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Review Article

A Review on Combating Antimicrobial Resistance: Probiotics and Microbiome Modulation as Next-Generation Therapeutics

K. Sairam[1], Neha[2], Yattam Manisha[3], Kallem Sirisha[4], K. Chandrashekar[5], P Munija[6]

[1,2,3,4,5] Student, B Pharmacy IV Year, Vision College of Pharmaceutical Sciences & Research
[6]Chief Coordinator, R&D & Vice Principal, Vision College of Pharmaceutical Sciences & Research.

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Abstract:
Antimicrobial resistance (AMR) has emerged as one of the most critical global public health threats of the 21st century, significantly compromising the effective treatment of infectious diseases and increasing morbidity, mortality, and healthcare costs worldwide. AMR develops when microorganisms acquire resistance mechanisms such as drug-degrading enzymes, efflux pumps, target modification, and biofilm formation, largely driven by irrational antibiotic use, inappropriate dosing, self-medication, and extensive agricultural applications. This review summarizes the major challenges associated with AMR, including limited surveillance, slow antibiotic discovery, and reduced therapeutic options, while emphasizing the World Health Organization (WHO) priority pathogen criteria and global action strategies. The consequences of higher antibiotic doses, although sometimes improving bacterial clearance, may lead to toxicity, microbiota disruption, and accelerated resistance selection. Therefore, alternative and adjunct therapeutic approaches are increasingly important. Innate immune-based therapies, probiotics, and microbiome modulation represent promising strategies by enhancing host defense, restoring microbial balance, and reducing pathogen colonization without exerting selective pressure for resistance. Additionally, advanced pharmaceutical formulations such as antibiotic adjuvants, efflux pump inhibitors, nanotechnology-based drug delivery systems, phage therapy, antimicrobial peptides, CRISPR-Cas systems, and combination therapies are being explored to overcome bacterial defense mechanisms and improve drug efficacy. A comprehensive "One Health" approach integrating rational antimicrobial use, infection prevention, surveillance, vaccination, and innovative therapeutics is essential to mitigate the growing AMR crisis. Coordinated global and national efforts are crucial to preserve existing antibiotics and safeguard future treatment outcomes.
Keywords: Microbiome therapy, antimicrobial resistance, probiotics, Drug-Degrading Enzymes, Efflux Pumps, Biofilm Formation, Innate Immunity, Host-Directed Therapy, Antimicrobial Peptides, Microbiota Disruption, Toxicity Risk,

Introduction

Antimicrobial resistance (AMR) is a quickly growing global health treat that deals the productive infectious diseases treatment and increases sickness, death rate, and healthcare costs [1-3]. AMR arises when bacteria develop mechanisms to hold the action of antimicrobial

agents, primarily due to irrational antibiotic use, incorrect dosing, self- medication, and large application in agriculture [5]. This review highlights the challenges associated with AMR, innate therapeutic responses against resistant bacteria, the impact of higher antibiotic doses, World Health Organization (WHO) criteria, and the increasing role of probiotics and microbiome-based therapies [8,9].

Addressing AMR is demanding due to the continuous development of bacterial resistance mechanisms such as drug-degrading enzymes, efflux pumps, target modification, and biofilm formation [6]. Limited public awareness, lack of surveillance, and the slow development of new antibiotics additional complicate AMR management. Innate immunity act as the first line of defence against resistant infectious agent through physical barriers, antimicrobial peptides, phagocytic cells, and inflammatory responses. Host-directed and innate immune-based therapies are being explored as additional strategies to diminish bacterial burden without increasing resistance pressure.

The use of higher antibiotic doses to reduce the resistance remains at issue. Although higher concentrations may increase bacterial killing, they increase the risk of toxicity, interrupting the normal microbiota, and may speed up the resistance development. The WHO Global Action Plan on AMR highlight rational antibiotic use, infection prevention, surveillance, public awareness, and research to fight resistance productively.

