Antibiotic Resistance from Zoonotic Point of View and Possible Alternative Treatments

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ABSTRACT

Globally, zoonotic infections are major contributor to the rise and spread of antibiotic resistance, and becomes a major threat to the public health. Infections may spread easily from animals to people due to close contact between the two species, which in turn foster the development of antibiotic resistance. Humane face an important risk to the potential transmission of animal originated, including milk, egg, meat and protein source. The need for alternative antibiotics is the deem need of current era. Bacteriophages, nanoparticle and antimicrobial peptides are proven to be effective. Results from different studies underscore the significance of these alternative treatments as a highly effective antibacterial for combating potentially pathogenic agents I animals, thereby enhancing their growth performance.

Key words: Zoonotic, Antibiotic resistance, Alternative, Bacteriophage, Nanoparticles.

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1. INTRODUCTION

The emergence and spread of various infectious diseases are influenced by the interactions between humans, animals, and the environment (Thompson and Kutz 2019). The majority of human infectious diseases are animal-borne. According to the "Asia Pacific strategy for emerging diseases: 2010" study, 60% of newly identified diseases affecting humans are zoonotic and 70% of these pathogens come from wildlife species (Rahman et al. 2020). The most recent human diseases were animal-related and directly linked to animal-derived food items (Slingenbergh 2013). Zoonosis comes from the Greek words "zoo" (animal) and "nosos" which means illness. Zoonoses are diseases or infections that may be transmitted from vertebrate animals to human beings or from humans to animals, according to the WHO (World Health Organization 2020). There are about 61% of human pathogens that are of zoonotic type (Taylor et al. 2001). Zoonosis poses a significant public health concern and represents a direct threat to human health, with potentially fatal outcomes. The majority of these diseases have a detrimental impact on animal well-being and result in a decline in livestock productivity (Grace et al. 2012). In this chapter, we summarized how Antibiotic resistance in livestock is spread? an alternative to these antibiotics: bacteriophages, nanoparticles, and antimicrobial peptides.

1.1. CLASSIFICATION OF ZOONOSES

Zoonotic diseases emerge as a result of a wide range of pathogens. Zoonoses are categorized based on their etiology into various groups, including bacterial zoonoses (e.g., Anthrax, Salmonellosis, Tuberculosis, Lyme disease, Brucellosis and Plague), viral zoonoses (e.g., rabies, acquired immune deficiency syndrome (AIDS), Ebola, and avian influenza), parasitic zoonoses (e.g., trichinosis, toxoplasmosis, trematodosis, giardiasis, malaria, and echinococcosis), fungal zoonoses (e.g., ringworm), rickettsial zoonoses (Q-fever), chlamydial zoonoses (psittacosis), mycoplasma zoonoses (*Mycoplasma pneumoniae* infection), protozoal zoonoses, and diseases caused by acellular non-viral pathogenic agents (e.g., transmissible spongiform encephalopathies and mad cow disease) (Schaechter 2009).

Zoonoses were formerly classified as anthropozoonoses, zooanthroponoses, amphixenoses, and euzoonoses (Hubálek 2003). Anthropozoonoses refers to a class of diseases originating in animals that have the potential to be transmitted to humans, exemplified by the case of rabies. Zoonotic diseases can pass from humans to animals, such as TB in cats and monkeys. The term "zooanthroponoses" describes this phenomenon. Amphizoonoses refers to diseases that have the potential to be transmitted bidirectionally, encompassing transmission from humans to animals as well as from animals to humans. An example of disease is staphylococcal infection. In some cases, humans assume the role of obligatory host for various parasitic diseases. Both Gram-negative and Gram-positive bacteria have the ability to induce zoonotic diseases. Zoonotic diseases are predominantly caused by bacteria, as per their etiology. According to estimates, 42% of zoonotic diseases with bovine origins are bacterial, 22% are viral, 29% are parasitic, 5% are fungal, and 2% are prion-base (McDaniel et al. 2014).

In the same way, it is noteworthy that zoonotic diseases can be attributed to both DNA and RNA viruses; however, RNA viruses cause Zoonosis more often than DNA viruses (Bae and Son 2011). Pathogens can be transmitted to humans directly or indirectly from animals. Diseases that are transmitted directly to humans from animals through media such as air are known as direct Zoonosis (Mortimer 2018). The majority of zoonotic diseases are transmitted to humans via animal hosts. Illustrative instances of such pathogens involve methicillin-resistant *Staphylococcus aureus* (MRSA), *Campylobacter spp.*, and *Salmonella enterica*. Furthermore, the term "reverse Zoonosis" is used to describe zoonotic diseases that arise from pathogens transmitted intermittently between humans and animals, with transmission occurring from humans to animals and subsequently from animals back to humans.

1.2. ANTIBIOTIC RESISTANCE IN ZOONOTIC PATHOGENS

One health approach identifies that most animals who serve as a reservoir for zoonotic diseases are domesticated with which man is commonly associated. Animal husbandry is an intrinsic part of the agricultural economy and plays a vital role to support the livelihood of the rural population. Animal husbandry provides milk, meat, eggs, and wool which directly interact with the human population. Despite the much risk of zoonotic diseases, livestock plays a crucial role in the income of many farmers, nutrition for households, and animal product consumption. Recently many zoonotic diseases have been reported to carry antibiotic resistant genes (ARGs) that reach the human population upon infection. The emergence of ARGs in zoonotic pathogens can be attributed to the inappropriate and irrational utilization of antibiotics (Dafale et al., 2020).

