How to Cite:
Berghiche, A., Asnoune, Z., Labiad, I., & Bouzid, R. (2023). Antibiotic resistance between theory and reality: Updated vision on the ecological phenomenon and the emerging crisis recommendations. *International Journal of Health Sciences*, *7*(S1), 2460–2475. Retrieved from https://sciencescholar.us/journal/index.php/ijhs/article/view/14531

Antibiotic resistance between theory and reality: Updated vision on the ecological phenomenon and the emerging crisis recommendations

Berghiche A
Institute of Agronomy and Veterinary Science, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria & Laboratory of Science and Technique of Living, Institute of Agronomic and Veterinarian Sciences, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria
Corresponding author email: amine_berghiche@yahoo.com

Asnoune Z
University Chadli Bend Djedid El Tarf, Algeria

Labiad I
Institute of Agronomy and Veterinary Science, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria & Laboratory of Science and Technique of Living, Institute of Agronomic and Veterinarian Sciences, University Mohamed Cherif Messaâdia, Souk Ahras, Algeria

Bouzid R
Laboratory of agriculture and ecosystems fonctionnary, University Chadli Bend Djedid El Tarf, Algeria & University Chadli Bend Djedid El Tarf, Algeria

***Abstract*---**Our work includes two aspects of resistance in consequence, the first one is the evolutionary side as it evolves in our ecosystem, as well as the estimative side for the future, where it poses a huge challenge that is still unpredictable. Our scientific opinion on this subject starts with a synthetic overview of mechanisms that may be recognized until now, and demonstrates the evolutionary concept in the context of resistance. The inadequate use of antibiotics for preventive or zootechnical purposes in animal production can lead to the presence of their residues as well as to the emergence of multi-resistant bacteria, even though the passage of this bacterial survival pattern among species and even across different species creates health risks and ecological disorders in general. However, the current problem, requiring urgent focus and attention, could become more

and more critical, and the timing of intervention can put our lives at risk. So the question arises, when will we take action?

***Keywords*---**antibiotics, resistance, risk, impact, ecological disorders.

Introduction

Actually, it is impossible to imagine medical treatment that cannot adequately control bacterial pathogens; medical specialties such as veterinary medicine and surgery would simply collapse without access to modern antibiotics. (Littmann *et al.*, 2020 ; Stuart B, 2013). Since the discovery of sulphonamides in 1932 and penicillin in 1945, the mortality rate due to infectious diseases has miraculously decreased, and this period is considered a turning point in human and animal health. (Søren Brøgger, 2021 ; Lesch, 2007). As human beings develop in their curative and preventive health status, the species known as pathogens, in spite of their primitiveness, have adapted to this progression and changed their survival strategies and mechanisms, which are still poorly known or less exploited by the most intelligent biological beings on the Earth !

An updated view of the biological phenomenon

The mechanisms of antibiotics are of five modalities, the first is the inhibition of nucleic acid synthesis, second is the inhibition of protein synthesis which acts on ribosomes, then inhibition of bacterial wall synthesis and disruption of membrane functions and blocking and inhibition of metabolic pathways such as that of folic acid (figure 1). (Elisabeth *et al.*, 2003 ; Garima et al., 2017 ; Walsh; 2003)

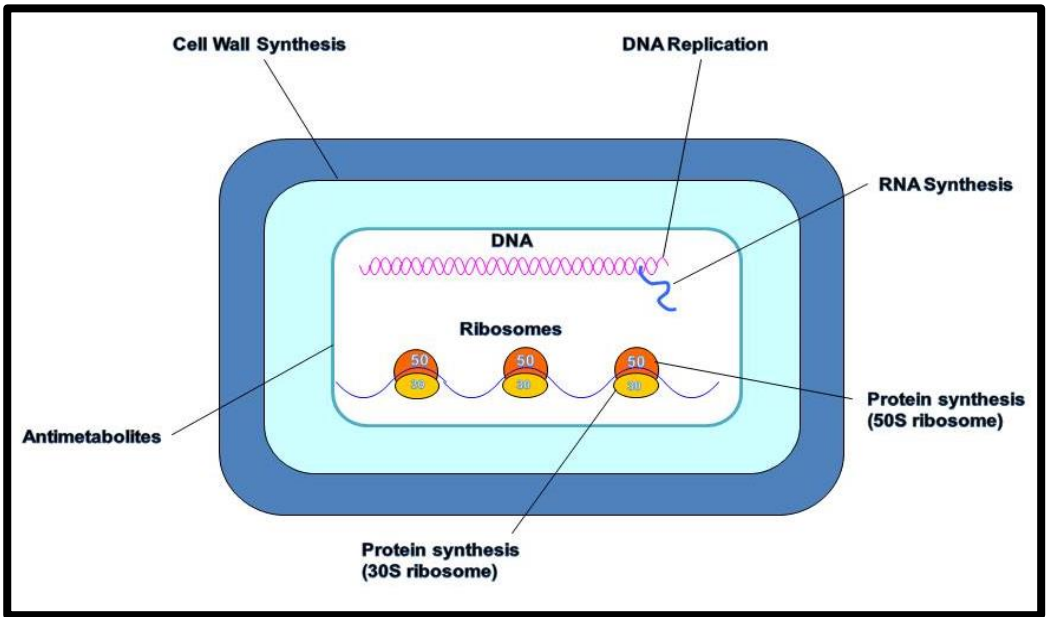

Figure 1. Locations of antiobiotics action at the cellular level

Today, this miracle of antibiotics is in jeopardy on all fronts, where bacteria are becoming increasingly resistant, even to our new antibiotics. (Nwobodo *et al.*, 2022). Antibiotics are integrated in our ecosystem more and more and this presence is an absolute imperative whose use goes from professionalism to total anarchism (Manyi-Loh *et al.*, 2018; Berghiche, 2019), and like all medicines, antibiotics have their own kinetics and dynamics and their fate in the environment as well as its metabolites will increase the risks related to its enormous use in sanitary and zootechnical matters for the living being in general and the animal in a special way. (Anadón *et al.*, 2018)

Our environment in general is becoming contaminated by various antibiotics (Diwan et *al.*, 2010), runoff from intensive farms and human sewage systems when we talk about the metabolites of these molecules that are excreted in urine and faeces, exposes more and more bacteria from all over the world to low levels of antibiotics. (Kraemer et *al.*, 2019). The phenomenon of resistance of bacterial strains to antibiotics was not necessarily related to its use or the era of its discovery. Reinforcing the assumption that some wild animals without apparent contact with man-made drugs, probably explains why most classes of compounds used clinically are also produced by microorganisms in the environment. (Davies & Davies., 2010 ; Holmes *et al.*, 2016)

