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Role of bacteria and fungi in antibiotic production

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Abstract
Many microbes, or microorganisms, are known to produce a wide variety of antibiotics that are produced and used to fight disease and life-threatening illnesses. Antibiotics are produced by many small groups such as bacteria, fungi, and actinomycetes as their immune system against other viruses that live near them. Improving the yield of antimicrobials in the industry has been achieved through the use of technologies and traditional programs to make a variety of varieties based on random mutation and testing. The development of DNA fusion techniques and their use in antibiotic-producing microorganisms has allowed for increased production and biosynthetic processes that create new antibiotics. In this review article, we will focus on how different types of bacteria and fungi help in producing different types of antibiotics.

Keywords: antibiotics, actinomycetes, bacteria, fungi, antimicrobials

1. Introduction
The term antibiotic, which means "fight against health," is often used methods by various investigators. antibiotics as molecular low weight-bearing compounds produced by micro-organisms that inhibit the growth of other creatures in the vicinity of the low-lying area (Gottlieb 1967) [1]. Similarly, Thomashow and his colleagues refer to antibiotics as distinct chemicals low-molecular compounds of cells produced by other micro-organisms to inhibit the growth and binding metabolic activity of other microorganisms (Thomashow *et al*., 1997) [2]. These compounds are produced by bacteria as secondary metabolites, which play no role in growth and reproduction. Instead, these secondary metabolites are produced in the stable phase and exist released in the environment (Koberl *et al*. 2013) [3]. Later it was fulfilled that higher species such as algae, plants, and animals also produce fewer molecular-weight substances such as secondary metabolites had antimicrobial activity (Berdy 1980) [4]. Therefore, Okafor described antibiotics as ingredients produced by any living species (microbes, algae, plants, or animals) that contained the ability to inhibit the growth of another species, in a low-lying area (Okafor 1987) [5]. In a broader sense, chemotherapeutic antibiotics prevent the growth of species such as bacteria, fungi, viruses, and protozoa (Chandra & Kumar, 2017) [6]. Antibiotics represent the most important group in the industry's secondary metabolites. Our ability to produce these compounds, in many cases fermentation has had an impact on the medical field surprisingly. Antibiotics comprise a broad group of chemicals it is combined with the various cellular targets in fighting infectious diseases. Some antibiotics are different of applications are therefore widely produced volumes, e.g. penicillins, and some only give applications and therefore only produced at small quantities prices, e.g. vancomycin. Of all the antibiotics there is, however, interest in getting high-quality products and high prices, as such will ensure less expensive production. This has always been the tradition obtained by the development of classical complexity, but by knowledge accumulating at the genomic level and in the cellular level, more understanding has been gained both local and global regulation of antibiotic production, therefore, opens up a lot directed methods (Rokem *et al.*, 2007) [7]. Natural products and their derivatives are very important in obtaining new medicines, for example, for the treatment of cancer, diabetes, inflammatory diseases, and infections caused by germs, fungi, viruses, or parasites (Wiese & Imhoff, 2018) [8].
Antibiotics were used for a long time before the advent of modern medicine. The effects of bread on which filamentous fungi grew for the treatment of wounds and burns have been known since ancient Egypt (Durand *et al*., 2018) [9]. The discovery of the first antibiotic occurred by accident when the plate of agar with the growth of stlococcici was introduced by Sir Alexander Fleming which was contaminated with mold.

A fungus colony showed a clear antimicrobial environment around it (Fleming 1980) [10]. The antibacterial agent was identified as penicillin, which was then used as an antimicrobial to treat many ailments and diseases bacteria (2006). The discovery of sulfonamides and antibiotics β-lactam in the 1930s leads to significant improvements in health and medical services such as disease as well the previously fatal bacterial infection was cured. The introduction of streptomycin in 1944 was another breakthrough in the treatment of tuberculosis. The golden era of antibiotic availability was marked until 1970 until the upper classes of antibiotics were found (Chandra & Kumar, 2017) [6]. "It was observed that around a large fungus pollutant the staphylococcus colonies were exposed and apparently undergoing lysis." History of Antibiotic Research the view, published by Alexander Fleming (1881-1955) in 1929, is often referred to as "the birth of the antibiotic period". The introduction of penicillin in medical treatment in 1941 became the next major milestone in this success story (Chain *et al*., 1940) [11]. 1945 Nobel Prize in Physiology or Medicine awarded Fleming, Chain, and Florey for “penicillin and treatment of various infectious diseases” and by the end of the Second World War Military, penicillin was available to US soldiers and civilians. It was the first time an antibiotic that can kill Gram-positive bacteria including pathogens that cause gonorrhea, syphilis, and puerperal infections (Mohr, 2016) [12].