Over the course of previous years, the well-being of both animals and humans has been put at risk by the presence of environmental pollution, the emergence of antimicrobial resistance, and the prevalence of chronic diseases, leading to increased rates of mortality and morbidity (Kalia et al. 2014). Most infectious diseases are considered to be serious health issues having a zoonotic origin. Zoonotic diseases may also be spread through consuming undercooked meat, unpasteurized milk, shellfish, and infected vegetables. In the field of animal husbandry, it is common practice to administer antibiotics to the entire herd, even if only some animals exhibit clinical symptoms, in order to mitigate the spread of infectious diseases within the herd. The practice of administering a large number of antibiotics for a brief duration is referred to as metaphylaxis, whereas prophylaxis involves the addition of antibiotics to animal feed in small doses over an extended period, typically spanning several weeks (Kalia and Purohit 2011).

Despite the absence of clinical symptoms in animals during this period, the risk of infection remains present. The unwise utilization of antibiotics gives rise to selective pressure in pathogens, leading to the development of antibiotic resistance at sub-therapeutic levels of antimicrobial concentration. Bacterial species acquire resistance through a range of mechanisms, which include mutation, alterations in cell permeability, horizontal gene transfer, drug efflux, and quorum sensing (Dafale et al. 2015). Zoonotic infections spread between people and animals through several methods. However, the most likely pathway for transmission occurs via the food chain (Fig. 1 Antibiotic resistant in the food chain). Humans face an important risk to the potential transmission of animal-originated antibiotic-resistant bacteria (ARBs) due to the consumption of animal-derived food products, including milk, eggs, meat, and protein sources. ARBs are more likely to be present in fermented, minimally processed, or raw food products that contain a higher concentration of microbial cells. Pathogenic bacteria in animal-derived food cause stomach problems and resistant strains in humans.

2. ALTERNATIVE TO ANTIBIOTICS

2.1. BACTERIOPHAGE THERAPY FOR ZOONOTIC PATHOGENS

Since antibiotic-resistant bacteria may continue to spread disease, there is an urgent need to identify and develop effective alternative treatments to antibiotics to prevent bacterial infections (Gambino and Brøndsted 2021). Bacteriophages (phages); are viruses that infect bacteria and have been used as medicines since before antibiotics were discovered (De-Melo et al. 2018). Bacteriophages, or phages, are highly prevalent and widely distributed entities across the planet, existing in both natural and artificial settings, particularly in environments conducive to the proliferation of their bacterial hosts (Golkar et al. 2014).

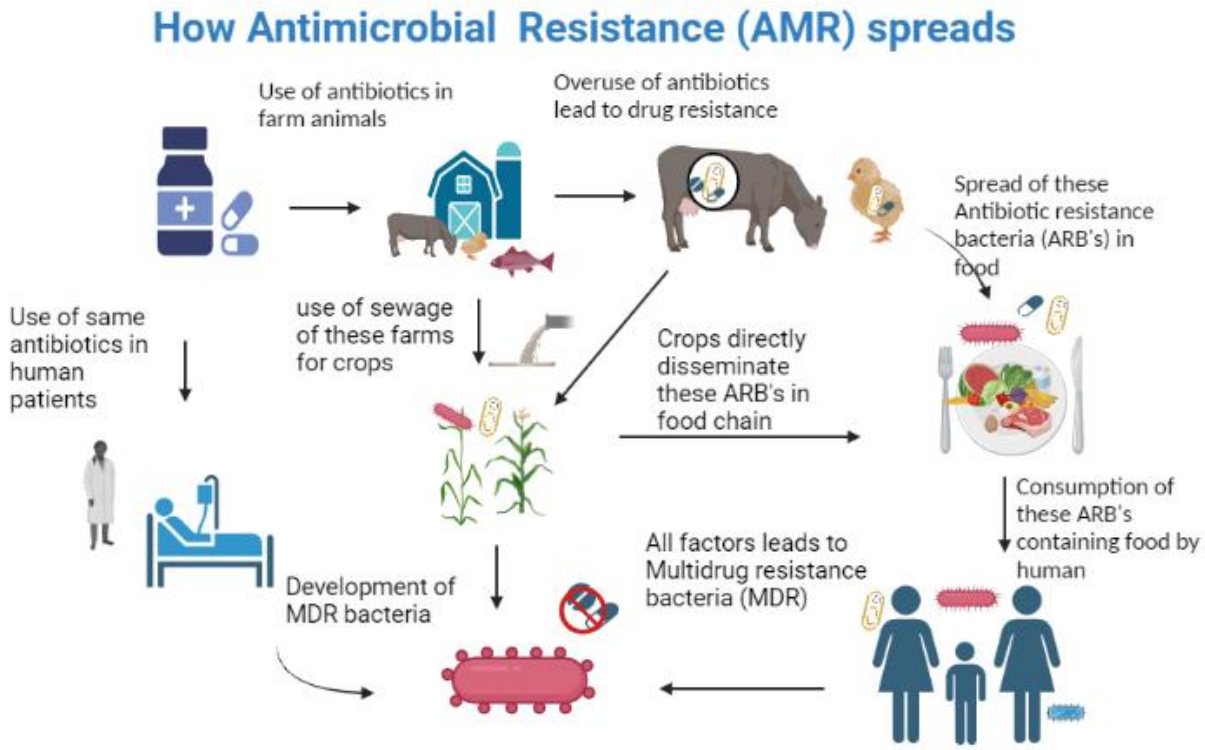

Fig. 1: Antibiotic resistance in the food chain

The discovery of bacteriophages can be attributed to Twort in 1915, who initially identified them as unknown entities capable of impeding bacterial growth. However, it was D'Herelle in 1917 who first succeeded in isolating and characterizing phages. Additionally, he pioneered the development of phage therapy, utilizing it for the treatment of fowl typhoid caused by *S. gallinarum* in poultry (Wernicki et al. 2015). Bacteriophages are widely believed to be the most prevalent life forms on Earth, boasting a population estimated to range from 10^{30} to 10^{32} virions within the biome (Rohwer and Edwards 2002). Extensive documentation exists regarding the prevalence of bacteriophages within the entirety of the human food chain. Certain phages exhibit the capacity to serve as advantageous biocontrol agents (LeLièvre et al. 2019). The primary focus of phage therapy experiments on animals used for food production has been on combating significant zoonotic pathogens, specifically *E. coli, Listeria* spp., *Campylobacter* spp., and *Salmonella* spp. The issue of AMR among certain bacterial strains is a significant and escalating concern (Threlfall et al. 2000).

