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Novel Strategies for Combating Antimicrobial Resistance: Alternative Agents on the Horizon

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A B S T R A C T

Antimicrobial resistance (AMR) is an escalating worldwide health emergency that jeopardizes our capacity to efficiently combat infectious infections. The escalation of antimicrobial resistance (AMR) can be associated with the boundless and inappropriate utilization of conventional antimicrobial agents. This pressing issue necessitates the exploration of alternative treatment modalities in order to effectively combat drug-resistant bacteria. This abstract focuses on innovative approaches and alternative substances that are now being developed to tackle this pressing matter. We offer a thorough examination of these methodologies, elucidating their modes of operation and prospective benefits, all substantiated by recent research discoveries and clinical observations. Bacteriophages, which are naturally occurring viruses, possess the ability to selectively target and eradicate particular kinds of bacteria, making them very precise antimicrobials. Recent research has demonstrated encouraging outcomes in utilizing phage therapy to address illnesses that are resistant to drugs, highlighting their potential as targeted antimicrobial agents [1]. The antimicrobial peptides, such as LL-37 and nisin, are a class of naturally occurring compounds that have garnered significant attention as possible substitutes to traditional antibiotics. The peptides under investigation display a wide array of effectiveness against various strains of fungi, bacteria, and even drug-resistant microorganisms. In addition, their distinct mechanisms of action reduce the probability of resistance development [2]. The utilization of the CRISPR-Cas9 mechanism has presented novel prospects for the meticulous modification of microbial genomes. This approach facilitates the development of genetically modified variants that exhibit increased vulnerability to conventional antibiotics, hence potentially reinstating its efficacy [3]. Antibiotic adjuvants, such as avibactam, can be employed alongside antibiotics to surmount resistance processes. According to existing research, the implementation of this particular approach has demonstrated the potential to enhance the efficacy of currently available antibiotics in combating drug-resistant bacteria [4]. Nanoparticle-Based Drug Delivery: The utilization of nanoparticles carrying antimicrobial agents can improve the durability of drugs and enhance their ability to specifically target bacteria. This technique shows potential for enhancing the effectiveness of current antibacterial agents [5].

Keywords: Antimicrobial resistance (AMR), Bacteriophage, Combination therapy, CRISPR/Cas, Immunotherapy, Pathogenic microbes.

1. Introduction

In the 21st century, the rapid emergence of antimicrobial resistance (AMR) has become a public health concern significantly, posing an increasing threat to our capacity to inhibit and treat various infections resulting from bacteria, parasites, viruses, and fungi [6]. These once-vulnerable microorganisms have developed an alarming capacity to withstand the very medicines that were once reliable in combating them, casting a pervasive doubt on our healthcare practices [7]. Within the expansive realm of AMR, antibiotic resistance in bacteria is particularly urgent. For many years, bacteria responsible for both common and serious infections have demonstrated a concerning capability to develop resistance to every novel antibiotic introduced to the market. This stark reality necessitates urgent action to prevent an imminent global healthcare crisis, where our primary tools for fighting infections are becoming increasingly ineffective [8]. As of the guidelines provided by the World Health Organization (WHO), AMR is not limited to bacteria alone; it encompasses a broader array of microbial adversaries, including viruses, fungi, and parasites, all gradually evolving to resist the medicines we once depended on [9]. This transformation makes infections more challenging to treat, leading to increased rates of disease transmission, more severe illnesses, and higher mortality rates. Our trusted medicines start to falter, allowing these pathogens to persist within the body and increasing the risk of contagion [10].

To address the increasing challenge of antimicrobial drug resistance, a range of innovative strategies has been suggested, each bringing distinct advantages and challenges. This thorough review investigates the diverse resistance mechanisms employed by pathogenic microbes in humans and introduces new approaches, such as therapeutic strategies involving a combination of treatments, immunotherapy, bacteriophage therapy, and approaches based on CRISPR/Cas are presented as potential solutions against these microbes. These innovative strategies demonstrate significant applications and benefits, aiding in the development of effective drugs and tools to address the arising problem of antimicrobial resistance (AMR). Notably, combination therapy stands out as a promising strategy to extend the effectiveness of drugs and control the spread of infections [11]. Bacteriophage therapy has gained

considerable recognition for its efficacy in treating a variety of multidrug-resistant pathogens [12], [13]. Additionally, immunotherapeutic approaches and CRISPR technologies have surfaced as valuable tools to bolster host defenses, providing crucial support in tackling the rapidly growing challenge of drug resistance posed by opportunistic microbial pathogens [14], [15].

This peer review aims to delve deeply into the intricate web of AMR, shedding light on its far-reaching consequences and the critical strategies needed to mitigate this growing threat to public health.

2. Antimicrobial Resistance

The study of evolution as it occurs in real time is a crucial goal within the realm of biological science. This can be accomplished by conducting experimental investigations on small fish species, like guppies, that experience predator-prey evolution. It's important to remember that the rise in antibiotic resistance (AbR) serves as, prime example of biological entities evolving in real time. Several research studies have emphasized this particular aspect. Enthrallingly, AbR can be perceived as a collective offsetting response by bacteria, aimed at restoring a harmonious equilibrium between the colonized hosts and their surrounding environment. Its behavior demonstrates the remarkable ability of bacteria and their ecological habitats to adapt and survive in the face of the significant release of antimicrobials into the environment by human activities. Various studies have highlighted the resilience of these intricate associations. It is proposed that natural antimicrobial agents primarily function as signals rather than weapons. These signaling molecules operate at extremely low concentrations, and exposure to high levels of signals not only negatively impacts bacterial cells but also disrupts its overall communication system of microbial communities.