2. Antibiotics produced by bacteria

2.1 Streptomycin

Streptomyces is a type of Gram-positive bacterium that grows in different habitats, and its structure resembles a filamentous fungus. The morphological variation of Streptomyces involves the formation of a hyphae layer that can divide into a series of letters. Streptomyces is a type of Gram-positive virus that grows in different places, with the same filamentous form as mold. Morphological differences of Streptomyces involves the formation of a hyphae crust that can split into a series of letters. The history of antibiotics taken from Streptomyces began with the discovery of streptothricin in 1942, and with the discovery of streptomycin two years later, scientists intensified their search for antibiotics within the species. (De Lima Procópio *et al*. 2012) [13]. The production of chromomycin by *Streptomyces flaviscleroticus* contributes to the survival of the producer. Indeed the chromomycin nonproducer mutant is characterized by a slow growth rate, reduced life expectancy associated with the concentration produced within the cells of the active oxygen species, and consequently high oxidative stress. This has led to metabolic changes such as redistribution of glycolytic flux to pentose phosphate pathway leading to an increase in the intracellular pool of NADPH, a cofactor used to combat oxidative stress. Chromomycin enhances oxidant activity (Procópio RE *et al*., 2012) [14]. Asukamycin, a new antibiotic, is isolated from the traditional culture - broth mycete designated as *Streptomyces nodosus* subsp. asukaensis. Antibiotic inhibits the growth of Gram-positive bacteria including Nocardia asteroids. Chemical Formula for the asukamycin antibiotic is represented as C29H22N2O9 (M.W. 542). The toxicity of antibiotics in mice is LD50 48.5 mg/kg by intraperitoneal injection and has no effect in mice when administered at 450 mg/kg per os (OMURA *et al.*, 1976) [15]. The isolation of streptomycin was the culmination of a critical situation in search of antimicrobial agents produced by actinomycetes, a group of organisms closely associated with bacteria. Eventually, it was found that 20 to 50 percent of all actinomycetes are found in soil and other substrates that have the ability to inhibit the growth of other organisms. *Streptomyces griseus*, a substance containing streptomycin, has been known in our laboratories since the beginning of our work in actinomycetes, although it was not tested at the time for its antimicrobial properties. Actinomyces, have shown how to form and differentiate themselves from the species of this group of other chemical substances containing antibodies. A new type of substance, chosen as streptothricin, was soon discontinued, in 1942. It was effective against both gram-positive and gram-negative bacteria and was not toxic to animals. Spatial structure in the *S. griseus–S. coelicolor* system acted in concert with the initial density of each species to determine conditions in which rare *S. griseus* could invade and outcompete larger streptomycin-susceptible *S. coelicolor* populations. *Streptomyces griseus* reached higher endpoint densities as the distance between colonies decreased (because the antibiotic reached susceptible cells with less diffusion) or as the initial density of *S. griseus* in the community increased (because more streptomycin was produced overall). Moreover, preserving spatial structure across multiple transfers allowed the benefits of streptomycin production to accrue over time, such that as few as 10 cells of *S. griseus* could invade large *S. coelicolor* populations. In contrast, if the spatial structure was broken up between transfers, then *S. griseus* required 100-fold higher starting densities to invade *S. coelicolor* (Singhal, 2020) [16].

