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ANTIMICROBIAL RESISTANCE: WILL THERE BE A SOLUTION?

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ABSTRACT

Antibiotics were unequivocally regarded as the pinnacle of the twentieth century's 'wonder drugs,' capable of transforming mortally dreadful bacterial infections into treatable conditions. The dawn of the antibiotic era not only heralded a period of relief for people who had been tormented by infections, but also enabled nations to prosper and reshaped the view of health as a moral obligation. However, the superiority of antibiotics over the potential infectious agents were rather brief. Antibiotic resistance has emerged as an international public health crisis of the twenty first century. Antimicrobial resistance (AMR) arises when antimicrobials exert selection pressure on microorganisms, causing them to mutate or adapt in ways that allow them to withstand antimicrobials. It is a natural phenomenon that is exacerbated by the imprudent use of antimicrobials in humans, animals and agriculture, as well as by global connection through travel and trade.

It is estimated that about 700,000 people die each year as a result of AMR. Without action, the death toll may grow to as many as ten million fatalities per year by 2050, resulting in a 3.8 percent drop in annual gross domestic product (GDP), according to a 2017 World Bank estimate. In an era of widespread resistance and a relatively dry pipeline for new antibiotic development, the therapeutic toolkit for most infections has reached its limit. Hence, in the present scenario of increasing antimicrobial resistance, novel strategies against multidrug resistant and persistent microorganisms, as well as methods to retain the efficacy of existing antimicrobials, their mechanism of action and challenges and prospects for their widespread translation into clinical practice are being discussed.

Keywords: Antimicrobial resistance, Multidrug resistance, Novel strategies

INTRODUCTION

Antibiotics, the 'magic bullets' that selectively targets only the microbes and

not the hosts, were a blessing to human civilization that saved millions of people. The golden era of antibiotics started with the classical discovery of penicillin by Alexander Flemming in 1928 followed by a whole lot of newer generation molecules. However, the successful use of these wonder drugs is threatened by the possible emergence of AMR. At this juncture, when the world responds to COVID-19, the hidden threat of AMR, one that has already killed hundreds of thousands of people around the world, lurks in the shadows. Antimicrobial resistance is still a concern because pathogens that cause resistant infections thrive in hospitals and medical facilities, putting all patients at risk, regardless of the severity of their medical conditions, and are frequently zoonotic. The World Health Organization (WHO) has cautioned AMR as one of the top ten threats to global health in 2019 (WHO, 2019). The United States Centre for Disease Control and Prevention (CDC) reported that antibiotic resistance in the United States accounts for more than 2 million infections and 23,000 deaths per year (CDC, 2013). Globally, 10 million deaths were projected to occur per year by 2050 if the current trend on indiscriminate use of antibiotics goes unchecked (O'Neill, 2014).

Resistance is a natural adaptive evolutionary phenomenon in which a previously susceptible population of bacteria develops resistance to an antibacterial agent under the selective pressure of using that agent. This can happen due to chromosomal mutation or by direct transfer of genes encoding resistance from other resistant organisms. Evolution of newer antibiotics and the development of the resistance to each antibiotic over decades is depicted in fig.1.