The European Union (EU) has implemented regulations that prohibit the routine administration of antibiotics in farm animals and impose limitations on the use of chemical treatments for carcasses during processing. Consequently, there is an urgent need for alternative interventions (Dibner and Richards 2005). The utilization of bacteriophages in combatting bacterial infections has yielded favorable outcomes, thereby fostering the advancement of investigations into the prospective application of bacteriophages as therapeutic agents for diseases affecting both humans and animals.

2.1.1. USE OF PHAGE-THERAPY IN POULTRY

Poultry has been widely employed as a primary model for Phage therapy in the context of food-producing animals. Poultry production is large-scale, high-throughput, and mechanized, unlike big animal meat

production, making phage treatment especially useful. Conventional chicken-rearing methods, that house hundreds of thousands of birds, increase disease transmission and economic losses. In a series of investigations, Phage therapy has been employed as a therapeutic approach for the treatment of chickens afflicted with experimental air sac infections caused by *E. coli*. In their initial investigation, the researchers employed an aerosolized solution comprising two distinct bacteriophages, resulting in a 50% reduction in chicken mortality when administered concurrently with the *E. coli* challenge (Huff et al. 2002).

The aerosol spray containing a higher concentration of phages demonstrated a notable decrease in mortality rates when chickens were exposed to *E. coli* three days after primary treatment. In a subsequent investigation, a comparable infection and treatment paradigm was employed, resulting in a notable decrease in mortality among the chickens subjected to phage therapy, with a rate of 7%, in contrast to the approximately 48% observed in the untreated specimens (Huff et al. 2006). The role of contaminated egg and poultry products as a significant reservoir of *Salmonella* spp. is widely acknowledged in academic literature. Furthermore, certain serovars of *Salmonella* have the capacity to induce illness and death in chickens, while also exhibiting the ability to persist in the agricultural setting for extended durations. Bacteriophages derived from human sewage were employed to mitigate the intestinal colonization of the poultry by *S. typhimurium* in experimental settings, resulting in a reduction of approximately 1 log10 cfu. Furthermore, the utilization of these phages led to a significant decrease in mortality rates when compared to untreated animals. Nevertheless, the phages exhibited persistence solely during the period in which *Salmonella* spp. may have been retrieved (Berchieri et al. 1991). Bacteriophage resistant *Salmonella* colonies were retrieved after undergoing phage treatment displayed a coarse physical structure and demonstrated reduced virulence compared to the original strain used for the challenge. Bacteriophages derived from free-range chickens were utilized in order to mitigate the colonization of broiler chickens by *S. enteritidis* PT4.

The experiment involved exposing one-day-old broiler chickens to *S. enteritidis* bacteria, followed by treatment with a mixture of three bacteriophages at a concentration of 10^{11} PFU seven days later. A reduction of 3.5 log10 in caecal carriage was observed five days following phage treatment, in comparison to the control group. A significant decrease in *Salmonella* colonization in the PT group was observed and persisted for the duration of 25 days following phage treatment (Fiorentin et al. 2005). Oral treatment of phage titer of 10^{11} PFU may inhibit caecal colonization of *S. enteritidis* and *S. typhimurium* in broiler chickens by up to 4.2 log10 cycles. A third serovar was targeted for reduction, but without success. Within 72 hours of being treated with bacteriophages, the birds were recolonized by phage-resistant subpopulations of salmonellas. Salmonellas collected from these hens seemed to return to a phage-sensitive phenotype after being challenged with phage-resistant mutants, indicating that phage resistance in this circumstance conferred a fitness cost (Atterbury et al. 2007).

Disease-causing strains of *E. coli* (pathogenic *E. coli*) are a major source of death and illness in chicken farms. When the death rate from *E. coli* septicemia in untreated hens reached about 100 percent, researchers turned to phages for an effective preventative measure. Phage therapy was remained very effective at reducing infection severity even when delayed until the beginning of clinical signs (Barrow et al. 1998). A research study was conducted to examine the impact of bacteriophages on the occurrence of neonatal diarrhea in poultry. A comparison was made between the impact of phage therapy and antibiotic on the chicken survival subjected to *E. coli* (strain 3-1) challenge. The application of phage therapy resulted in a notable decrease in the occurrence of diarrhea among the chicken population, with a reduction to 26% to that of 51.6% observed in the control group. The survival rate in the Phage therapy group exhibited a tenfold increase compared to the control group, and a six-fold increase compared to the group treated with antibiotics (Xie et al. 2005).

Campylobacter spp., an essential zoonotic origin pathogenic bacterium in poultry, has also a focus of phage therapy interventions. The prevalence of *Campylobacter* in poultry has long been recognized as a

major source of contamination in the human food chain (Skarp et al. 2016). One risk study revealed that reducing carcass *Campylobacter* contamination by 2 log10 cfu may reduce human Campylobacteriosis by 30 times (Rosenquist et al. 2003). After repeated phage dosages, broiler chicken caeca's contain 1–2 log10 cfu less *Campylobacter* (Wagenaar et al. 2005). The utilization of phages obtained from the same ecological niche as the host bacterium in numerous phage therapy trials raises inquiries regarding the cohabitation dynamics between viruses and their host organisms within their natural habitat. A recent study has revealed that the presence of phages in broiler chickens naturally colonized with *Campylobacter* which is associated with reduced populations of the bacteria in the caeca. This observation implies that phages may naturally prey upon *Campylobacter* within commercial flocks. The variability in bacteriophage titers observed in the intestinal tract could potentially be attributed to the dynamic nature of *Campylobacter* spp., as well as the presence of a susceptible host that is subject to change over time (Atterbury et al. 2005).

