computational techniques help extract relevant information regarding its performance and understand the structure-activity relationship. After the required information is extracted, the data is filtered based on given functionality (molecular mass, overall charge, hydrophobicity, target binding, etc.), Lipinski rule, etc., which is combined to form a new chemical entity [78]. Rational drug design can be applied broadly, from designing a molecule targeting an enzyme's specific pocket to creating drugs for hijacking a metabolic pathway [79]. This approach requires an in-depth understanding of bacterial biology, metabolic pathways, and the structure of the target.

The best example of rational design is linezolid, which is used as an alternative treatment for vancomycin-resistant bacteria *Enterococcus* and *Staphylococcus aureus* [80]. Linezolid is a drug designed from scratch with a different action mechanism than previously reported protein synthesis inhibitors [81]. Most protein synthesis inhibitors target the elongation phase. Still, linezolid, also a protein synthesis inhibitor, inhibits the beginning phase of the bacterial protein synthesis process, providing a new way to circumvent resistance [82]. Another example of process rational designed based anti-bacterial is the Diazabicyclooctane inhibitor, a beta-lactamase inhibitor used to overcome resistance in gram-negative bacteria [82]. The work of designing ETX0462, with potent in vitro and in vivo activity against Pseudomonas aeruginosa, gram-negative ESKAPE pathogens, *Stenotrophomonas maltophilia,* and bio-threat pathogens, makes it a promising candidate [83]. Another example of diazabicyclooctane is durlobactam, used in conjugation with sulbactam to treat *Acinectobacter* infections, and carbapenem-resistant *Enterobacteriaceae* with the highly unmet medical requirement [84, 85].

Combinatorial chemistry-

Combinatorial chemistry works on the same principle as traditional chemistry. The difference lies in speed, strategy, and the number of compounds synthesized. Combinatorial chemistry uses synthesis methods (solid-phase or liquid-phase) and strategies (multiple reactions at a time) to produce many compounds with common chemical scaffolds [86, 87]. It helps to analyze the effect of different motifs by substituting them systematically in a molecule. Virtual libraries help identify millions of fragments with all possible structures, combinations, and potential valuable targets [88]. Computer programs analyze the generated compound library, and the best hits are chosen based on requirements set by the researcher. Selected molecules are then synthesized, and physicochemical properties are determined (pharmacokinetics, pharmacodynamics, toxicity, etc.). A new type of antibiotic that is an inhibitor of bacterial peptidyl-deformylase was defined and evaluated with the use of a mixture-based combinatorial chemistry library [89]. Bacterial peptidyldeformylase catalyzes protein synthesis in bacteria by removing the N-formyl group from the Nterminal of methionine [90].

Retrobiosynthetic-

The retro-biosynthetic approach helps in designing de novo pathways of target compounds [91]. Algorithms are required to design an infinite number of synthetic routes; therefore, it is also known as the Retrobiosynthetic algorithm-based approach [92]. It can be applied to a large pool of antibiotic structures for identifying potential drug candidates with a new mode of action. Earlier, griselimycins and telomycins were synthesized by this approach [93, 94]. Griselimycins insert their activity by interacting with DNA clamp proteins such as DnaN, which is crucial in locking the beta clamp to Pol III during replication and increasing processivity. Preclinical studies have also exhibited anti-tubercular effects against *Mycobacterium abscesses* in mice. Telomycin acts on anionic phospholipids (cardiolipin) present in the mitochondrial membrane of bacteria [95]. Inhibition of these lipid proteins helps to enter the cell and disrupts essential processes such as signaling pathways, respiration, conservation of energy, etc.

Semi-synthetic approach-

Due to the development of AMR disruption, various essential pathways that were earlier

targeted for treating infections are being destroyed. It imparts several effects on drug molecules, but the majorly altered pharmacokinetic property is a major concern [96]. With the help of a semisynthetic strategy, new drugs are produced for the improvisation of pharmacokinetic activity and broad-spectrum inhibition. Alteration of different chemical and enzymatic methods is carried out for previously existing glycopeptides and lipopeptides such as vancomycin, teicoplanin, and daptomycin, which are derivatives of natural products [97]. This is used in the generation of new semi-synthetic drugs.

Easy modification of the C-terminus of vancomycin D-Ala-D-Ala successfully applies the semisynthetic approach [98]. This helped design several novel semi-synthetic vancomycin derivatives oritavancin, telavancin, and dalbavancin [99]. Apart from vancomycin, other antibiotics have been modified and synthesized, including an erythromycin derivative, 'clarithromycin,' and azithromycin [100]. Tetracycline derivatives such as doxycycline, minocycline, and rifamycin derivatives- rifampicin and tigecycline are also successful applications of this approach [101].

