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Antibiotics resistance - a stumbling block to antibiotics research

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ABSTRACT

Antibiotics are natural or synthetic substances that inhibit the growth of infectious microorganisms and prevent from them, causing serious infections. Though the discovery of penicillin was claimed to be accidental, later on, systematic procedures for antibiotic discovery was introduced by Waksman through his streptomycin discovery. Adopting Waksman's platform, many researchers are exploring natural sources in search of antibiotics. On the other hand, the development of resistance to antibiotics is growing at a rate faster than the discovery of new antibiotics. While a number of semi synthetic and synthetic compounds with antimicrobial properties are emerging to combat the above problem, the microorganisms are in no way working inferior to resist the actions of such substances. In fact, the development of resistance by microorganisms to above said alternatives are observed at an even faster rate than the natural antimicrobial compounds obtained from microbes. The reason behind such a faster resistance development is due to the similar structural features of semi-synthetic and synthetic compounds to natural antibiotics from microbes. The treatment of infectious diseases becomes a big task and requires a greater concern nowadays to avoid increased rates of mortality. This is an alarming condition demanding for the discovery and development of new antimicrobial compounds that would end up as a better solution for the existing problem and avoid the development of resistance. This review presents the background of antibiotics discovery and resistance development and also provides an insight into the available strategies to combat the problem.

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INTRODUCTION

Antibiotic Research: pre, golden and post-golden era

Antibiotics have been in use as life-saving medicines since ancient times, notably during World War II (Lerner, 2004). But the foundation for the golden era of antibiotics was laid only after the discovery of Penicillin in 1928. From then, a number of antibiotics were discovered from different natural sources and their potential to treat infections caused by various microorganisms were studied. During the period from 1940 to 1960, there was restless research to bring out the majority of the antibiotics now in the market. The discovery of drug classes like aminoglycosides, tetracyclines, cephalosporins, macrolides, glycopeptides, quinolones and carbapenems happened only during the golden era of antibiotics (Fernandes, 2006), (Chopra, 2012). They belong either to the class of natural compounds or

Table 1: Mode of action of antibiotics

Mechanism of action	Antibiotic class	Examples
Bacterial-cell-wall biosynthesis	Beta-lactam antibiotics, Glycopeptides	Penicillin and Vancomycin
Bacterial protein biosynthesis	Aminoglycoside and Macrolide	Gentamicin and Azithromycin
DNA and RNA replication	Quinolone and Rifamycin	Ciprofloxacin and Rifampin
Folate coenzyme biosynthesis	Sulfonamide	Sulfamethoxazole

analogues of natural substances. The mode of action of classes of antibiotics is characterized, as shown inTable 1. After 1960, the research and discovery of new classes of antibiotics dropped tremendously as evident with the number of antibiotics entered the market after 1960 (Kern, 2006). The reasons for such a curtailment were attributed to the failure of classical screening methods and rediscovery of known antibiotics (Bérdy, 2012; Sanchez and Demain, 2009). There was a lack of innovation in antibiotics research between 1960 and 2000. In the ballpark, antibiotics research appertain to four lines of discovery as shown inTable 2.

