ICONTECH INTERNATIONAL JOURNAL OF SURVEYS, ENGINEERING, TECHNOLOGY
ISSN 2717-7270
Journal homepage: http://icontechjournal.com/index.php/iij
Volume 7 (2023) Issue 4

# Alternative Approaches to Antimicrobials

**Buse Çağmel Turhal**

Department of Pharmacology and Toxicology, Institute of Health Sciences, Ankara University, Türkiye.

ORCID ID: https://orcid.org/0000-0002-2898-8124

**Ayhan Filazi**

Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ankara University, Türkiye.

ORCID ID: https://orcid.org/0000-0002-2800-6215

## Abstract

The extensive utilization of antibiotics over the last eighty years has rescued countless lives of individuals, accelerated technological advancement, and annihilated immeasurable quantities of microorganisms, encompassing both harmful and mutually beneficial species. Microbes associated with humans fulfill various vital roles, and we are currently only at the initial stages of comprehending the manners in which antimicrobial agents have restructured their ecological systems and the resulting functional implications of these alterations. Growing evidence indicates that antibiotics impact the performance of the immune system, our resistance to infections, and our ability to digest food. Hence, it is imperative, now more than ever, to reevaluate our antibiotic usage. In this review, we are going to summarize current research on alternative approaches to antibiotics.

**Keywords:** Bacteriophage, Bacteriocin, AMP, Predator Bacteria



## 1. Introduction

Antimicrobial substances, which can be natural, synthetic, or semi-synthetic, are widely used for antibacterial, antifungal, antiparasitic, or antiviral purposes in both humans and animals. It might propose that the future of humanity depends on the ability to prevent or treat diseases. The most important group of antimicrobials is constituted of antibacterial substances (generally referred to as antibiotics), which have been extensively used for many years as the preferred drug groups to enhance growth and feed utilization in animals, prevent subclinical diseases, and treat bacterial diseases in order to produce healthier, higher quality, and more cost-effective food (Sekkin and Kum, 2011). Nevertheless, their extensive usage has caused a progressive rise in the evolution of resistance over time (Filazi et al., 2015), formation of residues in consumed foods (Ergin-Kaya and Filazi, 2010; Ince and Filazi, 2007; Kaya et al., 1992), alteration in the ratio of beneficial/pathogenic microorganisms in the digestive system (Filazi et al, 2014) dampening of the immune response, toxicity in host organs, and the rise of environmental concerns (Kaya, 2014). The prevalence of resistance genes in pathogenic organisms, in particular, has raised concerns about the future effectiveness of existing antimicrobials (Projan and Shlaes, 2004). According to the Centers for Disease Control and Prevention (CDC) in the United States and its European counterpart, the European Centre for Disease Prevention and Control (ECDC), It has commonly been assumed that approximately 25,000 people die each year in the United States and Europe due to antibiotic-resistant bacterial infections (Laxminarayan et al., 2013; Reardon, 2015). It is estimated that this rate is not much lower in other countries and that many measures implemented to control antibiotic resistance have not been successful (Reardon, 2014). According to the World Health Organization (WHO), currently, 700,000 patients die each year worldwide due to

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

antimicrobial resistance (AMR). It is believed that these deaths will reach 10 million by 2050 (Gravitz, 2012). The Organisation for Economic Co-operation and Development (OECD) has unveiled a recent report which predicts that 2.4 million people in Europe, North America, and Australia will die from infections caused by resistant microorganisms in the next 30 years (OECD, 2018). The report indicates that among the nations included, those in Southern Europe are expected to have the highest mortality rate as a result of infections that are resistant to treatment. Moreover, it is stated that infections related to antibiotic resistance will disproportionately increase in many low- and middle-income countries. For example, it is estimated that an average of 50% of infections in Brazil, Indonesia, and Russia are caused by resistant microorganisms, and resistance is expected to increase 4-7 times faster in these countries compared to other OECD countries (Hofer, 2019).

Recent studies have concentrated on the advancement of new antimicrobial agents and the understanding of DNA gyrase inhibitors. As a result of this research, we could provide hopeful prospects for effectively managing the escalation of bacterial resistance and preventing the recurrence of past mistakes (Ling et al., 2015; Cociancich et al., 2015). However, it has been shown that microorganisms can develop resistance against newly developed antimicrobials when they are not used rationally (Baumann et al., 2014).