It should be emphasized that AbR genes have been present in bacteria since their evolution, but their concentration has been amplified as a result of the release of antibiotics in particular biological environments. To address the impact of AbR during infection treatment, novel approaches in antibiotic usage have been recommended. These approaches involve the utilization of narrow spectrum drugs that specifically target certain pathogens, as well as placing greater emphasis on regulating how an infection affects its host. The goal of these proposed "new paradigms" for antibiotic use is to reduce the negative consequences of AbR [16]. Its main goal of applying source attribution techniques to AMR genes or pathogens resistant to antibiotics is to pinpoint the main origins and routes of human exposure to AMR. The usage of antibiotics in animal production, which acts as a reservoir, is generally acknowledged to have a significant role in zoonotic bacteria developing resistance. Therefore, it's crucial to identify the key reservoirs of human AMR exposure in order to guide policies intended to lower AMR usage at its stage of initial production. Additionally, understanding the pathways through which prioritizing risk management techniques along the food chain is crucial because AMR is spread from reservoirs to humans. Even though there are numerous approaches available for attributing diseases to their original locations of infection or exposure in the case of foodborne pathogens, these techniques have only been used in a small number of studies in the context of AMR. Consequently, the complexity of employing source attribution approaches for AMR is further compounded by the fact that almost any disease can develop resistance to antimicrobials and that the zoonotic infections can be transmitted to humans through numerous foodborne and non-foodborne pathways. Up until now, the majority of source attribution has been concentrated on particular pathogens like E. coli or Salmonella. Coli, and determining the resistance patterns these pathogens exhibit from various sources [17], [18], [19], [20].

Plasmids commonly contain antimicrobial resistance (AMR) genes, which are interchangeable between diverse bacterial species by means of horizontal transfer genes. It means that AMR genes can be passed from harmless bacteria to harmful pathogens, like Klebsiella spp. Consequently, focusing solely on one bacterial species may result in an underestimation of the entire exposure and possible risk associated with AMR. In order to get around this restriction, it is more effective to identify the source of AMR determinants. This requires comprehensive information and data on the prevalence, abundance, and transmission of these genes, as well as the rates of horizontal gene transfer [21].

There are four separate categories into which it falls: active drug efflux, mitigation of the antimicrobial drugs target, drug substance inactivation, and limitation of medication uptake. Intrinsic resistance mechanisms involve changes in drug targets, drug deactivation, and drug efflux. Conversely, attained resistance systems entail alterations in drug targets, drug deactivation, and drug efflux. It is worth noting that gram negative bacteria employ different processes compared to gram positive bacteria as a result of structural differences and other variables. Gram-negative bacteria make use of each of the 4 main mechanisms, while gram positive bacteria exhibit a lower frequency of limiting drug uptake (due to the absence of an LPS outer membrane) and lack certain types of drug efflux mechanisms (as indicated by the presence of drug efflux pumps) [22], [23].

Its widespread abuse and overuse of antimicrobials, particularly antibiotics, exacerbates the global issue of antimicrobial resistance. As a result, there is a significant burden on a global level. Consequently, there is a continuous examination of antibiotic usage and consumption. In addition to the "One Health Approach," which acknowledges the interconnectedness of living organisms and the environment, there is a requirement for a multidisciplinary approach to achieve optimal health outcomes. With regard to the problem of antibiotic resistance, this article review seeks to provide an updated overview of the tactics used by international governmental organizations [24].

3. Antimicrobial Resistance Mechanism

Bacteria can acquire antibiotic resistance through various means, posing a significant public health concern due to the potential for treatment failure in bacterial infections. Mechanisms of resistance of antimicrobials can be categorized into four primary groups: (1) active drug-efflux; (2) altering the target of drug; (3) inactivating the drug; (4) limits the uptake of a drug [25].

3.1 Efflux Pumps

Both antibiotic-susceptible and antibiotic-resistant bacteria have efflux pump genes and proteins [26]. These specialized proteins are embedded in the cell membranes of bacteria and serve as efflux transporters. Efflux was initially discovered as a pathway of tetracycline resistance in Escherichia coli [27]. These proteins transport substances harmful to the cell from the interior to the exterior, and their primary function is to actively expel antimicrobial agents and other toxic compositions from the inside cell of the bacterial into the surrounding condition [28]. Bacteria possess five primary groups of pump efflux, categorized based on their form and usage of energy. Composed of the ATP binding cassette family, multi-antimicrobial extrusion protein, small transport multidrug resistance, the nodulation-cell division resistance superfamily, and major helper superfamily [25]. This expulsion of antibiotics decreases the intracellular drug concentration, rendering it less effective in inhibiting bacterial growth. Efflux pumps may either transport specific substrates or move a range of structurally distinct substances [29]. This phenomenon contributes greatly to the spread of antibiotic resistance, because bacteria that possessactive efflux pumps can sustain life and multiply even if antibiotics are present.

