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Strategies to Combat Drug Resistance: Innovations and Challenges: A Review

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Drug are used to treat the infection as antibiotics a low molecular weight molecule used to treat different bacterial infections. But the increasing drug resistance put danger to global healthcare and the treatment efficacy worsening the healthcare outcomes. Multidrug Resistance (MDR) by biofilm making the infection control complex. There are few prevention measures of this drug resistance but the use of technology with combination of the omics field may be used to develop the natural products faster than the already existing methods. This review focuses the golden era of antibiotics and how this era got shadow of resistance and strategy to overcome this. Also, the mechanism and future strategies which can be used to fight against this resistance threat is spotlighted. The use of technology collaboration and surveillance aspects are briefly explained.

Keywords: Antibiotics; Drug resistance; Mechanism of resistance Collaboration; Multi-drug resistance; Omics; Surveillance.

Drug resistance – "a superbugs" is a critical concern that is demanding the urgent attention and a powerfully built strategies for alleviation. The World Health Organization, identifies multidrug resistance as one of the top threats to global public health. (Hay et al., 2018).in response to the crucial issue of drug resistance, for researchers and healthcare professional, it is important for them to understand the underlying mechanisms for combating the drug resistance. Several studies are going on ESKAPPE pathogens to develop the effective strategies to combat drug resistance. There is promising tool which are now use to bypass the drug resistance (Indrawattana, 2016.).this review focuses on various approaches like efflux mediated resistance mechanism, nano-biotechnological and bioinformatics which are proving as the stepping stone to get ahead of the underscoring the urgent need of novel strategies to combat drug resistance. Antimicrobial materials are also gaining the acceptance due to their astonishing antimicrobial properties which as a potent activity against wide range of pathogens to elicit the resistance rather than traditional antibiotiocs. Inhibitors as adjuvants are also the growing demand. Targeted drug delivery with the combination of novel approaches is now wide spreading to reduce the chance of resistance in organisms. (J. Yao et al., 2023a)

Efflux pump mediated resistance basically involves the transport of antibiotics across the bacterial cell membrane through active mechanisms which leads to the decrease in the intracellular accumulation of the drugs. Thus, there is a decrease up to sub lethal levels.

Nano-biotechnology is a coming future to deal with drug resistance and due to its

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development the biofilms which is a major mechanisms through which bacteria develop resistance can be shed light on this .This gives a unique platform for scientist and researchers to develop the targeted drug delivery system .The development of nanoparticles based antimicrobial agents which can bypass efflux pump mediated resistance .Nano formulations are now striking the potential to enhance the mechanism by intracellular accumulation of antimicrobial agents .That why nano-scales delivery system facilitate the precise treatment with minimal or no side effect.

By integrating the nanos and biosensors we can develop a sensitive formulation and timely intervention and tailored treatment diagnostic tools which can also hold as a promising tool in disrupting the major cause – 'biofilm' (Saravanan et al., 2019)

As the bioinformatics are gaining too much attention in the real world of science we can predicting new targets, phage therapy or the repurposing the existing drugs. Docking and artificial intelligence are also gaining efforts which can predict and accelerates the different strategies for combating the drug resistance.

Also, the overuse of the antibiotics in humans' agriculture and animal husbandry resulted in the emergence of multidrug resistant pathogens to overcome this combination therapies are also gaining the attention due to the multifaced targeting side to make the inactivation of the drug by various

This review also focuses on the various therapeutic strategies like molecular application, bacteriophage therapy, avian egg model, probiotics and herbal medicine which can be used to combat drug resistance.

With the collaborating of researchers, scientists, health care professional, stakeholders with technology we are the stage where we can fight the drug resistance mechanisms implementing the NAP-AMP, public awareness campaign we can combat the leading superbugs 'Drug resistant pathogens.

Golden era of Antibiotics

Approximated 1940-1962 is a golden era of antibiotics where the development of new antibiotics takes places, where the medicine landscape changed.