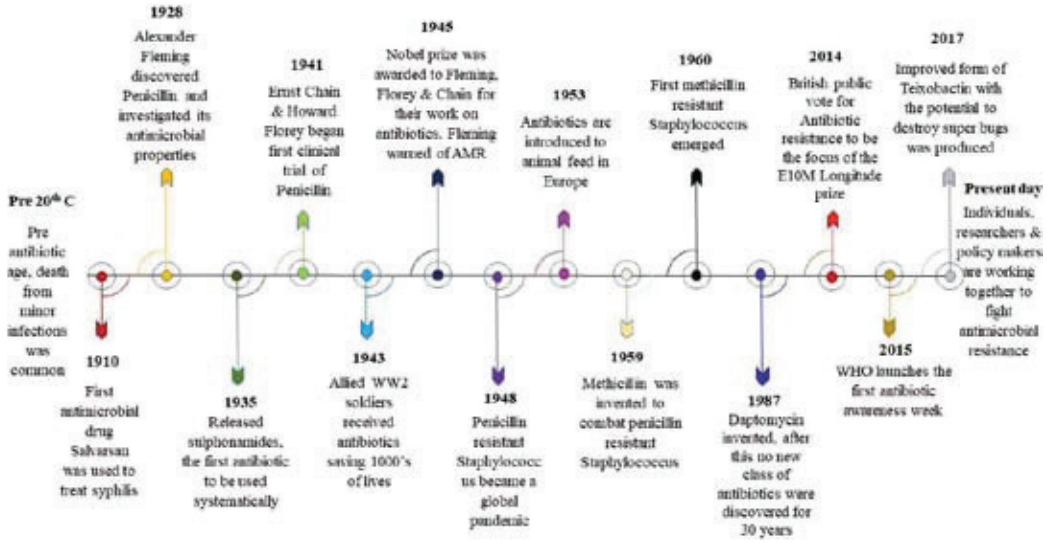

Fig. 1: A brief history of antibiotics and development of resistance

The most challenging MDR organisms currently encountered include the so called ESKAPE pathogens like *Escherichia coli*, vancomycin resistant MRSA strains, *Klebsiella pneumoniae* with extended spectrum β-lactamases (ESBL), *Acinetobacter baumannii, Pseudomonas aeruginosa*, and vancomycin resistant enterococci (VRE) and the extensively drug-resistant (XDR) *Mycobacterium tuberculosis* and New Delhi metallo beta lactamases (NDM) in Enterobacteriaceae (Khan and Khan, 2016). Zaman *et al*. (2017) portrayed antibiotic resistant organisms as 'superbugs' of which *S. aureus* being the most renowned owing to its intimacy with humans and the dramatic increase in resistance. Though ESKAPE bacteria were most often designated as a cause of nosocomial infections, six-year study by Singh (2018) on bacterial isolates from veterinary clinical cases revealed that 13.5 per cent of isolates belonged to "ESKAPE" group pathogens.

Sharma *et al*. (2018) opined that AMR is a silent pandemic that has the potential to undo a century of medical progress, and that it can only be addressed through coordinated global multidisciplinary efforts, such as developing strategies for prudent use of antibiotics, recharging the antimicrobial drug pipeline, or using alternative therapeutic strategies and novel diagnostic developments to identify the critical control points with respect to AMR in human medicine, animal sector and industrial agriculture.

Drivers of AMR Crisis

Although antimicrobial resistance is a natural phenomenon, the main drivers of both its development and spread are often man-made. Some of the factors that contribute to the development of resistance include the misuse and overuse of antimicrobials in humans, animals and plants, lack of diagnostics and effective treatment, lack of access to clean water, sanitation and hygiene, poor infection prevention and control strategies, transmission of resistant pathogens through the food chain and ineffective waste management systems. Moreover, many a times, bacteria can accumulate numerous multiple resistance traits over time and become multidrug resistant. As there were no spatial and geographical boundaries for resistant organisms and genes that impart resistance, the problem of AMR was globalised by increased international travel, import and export of foodstuffs (Read and Woods, 2014; Tenover, 2006).

The antibiotic resistance crisis had been exacerbated by the delay in novel drug discovery and development initiatives, often resulting from the huge

economics and time-consuming nature of the process (Roca *et al*., 2015). Although some incentive schemes such as increased investments have been proposed by the government, non-profit and public health organisations to arouse interest in novel drug discovery, there is a growing gap in the new drug discovery and development (Liu *et al*., 2021). Inappropriate prescription practices, self-medication, inadequate patient education, an increase in the number of elderly and immunocompromised people, limited diagnostic facilities, unauthorised antimicrobial sales, a lack of appropriate functioning drug regulatory mechanisms and non-human antimicrobial use, such as in animal production, agricultural and industrial sector were the driving factors behind the emergence of the AMR crisis (Prestinaci *et al.*, 2015).

Economic impacts

Unchecked antimicrobial resistance will have a significant negative economic impact on food systems, livelihoods, and health care costs, which will increase levels of poverty and inequality. The net economic effect of resistance was described as the cost attributable to treatment of an infection due to a resistant isolate ("treatment cost") minus the cost for preventing such infections ("prevention cost"). A joint report by the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) stated that the total annual social costs of infections caused by antibiotic-resistant bacteria were approximately £1.5 billion in European Union. The annual productivity losses due to lack of work and deaths of infected patients were estimated to be over £150 million and £450 million respectively (ECDC and EMA, 2009). Statistics from the World Bank indicated that AMR has a major impact on livestock due to mortality and morbidity which would reduce livestock production and trade, ultimately resulting in high protein prices that could be attributed to the restricted protein sources such as milk, egg and meat. Unless the ongoing AMR trends slow down, livestock production will lose 11 per cent by 2050, leading to a fall in revenue generation, exacerbating the economic crisis (World Bank, 2017).