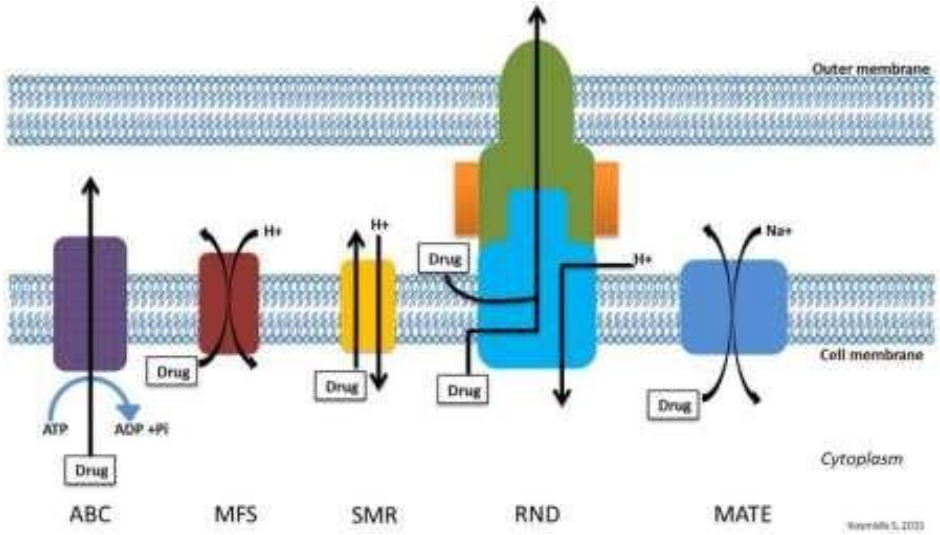

Figure 2. Illustrates the common structure shared among the primary families of efflux pumps, namely the ATP binding cassette, major-facilitator superfamily, small-multidrug resistance, resistance nodulation cell division, and multidrug and toxic compound extrusion. [25]

3.2 Modifying a drug target

In the context of antimicrobial resistance, modifying medication targets involves making alterations to the molecular structure or activity of the particular molecule that the antibiotic is intended to engage with. Changes in target locations are typically produced by natural occurrence of a mutation in a gene on the bacterial chromosome combined with antibiotic selection [30]. Antibiotic binding can be avoided by changing the target through mutation or post-translational modification [31]. Examples of target modifications involving genes coding point mutations in the target site, changes in the enzyme that bind to the site (such as the introduction of methyl compounds), and/or substitution or evasion of the initial target [32]. As a consequence, the antibiotic becomes less effective in inhibiting the growth or killing the microorganism it is meant to target.

Resistance to beta-lactam medications can occur through reconstruction of the form and/or quantity of penicillin binding proteins (PBPs). PBPs, which act as transpeptidases, partake in the cell wall synthesis of peptidoglycan—a process mainly employed by gram-positive bacteria [25]. The quantity of medication that can bind to a target site changes as the number of PBPs changes. PBP changes may include an increase in the number of PBPs with reduced drug binding or a reduction in the quantity of PBPs with regular drug binding [33]. This resistance mechanism frequently emerges due to the direct pressure imposed by the persistent antibiotics use. This selective pressure favors the survival and multiplication of microorganisms that have developed altered drug targets, reducing their susceptibility to the drug's effects. The continuous and widespread use of antibiotics is a crucial prerequisite for the rise of multidrug-resistant bacteria [34].

3.3 Inactivating a drug

One highly effective defense mechanism employed by bacteria in anticipation of antimicrobial agents in the making of enzymes. These enzymes can either deactivate the drug by attaching specific chemical groups to it or break down the antibiotic fragments itself, making it inadequate to react with its intended target [35]. Genes that are resistant are responsible for encoding enzymes that chemically alter an antibiotic, or can make antimicrobial hydrolyze, rendering it ineffective [36].

For example, bacteria may develop enzymes that can degrade or cleave the drug molecule, making it no longer capable of binding to its target within the microorganism. Pathogenic bacteria develop resistance to antibiotics in the aminoglycoside, beta-lactam (including penicillin and cephalosporins), and chloramphenicol classes through mechanisms such as enzymatic inactivation. This involves either hydrolysis of the antibiotic or the production of inactive derivatives [37]. As a result, the drug loses its potency, and the microorganism can continue to thrive despite the treatment. One of the most significant difficulties in antibiotic resistance is medication inactivation, as it diminishes the efficacy of existing treatments and necessitates the development of new drugs or combination therapies that are less susceptible to inactivation mechanisms.

3.4 Limiting the uptake of a drug

Bacteria have evolved tactics to hinder the absorption of antimicrobial fragments, preventing them from reaching their intracellular or periplasmic targets [35]. It involves the microorganism, often a bacterium, developing mechanisms to reduce the entry of the drug into its cells, thus decreasing the drug's effectiveness. This can occur through modifications in the bacterial cell membrane or transport proteins, leading to reduced drug penetration and allowing the microorganism to evade the drug's inhibitory or lethal effects. The structure and function of the cell wall layers containing lipopolysaccharides (LPS) serve as a barrier, preventing certain chemicals from penetrating gram-negative bacteria [33]. As a result, these bacteria exhibit intrinsic resistance to particular antimicrobial agent families [38]. Mycobacteria possess an outer membrane with a significant lipid content, enabling the movement of hydrophobic medications like rifampicin and fluoroquinolones to enter cells more effectively. Conversely, hydrophilic drugs face limitations in accessing the cells [39], [40].

Bacteria with thick outer cell walls frequently enable chemicals to pass via the channels of the porin cell [33]. Porin channels of the gram-negative microorganisms often enable access to hydrophilic substances [38]. Modifications in porins can diminish drug absorption through two mechanisms: a reduction of the quantity of porins and alterations in the selectivity of the porin channel. This is primarily caused by mutations influencing the structure or charge of the porin channel [39]. This resistance strategy hampers the drug's ability to reach its target inside the microorganism, making it less efficient in treating infections.