2.1.2. USE OF PHAGE-THERAPY IN LARGE FARM ANIMALS

Phage cocktails were administered to calves, piglets, and lambs as a potential treatment for enteritis, building upon their previous experiments with mice. The calves were subjected to either colostrum feeding or colostrum deprivation, followed by exposure to *E. coli* (strain O9:K30.99). All nine calves that were administered a phage titer (10^{11} PFU) cocktail of two distinct phages via colostrum did not exhibit any signs of illness, in contrast to the control group where 93% of the calves became ill. Among the cohort of 13 calves that were deprived of colostrum and subsequently administered phages upon the onset of diarrhea, a mortality rate of 15.4% was observed, in contrast to the control group which experienced a 100% mortality rate. The findings of this study provide evidence that the administration of phages can significantly decrease both the incidence of illness and the number of deaths, even when administered at the early stages of clinical manifestations. Comparable achievements were documented in the context of utilizing enterotoxigenic *E. coli* strains to induce challenges in piglets and lambs (Smith and Huggins 1983). Bacteriophages in combination can effectively diminish the population of *E. coli* O157:H7 within the gastrointestinal tract of sheep. In comparison to certain other studies on phage therapy (PT), it was observed that the utilization of higher phage MOI (multiplicity of infection) values, specifically 100 and 10, resulted in lower efficacy when compared to a MOI of 1(Callaway et al. 2008). Lytic bacteriophage exhibits specific affinity towards the *E. coli* K1 capsular antigen. This bacteriophage was utilized for the treatment of colostrum-deprived calves that had been subjected to *E. coli* challenge. The onset of bacteremia was observed to be postponed in animals subjected to phage treatment, resulting in a significant extension of their lifespan (Barrow et al. 1998). According to a study conducted by the application of phage therapy did not result in a reduction in the colonization of sheep by *E. coli* O157 (Sheng et al. 2006). It has been reported that an estimated 5% of bovine livestock are believed to harbor significant quantities of *E. coli* O157 in their gastrointestinal tract, thereby presenting the most substantial threat to human well-being (Matthews et al. 2006). Implementation of phage therapy to decrease the presence of this pathogen in a specific subset of highly colonized animals has the potential to generate significant advantages for public health.

2.2. NANOPARTICLE AS AN ALTERNATIVE OF AMR

To control the spread and emergence of antibiotic resistance, specifically resistance in humans against clinical antibiotics, an alternative approach is needed. In the past few years, nanoparticles have grabbed the attention worldwide due to their toxicity against microbes (Vidovic et al. 2015). Nanoparticles (NPs) are particulate substances having sizes ranging from 1 to 100nm on a nonmetric scale that permits

modification in the chemical and physical properties of materials. The size of NPs has a role in antimicrobial activity (Jeevanandam et al. 2018). NPs have been used in biological imaging, photo ablation therapy, biosensors, and drug administration (McNamara and Tofail 2015) and as an alternative in the reduction of antimicrobial resistance (Kanwar et al. 2021). NPs are categorized depending on their size, morphology, and chemical properties. Based on the chemical and physical characteristics of NPs, various classes of NPs are carbon-based NPs, metal NPs, polymeric NPs, Semi-conductor NPs, lipid-based NPs, and ceramics NPs (Khan et al. 2019).

Among them metal NPs showed higher antimicrobial activity (Jones et al. 2008) and no harmful effects to humans (Reddy et al. 2007). The reactivity of NPs depends on the size of NPs; the smaller the NPs, the greater the area-to-volume ratio resulting in high production of free metal and reactive oxygen species (Thakkar et al. 2010) resulting in the alteration of bacterial cellular components (Abdal et al. 2017). Absorption of the nanoparticles on the surface of bacteria causes damage that depends on the NPs size; the smaller the size greater will be the damage. The reason behind this damage is due to the interaction of the negative charge on the bacterial surface with the positive charge on the surface of NPs (Slavin et al. 2017; Gupta et al. 2019). There are 5 different mechanisms (Fig. 2 Antimicrobial action of metal Nano-particles) through which nanoparticles act on microbes, including the generation of reactive oxygen species, cell wall, and cell membrane interaction, adsorption at the cell membrane, blockage of protein synthesis, DNA destruction and disruption of the metabolic pathway (Pérez-Díaz et al. 2015; Nisar et al. 2019).