It was estimated that due to AMR, US incorporates a $20 billion surplus in its budget for direct healthcare expenses and also an annual productivity loss of around $35 billion (CDC, 2013). Taylor *et al*. (2014) created a theoretical model taking human capital approach to loss of productivity and predicted that in the absence of a modification in current trend of AMR, within ten years the world working-age population would decrease by two years.

An approximate estimated economic cost of AMR stratified by drug class and national income level revealed an overall economic cost of $0.5 billion and $2.9 billion respectively, in Thailand and United States due to resistance of five pathogens, namely *S. aureus, E. coli, K. pneumoniae, A. baumanii*, and *P. aeruginosa*. (Shrestha *et al.,* 2018).

Innes *et al*. (2020) developed and parameterised a model to quantify the external costs of enrofloxacin application to US broiler chickens on the fluoroquinolone resistance (FR) of Campylobacter in humans of US in 1999, prior to the ban of fluoroquinolone in the chicken industry. They found that the total excess human cost from FR Campylobacter infections was US$ 33 million, of which US$18 million was attributable to fluroquinolone usage in broiler industry. Cecchini *et al*. (2015) opined that resistant bacteria will double the risk of having a serious health condition compared to susceptible types and triple the likelihood of death.

The net economic effects of antimicrobial resistance are determined by a broad variety of factors from various viewpoints, such as prescribers, patients, healthcare providers, pharmaceutical companies and the society (McGowan Jr., 2001). Thus, the evaluation of the economic costs and benefits of an antimicrobial efficacy program should be based on all of these factors.

Mechanism of antibiotic resistance

Bacteria have evolved diverse genetic and biochemical mechanisms by which they manifest resistance against an antimicrobial agent (Fig. 2). The emergence of antimicrobial resistance is currently explained by two theories. First, the congenital theory which suggests that antibiotic resistance is ancient (Perron *et al*., 2015). According to this theory, antibiotic resistance is believed to be naturally occurring prehistorically, which includes antibiotic-producing organisms that have existed for millennia. For example, the complete vancomycin resistance determinant *VanA* was detected from 30,000-year-old Beringian permafrost sediments, which further supports this theory (D' Costa *et al*., 2011). A second theory claims that antibiotic resistance is an acquired biological phenomenon, as a result of the widespread and excessive use of antibiotics in clinical settings and agricultural activities.

In short, the intrinsic resistance is common to all members of a family and an inherent genetic property encoded in the chromosomal DNA, while acquired resistance is the result of any alteration in bacterial DNA that allows the expression of

