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Mechanism and challenges associated with adaptation and evolution of drug-resistant bacteria: an overview

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Abstract. Antimicrobial resistance is one of the leading challenges in the human healthcare segment. Advances in antimicrobial resistance studies have revealed various intrinsic, adaptive or acquired factors to be involved for pathogenicity. Antimicrobial agents are either bactericidal or bacteriostatic in action and prescribed according to the mode of action. Various factors are confined for the antimicrobial activity of these agents via biochemical, mechanical, physiological and molecular mechanisms. Microbial cell expresses a number of alternates responsible for the evolution of resistance against these agent activities involving cell surface modifications, enzyme inhibitions, modifications in efflux system, protein carriers and mutations in nucleic acids. Apart from this, the successful adaptations of such microbes have also been observed with the transfer of responsible genes through miscellaneous operations such as vertical evolution, horizontal gene transfer, co-selection, compensatory and random mutation. In addition, alterations or modifications in biochemical and physiological mechanisms at cellular levels are also responsible for antibiotic resistance. This article briefly shows the present scenario of antimicrobial resistance and the alternatives to overcome this global issue in future.

Keywords: Antimicrobial agents, antimicrobial resistance, multidrug resistance

INTRODUCTION

Antimicrobial resistance (AMR) is the capability of disease-causing microorganisms such as bacteria, viruses and parasite to survive in the presence of antimicrobials such as antibiotics, antiviral and antimalarial. Moreover, this AMR has been long perceived and is becoming an immense task to oversee (Antimicrobial resistance, 2017). World Health Organization (WHO) has published their single ever catalogue of antibiotic resistance "priority pathogens" – a catalogue of 12 families of bacteria which present the most serious danger to human health. According to the need, WHO in their catalogue enlisted antibiotic into three major groups on the basis of priority: critical, high and medium priority (Table 1). These bacteria have been turn out to be resistant to a great amount of antibiotic (WHO, 2017).

The recent data generated by WHO has presented most commonly reported resistant isolates such as *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus* and *Streptococcus pneumoniae*. Around 82% of bloodstream infection resistant isolates are present globally and shows to the most commonly used antibiotics. For penicillin and ciprofloxacin, the suspected proportion of resistant isolates fall between the range of 0-51% and 8-65% respectively (World Health Organization, 2018). Antibacterial resistance is a consortium of worldwide challenges that

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interrelates with high morbidity and mortality rate. Gram-positive and negative bacteria are using multifaceted approaches and becoming more reluctant to antibiotics. The dramatic increase in resistance emerges due to over usage of conventional broad-spectrum antibiotics, poor/unhealthy sanitary approaches and unhealthy environmental conditions. There are global issues which are associated with bacterial infection and emerging diseases. Lack of curative approaches, shortage of potential drugs and fewer novel antibiotics needs more consideration to overcome resistance challenges (Akova, 2016). Today's need for finding novel strategies to combat antimicrobial resistance is a major health care challenge (Mühlen & Dersch, 2015). Many crucial measures taken by WHO, has been leading many health care industries toward the seriousness of resistance and development of preventive measures against resistance (Chellat *et al.*, 2016). Establishment of updated epidemiological data and routine surveillance of resistance status is a useful approach not only in combating diseases but also for the development of a novel/potent medicines (Li & Webster, 2018). According to a survey, researchers have found a 65% rise in antibiotic usage till the year 2000-2015. In developing countries, greater access to antibiotics has lead resistance at the global level (van Hoek *et al.*, 2011). According to the 2014 analysis report, estimated deaths due to antibiotic resistance were half-million per year that could increase to several million by the year 2050 (Editor, 2018). According to a recent data report, India, Brazil and Vietnam have the highest diversity in resistant genes as compare to New Zealand and Australia. Researcher in their survey also reported antimicrobial resistance emergence due to the poor sanitary condition and individual health status (Science Daily, 2019).

Table 1. World Health Organization (WHO) priority pathogens list for the research and development of new antibiotics.

Pathogens	Antibiotics	Resistant genes	Priority
Acinetobacter baumannii	carbapenem-resistant	*OXA-23* and *OXA-51 β-lactamase*, *blaVIM*, *PER-1-like* and *GES-5* (Ibrahim, 2019)	Critical
Pseudomonas aeruginosa		*NDM*, *VIM*, *IMP* and *OXA-48* (Jabalameli *et al.*, 2018) *glnK* and *fstK* (Alvarez-Ortega *et al.*, 2011)	
Enterobacteriaceae	carbapenem-resistant	*NDM*, *VIM*, *IMP* and *OXA-48* (Jabalameli *et al.*, 2018)	
	ESBL-producing	*Bla*CTX-M-15 and *Bla*CTX-M-2 (Bevan *et al.*, 2017), *Bla*CTX-Ms and *Bla*KPCs (Mathers *et al.*, 2015), IS*Ecp1-Bla*CTX-M-9-like-IS903 and IS*Ecp1-Bla*CTX-M-1-like-orF477 (Zhao & Hu, 2013)	
Entercoccus faecium	vancomycin-resistant	*Van*R, *VanA*, *VanZ*, *VanX*, *VanS*, *VanH*, *VanD* and *VanC* (Ranotkar *et al.*, 2014)	
Staphylococcus aureus	methicillin-resistant, vancomycin-intermediate and resistant	*mecA*, *pbp1*, *pbp2*, *pbp3* and *pbp4* (Argudín *et al.*, 2016; Shore *et al.*, 2011)	High
Helicobacter pylori	clarithromycin-resistant	*23srRNA* (Matta *et al.*, 2018), *rpmJ*, *hp0605*, *hp0971* (Iwamoto *et al.*, 2014), *acrB* (Binh *et al.*, 2014)	
Campylobacter spp.	fluoroquinolone-resistant	*gyrA* (Tang *et al.*, 2017)	
Salmonellae		*gyrA*, *gyrB*, *parC* and *parE* (Ling *et al.*, 2003)	
Neisseria gonorrhoeae	cephalosporin-resistant, fluoroquinolone-resistant	*gyrA*, *gyrB* and *parC* (Aldred *et al.*, 2014)	
Streptococcus neumonia	penicillin-non-susceptible	*Pbp2X*, *pbp2b* and *pbp1a* (Chewapreecha *et al.*, 2014; Dewé *et al.*, 2019)	Medium
Haemophilus influenzae	ampicillin-resistant	*Fts* (Hoshino *et al.*, 2013), *TEM-1* and *ROB-1* type *β*-glactamase genes (Hasegawa *et al.*, 2003)	
Shigella spp.	fluoroquinolone-resistant	Aac(6')-Ib-cr, gyrA and *gyrB* (Pu *et al.*, 2009), *acrA* and *acrB* (Taneja *et al.*, 2015)	