Probiotics and microbiome-based therapies offer promising preference by renewing microbial balance, preventing pathogen colonization, and adjusting immune responses. However, challenges like safety, strain specificity, regulatory concerns, and intersubjective change must be addressed. A multidisciplinary approach merges immune-based strategies, improve antibiotic use, WHO guidelines, and microbiome therapy is fundamental to reduce the growing risk of AMR.

The term 'Antimicrobial Resistance' in bacteria is defined as to resist medicines (antibiotics) when the germs making infections harder to treat, disability, leading to longer illness and death with the excessive use of antibiotics in humans.

There are three types of that can develop resistance to antimicrobials:

1. Bacteria – Develops resistance to antibiotics.
2. Virus - Develops resistance to antiviral drugs.
3. Fungi- Develops resistance to antifungal drugs.

AMR come to the broader term antimicrobial resistance. This AMR bacteria includes all microorganisms which can develop noncompliance to the antimicrobial drugs. AMR bacteria cannot be killed or destroyed by the common usage of antibiotics. They are capable to live or else get multiplied in the presence of the antimicrobials. Bacteria which are resistant to many antibiotics are termed as multi-resistant organisms [MRO].

WHO Criteria

The WORLD HEALTH ORGANISATION(WHO) employs the particular criteria to recognise and emphasize antimicrobial resistance (AMR) bacteria firstly through its Bacterial Priority Pathogens List (BPPL), revised in 2024 and has established three groups of multi-resistant bacteria, according to their priority [4].

1. **Priority 1 Or Critical:** where all are resistant to carbapenems, the so-called broad-spectrum antibiotics, are Acinetobacter baumannii, Pseudomonas aeruginosa, some enterobacteria such as Klebsiella pneumonie, Escherichia Coli.
2. **Priority 2 Or High:** are Enterococcus faecium (vancomycin resistant), Staphylococcus aureus (methicillin and vancomycin resistant), Helicobacter pylori (immune to clarithromycin), Campylobacter spp. and Salmonella (both resistant to fluoroquinolones) and Neisseria

gonorrhoeae (cephalosporin and fluoroquinolone resistant).

3. **Priority 3 Or Medium:** which includes Streptococcus pneumoniae (penicillin-insensitive), Haemophilus influenzae (ampicillin- resistant) and Shigella spp. (fluoroquinolone-immune).

Challenges Encountered

AMR causes an economic threat and major global public health and made the infections harder to treat even with the help of many modern medical treatments.

- The drug-resistant microbes which cause infections are often also known as "Superbugs''. These are unable to respond to advanced treatments which leads to disability chronic illness and death.
- To prevent or treat infections, common medical treatments and procedures such as organ transplantation, surgeries and chemotherapies are become dangerous.
- The treatment to patients like second line treatment which are more costly, more toxic and less effective and few times highly impossible to distribute.

Impact of Higher Doses

- By the administration of higher doses of antibiotics may end up strengthening some bacteria in a time to tackle the problem of growing drug resistance.
- High doses or adequate doses aimed to achieve the concentration of antibiotics which remain above the minimum inhibitory concentration (MIC) required to kill the microorganisms which includes pre-existing subgroup of resistance mutants.

Severe Health Impacts on Humans:

- **Untreatable infections:** Common infections like urinary tract infections, pneumonia, tuberculosis, gonorrhoea, etc impossible to treat.
- **High mortality and morbidity:** Bacterial AMR was directly responsible for an estimated 1.27 million global deaths in 2019 and contributed to 4.95 million deaths without intervention, this could increase to 10 million deaths annually by 20502.
- **Increased risk in vulnerable populations:** The most affected patients are elderly, higher risk to children and immunocompromised patients.
- **Treatment Failure:** Leading to prolonged illness, the need for stronger, disability, more toxic "last resort drugs''.

Risks to Modern Medicine

- **Surgery and procedure:** Hip replacement, organ transplant and cancer are the routine lifesaving `procedures. Chemotherapy becomes remarkably more dangerous, as the ability to avoid and treat post-surgical illness is compromised.
- **Resurgence of disease:** Microorganisms illness that were one time managed may become influential risks reversing decades of medical development.

