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Antibiotics Action and Uses: Review

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Abstract

For the treatment of bacterial infections in a variety of settings, including as human health, agriculture, cattle breeding, and fish farming, antibiotics are a commonly used therapeutic approach. Four main modes of action are responsible for the effectiveness of antibiotics; these are covered in detail in this overview along with diagrammatic representations. Antibiotic resistance has become a major treatment challenge for bacterial infections, notwithstanding its effectiveness. Antibiotics are no longer effective against bacteria since they have defense mechanisms in place.. With diagrammatic graphics, this overview explores the specific strategies that bacteria have evolved to withstand antibiotics. Microorganism can acquire antibiotic resistance through a variety of means, making previously vulnerable bacteria resistant to antibiotics. Human antibiotic abuse is one of several causes contributing to the growing antibiotic resistance dilemma. The alternative strategies that have been suggested to lessen the escalation of antibiotic resistance are also highlighted in this review.

Keywords: antibiotics, antimicrobial, bacteria, antibiotic resistance, disease spreading

INTRODUCTION

The French terms "antibiose" and "antibiotic," which were established by Vuillemin in the late 19th century to describe compounds that have a harmful effect on living things, especially microbes, are where the name "antibiotic" originated [1]. Following this, Selman A. Waksman defined antibiotics broadly in 1947 as substances made by microorganisms with the ability to inhibit the growth and cause the death of bacteria and other microorganisms [2,3]. Antibiotics are used extensively in a wide range of industries, including fish farms, agriculture, human health, and cattle breeding [3,4]. The four distinct modes of action that underpin the effectiveness of antibiotics are as follows: preventing DNA replication [5]; protein biosynthesis [6]; cell wall biosynthesis [7]; and folic acid metabolism [8]. These mechanisms are outlined in Kaur Sodhi and Singh's 2022 study. But antibiotic resistance has become a serious worldwide problem [9,10]. This review article offers viable solutions for addressing the issue of antibiotic resistance in addition to a thorough discussion of the various variables that contribute to its spread. In addition, scientists have found creative ways to counteract antibiotic resistance, like using adjuvants and nanoantibiotics, finding new antibiotics, and investigating bacteriophages and botanicals as antibiotic substitutes. This review article explores the use of antibiotics in various industries, the debates surrounding their use, the mechanisms by which antibiotics work, the emergence of antibiotic resistance, the mechanisms controlling antibiotic resistance in bacteria, the spread of

resistance among bacterial populations, and the critical factors that lead to the escalation of resistance in addition to the previously mentioned topics. This article also outlines the successes to date and offers scientifically-discovered remedies to address the worldwide issue of antibiotic resistance.

1. USES OF ANTIBIOTICS

Numerous industries, including agriculture, aquaculture, animal husbandry, and human health, use antibiotics[3,4]. In order to prevent crop loss due to bacterial diseases, these compounds are used to treat bacterial infections in humans, animals, and crops [11,4]. Furthermore, antibiotics are frequently employed in animal husbandry as growth-promoting agents) [12]. Scientists divided the use of antibiotics in livestock into three categories: growth promoters, preventive agents, and therapeutic agents. Animals with infections are given therapeutic medicines in large dosages to address their ailments [13].In contrast, prophylactic medicines are administered in subtherapeutic doses through drinking water or feed to prevent illness in cases where infection signs are not immediately apparent. Animals receive antibiotics on a periodic basis over their life cycle An animal's growth rate and productivity can be increased using growth boosters, and it is periodically given a little amount of antibiotics through its feed [14]. Antimicrobial agents are used in aquaculture to treat fish illnesses. Antibiotics are fed to fish by mixing them with specially prepared feed, and the majority of the time the fish excrete the antibiotics into the surrounding water [15].