To prevent or minimize the problems caused by antimicrobials, many countries have prohibited the utilizing antimicrobials for the facilitation of growth, established national antimicrobial resistance and residue monitoring programs, emphasized preventive medicine, developed antimicrobial usage policies and promoted rational use (World Organization for Animal Health, 2016). In particular, in European countries, the use of certain antibiotics added to animal feed as growth promoters have been first restricted since June 1999 and then completely banned since 2006. However, their usage for therapeutic purposes is still allowed (Nollet, 2005). The prohibition of using antibiotics to promote growth in farm animals has increased the demand for alternative substances that can replace them, particularly in animal husbandry. Consequently, multidimensional approaches have been implemented, including vaccination for disease prevention, enhancing immunity, improving hygiene, regulating intestinal flora through nutrition strategies, and incorporating farm management practices (Conraths et al., 2011).



As a result of the aforementioned factors , there is an immediate need for the newest antimicrobial agents as we know. It has been reported that traditional methods used to discover new antimicrobials are inadequate. Additionally, to continue benefiting from existing antimicrobials, it is necessary to identify additional approaches that can serve as alternatives or support. Therefore, there is an imperative need for compounds that can serve as alternatives to antimicrobials. Since existing antimicrobials are used to treat diseases, prevent them, or facilitate growth in food-producing animals, the newly developed substances should also possess these properties.

Particularly in the context of alternative studies to antimicrobials in animal production, direct food microorganisms containing live or dead organisms or spores, bacteriocins, bacteriophages, and antimicrobial peptides have gained importance. Additionally, in recent years, various approaches to treatment such as fecal bacteriotherapy, or fecal transplantation have been reported as potential alternatives (Ricke et al., 2005; Tellez et al., 2012). However, it should be noted that in an environment where the appearance of new and intricate diseases remains uncontrollable, cross-resistance or the occurrence of multidrug resistance is identified, and the demand for drugs increases in clinical failures, the exploration and

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

development of new categories of antimicrobials will remain to be a priority (Edens, 2003; Filazi and Yurdakok-Dikmen, 2019).

In recent years, a variety of different substances from different groups have been developed that could potentially serve as alternatives to antibiotics. Due to the detailed nature of the topic, only those substances that specifically target certain microorganisms, thereby reducing the risk of resistance development, are discussed here. Therefore, they are partially distinguished from traditionally used antibiotics. In other words, this discussion will provide information about alternative antibiotics that are generally considered to have a narrow spectrum of activity.

## 2. Alternative Approaches Developed Target Microorganisms

### 2.1. Bacteriophages

Bacteriophage (phage) is an expression derived from Ancient Greek, meaning "*bacteria eater*." cells, and Bacteriophages are viral entities that specifically infect bacterial cells, and also they known as phages and they do not infect mammalian or plant cells. They are widely present in all environments where living organisms are routinely exposed to water or food. They are also known as "viruses that infect bacterial cells" or simply "bacterial viruses" (Filazi and Yurdakok-Dikmen, 2019). Structurally, they consist of genetic material, a protein coat surrounding it, and a tail region composed of proteins that aid in attaching to bacteria and transferring their genetic material (DNA or RNA) to infect the bacteria. Phages that are unable to infect mammalian cells possess the ability to bind to specific receptors on the bacterial surface to enter the host cell. The binding process exhibited by phages is highly specific, as it exclusively targets and attaches to a specific bacterial species or strain (Aydoğan and Hadımlı, 2016 and Baş, 2020).



Bacteriophages are found in places where bacteria are abundant, such as the digestive system, feces, sewage, lakes, streams, and fertilized soils. They can be easily isolated from these environments (Koskella et al., 2014). Fecal samples and liquids containing fecal matter are commonly preferred samples for phage isolation (Arda, 2011). As bacteriophage viruses invade bacteria, they damage bacterial metabolism and cause bacterial lysis (Abhilash et al., 2008 and Chevallereau et al, 2022). The genetic material of bacteriophages is contained within a protein shell called a capsid (Bauer et al, 2015). It is attached to a head-neck region and may or may not have a tail that can contract. The distal ends of the phages are in contact with tail fibers that bind to receptor sites on the bacterial cell surface (Wittebole et al., 2014).

Phages demonstrate their effects either in a lysogenic or lytic manner, depending on the type of phage applied. The lysogenic response is obtained from phages called temperate or moderate (Laganenka et al, 2019). In this case, the genetic material of the virus integrates into the bacterium's genome, and phage reproduction occurs at a later stage. In this situation, cell lysis does not occur, and the bacterium becomes immune to attacks from other phages of the same strain, turning into a lysogenic (and often more virulent) bacterium. Such a bacterium is characterized by having an inactive phage integrated into its genome, known as a prophage, and remains in a latent state during multiple divisions of bacterial cells. (Maura and Debarbieux, 2011 and Wittebole et al., 2014). The prophage becomes active by exiting the bacterial genome when the host is exposed to stress or cellular damage. Due to these characteristics, lysogenic phages are not preferred in phage therapy. However, considering the ability of lysogenic phages to transfer antibiotic-resistant genes to non-resistant bacteria,

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

genetically modified lysogenic phages have been considered. The aim is to insert specific genes into the resistant bacterium's genome, escalating its sensitivity to a particular class of antibiotics (Lu and Collins, 2009).