3. Pharmacological Based approaches-

Non-essential target inhibitors-

Antibiotic' adjuvants' or combination of antibiotics is used to tackle anti-microbial resistance. Deterioration of a person's Health during a bacterial infection is due to bacterial virulence. Antivirulence drugs were reported to inhibit bacterial virulence expressed during infection [102]. Pharmacological inhibition of such factors possibly suppresses the bacteria's ability to cause an infection in the host. This makes the work of the host's immune system successfully fight against less virulent bacteria. Examples of non-essential targets include biofilms, quorum sensing, and cysteine biosynthesis [103]. Targeting non-essential pathways reduces the evolutionary pressure of adaptation and the development of drug resistance.

Targeting biosynthesis of cysteine-

Amino acid biosynthesis inhibition generates harsh conditions for the proliferation and survival of bacteria [104]. This causes bacterial cells to develop new survival strategies, including advanced adaptation mechanisms and metabolic pathways. The enzyme SAT (serine acetyltransferase) and OASS (O-acetyl serine sulfurylase) catalyze the last step of cysteine biosynthesis, depending on the bacteria and environmental condition [105]. OASS is generally used and is crucial in transcriptional regulations, toxin generation, motility, etc. Fluoroalanine derivatives have been employed, which bind irreversibly to form a stable Schiff" s base and inhibit OASS but have poor efficiency [106].

Quorum sensing targeting-

Quorum sensing is a cell communication process in bacterial cells that controls bacteria growth and virulence [107]. In gram-positive bacteria signaling molecule for QS are present in peptides [108], whereas in gram-negative bacteria uses AHLs (N-acyl-homoserine lactones) [109]. pqsD transition state analogs which inhibit the quinolone signaling system of P.aeruginosa (PQS) have been reported, reducing the bacterial biofilm production and thereby inducing a bactericidal effect [110].

Anti-microbial peptides-

Conventional AMDs are on the verge of collapse due to increasing anti-microbial resistance cases and new mechanisms of acquiring resistance to pathogens. Just like pathogens are acting smart, there is an urgent requirement for new smart strategies to design and develop anti-microbials that are more efficient and reliable to fight this situation. One such approach which is extensively researched is the designing of anti-microbial peptides. AMPs are considered a next-generation strategy that can be used to tackle drug-resistant strains of pathogens [111]. These are charged peptides that humans produce as a defense mechanism against pathogens. Different ways can classify AMPs, but they are broadly classified into two classes based on the natural synthesis, independent ribosomal synthesis, and ribosome dependent synthesis [112]. Ribosomal dependence is observed in eukaryotes and ribosomal independence in prokaryotes.

Ribosomal-dependent anti-microbial peptides are now being studied for their therapeutic potential [113]. These AMPs are known to exhibit their effect by causing membrane dysfunction due to bacterial membrane disruption [114]. They are used to breach gram-negative bacterial membranes and are highly efficient for many pathogens. These peptides have a multi-target effect and are used with known glycopeptides for improvising the drug's efficacy. This helped to design lipoglycopeptides 'Vancapticins,' which is a combination of vancomycin and peptide and is known to augment the efficiency of vancomycin compared to unconjugated vancomycin variant against MDR *S.pneumoniae*, Methicillin-resistant *S.aureus* (MRSA) and Vancomycin-resistant

enterococcus (VRE) [115]. Recent research has shown several AMP with therapeutic potentials, such as P5 and P9, against MRSA with low cytotoxicity as anti-bacterial [116], AurH1 active against lethal C.albicans as anti-fungal peptides, defensins, maximin 3 as anti-HIV, Epi-1 for inhibiting Trichomonas vaginalis as anti-parasitic and Tritrpticin, puroindoline as anticancer peptides [117, 118, 119]. Even though active research is ongoing apart from enfuviritde, there is no commercialized AMP [120]. More research regarding methods, standardization, and validation of guidelines is required for making anti-microbial peptides a reliable alternative treatment. Apart from enormous advantages being costly and having a short half-life is a major setback. Hence new technologies are required to overcome inadequate ADME, toxicity, and cost-effectiveness properties. Different methods can be used to cross these obstacles. These methods can modify a peptidomimetic structure and protect a peptide from proteolytic enzymes. Encapsulation can be used to decrease AMP degradation by metabolic enzymes. In this, polymers, nanotubes, liposomes, etc., can be used to enhance the activity of AMP [121].

AMP has many benefits, which make them an excellent choice for the near future. These peptides are target selective, broad spectrum, less toxic, and have numerous mechanisms of action. In conjugation with antibiotics, AMP boosts the ability to fight against resistant pathogens and produce less resistance. Successful examples of synthetic AMPs and antibiotic combination includes- Nisin-Z, Lactoferricin B and Bac 7, Lactoferricin B, and PR-39 against various MDR bacterial strains [122, 123]. Another advantage of AMP is its ability to neutralize sepsis or endotoxemia (the presence of lipopolysaccharide in the bloodstream) and provide innate immunity to mammals [124]. They are also useful in stimulating innate immunity and reducing harmful inflammatory responses. IMX00C1 has been reported as a defensive synthetic peptide to fight against infectious bacterial disease. Various types of AMP, such as omadacycline, pyrrochorrycins, oncocins, apeadicins, and aminomethylcycline, have shown appreciable inhibitory activities against gram-positive and negative bacteria [125]. Pexiganan A, which exerts bactericidal activity against *Helicobacter pylori,* is also reported [126].