It has been seen that the drug resistance developed by microorganisms is a natural evolutionary existence and commences naturally over time. This phenomenon helps them to circulate their resistance to their progeny (Ashley & Brindle, 1960; Beceiro *et al.*, 2013). Furthermore, mutation at the genetic level plays a major role in many molecular mechanisms responsible for the resistance against the prescribed antibiotics (Munita & Arias, 2016). Mutations may involve vertical evolution i.e. gene transfer from parents to offspring e.g. such as Extended-spectrum β lactamase and plasmidic AmpC producing *Escherichia coli* found in poultry (Oikarainen *et al.*, 2019); obtaining new gene i.e. horizontal gene transfers from donor to recipient by transduction, transformation and conjugation e.g. *Citrobactor freundii* acquires metallo-β-lactamase NDM-1 (bla_{NDM-1}) and 16S RNA methylase ArmA genes by conjugation, on the similar plasmid pNDM-CIT and possess resistance to all aminoglycosides (Dolejska *et al.*, 2012); co-selection i.e. gene transfers due to the presence of mobile genetic elements such as plasmids, phages and transposons aids bacteria to attain variety of new traits to trigger antibiotic resistance (Jeters *et al.*, 2009) e.g. plasmid isolated from *Salmonella abortus* strain that were resistant to ampicillin and transposon CTnDOT, a carrier of tetracycline resistance genes i.e. *tetQ* and *ermF* in human colonic *Bacteroides* spp. (Jeters *et al.*, 2009; Ghosh *et al.*, 2000); compensatory mutations i.e. resistance due to dual mutation in a particular gene e.g. ribosomal mutations in *rpsL gene* which encodes rps12 protein of the ribosomal accuracy centre is responsible for the streptomycin resistance in *Escherichia coli* (Levin *et al.*, 2000); random mutations e.g. Hyper mutable (or mutator) e.g. dysregulated DNA mismatch repair system increases voluntary mutation rate up to 1000 times in *Pseudomonas aeruginosa* strains (Beceiro *et al.*, 2013; Maciá *et al.*, 2005). To date, only 13,293 genes from 933 species belongs to 124 genera are reported for 257 different antibiotics (Table-2) for treating AMR (Liu & Pop, 2008).

Along with genetic mutations various biochemical, mechanical and physiological mechanisms are accountable for the resistance (Munita & Arias, 2016). Bacteria have mechanisms to inactivate/modify antibiotics, remodel the antibiotic active site to reduce its binding ability, alter its own machinery to exclude out the effects of antibiotic and reduces the effect of antibiotic by regulating the efflux pump (McManus, 1997). Almost all pathogens assemble two properties: (a) toxicity, the extremities of causing damage and (b) invasiveness i.e. tendency of expansion after the invasion. Various proteomics studies have proven that antibiotic exposure is not only lethal to bacterial cell but also triggers various stress-tolerant mechanism in bacteria (Iyer & Delcour, 1997; Nabu *et al.*, 2017; Thorsing *et al.*, 2013; Vega & Delcour, 1996). Bacteria in response to antibiotics expresses a wide range of proteins required for different biological processes such as transport system, cell division, energy metabolism, stress response and virulence factor (Nabu *et al.*, 2017).

In addition to them, the final equilibrium of an infectious disease mechanism that every microbe hold depends on the virulence or pathogenicity of the microbes and also the human community condition such as immune condition, age, diet, and stress (Beceiro *et al.*, 2013). Nosocomial infections are also observed for the transmission of resistant bacteria. Long term exposures and wide usage of antibiotics also deplete the immune system and make patients more susceptible to mild diseases and eventually leading to the failure of antibiotics to treat the infection (Rakoff-Nahoum *et al.*, 2004). These factors in unification with genetic factors are also accountable for the rising and expansion of antimicrobial resistance. It is not all about the human community but we can also consider animals. Animal husbandry is the foundation of exploiting antibiotics and averting diseases (Chuma *et al.*, 2013; Antimicrobial resistance, 2018). The transfer of *ermA* and *ermC* resistant genes through transposition and transformation respectively, from poultry to human clinical *Staphylococcus aureus* strain is a better example of transfer to the resistance between same pathogenic isolate belongs to different ecological niche (Khan *et al.*, 1999).

Table 2. The summary of the method of action for the main classes is given in table (Hart & Kariuki, 1998).