2.2 Bacitracin

Endospore the rhizobacterium *Bacillus subtilis* - Gram-positive biological modeling system, is capable of producing more than a dozen antibiotics with a variety of amazing properties. Active anti-microbial compounds consist mainly of flexible and modified peptides (lantibiotic and lantibiotic-like peptides) or not ribosomally, as well as a few non-peptidic compounds such as polyketides, aminosugar, and phospholipid (Stein, 2005) [17]. Bacterium separated from the soil of the market field in Surrey in February 1946 and subsequently from the soil of Yorkshire and air was found to produce the most important antibiotic for treatment, as it appears to be unknown at present. Aerosporin is recommended (ainsworth *et al.*, 1947) [18]. *Subtilis*, which acts as a probiotic is not well understood. It is thought that *B. Subtilis* has positive probiotic effects, including the production of antimicrobials, boosting the immune system, and a complete improvement of the gut microflora. "Bacitracin" is filtered through Berkefeld or Chamberland filter. It’s neutral too it cannot be avoided from the first crop by removing the pH extracted by ether, chloroform, acetone or ethyl acetate. It dissolves in water and withstands heat 15 minutes to 100 'C. without much loss of titer. It does not eliminate the the feeling of blood in the suspension of salt. It is stable in acid. The solution, however, is not stable to an alkaline solution above pH9. It resists digestion with pepsin or trypsin (Waksman, 1953) [19]. Cell wall adhesion is inhibited by bacitracin produced by *Bacillus subtilis* and *Bacillus licheniformis*. It is often used as an additive in animal and poultry diets, which enhances feed performance and reduces infectious diseases. The bacterium bacilli are Gram-positive, sticky, and form lumps. They are saprophytes and live in aerobic or facultative anaerobic conditions. Bacilli are very

diverse, making them abundant in many areas, including hardy sands, hot springs, and Arctic soil. *Beptillic pepeptide* antibiotics such as bacitracin are harmful to Gram-positive bacteria, while compounds such as circulin, colistin, and polymyxin show special anti-Gram-negative antibodies (Hassan *et al*., 2020) [20]. Like many other peptides produced from Bacillus, bacitracin is synthesized by a large multienzyme complex using a thiotemplate method. It works by preventing cell wall biosynthesis in Gram-positive and other Gram-negative bacteria and has been used as an antibacterial feed supplement for over 50 years. Bacitracin contains at least ten different dodecapeptides with one or two amino acids, and bacitracin A is the most abundant and active among them. It contains four amino acids in D-suspension, including nonproteinogenic residues L-ornithine (Yu *et al*., 2019) [21].

2.3 Polymixin B

Polymyxins belong to the cationic lipopeptide antibiotic family produced by Gram-positive bacteria and work against many others germs. Although polymyxins are highly potent antimicrobials, their clinical use is limited by their nature, toxicity and the availability of other effective and non-toxic antibiotics. Polymyxins have a high concentration of lipopolysaccharide, and recently included in hemoperfusion cartridges used to remove lipopolysaccharide from blood and prevent the early stages of sepsis (Shaheen *et al*., 2011) [22]. Polymyxin is an antibiotic that occurs in cultural filters *Bacillus polymyxa*. The special thing is different in its definition of gram-free bacteria. A summary of the most significant effects obtained over several years, including chemotherapeutic and toxicity data, has been reported. The current contribution concerns the classification and identification of antibiotic-producing bodies and other early findings that identify and differentiate polymyxin from certain known antibiotics. *Bacillus polymyxa* was separated from the soil during a program designed to detect new chemotherapy antibiotics for non-gram-negative grams. The body of the test used in this search was *Salmonella schottmuelleri*. Our method of classifying antibiotic-containing products and specific types of work involves the preparation of soil fertility plates using various media and cultural contexts. Plates are also sprayed with a suspension body test machine designed for that purpose (Stansly PG *et al*., 1947) [23]. Members of the polymyxin family, isolated from strains of *Paenibacillus polymyxa* (formerly known as *Bacillus polymyxa*), it contains the heptapeptide nucleus and a specific series of tripeptide, bound to the N-terminus with fatty acyl groups of at least 7 carbon atoms. Polymyxins contain many traces of cationic amino acids, which contain α, γ-diaminobutyric acid (Dab) (Brown, & Dawson 2017) [24].