2. MECHANISMS OF ACTION OF ANTIBIOTICS

2.1 Antibiotics Inhibit DNA Replication

Bacteria adopt a kind of cell division called binary fission, which results in the production of two daughter cells [16]. However, bacteria must make precise copies of their circular DNA before that can occur. DNA replication is the procedure utilized to duplicate DNA[17]. The enzyme DNA helicase initiates this process by dividing a double helix strand of DNA into two single strands. Next, new complementary DNA strands are created by the enzyme DNA polymerase[18]. DNA helicase and DNA polymerase activity results in the accumulation of positive DNA helical twists. These positive helical twists prevent DNA replication from proceeding if they are not removed. DNA gyrase, sometimes referred to as topoisomerase II, is an enzyme that facilitates DNA replication by removing positive superhelical twists [19]. The 2A and 2B subunits make up DNA gyrase, an essential bacterial enzyme. Additionally, this enzyme is essential for the transcription of many genes and the initiation of DNA replication. The two newly formed daughter DNA molecules eventually bond and become interconnected. The enzyme topoisomerase IV, which is linked to DNA gyrase, allows the separation of the two coupled DNA molecules, allowing the bacterial cell to split into two new daughter bacterial cells.

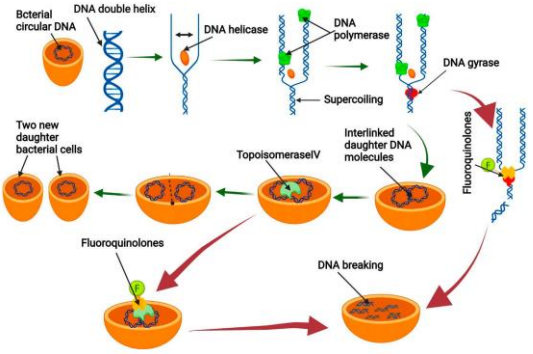

FIGURE 1. Mechanism of DNA replication process and mechanism of action of antibiotics that inhibit DNA replication.

2.2 Fluoroquinolones Antibiotics

Fluoroquinolone antibiotics stop the production of bacterial DNA by blocking the activity of DNA gyrase and topoisomerase IVAccording to [21],these antibiotics have a special propensity for attaching to the complex that DNA gyrase and DNA create. According to [22], this type of interaction destabilizes the enzyme-DNA complex, resulting in DNA breakage and, eventually, bacterial cell death (Figure 1). The main mechanism of action of fluoroquinolones against most gram-negative bacteria is their inhibition of DNA gyrase, On the other hand, fluoroquinolones primarily target topoisomerase IV in the majority of gram-positive bacteria[23]. But DNA gyrase also uses them as a secondary target.This leads to the formation of a complex by topoisomerase IV and the binding of fluoroquinolones to DNA, which disrupts the separation of the two daughter DNA molecules and ultimately causes DNA breakage [24].

2.3 Antibiotics Inhibit Protein Biosynthesis

Similar to all other organisms,bacteria are made of DNA, which is the genetic code for every protein required for survival. This comprises the protein required for growth,repair,reproduction and metabolism regulation,Furthermore, it encodes for three different forms of RNA necessary for carrying out protein synthesis: mRNA, rRNA, and tRNA [24].

The initial stage of protein biosynthesis involves the unwinding and separation of the DNA molecule at a location that codes for the required protein to be synthesized. Just one strand of DNA is used as a scaffold during transcription, the process that creates mRNA. Upon completion, the mRNA strand detaches from the DNA template and attaches itself to a ribosome. The bacterial ribosome is composed of the 50 s and 30 s ribosomal subunits. The synthesis of the polypeptide chain begins when these two subunits are joined along the mRNA strand. Until it receives the signal to cease along the mRNAthe ribosome continues to extend the polypeptide chain by adding amino acids. At this moment, the entire polypeptide chain is produced[25],(Figure 2). Accordingly, antibiotics cannot decrease protein synthesis unless they specifically target the ribosomal 30 or 50 subunits.