Antibiotic Class	Antibiotics name	Role of antibiotic	Mode of antibiotic action
B-lactam	Penicillins Cephalosporins Carbanepems Glycopeptides Fosfomycins	Bactericidal	Inhibit cell wall synthesis
Lipopeptides		Bactericidal	Inhibit membrane function
Polymixins	Polymixins A Polymixins B Polymixins C Polymixins D Polymixins E		
Quinolones	Ofloxacin Ciprofloxacin Norfloxacin	Bactericidal	Inhibits DNA synthesis
Furanes	Nitrofurantoin Metronidazole		
	Rifamycins		Inhibit RNA transcription
Aminoglycosides	Gentamicin Tobramycin Amikacin	Bactericidal	Inhibit protein synthesis
MLSK (macrolides, lincosamides, streptogramins, ketolides)	Erythromycin	Bacteriostatic	
Ansamycins	Rifampin Clindamycin Clarithromycin Azithromycin		
Tetracyclines	Tetracycline		
Phenocols	Chloramphenicol		
Oxazolidones	Linezolid		

This article recapitulates a brief overview on the alternatives used by bacteria to overcome antibiotic action and the severity of antibiotic resistance at the global scale. We mainly focus on the various paradigm from the literature and suggest that there is a need to educate people to develop various alternatives to overcome future challenges of antibiotic resistance.

Mechanistic action of resistance against antibiotics

The microorganisms in pursuit of having antimicrobial resistance are evolved either by intrinsic, adaptive or acquired resistance mechanisms (Figure 1). Intrinsic resistance is due to the inherent insensitivity in the microorganism that is insusceptible to antimicrobials. In intrinsic resistance, antimicrobial agents fails to cross pathogen's outer membrane due to which bacteria is able to survive in the presence of antibiotic stress (Munita & Arias, 2016). It is a universal trait of any bacteria which lies within the strain and is totally independent of gene transfer (Martinez & Baquero, 2000; Palmer *et al.*, 2010). MDR is a better conventional example of intrinsic resistance (Masi & Pagès, 2013). Bacteria can acquire resistance either through new genetic incorporation or getting external DNA from nearby species that is already resistant e.g. acquired vancomycin resistance VanG-type in

Enterococcus faecalis BM4518 (Tenover, 2006). *Enterococcus faecalis* BM4518 induces resistance due to the synthesis of peptidoglycan precursor ending in D-alanyl-D-serine (Weber *et al.*, 2009). Later on a transferable VanN-type resistance is reported in *Enterococcus faecium* (Hegstad *et al.*, 2010; Lebreton *et al.*, 2011). The basis of acquired resistance can describe by mean of horizontal or vertical gene transfer.

Microorganisms encounter with multitude of environmental factors during their evolutionary period which includes ecological niche, annual temperatures, seasonal variations, day-night cycles and nutrient burden. These changes are not instant but occur over a manifold timescale. Accordingly, microbes have evolved varied approaches to deal with extreme ecological niche, environmental variation and physiological adjustments. To survive microbes, maintain their cellular integrity by repairing and utilizing environmental resources during physical changes. Such type of physical responses against the cruelty of the environment is a natural selection procedure and occurs due to evolution (Galhardo *et al.*, 2007; Hochachka *et al.*, n.d.; Huisman & Kolter, 1994; Kennedy *et al.*, 2001; Kushner, 1978; Mitchell *et al.*, 2009; Ouyang *et al.*, 1998; Ram *et al.*, 2005; Woelfle *et al.*, 2004). Exposure to nonlethal antimicrobial doses, ion concentration and temperature are some other environmental factors which enhance their attribute of resistance (Fernández & Hancock, 2012).