2.4 Vancomycin

Vancomycin (VCM) is a tricyclic glycopeptide antibiotic produced by *Streptococcus orientalis*. It is widely used in hospitals, has been shown to fight serious infections caused by Gram-positive bacteria, especially with the arrival of MRSA (methicillin-resistant Staphylococcus aureus), penicillin-resistant pneumococci among others. In addition, it is indicated in the treatment of patients who are resistant to penicillin and cephalosporins. Recommendations for dosage, dosage levels, and types of dosage are controversial and cause toxic effects. The purpose of this paper was to review the literature on the therapeutic effects and side effects of vancomycin (Bruniera *et al*., 2015) [25]. Vancomycin is one of the antibiotics to treat life-threatening infections with gram-positive bacteria (Mcintyre *et al*., 2000) [26]. To identify aspects of moderate metabolism associated with vancomycin production, the interaction between vancomycin antibiotic production and intermediate products of the tricarboxylic acid (TCA), alpha-ketoglutarate dehydrogenase, and glyoxalate shunt isocitrate lyase activities, all play a major role in carbon metabolism, according to the glucose concentration of the *Amycolatopsis Orientalis* medium with respect to the incubation period. Antibiotic filtration was measured with a high-performance liquid chromatography (HPLC) gradient and selectively detected multiple wavelengths at 210 nm using the Varian Cromsep C8 column (Ayar-Kayali & Tarhan, 2006) [27].

3. Antibiotic produced by fungi

3.1 Penicillin

Industrial production of antibiotics-lactam antibiotic by filamentous fungus *Penicillium chrysogenum* is based on the successive cycle of developmental pressures. Genomic and transcriptional analysis of weight lines has led to the identification of a few important mutations in high-yielding species, including enlargement of the penicillin biosynthetic gene cluster group, high genetic enhancement involved in biosynthesis and penicillin precursors and amicinogen and genes that contain microbody growth factors, *P. chrysogenum* can be considered an excellent cell factory for β-lactam production antibiotics. Genetic analysis of industrial production has led to the identification of a number of important changes that have contributed to this increased production. A key factor is the enlargement of the genetic group of penicillin biosynthetic (Weber *et al*., 2011) [28]. Various events have led to that the use of Proteinics in penicillin which produces the fungus *Penicillium chrysogenum*, which has helped to understand industrial emergence types and processes for the production of penicillin. Looking back on facts, developments, needs or developments that have led to the use of Proteomics in *P. Chrysogenum* and penicillin production can be based on four pillars the homosexuality of Felming's cult nurtured by the need for antimicrobials for World War II casualties; the birth of deep tank fermentation technology due to citric acid production; mutagenesis and engineering processes that focus on genetic growth, precursor or reorganization of competing routes to increase penicillin titters; and improvements in road strength, such as cracks of proteins by SDS-PAGE and two electrophoresis (Ulrich K. Laemmli and Patrick H. O'Farrell, respectively), the use of mass spectrometry and spectrometers (2002 Nobel Prize in Chemistry was awarded for mass spectrometry and nuclear magnetic resonance spectroscopy) and the detection of ultrafast genome sequining (Barreiro, & García-Estrada, 2018) [29].

3.2 Cephalosporin

Once the properties of penicillin have been discovered; in the middle, in 1945, Giuseppe Brotzu (professor of hygiene at the University of Cagliari, Italy) asked why typhoid fever less powerful in his city than elsewhere. *Cephalosporium* sp. C.M.I. 49137 and changes found in this genus produces both penicillin N and cephalosporin C, which is 8- (D-a-aminoadipoyl) found in 6-aminopencillanic acid and 7-aminocephalosporanic acid respectively. *Cephalosporium* sp. it grows in a complex environment in flasks indicating that a-