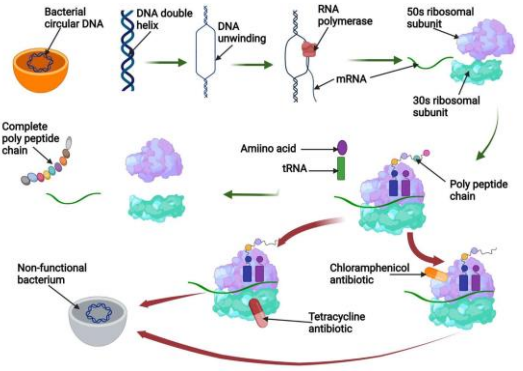

FIGURE 2: The process of protein biosynthesis and the way antibiotics that prevent protein biosynthesis work.

2.3.1 Antibiotics Inhibit Protein Biosynthesis by Targeting the Ribosomal 305 Subunits

2.3.1.1 Tetracycline Antibiotics

This class of antibiotics targets the ribosomal 30S subunit's highly conserved 16S rRNA sequence. For example, tetracycline works by preventing tRNA from attaching to the ribosome's A-site, which eventually prevents the production of proteins[31].

2.3.1.2 Aminoglycosides Antibiotics

Aminoglycoside antibiotics work by means of a particular mechanism. The positively charged nature of these antibiotics draws in the negatively charged bacteria's outer membrane, which results in the membrane's development of huge pores [27]. These pores subsequently allow the aminoglycosides to enter the bacterial cell. Furthermore, by harnessing the energy of active bacterial transport, aminoglycosides can cross the bacterial cytoplasmic membrane [28].Aminoglycosides bind via hydrogen bonds to the 16s rRNA of the 30s, which is their target. Protein production is prevented from proceeding by this binding[29].

Aminoglycosides work well against a wide variety of bacteria, however they are less effective against anaerobic bacteria since these bacteria need oxygen to operate their active transport pathways [30]. Nonetheless, it has been discovered that aminoglycosides can more effectively enter bacterial cells at low concentrations when paired with an antibiotic that prevents the formation of cell walls[29]. (Figure 2).

2.3.2 Antibiotics Inhibit Protein Biosynthesis by Targeting the Ribosomal 50s Subunit

2.3.2.1 Macrolides Antibiotics

Macrolide antibiotics block the synthesis of proteins and polypeptide chains by binding to the 50S component of the ribosome[6].

2.3.2.2 Chloramphenicol Antibiotics

The enzyme peptidyl transferase, which is present on the 50S ribosomal subunit and required for protein synthesis, is inhibited by chloramphenicol antibiotics. Protein synthesis is inhibited as a result of this inhibition, which stops t-RNA from attaching to the ribosomal A site[32]. (Figure 2).

2.3.2.3 Oxazolidinone Antibiotics

Antibiotics called oxazolidinones bind to the ribosome's 50S component and stop the initiation complex from synthesizing, which stops the synthesis of proteins [33]. (Figure 2).

2.4 Antibiotics i\Inhibit Cell Wall Synthesis

While some bacteria additionally have an additional outer layer, most bacteria are made up of a cell membrane encased in a cell wall. The two functions of the bacterial cell wall are to maintain the bacteria's unique structure and to prevent the cell from rupturing when fluid is introduced into it by osmosis[34] The most important component of the cell wall is the peptidoglycan. The polymer known as peptidoglycan is made up of chains of amino acids that link N-acetyl muramic acid (NAM) and N-acetyl glucosesamine (NAG), which alternately create the polymer [35]. . The peptidoglycan manufacturing process involves multiple phases and ultimately leads to the production of bacterial cell walls. N-acetyl muramic acid and N-acetyl glucosamine (NAG) combine to form a precursor to peptidoglycan. This peptidoglycan precursor is transported across the membrane and subsequently bound by cell wall acceptors in the periplasm. Peptidoglycan precursors undergo extensive cross-linking after adhering to periplasmic cell wall receptors In cross-linking, the two primary enzymes involved are trans peptidase and carboxy peptidase. Many cross-linked peptidoglycan layers finally combine to form a cell wall[36].