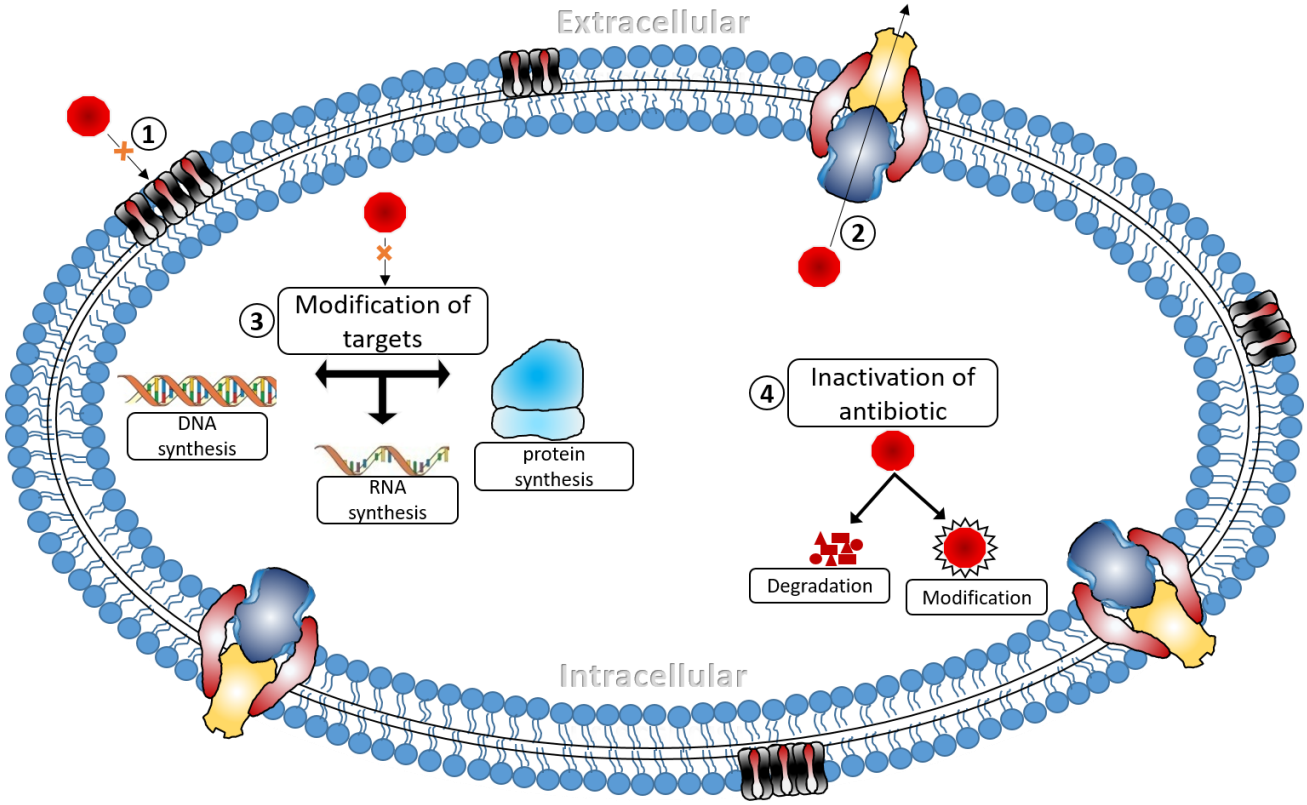

Figure 1. Mechanisms responsible for antibiotic resistance in bacteria includes antibiotic alteration antibiotics; Ribosomal alteration; altered efflux pump; Porins alteration (first line of defense in bacteria that blocks antibiotic entry in host cell). In the given figure legends are depicting as follow (1) Several mutations in the coding genes of porins and their down regulation leads to its alteration that block antibiotic entry, (2) Efflux pump, active transporter and are responsible for the removal of toxic substances out of the cell. Hence alteration in efflux pump due to continuous exposure to antibiotic leads to antibiotic resistance, (3) Ribosomal alteration leads to target site alteration which in response inhibit antibiotic binding to target site, (4) Antibiotic inactivation either by its modification or degradation respectively by host enzymes.

Prevention of antibiotic access across the bacterial cell

Loss of porins

Bacteria have an inbuilt mechanism for uptake of hydrophilic compounds of a specific size (Danilchanka *et al*., 2008). These compounds travel through water-filled channels known as porins present on the outer membrane of their cell wall (Silhavy *et al*., 2010). For the first time in 1976, these proteins were identified in *Escherichia coli* strain (Nakae, 1976). Porins lacking a classic hydrophobic region and allow less hydrophilic antibiotic uptake inside the cell (Kojima & Nikaido, 2013; Lambert, 2002; Lambert, 2005; Vargiu & Nikaido, 2012). Hence downregulation or replacement of porins is associated with certain types of antibiotic resistance. These dysregulated porins reduce membrane permeability and hence restricting antibiotic entry inside the bacterial cell (Tamber & Hancock, 2003) (Table 3).

Table 3. There are different types of porins channels present in each bacterial species. Some of them responsible for antibiotic resistance are listed in the table (Fernández & Hancock, 2012).

Bacterial species	Porins responsible for antibiotic resistance
Pseudomonas aeruginosa	OprD
Escherichia coli	OmpC, OmpF
Serratiamarcescens	OmpF, OmpC
Klebsiellapneumoniae	OmpK35, OmpK36
Enterobacter cloacae	OmpF
Enterobacteraerogenes	OmpC, OmpF, Omp36
Klebsiellaoxytoca	OmpK36
Neisseriagonorrhoeae	PIB
Salmonella enteric	OmpC, OmpF
Vibrio cholera	OmpU
Acinetobacterbaumannii	CarO

Loss of outer membrane protein (porins) expression has been proposed as an important mechanism of carbapenem resistance. Mutation in coding sequences and overexpression of bacterial small RNA (sRNAs), down-regulate the porins expression in carbapenem-resistant isolate *Enterobacter aerogenes* (Hao *et al*., 2018). Porins are beta proteins and are of different types (Table 4) in which general porins are highly subjected to antibacterial vulnerability and resistance. These are non-selective channels and allow preferences for positively or negatively charged molecules.

In the case of *Escherichia coli* certain general porins such as OmpF and PhoE act as a gateway for the diffusion of hydrophilic molecules (Achouak *et al*., 2001; Fernández & Hancock, 2012). In some cases the regular dosage of antibiotic pressure initiate certain mutational changes on transcription factor leading to the loss of porins expression as indicated by the development of carbapenem resistance in *Escherichia coli* trans conjugant (Kong *et al*., 2018). Carbapenem belongs to a class of β-lactam antibiotics which is also effective against disease caused by *Pseudomonas aeruginosa* (Hong *et al*., 2015). However, carbapenem-resistant *Pseudomonas* isolates are constantly reported worldwide due to loss of substrate-specific outer membrane porin protein OprD (Hancock & Brinkman, 2002; Trias & Nikaido, 1990). *Serratia marcescens* is a Gram-negative bacteria and reported for the β-lactam resistance due to reduction in outer membrane porins protein (Grimont & Grimont, 1984; Sanders & Sanders Jr, 1992). *Serratia marcescens* exhibit OmpF and OmpC porins regulation in response to environmental stress conditions such as osmotic pressure, temperature and pH variability. Both of the porins protein is highly regulated by RNA transcript micF which inhibit porins translation under these environment stress (Begic & Worobec, 2006). In addition, micF is also reported to reduce the expression of ompK35 (ompF) in ceftazidime resistance in *Klebsiella pneumonia* (Shen *et al*., 2017). Acquisition of *Klebsiella pneumonia*, a major cause of nosocomial infection become a major problem due to its resistance against a number of β-lactam antibiotics due to loss or modifications of OmpK35 and OmpK36 porins proteins (García-Fernández *et al*., 2012). In the late 1970s and early 1980s *Neisseria gonorrhoeae* become more resistant to penicillin and tetracycline. Studies have shown porin protein PIB, encoded by *penB* gene is responsible for the gradual increase in resistance (Gill *et al*., 1998; Olesky *et al*., 2002). Mutations in the amino acids sequence of *penB* at position 120 and 121 in association with mutation in *mtr*R were preferred for the increased resistance to penicillin and tetracycline (Olesky *et al*., 2006)

Table 4. There are some different classes of porins and their function are given in the table (Fernández & Hancock, 2012).

