Novel Alternatives to Antibiotics in Veterinary Medicine

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Abstract

Antibiotics have long played an important role in the treatment of bacterial illnesses in people and animals. However, the rising issue of antibiotic resistance, enhanced by their extensive usage in animal husbandry, has created an urgent need for alternate approaches for addressing infectious diseases. Overuse of antibiotics in livestock raises issues about food safety, public health, and the viability of animal production systems. As a result, much of the focus has switched to developing novel antibiotic alternatives that may successfully control infections while reducing the danger of resistance. This chapter discusses developing technologies and research in the realm of alternative antimicrobials, such as bacteriophages, bacteriocins, phytochemicals, probiotics and prebiotics, vaccines, nanoparticles, and predatory bacteria. The focus is to provide a comprehensive overview of these novel approaches, with particular emphasis on their potential to replace or complement traditional antibiotic therapies, ensuring a more sustainable and effective future for animal health and food security.

Keywords: Antibiotic resistance, Animal husbandry, Antibiotic alternatives, Bacteriophages, Probiotics, Vaccines, Nanoparticles

1. Introduction

The first antibiotic, Salvarsan, was developed in 1910. Antibiotics have considerably improved contemporary medicine during the past century, increasing human life expectancy by an average of 23 years. Alexander Flemming's 1928 discovery of penicillin launched the golden period of antibiotic discovery from natural chemicals, which lasted until the mid-1950s. (Hutchings et al., 2019). Several novel antibiotics were found during this antibiotic era, and the period from 1950s to 1970s were named as "the golden age of discovering new antibiotics."(Adedeji, 2016). Antibiotics are microbial molecules with low molecular weight that, in little quantities, impede the growth of other microbes (Lancini et al., 1995). Antibiotics are critical for treating bacterial infections in livestock, which impact their health, productivity, and well-being (Van et al., 2020). Antibiotics are seen as critical for treating and preventing infectious diseases in agricultural animals used in food production, as well as safeguarding public health from foodborne illnesses (Ungemach et al., 2004). Antimicrobials are also needed to treat infections of the skin, wounds, respiratory system, and urinary tract in companion animals. They are also crucial in reducing the risk of sepsis and surgical site infections (Vasseur et al., 1988). However, recent trends show a decline in antibiotic potency in battling hazardous bacteria, despite significant accomplishments against microorganisms (Richardson, 2017). Antibiotic resistance occurs when a pathogen or commensal bacterium that was previously responsive to an antibiotic loses its susceptibility following exposure (Canteschi et al., 2023).

Antibiotic overuse and inappropriate use causes resistance (Ferri et al., 2017). Bacteria use evolutionary methods to adapt to antibiotic selection pressure, lowering their efficacy against human and animal infections (Palma et al., 2020). The veterinary industry, animal welfare, and food and feed production systems may be jeopardized if bacteria acquire antibiotic resistance (FAO, 2016). AMR is a major One Health issue that is expanding globally (Forsberg et al., 2012; Mather et al., 2013). Humans,

animals, and the environment interact, allowing resistance genes to spread between species. This technology allows for bidirectional transfer of resistance genes between humans and animals (Fernández et al., 2018). The process of discovering new antibiotics is both technically difficult and financially unfeasible due to the high time, effort, and expenditure requirements, as well as the low ROI. The most effective long-term remedy to this problem is to limit and rationalize antibiotic use (Holmes et al., 2016).

It is critical to explore new antibiotics with unique mechanisms of action (MOAs) that prevent infections, delay the development of resistance, or enhance effectiveness of current antibiotics (Allen et al, 2014). Using these techniques for infections contracted in the community would eventually reduce reliance on antibiotics.

2. Novel Alternatives to Antibiotics

Alternatives to antibiotics are designed to help minimize disease and improve animal well-being while minimizing resistance (Rello et al., 2019). New antibacterial drugs can help treat or prevent infections related to bacterial pathogens, just like the common antibiotics (Allen et al., 2014). These agents may also be used in combination with traditional antibiotics, to enhance their activity, and to resensitize them for use against antibiotic-resistant bacteria, to increase the spectrum of activity against other bacterial species, and to extend their life span, in both human and veterinary medicine (Betts et al., 2018).

2.1. Bacteriophages

Bacteriophages are viruses that specifically target bacteria, and they can be genetically engineered to have antibacterial properties through various methods (Allen et al., 2014). Phage treatment is the use of lytic phages to kill harmful microorganisms. To cure diseases in humans and animals, lytic phages of specific pathogens have been designed and given. Although some evidence suggests that phage therapy is useful against systemic infections, it has primarily been developed and utilized to treat easily accessible topical disorders, such as those of the paranasal sinuses or the skin (Biswas et al., 2002).