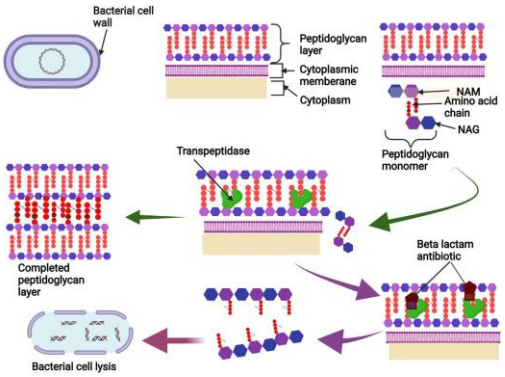

FIGURE 3. The synthesis of cell walls and the mode of action of antibiotics that prevent the formation of cell walls.

The most important component of the bacterial cell wall is the peptidoglycan. The two main enzymes involved in cross-linking during cell wall biosynthesis are transpeptidase and carboxypeptidase[36]. (Figure 3).

2.4.1 Beta-lactams Antibiotics

This group comprises all cephalosporins and penicillins having the beta-lactam ring chemical structure[37]. Because of their unique structure, they can bind to enzymes that cross-link peptidoglycans, like transpeptidase and carboxypeptidase, which inhibits the formation of bacterial cell walls and prevents cross-linking,The bacterial cell is destroyed as a result of this prevention of cell wall production, as Figure 3[7]. illustrates.

2.4.2 Glycopeptides Antibiotics

These antibiotics stop peptidoglycan precursors from cross-linking by forming non-covalent connections with the terminal carbohydrates. In the end, this process results in the breakdown of bacterial cell walls, which destroys and gets rid of bacterial cells [38].

2.5 Antibiotics inhibit folic acid metabolism

These antibiotics are made to specifically block an important enzyme that is part of the folic acid metabolism pathway. Dihydropteroate synthase is an enzyme in the metabolic pathway that is the target of sulfonamide antibiotics. However, dihydrofolate reductase is another enzyme in the same pathway that is the target of trimethoprim antibiotics[39]. (Figure 4).