4. Old/Usual Strategies in Combating Antimicrobial Resistance

4.1 Antimicrobial Stewardship

Antimicrobial stewardship (AMS) is described as "an organizational or healthcare-system-wide approach to encouraging and monitoring the prudent use of antimicrobials to preserve their effectiveness" [41]. In 2007, the Infectious Diseases Society of America (IDSA) presented an overview of AMS for the first time. It was once described as planned interpositions meant to improve the use of antibiotics by choosing the most appropriate drugs, dosages, delivery methods, and treatment durations without endangering patient outcomes [42]. Antimicrobial stewardship (AMS) is a healthcare method that promotes, develops, monitors, and evaluates antimicrobial stewardship to protect future efficacy and promote and maintain public health [43].

Antibiotic stewardship is an essential component in combating Antimicrobial Resistance (AMR). Encouraging the prudent use of antibiotics reduces bacteria's exposure to these medications [44]. This reduces the likelihood of their establishing resistance mechanisms, impeding their capacity to spread

and prosper. Appropriate antibiotic administration results in more tailored therapy, improving efficacy while reducing unwanted side effects [45]. This results in speedier healing times for individuals and less strain on healthcare systems. Antibiotics with a broad spectrum of action frequently upset the delicate balance of good and harmful bacteria in our gut and other mucosal surfaces [46]. Stewardship activities aid in preserving this natural defensive mechanism, decreasing susceptibility to infections and improving general health. However, it is critical to recognize that while antibiotic stewardship is vital, it is not a solution. To effectively tackle AMR, we need a multifaceted approach that involves investing in new antibiotic research and development and alternative medicines [47]. Strategies for preventing and controlling infections in hospital settings and beyond are being strengthened, and environmental and agricultural issues that lead to the spread of resistance are being addressed. Patients for viral illnesses frequently request antibiotics, while doctors may prescribe them to prevent missing a bacterial diagnosis [48].

Many people are unaware of the consequences of antibiotic abuse and misuse, and even healthcare professionals may require ongoing training. Financial incentives for healthcare practitioners or restricted access to diagnostics may lead to overprescribing in particular contexts. There needs to be more than stewardship alone to solve the complicated problem of AMR. It is primarily concerned with human behavior and healthcare settings, failing to address broader environmental and agricultural issues [49]. While it can decrease the formation of resistance, it cannot reverse it, especially for already resistant bacteria [50]. It depends on the availability of effective antibiotics, which is becoming increasingly constrained as development pipelines dwindle. To summarize, while antibiotic stewardship remains an essential tool in the battle against AMR, it is critical to recognize its limits and include it within a holistic strategy that addresses the problem from many perspectives. We can only hope to control and minimize the rising issue of antimicrobial resistance successfully if we work together.

5. Novel Strategies to Combat the Emerging Antimicrobial Drug Resistance

5.1 Bacteriophage Therapy

Comparatively speaking, bacteriophages are based on natural selection, environmentally safe, and quickly isolate and identify bacteria. This is in contrast to the development of innovative drugs. It might be cost-effective, take years, and need millions of dollars in clinical trials [51]. Bacteriophage injection was suggested as a preventive and therapeutic measure for bacterial illnesses before identifying and generally using antibiotics. Phage use continued across the former Soviet Union and Eastern Europe, even though early therapeutic investigations using bacteriophages were not actively explored in the United States and Western Europe [52]. However, because the biology of bacteriophage was little known, the early trials of bacteriophage treatment for infectious disorders were complicated. The preliminary research examined here suggests solid grounds for anticipating that phage treatment may benefit some situations. Until recently, there were no thorough reviews of phage treatment due to the development of antibiotics and the "Soviet taint" it acquired during the postwar period [53].

Phage therapy, sometimes called using bacteriophages (phages) to cure bacterial illnesses, has a much older history than antibiotics. However, antibiotics have been the preferred form of treatment in the West for more than 60 years due to their effectiveness, low toxicity, and simplicity of manufacture. Antibiotic-resistant bacteria are emerging, while research efforts to find new treatments have significantly decreased. Over billions of years, phages and their hosts co-evolved, creating defense mechanisms against bacterial defenses such as extracellular biofilm development, considerably lowering conventional antibiotics' effectiveness. Current research on humans and animals indicates that phages are safe, well-tolerated agents that may one day replace chemical agents [54]. Recently, there has been a resurgence of interest in bacteriophages due to the increasing occurrence of fatal bacterial infections and antibiotic resistance. Despite these initiatives, bacteriophage treatment still needs to be widely used in Western medicine due to several obstacles, including delivery problems, bacterial lysis side effects, host range limitations, bacterial resistance to phages, and regulatory limits [55].

Though phage treatment has been extensively studied, the pharmacokinetics of therapeutic phage formulations have been covered in relatively few papers. The limited literature on the subject states that phages reach the bloodstreams of experimental animals (after a single oral dosage) between two and four hours after exposure, and ten hours later, they originate in their internal organs (such as the liver, spleen, kidney, etc.) [56,57]. Based on information regarding the presence of injected phages, it has been observed that phages can remain in the human body for prolonged durations, ranging up to several days [58].