Diseases Caused by Amr Bacteria

- The bacterium that causes TB
- Vancomycin resistant cocci
- Methicillin Resistant Enterobacteriaceae
- The bacterium that causes Gonorrhoea .
- Carbapenem resistant Enterobacteriaceae

Long-Term Impacts on Amr Pathogens

Pathogens Specific pathogen threats:

- **Gram – Negative bacteria: -** Drugs like carbapenems in bacteria like Klebsiella pneumoniae and Acinetobacter baumannii is a main issue.
- **Drug Resistant Tuberculosis [MDR-TB]: -** Extremely drug-resistant TB[XDR-TB] depart nearly not efficient therapy alternatives.
- **Drug Resistant Fungi: -** The main risk to the immunocompromised patients in the spread of Candida auris.

Socioeconomic impact:

- **Economic loss: -** AMR is predicted to produce global GDP losses of US 1 trillion to US 3.4 trillion per year by 2030.

- **Increased poverty: -** sIn places with extreme away from pocket medical care expenses curing resistant illness could operate families into liability.

Environmental And Food Safety Risks:

- **Contaminated food supply: -** AMR bacteria can be transferred through food web with important farming impacts.
- **Water contamination: -** Raw sewage and pharmaceutical debris can diffuse AMR bacteria into water origins.

Innate Therapy for Antimicrobial Resistance Bacteria (AMR)

A. **Probiotics And Microbiome Therapy:**

- Probiotics and microbiomes combine crucially with AMR bacteria by acting as a natural defence mechanism in which a healthy gut flora (microbiome)limits pathogen growth and decreases the need of antibiotics [8,9]. Meanwhile, Probiotics helps to reimpose balance after antibiotics use, possibly reducing the growth of AMR genes.
- Probiotics apply antimicrobial responses by multiple synergistic process, appear as a promising natural alternative to standard antibiotics while primarily avoids the resistance development.[9]
- Probiotics work as the effective bio-preservatives in food processing applicable antibiotic substitutes in livestock manufacturing and the therapeutic agents for infections of clinical.
- The lactobacillus is the most commonly used in food and supplements as the probiotic genera.
- In genomic architecture, phenotypic traits and functional properties the probiotic strains reveal substantial variety.
- The probiotics are widely introduced into fermented foods (example.: yoghurt, kimchi etc)
- Probiotics increase the gut microbiota physiological activity with the increase in bioavailability of short chain vitamins, amino acids, peptides and fatty acids [1].

The Microbiome and AMR:

1. **Reservoir for ARGs:** The gut microbiomes particularly the dependent bacteria work as the large pool (resistome) of antibiotic resistance genes (ARGs)that pass out the harmful pathogens by horizontal gene transfer (HGT)
2. **Antibiotic disruption:** the particular antibiotics which are having broad spectrum kills the profitable microbes, destroying the microbiomes balance and allows the resistant bacteria

Mechanism Of Action Against Amr Bacteria:

- **Competitive exclusion:** Probiotics strains such as Lactobacillus and bifidobacterium live in niche sites on the intestinal mucosa, stop the adhesion and colonisation of AMR bacteria such as E Coli and Salmonella.
- **Production of Antimicrobial Metabolites:** advantageous bacteria produce substances that stop bacteria growth such as
  a. **Organic acids:** Short -chain fatty acids (SCFAs) like butyrate and propionate decrease intestine pH, which stops the growth of resistance Enterobacteriaceae.
  b. **Bacteriocins:** Ribosomal synthesized peptides, such as nisin, directly kill or inhibit Gram - positive and Gram-negative pathogens by damaging their cell membrane.
  c. **Hydrogen peroxide:** produced by certain probiotics to damage pathogens cell membrane.

Challenges and Considerations:

1. **Probiotic ARGs:** Few probiotic strains themselves transfer ARGs and there's concern they could carry these genes to microorganisms
2. **Strain specificity:** All the probiotics are not same their responses vary and rigorous screening for safety and efficacy.