The lytic response, also known as virulent phages, is obtained from lytic phages (Filazi and Yurdakok-Dikmen, 2019). Utilizing lytic phages for the inactivation of bacteria can be served as an alternative approach to addressing bacterial infections (Valerio et al., 2017). In this case, the target is the host bacterium's metabolism, and the generation of new phage particles is aimed. The viral genetic material is replicated in the cytoplasm. Consequently, the synthesis of lytic phage particles is achieved by stimulating the production of holins and lysins in 30-minute cycles. Eventually, the bacterium undergoes lysis. These types of phages are preferred for phage therapy because they replicate their own DNA, lyse bacterial cells, especially within a short replication period, and can transfer the phage's genetic information to other cells without integrating into the host genome, thereby spreading it (Filazi and Yurdakok-Dikmen, 2019). Although there are many phages named within this scope, the phages that have undergone clinical trials and are considered usable in human and animal production are quite limited. Excessive use of antibiotics over the years has significantly raised the emergence of antimicrobial multidrug-resistant bacteria. Most bacterial strains have developed resistance to various drugs, including most available antibiotics, with various mechanisms of action (Valerio et al., 2017). In humans, phage therapy has been used primarily for *Streptococcus pneumonia*, *Mycobacterium tuberculosis* (lung infections), *Haemophilus influenzae type-B* (pneumonia, bacteremia, and meningitis), or *Shigella spp*. (dysentery), *Vibrio cholerae*, and certain types of *E. coli*-induced diarrhea (gastrointestinal) and skin infections. In animals, it has been noted that phage therapy is used for the prevention or reduction of infections caused by neonatal *E. coli* (septicemia) in cattle, sheep, pigs, and poultry production, *S. aureus* (mastitis), *Salmonella pullorum* (pullorum disease in poultry), *S. typhimurium*, and *Campylobacter jejuni* (gastroenteritis in animals) (Johnson et al., 2008; Rodrigues-Rubio et al., 2013 and Sorensen et al., 2015)



**Table 2.1.1.** Differentiation Between Antibiotic and Phage (Aydoğdu and Hadımlı, 2016; Baş, 2020).

| **Antibiotics** | **Phages** |
|---|---|
| Broad spectrum | Narrow spectrum and also species specific |
| Metabolizes and eliminates in body | Replicate where infection occurs and reproduce where needed (auto-dosing) |
| Bacterisid/Bacteriostatic | Rapid bactericidal action |
| Many side effects | No reported serious side effects, but they can stimulate the immune system |
| Antibiotic resistance is not limited to the targeted bacteria | Phage-resistant bacteria may remain susceptible to other phages with the same target |
| Developing new antibiotics takes time and costs | New phage selection is a quick process and can be done in days to weeks<br>It is quite low cost |
| Biofilm-forming bacteria are resistant to antibiotic treatment with many tolerance mechanisms | It is very effective in biofilm forms |

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

| | |
|---|---|
| Their standardization has been done quite well | They may be exposed to factors that reduce phage activity in the human body |
| They can be used in the treatment of intracellular pathogens | They are not effective against intracellular pathogens |

## 2.2. Antimicrobial Peptides

Antimicrobial peptides (AMPs), also commonly called host defense peptides (HDPs), are protein molecules found in almost all forms of life (including microorganisms, arthropods, and plants) that constitute a part of the natural immune system (Thakur et al, 2022). They possess strong and broad-spectrum antimicrobial activity against pathogenic bacteria and fungi. AMPs are natural host defense peptides that contain an amino acid sequence and are considered promising candidates (Hancock et al, 2021) that could serve as an alternative to conventional antibiotics, which are developing resistance (Onbaşılı et al., 2020). AMPs have gained attention in the field of antimicrobial resistance (AMR) as notable natural host defense peptides. Over the past few years, there has been a notable emphasis on studying synthetic antimicrobial peptides (AMPs) to address the limitations associated with their natural counterparts (Mukhopadhyay et al., 2020).