According to the stakeholders who attended, and given the number of instances that have been reported, phage therapy is a good treatment choice for a number of bacterial illnesses, whether or not they are multi-resistant. Phages are now utilized in complicated cases for patients who have reached the end of their treatment, and they are always used in conjunction with antibiotic therapy due to a lack of RCT evidence. [59]. However, the applications are numerous, and it is absolutely possible that they may be employed instead of antibiotics in some circumstances. As a consequence, by lowering antibiotic use, they will be able to manage while limiting the emergence of new ones [60]. However, as we have demonstrated, phages are framed, classed, and categorized like chemical compounds. Building upon Chandler's perspective, our aim was to illustrate that antibiotics can be considered an epistemological framework that hinders the progress of phage therapy. This hindrance is attributed to predefined concepts and limitations related to treatment and cure, where eradications serve as the fundamental reference point [61]. Hannah Landecker describes how the invention of antibiotics, followed by their manufacturing and widespread use, has played a role in altering the biological characteristics of bacteria. "The bacteria of today are not the bacteria of yesterday, whether that change is registered culturally, genetically, physiologically, ecologically or medically" [62]. The denial of the capacity of living organisms to act and respond is evident. Phages, owing to their extensive co-evolutionary relationship with bacteria, stand out as a valuable resource. However, when integrated into other anti-infective categories composed of chemical compounds rather than living entities, it results in the objectification of living beings. This process substantially diminishes the recognition of their inherent agency [63]. The current constraints on incorporating phages into commercial pharmaceutical products effectively lead to the commodification of living entities and a form of imposed scaling,

a situation in which phages exhibit resistance. Nevertheless, the obstacles presented by this commercialization are not impossible to overcome [64]. Subsequently, phages would be converted into antibiotics, providing physicians with a "product" that only partially aligns with the standards and practices adhered to by the infectiologists we have encountered. These doctors possess a more dynamic and ecological comprehension of infection [65].

5.2 Combinatorial Therapy Approach

Consistent evidence affirms that the effectiveness of antimicrobial agents is improved through the combination of therapies. To address the escalation of drug resistance, it is crucial to carefully assess the utilization of drug combinations. The increasing occurrence of serious illnesses caused by multi-drug resistant bacterial strains emphasizes the insufficiency of single-agent treatments for such conditions. This underscores the growing significance of implementing combination therapies [66] [67].

As an example, a prevalent treatment approach for Gram-negative diseases resistant to multiple drugs includes pairing the nephrotoxic drug colistin with another antibiotic [68]. However, in the context of treating M. tuberculosis infections, the standard practice is exclusively employing combination therapy, typically involving the concurrent use of approximately four conventional drugs. Antibiotic combination therapy is commonly divided into three primary groups: a) Addressing distinct pathways, as exemplified by the combination of isoniazid (an enoyl reductase inhibitor), rifampicin (a compound that inhibits RNA polymerase), ethambutol (a substance that inhibits arabinosyl transferase), and pyrazinamide in the treatment of M. tuberculosis. b) Concentrating on the same pathway is exemplified by the combination of sulfamethoxazole and trimethoprim, both acting as inhibitors of the folic acid biosynthetic pathway. c) Targeting the same target but utilizing distinct methods, such as the use of streptogramins [69] [70].

Employing a combinatorial approach enables the merging of two or more compounds in a manner where one substance enhances the efficacy of another (such as an antibiotic) through synergy, affecting the entire resistance or defense system. [71]. Utilizing combination therapy presents a more beneficial strategy to extend the effectiveness of current antifungal agents. The combined action of two agents produces a more potent toxic effect, reduces pathogenic growth, and consequently diminishes the likelihood of the emergence of pathogenic variations [71] [72] [73].

Recently, the screening process involved identifying potent drug combinations with optimal inhibitory effects against various pathogenic fungi by utilizing a diverse array of compounds [74]. For example, roughly 3,600 bioactive compounds underwent evaluation for their respective synergistic effects with six different antifungals across diverse fungal species. As a result of this screening, approximately 1,550 combinations were identified, effectively inhibiting fungal growth under at least one specific set of conditions [73]. Likewise, analyzing an additional 1,280 active compounds revealed a strong synergy between echinocandins and diethylenetriaminepentaacetic acid. This combination effectively tackles echinocandin-resistant C. albicans strains, demonstrating its efficacy in both laboratory settings and a live mouse model of candidiasis [74].

In tuberculosis treatment, the effectiveness of combining multiple drugs is evident. Initially, in 1948, patients with tuberculosis (TB) were treated with streptomycin alone, showing initial improvements but leading to eventual fatalities due to the emergence of streptomycin-resistant TB [75], [76]. The British Medical Research Council played a pivotal role in establishing documented antibiotic combination therapy for TB by combining streptomycin with para-amino salicylic acid. This approach not only resulted in patient recoveries but also impeded the development of resistance. After conducting numerous randomized controlled trials (RCTs), a regimen consisting of four drugs was developed [75], and the current recommendation from the World Health Organization (WHO) is a 6–9-month combination therapy for tuberculosis (TB) [77]. These medications act on distinct metabolic pathways: isoniazid inhibits fatty acid synthase, resulting in the production of harmful free radicals [78]; rifampicin interferes with RNA polymerase [79]; ethambutol hinders arabinosyl transferase, crucial for cell wall synthesis [80]; and pyrazinamide focuses on persistent TB bacilli [81]. In spite of the extensive application of combination therapy, resistance to TB has arisen, probably because of inadequate compliance with challenging and expensive treatment protocols [75], [76], [81], [82]. To tackle this issue, there is a need to innovate and create novel medications and combinations with the aim of reducing the duration of the 6–9-month chemotherapy regimen, thereby enhancing disease control more effectively [75], [76], [83].