Mode of action

Lysogenic phages integrate into the bacterial genome and replicate passively, without creating virions; yet, they can enter the lytic cycle and kill the host cell (Cheng et al., 2014). Lytic phages, on the other hand, enter bacterial cells by binding to various receptors, multiplying with host cell machinery, and causing cell lysis (Gordillo et al., 2019). Lysogenic phages or phagemids (plasmids that carry bacteriophage genes) are genetically modified to express some proteins, enzymes, antimicrobial peptides (AMPs), or toxins, which interfere with bacterial metabolism and delete pathogenicity or resistance genes. Bacteriophages are known to express several enzymes such as endolysin and holin that degrade the bacterial cell wall for the entry of phage or the release before cell lysis (Gupta et al., 2022).

Advantages of Phage Therapy

Specificity: Phages are very specific, typically targeting only one type of bacterium or even specific strains within a species (Górski, et al., 2007). Unlike broad-spectrum antibiotics, which can kill both good and bad bacteria, this keeps the host's beneficial microbiota intact (Carlton, 1999).

Phage modification for resistance: Although bacteria can acquire resistance to phages, the intrinsic diversity of phages in the environment enables the selection or synthesis of novel phages capable of overcoming resistance mechanisms (Pirnay et al., 2011). Because of its flexibility, it is less likely to create long-term resistance than antibiotics.

Protection: When phages have finished attacking bacteria, they are typically eliminated from the body and rarely cause harm to human or animal cells. This safety profile has greatly aided research and applications involving food animals and aquaculture (Sulakvelidze et al., 2001).

Applications of Phage Therapy

Bacteriophages multiply solely in their target bacteria, leaving little impact on the remainder of the microbiome (Kakasis, A., & Panitsa, G. et al., 2019). They are cheaper than antibiotics and have better safety profile, tolerability and convenient to administer (Principi et al., 2019). These have been established for their safety and for therapeutic potential in the management of various bacterial infections in man and animals, through local or systemic administration (Torres-Barceló, 2018). Bacteriophages have been found to effectively treat diabetic foot ulcers, burns, wound infections, and systemic infections

caused by a wide range of pathogens. Phage therapy could be an alternative method of reducing diseases in chicken farms, livestock, and aquaculture. Phage treatment is routinely used to treat salmonellosis, colibacillosis, and campylobacter infections in chickens (Johnson et al., 2008). The majority of research on the use of phage treatment in cows focused on treating mastitis. Mastitis is a prevalent disease that causes considerable financial issues for animal farms. Petrovski et al. (2006) discovered that Staphylococcus aureus and Streptococcus agalactiae act as reservoir hosts for mammalian glands in bovine species. Protein phages, such as endolysins, have been useful in the treatment of mastitis (Shan et al., 2020).

Challenges and limitations

Despite all of the features of lytic phages that appear to support their clinical usage, their use is still debatable, and they are not widely employed therapeutically or prophylactically around the world (Loponte et al., 2022). Because of phages' restricted host range, developing a single phage therapy capable of curing all pathogenic subspecies in multiple animals and humans can be difficult. Phage activity may have been overlooked because phage preparations were not adequately purified (Luong et al., 2020).Some researchers may have used lysogenic phages, which are substantially less successful than lytic phages, because they couldn't tell the difference between the two types of phages (Kuchment, 2011).Furthermore, it is unknown how effectively phages can treat illnesses caused by intracellular infections (such as Salmonella species), which are bacteria that often live inside human cells and are resistant to phages (Khan, M. A. S., & Rahman, S. R, et al., 2022)

2.2. Antimicrobial proteins (Bacteriocins)

All living things produce antimicrobial proteins (AMPs), which are also known as antimicrobial peptides because of their short size. Antibiotics are predicted to be replaced by AMP-based therapies because of their broad-spectrum antibacterial, antiviral, and antifungal properties (Kirienko et al., 2019). Bacteria produce two types of antimicrobial peptides (AMPs): those synthesized by ribosomes, known as bacteriocins, and those created without ribosomes, which lack structural genes that code for them (Chikindas et al., 2018). Antimicrobial peptides (AMPs) are increasingly being used as alternatives to traditional antibiotics. However, non-ribosomal AMPs are unsuitable for therapy since many of them are harmful to mammalian cells.
Bacteriocins address this disadvantage by preventing closely related organisms from forming (Snyder and Worobo 2014). Bacteriocins, like phage-encoded endolysins, permeate the target bacteria's plasma membrane, creating holes and finally causing lysis. The term "narrow-spectrum bacteriocin" refers to bacteriocins produced by a bacterium that inhibit other bacteria in its species. It is worth noting that bacteriocin-producing bacterial cells are resistant to the antimicrobial peptides that are mediated by host cell immune proteins (Juturu et al., 2018).