**Table 2.2.1.** Advantages and Disadvantages of AMPs (Rios et al., 2016; Bruhn et al., 2011; Cheema et al., 2011; Uppu et al., 2015; Brogden et al., 2003; Brogden, 2005; Brogden et al., 2011; Bruhn et al., 2009; Park et al., 2011 ve Yeung et al., 2011).

| **Some examples of AMP** | **Advantages** | **Disadvantages** |
|---|---|---|
| Buforin II<br>Plörosidin<br>Dermaseptin<br>Sekropin P1<br>Defensin<br>Prikrosin<br>Baktenesin<br>papiliyosin | ImmuImnomodular effect<br>Anti- Antiflammatory effect<br>B Bactericidal effect | It is costly to produce and purify,<br>Storage conditions are difficult,<br>It is toxic to eukaryotic cells. |



Plant AMPs are potential candidates for the discovery of new antibiotics that could prove effective against Multi-Drug Resistant (MDR) infections, particularly due to their versatile effects on pathogenic microorganisms, by inhibiting MDR pumps (Zhu et al, 2022). They have been proposed as a promising alternative approach to combat microbial infections. Despite the identification of over 5000 general AMPs (Ben Brahim et al, 2022) from various sources, many of these identified AMPs have been tested in clinical trials, and some that have reached the clinical stage have failed due to toxicity or lack of efficacy. Therefore, there is a need to explore new AMPs to expand the available variety of AMPs for potential therapeutic and similar uses (Onbaşılı et al., 2020).

Antimicrobial peptides are small, cationic peptides encoded by genes (Datta et al, 2021) and produced by various tissue and cell types in humans, animals, and plants. They play a substantial role in providing natural immunity. Some of the most important types of these peptides include cathelicidins, defensins, histatins, granulins, lactoferrin, and hepcidins (Akar and Çetin Uyanıkgil, 2020).

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

### 2.3. Bacteriocins

Bacteriocins can be broadly defined as peptides that are produced by bacteria and are synthesized by small ribosomes before being secreted. Indeed, these compounds exert their effects by inserting themselves into the plasma membrane of target bacteria, resulting in the formation of pores and ultimately leading to bacterial lysis. (Rios et al., 2016).

Bacteria can produce bacteriocins in almost every generation, and it has been suggested that at least 99% of all bacteria generate at least one bacteriocin. Indeed, among these compounds, there is a wide range that could potentially be utilized for therapeutic purposes. Many commensal bacteria have been found to endogenously produce bacteriocins, and their use as alternatives to antibiotics is being considered (Cotter et al., 2013).

In the food industry, bacteriocins synthesized from lactic acid bacteria (LAB), or known as "lantibiotics" are predominantly used as preservatives. These bacteria are found in cheese, yogurt, and other fermented dairy products and are generally considered safe. For example, nisin A is bactericidal and is used as a food preservative in more than 50 nations (Setiarto et al, 2023). Furthermore, it is believed that certain LAB bacteriocins could be used for the treatment of infections caused by pathogens such as Helicobacter pylori, E. coli, and Salmonella in the digestive system (Nishie et al., 2012).

Bacteriocins in food are used not only in basic food items such as meat and milk but also in various other forms. For instance, they can be incorporated into protective packaging materials. Nisin, derived from lactic acid bacteria, is widely used due to its pH and temperature stability. The U.S. Food and Drug Administration (FDA) has determined the daily acceptable amount of nisin for adults as 2.9 mg (Üstündağ-Çayır and Yalçın, 2017).



The incorporation of bacteriocin-producing bacteria as probiotics provides an economically viable approach that enables the precise targeting of specific pathogens while maintaining the beneficial bacteria population. The utilization of bacterial strains that produce bacteriocins in combination can consequence in greater efficient targeting of pathogenic bacteria. Moreover, bacteriocins could also be applied to minimize the number of probably pathogenic bacteria in wastewater and manure, limiting their transmission to humans. Lauková and colleagues conducted an assessment effectiveness of bacteriocin CBE V24 produced by E. faecalis V24 in reducing the number of pathogenic bacteria in humans in cattle manure. It was suggested that bacteriocins like CBE V24 could be used to manage animal feces and wastewater without resorting to antibiotics. These applications are thought to be easily transferable to poultry farming and the swine industry, but further research is needed to validate this possibility (Lagha et al., 2017).

Durancin 61A, a broad-spectrum bacteriocin, inhibits highly resistant pathogens such as *S. aureus*, *C. difficile*, and *Streptococcus spp*. when combined with antibiotics and other bacteriocins, demonstrating a synergistic effect. Utilizing synergistic combinations of antimicrobial agents can provide a practical solution to antibiotic resistance and cytotoxicity issues (Hanchi et al., 2017).