MATERIALS AND METHODS

Antibiotics resistance development – The rationale behind

The accelerated the need for antibiotics over the years is unavoidably accompanied by a major drop in the discovery and development of new antibiotics for a number of reasons including huge time and money investments. On the other hand, infectious microorganisms have built up resistance mechanisms to evade the actions of antibiotics. Antibiotics or antimicrobials have become vital in maintaining the health of human beings by way of treating infections caused by several microorganisms. The major causes of resistance development are stated as inappropriate prescribing of antibiotics (Silva and Palomino, 2011; Arnold *et al.*, 2011) extensive usage in agricultural fields (Gross, 2013; Howard, 2013) availability of few antibiotics in the market (Gould and Bal, 2013; etal Golkar, 2014; Wright, 2014), and stringent regulatory principles. Since only a very few classes of antibiotics are natural and the rest belong to either synthetic or semi-synthetic forms of those obtained from natural sources, they possess similar structural characteristics. Hence the target microorganisms have developed resistance to almost all these antibiotics in the commercial market in a relatively very shorter span of time (Kumarasamy, 2010; Lee, 2010). The development of resistance to antibiotics is clearly understood in a number of studies performed with respect to hospital-associated infections at a different time (Fish, 1995; Espersen, 1998). The inappropriate and over the use of antibiotics are reported to be the major reasons of resistance development in all these studies (Lushniak, 2014; Rossolini *et al.*, 2014). It is more distressing that even before some of the antibiotics reach the commercial market, the target microorganisms have gained resistance. This is owing to the exposure of target organisms to antibiotics in the natural environment (Kim, 2013). The detailed mechanisms of antibiotic resistance development are understood and explained by several scientists. The resistance developed may be attributed to the biochemical or genetic changes that take place in the target microorganisms after repeated exposure to the same antibiotics. This, in turn, leads to mutations that would happen spontaneously either in the dividing or non-dividing cells (Hooper, 2001; E.Peterson and Kaur, 2018). Horizontal gene transfer is claimed to be the prominent reason for the fast and easy spread of antibiotic resistance between target organisms of different classes (Nordmann and Poirel, 2002). The biochemical changes are accredited to enzyme modification, redox changes, target alteration and membrane permeability factors (Ramirez and Tolmasky, 2010; Delcour, 2009). Hence the infectious microorganisms undergo any of the above changes to acquire resistance to the antibiotics. As new classes of antibiotics emerge to combat the current resistance issue, the same target develops mutations to overcome the challenge of the new class of antibiotics. Thus, it leads to the emergence of multidrug-resistant microorganisms. Moreover, the microorganisms form biofilms with instinctive resistance to the antibiotics due to the reduced rate of movement of the antibiotics into such biofilms formed (J.Davies and D.Davies, 2010; Nikaido, 2009). The development of multidrug-resistant microorganisms and superbugs move the issue to a critical state which needs to be addressed at a faster rate with a long

Table 2: Summary of lines of antibiotics discovery

S.No	Line of discovery	Examples	References
1	Natural sources	Penicillin, Streptomycin	(Johnson, 1983), (Owa, 1999)
2	Synthetic	Sulfa drugs, Quinolones	(Silva, 2003)
3	Semi-synthetic	Carbapenems, Azithromycin	(J.ApSimon and Goldsmith, 1973) , (Nicolaou, 2001) , (Nicolaou, 2009)
4	Combination of therapies	Isoniazid, pyrazinamide and rifampicin	(Gillespie, 2002) (Silva and Palomino, 2011)

time viable solution.

Antibiotic resistance – Strenuous challenge

Majority of the pharmaceutical companies abstain from spending huge money and time to prove newer classes of antibiotics, but rather they counteract to this problem by way of developing an abundant number of synthetic and semi-synthetic antibiotics (Harvey, 2008; Projan, 2003). They also employ high throughput technologies to combat the problem of figuring out the right candidate for development. But then a number of unanswered challenges remain in the path of antibiotics research. The ability of synthetic antibiotics to penetrate the cell walls of infectious microorganisms is poor, and they fail to adopt 'Lipinski's rule of five' for drug likeliness. In order to achieve efficient treatment, higher doses of synthetic antibiotics need to be administered, which increase the inherent toxicity associated with drug administration (Payne, 2007). When new antibiotics are out into the commercial market, they reach the peak of their sale and start to drop over a very short period of time for the reason of resistance development. Thus, the companies must constantly look for new antibiotics replacing the old ones in order to hold on their sales number. For these reasons, the return on the investment made was poor which urge the pharmaceutical companies to take other decisions to focus on manufacturing of generic drugs which would, in turn, bring them up to huge monetary benefits (Park and Kim, 2003). Hence the research on new antibiotic discovery and development failed to happen with the most interest during the last few decades (Finberg, 2004; Grossman, 2012; Jabes, 2011). The era is now reverting back to the pre-antibiotic period leading to the increased numbers of death due to the inability of available antibiotics to treat infections in the thick of these resistance issues. The development of multidrug-resistant pathogens is the epitome of this issue, making the problem rather more complicating. It was predicted by WHO that nearly 35 million people would die from tuberculosis by 2020. The problem has now become the most threatening public crisis and looking at a suitable solution is the need of the hour.