3. **Holistic approach:** probiotics are the hopeful tool but not a complete solution.

B. **Formulations Against Amr Bacteria**

Formulation and strategies to fight Antimicrobial Resistance (AMR) focus on improving the efficacy to existing drugs, developing antimicrobial agents and using innovative drug delivery system to bypass bacterial defence mechanism.

Advanced Formulation and Stratgies Against AMR

- **Antibiotics Adjuvants:** These are agents that, while having a weak or no antimicrobial activity themselves, enhance the effectiveness of antibiotics by stopping resistance mechanisms. Antibiotics adjuvants are non -antibiotic compound that are enhances the efficacy of existing antibiotics and combat antimicrobial resistance by targeting bacterial defences mechanisms or boosting the host's immune response [11]. This strategy helps prolong the lifespan of existing drugs and is an important approach in the fight against multi-drug resistance (MDR) pathogens. Classes of antibiotics adjuvants:

a) Beta- Lactamase inhibitors:

They are the most successful and clinical used adjuvants. Compounds like clavulanic acid, sulbactum and tazobactum are combined with beta lactam antibiotics to hinder enzymatic inactivation of the drug.

b) Other example include:

Avibactum(with ceftazidime in Avycaz), relebactum (with imipenem/cilastatin), and vaborabactum (with merpenem).

- **Efflux pump inhibitors (EPIs):** Small molecule such as phenylalanine – arginine - beta naphthylamide are used to block pumps that expel antibiotics from the bacterial cell, thereby increasing the intracellular concentration of the antibiotics to effective levels. Examples include: phenylalanine-arginine beta -naphthylamide is a well-studied example in laboratory, but it is not currently in a clinical use due to toxicity concerns. Other potentials EPIs such as specific derivatives, are under investigation.
- **Membrane permeabilizer:** Cationic peptides like polymyxin B are used to disrupt the outer membrane of Grame-negative bacteria, ease drug entry. Examples include: -polymyxin such as cliostin(used as a last -resort antibiotics,but also acys as a permeabilizer) and the less toxic derivative polymyxin B nanopeptides (PMBN) have been explored, though PMBN also showed preclinical toxicity issues.
- **Nanotechnology:** Organised nanoparticles (metals oxide, polymer), improve drug delivery, decrease toxcity, and have basic antimicrobial properties, enhancing vaccines and developing novel diagnostictools loke nano-biosensors. Metal nanoparticles such as Silver, gold, zinc oxide and copper etc nanoparticles are used to impair bacterial membranes and produce oxidative stress [12,13]. They have been specifically inspected for the intrinsic antimicrobial properties and they are importantly used as antimicrobial agents during the last two decades.

- **Lipid-based Carriers:**

Solid lipid nanoparticles can enclose antibiotics to provide endure targeted release at infections sites .lipid carriers act by improving bioavailability, drug stability, and penetration into bacteria biofilms often by imitating cell membranes for targeted fusion and enhanced intracellular delivery these nanocarriers control issues with free antibiotics like deactivation and poor solubility by securing them and detaching high concentrations directly inside bacteria by making treatments more productive. Ex: Liposomes, solid lipid nano particles, nano emulsions.

- **Polymeric Nanoparticles:**

These deliver drugs directly enter into infection sites, improving

Concentration while minimizing side effects. There are two types of nano particles

1. Reservoir system
2. Matrix system

Examples of polymeric nanoparticles: - PLGA [poly lactic co-glycolic acid], natural polymers like chitosan and dextran etc.

- **Combination therapy:**

Combination therapy is termed as using more than one therapy to cure a single disease. Combining many antibiotics that target different pathways in a common strategy specially for treating illness like TB. Multiple drugs act by improving the therapeutic effect and then slows the drug resistance of tumors and decreases the toxicity of drugs. the combination therapy used for the purpose of increasing efficacy.