General properties of bacteriocins

Bacteriocins are particularly appealing for a wide range of applications due to their many positive qualities. LAB bacteriocins are well-known for their ability to work across a wide pH range and their natural tolerance to high heat stress. These antimicrobial peptides are colorless, odorless, and tasteless, which increases their potential value. Because they are proteinaceous, proteolytic enzymes can easily break them down (Perez and Zendo 2014). Bacteriocin fragments have a short lifespan in the environment and in the human body, therefore target strains are less likely to interact with degraded antibiotics. Bacteriocins are "designer drugs" that treat certain bacterial infections. Bacillus species are gram-positive bacteria that generate bacteriocin, while Escherichia coli and other Enterobacteriaceae are gram-negative (Prabhakar et al., 2013).

Mode of Action

Bacteriocins reduce the growth of their target organisms in a variety of ways. Bacteriocins can suppress gram-positive bacteria by targeting and damaging their cell envelopes. They inhibit the synthesis of peptidoglycan by targeting lipid II on the cell membrane (Cotter et al., 2013). Other bacteriocins form pores and bind to the mannose phosphotransferase system (Man-PTS), thereby inhibiting or killing their target bacteria. Many bacteriocins used to treat gram-negative bacteria disrupt their DNA, RNA, and protein metabolism.

Applications of Bacteriocins

Bacteriocins are naturally produced by a large variety of commensal bacteria, therefore they could be manipulated or exploited (Cotter et al., 2013). Lactic acid bacteria (LAB), a type of commensal bacterium, produce the bacteriocin nisin A, which is utilized as a food preservation in over 50 countries due to its antibacterial properties. Nisin has also been studied as a preventive and therapeutic agent for cow mastitis. Nisin-based injectable therapies have been shown to effectively eradicate approximately 99.9% of mastitis-causing bacteria, including Streptococcus agalactiae and Staphylococcus aureus, after medication administration (Kitazaki et al., 2010).

2.3. Phytochemicals

Phytochemicals, also known as phytobiotics, phytogenics, herbal medicines, or functional foods, are biologically active compounds found in plants. They are produced during metabolism and are essential to plant survival (Górniak et al., 2019). Numerous phytochemicals have been studied and found to have a wide range of properties, including antibacterial, antioxidant, anticancer, immune-stimulating, anti-inflammatory, provitamin, enzymatic, anti-stress, and hormone regulating activities (Barbieri et al., 2017). These substances consist of carotenoids, curcumin, organosulfur compounds, phytosterols, and flavonoids (Yang, 2022).

Mode of Action:

The main way phytochemicals promote health and growth is through immunomodulation, enhancing the immune function of host cells. Various compounds have antibacterial activity through a variety of mechanisms, such as rupturing bacterial membranes, inhibiting virulence factors, interacting with membrane proteins, causing ion leakage, coagulating cell content, and preventing bacterial biofilm formation (Almodaifer et al., 2017). Certain compounds can also alter bacteria's antibiotic resistance mechanisms, potentially lowering antibiotic dosage or enhancing antibiotic efficacy (Chandra et al., 2017).

Applications

Carotenoids, flavonoids, and benzoic acid are some of the phytochemicals that have been identified to exhibit extensive antibacterial activity against facultative anaerobic, aerobic, both gram positive and negative, and MDR bacterial strains (Weber et al., 2012). They are prescribed to cure inflammation and to prevent and treat microbial infections. Topical applications of natural plants such as aloe vera, curry leaf and calcium hydroxide are often applied on the affected cattle with SCM due to their broader-spectrum antibacterial, anti-inflammatory and immunomodulatory factors (Saidi et al., 2019).

Challenges and limitations

Despite the fact that both herbal medicines and phytochemicals are used singly and in combination with antibiotics for therapeutic and preventive intents and purposes, clinical evidence on the efficacy and safety profile of these products remain scarce. Like with antibiotics, there have been cases of lack of sensitivity or intolerance and even resistance to phytochemicals and herbal therapies (Singh et al., 2020). Herbal treatments have traditionally been regarded to be innocuous and non-toxic in comparison to allopathic medications; however, there are mounting instances of users being put at unacceptable risk for health problems due to contamination with hazardous amounts of metals and carcinogens (bode et al., 2015).