In some cases, resistance has proven to be a complicated task and its development took three decades and involved a series of genetic events that were perfected until levels of resistance of medical interest were obtained (figure 2). (Fair *et al.*, 2017 ; Wright; 2003 ; Gootz; 1990)

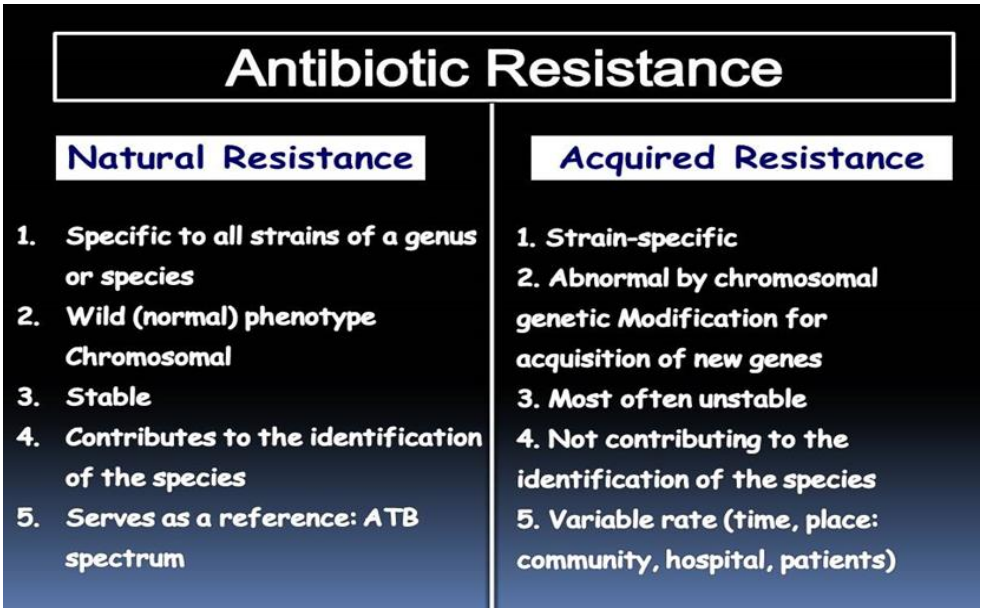

Figure 2. Differential analysis between natural and acquired resistance profile.

If we look at the examples of natural resistance in *Enterobacteria*, we find this taxonomy of bacteria in the following distribution; Group one contains species naturally sensitive to all b-lactam antibiotics such as *Escherichia coli, Proteus mirabilis, Shigella sp, Salmonella sp, Yersinia pestis*, second group contains species resistant to amino and carboxypenicillins. *Klebsiella sp, Citrobacter koseri, amalonaticus*, third group includ species resistant to aminopenicillins not recovered by clavulanic acid as *Enterobacter sp, Citrobacter freundii, Serratia sp, Morganella* sp, the fourth group typify by accumulation of natural resistance from groups 2 and 3 as *Yersinia enterocolitica*, *Pseudotuberculosis*. (Yao & Moellering Jr., 2011 ; Shahid et al., 2009)

Selective preferential antibiotic resistance processes are divided into three ecosystem interactions: Natural environment (resistome) where microbes surround small concentrations of antibiotics produced by other microorganisms and where resistance is low in this case; Non-clinical environment where human presence that increases the selective pressure "medium resistance" and clinical environment high resistance (figure 3). (Yılmaz & Özcengiz., 2017 ; Waglechner & Wright., 2017)

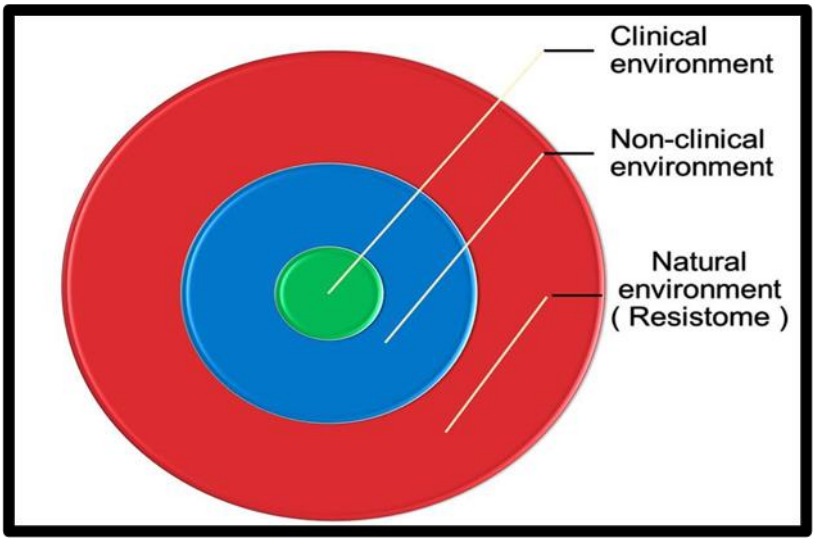

Figure 3. Schematic organization of preferential ecosystem interactions for antimicrobial resistance

At the lethal concentration used to treat an infection, antibiotics impose an intense selective flare-up that can be overcome by several types of pathogen resistance. (Dhama *et al.*, 2013 ; Baumgartner *et al.*, 2008)

Chronic exposure to a minute dose of an antibiotic that is present as a growth promoter in food sewer systems and in a contaminated microenvironment causes a stress response in bacteria that are the result of mutation, on the other hand, bacteria exposed to a sublethal dose of a bactericide produce increased levels of reactive oxygen species that can mutate and increase the efficiency of recombination in the affected bacteria, as well as emergency response via the

error-prone DNA polymerase, which creates a new mutation (figure 4). (Mack *et al.*, 2011 ;Donné & Dewilde., 2015)