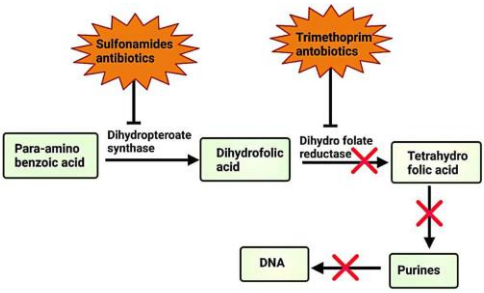

FIGURE 4. Mechanism of action of antibiotics that limit folic acid metabolism

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1-Laskin, A. I., Bennett, J. W., and Gadd, G. M. (2002). *Adv. Appl. Microbiol.* 51.
2-Waksman, S. A. (1947). What is an antibiotic or an antibiotic substance? *Mycologia* 39 (5), 565–569. doi:10.1080/00275514.1947.12017635
3-Kaur Sodhi, K., and Singh, C. K. (2022). Recent development in the sustainable remediation of antibiotics: a review. *Total Environ. Res. Themes* 3–4, 100008. May. doi:10.1016/j.totert.2022.100008
4-Okocha, R. C., Isaac, O. O., and Olufemi, B. A. (2018). Food safety impacts of antimicrobial use and their residues in aquaculture. *Public Health Rev.* 39 (1), 1–22. doi:10.1186/s40985-018-0099-2
5-Fàbrega, A., Madurga, S., Giralt, E., and Vila, J. (2009). Mechanism of action of and resistance to quinolones. *Microb. Biotechnol.* 2 (1), 40–61. doi:10.1111/j.1751-7915.2008.00063.x
6. Gould, K. Antibiotics: From prehistory to the present day. J. Antimicrob. Chemother. **2016**, 71, 572–575. [CrossRef]
7. Clardy, J.; Fischbach, M.A.; Currie, C.R. The natural history of antibiotics. Curr. Biol. **2009**, 19, R437–R441. [CrossRef]
8. Fleming, A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. influenzæ. Br. J. Exp. Pathol. **1929**, 10, 226–236. [CrossRef]
9. Hodgkin, D.C. The X-ray analysis of the structure of penicillin. Adv. Sci. **1949**, 6, 85–89.
10. Sheehan, J.C.; Henery-Logan, K.R. The Total Synthesis of Penicillin, V.J. Am. Chem. Soc. **1959**, 81, 3089–3094. [CrossRef]
11. Von Döhren, H. Antibiotics: Actions, Origins, Resistance, by C. Walsh. 2003; ASM Press: Washington, DC, USA, 2009; Volume 13, p. 345.
12. Abraham, E.P.; Chain, E. An Enzyme from Bacteria able to Destroy Penicillin. Nature **1940**, 146, 837. [CrossRef]
13. Aminov, R.I. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. Front. Microbiol. **2010**, 1, 134. [CrossRef] [PubMed]
14. Durand, G.A.; Raoult, D.; Dubourg, G. Antibiotic discovery: History, methods and perspectives. Int. J. Antimicrob. Agents **2019**, 53, 371–382. [CrossRef] [PubMed]
15. Iskandar, K.; Murugaiyan, J.; Hammoudi Halat, D.; Hage, S.E.; Chibabhai, V.; Adukkadukkam, S.; Roques, C.; Molinier, L.; Salameh, P.; Van Dongen, M. Antibiotic Discovery and Resistance: The Chase and the Race. Antibiotics **2022**, 11, 182. [CrossRef] [PubMed]
16. Christensen, S.B. Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and_-Lactams. Molecules **2021**, 26, 6057. [CrossRef]