2.4. Probiotics and Prebiotics

The gut microbiome is made up of over 1,000 different species of commensal microbes that regulate the gut-brain axis and aid in energy consumption, digestion, and immunological responses (Kerry et al., 2018). Probiotics are live microorganisms that improve the host's gut microbial balance. Probiotics are typically from the Bifidobacterium, Lactobacillus, Saccharomyces, or Bacillus genera (Ghosh et al., 2019).

Probiotic bacteria work by altering the composition of the gut microbiome. Prebiotics are naturally occurring, indigestible nutrients such as fruits, vegetables, fiber, and natural sugars that nourish and encourage commensal bacteria. Prebiotics allow probiotics to survive in the human digestive system for longer lengths of time than they would otherwise. Prebiotics mostly target bacteria in the colon and large intestine, whereas probiotics often target bacteria in the small intestine. Synbiotics are dietary supplements that contain both probiotic microorganisms and prebiotic food components. Synbiotic solutions can be designed to target certain probiotic strains, enhancing health benefits (Gu et al., 2022).

Mode of Action

These microbes employ a variety of mechanisms, including improving mucosal barriers, producing antibacterial substances such as bacteriocins and organic acids, (Ghosh et al., 2019) removing toxins, restoring gut dysbiosis, and inducing immunomodulation by increasing pro-inflammatory cytokines and inhibiting protective cytokines (Gupta et al., 2022).

Applications

Probiotics play a significant role in the gut-brain axis and exhibit various beneficial properties, including anti-pathogenic, anti-inflammatory, antidiabetic, anticancer, anti-allergic, anti-obesity, and angiogenic effects (Kerry et al., 2018). They are medically applied to enhance lactose tolerance and diarrhea prevention. They are also used in preventing certain conditions such as antibiotic-associated diarrhea, vaginitis, sepsis, and atopic dermatitis. They are also administered to patients which are suffering from acute bacterial diseases and also including Clostridium difficile infections (CDIs), diarrhea and constipation and chronic illnesses for example irritable bowel syndrome, and hepatic encephalopathy. Apart from these, they even aid to prevent side effects associated with chemotherapy or conventional antibiotic therapies (Imperial, I. C., & Ibana, J. A. et al., 2016

Research indicates that probiotics might play a role in cancer prevention, help manage inflammatory gut disorders, reduce allergic responses, and strengthen the immune system (Liu et al., 2018). Tests have also shown that bacteriocins, which many Lactobacillus probiotics produce, can help to stop MRSA biofilm from forming (Lee et al., 2020).

Challenges and Limitations

It is hard to know which probiotic product to choose because probiotic effectiveness depends on strain, condition as well as dosage. This is so because different infections have different probiotic modes of action, and while a certain strain or combination of strains may be helpful in one disease application, it may not be same in another. For instance, Lactobacillus rhamnosus GG is useful to prevent antibiotic-associated diarrhea in children but bursts infections such as Crohn's disease, CDIs, traveler's diarrhea, and nosocomial infections (McFarland et al., 2018).

2.5. Vaccines and Antibodies

Vaccines cause a strong, fast, and highly specific immune response in the event of re-infection Kim, W. H., & Lillehoj, H. S et al., 2019). If an infection occurs, these either prevent it or mitigate its severity (Hoelzer et al., 2018). Furthermore, immunizations prevent unvaccinated people from disease and foster herd immunity (Bhatia, 2019). Because of the lack of diagnostic precision, antibiotics are frequently misused for viral illnesses. Furthermore, these persons are routinely given antibiotics to avoid further bacterial infections.

The immune system produces antibodies, also known as immunoglobins. These 150 kDa Y-shaped proteins target and destroy certain pathogen components, preventing invasion. They are made up of two identical heavy chains (IgA, IgD, IgE, IgG, and IgM) that distinguish the isotype and two identical light chains (kappa or lambda) (Bebbington et al., 2008). To cure bacterial illnesses, they can either directly target the bacterial surface or indirectly eliminate the virulence factors and bacterial toxins that cause the illness (Saylor et al., 2009). Antibodies have gained appeal as antibiotic alternatives in recent years due to their low side effects and high specificity (Lu et al., 2020).

Applications

The introduction of vaccines for pet diseases such as parvovirus, rabies, distemper, and viral hepatitis, as well as vaccines for livestock such as necrotic enteritis, coccidiosis, infectious bronchitis, Escherichia coli, rotavirus, pink eye, and brucellosis, has resulted in a significant reduction in antibiotic prescriptions (Kim et al., 2019).