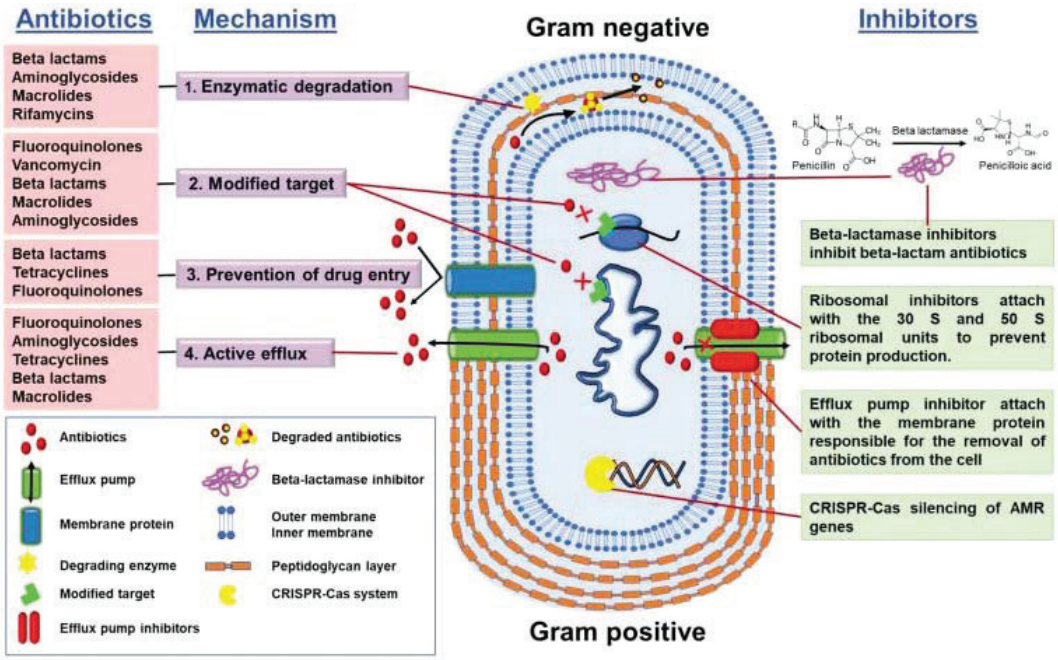

Fig.2: Mechanism of antibacterial resistance (Murugaiyan *et al.*, 2022)

a new phenotypic trait (McManus, 1997). Mobile genetic elements (MGEs) such as bacteriophages, plasmids, naked DNA, transposons or integrons that integrates different AMR genes mediates the transfer of acquired resistance (Levy and Marshall, 2004).

The common bacterial resistance mechanisms includes enzymatic inactivation and modification of the antibiotic molecule, modification of the antibiotic target site like metabolic enzymes, bacterial cell-wall components, nucleic acids and ribosomal subunits due to post translational modification or genetic mutation of the target and reduction of the intracellular concentration of antibiotic needed to produce the therapeutic action either by means of antibiotic efflux pumps or reduced cell membrane permeability (Aslam *et al*., 2018).

A multi-layered defence mechanism against antimicrobials was by formation of biofilms which were the organised sessile aggregates of microorganisms encased in a self-produced polymeric matrix composed of exopolysaccharides, DNA and proteins (Hoiby *et al*., 2010). Biofilm formation is the result of expression of a complex network of signal molecules orchestrated under the coordinated expression of certain genes and bacterial quorum sensing (QS) system (Aricola *et al*., 2012). The decreased antimicrobial susceptibility of biofilms was due to tolerance and resistance owing to the reduced antimicrobial penetration into

biofilms, composition, genetic basis and interactions among organisms of biofilms, occurrence of persister cells, nutritional limitation, reduced growth and biofilm-specific protective stress responses (Hall and Mah, 2017).

Strategies to combat antimicrobial resistance

The importance of the prudent access and use of antimicrobials worldwide is being clearly expressed in the words of Sir Liam Donaldson, who stated that 'Every antibiotic expected by a patient, every unnecessary prescription written by a doctor, every uncompleted course of antibiotics, and every inappropriate or unnecessary use in animals or agriculture is potentially signing a death warrant for a future patient' (Chief Medical Officer, 2008). Hence, the use of the right drug at the right time at the right dose for the right duration is being advocated as an approach to prolong the lifespan of lifesaving drugs along with optimal patient care (Dryden *et al*., 2011).

Any strategy for the prevention and containment of AMR should be aimed at reducing un-intended contact between pathogenic microorganism and antibiotics, restricting the spread of resistant strains, and treating infections with rational use of antibiotics to cure (Sharma *et al*., 2018). According to Kaur (2016) to be in pace with the emergence of AMR, rejuvenating the already existing antimicrobials were a more realistic and better approach than investing in novel drugs, as the process is more complicated, expensive and time consuming.

Different approaches are being used by different authors to classify the various alternative strategies to combat antimicrobial resistance. The following are some of the novel therapeutic strategies to combat and mitigate the spread of antimicrobial resistance:

a. Drug repurposing and combination therapy

The surging antimicrobial resistance crisis coupled with the dismantled antibiotic discovery programmes due to the low output to input ratio, necessitates novel strategies to generate more viable and effective pharmaceuticals from the existing arsenal. Drug repurposing or repositioning is heralding a new therapeutic avenue to bypass the huge investment in the development of new drug. Drug repurposing, also called drug repositioning, reprofiling or re-tasking is a novel strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication (Pushpakom *et al*., 2019).

