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A MINI REVIEW ON NON-ANTIBIOTIC THERAPIES TO TARGET EMERGING ANTIMICROBIAL RESISTANCE DURING POST COVID ERA

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AUTHORS' CONTRIBUTIONS

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ABSTRACT

Antibiotics considered as miracle drugs and as one of the most demanding life-saving discoveries of the twentieth century have now imposed a threat to society due to its overuse and misuse. Antimicrobial resistance (AMR) is a growing global problem to which the current COVID-19 pandemic may fuel further. The high number of patients suffering from Covid-19 worldwide have been reported to suffer further from secondary microbial infections. This has become a challenge for the medical community. Hence, various non-antibiotic strategies have been sought after and their mechanisms have been evaluated to mitigate the rise of AMR. This review gives an overview of the success of the alternate methods to combat AMR.

Keywords: Antibiotic resistance; COVID 19; phytotherapy; phage therapy; CRISPR.

1. INTRODUCTION

The World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic in March 2020 [1]. Majority of patients affected with Coronavirus (COVID-19) worldwide are indeed most vulnerable for secondary infections. The advent of COVID-19 has seen an increase in microbial infections as secondary infections, which witnessed an increase in antimicrobial resistance (AMR) [2,3]. World Health Organization has reported that human deaths caused by drug-resistant microorganisms could rise from approximately 700,000 per year to 10 million per year by 2050 [4]. The increased antibiotic administration during covid outbreak has added to the burden of AMR. However, the emergence of antimicrobial resistance may be attributed to high rates of inappropriate antimicrobial prescribing, misuse of biocides and the interruption of treatment for other conditions. Increased use of antibiotics has led to the emergence and dissemination of antimicrobial resistance (AMR), which is a major global health challenge. One of the main recommendations to combat the AMR is to minimise the use of antibiotics, which is a part antimicrobial stewardship programs [5]. Failure of currently available antibiotics to treat some infections is worrying biomedical problem [6,7]. The World Health Organization has stressed the significance of integrating antimicrobial stewardship measures with COVID-19 response of the healthcare system.

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1.1 Factors Favouring the Emergence of Antimicrobial Resistance

The success of antibiotics is governed by several factors including, bacterial genetics, mutation rate, capacity to form biofilm, inoculum size, antimicrobial concentrations, host factors and its interplay with gut micro-biota. Overuse and misuse of antibiotics and self- medication also favour the emergence of bacteria resistant to drugs.

Antibiotic treatments are mostly applied as prophylaxis to prevent further bacterial co-infections among hospitalized patients. Antibiotic resistance is not the only prevalent problem. Another undesirable effect of the use of antibiotics in patients may be alterations in the gastrointestinal tract (GIT) microbiota. Moreover, disturbances in the GIT microbiota may facilitate worse outcomes in patients with COVID-19. Interestingly, there are reports that COVID-19 patients with gastrointestinal (GI) complications experience greater respiratory distress compared to COVID-19 patients without GI symptoms [8,9].

1.2 Use of Hand Sanitizers and Disinfectants

The use of hand sanitizers and disinfectants frequently during covid infection exposes the user to pharmaceutical and non-pharmaceutical agents at varying frequencies, concentrations, and doses [10]. Most available sanitizers contain phenol and hydrogen peroxides, that induce microbial DNA damage [11-13].