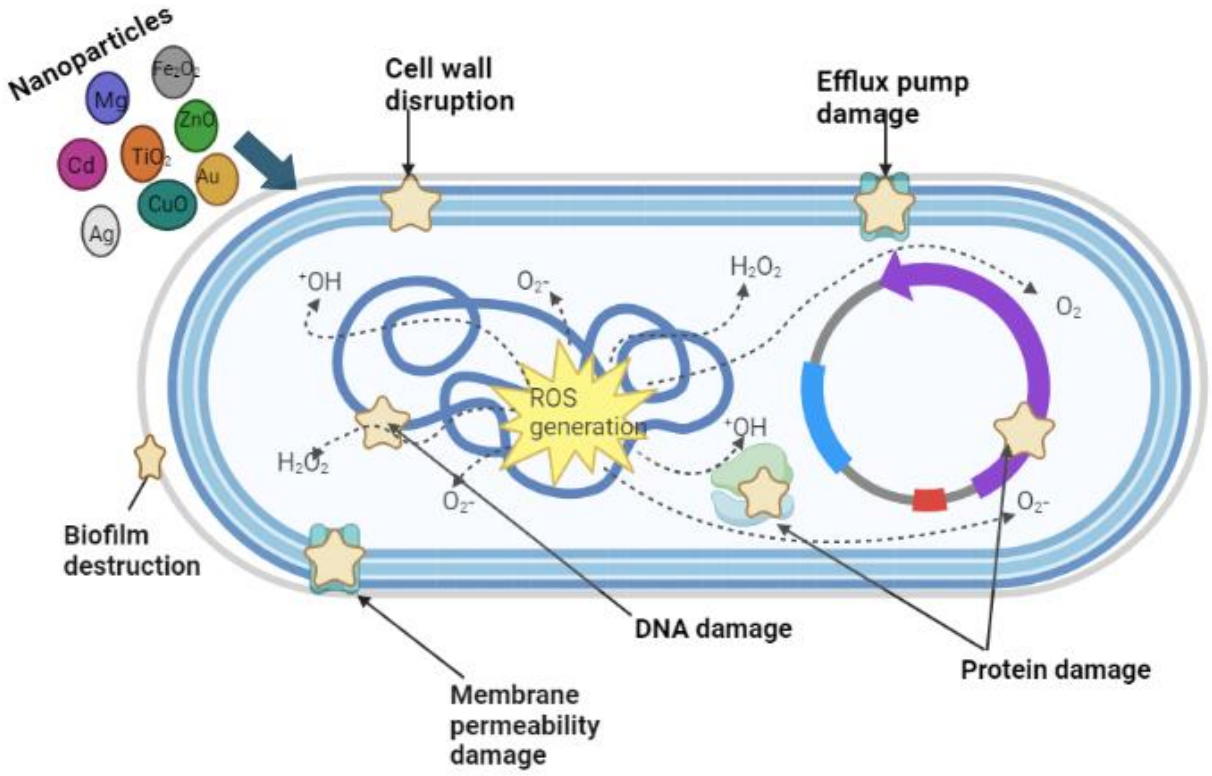

Fig. 1: Antimicrobial action of metal Nano-particles

Antimicrobial resistance against zoonotic diseases is an alarming situation for both animals and humans. The antimicrobial activity of various NPs against zoonotic pathogens has been evaluated. The efficacy of NPs can be enhanced when combined with antibiotic drugs. Silver nanoparticles were combined with

various drugs like ioniazid, ofloxacin, rifampicin, and various others. All these drugs except kanamycin showed greater growth inhibitory activity along with silver nanoparticles (AgNPs). Through these combinations, a minimal dose can be found to overcome antimicrobial resistance (Kreytsberg et al. 2011). The effects of bacterial-resistant antibiotics were evaluated in combination with AgNPs against *P. multocida, S. enterica, S. aureus,* and *E. coli*. Due to the combination of antibiotics such as gentamicin, colistin, amoxicillin, etc. with the AgNPs bacteria like *P. multocida* resistant to these antibiotics became sensitive to these antibiotics and the antimicrobial effect of AgNPs was enhanced (Smekalova et al. 2016). Administration of drugs in combination with nanoparticles showed higher antimicrobial activity as compared to free drug administration. The research was conducted in which chitosan nanoparticles were combined with tetracycline and silica nanoparticles with chlorpromazine to evaluate their efficacy against multi-drug resistant (MDR) *S. enterica* and *S. aureus*. These combinations reduce the microbial load by 83.02±14.35% by inhibiting the AMR mechanism (Brar et al. 2022).

The antimicrobial activity of AgNPs was evaluated against MDR *S. enterica* and *S. typhimurium*. These isolates were sensitive against only meropenem but resistant against tetracycline, ampicillin, and amoxicillin. Proteins present in the bacterial membrane contain sulphur that interacts with AgNPs resulting in bacterial death. During different storage times, the growth was seen to be decreased while after 48hrs no bacterial growth was present (Abou-Elez et al. 2021). The growth of both MDR *Salmonella* spp. and *E. coli* was inhibited due to the antimicrobial property of gold nanoparticles (AuNPs) (Abdalhamed et al. 2021). Some biofilm-producing bacteria induce chronic mastitis resulting in inflammation of the udder. Due to the antimicrobial resistance an alternative treatment is needed for bovine mastitis. Plant-derived drugs having antimicrobial activity are naturally effective agents. Quercetin and AgNPs (QA NPs) together inhibit the growth of MDR *E. coli.* QA NPs efficiently decreased the transcription of genes associated with biofilm formation resulting in the inhibition of *E. coli* biofilm formation (Yu et al. 2018).

Another bacterial pathogen that causes bovine mastitis is *S. aureus*. Various kinds of Nanoparticles like polymeric nanoparticles, nanogels, liposomes, inorganic nanoparticles, and solid lipid nanoparticles are developed to enhance intracellular drug delivery and inhibit biofilm formation. NPs have played a key role in the treatment of bovine mastitis (Algharib et al. 2020). AgNPs when combined with vancomycin could overcome the resistance in *S. aureus* and increase cell death (Esmaeillou et al. 2017; Mohamed et al. 2020). Zinc oxide (ZnO) can also be used to treat mastitis. Also, Saeb et al. (2014) suggested that the AgNPs can make methicillin-resistant *S. aureus* sensitive and inhibit their microbial activity (Abd EL-Tawab et al. 2018). Both AgNPs and AuNPs have enhanced activity when combined with ampicillin against *S. aureus*. However, the activity of AuNPs increases when ampicillin attaches to their surface (Brown et al. 2012). Brucellosis caused by *Brucella* spp. is difficult to treat. Virulence of *Brucella* spp. is associated with intra-macrophage survival. The antimicrobial activity of AgNPs of a concentration of 4-6 ppm is effective even inside macrophage cells (Alizadeh et al. 2013). Solid-liquid nanoparticles encapsulated with doxycycline significantly decrease the load of *B. melitensis* in macrophages by 3.5 log as compared to free doxycycline (Hosseini et al. 2019). AgNPs and AuNPs have toxic effects against *B. melitensis* and *B. abortus* and have no side effects on organs and bacteria showed no resistance against these NPs even after extensive exposure (Elbehiry et al. 2022). Glutathione combined with AgNPs can be used effectively against MDR *Campylobacter* spp. in chickens (Silvan et al. 2018).