Early discoveries

In 1900, The potential targeted therapies treatment for syphilis by Paul Ehrlich with salvarsan in1900 ground worked was laid before the discovery of the penicillin in 1928 by Alexander Fleming and also the 'Prontosil' a sulpha drug in 1930 is a commercialized first antibiotics (Lyddiard et al., 2016)

The Waksman platform Bursting of Antibiotics

The true bursting of the antibiotics takes place by the work done by Waksman and his colleagues in the 1940s. systematic screening the soil microorganism, *'actinomycetes'* led to the isolation of streptomycin, first effective treatment for tuberculosis termed as 'Waksman platform' known to be the new start for the antibiotic discoveries (Lyddiard et al., 2016)

A new era in Medicine

After that -tetracycline, chloramphenicol, neomycin, erythromycin, vancomycin goes on for bringing the mortality down the life threating illness like pneumonia, meningitis and others. (Lyddiard et al., 2016)

New era in medicine

New era become the golden era because once the disease which was deadly become the now available due to advancement which led to the reduced risk of post-operative infective this is possible because antibiotics ushered in the era of preventive and curative medicines. (Lyddiard et al., 2016)

Shadow of resistance

Overuse of medicine and lack of new antibiotics from 2000 shows the resistance of bacteria against the developed antibiotics and this causes the significant threat to public health. (Lyddiard et al., 2016)

National Policies of India for combatting Drug resistance

As India is struggling with the growing drug resistance among its population, thus the government implement several national policies to curb the issue

National Action Plan on AMR

The NAP-AMR, formed in 2017 serves as a guideline to address AMR in India. This outlines 6 key priorities: Surveillance, Awareness Stewardship, Infection prevention and control [IPC], Research and development, international collaboration (Ranjalkar & Chandy, 2019)

Schedule H1 drug warning

This policy restricts the scale of certain

antibiotics which were classified under scheduled H1. This practice overcome the over-the-counter purchase and misuse of drugs and thus sold under the prescription from a registered medical practitioner. (Singhal et al., 2016)

Regulation of Fixed Dose combinations [FDCs]

Based on Indian council of medical research [ICMR], the Drug controller general of India [DCGI] has banned the sale of some of the fixed dose combination drugs to be in appropriate combining with other medicines may increase the risk of resistance (Ranjalkar & Chandy, 2019)

Mechanism of resistance

Drug resistance has many mechanisms evolved in it which mainly comprise of the four main categories :-(1) Limiting uptake of a drug (2) Modifying a drug target (3) Drug inactivation (4) Active drug efflux

Table 1. Classification of traditional antibiotics (J. Yao et al., 2023b)

Name	Representative Drugs	Description
β-lactam antibiotics	Penicillin, Cephalosporin, Carbapenem, Monobactams	Widely used in clinical treatment, mainly for infectious diseases caused by sensitive bacteria
Glycopeptides	Vancomycin	Clinical "last resort" for the treatment of serious infections caused by Gram-positive bacteria
Oxazolidinones	Linezolid	The first FDA-approved oxazolidinone antibiotic, a broad-spectrum Gram-positive drug
Quinolones	Norfloxacin, Ofloxacin, Ciprofloxacin, Flurofloxacin	The most used and effective clinical application is the treatment of genitourinary tract infections; they are also widely used in the respiratory system, as well as the intestinal system.
Ansamycins	Geldanamycin, Herbimycin	This class of antibiotics has a variety of biological activities such antibacterial, antitumor and antiviral. Some of them are currently clinically important anti-tuberculosis drugs.

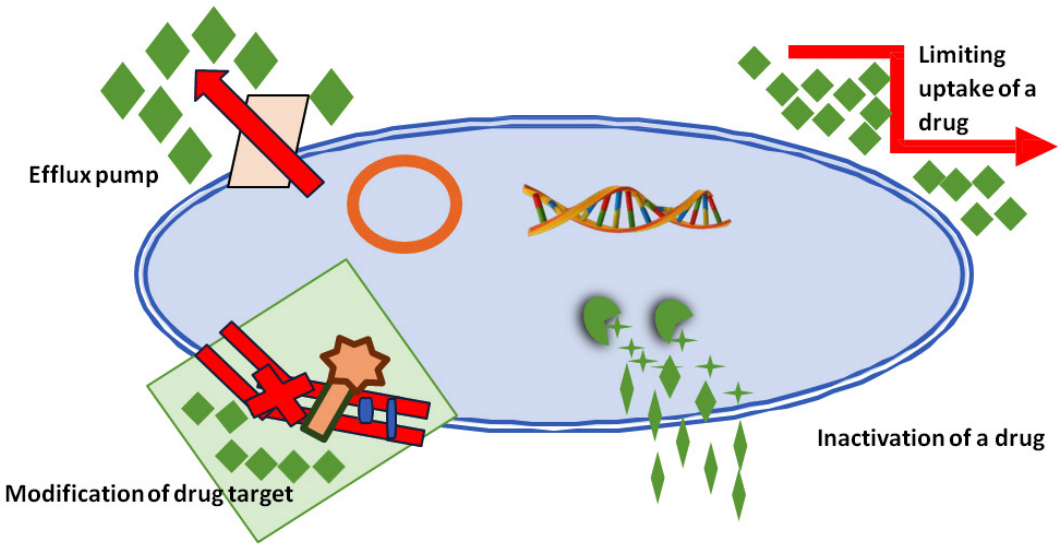

Fig. 1. Mechanism of drug resistance

Limiting drug uptake

There is a natural difference in the ability of bacteria to limit the uptake of antimicrobial agent the gram-negative bacteria having LAP layer provides a barrier for certain molecules typer. This; provide the innate resistance for some antimicrobial agents (Blair, Richmond, et al., 2014)