Classes of porins	Function
General porins	Determining the permeability barrier
More specific porins	Involve in the uptake of specific substrates (e.g., LamB, which is involved in the uptake of maltose and maltodextrins)
Iron-regulated outer membrane proteins (OMPs)	Energize cytoplasmic membrane system to enable the specific uptake of relatively rare iron complexes with secreted bacterial siderophores (e.g., the ferric enterochelin channel FepA)

Dysregulated efflux pump

Bacteria also consist of energy derived channels to eject toxic compound out of the cell (Table-5). This mechanism helps bacteria to pump out antibiotic out of the cell efficiently instead of altering it. Reduction in tetracycline aggregation in *Escherichia* coli was identified in 1978 by Levy and McMurry (Levy & McMurry, 1978). Later studies have proven the role of an efflux pump that have intrinsic resistance in *Pseudomonas* (Galhardo *et al.,* 2007; Kennedy *et al*., 2001; Kushner, 1978).

Furthermore, altered membrane permeability as a result of porins alterations and efflux pump over expression stays constantly associated with multidrug resistance (MDR) (Masi & Pagès, 2013). Most multi-resistance systems are chromosomally encoded. Active multidrug efflux pump supports intrinsic resistance of a bacterial pathogen. Efflux pump has a self-regulatory gene to control expression (Thanassi *et al*., 1997). For instance, overexpression of several genes such as *mdfA*, *marA*, *yhiU* and *yhiV* in *Escherichia coli* are reported to exhibit resistance against fluoroquinolones (Bohnert *et al*., 2007; Keeney *et al*., 2008). Hence, mutational changes in repressor genes increased expression that leads to resistance (Levy & McMurry, 1978) or may result from global transcriptional regulator activation (Ball *et al*., 1980; Pomposiello & Demple, 2000). Several time bacteria harness these mutations coherently for antibiotic exclusion and resistance emergence (Fernández & Hancock, 2012). In particular, many bacteria possess intrinsic resistance to many antibacterial agents due to the presence of multidrug efflux transporters system (Nikaido, 1994). The emergence and spread of multidrug-resistant *Pseudomonas aeruginosa* have been recognized as perturbing species in the health care industry as very few agents are effective against these strains (Fischbach & Walsh, 2009; Poole, 2011). Up regulation of MexXY pump is the reported mechanism of aminoglycoside resistance in cystic fibrosis lung isolates *Pseudomonas aeruginosa* (Armstrong & Miller, 2010; Poole, 2011).

Among all the given efflux pumps (Table-5), the over expression of RND (resistance-nodulation-division) family of MDR system has proven for the removal of extremely broad categories of clinical substances (Blair *et al*., 2015). In which MexXY pump was found for the first time in *Pseudomonas aeruginosa* PAO1 strain (Mine *et al*., 1999). Another study on *Pseudomonas aeruginosa* PA154197 strain revealed the over expression of several MDR efflux pump such as MexAB-OprM, MexEF-OprN and MexGHI-OpmD. Major virulence factor in *Pseudomonas aeruginosa* PA154197 strain is controlled by a secondary quorum-sensing system which involved in antibiotic resistance (Cao *et al*., 2019). Further studies have revealed that there are additional MDR efflux pumps like MdeA in *Streptococcus mutans*, FuaABC in *Streptococcus maltophilia*, KexD in *Klebsiella pneumoniae* and LmrS in *Staphylococcus aureus* (Floyd *et al*., 2010; Hu *et al*., 2012; Kim *et al*., 2013; Ogawa *et al*., 2012). HasF, one of the efflux system of RND efflux super family linked with MDR has found in *Serratia marcescens* strain against KAM32 (Toba *et al*., 2019).

Mutational modification of antibiotic target site

Microbes acquire resistance either by inheriting new genetic components or mutations in the existing gene. In such events, the genetic transmission is held either by conjugation, transduction, or transformation (Lambert, 2005). The alteration due to transmission in target structure, reduces the antibiotic binding affinity but does not affect the microbes itself to carry their normal function. For example, resistance in *Streptococcus pneumonia* strain due to mutation in penicillin-binding protein gene (*pbp)* such as (*1A, 1B, 2A, 2X* and *2B*) encodes for the penicillin-

insensitive enzyme (Unemo *et al*., 2012). Hence, alteration events in these high molecular weight PBPs have led to low affinity for antibiotics. Results were validated by protein electrophoresis assay using radio labelled penicillin (Hakenbeck *et al*., 1980; Zighelboim & Tomasz, 1980). More recently, it has been identified that this modified trait of PBPs has arisen due to interspecies recombination by transformation and localized recombination between homologous genes at least from two unidentified closely related species (DowsON *et al*., 1990) that results in mosaic gene *PBP2B* formation (Unemo *et al*., 2012).