The two approaches involved in drug re-purposing are combination therapy and antibiotic adjuvant approaches. Most antibiotics work primarily on a specific target. As a result, protection of these targets has been a comparably simpler and therapeutically relevant mechanism of resistance generated by certain bacteria. Hence, various combinations of antibiotics and non-antibiotic substances that can suppress bacterial resistance factors or increase antibiotic action provide a sustainable and successful method for dealing with multidrug resistant microorganisms. The following three objectives must be met for an ideal drug combination; should have a synergistic effect, suppress the emergence of spontaneous resistance and attenuate drug toxicity in host cells. In particular, repurposing antibiotics or non-antibiotic drugs (also known as antibiotic adjuvants) that have undergone extensive toxicological and pharmacological analysis is an effective method to reduce the time, cost and risks associated with conventional antibiotic innovation.

b. Phytocompounds

Plants have evolved unique mechanisms to protect themselves from microorganisms via natural phytochemicals (secondary metabolites) found in seeds, roots, leaves, stems, flowers, and fruits. Furthermore, plants synthesize a wide range of structurally distinct compounds, each of which plays a distinct role in their defense against microbial invasion. As a result, the potential usefulness of plant-derived chemicals as therapeutic candidates has drawn the attention of the pharmaceutical and scientific communities, who have examined a wide range of plant extracts and oils as antibacterial and antibiotic resistance-modifying agents. Random, algorithmic and ethnopharmacological techniques are among the screening procedures used for such novel drug development.

Dhama *et al*. (2014) reviewed the multidimensional health benefits of a wide variety of phytocompounds and concluded that they could serve as promising antibacterial by influencing the pathogenicity of the pathogen, improving the immune status of the host and modulating the macro and micro environment of disease.

c. Antimicrobial peptides and bacteriocins

Many multicellular organisms produce antimicrobial peptides (AMPs) and host-defense peptides (HDPs) as the first line of defense against invading pathogens. They have a broad range of activities, involving immunomodulation, antiplasmodial, antiprotistal, anticancer,

antifungal, antiviral, insecticidal and spermicidal. Although most of these peptides bear a net positive charge, anionic antimicrobial peptides have also been reported. Being facially amphiphilic, the cationic domain of the peptide interacts with negatively charged bacterial cell surface, while the hydrophobic domain interacts with the lipids of the bacterial membrane, causing the cell membrane to disintegrate, eventually resulting in bacterial death.

Mammalian cells are zwitter ionic in nature and hence do not interact well with the positively charged AMPs, rendering them selectively toxic toward bacteria. Aside from membrane activity, intracellular targets are increasingly being probed. Reports of bacteria developing resistance against AMPs do exist. However, disintegration of the bacterial cell membrane is energetically too unfavorable for bacteria to easily develop resistance. The broad range of properties and the aforementioned advantages have prompted the scientific world to consider AMPs as future antibiotics. Zhang *et al*. (2007) observed that the intramammary delivery of mammary gland tissue - specific expression vector carrying the antimicrobial peptide genes coding for bovine lactoferricin (LfcinB) and bovine tracheal antimicrobial peptide (bTAP) into goats enabled their mammary cells to produce exogenous antibacterial proteins. The expressed antibacterial proteins exhibited significant inhibitory activity against *S. aureus* and *E. coli* by bacterial growth inhibition zone assay indicating a broad spectrum of antibacterial activity against both gram-negative and gram-positive bacteria.

c. Phage therapy and enzybiotics

Before the therapeutic conventional antibiotics were put in to therapeutic use, 'bacteriophages' or viruses that propagate at the expense of bacteria were used to treat the infected livestock. Initially they anchor on to bacterial cell surface and inject the phage genetic material on to bacterial cytoplasm. This subsequently takes over the host cell machinery, resulting in synthesis of phage components and assembly of new phages within he infected bacteria. This eventually leads to bacterial lysis and the release of phage progeny that can commence a second infection cycle. Phages are known to select between mixed populations of bacteria. Thus, exploitation of the lytic cycle of bacteriophages can be used to develop an alternative but selective approach to target pathogenic bacteria over commensal bacteria (Ghosh *et al*., 2019).