RESULTS AND DISCUSSION

Expedient resources for antibiotics research

Microorganisms had been the most preferred sources of antibiotics research for a long time as known with the contribution of Fleming and Waksman. The phenomenon of antagonism for the existence of life in a habitat is the basis for the production of antibiotics. In the natural conditions, different microorganisms produce numerous forms of secondary metabolites, which in turn, specifically inhibit the growth of other related forms of microorganisms (Silva, 2017). This approach is later adapted for use in the treatment of infectious diseases caused by susceptible microbial targets. With the success stories in line, researchers started exploring different natural sources, including soil samples, to isolate microorganisms competent to produce such antibiotics. But lamentably the levels of antibiotics produced are not sufficient to meet up the commercial needs of the society. Hence, the advent of fermentation technology proves to achieve necessitous levels of useful antibiotics (Robinson, 2001). With this animus, the search for new classes of antibiotics continued to reconnoiter the natural sources. The domain bacteria was burrowed in-depth with this idea, and the research dropped after a few decades for the reason that now or very rare number of new classes of antibiotics were discovered. This is because the theoretical numbers proposed for the screening of one actinomycete strain, the most active antibiotic producer ranges from 10^8 to 10^9 strains (Baltz, 2006). That is the researcher should work with at least 10^8 strains before screening a single strain that actively produces a new antibiotic. Also, higher numbers of such compounds screened belonged to any of the known classes of antibiotics for which the organism had already gained resistance. The principle of antibiotic research becomes less significant since no new class of antibiotics efficient to inhibit the resistant organisms is obtained (Fox, 2006). This

fact naturally pulls back pharmaceutical companies to get out of these cumbersome screening processes which would demand large investment and time with relatively modest returns. But the literatures suggest that majority of the natural population capable of producing secondary metabolites like antibiotics remain unexplored (Peláez, 2006).

Future Prospects

Greater numbers of the unexplored or least explored population belong to habitats like marine and extreme environments. Microorganisms living in extreme environments are of considerable importance on this subject (Imhoff, 2011). Majority of these populations belong to the domain Bacteria and Archaea. Marine or halophilic/haolotolerant bacteria and archaea account for nearly 20 - 30% of the total biomass (Allers and Mevarech, 2005). The members of these haophiles thrive in extreme conditions like high salt. Their metabolites are highly valued for their stability compared to similar metabolites from the other members of the domain Bacteria (Margesin and Schinner, 2001). Recently there are reports on the use of Archaeocins to inhibit the growth of members of the domain Bacteria (Pidot, 2014). The least explored population belonging to halophilic/halotolerant classes of microbes are the promising sources of antibiotics research. Also since only less than 1% of the microbial population is culturable, the metagenomic approach appears to be a better alternative to discover useful antibiotics from uncultured microorganisms (Mann, 2005; Singh and Pelaez, 2008).

CONCLUSION

Nature always offers positive hands to provide perfect and unimaginable answers for all complex tabled questions. What then appears as the need of the hour is researchers and pertinacious research to bring out unblemished solutions. In this respect, the research on antibiotics and resistance development has to be thoughtfully scrutinized, and more viable solutions in terms of new classes of antibiotics must be obtained to fight the existing problems of antibiotic scarcity and antibiotic resistance.

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