Modifying a drug target

Resisting the drugs by modifying the target molecule or binding sit for instance some bacteria modify their cell components just because to resist them from drug effects

Gram positive bacteria, like *S. aureus* car their penicillin binding protein (PBPS) which makes the drug like B-lactamase less effective also drug like vancomycin and daptomycin are resisted by altering the membrane structure.

Also, the mutations or change in enzymatic results in resistance. For instance, bacteria can modify enzymes involved in folate biosynthesis, which affects making it harder for drug to bind to their target. (Reygaert, 1900)

Drug Inactivation

This mechanism has two ways to make drugs ineffective which have developed by bacteria. One way is by using B-lactamases like enzymes to break down penicillin like tet X, which deactivates tetracycline (Blair, Webber, et al., 2014; Reygaert, 1900)

Additionally, bacteria can also attach to chemical group like acetyl, phosphoryl and deny of drug making them useless. (Reygaert, 1900)

Efflux Pumps

The membrane bound transport proteins found in bacteria actively pump out the drugs or antimicrobial agents out from the bacterial cell leading to the decrease of drug level for action and this confer resistance to the multiple classes of drug.(Blair, Richmond, et al., 2014)

Strategies for combating drug resistance

Focusing mainly on the four strategies.

1) Nano-biotechnology.
2) Bioinformatics.
3) Antimicrobial materials.
4) Molecular mechanism

Nano-biotechnology

As nano-biotechnology is a growing field with the advancement to fight against drug resistances. The nano system can target the pathogens with precision and help for the site supply. Nanoscale drug delivery system has also the promising application for the antibiotics as well as antimicrobial agents.(Y. Yao et al., 2020) Nano formulations are helping in field of pharmacokinetics and bio-distribution of drug enabling enhanced penetration in the intracellular cell compartment as well as biofilms where the conventional antibiotics may not reach Nano carries are also playing roles as they are protection of encapsulated drugs from degradation which facilitate target delivery to the site of infection and cancer.(Ulldemolins et al., 2021)

Minimizing the systemic toxicity and enhancing binding affinity, surface modification of nano particle with ligands targeting bacterial cell surface receptor be used (Lemire et al., 2013)

Designing of nanomaterial based antimicrobial agents with unique mechanism of action is also another aspect engineered nano particles, such as silver nano particle (AGNPs), copper nano particles (CUNPs) and the most advanced quantum dots (QA) exhibit strong antimicrobial activity against the broad spectrum of drug resistance pathogen by a different mechanism such as membrane disruption, oxidative stress in duction and with interfering the microbial process. This proved to the best approach to overcome the conventional resistance mechanisms. (Gupta et al., 2019)

The nano-based biosensors such as gold nano particles (CUNPs) or carbon nano tubes (CNTs) can able to detect specific biomarkers which as associated with drug resistance making them best tools for diagnostic and rapid identification test. These point of case diagnostic device (biosensors) enable timely identification selection of antibiotics and treatment strategies to overcome. (McKeating et al., 2016)

Also, Nano particles based immune-modulatory agents likes immune stimulating adjuvants and immune-modulatory cytokines can boost innate as well as adaptive response to infections reducing the risk of recurrent infections (Chand & Kushawaha, 2023)

Moreover, nano vaccines design to mimic pathogen structures or deliver antigenic peptides to APCs (Antigen presenting cells) can remove in destructive immune response against the pathogens providing a year of protection against regaining the infection. (Khatun et al., 2023)

Bioinformatics

Bioinformatics has emerged as a valuable tool for studying and combating drug resistance there are 4ways in which bioinformatics is revolutionizing against drug resistance.

Unveiling resistance mechanisms

Genome sequencing- Allows rapid and cost-effective bacterial genome sequencing which help to identify mutation and genes associated with resistance and how bacteria evade antibiotics.

Comparative genomics – To develop crucial strategies to target the vulnerabilities, by comparing the genomes of resistance and susceptible bacteria, bio-informaticians can pinpoint specific genetic change responsible for resistance.