2.3. ANTIMICROBIAL PEPTIDES

The identification of antimicrobial peptides (AMPs) has provided insights into the mechanisms by which plants or insects, which do not possess adaptive immune systems, are capable of defending themselves

against microbial infections (Nayab et al. 2022). The increase in antibiotic resistance has prompted an extensive investigation into the exploration of alternative options to existing antibiotics. Antimicrobial peptides (AMPs) are being increasingly recognized as potential candidates for standalone or adjunctive use with existing antibiotics, thereby getting renewed attention (Fox 2013).

Nisin is a cationic peptide with antimicrobial properties that is synthesized by *Lactococcus* and certain species of *Streptococcus*. In 1969, nisin achieved the distinction of being the inaugural antimicrobial agent to attain the status of a food-safe additive. Nisin has been employed as a therapeutic intervention for bovine mastitis resulting from a diverse array of bacterial pathogens, including *Enterococcus*, *Streptococcus*, and *Staphylococcus*. One primary benefit is that the presence of nisin in milk is limited to a duration of 12 hours following its application, at concentrations that pose no discernible risk to consumers. Additionally, the application of nisin helps to mitigate the development of bacterial resistance (Cao et al. 2007).

The concurrent application of the nisin or another bacteriocin, enterocin DD14 in conjunction with colistin exhibited a synergistic impact on colistin-resistant strains of *E. coli* that were obtained from porcine sources. The observed phenomenon can be attributed to the destabilization of the cell membrane caused by the interaction between colistin and LPS, which subsequently facilitates the penetration of bacteriocins into the cell wall, resulting in its damage (Al-Atya et al. 2016). The effective application of bacteriocins' antimicrobial characteristics has been employed for the purpose of managing the harmful microflora in poultry. Plantaricin, derived from *L. plantarum* F1, has been suggested as a potential substitute for antibiotics in the treatment of colibacillosis in grill chickens (Ogunbanwo et al. 2004). New bacteriocins with potential application in poultry have been discovered within the microbiota of the gastrointestinal tract of domestic broiler chickens. The bacteria *P. polymyxa* NRRL B-30509 was obtained from domestic Russian grill chickens and found to produce the bacteriocin ribosomally synthesized AMPs “paenicidin A”. This bacteriocin has demonstrated antimicrobial activity specifically against *C. jejuni* (Stern et al. 2005).

Pediocin A was given in the feed of broilers infected with *C. perfringens* type A, which is known to produce the Net B toxin and is associated with the development of necrotic enteritis. The administration of the treatment resulted in a notable enhancement in the development and performance of the avian subjects. Nevertheless, the bacterial load did not exhibit a decrease (Keyburn et al. 2008). The application of microencapsulation techniques to bacteriocin can potentially mitigate the degradation of bacteriocin caused by digestive processes in broilers (Grilli et al. 2009). The application of the divercin AS7 along with nisin as dietary additive for broilers has demonstrated a positive impact on the enhancement of body weight gain (Jozefiak et al. 2011). Nisin exhibits antimicrobial properties against microbiota that are associated with reduced productivity in grill chickens, akin to the ionophore monensin. The addition of nisin had a beneficial impact on the gut microbiota by decreasing the presence of potentially harmful bacterial populations in the jejunum and ceca (Kierończyk et al. 2020). These results underscore the significance of bacteriocins as a highly effective antibacterial alternative for combating potentially pathogenic agents in animals, thereby enhancing their growth performance.

3. CONCLUSION

Antibiotic-resistant zoonotic diseases threaten human and animal health. It reduces antibiotic efficacy, prolongs sickness, increases healthcare expenditures, and potentially kills patients. It also hinders our capacity to fight infectious illnesses, undermining modern medicine and public health. Promoting appropriate antibiotic use in people and animals is vital. Antibiotics should be used sparingly in veterinary medicine. Novel therapeutics like phage therapy, bacteriocins, or nano-particles are intriguing alternatives. These focused methods may solve certain problems without causing general resistance.

REFERENCES

Abd EL-Tawab A et al., 2018. Effect of Zinc Oxide Nanoparticles on Staphylococcus Aureus Isolated from Cows' Mastitic Milk. Benha Veterinary Medical Journal 35: 30-41.

Abdal DA et al., 2017. The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. International Journal of Molecular Sciences 18: 120-141

Abdalhamed AM et al., 2021. Therapeutic effect of biosynthetic gold nanoparticles on multidrug-resistant *Escherichia coli* and Salmonella species isolated from ruminants. Veterinary World 14: 3200-3210

Abou-Elez RM et al., 2021. Antimicrobial Resistance of Salmonella enteritidis and Salmonella typhimurium Isolated from Laying Hens, Table Eggs and Humans with Respect to Antimicrobial Activity of Biosynthesized Silver Nanoparticles. Nanotechnology in Animal Science 11: 3554-3571

Al-Atya et al., 2016. Effects of colistin and bacteriocins combinations on the in vitro growth of Escherichia coli strains from swine origin. Probiotics and Antimicrobial Proteins 8: 183-190.

Algharib SA et al., 2020. Nanoparticles for treatment of bovine *Staphylococcus aureus* mastitis. Drug Delivery 27: 292-308

Alizadeh H et al., 2013. Intramacrophage antimicrobial effect of silver nanoparticles against Brucella melitensis 16M. Scientia Iranica 20: 1035-1038.

Atterbury et al., 2005. Correlation of Campylobacter bacteriophage with reduced presence of hosts in broiler chicken ceca. Applied and Environmental Microbiology 71: 4885-4887.

Atterbury RJ et al., 2007. Bacteriophage therapy to reduce Salmonella colonization of broiler chickens. Applied and Environmental Microbiology 73: 4543-4549.