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

**Table 2.3. 1.** Advantages and Disadvantages of Some Bacteriocins (Biswas ve et al., 2012; Rios et al., 2016; Synder et al., 2014 and Cotter et al., 2013).

| Some examples of Bacteriocins | Advantages | Disadvantages |
|---|---|---|
| Nisin A<br>Mersasidin Pediosin PA-1<br>Plantarisin S<br>Thurisin CD | They show a synergistic effect when used with antibiotics. They have show potential for resistance develo development | They are very costly to manufacture and purify. Legislation is still unclear. |

## 2.4. Predator Bacteria

Predator bacteria such as Bdellovibrio and similar organisms (BALOs) have been proven to have the potential to act as substitues for antimicrobials and even possess more advantageous therapeutic effects compared to antibiotics and other antibiotic alternatives. BALOs are Delta-proteobacteria that specifically invade gram-negative pathogens such as *E. coli, Salmonella, Legionella,* and *Pseudomonas*, reproducing within them (Dwidar et al, 2012). BALOs are capable of lysing biofilms through various hydrolytic enzymes, including DNAases and proteases. Due to this ability, they are more effective against biofilm-forming bacteria compared to traditional antimicrobials (Cavallo et al, 2021). They create a localized pore and penetrate the periplasm of the target bacterium, forming a hybrid structure called a "*bdelloplast*." They subsequently deform the cells through the breakdown and reshaping of the peptidoglycan layer (Pasternak et al., 2013).



BALOs are highly favorable in controlling diseases caused by complex microbial structures where access to antimicrobials is challenging, such as polymicrobial infections in cystic fibrosis patients and periodontal diseases caused by microorganisms (Filazi & Yurdakok-Dikmen, 2019).

In an experimental infection with *Salmonella enterica* serovar Enteritidis in chickens, oral administration of BALOs resulted in a decrease in cecal *S. enterica* populations and inflammation (Filazi & Yurdakok-Dikmen, 2019).

Although the clinical use of BALOs in the treatment of persistent pathogens is not yet widespread, their effectiveness against a wide range of bacteria, low immunogenicity, and low toxicity make them promising candidates for the treatment of infections. Further research is needed to explore their potential and advance their clinical application (Attebury et al., 2011).

## 2.5. Fecal Microbiota Transplantation

Fecal bacteriotherapy or fecal microbiota transplantation (FMT) is the process of transferring fecal matter obtained from a healthy donor, which undergoes preparation stages, to patients (Nicco et al, 2020). In human medicine, FMT has been used as a method for the treatment of recurrent Clostridium difficile infections, and positive responses have also been observed in the treatment of other gastrointestinal and non-gastrointestinal diseases (Ural et al., 2019). FMT is an ancient practice that has been used in China since the 4th century for the therapeutic intervention of intestinal diseases. In the early 17th century, it was employed in the West for the treatment of rumen acidosis (Borody et al., 2011).

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

## 3. Conclusion

Various alternatives have been developed in response to antimicrobial resistance and the need to effectively treat bacterial infections, moving away from traditional antibiotics. As bacteria develop resistance to traditional antibiotics, researchers are exploring alternative approaches to combat infections. These alternatives being investigated include bacteriophages (viruses that target bacteria), bacteriocins (peptides produced by bacteria), predator bacteria, and antimicrobial peptides. These alternatives are currently undergoing clinical trials to assess their effectiveness in treating bacterial infections (Ghosh et al, 2019). This review offers a concise overview of potential therapeutic alternatives to antibiotics.

## 4. References

Akar, S., & Çetin Uyanıkgil, E. Ö. (2020). Antimikrobiyal Peptitlerin Proinflamatuvar Yanıttaki Potansiyelleri. Medical Journal of Suleyman Demirel University, 27(1).

Arda M (2011). Bakteriyofajlar (Bakteriyel Viruslar). Temel Mikrobiyoloji. Medisan Yayınevi-Ankara. 182-194.

Atterbury, R. J., Hobley, L., Till, R., Lambert, C., Capeness, M. J., Lerner, T. R., ... & Sockett, R. E. (2011). Effects of orally administered Bdellovibrio bacteriovorus on the well-being and Salmonella colonization of young chicks. Applied and environmental microbiology, 77(16), 5794-5803.

Aydogan DY, Hadımlı HH (2016). Bakteriyofaj Tedavisi. Etlik Vet Mikrobiyal Derg. 27(1): 38-47.



Bauer, D. W., Li, D., Huffman, J., Homa, F. L., Wilson, K., Leavitt, J. C., ... & Evilevitch, A. (2015). Exploring the balance between DNA pressure and capsid stability in herpesviruses and phages. Journal of virology, 89(18), 9288-9298.