Predicting new targets

Protein structure analysis- Analysing three-dimensional structure of proteins involved in antibiotic resistance. This structural analysing helps to identify potential weakness which can be exploited by new drugs.

Metabolic pathway modelling. - To identify novel targets for antibiotic action, modelling of bacterial metabolic pathway can research.

This results in the development of new drugs which disrupt process for bacterial survival bypassing existing mechanism of resistance.

Repurposing existing drugs

Virtual screening: - Allows researchers to virtually screen vast libraries of already against resistant bacteria. By repurposing already approved drugs makes it easier for the researchers to get information easy and fast.

Drug target interaction analysis: -By analysing the existing drug mechanisms for resistant bacteria that how interaction between drug and targets are there, researchers can predict the effectiveness of drug and may leading to the identification of new uses for established medication.

Accelerating drug discovery

Insilico docking helps to simulate the docking of potential drug candidate with target bacteria. This helps to gain the resources during drug discovery.

Combining machine learning and artificial intelligence (A1) helps to analyse the huge datasets of genetic as well as chemical information to predict the repurposing or the effectiveness of new antibiotics. (Ndagi et al., 2020)

Antimicrobial material

Antimicrobial peptide

Antimicrobial peptide is gaining attention for their remarkable antimicrobial properties which has a strong activity against a wide range of pathogens and reduced the activity of resistance compared to traditional antibiotics or drugs some examples like short Bacillus peptide and polymyxin, have already been approved in the clinical and therapeutic use as a class of molecules in clinical trial. One major challenge is the degradation by enzymes due to the peptide like structure which limits thar effectiveness and their extraction process is also a complex and resources intensive. Also, the natural source of AMPs is limited and then extraction process is also a complex and resource intensive. Also, the chemically synthesizing AMPs offers a potential solution but it adds cost and scaling up as a major drawback.(Mwangi et al., 2019)

Researchers are now working to enhance their stability and efficacy by protecting the AMPs from enzymatic degradation by use of engineering modification. (Mwangi et al., 2019; Xuan et al., 2023)

Drug delivery system (DDSs)

This basically focuses on the practical approach to address drawbacks associated with systemic administration of antibiotics lifespan, scientist proposes a strategy in (DAS) design known as 'Trojan horse' In Trojan horse, the antimicrobial agents are combines with various carries such as liposomes, erythrocytes exosomes, polymers and self-assembled peptide to achieve efficient drug delivers which overcomes the barriers posed drug resistance bacteria various DDSs are now be as developed like.

1. Carbon based nano delivery systems
2 .Liposomal drug delivery systems
3. Biomimetic nano delivery systems
4. Polymer based antibiotic delivery systems (PADSs)
5. Self assembled peptide drug delivery systems (J. Yao et al., 2023c)

Molecular application

As resistance bacteria are emerging quickly, it's difficult to fight infections diseases as well as making new antibiotics. CRISPR associated

system (CRIPR-case) known to be a one of the methods to fight against the diseases. The short palindromic repeats-case nuclease when used against bacterial genome may be lethal which help to decrease the AMR counts. This system is used as an adaptive immune system in bacteria. As in eukaryotic cells, RNAI (interference) works same way the CRISR system work. (Gholizadeh et al., 2020)

In bacterial species, the CRISPR-case has been used to target the harmful genes, many configurations of CRISPR system like CRISPR-case in enterococci, are associated. This become contradictory as, Plasmid in E-coli has no impact on of antimicrobial resistance (Touchon et al., 2012)

Recent research shown that when we attack the genome of bacteria wine CRISPR-case system, resulted in the cytotoxic of the cell leading to the death.

In current situation where bacterial genome is immune to antimicrobial agents a substitute like phagemid can be the alternate option but the lack behind this technology is the diverse microbial community (Gholizadeh et al., 2020; Roach et al., 2017)

Therapeutic strategy

Bacteriophage

As the most challenging issues are facing to treat common or devasting bacterial infecting, thus the world is moving towards an alternative option. There have been many advantages stated to use phage therapy over the chemotherapy of the different antimicrobial agent. As these phage's are different from antibacterial agents in several way, like production of virolysin, encoding antimicrobial peptides delivery mechanism and ability to infect bacteria as living phages (Ghannad & Mohammadi, 2012). Some cases shown that, lytic phages shown best activity against the target pathogen result in the elimination of contaminated bacterial debris and endotoxins. (Young & Gill, 2015) The host range vary for the phages for adsorption and penetration in bacteria and only several receptors and phage interactions are there but now as we are stepping ahead the list is continually expanding. And human disease is linked to bulk of lytic phage. (Lin et al., 2017)