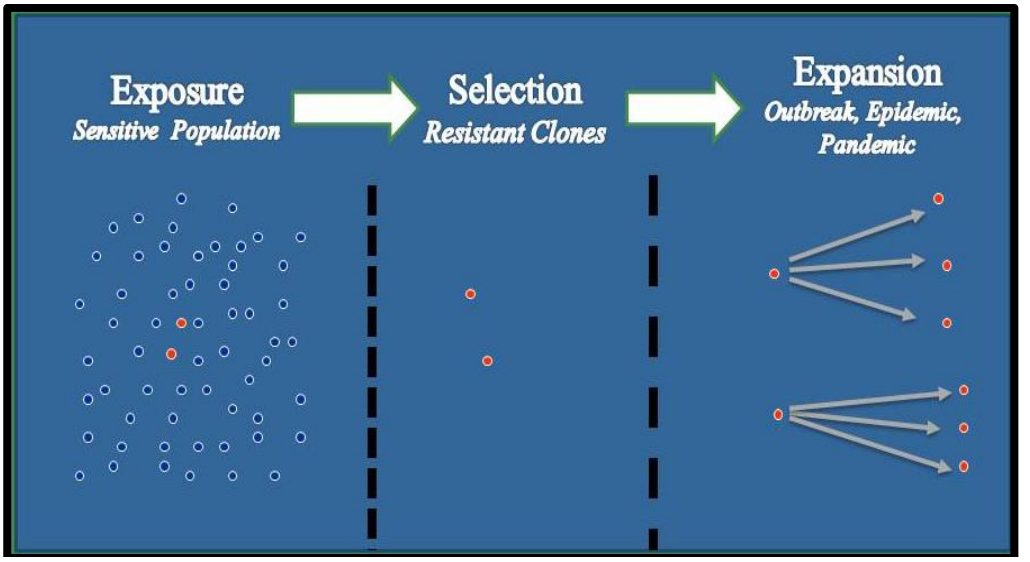

Figure 4. Impact of chronical exhibition on the appearance of the resistant gene

Genetically, two mechanisms have been identified, intrinsic resistance or a chromosomal mutation involving resistance passed on from the descendants or the vertical transmission at this level an acquisition of genetic information from another bacterium and extrinsican resistance or a extrachromosomal mutation which resistance transmitted from one bacterium to another or horizontal transmission more or less vertical. (Christaki *et al.*, 2020)

Some bacteria are inherently insensitive to antibiotics, and were so before generalization of these products. Most resistant bacteria, however, emerged as a result of acquired genetic modifications by mutation or by transfer of genetic material from resistant bacteria to sensitive bacteria. It is generally recognized that bacteria can develop resistance to virtually any antibiotic in response to its use. Exposure to antimicrobials leads to a selective multiplication of resistant bacteria which may persist and replace sensitive bacteria. (Jian *et al.*, 2021 ; Levy, 2013)

Resistance genes are encoded either by or outside of chromosomes by plasmids, transpose and integrate. The ease of transfer of genetic material plays an important role in the spread of antibiotic resistance from one bacterial strain to another. Resistance genes therefore have a high potential for diffusion among bacteria. It follows that antimicrobials may be responsible for the multiplication of resistant bacteria, both among virulent strains and in normal bacterial flora. (McManus, 1997 ; Amábile-Cuevas & Chicurel., 1992)

Three mechanisms of horizontal gene transfer that occur in nature are transduction, transformation and conjugation. Conjugation is essentially the transfer of bacterial DNA from one bacterium to another after contact, this

transfer pathway being particularly widespread in the digestive tract, a place rich in microorganisms allowing close contact with pathogens, transformation is the transfer of bacterial DNA after fixation and absoprtion by competent recipient bacteria and transduction is the transfer of partial bacterial DNA via a bacteriophage (figure 5). (McManus, 1997 ; De la Cruz & Davies., 2000)

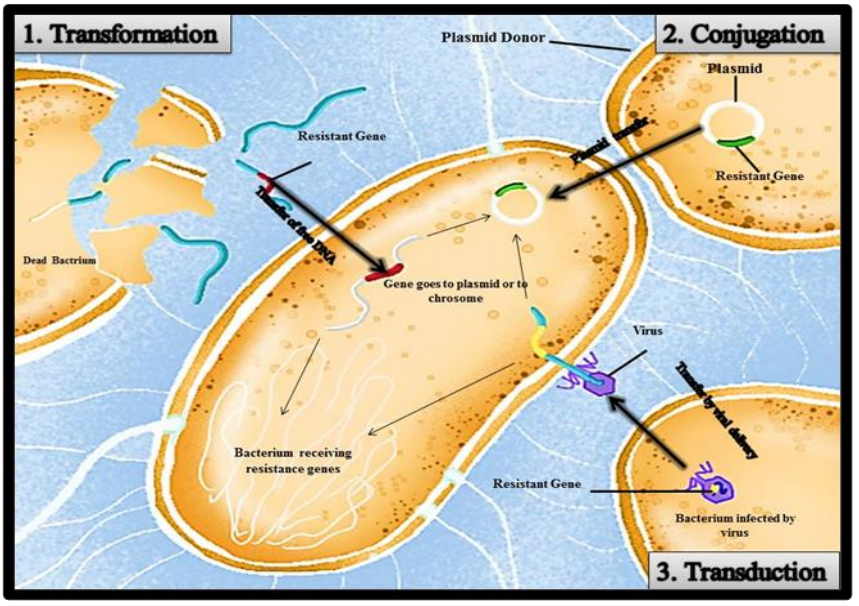

Figure 5. Horizontal and vertical models of resistant gene exchange

The chromosomal resistance mechanisms are classified as follows:

1. Drug inactivation: an enzyme that cleaves part of the molecule and makes it inactive like penicillin by penicillinase (figure 6). (Foster, 1983 ; Todar, 2011 ; Neu & Gootz., 1996)

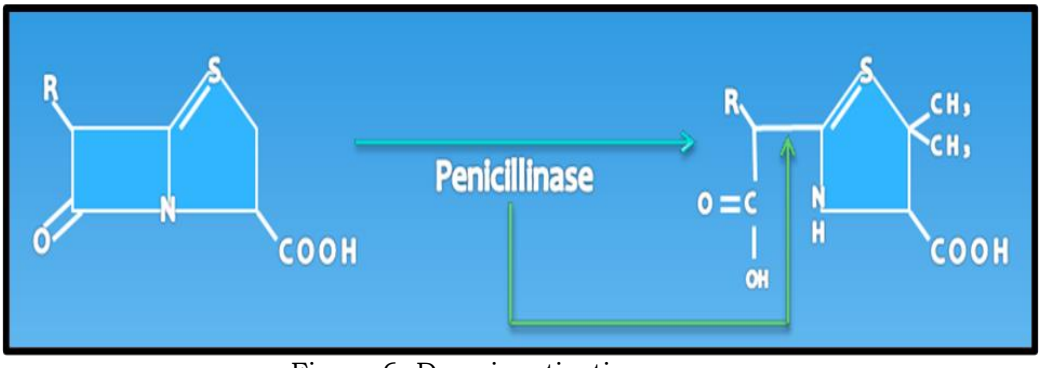

Figure 6. Drug inactivation process

2. Decreased permeability: the receptor that carries the drug is altered so that the drug cannot enter the cell (figure 7). (Jarlier & Nikaido., 1994)

