

Microbial Amensalism: A Natural Process for the Revival of Antibiotics

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Abstract

Pathogenic microorganisms are developing antibiotic resistance against lifesaving drugs. Many pathogenic bacteria have now developed multi-resistance that is a significant concern over the failure of antibiotics. There is a pressing need to work on a natural amensalism strategy to cope with these resistant pathogenic strains. Pathogenic microorganisms are developing resistance against old antibiotics with the help of evolutionary mechanisms, in the same way; the microorganism that previously produced antibiotics can also upgrade their defensive antibiotic compound through evolutionary mechanisms. Microbial amensalism is a negative ecological relation that can be a pleasing strategy to upgrade failed antibiotics. Re-culturing of antibiotics producing microorganisms with antibiotic-resistant pathogenic strains can produce upgraded antibiotic compounds against these resistant strains.

Keywords: Amensalism; Antibiotics resistance; *Staphylococcus aureus*; Superbugs

Abbreviations: MRSA: Methicillin-Resistant *Staphylococcus aureus*; VRSA: Vancomycin-Resistant *Staphylococcus aureus*

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Introduction

Antibiotics have saved thousands and millions of lives since their discovery. Until 1950, a majority of bacterial infections were curable by using antibiotics [1,2] but now we have learned a new term known as antibiotic resistance. Bacteria are evolving their own defense against these antibiotics; as a result, it abates the likelihood of curing bacterial infections and escalates the mortality and morbidity linked with bacterial infections [3].

Antibiotic resistance is an intricate ecological phenomenon that depends on mechanisms of resistance, bacterial strains and individuals [4]. Despite targeting numerous critical pathways, antibiotics have vanished their efficacy against bacterial infections through the evolution of resistance mechanisms in these bacteria [5-7].

Due to the continuous upsurge in resistance to synthetic antibiotics, there is a need to change our attention toward natural antibiotics. The gap between new antibiotics development and the development of antibiotic resistance has drawn consideration to old antibiotics whose spectrum of cure commonly contains highly resistant bacteria [8].

Amensalism is a type of interaction between two organisms,

where one causes harm to another organism without any benefits [9,10]. The discovery of the first natural antibiotic named penicillin was the accidental result of this process of amensalism [11]. Therefore, the aim of this review is to draw attention to a natural process of microbial amensalism to revive antibiotics against bacteria that have become resistant to old natural antibiotics. The interactions between bacteria and fungi have been extensively utilized effectively over the years by humans for making antibiotics and other several biochemicals that can be used in biotechnology and pharmacology [12].

The Emergence of Antibiotic Resistance

Antibiotic resistance was recognized soon after the discovery of penicillin. In 1941, penicillin was released for clinical use, and just after a year (in 1942), *Staphylococcus aureus* became resistant to it. *Staphylococcus aureus* started making the penicillinase which breaks the beta-lactam ring of penicillin [2].

Antibiotic resistance develops naturally, but misuse of antibiotics is speeding up the process [13]. The irrational use of antibiotics generates selection pressure favoring the development of resistant mutants against these antibiotics [14]. However, this problem is becoming perilous due to the development of new

bacterial strains having multiple resistances to a great range of antibiotics [15]. An increasing number of infections such as salmonellosis, tuberculosis, gonorrhoea, tuberculosis, and pneumonia are becoming tougher to treat because of the less effectiveness of antibiotics [16].

One of the well-known examples of multiple-resistant bacterial strains is *Staphylococcus aureus* (or golden staph). It is distressing that the bacterium (*Staphylococcus aureus*) that acquaint with the discovery of the first antibiotic, could also be the first to develop multiple resistance and become incurable with a huge collection of antibiotics developed and discovered over the past six decades. Antibiotic resistance is now becoming a risk for the health-related achievements of modern medicine [17]. Chemotherapy surgeries and organ transplantations become much risky without antibiotics for the treatment and prevention of infections [16].

New Discoveries and Revival of Old Antibiotics

In the era of rising antimicrobial resistance, and the scarcity of novel antibiotics, new strategies for the development of novel antibiotics are instantly needed. One of the prolific strategies is to revive old antibiotics with the help of the natural amensalism process. Amensalism (also antibiosis) aids in the making of antimicrobial compounds by one microorganism which may be harmful to the others [18]. Although hundreds of antibacterial agents have been extracted from different microorganisms, only a few of them are clinically valuable. New discovered antimicrobial compounds should be highly effective against microorganisms and minimally toxic to humans. Several different antibiotics have been isolated from microorganisms to combat microbial infections, but the irrational use of these antibiotics provided a chance for microorganisms to develop resistance against these antibiotics [19,20]. With the discovery of new natural antibiotics, old antibiotics can also be revived.

