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Applications in microbiology contribute to the development of antibiotics

Review article

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Abstract

Many people consider antibiotic treatment to be one of the most successful medical interventions ever developed. They have been able to treat bacterial diseases in humans, animals, and, to a lesser extent, plants, resulting in millions of lives being saved. They have demonstrated their efficacy in a variety of applications, such as food preservation, animal nutrition, and others. In addition to their notoriety as pathogens, bacteria are also the primary and most important source of antibiotics. Antibiotics were first discovered in bacteria. Microbes such as fungi, bacteria, and actinomycetes make antibiotics on their own to protect themselves from other microbes that may be in their environment. Soil microorganisms employ these adaptive strategies to live and reproduce in a wide variety of biotic and abiotic environments. Therefore, it is not surprising that bacteria can adapt to evade antibiotic elimination or develop resistance to the medicines they produce. Due to the growing need to fight diseases and stop the exponential spread of antibiotic resistance in the ever-changing microbial family, antibiotic research and production have become the most promising fields.

Keywords: Actinomycetes. Antibiotic-producing. Aspergillus. Bacteria Cephalosporin. Gene cluster.

Introduction

The ecosystem cannot function without the presence of microorganisms. Although they are known to spread diseases that could result in death, they also offer many benefits to the ecosystem. Their benefits include the production of oxygen, which is essential for human existence, and the release of nutrients into the environment, which is beneficial to both plants and animals. Both are beneficial for the environment [1]. In addition to bacteria, viruses, algae, protozoa, and fungi are also considered types of microorganisms. Specifically, microorganisms play a crucial role in forming symbiotic relationships with other creatures, such as plants and animals. The human digestive tract contains a wide variety of bacteria. 2017 Previous and subsequent Wednesdays Researchers have found that only a few hundred of the approximately 1.5 million different bacteria pose a threat to human health. We call bacterial infections "communicable" because they spread between hosts. In contrast to viruses, bacteria and other types of microorganisms can reproduce without the assistance of an outside virus. Infections caused by bacteria are the leading contributor to mortality on a global scale. The bacterial infection known as tuberculosis (TB) is one of the top 10 leading causes of death on a global scale [2]. Pathogens can cause tuberculosis. The mycobacterium that causes tuberculosis spreads slowly and mostly attacks the lungs. Its growth rate is moderate. You can avoid many infectious diseases, such as pneumonia [3]. pneumococcal bacterial meningitis [4]. Shigella sp. food poisoning [5]. and Campylobacter spp [6]. The production of endotoxin and exotoxin is the primary

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focus of bacterial pathophysiology in the host. Case in point: Toxins cause tissue damage and can throw off the body's homeostatic balance. On the contrary, bacteria get their nutrients for reproduction from the tissues they infect, which can lead to tissue breakdown. *Staphylococcus* species, *Streptococcus* species, and *E. coli* are all examples of bacteria that are known to cause disease. In most cases, the immune system can successfully combat bacterial infections well before they cause any damage or illness. However, they can avoid detection by the immune system, which is a process that is often sped up in settings where the immune system is impaired. In most cases, antibiotics are required for therapy in these types of cases, since they can kill bacteria and inhibit their growth [7-9].

Antibiotics

Antibiotics are low molecular weight compounds or drugs that are used to treat bacterial infections. Actinomycetes are responsible for 85% of antibiotic production, whereas bacteria and fungi are responsible for 11% and 4%, respectively, of antibiotic production [10]. During reproduction, the primary metabolites that are created are secondary ones. Metabolites have been put to a variety of uses, including in the treatment of viral infections, cancer, and bacterial infections, respectively. It is common for them to be created during the late logarithmic phase of reproduction, but their presence is not necessary for the development of bacteria. Antibiotics have been administered to gram-negative and gram-positive pathogen strains to eradicate or stop the pathogen's ability to reproduce. Antibiotics can either cause the death of bacterial cells or stop the growth of bacterial cells when they encounter them. How they eradicate germs determines how we classify them [11]. Common mechanisms of action include blocking the production of bacterial proteins, interfering with DNA replication and transcription, and inhibiting the formation of bacterial cell walls. Other antibiotics go after cell membranes, disrupt folic acid metabolism, and interfere with the production of DNA and RNA. It is common knowledge that aminoglycosides, macrolides, and other types of chemicals kill bacterial cells by inhibiting protein synthesis, which is necessary for bacterial cells to maintain their homeostasis. Antibiotics have been used for a very long time to suppress the synthesis of bacterial cell walls, particularly glycopeptides. This is one of their primary functions. Penicillin is effective against bacteria because it blocks the activity of the Trans peptidase enzyme, which is responsible for the completion of the peptidoglycan cross-linking process and the formation of the bacterial cell wall [12].