Moreover, bacteria smartly acquire similar gene as that of the target protein and render its own mechanism to resist the target protein effect. In the case of methicillin resistance, *Staphylococcus aureus* attains *Staphylococcal cassette* chromosome *mec* (SCC*mec*) element encoding for PBP2 protein, has led its emergence (Katayama *et al*., 2000; McManus, 1997). By attaining this trait MRSA is able to form specific penicillin-binding protein *PBP 2a* and hence reduces binding affinity to β-lactam antibiotics (Brown & Reynolds, 1980; Hartman & Tomasz, 1984; Utsui & Yokota, 1985). These MRSA strains encoding *PBP 2a* proteins are basically originated from hospitals in all over the world (Ito *et al*., 1999; Ito *et al*., 2001; Kuroda *et al*., 2001).

Other than gene mutation bacteria utilize other mechanisms for their survival. One of the examples is an erythromycin ribosome methylase (*erm*) family of genes in bacteria (Khan *et al*., 1999). Bacteria utilize these genes to methylate 16s rRNA ribosomal subunit to reorient active drug binding sites. Thereby, averts the binding of some class of antibiotics such as macrolides, lincosamines and streptogramins (Long *et al*., 2006). Recently a study has reported the association of *erm* gene in reduced solithromycin susceptibility against *Staphylococcus aureus* strain (Yao *et al*., 2019). Interestingly, the characterization of chloramphenicol–florfenicol resistance (*cfr*) methyltransferase unveils that methylation of *A2503* gene in 23S rRNA results in resistance against the majority of drugs such as phenicols, pleuromutilins, streptogramins, lincosamide and oxazolidonones (including linezolid) (Long *et al*., 2006). Both the genes *erm* and *cfr* are transmitted together on plasmid for the distribution among bacteria (Leclercq, 2002; Zhang *et al*., 2013). Molecular distribution and resistance mechanism in *Campylobacter coli* reveal the presence of a broad array of resistance mechanisms against a number of antibiotics such as ciprofloxacin, nalidixic acid, tetracycline and erythromycin. Antibiotic ciprofloxacin and nalidixic isolates express gyrA T861 substitution, tet(O) gene among tetracycline-resistant isolates and 23rRNA A2075G mutation among erythromycin-resistant isolates (Elhadidy *et al*., 2019). The high mutation rate in gyrA among Uropathogenic isolates *Escherichia coli* is also associated with quinolone resistance (Shenagari *et al*., 2018). Another class of antibiotic fluoroquinolones resistance is also associated with a mutation in DNA gyrase or topoisomerase IV genes in *Mycoplasma hominis* strain (Zhang *et al*., 2019).

Modification of antibiotics

Further studies on the antibiotic resistance have revealed various examples of antibiotic alteration which is done by enzyme-catalyzed reactions that hydrolyses the antibiotics (Abraham & Chain, 1940). For the fulfillment of survival, microbes expresses several class of β-lactamases enzymes such as penicillinase (hydrolyzes penicillin and early generation cephalosporin), extended-spectrum β-lactamases (ESBL) (hydrolyzes late generation cephalosporin), Class-A carbapenemases (hydrolyzes penicillins, cephalosporins and carbapenem), cephalosporinases (hydrolyzes cephalosporin), oxacillinase (hydrolyzes cloxacillin or oxacillin) and metallo-β-lactamases (hydrolyzes broad spectrum of β-lactam ring of antibiotic such as penicillins, cephalosporins, monobactams, carbapenems and cephamycins etc.) (Chuma *et al*., 2013; Jacoby & Munoz-Price, 2005). Hydrolysis of β-lactam antibiotics is the most common resistance mechanism reported in Gram-negative bacteria. There are mainly four known mechanisms of β-lactam antibiotic resistance; hydrolysis of the β-lactam ring by β-lactamase; production of PBPs to maintain bacterial cell wall; porins channels modification; efflux protein initiation (Fisher *et al*., 2005; Massova & Mobashery, 1998). PBPs and β-lactam antibiotics cluster together and possess a public health threat that causes β-lactam antibiotic resistance (Massova & Mobashery, 1998). These enzymes also modify antibiotics by adding several chemical

groups on their active site. Hence avert antibiotic binding due to steric hindrance. So far it can be said that these traits enhance pathogen's ability and widespread their resistance at a larger scale (Wright, 2005). Enzymatic modification of aminoglycoside is also another example of the emergence of resistance. Aminoglycoside acts synergistically in combination either with vancomycin or β-lactam (Fatholahzadeh *et al*., 2009). Several classes of aminoglycosides structure modifying enzyme such as aminoglycoside phosphotransferase, acetyltransferase and nucleotidyltransferase (Seyedi-Marghaki *et al*., 2019).

Table 5. Different bacterial efflux transporters are classified into five major super families based on their amino acid sequence and the energy source used to export their substrates, given in table 5 (Ayaz, 2017; Tseng *et al*., 1999).

Major super family		Sub family	Efflux pumps observed in superfamilies
The major facilitator superfamily (MFS)	Secondary active transporter	The Sugar Porter (SP) Family The Drug: H+ Antiporter-1 (12 Spanner) (DHA1) Family The Drug: H+ Antiporter-2 (14 Spanner) DHA2) Family The Organophosphate: Pi Antiporter (OPA) Family The Oligosaccharide: H+ Symporter (OHS) Family The Metabolite: H+ Symporter (MHS) Family fructose-glucose-galactose H+ symporter (FGHS)Family The Nitrate/Nitrite Porter (NNP) Family The Phosphate: H+ Symporter (PHS) Family The Nucleoside: H+ Symporter (NHS) Family The Oxalate: Formate Antiporter (OFA) Family The Sialate: H+ Symporter (SHS) Family The Monocarboxylate Porter (MCP) Family The Anion: Cation Symporter (ACS) Family The Aromatic Acid: H+ Symporter (AAHS) Family "unknown major facilitator super-family" (UMFS) Family The Cyanate Permease (CP) Family The Proton-dependent Oligopeptide Transporter (POT) Family	XylE transporter of *Escherichia coli* QacA of *Staphylococcus aureus* Bmr transporter of *Bacillus subtilis* UhpT transporter of *Escherichia coli* LacY transporter, Kgt transporter, FucP transporter and NarK transporter of *Escherichia coli* Pho-5 transporter of *Neurospora crassa* NupG transporter of *Escherichia coli* OxlT transporter of *Oxalobacter formigenes* NanT and ExtU transporter of *Escherichia coli* PcaKo transporter of *Pseudomonas putida*
The small multidrug resistance family (SMR)		The small multidrug pumps (SMP) Suppressor of groEL mutation proteins (SUG), and a third group Paired small multidrug resistance proteins (PSMR).	EmrE of *Escherichia coli*