aminoadipic acid, cysteine and valine were placed in a chain, f3-lactam ring and dihydrothiazine ring in the sequence of cephalosporin C. Additional tests are indicated that the 8- (D-a-aminoadipoyl) series of this antibiotic is composed of acetate and oc-oxoglutarate and that the acetoxy group is derived from acetate. Chemically-defined media has been described as growing *Cephalosporium* sp. and the formation of penicillin N and cephalosporin C, and the production of both antibiotics has been shown to be stimulated by D- or DL-methionine. (Smith *et al*., 1967) [30]. Sometime after the discovery of cephalosporin C, the Sardinian version of *Cephalosporium acremonium* appeared to be the only body capable of producing this type of antibiotic. Later, a few species of Emericellopsis (Acremonium), a sexual form of Cephalosporium, have been shown to combine cephalosporins. Minor components that produce Cephalosporin have been found by Kitano and others to be widely distributed and to include a variety of fungi, such as members of the genus Anixiopsis, Arachnomyces, Diheterospora, Paecilomyces, Scopulariepsis and Spiroidium, and several species of *Streptomyces P.* was only effective against several Gram-positive bacteria, indicating that it alone would not be able to cope with the wide range of activity observed by Brotzu. Hydrophilic cephalosporin N did not work with preparation of penicillinase from *Bacillus cereus* (Abraham, 1987) [31].

3.3 Griseofulvin

The antibiotic griseofulvin (GF), isolated in 1939 by Oxford began construction as fungicic systemic use of horticultural in the treatment of Botrytis and Alternaria diseases Grove, 1963. GF is an antimicrobial drug produced by a variety of Penicillium. First discovered as a metabolic product from the culture of *Penicillium griseofuluum* Dierckx. Chemically written as 7-chloro-2 ', 4,6-trimethoxy-6', j3-methylspiro benzofuran-2 (3H), l '- [2] - cyclohexene] -3,4 dione (De Carli & Larizza, 1988) [32]. Many species of fungi contaminate the growth of *Penicillium nigricans* and the production of griseofulvin. This may have their effect on the production of *P. nigricans* antibiotics or competing with genetics or space. Of the six fungal species known to produce antibiotics in artificial culture, four inhibited *P. nigricans* in the ground; of the two who were absent, *P. albidum* produces an extremely unstable disinfectant and not a single one was found in the soil, either *P. stoloniferum* has a slow growth rate and the yield of antimicrobials in the soil has been very low and insufficient to have an effect on *P. Nigricans* growth (Wright, 1955) [33]. Antibiotics, commercially produced by fermentation of highly potent variants of *P. patulum*, made up of acetate blocks. It contains chlorine, which is released during fermentation as potassium chloride; in its absence is made dechlorogriseofulvin, which has no fungicidal activity. Early growth is productive category in GF fermentation. Unlike penicillin and streptomycin, GF remains intracellular; yield is 6000 mg / kg. As an antibiotic is given orally, for therapeutic use, the particle size is pressed into the back water the release of acetone is a very important parameter, which affects the absorption of drugs.GF can be produced in the environment by a fungus that pollutes food; for example it is found in traditional filtrate and in mycelium fragments of *Penicillium urticae* separated from flour and moromi (mash). However, it was not found in samples of ripe soybeans attached to Japan. In any case the pollution is not harmful to the health of animals and humans (De Carli & Larizza, 1988) [32]. During research into metabolites produced by different fungi isolated from vegetable plants, a type of *Penicillium griseofulvum* was discovered or to produce patulin and griseofulvin. One milliliter of spore suspension (2 x 106 / ml) was placed in a 500 ml Erlenmeyer container containing 100 ml of one of the media described below and included in static culture at 28 degrees (Torres *et al*., 1987) [34].