Bae SE and Son HS, 2011. Classification of viral zoonosis through receptor pattern analysis. BMC Bioinformatics 12: 1-7.

Barrow P et al., 1998. Use of lytic bacteriophage for control of experimental Escherichia coli septicemia and meningitis in chickens and calves. Clinical Diagnostic Laboratory Immunology 5: 294-298.

Berchieri Jr et al., 1991. The activity in the chicken alimentary tract of bacteriophages lytic for Salmonella typhimurium. Research in Microbiology 142: 541-549.

Brar A et al., 2022. Nanoparticle-enabled combination therapy showed superior activity against multi-drug resistant bacterial pathogens in comparison to free drugs. Nanomaterials. 12: 2179-2195.

Brown AN et al., 2012. Nanoparticles functionalized with ampicillin destroy multiple-antibiotic-resistant isolates of *Pseudomonas aeruginosa* and *Enterobacter aerogenes* and methicillin-resistant *Staphylococcus aureus*. Applied and Environmental Microbiology 78: 2768-2774.

Callaway TR et al., 2008. Bacteriophage isolated from feedlot cattle can reduce *Escherichia coli* O157: H7 populations in ruminant gastrointestinal tracts. Foodborne Pathogens and Disease 5: 183-191.

Cao LT et al., 2007. Efficacy of nisin in treatment of clinical mastitis in lactating dairy cows. Journal of Dairy Science 90: 3980-3985.

Dafale NA et al., 2015. Development and validation of microbial bioassay for quantification of Levofloxacin in pharmaceutical preparations. Journal of Pharmaceutical Analysis 5: 18–26.

Dafale NA et al., 2020. Zoonosis: an emerging link to antibiotic resistance under "one health approach". Indian Journal of Microbiology 60: 139-152.

De-Melo et al., 2018. Phages as friends and enemies in food processing. Current Opinion in Biotechnology 49: 185-190.

Dibner JJ and Richards JD, 2005. Antibiotic growth promoters in agriculture. history and mode of action. Poultry Science 84: 634-643.

Elbehiry A et al., 2022. Brucella species-induced brucellosis: Antimicrobial effects, potential resistance and toxicity of silver and gold nanosized particles. Plos one 17: e0269963.

Esmaeillou M et al., 2017. Vancomycin capped with silver nanoparticles as an antibacterial agent against multi-drug resistance bacteria. Advanced Pharmaceutical Bulletin 7: 479-483.

Fiorentin L et al., 2005. Oral treatment with bacteriophages reduces the concentration of *Salmonella Enteritidis* PT4 in caecal contents of broilers. Avian Pathology 34: 258-263.

Fox JL, 2013. Antimicrobial peptides stage a comeback: Better understanding of the mechanisms of action, modification and synthesis of antimicrobial peptides is reigniting commercial development. Nature biotechnology 31: 379-383.

Gambino M and Bronsted L, 2021. Looking into the future of phage-based control of zoonotic pathogens in food and animal production: Current Opinion in Biotechnology 68: 96-103.

Golkar Z et al., 2014. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. The Journal of Infection in Developing Countries 8: 129-136.

Grace D et al., 2012. Mapping of poverty and likely Zoonosis hotspots. Zoonoses Project 4 Report to the UK Department for International Development, Nairobi, Kenya.

Grilli E et al., 2009. Pediocin A improves growth performance of broilers challenged with Clostridium perfringens. Poultry Science 88: 2152-2158.

Gupta A et al., 2019. Combatting antibiotic-resistant bacteria using nanomaterials. Chemical Society Reviews 48: 415-427.

Hosseini SM et al., 2019. Doxycycline-encapsulated solid lipid nanoparticles as promising tool against Brucella melitensis enclosed in macrophage: a pharmacodynamics study on J774A. 1 cell line. Antimicrobial Resistance and infection control 8: 1-12.

Hubálek Z, 2003. Emerging human infectious diseases: anthroponoses, Zoonosis, and sapronoses. Emerging Infectious Diseases 9: 403-404.

Huff WE et al., 2006. Evaluation of the influence of bacteriophage titer on the treatment of colibacillosis in broiler chickens. Poultry Science 85: 1373–1377.

Huff WE et al., 2002. Prevention of Escherichia coli respiratory infection in broiler chickens with bacteriophage (SPR02): Poultry Science 81: 437-441.

Jeevanandam J et al., 2018. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein Journal of Nanotechnology 9: 1050-1074.

Jones N et al., 2008. Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms. FEMS Microbiology Letters 279: 71-76.

Jozefiak D et al., 2011. Dietary divercin modifies gastrointestinal microbiota and improves growth performance in broiler chickens. British Poultry Science 52: 492-499.

Kalia VC and Purohit HJ, 2011. Quenching the quorum sensing system: potential antibacterial drug targets. Critical Reviews in Microbiology 37: 121–140.

Kalia VC et al., 2014. Evolution of resistance to quorum-sensing inhibitors. Microbial Ecology 68: 13–23.

Kanwar R et al., 2021. 2. Biological, physical and chemical synthesis of silver nanoparticles and their non-toxic bio-chemical application: A brief review. Pure and Applied Biology 11: 421-438.

Keyburn AL et al., 2008. NetB, a new toxin that is associated with avian necrotic enteritis caused by Clostridium perfringens. PLoS Pathogens 4: e26.

Khan I et al., 2019. Nanoparticles: Properties, applications and toxicities. Arabian Journal of Chemistry 12: 908-931.

Kierończyk B et al., 2020. Nisin as a novel feed additive: The effects on gut microbial modulation and activity, histological parameters, and growth performance of broiler chickens. Animals 10: 101-116.

Kreytsberg GN et al., 2011. Antituberculous effect of silver nanoparticles. Journal of Physics, Conference Series 291: 012030.