Table 1. presents the most prevalent naturally occurring antibiotics that are created by bacteria, in addition to the antibacterial actions that are carried out by these organisms.

Class	Mode of action	examples	Production species	References
β-Lactams	Inhibits bacterial cell wall synthesis	penicillin	Penicillium sp.	[13]
β-Lactams (Carbapenems)	inhibits bacterial cell wall synthesis	cephalosporin	Streptomyces cattleya	[14]
Tetracyclines	inhibits protein synthesis;	Thienamycin	Streptomyces rimosus	[15]
Quinolones	Interferes with the replication and transcription of bacterial DNA	Chlortetracycline	Pseudomonas sp	[16]
Lincosamide	inhibits bacterial protein synthesis	Oxytetracycline	Streptomyces lincolnensis	[17]
Macrolides	Inhibits bacterial protein synthesis	Lincomycin	Arthrobacter sp	[18]
Glycopeptides	Inhibits bacterial cell wall synthesis	Vancomycin	Streptomyces griseus	[19]
Aminoglycoside	Inhibits bacterial protein synthesis, leading to cell death.	Streptomycin	Streptomyces fradiae	[20]

The Role of Soil Microorganisms in the Manufacturing of Antibiotics

Many different bacterial species often produce antibiotics as secondary metabolites [21]. Most of the bacteria that are antagonistic to these pathogens and antipathogenic come from soil cultures. Currently, we can produce antibiotics through semi-synthesis and chemical synthesis of natural product analogs. The intricate and diverse ecology of the soil makes it ideal for the growth of bacteria that can produce antibiotics. In 1904, Frost was one of the first scientists to explore the role of soil microbes in preventing or eliminating the onset of disease [22]. The journal Science published his research. Since then, researchers have conducted extensive research on the role of soil microorganisms in preventing, retarding, or curing disease progression, leading to the development of several innovative antibiotics. According to the study's authors, the "disappearance" of soil pathogens was the driving force behind this [23]. Microorganisms, particularly those in the soil, produce antibiotics to inhibit or kill bacteria that compete with them for food, water, and nutrients. A single teaspoon of soil can hold anywhere from hundreds to billions of different species of bacteria. The soil contains bacteria [24]. It produces more than 60% of all known antibiotics. Microbes produce antibiotics as a defense

mechanism to keep them alive. This way of treating infectious diseases that can affect animals, plants, and people has become the gold standard.

Actinomycetes are responsible for the production of antibiotics.

They provide food, water, and nutrients. A single teaspoon of soil can hold anywhere from hundreds to billions of different species of bacteria. Strains belonging to the genus Actinomycetes include Nocardia, Streptomyces, and Actinomyces. In the nineteenth century, actinomycetes were responsible for the discovery of a wide variety of antibiotics. These antibiotics included, among others, streptothricin, tetracyclines, and erythromycin [25]. Throughout the 20th century, researchers actively continued to develop antibiotics, notably daptomycin, thienamycin, and petrobactin [26]. The most important genus of Actinomycetes, Streptomyces sp., is responsible for the production of almost two-thirds of all antibiotics, including the well-known medication streptomycin [27,28]. Streptomyces produces natural antibiotics such as chloramphenicol and neomycin, which are used in medicine. Table 2 shows that the Streptomyces species produce many antibiotics used in clinical settings.

Table 2 outlines the antibiotics found in actinomycetes. Research on Bacillus and Actinomycetes has led to the discovery of many new antibiotics [29].

Actinomycetes	**Antibiotics**	**References**
Streptomyces kanamyceticus	kanamycin	[30]
Amycolatopsis mediterranei	Rifamycin	[31]
Streptomyces rose sports	Daptomycin	[32]

Antibiotics generated by fungi

On Earth, there are around 1.5 million different species of fungi, 95% of which remain unidentified [33]. Fungi are the organisms with the most architectural diversity when it comes to producing medicinal compounds. The production of some of the most powerful antibiotics currently on the market involves this bacterium. Antibiotics similar to those produced by soil bacteria help fungi compete with soil microorganisms. Fungi that grow in the soil are responsible for approximately 20% of all antibiotics produced by fungi [34]. It is believed that the first antibiotic, penicillin, was created by fungus. Penicillium (P) fungus was the catalyst for penicillin's discovery. Researchers have discovered many species of Penicillium, including P. chrysogenum, P. nalgiovense [35]. and P. notatum [36]. The scientific name for a species of the genus Penicillium known for its high levels is P. chrysogenum [37]. Fungi are responsible for producing both penicillin and cephalosporin. They belong to the beta-lactam class of antibiotics and have properties similar to penicillin. The microorganism Cephalosporium acremonium, also known as Acremonium chrysogenum, produces the broad-spectrum antibiotic cephalosporin [38]. Soil matrices widely contain Acremonium chrysogenum. This is especially true in humid conditions. Cephalosporin is an antibiotic that acts as an inhibitor to prevent the production of bacterial cell walls.