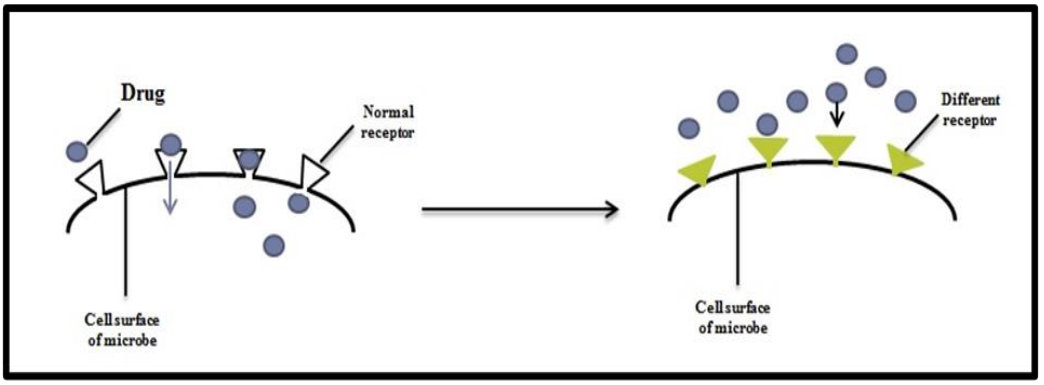

Figure 7. Decreased permeability device

3. Activation of the drug pump: specialized membrane proteins are activated and continuously pump the drug out of the cell (figure 8). (Land & Johnson., 1999)

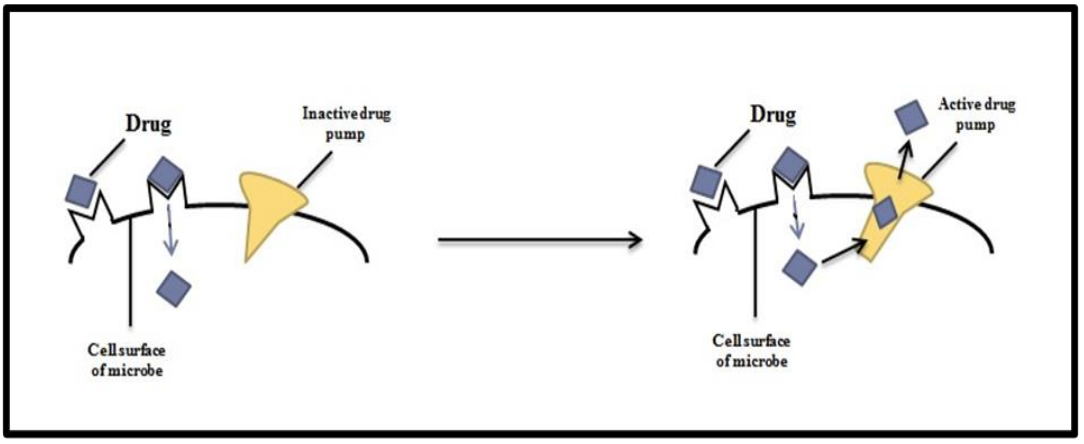

Figure 8. Activation of the drug pump mechanism

4. Modification of the drug binding site: the binding site on the target (ribosome) is altered so that the drug has no effect (figure 9). (Foster, 2017 ; Hansen *et al.*, 1999)

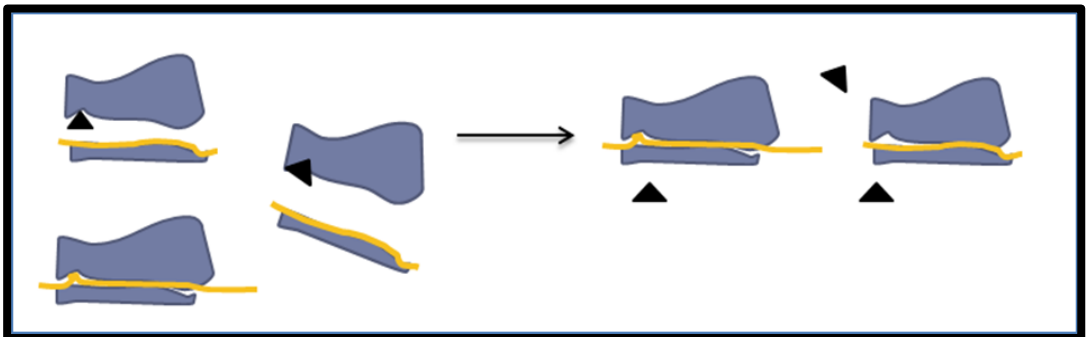

Figure 9. System of modification of the drug binding site

5. Use of the alternative metabolic pathway: the drug has blocked the usual metabolic pathway so that the microbe bypasses it by using an unblocked alternative pathway that achieves the desired result (figure 10). (Yi *et al.*, 2021 ; Onorato, 2021)

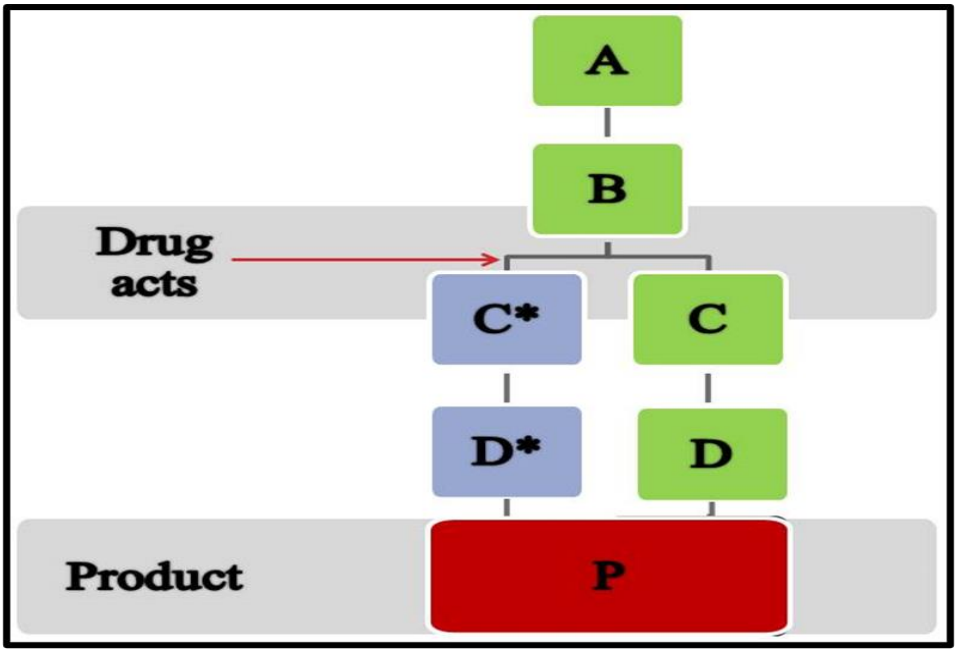

Figure 10. Use of the alternative metabolic pathway

What are the possible alternatives to conventional antibiotics?