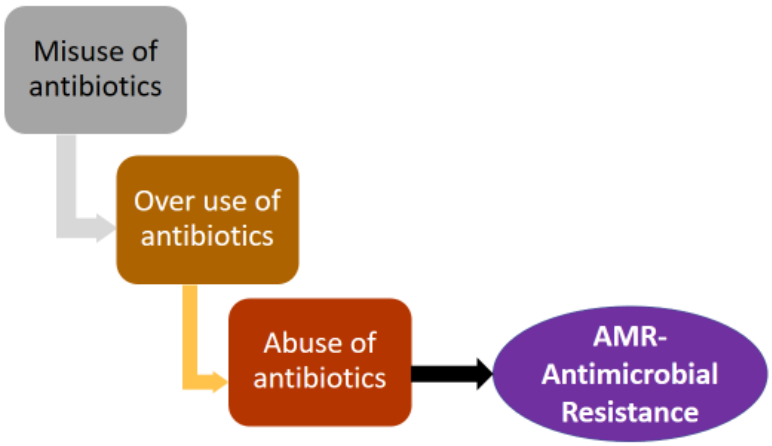

Fig. 1. Factors leading to Antibiotic Resistance

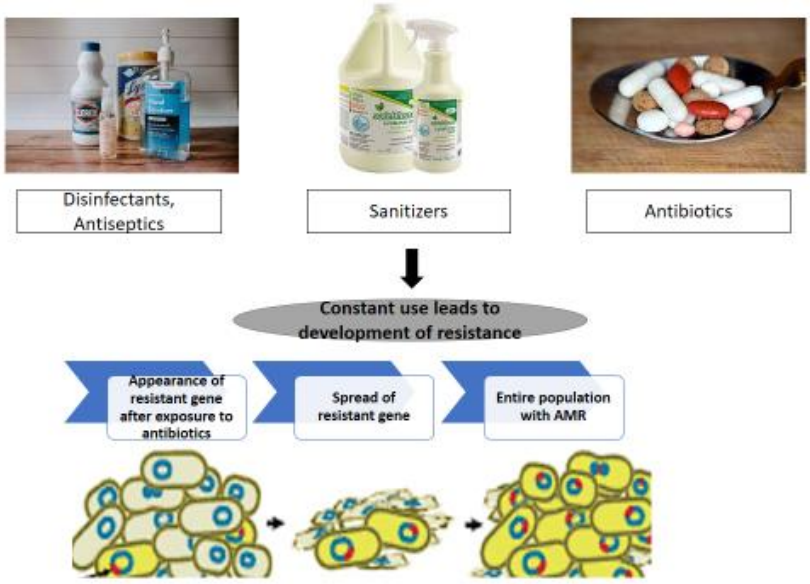

Fig. 2. Mechanism of spread of Antibiotic resistance gene

1.3 Mechanisms of Antibiotic Resistance

The main mechanisms of antibiotic resistance are alteration in membrane components leading to reduced permeability of the cell membrane, modification in cell wall proteins as the common antibiotic targets, inhibiting or limiting uptake of a drug, bypassing the pathway (compensatory tack) inhibited by a drug, degrading and inactivation of a drug by modification/ degradation enzymes, and pumping out of a drug by various types of active efflux pumps [14].

2. NON-ANTIBIOTIC THERAPIES TO TARGET AMR

Appropriate, alternatives to antibiotics need to be considered to address the problem of AMR. There are several non-antibiotic approaches to treat and prevent various infections, including probiotics, phages and phytomedicines [15].

2.1 Probiotics and Prebiotics

Probiotics have been in use as an alternative therapy for the treatment of several intestinal infections such as gastroenteritis and antibiotic-associated diarrhoea. Probiotics exhibit a beneficial effect on the on the digestive and other systems by conferring resistance to infection or eliminating infectious agents. Several bacterial species and yeasts have been used as probiotics [16].

Prebiotics. They are non- absorbable polysaccharides (like inulin and fructo-oligosaccharides) that exhibit health benefits in host by stimulating biodiversity of human gut microbiome. Studies have reported that administration prebiotics by patients with antibiotics-associated diarrhoea has proven effective.

2.2 Bacteriophages as Antimicrobial Agents

Bacteriophage therapy is one where phages are used to lyse bacterial pathogens. There has been renewed interest in bacteriophage therapy with the emergence of antibiotic resistance as a major problem in modern medicine [17].

2.3 Phytomedicines

Phytomedicines are plant-derived bioactive compounds used as remedies. Several phytocompounds are used as lead molecules to treat various infections. Today it is estimated that more than two thirds of the world's population relies on plant derived drugs; In the USA approximately 25% of all prescription drugs used contain one or more bioactive compounds derived from vascular plants [18]. It is estimated that today, plant materials are present in, or have provided the models for 50% Western drugs [19]. Many commercially proven drugs used in modern medicine were initially used in crude form in traditional or folk healing practices, or for other purposes that suggested potentially useful biological activity. Also Ahmad and Aqil [20] have reported that fractions from 15 traditionally used Indian medicinal plants were active against ESBL-producing multidrug-resistant enteric bacteria. Ahmad and Beg [21] had reported 45 Indian medicinal plants having activity against multi drug-resistant human pathogens. Also, certain bioactive plant extracts on beta-lactamase producing methicillin resistant *Staphylococcus aureus* was reported [22]. Several researches have been performed to validate the claims made for alternative therapies.