Baumann S, Herrmann J, Raju R, Steinmetz H, Mohr KI, HutteL, S., ... ve Muller R (2014). Cystobactamids: myxobacterial topoisomerase inhibitors exhibiting potent antibacterial activity. Angewandte Chemie International Edition, 53(52): 14605-14609.

Bas B (2020). Bakteriyofajlar (Bakteri Virusları): Antibiyotiklere Alternatif Tedavi. Veteriner Farmakoloji ve Toksikoloji Derneği Bülteni. 11(1): 38-43.

Ben Brahim, R., Ellouzi, H., Fouzai, K., Asses, N., Neffati, M., Sabatier, J. M., ... & Regaya, I. (2022). Optimized Chemical Extraction Methods of Antimicrobial Peptides from Roots and Leaves of Extremophilic Plants: Anthyllis sericea and Astragalus armatus Collected from the Tunisian Desert. Antibiotics, 11(10), 1302.

Biswas S, Brunel Jm, Dubus Jc, Reynaud-Gaubert M, Ve Rolain Jm (2012). Colistin: an update on the antibiotic of the 21st century. Expert review of anti-infective therapy. 10(8): 917-934.

Borody T, Campbell J, Torres M, Nowak A, Leis S (2011). Reversal of idiopathic thrombocytopenic purpura [ITP] with fecal microbiota transplantation [FMT]. Am J Gastroenterol. 106-941.

Brogden Ka, Ackermann M, Mccray Jr Pb and Tack Bf (2003). Antimicrobial peptides in animals and their role in host defences. International journal of antimicrobial agents, 22(5): 465-478.

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

Brogden KA (2005). Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nature reviews microbiology, 3(3): 238-250.

Brogden NK and Brogden KA (2011). Will new generations of modified antimicrobial peptides improve their potential as pharmaceuticals? International journal of antimicrobial agents. 38(3): 217-225.

Bruhn O, Cauchard J, Schlusselhuber M, Gelhaus C, Podschun R, Thaller G, ... And Grotzinger J (2009). Antimicrobial properties of the equine α-defensin DEFA1 against bacterial horse pathogens. Veterinary immunology and immunopathology. 130(1-2): 102-106.

Bruhn O, Grotzinger J, Cascorbi I, and Jung S (2011). Antimicrobial peptides and proteins of the horse-insights into a well-armed organism. Veterinary research. 42(1): 1-22.

Cavallo, F. M., Jordana, L., Friedrich, A. W., Glasner, C., & van Dijl, J. M. (2021). Bdellovibrio bacteriovorus: a potential 'living antibiotic'to control bacterial pathogens. Critical Reviews in Microbiology, 47(5), 630-646

Cociancich S, Pesıc A, Petras D, Uhlmann S, Kretz J, Schubert V, ... ve Sussmuth RD (2015). The gyrase inhibitor albicidin consists of p-aminobenzoic acids and cyanoalanine. Nature chemical biology. 11(3): 195-197.

Conraths FJ, Schwabenbauer K, Vallat B, Meslın FX, Fussel AE, Slıngenbergh J ve Mettenleıter TC (2011). Animal health in the 21st century—a global challenge.

Cotter Pd, Ross Rp, Hill C (2013). Bacteriocins – a viable alternative to antibiotics? Nat Rev Microbiol. 11(2): 95-105.

Cheema Ub, Younas M, Sultan Ji, Iqbal A, Tariq M, and Waheed A (2011). Antimicrobial peptides: an alternative of antibiotics in ruminants. Adv Agric Biotechnol. 2: 15-21

Chevallereau, A., Pons, B. J., van Houte, S., & Westra, E. R. (2022). Interactions between bacterial and phage communities in natural environments. Nature Reviews Microbiology, 20(1), 49-62.

Datta, S., & Roy, A. (2021). Antimicrobial peptides as potential therapeutic agents: a review. International Journal of Peptide Research and Therapeutics, 27, 555-577.

Dwidar M, Monnappa AK, Mıtchell RJ (2012). The Dual Probiotic and Antibiotic Nature of Bdellovibrio Bacteriovorus. Biosensors and Bioelectronics. 15(1-2): 23-30.

Edens FW (2003). An alternative for antibiotic use in poultry: probiotics. Rev Bras Cienc Avic. 5(2): 1-17.

Ergin-Kaya S, Fılazı A (2010). Determination of antibiotic residues in milk samples. Kafkas Univ Vet Fak Derg. 16(Suppl-A): S31-5.

Filazi A, Yurdakok-Dikmen B, Kuzukıran O (2015). Antibiotic resistance in poultry. Turkiye Klinikleri J Vet Sci-Pharmacology and Toxicology-Special Topics. 1(2): 42-51.