Pathoblockers-

Pathoblockers are an alternative strategy used to target virulence factors in bacteria. Virulence factors such as cytosolic, secretory or membrane associated in nature play an important role in exhibiting pathogenesis [127]. This factor could be enzymes, proteins, and small molecules which pathogenic bacteria can use to colonize or infect the host cells. The role of pathoblockers is to aim at virulence factors and thereby disarm bacteria instead of bactericidal action [128]. They are very useful for reducing pathogen-induced damage and facilitating the immune system's clearance of the infective agent.

Virulence factors are considered non-essential agents that decrease resistance evolution in a species. Screening therapeutic agents targeting virulence factors is quite challenging, but in vivo infection models, preclinical studies, and biochemical assays are some demonstration tools. There are various virulence factor targets, such as Elastase B (pseudospin) [129], a broad spectrum exometalloprotease enzyme which plays an essential role in host-pathogen interaction for *P. aeruginosa,* a gram-negative bacterial strain. Gene LasB encodes this. Some known inhibitors for LasB include hydroxamic acid based tools, pentetic acid [130, 131, 132]. Several other virulence factors are present in P. aeruginosa, such as lectins A and B, responsible for biofilm production and potential targets [133]. This can be inhibited by carbohydrate derivatives that inhibit the pqs system and activate the pqsR transcriptional regulator and process of iron-salvation [134]. These pathoblockers are at various stages and have reached preclinical development.

4. Other techniques- Genome mining technique-

With the constant evolution of superbugs, novel anti-microbials are required. Anti-microbial drugs of natural origin provide an artistic way. But due to less targeted research, this field provides a challenge to overcome resistance. The genome mining technique helps in designing new antimicrobials of plant origin [135]. More targeted digging into the biosynthetic potential of natural origins can be carried out with the help of genome mining techniques. Drug isolation is guided by biosynthetic gene cluster (BGC). Identification of BGC can be carried out with anti-SMASH and PRIS [137]. Several strategies for genome mining can be used, such as CRISPR-Cas9 mediated insertion, cultural condition optimization, genetic material manipulation of transcriptional regulators, heterologous expression, small molecule elicitors, and epigenetic control perturbation [139]. The latest studies have shown the degrading potential of polysaccharides of *Paenibacillus jilinensis*, an intestinal bacteria [138].

Phage therapy-

Phage therapy is an ancient technique that has been practiced even before penicillin. Phages or bacteriophages are viruses responsible for infection in bacterial cells [140]. An example of phage therapy includes treatment for cholera in the 1890s in Ganges due to *Vibro cholerae* killer phages. With time phages and bacteria have co-evolved to outcompete each other. Dr. Tom Patterson used Personalized ΦPC phage intravenously 2017 against multidrug-resistant systemic infection caused by *A.baumannii* [141}. Mass production, cost, labor-intensive output, lack of knowledge about phage functioning, and strain specificity are obstacles that must be crossed for successful global phage therapy [142]. Even though phages can be used as an alternative treatment, they are still responsible for transferring anti-microbial resistance through transduction, providing a major concern [143].

Conclusion-

Anti-microbials are one of the excellent discoveries, but because of acquired resistance due to mutations in the pathogen, it is initiating a war with humanity. The spread and emergence of antimicrobial resistance are complex and disregard regional and international rim; thereby, it can only be tackled by taking global action. The differential drivers of resistance, primarily agricultural, self-medication, misuse or overuse of the prescribed medicine, COVID-19, environmental factors like pollution, etc., fuel up a pathogen's unresponsiveness towards the anti-microbial agent (AMA). Due to the development of resistance affinity of a drug molecule toward the target is reduced significantly. This reduced affinity results in the inactivation of the drug and could cause no pharmacological response. The rise in AMR requires diversification in strategies to obtain new chemical entities of synthetic and natural origin.

A possible strategy for overcoming drug resistance can be achieved by restoring the affinity of drug molecules with receptors or by increasing the potency of the drug molecule. This can be accomplished by (1) designing new chemical entities, biologics, etc., (2) modifying the existing scaffold by keeping the pharmacophore intact (3) siderophore conjugated antibiotics (SAC). With the advancement in technologies, various new techniques are in process which can be used to kill these drug-resistant superbugs. One existing method that needs more attention is the Trojan horse strategy often used in designing SAC. These conjugates break the traditional belief of using covalent linkers by designing a successful methotrexate-siderophore conjugate. Another approved SAC is cefiderocol, sold under the fetroja brand, used in treating complex UTIs. Newer techniques, such as genome mining, semi-synthetic strategy, non-essential target inhibitors, etc., also require attention to overcome resistance.

WHO census has reported a higher rate of AMR in less-reporting countries. It can be well understood by the statement that global median AMR levels for MRSA and E.coli are 35% and 42%. AMR levels for high testing coverage countries were comparatively lower for these indicators and reported at 6.8% and 11% only. Close monitoring and testing are also required to combat resistance to evolving AMR threats.

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