3.4 Amphoterecin

Polyene macrolide amphotericin B is a treatment of an important antibiotic produced by *Streptomyces nodosus*. Polyenes disrupts the eukaryotic lining after mixing with sterols to form channels allow the loss of small molecules and ions and eventually caused cell death. Amphotericin B has selective toxicity in relation to fungal cells because they show high proximity to Ergosterol, the most prominent sterol in the fungal cell membrane (Caffrey *et al*., 2001) [35]. *Streptomyces nodosus*, previously separated from the soil of the Venezuelan Orinoco River region, produces two polyene antibiotics, tetraene amphotericin A and heptaene amphotericin B. Amphotericin B and other polyene macrolides are signals of interaction with membrane sterols of sensitive substances. In addition they show an amazing vivo effect on sterol and steroid metabolism in animals and humans. Clinical use has been available since it was first approved by the FDA in 1959. Amphotericin B itself does not dissolve salts at normal pH; as a result, it is formulated as a combination of 50 mg amphotericin B and 41 mg of detergent, sodium deoxycholate, resulting in a ribbon-like compound that creates a colloidal mixed distribution (Hamill, 2013) [36]. Considerations of therapy for invasive candidiasis must include the extent and area of infection (Meyer *et al*. 1992) [37]. *Aspergillus terreus* is of great concern due to its high distribution in *in vitro* and *in vivo* resistance to Amphotericin B (AmB) (Blum *et al*., 2013) [38]. Amphotericin B provides advanced treatment for visceral leishmaniasis (VL) caused by *Leishmania donovani*, with a single dose of liposomal-encapsulated ambisome providing the highest levels of treatment. Visceral leishmaniasis (VL), also known as kala-azar, is a potentially fatal disease caused by the intracellular parasites of the *Leishmania donovani* complex. VL is a major public health problem in rural India, causing high morbidity and mortality, as well as huge costs in local and national health budgets. Amphotericin B provides advanced VL treatment with a single liposomal-encapsulated Ambisome, now cheaper with reduced prices, providing excellent therapeutic value. B compared to most non-liposomal amphotericin B tablets over 30 days (Fakiola *et al*., 2019) [39]. The implant unit developed internal pneumonitis (e.g. spreading pulmonary infiltration into hypoxia) during treatment; of these 50 patients, 37 (33% of the total) suspected fungal pneumonitis (Chopra *et al*., 1991) [40]. Amphotericin A and B are the natural fermentation products of the actinomycete found in the soil collected in Venezuela in 1953. The body was later renamed *Streptomyces nodosus*. Both of these computers were found to have many types of lethal actions, but amphotericin A was not developed. Amphotericin B remains the drug of choice for many types of deep-seated infections, underestimating its side effects and the continuous development of new chemicals. The chemical composition of amphotericin B was clarified in 1970. The molecule contains macrolide lacton in the ring of 3 7 carbon atoms. One side of the macrolide ring is made up of a strong lipophilic series of seven bonds bound and on the other side there are the same numbers of hydroxyl groups. Therefore,

the molecule is amphipathic and this element o its structure is believed to be important in its biological function. The macrolide ring contains a six-part ketalic ring and the amino sugar mycosamine is attached to the ring by a-glycosidic bonding (Warnock, 1991) [41].