Kwiatek *et al*. (2012) isolated and characterised a bacteriophage, MSA6 from bovine mastitic milk samples and demonstrated its lytic activity against

staphylococcus associated with bovine mastitis and MRSA associated with human infections. Tiwari *et al*. (2014) reviewed the potential of phages and purified phage gene products and concluded that they were able to selectively control the cellular or replicative machinery of the host cell owing to their lytic or lysogenic mode of replication and can be employed for treatment of bacterial, viral, fungal, and algal infections in humans and animals. Moreover, they could serve as potential biocontrol agents safeguarding the biosphere and a promising therapeutic tool in the scenario of AMR.

e. CRISPR Cas genes

The CRISPR (clustered, regularly interspaced, short palindromic repeats)-Cas9 (CRISP-associated protein 9) system are key components of a bacterial immune system wherein a 20nt small RNA acts as a guide for Cas9 to cleave foreign genetic elements, such as those present in plasmids and phages, at specific sites. The CRISPR-Cas9 system has been used in a variety of biological applications and the benefits are now being extrapolated to the field of antimicrobial therapeutics. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-Cas (CRISPR-associated) systems, the adaptive immune systems native to bacteria and archaea which employs CRISPR RNAs to specifically recognize the complementary nucleic acids of foreign invaders without affecting the microbiome, leading to sequence specific cleavage or degradation of the target nucleic acids offers a promising solution to the antimicrobial resistance crisis (Beisel *et al*. 2014).

Singh *et al*. (2018) reviewed the recent developments in CRISPR-Cas genome editing technology and proposed that they could serve as simple, efficient, and versatile tool for targeted genome editing in a wide range of organisms and cell types. They worked upon a targeted site by generating a double strand breaks in the target site, modifying or permanently replacing the target sequence of interest which could be viral targets, antibiotic resistant genes, single-mutation genetic diseases or multiple-site corrections for wide scale disease states, offering the potential to manage and cure a number of biomedical hazards.

f. Nanoparticles

Nanomaterials, also known as nanostructured materials are organic, inorganic or hybrid particles that have at least one dimension falling in a nanometer scale (1 to 100 nm) (Makabenta *et al*., 2021; Pathakoti *et al*., 2017). They seem to have an infinite variation of structure and morphology and is classified as

nanoparticles (NPs), nanorods, nanowires, thin films and bulk materials made of nanoscale building blocks or consisting of nanoscale structures. Nanoparticles are the building blocks of the nanostructured materials.

Antimicrobial actions of nano-particles (NPs) might be mediated through their attachment to the bacterial membrane by electrostatic interaction which could disrupt the bacterial membrane integrity, alters the cell wall or blocks vital enzyme pathways. NPs and their ions could also induce oxidative stress mediated through generation of reactive oxygen species, that damaged the bacteria cellular components irreversibly resulting in death (Hajipour *et al*., 2012). Kar *et al*. (2016) studied the antibacterial property of silver nanoparticles (AgNPs) and a plant derived compound capsaicin against MDR-ESBL producing *E. coli* of bovine and poultry origin and observed that 1000mmol/L of AgNPs and 25mmol/L of capsaicin reduced the bacterial viability to 0-3 per cent and 0-8 per cent respectively. Gao *et al*. (2018) proposed that the NP based drug delivery systems promotes antibiotic localization in pathogen, modulates drug-pathogen interaction against AMR and enables novel anti-virulence approaches. The improved pharmacokinetic profile and therapeutic index of NP based drug delivery systems compared to their free counterparts could be attributed to the enhanced drug solubility, stealth against immune evasion, modulated drug release characteristics and their ability to deliver multiple drugs simultaneously to desired sites.

g. Antivirulence therapy

Anti-virulence therapy is a promising option against AMR as it specifically interferes with the expression or activity of virulence traits without killing of the bacteria, allowing the host immune system, including the normal microbiota, to prevent bacterial colonization or clear any established infection thereby reducing the evolutionary pressure for the development of resistant clones. In addition, it could potentially be used in combination with established drugs or novel antimicrobials in a synergistic manner to extend the lifespan of these drugs (Rasko and Sperandio, 2010). Zhao *et al*. (2020) suggested that quorum quenchers interfered with the microbial cell to cell communication system and offers a novel strategy for treatment of drug resistant bacteria either by inhibition of signal molecule production, degradation of signal molecule or by interfering with its conduction and receptor binding which arrests the cellular processes of microorganisms, such as pathogenic gene expression, toxin production, extracellular polysaccharide synthesis, biofilm formation and regulation of drug efflux pumps.