LeLièvre V et al., 2019. Phages for biocontrol in foods. What opportunities for Salmonella sp. control along the dairy food chain: Food Microbiology 78: 89-98.

Matthews L et al., 2006. Super-shedding cattle and the transmission dynamics of *Escherichia coli* O157. Epidemiology and Infection 134: 131-142.

McDaniel CJ et al., 2014. Humans and cattle: a review of bovine Zoonosis. Vector-Borne and Zoonotic Diseases 14: 1-19.

McNamara K and Tofail SA, 2015. Nanosystems: the use of nanoalloys, metallic, bimetallic, and magnetic nanoparticles in biomedical applications. Physical Chemistry Chemical Physics 17: 27981-27995.

Mohamed MS et al., 2020. Combination of silver nanoparticles and vancomycin to overcome antibiotic resistance in planktonic/biofilm cell from clinical and animal source. Microbial Drug Resistance 26: 1410- 1420.

Mortimer PP, 2018. Influenza: the centennial of a zoonosis. Reviews in Medical Virology 29: e2030-e2030.

Nayab S et al., 2022. A review of antimicrobial peptides: its function, mode of action and therapeutic potential. International Journal of Peptide Research and Therapeutics 28: 1-15.

Nisar P et al., 2019. Antimicrobial activities of biologically synthesized metal nanoparticles: an insight into the mechanism of action. Journal of Biological Inorganic Chemistry 24: 929-941.

Ogunbanwo ST et al., 2004. Influence of bacteriocin in the control of Escherichia coli infection of broiler chickens in Nigeria. World Journal of Microbiology and Biotechnology 20: 51-56.

Pérez-Díaz MA et al., 2015. Silver nanoparticles with antimicrobial activities against Streptococcus mutans and their cytotoxic effect. Materials Science and Engineering 55: 360-366.

Rahman MT et al., 2020. Zoonotic diseases: etiology, impact, and control. Microorganisms 8: 1405-1438.

Reddy KM et al., 2007. Selective toxicity of zinc oxide nanoparticles to prokaryotic and eukaryotic systems. Applied Physics Letters 90: 2139021-2139023.

Rohwer F and Edwards R, 2002. The Phage Proteomic Tree. a genome-based taxonomy for phage. Journal of Bacteriology 184: 4529-4535.

Rosenquist H et al., 2003. Quantitative risk assessment of human campylobacteriosis associated with thermophilic Campylobacter species in chickens. International Journal of Food Microbiology 83: 87-103.

Saeb A et al., 2014. Production of silver nanoparticles with strong and stable antimicrobial activity against highly pathogenic and multidrug resistant bacteria. The Scientific World Journal 2014: 1-9.

Schaechter M, 2009. Encyclopedia of microbiology. Academic Press.

Sheng H et al., 2006. Application of bacteriophages to control intestinal Escherichia coli O157: H7 levels in ruminants. Applied and Environmental Microbiology 72: 5359-5366.

Silvan JM et al., 2018. Antibacterial activity of glutathione-stabilized silver nanoparticles against Campylobacter multidrug-resistant strains. Frontiers in Microbiology 9: 458-467

Skarp CPA et al., 2016. Campylobacteriosis. the role of poultry meat. Clinical Microbiology and Infection 22: 103-109.

Slavin YN et al., 2017. Metal nanoparticles: Understanding the mechanisms behind antibacterial activity. Journal of Nanobiotechnology 15: 1-20.

Slingenbergh J, 2013. World Livestock: changing disease landscapes. Food and Agriculture Organization of the United Nations (FAO).

Smekalova M et al., 2016. Enhanced antibacterial effect of antibiotics in combination with silver nanoparticles against animal pathogens. The Veterinary Journal 209: 174-179.

Smith HW and Huggins MB, 1983. Effectiveness of phages in treating experimental *Escherichia coli* diarrhoea in calves, piglets and lambs. Microbiology 129: 2659-2675.

Stern NJ et al., 2005. Paenibacillus polymyxa purified bacteriocin to control *Campylobacter jejuni* in chickens. Journal of Food Protection 68: 1450-1453.

Taylor LH et al., 2001. Risk factors for human disease emergence. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 356: 983-989.

Thakkar KN et al., 2010. Biological synthesis of metallic nanoparticles. Nanomedicine: Nanotechnology, Biology and Medicine 6: 257-262.

Thompson A and Kutz S, 2019. Introduction to the special issue on 'Emerging Zoonoses and Wildlife'. International Journal for Parasitology: Parasites and Wildlife 9: 322.

Threlfall E et al., 2000. The emergence and spread of antibiotic resistance in food-borne bacteria: International Journal of Food Microbiology 62: 1-5.

Vidovic S et al., 2015. ZnO nanoparticles impose a panmetabolic toxic effect along with strong necrosis, inducing activation of the envelope stress response in *Salmonella enterica* serovar Enteriditis. Antimicrobial Agents Chemotherapy 59: 3317–3328.

Wagenaar JA et al., 2005. Phage therapy reduces *Campylobacter jejuni* colonization in broilers. Veterinary Microbiology 109: 275-283.

Wernicki A et al., 2017. Bacteriophage therapy to combat bacterial infections in poultry: Virology Journal 14: 1-13.

World Health Organization, 2020. WHO Health Topic Page: Zoonosis. World Health Organization, Geneva. Available from: https://www. who. int/topics/Zoonosis/en/Retrieved on 20-07.

Xie H et al., 2005. Bacteriophage Esc-A is an efficient therapy for *Escherichia coli* 3-1 caused diarrhea in chickens. The Journal of General and Applied Microbiology 51: 159-163.

Yu L et al., 2020. The anti-biofilm effect of silver-nanoparticle-decorated quercetin nanoparticles on a multi-drug resistant Escherichia coli strain isolated from a dairy cow with mastitis. Peer J 6: e5711-1524.