Currently, research is focused on the alternatives for classical therapy with antibiotics, aiming at reducing the use of antibiotics in order to reduce the harmful effects and at finding a new approach in the case of multi-resistant bacteria dominance.

A. Natural resources
   Recent studies have shown a renewed interest in alternative therapies (phytotherapy, aromatherapy, homeopathy), as consumers consider them to be less aggressive and more respectful of nature than conventional medicines; These researches are great and especially in their application as antimicrobial compounds are tremendous and very representative, but they require more interesting and valorisation as well as toxicological studies for these organic products are obligatory. (Valladão *et al.*, 2015 ; Marini *et al.*, 2015)
B. Nano-antibiotics
   Nanoparticle antibiotics are defined as drugs modified at the nano-level to improve their effects on bacterial infections. These materials include nanometallic particles, polymeric nanoparticles and liposomes. (Kumar *et al.*, 2019 ; Srivastava, 2016). The advantage of nano-antibiotics is that they can be designed to specifically target pathogenic bacteria, while minimising

damage to healthy cells. In addition, nanoscale antibiotics can more easily penetrate infected tissues and reach places that are difficult for conventional types to penetrate; however, it is important to note that nanoscale antibiotics can also have adverse impacts on the environment and human health if they are released into nature in large quantities. Therefore, their use should be carefully monitored and regulated to minimise any negative consequences. (Le *et al.*, 2021 ; Pormohammad *et al.*, 2021 ; Abeer, 2012)

C. Bacteriocin

Lactic acid bacteria are micro-organisms used in the production of many fermented foods, such as yoghurt, cheese and sauerkraut. In addition to their food use, lactic acid bacteria also possess antimicrobial properties that make them promising for use as an alternative to antibiotics. (Das & Goyal., 2012 ; Khan *et al.*, 2010) Lactic acid bacteria produce substances called bacteriocins that have antimicrobial activity against pathogenic bacteria. The bacteria can act in different ways, preventing the growth of pathogenic bacteria or destroying them; Bacteriocins can be classified into two categories: class I bacteriocins, which are linear peptides, and class II bacteriocins, which are cyclic peptides. Class II bacteriocins are more stable and active than class I bacteriocins, making them a preferred choice for use as alternatives to antibiotics. (Parada *et al.*, 2007 ; Šušković *et al.*, 2010 ; Zimina *et al.*, 2020). By using lactic acid bacteria as an alternative to antibiotics, it is possible to specifically target pathogenic bacteria without harming the beneficial bacteria present in the human body. In addition, the use of lactic acid bacteria is considered safe and without undesirable side effects. (Perez *et al.*, 2014). However, it is important to note that the use of lactic acid bacteria as an alternative to antibiotics is not always effective against all bacterial infections. Furthermore, the production of bacteriocins by lactic acid bacteria can be influenced by different environmental factors, such as temperature, pH and available nutrients, which can affect their effectiveness. Finally, it is important to stress that the use of lactic acid bacteria must be carefully controlled to avoid any risk of bacterial resistance. (Gilliland, 1990 ; Zeise *et al.*, 2021)

D. Cyclopeptid

Cyclopeptides are small molecules composed of amino acids that are bound as a ring. They occur naturally in some bacteria and fungi and have been studied for their potential as alternatives to antibiotics, cyclopeptides have antimicrobial properties, which means that they are able to kill or inhibit the growth of pathogenic bacteria. Unlike traditional antibiotics, cyclopeptides have a unique molecular structure that allows them to specifically target pathogenic bacteria without affecting beneficial bacteria in the body; In addition, they have advantages in terms of bacterial resistance. Pathogenic bacteria tend to develop resistance to antibiotics quickly, which limits their long-term effectiveness, on the other hand, have a unique molecular structure that makes them less susceptible to the emergence of bacterial resistance. (Berdy, 2005 ; Jin, 2020 ; Lai *et al.*, 2023). However, it is important to note that cyclopeptides are still under investigation and their use as alternatives to antibiotics has not yet been widely adopted. Pre-clinical and clinical studies are on-going to assess their efficacy and safety and have also higher production costs than traditional antibiotics, which

may limit their accessibility. In sum, those molecules have great potential as alternatives to antibiotics, but their use still requires further research and development to be widely adopted.

E. Bacteriophages

Bacteriophages are specific viruses that infect and destroy bacteria; they are used as an alternative to antibiotics in the treatment of bacterial infections, the use of bacteriophages as antibiotics involves the identification of specific phages that can target and destroy the pathogenic bacteria responsible for the infection. The phages are then multiplied in the laboratory to produce enough phages to treat the infection. (figure 10) (Allen *et al.*, 2014 ; Loc-Carrillo & Abedon., 2011)

Phages have several advantages as alternatives to antibiotics. Firstly, phages have high specificity for target bacteria, which means that they do not harm beneficial bacteria in the body. In addition, bacteria are less likely to develop resistance to phages than to antibiotics. (Defoirdt *et al.*, 2011)

However, the use of phages as antibiotics also presents challenges. Identifying appropriate phages can be difficult and time-consuming, and their use requires rigorous safety and efficacy testing. In addition, producing phages in large quantities can be expensive and requires specialised equipment and infrastructure. (Svircev *et al.*, 2018)