h. Other recent strategies

Asahara *et al*. (2016) established the protective effect of a probiotic, *Bifidobacterium breve* strain Yakult (Bby) with and without synbiotic potentiation using the prebiotic, galacto-oligosaccharide (GOS) against MDR *A. baumannii* (MDRAb) in a murine infection model and found that the synbiotic strategy increased the survival rate of murines and inhibited the intestinal growth and invasion by MDRAb. The findings of the study offer a promising alternative towards the dietary use of antimicrobials in animals that might contribute to the development of AMR. Buckner *et al*. (2018) reviewed the plasmid localisation of mobile AMR genes and documented a novel strategy that involved drug, incompatibility, phage or CRISPR Cas based plasmid curing and inhibition of plasmid replication or segregation as an important tool against AMR.

Kottil and Jakobsson (2019) opined that targeting the ecological evolution of AMR genes using antisense molecules will help to elucidate an effective solution to curb the menace of AMR. Antisense molecules are nucleic acid analogues that base pairs with its targeted mRNA (sense strand) to impede translation and expression of AMR genes.

The major steps to be undertaken to prevent the emergence and spread of drug resistance includes implementation of antibiotic stewardship programs and infection control measures, rapid and affordable diagnostic tests, development of novel treatment strategies, banning antibiotic use as growth promoters, reinforcement of national and international regulations, conduct of awareness programmes and antibiotic resistance surveillance among humans and animals (Roca *et al*., 2015). Ayukekbong *et al*. (2017) proposed that apart from the rational use of antibiotics in health care, livestock and agriculture sector, long-term solutions against development of resistance should be focused on methods to prevent the circulation and dissemination of resistant organisms. This could be accomplished by enhancing the basic hygiene and sanitation as well as by upgrading biosecurity measures to prevent and manage nosocomial and infectious diseases through vaccination, and alternative therapeutic strategies.

CONCLUSION

Antimicrobial resistance still remains a malady in that the pathogens causing resistant infections continues to thrive in hospitals and medical facilities, putting all patients at risk, irrespective of the severity of the ailment they suffer from and thus complicating the management of other infections. The existing scientific

and commercial challenges in novel drug development coupled with the historic abuse of antibiotics may soon lead to an era of scarcity of effective antibiotics. As a result, strategies involved in prudent use of antimicrobials as per dose and schedule encompassing the identification of the pathogen and assessing the antimicrobial sensitivity needs to be legally enforced. Genomic, proteomic, transcriptomic and metabolomic studies concentrating on the dynamics of the molecular mechanisms of resistance and its phenotypic expression could help to fill gaps in addressing the challenges of AMR and guides in development of strategies to ameliorate its emergence and transmission. This also helps in establishment of novel therapeutic alternatives and diagnostic innovations, tailored to local needs. Moreover, it is of paramount importance to inculcate and nurture a "One Health One Welfare" practice, through collaboration between different sectors at the regional, national and international level in making crucial decisions to effectively combat and mitigate the spread of these pathogens.

Future prospects

Protecting the already available arsenal is critical in the war against resistance. Hence, strong political commitment can play a vital role in formulating policy, implementation, and regular educational updates based on scientific evidence to better regulate the use and sale of antibiotics for both humans and animals. Unethical use of antibiotics must not be promoted and strategies must be adopted to prevent their imprudent use.

In spite of many new avenues that are being explored day by day to combat current and emerging resistance, the field of novel antimicrobial therapies against multi drug resistant organisms is in nascent stage and further research must be invested for development of next generation therapeutic options. More long term *in vitro* as well as *in vivo* studies has to be carried out with regard to the safety, cytotoxicity and biocompatibility of each therapeutic modality. The predominance of different antibacterial mechanisms on these alternative therapeutic strategies under different conditions has to be focused. Genomic, transcriptomic, proteomic and metabolomic studies have to be carried out with regard to the emergence of resistance against them. Above all, an interdisciplinary collaboration between fundamental, translational, and industrial organisations with sufficient financial back up will be critical in the clinical translation of these molecules.

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