The resistance nodulation-cell division superfamily (RND)		The heavy metal efflux (HME) The hydrophobe/amphiphile efflux-1 (gram-negative bacteria) The nodulation factor exporter family (NFE) The SecDF protein-secretion accessory protein family The hydrophobe/amphiphile efflux-2 family The eukaryotic sterol homeostasis family And the hydrophobe/amphiphile efflux-3 family.	MexB of *Pseudomonas aeroginosa* AcrB *of Escherichia coli* MexAB-OprM, MexEF-OprN, MexXY, MexJK and MexEF-OpmD of *Pseudomonas aeruginosa*
The Multi antimicrobial extrusion protein family (MATE)		MATE transporter proteins like NorM in V. parahaemolyticus, a prototype transporter Eukaryotic MATE proteins Subfamily - 2A represents fungal and yeast MATES 2B represents plant MATES 2C comprises animal MATES and 2D consists of protozoal MATES Bacterial and archaeal MATES	NorM of *Vibrio parahaemolyticus* PmpM of *Pseudomonas aeruginosa* HmrM of *Haemophilus Influenza* YdhE of *Escherichia coli* NorM of *Brucella melitensis* MepA of *Staphylococcus Aureus* AbeM of *Acinetobacter baumannii* CdeA of *Clostridium difficile* VcmA, VcrM, etc of *Vibrio cholerae* BexA of *Bacteroides thetaiotaomicron* Erc1 of *Saccharomyces cerevisiae* NorM of *Erwinia amylovora*
The ATP-binding cassette superfamily (ABC)	Primary active transporters	ATP binding cassette subfamily A (ABCA) ATP binding cassette subfamily B (ABCB) ATP binding cassette subfamily C (ABCC) ATP binding cassette subfamily D (ABCD) ATP binding cassette subfamily E (ABCE) ATP binding cassette subfamily F (ABCF) ATP binding cassette subfamily G (ABCG) ATP binding cassette subfamily H (ABCH)	Ard1 of *Streptomyces capreolus* TnrB of *Streptomyces longisporoflavus* LmrA of *Lactococcus lactis*

Approaches to enhance the antibacterial activity

Bioprospecting of natural products that have useful pharmacological compounds are in trends nowadays. Majority of antibiotic resistance against routinely utilized antibiotics has to lead the exploitation of natural sources such as plants, microorganisms and fungi (Simoes *et al.*, 2009). Due to antibacterial activities, these naturally derived phytochemicals can restore the potency of older antibiotics as a consequent and can be served as an alternative approach to treat resistance (Savoia, 2012).

Although the number of phytochemicals are present in natural resources, only few have been identified (Cao *et al.*, 2017; Singh & Chaudhuri, 2018). The most common phytoconstituents are anthraquinones, carotenoids, catechins, flavonoids, ginsenosides, indoles, lignans, polyphenol, phenolic acids, phenylpropanoids, saponins etc. (Xiao, 2017; C. Zhao *et al.*, 2017). Various classes of alkaloids have been investigated for their antibacterial mechanism of action. It has been proposed that indolizidine class of alkaloids inhibit nucleic acid synthesis by inhibiting dihydrofolate reductase enzyme (Rao & Venkatachalam, 2000). Moreover, polyamide alkaloid compromises outer and cytoplasmic membrane integrity and can cause leakage of cytoplasmic content (Alhanout *et al.*, 2010; Salmi *et al.*, 2008). Berberine, an isoquinoline alkaloid isolated from roots and stem-bark of Berberies plant species is known to inhibit nucleic acids synthesis of various pathogens such as bacteria, fungi and protozoa (Domadia *et al.*, 2008; Yi *et al.*, 2007). Besides their antibacterial activity these phytochemicals in combination with conventional antibiotics may possess a different mode of action through different target sites of bacteria and hence can be utilized as an additional therapy to improve conventionally available antibiotics. For example, the antibacterial activity of sulfur-containing phytochemicals such as allicin, dialkenyl, S-allele-cysteine, dialkyl sulphides and isothiocynates from plants against both Gram-positive and Gram-negative bacteria (Barbieri *et al.*, 2017; Sobolewska *et al.*, 2015). An organosulfur compound Allicin (diallyl thiosulfinate) obtained from garlic has been studied for its antibacterial activity against a variety of bacteria such as *Staphylococcus epidermidis, Pseudomonas aeruginosa* and MRSA (Reiter *et al.*, 2017). The antibacterial mechanism of action of allicin has been reported to inhibit sulfhydryl-dependent enzymes such as alcohol dehydrogenase and RNA polymerase (Lanzotti *et al.*, 2014). Further allicin is also reported to target RNA synthesis in the host organism (Feldberg *et al.*, 1988). Resveratrol, a phenolic compound is known to inhibit efflux pump *CmeABC* of *Campylobacter jejuni* and *Mycobacteriaum smegmatis* (Klančnik *et al.*, 2017; Lechner *et al.*, 2008). Moreover, phenolic compound biochanin A is able to reduce the expression of *NorA* efflux pump of MRSA (Zou *et al.*, 2014). Nonetheless, curcumin a well-known phenolic compound obtained from Turmeric plant shows antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* by disrupting their cell membrane (Tyagi *et al.*, 2015).