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5. References

1. Gottlieb D. Antibiotics and cell metabolism. Hindustan Antibiot Bull, Hmmond SM, Lambert PA. Antibiotics and antimicrobial action. Edward Arnold, London 1967-1978;10:123-134, 5-52.
2. Thomashow LS, Bonsall RF, Weller DM. Antibiotic production by soil and rhizosphere microbes in situ. In: Hurst CJ, Knudsen GR, MJ MI, Stetzenbach LD, Walter MV (eds) Manual of environmental microbiology. American Society of Microbiology, Washington 1997.
3. Koberl M, Schmidt R, Ramadan EM, Bauer R, Berg G. The microbiome of medicinal plants: diversity and importance for plant growth, quality and health. Front Microbiol 2013;4:400.
4. Berdy J. Recent advances and prospects of antibiotic research. Process Biochem 1980;15:28-35.
5. Okafor N. Antibiotics and anti-tumour agents. In: Industrial microbiology 1987, 336-369.
6. Chandra N, Kumar S. Antibiotics Producing Soil Microorganisms. Antibiotics and Antibiotics Resistance Genes in Soils 2017, 1-18. doi:10.1007/978-3-319-66260-2_1
7. Rokem JS, Lantz AE, Nielsen J. Systems biology of antibiotic production by microorganisms. Natural Product Reports 2007;24(6):1262. doi:10.1039/b617765b
8. Wiese J, Imhoff JF. Marine bacteria and fungi as promising source for new antibiotics. Drug Development Research 2018. doi:10.1002/ddr.21482
9. Durand GA, Raoult D, Dubourg G. Antibiotic discovery: History, methods and perspectives. International Journal of Antimicrobial Agents 2018. doi:10.1016/j.ijantimicag.2018.11.010
10. Fleming A. Classics in infectious diseases: on the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae by Alexander Fleming, Reprinted from the British Journal of Experimental Pathology 10:226-236, 1929. Rev Infect Dis 1980;2:129-139.
11. Chain E, Florey HW, Gardner AD, Heatley NG, Jennings MA, Orr-Ewing J *et al*. Penicillin as a chemotherapeutic agent. Lancet ii 1940, 226-228.
12. Mohr KI. History of Antibiotics Research. How to Overcome the Antibiotic Crisis 2016, 237-272. doi:10.1007/82_2016_499
13. De Lima Procópio RE, da Silva IR, Martins MK, de Azevedo JL, de Araújo JM. Antibiotics produced by Streptomyces. The Brazilian Journal of Infectious Diseases 2012;16(5):466-471. doi:10.1016/j.bjid.2012.08.014
14. Procópio RE, Silva IR, Martins MK, Azevedo JL, Araújo JM. Antibiotics produced by Streptomyces. Braz J Infect Dis 2012;16(5):466-71. doi: 10.1016/j.bjid.2012.08.014. Epub 2012 Sep 11. PMID: 22975171.
15. Omura S, Kitao C, Tanaka H, Oiwa R, Takahashi Y, Nakagawa A *et al*. A new antibiotic, asukamycin, produced by Streptomyces. The Journal of Antibiotics 1976;29(9):876-881. doi:10.7164/antibiotics.29.876
16. Singhal S. Digest: Structuring interactions in Streptomyces. Evolution 2020;74(1):207-209. doi: 10.1111/evo.13874. Epub 2019 Dec 10. PMID: 31705652.
17. Stein T. *Bacillus subtilis antibiotics*: structures, syntheses and specific functions. Molecular Microbiology 2005;56(4):845-857. doi:10.1111/j.1365-2958.2005.04587
18. Ainsworth GC, Brown AM, Brownlee G. Aerosporin, an Antibiotic Produced by *Bacillus aerosporus* Greer. Nature 1947;160(4060):263-263. doi:10.1038/160263a0
19. Waksman SA. Streptomycin: background, isolation, properties, and utilization. Science 1953;118(3062):259-266.
20. Hassan A, Ali S, Farooq MA, Tahir HM, Awan MU, Mughal TA. Optimization of enhanced microbial production of zinc bacitracin by submerged fermentation technology. J Basic Microbiol 2020;60(7):585-599. doi: 10.1002/jobm.201900694. Epub 2020 May 4. PMID: 32364268.
21. Yu W, Li D, Jia S, Liu Z, Nomura CT, Li J, Wang Q. Systematic metabolic pathway modification to boost l-ornithine supply for bacitracin production in Bacillus licheniformis DW2. Applied Microbiology and Biotechnology 2019. doi:10.1007/s00253-019-10107-7
22. Shaheen M, Li J, Ross AC, Vederas JC, Jensen SE. *Paenibacillus polymyxa* PKB1 Produces Variants of Polymyxin B-Type Antibiotics. Chemistry & Biology 2011;18(12):1640-1648. doi:10.1016/j.chembiol.2011.09.017
23. Stansly PG, Schlosser ME. Studies on Polymyxin: Isolation and Identification of *Bacillus polymyxa* and Differentiation of Polymyxin from Certain Known Antibiotics. J Bacteriol 1947;54(5):549-556. doi:10.1128/JB.54.5.549-556.1947
24. Brown P, Dawson MJ. Development of new polymyxin derivatives for multi-drug resistant Gram-negative infections. The Journal of Antibiotics 2017;70(4):386-394. doi:10.1038/ja.2016.146
25. Bruniera FR, Ferreira FM, Saviolli LR, Bacci MR, Feder D, da Luz Goncalves Pedreira M *et al*. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci 2015;19(4):694-700.
26. McIntyre JJ, Bull AT, Bunch AW. Vancomycin production in batch and continuous culture. Biotechnology and Bioengineering 2000;49(4):412-420. doi:10.1002/(sici)1097-0290(19960220)49:4<412::aid-bit8>3.0.co;2-s
27. Ayar-Kayali H, Tarhan L. Vancomycin antibiotic production and TCA-glyoxalate pathways depending on the glucose concentration in *Amycolatopsis orientalis*. Enzyme and Microbial Technology 2006;38(6):727-734. doi:10.1016/j.enzmictec.2005.07.023
28. Weber SS, Bovenberg RAL, Driessen AJM. Biosynthetic concepts for the production of β-lactam antibiotics in *Penicillium chrysogenum*. Biotechnology Journal 2011;7(2):225-236. doi:10.1002/biot.201100065
29. Barreiro C, García-Estrada C. Proteomics and *Penicillium chrysogenum*: Unveiling the secrets behind penicillin production. Journal of Proteomics 2018.