5.3 CRISPR/Cas

Genome editing refers to the precise manipulation of genomic DNA at a targeted location within various cellular and organismal contexts. The process under consideration involves the manipulation of DNA through various techniques such as introduction, removal, or substitution. The actions mentioned have the capacity to deactivate specific genes, enable the acquisition of new genetic traits, and correct harmful gene mutations [84], [85], [86]. The CRISPR/Cas system, acronym for Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated proteins, is a revolutionary gene and is also a cutting-edge technique for modifying genomes, originating from the inherent defense systems of bacteria and archaea [87]. The Cas9 protein, a molecular cutting tool, is employed by scientists in tandem with a guide RNA molecule to achieve accurate modifications to the DNA of various animal species. The guide RNA assumes a pivotal function in facilitating the accurate localization of the Cas9 enzyme to the precise genomic locus necessitating alteration.

The CRISPR-Cas system represents an intrinsic immune mechanism that is widely distributed among bacteria and archaea, serving as a defense against phages, viruses, and exogenous genetic elements [88], [89]. A set of CRISPR repeat-spacer arrays will be included in the CRISPR system, which possess the capacity to undergo transcription into two discrete RNA molecules: CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA) represent the two distinct RNA types. Additionally, it should be noted that the system under consideration consists of a collection of CRISPR-associated (cas) genes, which are responsible for encoding Cas proteins that exhibit endonuclease activity [90]. By employing the Cas9 enzyme to introduce double-strand

breaks in DNA at specific spots, the CRISPR/Cas9 approach has been established to enable precise modification of genes. This has been accomplished through the utilization of technology, thereby leading to modifications in the genetic sequence [91].

Within the realm of molecular biology, the exploitation of CRISPR-Cas systems has garnered a large amount of attention and is now the technology that is most often used for genome editing. This surge in popularity can be attributed to the groundbreaking discovery of their genome editing potential in 2012 [92]. Significant advancements have been achieved in the field of rectifying deleterious mutations, determining which genes are essential for immunotherapy against cancer, and tackling significant challenges in organ xenotransplantation [93], [94], [95]. Regrettably, additional constraints persist within CRISPR-Cas systems that necessitate further investigation and resolution. Several factors contribute to the challenges associated with genome editing techniques. One such factor is the potential for off-target effects, which refers to unintended modifications in regions of the genome that were not intended to be targeted. Additionally, the range of genome targeting is constrained as a result of the existence of sequences that constitute the protospacer adjacent motif (PAM), which restrict the sites where editing can occur. Moreover, the effectiveness and precision of genome editing techniques are relatively limited, as emphasized in earlier research [96], [97].

5.4 Microbiome-based Therapies

The investigation and exploration of microbiome-based therapies represent a burgeoning area of scholarly investigation and medical exploration. These therapies seek to leverage the complex assemblage of microorganisms that inhabit the human body, both internally and externally, with the objective of promoting overall health and ameliorating various disorders. Fecal Microbiota Transplantation (FMT) has been widely recognized as a method that is very effective in the treatment of recurrent C. difficile infection (the acronym CDI). The procedure entails the transfer of fecal matter from a donor who possesses good health to the recipient patient [98]. The objective of this therapeutic intervention is to reinstate a harmonious and robust microbiome in individuals exhibiting perturbed microbial ecosystems.

Probiotics, which are classified as living microorganisms, have the potential to bestow positive health effects upon individuals when ingested in adequate quantities. There has been a substantial amount of research carried out in order to investigate the potential beneficial effects that the topic may have on the microbiome, as documented in reference [99]. Prebiotics, on the other hand, are non-digestible fibers that have the capacity to encourage the growth and activity of beneficial microbes within the gastrointestinal tract. This quality makes prebiotics an important component of a healthy diet. When it comes to ensuring that probiotics are able to perform their functions, these chemicals are quite important [100]. Postbiotics, a term used to describe the bioactive compounds produced by probiotics through the process of fermentation, have been found to exhibit beneficial effects on human health [101]. These postbiotics include short-chain fatty acids, among other bioactive chemicals.

The advancement in microbiome-centered therapeutics has also encompassed the development of antibiotics that selectively focus on the microbiota, aiming to eradicate harmful bacteria while safeguarding the advantageous microbiome [102]. Engineered bacteriophages, which are viruses that have been deliberately developed to target and kill bacteria, offer a very precise and targeted technique for the elimination of dangerous infections [103]. The present approach exhibits promising potential in mitigating disruptions to the microbiota induced by antibiotic therapy.

In addition to infectious disorders, recognizing that the microbiome has a significant impact on a variety of aspects of human health is an important point to bring up. There is evidence to imply that the microbiome plays a substantial role in modifying the body's response to cancer treatment, as indicated by the research that has been conducted up until this point [104]. In addition, ongoing investigations by researchers are focused on the exploration of personalized microbiome therapeutics. This emerging field aims to tailor interventions based on an individual's unique microbiome composition, with the ultimate goal of maximizing therapeutic efficacy [105].

The burgeoning body of research indicates that the impact of the microbiome extends beyond the realm of physical health, encompassing a significant influence on mental well-being. A number of recent studies have been conducted to investigate the complex relationship that exists between the gastrointestinal tract and the central nervous system, alongside the profound impact exerted by the microbiome on mental well-being, have unveiled promising avenues for novel therapeutic interventions [106]. Furthermore, it has been established that there is a strong association between the microbiome and metabolic disorders such as obesity and diabetes. This suggests that by manipulating the microbiome, novel approaches for managing and controlling these conditions could potentially be developed [107].