Bacterial infection leading to animal death are also a major concerns associated with economic loses. Hence there is a critical need of a potential alternative to antibiotics which can further elevate its present ability. In this regards a study in which nisin in combination with essential oil from herbal plants brought evidence of potential inhibitor against respiratory tract pathogen *Streptococcus suis* (LeBel *et al.*, 2019). Nonetheless essential oils isolated from *Santalum spp.* and *Vetiveria zinzanioides* plants alone and in combination showed considerable antimicrobial activity and presented as a feasible approach in wound healing therapy (Orchard *et al.*, 2018). Respiratory tract infections and cancer-related deaths are dominating all over the world and hence there is a demand of effective chemotherapy compounds with reduced side effects is needed. Phytochemical tanshinones, abietane diterpenes extracted from *Salvia miltiorrhiza* exhibits versatile anticancer activity against doxorubicin resistant gastric cancer cells (Xu *et al.*, 2018). According to the WHO fact sheet 2018, resistance to malaria become a major public health concern nowadays and the majority of the strains are getting resistant to the number of anti-malarial medicines. Plant extract from *Zingiber officinale* and *Echinops kebericho mesfin* is reported for exhibiting anti-plasmodial activity suggesting its usage in treating malaria (Biruksew *et al.*, 2018). Phyllanthin compound extracted from *Phyllanthus amarus* plant is able to modulate fluoroquinolone-resistance by

inhibiting NorA efflux pump in *Staphylococcu aureus* SA1199-B strain and could be a potential agent to treat infection (Ribeiro *et al*., 2019). A number of studies also reporting the antimicrobial activities of the number of extracts, essential oils, resins and various compounds derived from herbal plants in recent years (Kokoska *et al*., 2019).

Recently characterization of vaginal microbiota *Lactobacillus* strain is studied for lactic acid and bacteriocin production (Fuochi *et al*., 2017). These substances are not only with antibacterial activity but can be utilized as a co-therapy in combination with antibiotics prescribed (Fuochi *et al*., 2019; Tachedjian *et al*., 2017). Modern techniques indeed led our knowledge to stimulate developments of alternative therapies. Bioengineered lysin-bacteriocin amalgamated molecule termed as lysocins does not only disrupt peptidoglycan in *Pseudomonas aeruginosa* but also degrade biofilm efficiently. This modern approach can be a suitable module to target other pathogenic Gram-positive strains (Heselpoth *et al*., 2019). Nonetheless usage of probiotics also has proven effective against several Gram-negative strain (Öncül & Yıldırım, 2019). Moreover, the pathogenicity of *Mycobacterium paratuberculosis* has the account to dairy animals as well as a human being (Naser *et al*., 2014). Therefore, nisin treatment could be an improving approach not only by decreeing *Mycobacterium paratuberculosis* cell number in milk products but also in animals too (Ali *et al*., 2019). Recently characterized BaCf3 bacteriocin isolated form *Bacillus amyloliquefaciens* strain has been proved as a probable biofilm and growth inhibitor against certain food borne pathogens (Bindiya *et al*., 2019).

In addition to this utilization of nanoparticles is in trend nowadays (Nejabatdoust *et al*., 2019). Tobramycin conjugated to Fe_3O_4 (iron oxide) nanoparticles was investigated against *Pseudomonas aeruginosa* in cystic fibrosis diseases (Brandt *et al*., 2013). Therefore, nanoparticles such as zinc oxide, iron oxide and silver can be a novel approach to treat pathogenic infection due to their broad-spectrum antimicrobial activity (Alam *et al*., 2019; Nejabatdoust *et al*., 2019; Rafińska *et al*., 2019). Nonetheless, several D-amino acids are also cited as a therapeutic agent against several Uropathogenic bacteria (Korte-Berwanger *et al*., 2013).

CONCLUSION

The emergence of antibiotic has revolutionized the treatment of major infectious diseases and from there on numerous mechanisms have been learnt up to develop several novel antibiotics. However, the early era of antibiotic generations has successfully treated the infectious diseases but with the passage of time continuous exposure of antibiotic has led them to develop alternative pathways alterations/modification at the cellular level to survive against various classes of antibiotics, which indeed have challenged the health of people all around the world. For that pursuance more studies on the mechanism (physiological, metabolic and genetic) pertaining to their adaptations are required to develop novel antibiotics.

Microbes obtain resistance against antibiotics is entirely hinge on the method of action of antibiotics. This include membrane permeability, active efflux pump lead to MDR, modification in target site, inactivation of antibiotic via enzyme production or additional intermediary materials then finally alterations within genetic material which entirely impact in resistance production. Hence, there is a necessity of novel antibiotic along with novel microbe's extermination mechanisms or else through a modified mechanism. Some additional approaches like the addition of stable products, using antibiotics in combination or by modifying their characteristics which in turn enhance antibiotic capability. These new approaches can be helpful in inactivating bacterial protein synthesis destruct their DNA synthesis and inhibit their self-defense mechanism. In fact, some researchers are using antibodies, herbal plants extract and probiotics to enhance antibiotic capability. However, there is a need for in-depth studies to ensure the mechanism of action and safety of antibacterial phytochemicals.

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