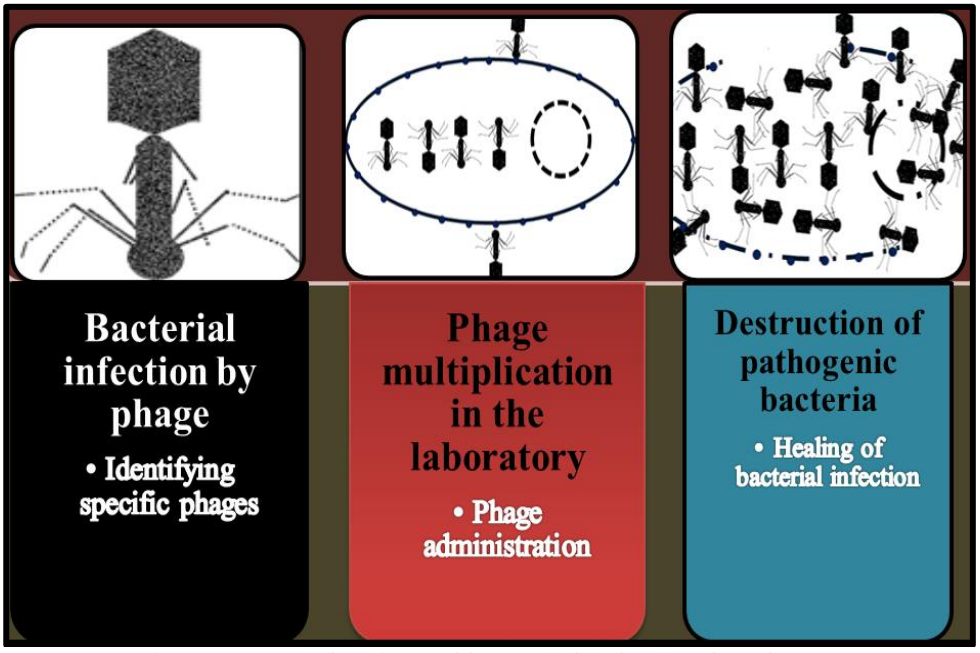

Figure 11. Mechanism of bacterial infection by phages

F. Synthetic biology and predatory bacteria

For antibiotics, synthetic biology has been proposed as a valuable alternative to conventional antibiotics. Scientists explored the feasibility of developing predatory bacteria that could target and kill pathogenic bacteria,

but without the side effects associated with antibiotics. Predatory bacteria are organisms that occur naturally in the soil and have the ability to kill other bacteria by releasing enzymes that break down the cell walls of the target bacterium; Synthetic biology has been used to design predatory bacteria that can be controlled using external signals, such as light or specific molecules. This would allow specific targeting of pathogenic bacteria without affecting the beneficial bacteria in the host organism. However, much work remains to be done to develop this approach and make it effective and safe for use in humans. (Pérez *et al.*, 2020 ; George et *al.*, 2023). To summarise, synthetic biology and predatory bacteria are promising areas of research for developing new alternatives to antibiotics. However, more research is needed to evaluate their efficacy and safety before they can be used as treatments in clinical practice.

Antibiotic resistance' Real or predicted crisis?

Through several researchers and after consulting hundreds of scientific papers, we synthesize the opinions in two ways, firstly that antibiotics since are only effective against foreign cells and bacteria and should have no effect on our own cells and tissues, they are not pharmacologically active, except for the side effects that many of them have when taken in high doses. This means that they can be prescribed with less rigour than other drugs. In many patients who show signs of infection, they are given simply for safety reasons, without strict bacterial diagnosis. This has contributed greatly to the extremely high consumption of antibiotics; this can be estimated from sales figures, which can be used as good indicators of actual consumption. (Bouvet *et al.*, 2022 ; Daubin , 2010) Antibiotic resistance has evolved among pathogenic bacteria in a short time and in many ways faster than expected. This can be explained in part by the short reproductive period of the bacteria, which allows them to succumb to antibiotic resistance.

Evolutionary theory in a much shorter time than would have been possible for animals and other organisms, and bacteria have the ability to manipulate their genetic make-up, resulting in more rapid adaptation to the toxic effects of antibiotics: this is any resistance development that can be envisaged a natural hereditary of bacteria, including the absorption and integration of resistance genes from related organisms by adapting old evolutionary genetic mechanisms to the new ecological situation of high antibiotic presence. No microbial scientist can escape the wonder. We wonder then that these phenomena are constantly taking place. (Christaki *et al.*, 2020 ; Uddin *et al.*, 2021)

Secondly, we notice that there are other viewpoints that justified this development of resistance as normal. It is explained by our existence until now, and the fact that antibiotics were found not that long past relative to our existence and this continues to evolve with our state of health and sanitary conditions, and this phenomenon is considered natural. It is natural even if the causation is anthropogenic, and although this vision is a little optimistic and superficial in terms of estimation, it cannot be said that there is a lack of predictive meta-analysis on the subject. (Stearns *et al.*, 2010 ; Ravelli, 2014 ; Ruppé, 2018)

Whatever your scientific opinion, antibiotic resistance is a major global public health concern. Antibiotic resistance is a natural phenomenon that occurs when bacteria develop ways to survive antibiotics. However, the excessive and inappropriate use of antibiotics by humans accelerates the process of resistance development. Antibiotic resistance poses a number of public health problems, as it can make infections more difficult or impossible to treat. This can lead to serious health complications, increased treatment costs and increased mortality. Antibiotic resistance is an issue that affects everyone, from health professionals and researchers to policy makers and the general public. It is therefore important to take measures to prevent antibiotic resistance, such as promoting the judicious use of antibiotics, developing new antibiotics, implementing better hygiene practices and raising public awareness of antibiotic resistance. Antibiotic resistance is a complex problem that requires a comprehensive and coordinated approach to solve.

Conclusion

This review makes reference to predictive meta-analyses on the subject, which suggests that there is on-going scientific research to better understand and predict the evolution of antibiotic resistance. This work can help guide public health policies and interventions to prevent and control the spread of antibiotic resistance. Through this work we have detailed the mechanisms of resistance to antibiotics as a phenomenon danger, with all the existing information available summarized, antibiotic therapy currently with the use of correct or inconsiderate is a double-edged sword because our vision of these components is limited to their therapeutic role without accounting for their role in the environment and the organism over time.

Understanding the phenomenon of resistance is a necessity and an absolute must, and the adverse effects are getting more and more closer to us, and the alarming phenomenon has entered the danger phase with no sign of monitoring and no way to prevent its spread; if antibiotics have wiped out humanity many times, they can harm it just as much, and perhaps more. Combining the efforts of experts and researchers in the fields related to the phenomenon of antibiotic resistance is mandatory, and working on a global system to study and monitor the spread of the phenomenon is an urgent necessity before the beginning of a pandemic that will be the most damaging in the world' history.

References

1. Abeer, S. (2012). Future medicine: nanomedicine. *Jimsa*, *25*(3), 187-192.
2. Allen, H. K., Trachsel, J., Looft, T., & Casey, T. A. (2014). Finding alternatives to antibiotics. *Annals of the New York Academy of Sciences*, *1323*(1), 91-100.
3. Amábile-Cuevas, C. F., & Chicurel, M. E. (1992). Bacterial plasmids and gene flux. *Cell*, *70*(2), 189-199.
4. Anadón, A., Martínez-Larrañaga, M. R., Ares, I., & Martínez, M. A. (2018). Regulatory aspects for the drugs and chemicals used in food-producing animals in the European Union. In Veterinary toxicology (pp. 103-131). Academic Press.