Filazi A, Yurdakok-Dikmen B (2019). Alternative Approahes to Antimicrobials. Frontier in Clinical Drug Research. Vol 5: 111-157.

Filazi A, Sireli UT, Yurdakok B, Aydın FG, Kucukosmanoglu AG (2014). Depletion of florfenicol and florfenicol amine residues in chicken eggs. Br Poult Sci. 55(4): 460-5.



Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

Ghosh, C., Sarkar, P., Issa, R., & Haldar, J. (2019). Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends in microbiology, 27(4), 323-338.

Gravitz L (2012). Turning a new phage. Nat. Med. 18: 1318–1320

Hanchi H, Hammami R, Gingras H, Kourda R, Bergeron MG, Ben Hamida J, ... ve Fliss I (2017). Inhibition of MRSA and of Clostridium difficile by durancin 61A: synergy with bacteriocins and antibiotics. Future microbiology. 12(3): 205-212.

Hancock, R. E., Alford, M. A., & Haney, E. F. (2021). Antibiofilm activity of host defence peptides: Complexity provides opportunities. Nature Reviews Microbiology, 19(12), 786-797.

Hofer, U (2019). The cost of antimicrobial resistance. Nature Reviews Microbiology, 17(1), 3-3.

Ince S, Fılazı A (2007). Bound residues. Turk Vet Hekim Bir Derg. 7: 79-85.

Johnson RP, Gyles CL, Huff WE, et al (2008). Bacteriophages for prophylaxis and therapy in cattle, poultry and pigs. Anim Health Res Rev. 9(2): 201-15.

KAYA S (2014). Kemoterapotikler.Veteriner Farmakoloji. Ankara: Medisan Press Vol 5: 323-665kaya

Kaya S, Yavuz H, Akar F, Liman BC, Filazi A (1992). Antibiotic residues in meat, liver and kidney samples from slaughter cattle. Ankara Univ Vet Fak Derg. 39(1-2): 13-29.

Koskella, B., & Brockhurst, M. A. (2014). Bacteria–phage coevolution as a driver of ecological and evolutionary processes in microbial communities. FEMS microbiology reviews, 38(5), 916-931.



Laganenka, L., Sander, T., Lagonenko, A., Chen, Y., Link, H., & Sourjik, V. (2019). Quorum sensing and metabolic state of the host control lysogeny-lysis switch of bacteriophage T1. MBio, 10(5), e01884-19.

Lagha AB, Haas B, Gottschalk M ve Grenier D (2017). Antimicrobial potential of bacteriocins in poultry and swine production. Veterinary research. 48(1): 22.

Laxminarayan R, Duse A, Wattal C, et al (2013). Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 13(12): 1057-98.

Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, ... ve Lewis K (2015). A new antibiotic kills pathogens without detectable resistance. Nature. 517(7535): 455-459.

Lu TK, Collins JJ (2009). Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy. Proc Natl Acad Sci USA. 106(12): 4629-34.

Maura D, Debarbieux L (2011). Bacteriophages as twenty-first century antibacterial tools for food and medicine. Appl Microbiol Biotechnol. 90(3): 851-9.

Mukhopadhyay S, Prasad AB, Mehta CH ve Nayak UY (2020). Antimicrobial peptide polymers: No escape to ESKAPE pathogens—A review. World Journal of Microbiology and Biotechnology. 36(9): 1-14.

Nicco, C., Paule, A., Konturek, P., & Edeas, M. (2020). From donor to patient: collection, preparation and cryopreservation of fecal samples for fecal microbiota transplantation. Diseases, 8(2), 9.

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

Nishie M, Nagao J, Sonomoto K (2012). Antibacterial peptides 'bacteriocins': overview of their diverse characteristics and applications. Biocontrol Sci. 17(1): 1-16. [http://dx.doi.org/10.4265/bio.17.1] [PMID: 22451427]

Nollet L (2005). AGP alternatives-part I. EU close to a future without antibiotic growth promoters. World Poult. 21(6): 14-5.

OECD.(2018). 'Stopping Antimicrobial Resistance Would Cost USD 2 per person a year'. (Access Date: 27.05.2023). https://www.oecd.org/newsroom/stopping-antimicrobial-resistance-would-cost-just-usd-2-per-person-a-year.html

Onbasili D, Yuvali-Çelik G, Turk-Katırcıoglu H (2020). ERÜ Sağlık Bilimleri Fakültesi Dergisi. 7(1): 51-57.

Park Sc, Park Y, Hahm Ks (2011). The role of antimicrobial peptides in preventing multidrug-resistant bacterial infections and biofilm formation. International journal of molecular sciences. 12(9): 5971-5992.