Table 3 includes fungi with the ability to produce antibiotics. There are four different species of Aspergillus [39].

Species	Antibiotics	References
Penicillium	griseofulvin Patulin	[40]
Aspergillus	fumigatus Aspergillin	[41]
Aspergillus awamori	Emodin	[42]
Aspergillus sp.	Xanthoascin	[43]

Considerations in Biochemistry and Genetics Regarding the Production of Antibiotics

During antibiotic-producing microbe screening, we use techniques with a high degree of selectivity to detect and isolate bacteria of interest from a large pool of other types of microorganisms. Environmental parameters, such as temperature and the amount of water and nutrients available, have a considerable impact on the ability of microorganisms to live and thrive in their surroundings. The process of cultivating the specified microorganisms also requires consideration of these aspects. Advances in microbial molecular genetics have greatly simplified the production of antibiotics. Mutagenesis, a technology that modifies genes, uses ultraviolet radiation, X-rays, and substances that are themselves mutagenic. The resistant mutation strategy can also increase the number of antibiotic-producing microorganisms in a population [44]. The genetic material of bacteria that can produce antibiotics is jam-packed with genes that code for the enzymes involved in antibiotic production. To prevent drug autotoxicity, bacteria encode antibiotic-resistance genes as a precaution. It makes sense that there is a connection between the expression of the gene that codes for antibiotics and the gene that confers resistance. The presence of antibiotics or transformation chemicals that are necessary for antibiotic manufacture is what activates the resistance gene most of the time. Even if the antibiotic-associated gene is absent, it is possible to produce the gene for antibiotic resistance. For instance, if we prevent the expression of the erythromycin gene, we will express the erythromycin-resistant gene. A wide variety of resistance and defense mechanisms, such as drug receptor alteration and metabolic shielding, impede the pharmacological target response [45]. Microorganisms that produce antibiotics also create enzymes that break down antibiotics in the environment. Enzymes such as N-acetyl transferases, O-phosphotransferases, and O-adenyl transferases are essential to the production of antibiotics [46]. The strain Streptomyces griseus, responsible for manufacturing streptomycin, produces a modification enzyme, a subject of extensive investigation. The enzyme streptomycin-6-phosphotransferase is responsible for the conversion of active streptomycin to the inactive form streptomycin-6-phosphate [47]. Butyrolactone, a signaling molecule, triggers the production of streptomycin in bacteria by stimulating the A-factor signaling cascade [48]. It does this by interacting with a member of the TetR family called Arp, which in turn releases the target promoter [49]. AdpA and the str gene cluster, which is unique to streptomycin production, are key regulators of secondary metabolites (Ohnishi et al., 2005). Within the str-gen cluster, A dpA can form a binding complex with the strR-aphD promoter. This causes the transcription factors StrR and AphD to become more active, which in turn activates the biosynthetic gene and the streptomycin-resistant gene, respectively [50]. The AphD gene encodes a protein that inactivates streptomycin-6-phosphotransferase. Because it

removes the phosphate group, StrK phosphatase can reconstruct phosphorylated streptomycin. Both the mechanisms by which antibiotics accomplish their goals and the genes responsible for resistance are tightly intertwined. Nature does not synthesize antibiotics simultaneously, potentially leading to shared toxicity among different strains of bacteria. On the other hand, nonproducing cells acquire resistance through communication within the same strain. Antibiotic-producing microorganisms can produce antibiotics through a process known as antibiotic efflux, which is an additional significant and favorable technique. Microbes use this process to rid their cells of medications, which lowers the toxicity of the pharmaceuticals within the cell while simultaneously increasing the toxicity of the chemicals to nearby pathogens. Efflux is beneficial for commercial antibody manufacturing, which is in contrast to the inactivation process. The inactivation method requires the activation of antibiotics before injection, while the efflux method successfully removes active antibiotics [51].

Utilization of microorganisms in the production of antibiotics in an industrial setting

Industrial microbiology has developed methods to expand the production of antibiotics due to the importance of antibiotics and the growing demand for them. One method of enhancing gene expression is amplification. During the amplification phase, vectors such as phages and plasmids reproduce these genes and reintroduce them into microorganisms. During the research and development phase of the process, scientists modify the gene that stores instructions for producing antibiotic-producing enzymes and grow antibiotic-producing bacteria in Petri plates and tubes with a growth medium capacity of only 100 milliliters. In an industrial environment, the source microorganisms are cultivated in containers that accommodate more than 100,000 liters (L) of growth material. The fermentation technique enables production on a large scale. In most cases, the microbial strains used in fermentation are genetically engineered to enhance antibiotic production. We constantly improve strains because we need high-yielding strains to produce antibiotics [52].