doi:10.1016/j.jprot.2018.11.006
30. Smith B, Warren S, Newton G, Abraham E. Biosynthesis of penicillin N and cephalosporin C. Antibiotic production and other features of the metabolism of a *Cephalosporium* sp. Biochemical Journal 1967;103(3):877-890. doi:10.1042/bj1030877
31. Abraham EP. Cephalosporins 1987, 1945-1986. Drugs, 34(Supplement2):1-14. doi:10.2165/00003495-198700342-00003
32. De Carli L, Larizza L. Griseofulvin. Mutation Research/Reviews in Genetic Toxicology 1988;195(2):91-126. doi:10.1016/0165-1110(88)90020-6
33. Wright JM. The production of antibiotics in soil: *II*. production of griseofulvin by Penicillium Nigricans. Annals of Applied Biology 1955;43(2):288-296. doi:10.1111/j.1744-7348.1955.tb02477
34. Torres M, Canela R, Riba M, Sanchis V. Production of patulin and griseofulvin by a strain of *Penicillium griseofulvum* in three different media. Mycopathologia 1987;99(2):85-89. doi:10.1007/bf00436910
35. Caffrey P, Lynch S, Flood E, Finnan S, Oliynyk M. Amphotericin biosynthesis in Streptomyces nodosus: deductions from analysis of polyketide synthase and late genes. Chemistry & Biology 2001;8(7):713-723. doi:10.1016/s1074-5521(01)00046-1
36. Hamill RJ. Amphotericin B Formulations: A Comparative Review of Efficacy and Toxicity. Drugs 2013;73(9):919-934. doi:10.1007/s40265-013-0069-4
37. Meyer RD. Current Role of Therapy with Amphotericin B. Clinical Infectious Diseases 1992;14(Supplement_1):S154-S160. doi:10.1093/clinids/14.supplement_1.s154
38. Blum G, Kainzner B, Grif K, Dietrich H, Zeiger B, Sonnweber T, Lass-Flörl C. *In vitro* and *in vivo* role of heat shock protein 90 in Amphotericin B resistance of Aspergillus terreus. Clinical Microbiology and Infection 2013;19(1):50-55. doi:10.1111/j.1469-0691.2012.03848
39. Fakiola M, Singh OP, Syn G, Singh T, Singh B, Chakravarty J *et al*. Transcriptional blood signatures for active and amphotericin B treated visceral leishmaniasis in India. PLOS Neglected Tropical Diseases 2019;13(8):e0007673. doi:10.1371/journal.pntd.0007673
40. Chopra R, Blair S, Strang J, Cervi P, Patterson KG, Goldstone AH. Liposomal amphotericin B (AmBisome) in the treatment of fungal infections in neutropenic patients. Journal of Antimicrobial Chemotherapy 1991;28(supplB):93-104. doi:10.1093/jac/28.suppl_b.93
41. Warnock DW. Amphotericin B: an introduction. Journal of Antimicrobial Chemotherapy 1991;28(suppl B):27-38. doi:10.1093/jac/28.suppl_b.27