In 1928, the finding of the first antibiotic (penicillin) started the golden age of antibiotics discovery that remained undefeatable till the mid-1950s. Afterward, a gradual decline started in the discovery and development of novel antibiotics and the evolution of drug resistance have led to the contemporary antimicrobial resistance crisis. In the early 1940s, Penicillin-Resistant *Staphylococcus aureus* (PRSA) was reported just after a few years of the first clinical use of penicillin [21,22] including MRSA. To find new antibiotics for *Staphylococcus aureus*, it can be reinfected with *Penicillium* species to develop an updated version of penicillin to treat this superbug. Several studies have been conducted on different *Penicillium* species to find penicillin antibiotics for the direct treatment of treat wounds infected by *Staphylococcus aureus*.

Vancomycin is another important antibiotic for multi-resistant bacterial infections. In the 1980s, resistance to vancomycin was revealed in enterococci, and this detection prompted substantial concern for the use of vancomycin in the future as

a suitable treatment for Methicillin-resistant *Staphylococcus aureus* [23]. Soon thereafter, *Staphylococcus aureus* was isolated with less susceptibility to teicoplanin (a structural relative of vancomycin) appeared in Europe [24,25]. The first VRSA (Vancomycin-Resistant *Staphylococcus aureus*) was reported in the USA in 2002 [26]. Providentially, VRSA strains with complete resistance to vancomycin are still rare, regardless of extensive use of vancomycin for treating MRSA (Methicillin-Resistant *Staphylococcus aureus*) infections [27].

Many different old antibiotics were lifesaving drugs at a time and then microorganisms developed different mechanisms to get resistant against them. There is a pressing need for the health research sector to find new antibiotics as well as revive old antibiotics to compete with superbugs in the future.

Why do Microbes Produce Antibiotics?

Microorganisms usually live in harsh environments with their competitors. To get sufficient water, food, space, and other limited resources, they have to compete with their competitors. Huge variation in abiotic and biotic conditions makes microbial populations acclimatize and develop tactics for successful reproduction and survival and antibiotics are one of the most effective strategies for this adaptation [28]. All microorganisms including bacteria, and fungi developed chemical interactions either associative or competitive, and amensalism is one of these interactions which help one organism to harm or kill another by using antimicrobial compounds.

Why Amensalism Process for the Revival of Antibiotics?

The main reason to choose this strategy of amensalism is to allow the natural process of producing improved antimicrobial compounds with the help of natural mechanisms of the microorganisms. As pathogenic organisms develop defense mechanisms against the antimicrobial compounds by using their genomic tools. In this same way, other organisms can also improve their antimicrobial compounds against resistant strains with the help of evolutionary mechanisms. As amensalism is a negative ecological association between two different organisms, in which one is destroyed and the other remain unaffected [29] thus, culturing a resistant strain of any microorganism with its enemy (either a bacterium or fungus) which can reproduce an upgraded version of antimicrobial compounds with the help of evolutionary mechanisms to kill again the resistant strains of microorganism.

For example, *Staphylococcus aureus* has become resistant against penicillin, but reculturing of *Staphylococcus aureus* with *Penicillium* species can reinitiate the process of amensalism, and *Penicillium* species will try to kill *Staphylococcus aureus* by upgrading their antimicrobial compounds with the help of evolutionary mechanisms. After several interactions of both these organisms, *Penicillium* species can develop some evolutionary mechanisms to change the version of penicillin to kill the resistant strains of *Staphylococcus aureus* resulting in the revival of old penicillin,

which is currently unserviceable against *Staphylococcus aureus*. The best results can be attained by providing a natural environment to both organisms in controlled conditions without fudging biosafety and biosecurity rules.

Conclusion

Antibiotics are playing an important role in saving lives since the discovery of penicillin. But due to the irrational use of antibiotics, microorganisms are developing resistance against these lifesaving drugs. The serious concern is that now bacteria are developing multiple resistances. It is estimated that due to antibiotic resistance 10 million people will die each year by 2050, and this estimated number of casualties will be more than that of dying by cancer. Therefore, a suitable strategy is required to cope with antibiotic resistance. The natural process of amensalism is a natural way to develop upgraded antibiotics. Resistance strains should re-infect with those which previously produced antibiotics against them e.g., *Penicillium* species can be re-cultured with resistant strains of *Staphylococcus aureus*. The main reason for choosing this strategy is that if pathogenic microorganisms are developing resistance against old antibiotics, then organism that previously produced antibiotics can also upgrade their defensive antimicrobial compound through the same evolutionary mechanisms.

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