5. Bandow, Julia Elisabeth, et al. "Proteomic approach to understanding antibiotic action." *Antimicrobial agents and chemotherapy* 47.3 (2003): 948-955.
6. Baumgartner, J. C., Siqueira, J. F., Sedgley, C. M., & Kishen, A. (2008). Microbiology of endodontic disease. *Ingle's endodontics*, *6*, 221-308.
7. Berdy, J. (2005). Bioactive microbial metabolites. *The Journal of antibiotics*, *58*(1), 1-26.
8. Berghiche, A. (2019). Special attention is needed for reduce antibiotic residue risk in the white meat produced in Algeria. *Journal of food quality and hazards control*, *6*(2), 44-44.
9. Bouvet, P., Cavaillon, J. M., Dussaule, J. C., Gay, S., Gosselin, M. P., Merel, Q., ... & Senni, N. (2022). La résistance aux antibiotiques. *Les Cahiers de l'ANR*.
10. Chinemerem Nwobodo, D., Ugwu, M. C., Oliseloke Anie, C., Al-Ouqaili, M. T., Chinedu Ikem, J., Victor Chigozie, U., & Saki, M. (2022). Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. *Journal of Clinical Laboratory Analysis*, *36*(9), e24655.
11. Christaki, E., Marcou, M., & Tofarides, A. (2020). Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence. *Journal of molecular evolution*, *88*, 26-40.
12. Christaki, E., Marcou, M., & Tofarides, A. (2020). Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence. *Journal of molecular evolution*, *88*, 26-40.
13. Christensen, Søren Brøgger. "Drugs that changed society: History and current status of the early antibiotics: Salvarsan, sulfonamides, and β-lactams." *Molecules* 26.19 (2021): 6057.
14. Das, D., & Goyal, A. (2012). Lactic acid bacteria in food industry. *Microorganisms in sustainable agriculture and biotechnology*, 757-772.
15. Daubin, V. (2002). *Phylogénie et évolution des génomes procaryotes* (Doctoral dissertation, Université Claude Bernard-Lyon I).
16. Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and molecular biology reviews*, *74*(3), 417-433.
17. De la Cruz, F., & Davies, J. (2000). Horizontal gene transfer and the origin of species: lessons from bacteria. *Trends in microbiology*, *8*(3), 128-133.
18. Defoirdt, T., Sorgeloos, P., & Bossier, P. (2011). Alternatives to antibiotics for the control of bacterial disease in aquaculture. *Current opinion in microbiology*, *14*(3), 251-258.
19. Dhama, K., Chakraborty, S., Kapoor, S., Tiwari, R., Kumar, A., Deb, R., ... & Natesan, S. (2013). One world, one health-veterinary perspectives. *Adv Anim Vet Sci*, *1*(1), 5-13.
20. Diwan, V., Tamhankar, A. J., Khandal, R. K., Sen, S., Aggarwal, M., Marothi, Y., ... & Stålsby-Lundborg, C. (2010). Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital in Ujjain, India. *BMC public health*, *10*(1), 1-8.
21. Donné, J., & Dewilde, S. (2015). The challenging world of biofilm physiology. In *Advances in microbial physiology* (Vol. 67, pp. 235-292). Academic Press.
22. Fair, R. J., & Tor, Y. (2014). Antibiotics and bacterial resistance in the 21st century. *Perspectives in medicinal chemistry*, *6*, PMC-S14459.

23. Foster, T. J. (1983). Plasmid-determined resistance to antimicrobial drugs and toxic metal ions in bacteria. *Microbiological reviews*, *47*(3), 361-409.
24. Foster, T. J. (2017). Antibiotic resistance in Staphylococcus aureus. Current status and future prospects. *FEMS microbiology reviews*, *41*(3), 430-449.
25. George, S., Sharma, R. K., Hazarika, R., Hazarika, S., Ahmed, R., & Phangchopi, D. (2023). Predatory Bacteria: A Novel Approach to Antibiotic Substitution. *International Journal of Bio-Resource & Stress Management*, *14*(1).
26. Gilliland, S. E. (1990). Health and nutritional benefits from lactic acid bacteria. *FEMS Microbiology reviews*, *7*(1-2), 175-188.
27. Gootz, T. D. (1990). Discovery and development of new antimicrobial agents. *Clinical microbiology reviews*, *3*(1), 13-31.
28. Hansen, L. H., Mauvais, P., & Douthwaite, S. (1999). The macrolide–ketolide antibiotic binding site is formed by structures in domains II and V of 23S ribosomal RNA. *Molecular microbiology*, *31*(2), 623-631.
29. Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., ... & Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, *387*(10014), 176-187.
30. Jarlier, V., & Nikaido, H. (1994). Mycobacterial cell wall: structure and role in natural resistance to antibiotics. *FEMS microbiology letters*, *123*(1-2), 11-18.
31. Jian, Z., Zeng, L., Xu, T., Sun, S., Yan, S., Yang, L., ... & Dou, T. (2021). Antibiotic resistance genes in bacteria: Occurrence, spread, and control. *Journal of Basic Microbiology*, *61*(12), 1049-1070.
32. Jin, K. (2020). Developing cyclic peptide-based drug candidates: an overview. *Future medicinal chemistry*, *12*(19), 1687-1690.
33. Kapoor, Garima, Saurabh Saigal, and Ashok Elongavan. "Action and resistance mechanisms of antibiotics: A guide for clinicians." *Journal of anaesthesiology, clinical pharmacology* 33.3 (2017): 300.
34. Khan, H., Flint, S., & Yu, P. L. (2010). Enterocins in food preservation. *International journal of food microbiology*, *141*(1-2), 1-10.
35. Kraemer, S. A., Ramachandran, A., & Perron, G. G. (2019). Antibiotic pollution in the environment: from microbial ecology to public policy. *Microorganisms*, *7*(6), 180.
36. Kumar, A., Gupta, K., Dixit, S., Mishra, K., & Srivastava, S. (2019). A review on positive and negative impacts of nanotechnology in agriculture. *International Journal of Environmental Science and Technology*, *16*, 2175-2184.
37. Lai, S., Zhang, Q., & Jin, L. (2023). Natural and Man-Made Cyclic Peptide-Based Antibiotics. *Antibiotics*, *12*(1), 42.
38. Land, K. M., & Johnson, P. J. (1999). Molecular basis of metronidazole resistance in pathogenic bacteria and protozoa. *Drug Resistance Updates*, *2*(5), 289-294.
39. Le, H., Karakasyan, C., Jouenne, T., Le Cerf, D., & Dé, E. (2021). Application of polymeric nanocarriers for enhancing the bioavailability of antibiotics at the target site and overcoming antimicrobial resistance. *Applied Sciences*, *11*(22), 10695.
40. Lesch, John E. *The first miracle drugs: how the sulfa drugs transformed medicine*. Oxford University Press, USA, 2007.
41. Levy, S. B. (2013). *The antibiotic paradox: how miracle drugs are destroying the miracle*. Springer.