In addition, while stopping infections, vaccinations contribute to growth and eventually good health and indirectly reduces the demand for antibiotics (Hancock et al., 2012). Due to their high specificity and the inability of bacterial pathogens to develop resistance to antibodies during acute infections, antibodies are being evaluated scientifically for participation in prevention or treatment of bacterial infections as a passive immunization that is presumably more effective than primary, or as an additional to antibiotics, or in some cases – instead of the antibiotic treatment (Zurawski et al., 2020).

Challenges and Limitations

Most of the licensed vaccines are directed towards viruses while there are minimal vaccines for bacterial diseases (Hoelzer et al., 2018). Antibodies provide little protection across the board for some diseases and immunization of human or animals is costly (Van Panhuis et al., 2013). There are two major drawbacks associated with the use of antibodies for antibacterial treatment, including its expensive manufacture and reduced shelf life (Chames et al., 2009).

2.6. Nano particles

Recent studies have shown that nanomaterials including; nanoparticles (NPs) and nano drug carriers provide a better solution in treating diseases, especially those caused by MDR bacteria. Such nanoparticles can cross bacterial cell membranes and can function as antibiotics (Baptista et al., 2018). Nanoparticles can be mixed with metals including silver, gold, zinc oxide, and copper and other nanoparticles (Gao et al., 2021).

Mechanism of action

There are two types of nanoparticle processes. The nanoparticles that enhance the activity of preexisting antibiotics and those that demonstrate novel, non-antibiotic-dependent bactericidal effects (Kaweeteerawat et al., 2017). This is because when an antibiotic goes through a nanoparticle, a greater concentration of the antibiotic can enter a bacterial cell, which removes the need for massive doses, and unpleasant side effects while enhancing the drug's pharmacokinetics, therapeutic index, and cost-effectiveness. This interaction generates ROS that brings about oxidative stress, disruption of cell wall, inhibition of biofilm formation, deactivation of proteins, DNA distortion, inefficiency of bacterial efflux pump, and inactivation of plasmid (Hemeg, 2017).

The second category of nanoparticles forms bactericidal properties utilizing physical and biological mechanisms (Wang et al., 2017). The surface of the bacterial cell wall is generally negatively charged. Nanoparticles are often coated with a positively charged polymer to facilitate electrostatic interactions with the negatively charged cell membrane. This helps the proper adhesion of the nanoparticles to the membrane of the bacterial cell (Sánchez-López et al., 2020).

Applications

Various metal-based NPs have been investigated in animal models and in vitro for the antibacterial properties and efficiency. Thus, chemically produced gold nanoparticles were examined to be highly efficient against several antibiotic-resistant bacterial strains such as Staphylococcus aureus, Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Vibrio cholerae and Salmonella typhimurium. Zinc oxide nanoparticles are antimicrobial against both gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa, as well as gram-positive bacteria such as Bacillus subtilis and Staphylococcus aureus (León-Buitimea et al., 2020).

Challenges and Limitations

Because NPs penetrate so well across cells, tissues, and organs, calculating dosage and establishing the best routes of delivery is difficult (Deshmukh et al., 2019). Numerous studies have demonstrated that after injection or inhalation, NPs concentrate in the liver, heart, lungs, and spleen (Wang et al., 2017).

2.7. Predatory bacteria

Multidrug-resistant gram-negative bacteria (MDR) pose a significant threat to human and animal health. Bdellovibrio and Micavibrio are gram-negative bacteria that consume other gram-negative bacteria (Kadouri et al., 2013). The genomes of these predatory bacteria contain the code for various hydrolases, including DNases and proteases. This collection of enzymes plays a crucial role in breaking down prey and works well against bacterial biofilms (Lambert, C., & Sockett, R. E. et al., 2013).

Conclusion

The problem of increasing antibiotic resistance rates is a major threat to the development of the veterinary business. While the antibiotics have helped to enhance animal health, its unauthorized use and abuse has led to the emergence and development of drug-resistant organisms. There are various potential substitutes for antibiotics in veterinary medicine such as bacteriophages, antimicrobial peptides, probiotics, vaccines, nanoparticles, and predatory bacteria. All of these approaches offer substantial benefits for infection prevention and control and, at the same time, reduce the risk of resistance emergence. Nevertheless, they have not yet received as much attention as they should, and require future investigation as well as further approval from relevant authorities to be optimized. These solutions are particularly helpful for veterinarians who want to protect the health of the animals, support agriculture production and reduce antibiotic resistance in the world.

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