- **Phage Therapy:**

Using bacteriophages to target particular, resistance bacteria strains. there are two types of phages i.e DNA phage and RNA phage. Phage therapies could offer a substitute to the traditional antibiotics [14].

- **Antibacterial peptides (AMPs):** Organized peptides, such as cationic steroidal antibiotics (CSAs), can quickly depolarize bacterial membrane and work against resistant gram-negative bacteria. AMPs inhibit cell division by reducing DNA replication and DNA damage response by obstruct by obstructing cell division or leading to the chromosome failure.
- **Antivirulence Agents:** Rather than killing bacteria, these agents disable bacterial virulence factors by decreasing their capability to cause disease and making them more susceptible to the immune system. Antivirulence agents operate differently from antibiotics and have distinct benefits. For instance, the development of resistant or tolerance strains may be challenging for this class of drug. Thus, different from traditional antibiotics adjuvants, antivirulence agents may satisfy for the fault of antibiotics and supress S. aureus pathogenicity productively.
- **CRISPR- Cas Systems:**
    a. The CRISPR Cas system [15] prokaryotic immune defence, is being repurposed to combat resistance of antibiotics by precisely targeting and destroying antibiotic resistance genes or plasmids in bacteria.
    b. It is used as a gene editing tool to specifically remove antibiotic genes with bacterial populations.

Targeted Drug Delivery Systems:

- **Smart delivery systems:** These respond to environmental stimuli to release antibiotics only when needed decreasing the risk of resistance. Targeted delivery, stimuli responsive, biofilm disruption are the smart delivery systems against AMR.
    a) Ph sensitive nanoparticles release drugs in the acidic environmen.
    b) Temperature responsive micelles they release the drugs when warmed.
    c) Long-acting formulations such as Implants or adapt release formulations reform sustained drug presence with modifying patient adherence.

Alternative agents:

- **Plant based compounds:** Curcumin and various essential oils are being analysed for their antimicrobial properties and synergistic action with existing antibiotics.
- **Metal based Antimicrobials:** Compounds containing gold, copper and platinum are being evolve as alternatives or adjuvants.

Global and National Strategic Actions

- **One health approach:** The combining framework approved by the WHO, FAO, and UNEP that unifies human, animal, and environmental health sectors to address AMR collectively.
- **National Action Plans:** Countries like INDIA have formulates specific NAP AMR frameworks to monitor antibiotic use and

execute infection control policies at state level.

- **Vaccination programs:** Vaccines are emphasized as a formulation to prevent infections, thereby reducing the overall and slowing the appearance of resistance.

Conclusion:

Antimicrobial resistance (AMR) bacteria describe one of the most serious global public health challenges of the 21st century. The rapid appearance and spread of resistant pathogens have consequentially reduced the effectiveness of existing antibiotics, leading to increased sickness, death rate, prolonged hospital stays, and higher healthcare costs. Factors such as irrational antibiotic use, lack of observance to treatment guidelines, poor infection control practices, and limited growth of new antimicrobials have accelerated this emergency.

This review highlights the complex mechanisms fundamental AMR, involve genetic mutations, horizontal gene transfer, and biofilm organisation, which enable bacteria to exist and adapt in the presence of antimicrobial agents [1,16]. The result of AMR extend beyond human health, affecting veterinary medicine, agriculture, and the environment, thereby underline the link up “One Health” perspective.

To combat AMR bacteria, a multifaceted approach is essential. This includes strengthening antimicrobial management programs, promoting rational drug use, improve infection prevention and control measures, investing in research and evolution of novel antibiotics and preference therapies (such as probiotics, phage therapy, and immunomodulators), and increasing public and professional realization [16]. Coordinated global action, robust surveillance systems, and supportive policies are crucial to limit the spread of resistance.

In conclusion, addressing AMR bacteria requires assist assurance from healthcare professionals, researchers, policymakers, and society at large. Without urgent and collaborative involvement, AMR threatens to undermine decades of medical progress; however, with critical and timely action, its impact can be efficiently controlled and future treatment options preserved.

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