Avian egg model

Avian immunoglobulin can be demonstrated to meet all the criteria which fight against the resistance pathogens. The avian immunoglobulin can be said to be 'Superdrug using the eggs as a source for generating the polyclonal antibodies for a wide of rang of infections pathogens which not harm normal flora (Threlkeld & Webster, 1989)

Probiotics

The antibiotics and probiotics together used has resulted to less severity and duration of antibiotic associated diarrhoea up to how much extent probiotics help to reduce the resistance is still ongoing research but maintaining healthy microbiome with antibiotic resistance but using may reduce it only. Mainly lactobacillus and bifidobacterium are present in probiotics (Ouwehand et al., 2016).

Herbal medicine

There are many infectious and non-infectious diseases are treated from herbal remedies since ancient times. These herbal remedies treat in the same way as the antimicrobial did by kill or preventing the infections bacteria growth. But there are research findings that may show resistance towards herbal antimicrobial components making it more difficult because of the meta-analysis of large data set.(Bhardwaj, 2015)

The Role of Technology in Addressing Drug Resistance Issue

One of the best approaches is the screening of libraries of previous approved drugs the identify non obvious antimicrobial adjuvants. This adjuvant helps to enhance the existing antimicrobial agents. (Gill et al., 2015)

Another strategy involves the combination therapies where a target the different pathway one such example is the gram-negative bacteria *Pseudomonas spp*, which included broad spectrum beta lactam and an amins glycoside or fluoroquinolone now a days colistin combination increasingly used as a last resort treatment for multi drugs resistant strains.(Vestergaard et al., 2016)

Novel therapy that only target specific mechanisms of drug resistance is also an approach. As instance, researcher is exploring the use of inhibitors that can specifically target and inhibit the active multi drug efflux pumps preventing them from expelling antimicrobial agents and allowing the drugs to effectively kill the pathogens. (Lamut et al., 2019)

Tactics for enhancing antibiotics efficacy

Enhancing antibiotic efficacy is a crucial role for the fight against drug resistance.

Optimizing Antibiotic use: -To preserve the effectiveness of antibiotics and minimizing the drug by promoting responsible prescribing practices, banned over the counter (OTCs) medicine and implementing antibiotic stewardship. (Ranjalkar & Chandy, 2019)

Exploring Alternative treatment options: -Use of phage therapy or immunotherapy proved as an alternative treatment mechanism which by pass the traditional way of approaching by antibiotics. (Ranjalkar & Chandy, 2019)

Challenges

The good come with its own challenges. One of the major challenges is the lack of standardization and harmonization of procedure which also include standardized breakpoints for determining susceptibility of resistance to antibiotics. This detoriate the interpretation of data between the different regions and heath care. This challenge must be addressed by the creation of new international breakpoint encompassing all stake holders. The other major challenges are the economic which include limited investment and commercial viability of the discovered drug. As new drug development takes times with less commerciality and required investment which my hampers the commerciality profit of the company which lacks the interest develop new drugs. This resulted in the gap of discover of new drugs. To overcome this, government must try to encourage research and development and funding mechanisms in the field of drug discovery.(Gelband & Laxminarayan, 2015a; Harbarth et al., 2015)

Fighting Back against drug resistance

As the world is facing an issue, where the bacterial infections which are once treatable became now untreatable. This is due to the resistance mechanism of bacteria towards a specific drug. This problem should require global as well as national effort.(Gelband & Laxminarayan, 2015b)

The WHO (world health organization) has plan to address this. The WHO encourage country to develop their own plans that focus on resistance tracking, spreading antimicrobial stewardship program educating people, preventing infections and finding new treatment option.(Fishman, 2006)

Countries can also take action on their own for the wisely of antibiotics, arranging public awareness campaigns regulating how antibiotics are sold, banning over the counter drug. Everyone has their own role. To c urb this issue everyone must be worked individually by taking prescribed. Farmers should only give drugs or antibiotics to animals when vet prescribed. By working, globally, nationally and individually we can keep this lifesaving drugs effective for longer period. (Harbarth et al., 2015)

CONCLUSION

Drug resistance is increasingly in the local as well as global scale mainly in the developing countries. This emergence is a now treated with the innovative strategies mentioned above and banning the over the counter (OTC) drug or antibiotic and educating people collaboration of researcher, scientist and healthcare professional should be way to approach usage and resistance must be improved via antibiotic stewardship program. To keep the pace like increasing the antibiotic as the increasing resistance should be thought.

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