5.5 Immuno-therapeutic Approaches

For almost two centuries, active immunotherapeutic techniques have been at the forefront of attempts to avoid infectious illnesses that plague humanity. Ten percent of fatalities in Europe throughout the eighteenth century were caused by smallpox. But Edward Jenner employed cowpox vaccination in 1796 to create smallpox protection. 180 years after these efforts began, the smallpox virus was eradicated. Using an analogous approach incorporating dead or attenuated microorganisms, effective vaccinations were created for acute self-limiting infectious agents such as cholera, plague, poliomyelitis, mumps, rabies, typhoid, varicella, mumps, hepatitis B, and the toxins of tetanus and diphtheria [108].

Tuberculosis (TB) is an alarming contagious illness primarily triggered by the Mycobacterium tuberculosis (Mtb) that infects the host. According to WHO report in 2021, it has been projected that there will be an approximate count of 10.9 million fresh instances and 1.28 million fatalities in the year 2020. Although there are available treatment regimens and antibiotics that prove to be effective, chemotherapy is accompanied by several unavoidable negative consequences. These include a lengthy treatment duration, severe adverse effects, challenges in patient compliance, and the emergence of multidrug resistance [109].

The interplay of innate and adaptive immune cells during the response to tuberculosis (TB) is shaped by a combination of environmental factors and the host's genetic composition. The initial stages of TB infection rely heavily on a strong innate immune response for the elimination of Mycobacterium tuberculosis. The initial barrier against pathogens involves a diverse array of immune cells, including γδ T cells, neutrophils, natural killer cells, dendritic cells, macrophages, and other phagocytes. Of these, macrophages are particularly significant in their ability to hinder the proliferation and dissemination of Mtb [110].

Mycobacterium tuberculosis primarily thrives and reproduces within the host's innate immune cells, specifically alveolar macrophages. The interaction between Mtb and the immune system results in a dynamic process. At the onset, when the invasion of mycobacterium tuberculosis is less than the defensive reaction of the host, alveolar macrophages effectively eliminate this and eradicate the bacterium [111], [112]. Following subsequent encounters with Mtb, macrophages, natural killer cells, and other intrinsic resistant cell culture can develop a phenomenon known as "trained immunity." This phenomenon results in a more rapid and powerful immunological defense [113]. In cases where the invasiveness of mycobacterium tuberculosis exceeds the host's immune capabilities, the bacterium can replicate within granulomas and potentially undergo caseous necrosis, liquefaction, and cavitation. These processes may contribute to the dissemination of mycobacterium tuberculosis and the onset of progressive tuberculosis [114]. When the invasiveness of mycobacterium tuberculosis is in equilibrium with the immune response of the host, the bacterium has the ability to enter a dormant phase, thereby avoiding immune detection and establishing a mutually beneficial relationship with the host [115], [116].

MV, which is derived from inactivated M. vaccae, serves as an immunomodulatory agent that is used as an adjuvant therapy for active TB. In a mouse model, the MV vaccine demonstrated efficacy in safeguarding against pulmonary Mycobacterium tuberculosis (Mtb) infection within the lungs [117]. A comprehensive scrutiny has revealed that MV can effectively enhance the rate of sputum bacteria-negative outcomes. However, the impact on lesion absorption, cavity closure, and mortality has shown inconsistency, which could potentially be attributed to variations in the recurrence and hiatus of MV administration. Accordingly, it is crucial to arbitrate the optimal drug delivery regimen and evaluate the deep-rooted repercussion of MV [118]. In 2013, a phase 3, a double-blind, randomized clinical trial investigating the LTBI regimen with MV revealed a promising trend of reduced TB prevalence accompanied by minimal adverse effects. Nevertheless, the data from the accomplished phase 3 trial have not been made publicly available [119]. Another phase 2 trial demonstrated significant elimination of Mtb in sputum smears after a month of medication with an MV (V7) pill in TB patients. However, further observation is necessary to assess the long-term effects [120], [121].

TB subunit vaccines, derived from specific components of Mtb, can serve as effective adjuvant therapy for TB patients and as a preventive measure for individuals with LTBI. Among the immunotherapeutic vaccines available, Bacillus Calmette-Guerin, polysaccharide nucleic acid injection (BCG-PSN, with the trade name SIQIKANG) holds the sole license for TB treatment (Approval No: S20020019). However, its usage has predominantly shifted towards non-TB weak immune system conditions in recent years [122], [123]. Additionally, four other recombinant protein vaccines which are the Mtb72f/AS01, H56/IC31, ID93/GLA-SE, and AEC/BC02 are currently undergoing phases 1 and 2 clinical trials.

The vaccine candidate Mtb72f/AS01E is created by incorporating a recombinant chimeric protein (M72), which is a combination of Mtb39 and Mtb32. Used to enhance resistance reaction, it is adjuvanted with AS01E [124], Phase 1/2a clinical trials demonstrated that Mtb72f/AS01E was well tolerated and induced robust humoral immune responses and CD4+ T cell responses specific to M72. However, the vaccine showed weaker CD8+ T cell responses. These findings were reported in two separate clinical trials with the identifiers NCT00730795 and NCT00397943 [125], [126], [127]. Furthermore, subsequent phase 2 b clinical trials, identified by the identifier NCT01755598, revealed that Mtb72f/AS01E provided 54% protection against HIV-negative LTBI adults, resulting in a reduced incidence of PTB [128], [129].