Fermentation

The fermentation process requires the isolation of the appropriate source bacterium under sterile conditions to prevent contamination by other types of microorganisms. Glycerol yeast extract and Seaboard dextrose agar can help isolate bacteria and fungi, respectively. Carefully regulating the oxygen content, temperature, and pH of the growing medium, along with the amount of fertilizer and the plant population, can achieve optimal yield. Fermentations in batch, fed-batch, or continuous culture are the most common approaches utilized when accomplishing this goal. We suspend reproducing microorganisms in a solution before submerging them into their growth medium. Once production is complete, a significant amount of work remains. To acquire and purify essential by-products, the fermentation process that occurs after the production of antibiotics includes several critical phases. One can utilize processes such as crystallization, ion exchange, adsorption, and chemical precipitation. In most cases, these require a significant investment of both time and money. In response to the challenge, scientists developed solid-state fermentation [53]. Both distinct approaches employ the fundamental principles. Solid-state fermentation, on the other hand, is characterized by the immobilization of microorganisms on the surface of the fermenting reactor. This makes subsequent filtration and processing much more effective. Furthermore, solid-state manufacturing enhances the stability of the final product. Most of the time, the methods outlined in the previous paragraph enable the acquisition of the necessary antibiotics. Sometimes, researchers alter antibiotics to enhance their effectiveness, adding functional groups such as an amino group and two methoxy groups to produce ampicillin and methicillin [54].

According to Stapleton and Taylor, these antibiotics are more useful than penicillin because they work on a wider range of infections. They are especially helpful for treating infections that have become resistant to penicillin.

Considering both the near and distant futures, as well as the most recent events

The peak of the search for new antibiotics occurred during this period and continued through the end of the 1960s. Infectious diseases that are resistant to antibiotics have made it more difficult to discover new effective antibiotics. The demand for efficient and innovative therapies has increased significantly in recent years due to the proliferation of previously unknown diseases and the development of pathogens that are resistant to standard antibiotics. The emergence of novel viral strains that can cause diseases with a risk of death is a significant danger to the health of the general population. Throughout history, advances in technology have led to better conditions for the manufacture of antibiotics. When there was a lull in the discovery of new antibiotics, developments in technology, notably in the field of genetic sequencing, were an essential factor in the rise in antibiotic production. Editing the genome and direct cloning were both components of the experiment that Du and his colleagues carried out [55]. Because of the substantial costs connected with operating in this market, pharmaceutical companies and research institutes have only conducted a very small amount of research and development on the discovery of new medicines. Because disease-causing bacteria frequently undergo mutations and can acquire resistance to antibiotics, this may have a significant influence on the public health industry throughout the world. This shows how important it is to keep doing research in the field of medicine discovery, especially when it comes to finding new antibiotics and new ways to treat them [56].

Conclusions

For more than a century, scientists have widely acknowledged bacteria as the root cause of most of the world's deadliest infectious diseases. On the other hand, they played an important role in the development of antibiotics that have prevented the loss of millions of lives throughout the world. According to the researcher's findings, the fact that naturally occurring antibiotics in humans can cause toxicity and other unpleasant side effects has slowed the development of effective antibiotic medicines. In addition to the factors of antibiotic usage, misuse, and abuse that continue to contribute to the emergence of antibiotic resistance in bacteria, the issue of intrinsic or acquired resistance has also been a significant concern. This is due to the transmission of antibiotic resistance from generation to generation. Because of this discovery, scientists have been able to modify microbes so that they can manufacture antibiotics genetically. Changing the composition of the growing medium simultaneously enhances antibiotic production. Structural alteration of antibiotics, as well as the individualization of growth media, have led to increased activity with fewer adverse effects and higher overall production. Antibiotic-producing microorganisms are resistant not only to the antibiotics they manufacture but also to other types of broad-spectrum antibiotics, such as tetracycline, chloramphenicol, streptomycin, and others. Research on the antibiotic-producing capabilities of soil bacteria is still ongoing However, only around 100 of the 5,000 antibiotics discovered were useful, and the effectiveness of the antibiotics that were still available gradually declined as bacteria became resistant to them. To address this issue, scientists are chemically modifying existing antibiotics and developing new antibiotics to create more effective alternatives. Additionally, scientists are still in the process of discovering new and uncommon microorganisms capable of manufacturing antibiotics and conducting research into the development of novel antibiotics. and plasmid. This process requires increasing the amount of the gene that encodes enzymes that

generate antibiotics. Researchers and developers cultivate antibiotic-producing bacteria in Petri plates and tubes with a growth medium capacity of only 100 milliliters. The industrial environment cultivates the source microorganisms in containers that hold more than 100,000 liters (L) of growth material. The fermentation technique enables production on a large scale. Most microbial strains used in fermentation undergo gene modification to enhance their antibiotic production. We always strive to improve strains because we need high-yielding strains to produce antibiotics.

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