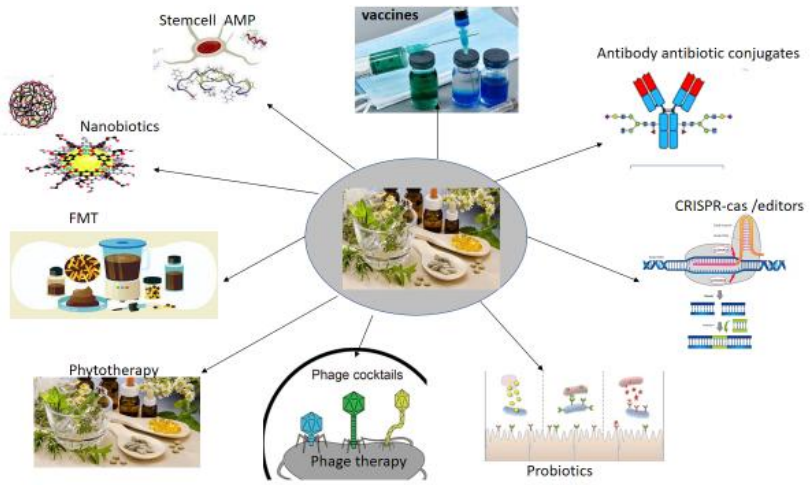

Fig. 3. Various approaches to combat Antimicrobial resistance

2.4 Faecal Microbiota Transplantation (FMT)

In FMT, faeces from a healthy person is transferred to a patient to restore gut microbiome which is disrupted in a sick patient. This FMT was found to treat infections caused by drug-resistant bacteria like vancomycin-resistant enterococci or multidrug-resistant *K. pneumonia* [23].

2.5 Stem Cell-Derived Antimicrobial Peptides

Mesenchymal stem cells (MSCs) have been extensively studied towards development of a safe and promising therapeutic product against several chronic diseases. MSCs exhibit promising ability to promote immunomodulation, tissue healing and control of excessive inflammation [24]. Recently, it was reported that human MSCs serve as antimicrobial peptides (AMPs) that eradicate the bacteria through multiple mechanisms including inhibition of bacterial cell wall synthesis [25,26].

2.6 Hemofiltration Devises

Subsiding the cytokine storm is essential to prevent organ damage in several cases of infections. Hemofiltration or renal replacement therapies utilize the devices that bind to and remove circulating bacterial products, inflammatory mediators and cytokines [27] and some pathogens circulating in blood. Two of the devices popularly used include the mannose-binding lectins [28] or bound heparin [29]. It is thought that if substantial reduction in the pathogenic bacterial load is achieved by these hemofilters, the host immune system will be able to tackle the remaining pathogens even in cases of multidrug resistance.

2.7 Quorum Sensing Inhibitors

Formation of biofilms and quorum sensing are the two important attributes of bacterial species enhancing the chances of their survival under adverse environments. Several natural and synthetic molecules have been proved and reported to block quorum sensing [30].

2.8 Role of CRISPR-Cas against AMR

CRISPR-cas is a distinctive adaptive immune feature in archaea and bacteria that provides protection against invading bacteriophages [31].

2.9 Significance of Nanoantibiotics to Combat AMR

Nanoparticles can be employed to deliver antimicrobial substances or may themselves contain antimicrobialsubstances. The metal and metal oxide-based nanoparticlesand antibioticsare regarded as promisingtherapeutic candidates for future applications in biomedicalsciences since they exhibit low toxicity, enhanced antimicrobial and anticancer activity [32]. Nanoparticles can serve as carriers for targeted drug delivery and also possess antibacterial properties through several mechanisms suchas disruption of bacterial wall, biofilm inhibition, modulation ofimmune response in host, generation of reactive oxygen speciesand damage to key DNA and protein molecules of the resistantbacteria [33].

3. MODULATION OF HUMAN MICROBIOME

Human microbiota is the total microorganisms found in human body, where microbiome represents all their genomes. In a healthy adult gut there are more or less 160 bacterial species (mainly *Bacteroidetes* and *Firmicutes*) which are known to regulate physiological functions [34]. Dysbiosis of this ecosystem has been associated with many illnesses like diabetes mellitus, cardiovascular diseases, asthma, autism, inflammatory bowel disease (IBD), antibiotics-associated diarrhoea and cancer.

4. CONCLUSION

Antibiotic resistance can become life threatening and hence it is advisable to develop alternative therapies to reduce the dependence on antibiotics. The efficacy of antibiotics is waning due to the emergence of drug resistance. It is therefore imperative to evolve newer strategies and develop novel therapeutics to tackle the problem and reduce the use of antibiotics by increasing the use of non antibiotic alternative therapeutics.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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