The National Research Council has advocated for immune boosting strategies as a non-conventional approach to combat antimicrobial resistance. These strategies focus on enhancing the clearance of pathogens by targeting antimicrobial pathways within the immune system, rather than individual species of microbes. While immune boosting agents may not match the antimicrobial efficacy of antibiotics, they can work in synergy with antibiotics to improve the outcomes of difficult-to-treat infections. However, there are several challenges associated with immune-based strategies that may render them unsuitable for clinical use [130]. The effectiveness of these strategies heavily relies on the state of the host's immune system, making them dependent on factors such as the availability of neutrophils for recruitment in patients undergoing chemotherapy. Additionally, excessive inflammation induced by immune stimulation could lead to immunopathology that is more severe than the infection itself [130]. Furthermore, pathogens have the potential to develop resistance to the immune pathway and the reagents used, resulting in a compromised immune response against the pathogen. These limitations, along with factors like cost, favorable pharmacokinetics, and stability, further restrict the number of immune boosting agents that can be effectively used in clinical settings [130].

6. Discussion

Antibiotic resistance, or antimicrobial resistance (AMR) to put it more broadly, is still evolving and spreading unchecked [131]. It is the ability of microorganisms, including bacteria, viruses, fungi, and parasites, to resist the effects of treatment. If left unchecked, it is predicted to be a worldwide health issue that results in 10 million fatalities by 2050 [132]. While AMR can happen on its own, improper usage and abuse of antibiotics and other antimicrobial medications speed up the process. Agriculture, animals, and people may all experience this [133]. The World Health Organization (WHO) states that AMR is not just a bacterial-only problem. It includes a greater range of microbial adversaries, like fungus, viruses, and parasites, which all eventually learn to resist the drugs that humans once depended on [134]. Microorganisms that cause disease in humans are known as pathogenic microbes.

Bacteria, viruses, fungus, and parasites are all examples of pathogens. Pathogenic bacteria have developed a number of strategies to avoid detection by the immune system and cause illness. These pathways can also render them resistant to anti-infective medications [135]. Pathogenic microbes can acquire

medication resistance through a number of processes, including enzyme modification, which occurs when a bacterium produces enzymes that break down pharmaceuticals before they reach their target site. Some bacteria, for example, create enzymes that break down beta-lactam medicines like penicillin [136]. Second, this bacterium has the ability to modify the target site of a medicine, rendering it less effective. Some bacteria, for example, modify penicillin-binding proteins, making them less vulnerable to penicillin [137].

There are four main ways that drugs become resistant: drug inactivation, drug target modification, drug uptake restriction, and drug active efflux [138]. As opposed to earlier periods, efficient and motivating institutions such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have taken the lead in organizing multiple measures to assess the risk, pinpoint the contributing factors, and proficiently handle this worldwide issue [139]. Alternative therapeutic modalities are desperately needed to address the AMR crisis. It is evident that pathogen-oriented therapy (POT) is emerging as a viable antibiotic resistance countermeasure. POT is predicated on using antimicrobial materials or agents. These strategies try to get around bacterial resistance to antibiotics by directly applying antimicrobial compounds or materials to specific bacterial species, strains, or infected sites [140]. It is more important than ever to continue developing antibiotics because of the rise of drug-resistant bacteria [141]. Preventing serious drug-resistant bacterial infections requires the development of alternative therapeutic approaches or the use of new antibiotics [142]. Its overall impact of innovative medicines in the fight against AMR is positive, although there are complexity and ongoing research requirements. Novel medicines provide new ways to combat microorganisms that are resistant to standard antibiotics [143].

This is critical since AMR is spreading and endangering the effectiveness of modern medicine. Some innovative medicines, such as phage therapy and monoclonal antibodies, target the troublesome germs selectively, limiting injury to healthy cells and perhaps lowering adverse effects [144]. The emergence of AMR has rekindled interest and funding in antimicrobial research, resulting in a broad pipeline of innovative medicines in the works. Many innovative medications are still in early clinical trials or pre-clinical research, implying that mainstream adoption will take years [145]. Access to current solutions may also be limited owing to financial and legal barriers. While innovative medicines are promising, they may not be uniformly effective against all resistant microorganisms. Furthermore, bacteria may acquire resistance to these novel techniques, demanding continual innovation. For the safe and responsible development and deployment of innovative medicines, clear regulatory processes and criteria are required [146]. The impact of innovative medicines in the fight against AMR is positive, offering much-needed optimism in the face of a growing worldwide danger. Continuous research, development, and appropriate implementation, on the other hand, are required to optimize their potential and provide equal access to these life-saving measures.

7. Conclusion

7.1 Conclusion and Future Perspectives

In conclusion, the battle against antimicrobial resistance (AMR) is a complex and urgent challenge that requires innovative solutions and concerted efforts. The novel strategies and alternative agents discussed in this paper provide hope for addressing this global health crisis. As we look to the future, interdisciplinary collaboration, robust regulation, and vigilant surveillance are essential components of our strategy. Education and awareness play a critical role in promoting responsible antibiotic use and garnering support for research in this field. Combination therapies, economic incentives, and global cooperation are all integral to the fight against AMR. By collectively embracing these principles and focusing on the development and implementation of these novel strategies, we can make significant progress in preserving the effectiveness of antimicrobial agents and safeguarding public health against the growing threat of antimicrobial resistance.

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