Pasternak Z, Pietrokovski S, Rotem O, Gophna U, Lurie-Weinberger MN, Jurkevitch E (2013). By their genes ye shall know them: genomic signatures of predatory bacteria. ISME J 2013. 7(4): 756-69. [http://dx.doi.org/10.1038/ismej.2012.149] [PMID: 23190728]

Projan SJ, Shlaes DM (2004). Antibacterial drug discovery: is it all downhill from here? Clin Microbiol Infect. 10 (Suppl. 4): 18-22.

Reardon S (2014). Antibiotic resistance sweeping developing world. Nature. 509(7499): 141-2.



Reardon S (2015). Dramatic rise seen in antibiotic use http://www.nature.com/news/dramatic-rise-seen-[http://dx.doi.org/10.1038/nature.2015.18383]

Ricke SC, Kundinger MM, Miller DR, Keeton JT (2005). Alternatives to antibiotics: chemical and physical antimicrobial interventions and foodborne pathogen response. Poult Sci. 84(4): 667-75.

Rios AC, Moutinho CG, Pinto FC et al (2016). Alternatives to overcoming bacterial resistances: State-of-the-art. Microbiol Res. 191: 51-80.

Rodríguez-Rubio L, Martínez B, Rodríguez A, Donovan DM, Gotz F, García P (2013). The phage lytic proteins from the Staphylococcus aureus bacteriophage vB_SauS-phiIPLA88 display multiple active catalytic domains and do not trigger staphylococcal resistance. PLoS One. 8(5): e64671.

Sekkin S, Kum C (2011). Antibacterial drugs in fish farms: Application and its effects. Recent Advances in Fish Farms. Croatia: InTech. Pp: 217-50.

Setiarto, R. H. B., Anshory, L., & Wardana, A. A. (2023, April). Biosynthesis of nisin, antimicrobial mechanism and its applications as a food preservation: A review. In IOP Conference Series: Earth and Environmental Science (Vol. 1169, No. 1, p. 012105). IOP Publishing.

Sørensen MC, Gencay YE, Birk T et al (2015). Primary isolation strain determines both phage type and receptors recognised by Campylobacter jejuni bacteriophages. PLoS One. 10(1): e0116287.

Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926

Snyder Ab, Worobo Rw (2014). Chemical and genetic characterization of bacteriocins: antimicrobial peptides for food safety. Journal of the Science of Food and Agriculture. 94(1): 28-44.

Tellez G, Pixley C, Wolfenden RE, Layton SL, Hargis BM (2012). Probiotics/direct fed microbials for Salmonella control in poultry. Food Res Int. 45(2): 628-33.

Thakur, A., Sharma, A., Alajangi, H. K., Jaiswal, P. K., Lim, Y. B., Singh, G., & Barnwal, R. P. (2022). In pursuit of next-generation therapeutics: Antimicrobial peptides against superbugs, their sources, mechanism of action, nanotechnology-based delivery, and clinical applications. International Journal of Biological Macromolecules.

Uppu Ds, Ghosh C, Haldar J (2015). Surviving sepsis in the era of antibiotic resistance: Are there any alternative approaches to antibiotic therapy? Microbial pathogenesis. 80: 7-13.

Ural K, Erdogan H, Adak HI et al (2019). Ataksik Kedilerde Fekal Mikrobiyata Transplantasyonu. MAKÜ Veteriner Fakültesi Dergisi. 4(1): 34-36.

Valerio N, Oliveira C, Jesus V, Branco T, Pereira C, Moreirinha C, Almeida A (2017). Effects of single and combined use of bacteriophages and antibiotics to inactivate Escherichia coli. Virus Research. http://dx.doi.org/10.1016/j.virusres.2017.07.015

Wittebole X , Roock S, Opal Sm (2014). A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence. 5: 1.

World Organization For Animal Health (OIE) (2016). Chapter 6. Responsible and prudent use of antimicrobial agents in veterinary medicine. Terrestrial Animal Health Code. http://www.oie.int/internationalstandard-setting/terrestrial-code/access-online/ [cited: 24th October 2016].

Yeung At, Gellatly Sl, Hancock Re (2011). Multifunctional cationic host defence peptides and their clinical applications. Cellular and Molecular Life Sciences. 68(13): 2161.

Zhu, Y., Hao, W., Wang, X., Ouyang, J., Deng, X., Yu, H., & Wang, Y. (2022). Antimicrobial peptides, conventional antibiotics, and their synergistic utility for the treatment of drug-resistant infections. Medicinal Research Reviews, 42(4), 1377-1422.



Received 28 May 2023; Received in revised form 13 June 2023;
Accepted 28 September 2023; Available online 31 December 2023;
doi: 10.5281/zenodo.8130926