17. Chait, R.; Vetsigian, K.; Kishony, R. What counters antibiotic resistance in nature? Nat. Chem. Biol. **2012**, 8, 2–5. [CrossRef] Pharmaceuticals **2023**, 16, 1615 45 of 54
18. Blair, J.M.A.;Webber, M.A.; Baylay, A.J.; Ogbolu, D.O.; Piddock, L.J.V. Molecular mechanisms of antibiotic resistance. Nat. Rev. Microbiol. **2015**, 13, 42–51. [CrossRef] [PubMed]
19. Livermore, D.M.; Blaser, M.; Carrs, O.; Cassell, G.; Fishman, N.; Guidos, R.; Levy, S.; Powers, J.; Norrby, R.; Tillotson, G.; et al. Discovery research: The scientific challenge of finding new antibiotics. J. Antimicrob. Chemother. **2011**, 66, 1941–1944. [CrossRef]
20. Saga, T.; Yamaguchi, K. History of antimicrobial agents and resistant bacteria. Japan Med. Assoc. J. **2009**, 52, 103–108.
21. Hwang, I.Y.; Tan, M.H.; Koh, E.; Ho, C.L.; Poh, C.L.; Chang, M.W. Reprogramming Microbes to Be Pathogen-Seeking Killers. ACS Synth. Biol. **2014**, 3, 228–237. [CrossRef]
22. Orfali, R.; Perveen, S.; AlAjmI, M.F.; Ghaffar, S.; Rehman, M.T.; AlanzI, A.R.; Gamea, S.B.; Essa Khwayri, M. Antimicrobial Activity of Dihydroisocoumarin Isolated from Wadi Lajab Sediment-Derived Fungus Penicillium chrysogenum: In Vitro and In Silico Study. Molecules **2022**, 27, 3630. [CrossRef] [PubMed]
23. Davies, J.; Davies, D. Origins and Evolution of Antibiotic Resistance. Microbiol. Mol. Biol. Rev. **2010**, 74, 417–433. [CrossRef]
24. Bartlett, J.G.; Gilbert, D.N.; Spellberg, B. SevenWays to Preserve the Miracle of Antibiotics. Clin. Infect. Dis. **2013**, 56, 1445–1450. [CrossRef] [PubMed]
25. Velez, R.; Sloand, E. Combating antibiotic resistance, mitigating future threats and ongoing initiatives. J. Clin. Nurs. **2016**, 25, 1886–1889. [CrossRef] [PubMed]
26. D'Costa, V.M.; McGrann, K.M.; Hughes, D.W.; Wright, G.D. Sampling the Antibiotic Resistome. Science **2006**, 311, 374–377. [CrossRef] [PubMed]
27. Peterson, E.; Kaur, P. Antibiotic Resistance Mechanisms in Bacteria: Relationships Between Resistance Determinants of Antibiotic Producers, Environmental Bacteria, and Clinical Pathogens. Front. Microbiol. **2018**, 9, 2928. [CrossRef]
28. Vega, N.M.; Gore, J. Collective antibiotic resistance: Mechanisms and implications. Curr. Opin. Microbiol. **2014**, 21, 28–34. [CrossRef] [PubMed]
29. Darby, E.M.; Trampari, E.; Siasat, P.; Gaya, M.S.; Alav, I.;Webber, M.A.; Blair, J.M.A. Molecular mechanisms of antibiotic resistance revisited. Nat. Rev. Microbiol. **2023**, 21, 280–295. [CrossRef]
30. Chellat, M.F.; Raguž, L.; Riedl, R. Targeting Antibiotic Resistance. Angew. Chemie Int. Ed. **2016**, 55, 6600–6626. [CrossRef]
31-Brodersen, D. E., Clemons, W. M., Carter, A. P., Morgan-Warren, R. J., Wimberly, B. T., and Ramakrishnan, V. (2000). The structural basis for the action of the antibiotics tetracycline, pactamycin, and hygromycin B, on the 30S ribosomal subunit. *Cell* 103 (7), 1143–1154. doi:10.1016/S0092-8674(00)00216-6
32-Syroegin, E. A., Flemmich, L., Klepacki, D., Vazquez-Laslop, N., Micura, R., and Polikanov, Y. S. (2022). Structural basis for the context-specific action of the classic peptidyl transferase inhibitor chloramphenicol. *Nat. Struct. Mol. Biol.* 29 (2), 152–161. doi:10.1038/s41594-022-00720-y
33-Foti, C., Piperno, A., Scala, A., and Giuffrè, O. (2021). Oxazolidinone antibiotics: chemical, biological and analytical aspects. *Molecules* 26 (14), 4280. doi:10.3390/molecules26144280
34-Gupta, R., and Gupta, N. (2021). *Fundamentals of bacterial physiology and metabolism*. Singapore: Springer
35-Meroueh, S. O., Bencze, K. Z., Hesek, D., Lee, M., Jed, F. F., Timothy, L. S., et al. (2006). Three-dimensional structure of the bacterial cell wall peptidoglycan. *Proc. Natl. Acad. Sci. U. S. A.* 103 (12), 4404–4409. doi:10.1073/pnas.0510182103
36- Liu, Y., and Breukink, E. (2016). The membrane steps of bacterial cell wall synthesis as antibiotic targets. *Antibiotics* 5 (3), 28. doi:10.3390/antibiotics5030028
37- Fernandes, R., Amador, P., and Prudêncio, C. (2013). ß-Lactams: chemical structure, mode of action and mechanisms of resistance. *Rev. Res. Med. Microbiol.* 24 (1), 7–17. doi:10.1097/MRM.0b013e3283587727
38- Kang, H. K., and Park, Y. (2015). Glycopeptide antibiotics: structure and mechanisms of action. *J. Bacteriol. Virology* 45 (2), 67–78. doi:10.4167/jbv.2015.45.2.67
39- Capasso, C., and Supuran, C. T. (2014). Sulfa and trimethoprim-like drugs-antimetabolites acting as carbonic anhydrase, dihydropteroate synthase and dihydrofolate reductase inhibitors. *J. Enzyme Inhibition Med. Chem.* 29 (3), 379–387. doi:10.3109/14756366.2013.787422