42. Levy, Stuart B. *The antibiotic paradox: how miracle drugs are destroying the miracle*. Springer, 2013.
43. Littmann, Jasper, Adrian M. Viens, and Diego S. Silva. "The super-wicked problem of antimicrobial resistance." *Ethics and drug resistance: Collective responsibility for global public health* 5 (2020).
44. Loc-Carrillo, C., & Abedon, S. T. (2011). Pros and cons of phage therapy. *Bacteriophage*, *1*(2), 111-114.
45. Mack, A., Relman, D. A., & Choffnes, E. R. (Eds.). (2011). *Antibiotic resistance: implications for global health and novel intervention strategies: workshop summary*. National Academies Press.
46. Manyi-Loh, C., Mamphweli, S., Meyer, E., & Okoh, A. (2018). Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules*, *23*(4), 795.
47. Marini, E., Di Giulio, M., Magi, G., Di Lodovico, S., Cimarelli, M. E., Brenciani, A., ... & Facinelli, B. (2018). Curcumin, an antibiotic resistance breaker against a multiresistant clinical isolate of Mycobacterium abscessus. *Phytotherapy research*, *32*(3), 488-495.
48. McManus, M. C. (1997). Mechanisms of bacterial resistance to antimicrobial agents. *American Journal of Health-System Pharmacy*, *54*(12), 1420-1433.
49. Neu, H. C., & Gootz, T. D. (1996). Antimicrobial chemotherapy. *Medical Microbiology. 4th edition*.
50. Onorato, M. R. (2021). *Genome-Scale Metabolic Modeling of Mycobacterium tuberculosis* (Doctoral dissertation, San Diego State University).
51. Parada, J. L., Caron, C. R., Medeiros, A. B. P., & Soccol, C. R. (2007). Bacteriocins from lactic acid bacteria: purification, properties and use as biopreservatives. *Brazilian archives of Biology and Technology*, *50*, 512-542.
52. Pérez, J., Contreras-Moreno, F. J., Marcos-Torres, F. J., Moraleda-Muñoz, A., & Muñoz-Dorado, J. (2020). The antibiotic crisis: How bacterial predators can help. *Computational and Structural Biotechnology Journal*, *18*, 2547-2555.
53. Perez, R. H., Zendo, T., & Sonomoto, K. (2014). Novel bacteriocins from lactic acid bacteria (LAB): various structures and applications. *Microbial cell factories*, *13*(1), 1-13.
54. Pormohammad, A., Monych, N. K., Ghosh, S., Turner, D. L., & Turner, R. J. (2021). Nanomaterials in wound healing and infection control. *Antibiotics*, *10*(5), 473.
55. Ravelli, Q. (2014). Résistances aux antibiotiques: la fin du scientisme de l'innovation. *Bulletin d'histoire et d'épistémologie des sciences de la vie*, *21*(2), 149-161.
56. Ruppé, É. (2018). *Les antibiotiques: c'est la panique!: Les solutions pour lutter contre la résistance des bactéries…*. Editions Quae.
57. Shahid, M., Sobia, F., Singh, A., Khan, H. M., Hawkey, P. M., Huq, A., & Khardori, N. (2009). AmpC β-lactamases and bacterial resistance: an updated mini review. *Reviews and Research in Medical Microbiology*, *20*(3), 41-55.
58. Srivastava, S. K. (2016). Nano particles: emerging warheads against bacterial superbugs. *Current Topics in Medicinal Chemistry*, *16*, 1963-1975.
59. Stearns, S. C., Nesse, R. M., Govindaraju, D. R., & Ellison, P. T. (2010). Evolutionary perspectives on health and medicine. *Proceedings of the National Academy of Sciences*, *107*(suppl_1), 1691-1695.
60. Šušković, J., Kos, B., Beganović, J., Leboš Pavunc, A., Habjanič, K., & Matošić, S. (2010). Antimicrobial activity–the most important property of

probiotic and starter lactic acid bacteria. *Food Technology and Biotechnology*, *48*(3), 296-307.
61. Svircev, A., Roach, D., & Castle, A. (2018). Framing the future with bacteriophages in agriculture. *Viruses*, *10*(5), 218.
62. Todar, K. (2011). Bacterial resistance to antibiotics (page 3). *Todar's online textbook of bacteriology*, *4*.
63. Uddin, T. M., Chakraborty, A. J., Khusro, A., Zidan, B. R. M., Mitra, S., Emran, T. B., ... & Koirala, N. (2021). Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *Journal of infection and public health*, *14*(12), 1750-1766.
64. Valladão, G. M. R., Gallani, S. U., & Pilarski, F. (2015). Phytotherapy as an alternative for treating fish disease. *Journal of veterinary pharmacology and therapeutics*, *38*(5), 417-428.
65. Waglechner, N., & Wright, G. D. (2017). Antibiotic resistance: it's bad, but why isn't it worse?. *BMC biology*, *15*(1), 1-8.
66. Walsh, Christopher. *Antibiotics: actions, origins, resistance*. American Society for Microbiology (ASM), 2003.
67. Wright, G. D. (2007). The antibiotic resistome: the nexus of chemical and genetic diversity. *Nature reviews microbiology*, *5*(3), 175-186.
68. Yao, J. D., & Moellering Jr, R. C. (2011). Antibacterial agents. *Manual of clinical microbiology*, 1041-1081.
69. Yi, D., Bayer, T., Badenhorst, C. P., Wu, S., Doerr, M., Höhne, M., & Bornscheuer, U. T. (2021). Recent trends in biocatalysis. *Chemical Society Reviews*, *50*(14), 8003-8049.
70. Yılmaz, Ç., & Özcengiz, G. (2017). Antibiotics: Pharmacokinetics, toxicity, resistance and multidrug efflux pumps. *Biochemical pharmacology*, *133*, 43-62.
71. Zeise, K. D., Woods, R. J., & Huffnagle, G. B. (2021). Interplay between Candida albicans and lactic acid bacteria in the gastrointestinal tract: impact on colonization resistance, microbial carriage, opportunistic infection, and host immunity. *Clinical microbiology reviews*, *34*(4), e00323-20.
72. Zimina, M., Babich, O., Prosekov, A., Sukhikh, S., Ivanova, S., Shevchenko, M., & Noskova, S. (2020). Overview of global trends in classification, methods of preparation and application of bacteriocins. *Antibiotics*, *9*(9), 553.