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The Alternatives of Antibiotics in Poultry Production for Reducing Antimicrobial Resistance

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ABSTRACT

Antibiotics are natural, semi-synthetic, or chemical compounds that have anti-microbial activity and are used in livestock and poultry production for a variety of reasons, including therapeutic and growth promotion. The use of antibiotics in poultry production has been associated with the development of resistant bacteria. The present study attempted to explain the role of antibiotics as poultry growth promoters, bacterial resistance, and risks for human health, with a special focus on some selected bacterial species isolated from poultry farms and products. Furthermore, the manuscript reviewed the literature on alternative feed additives to reduce the reliance on antibiotics. Microbial resistance is a significant global health concern that has been a top global threat in the 21st century. The use of antibiotics in poultry production as non-therapeutic or growth promoters is at low doses and continuously, associated with developing resistant bacteria. Meanwhile, antibiotic-resistant genes in humans may have their roots in the diets of animals treated with antibiotics. Developing bacterial resistance has encouraged researchers to reduce the reliance on antibiotics by identifying potential feed additives, such as essential oils, bacteriophages, antimicrobial peptides, probiotics, prebiotics, organic acid, and enzymes that improve the immune system functions, reduce morbidity and mortality, improve the growth performances of poultry, and preserve consumer health.

Keywords: Antibiotic, Antimicrobial resistance, Feed additive, Human, Poultry

INTRODUCTION

Poultry production is an important source of the human diet globally providing essential animal protein with a suitable nutritional composition for humans. However, it also poses potential health concerns in some cases. Antibiotics, which are created in laboratories or produced by a wide range of microorganisms, including fungi and bacteria (Sahu and Saxena, 2014; Abreu et al., 2023), vary in their antibacterial effects, mode of action, and physical, chemical, and pharmacological characteristics (Dutta et al., 2019). The bactericidal or bacteriostatic mechanisms of antibiotics are inhibition of protein synthesis, cell wall synthesis, cytoplasmic membrane synthesis, and DNA synthesis (Sahu and Saxena, 2014; Diaz-Sanchez et al., 2015; Abreu et al., 2023).

Antibiotics have been used for a wide range of purposes in livestock and poultry for the past few decades. As therapeutic agents, antibiotics treat infectious diseases with high doses applied for short periods against specific diseases. As prophylactic agents, antibiotics prevent certain infections at the subclinical stage, using low (sub-therapeutic) doses periodically for several days. In addition, antibiotics are used as growth promoters, administered at a very low dose regularly in livestock feed. According to the literature, global antibiotic use increased by 39% between 2000 and 2015 (Klein et al., 2018). This surge in antibiotic demand, especially in low- and middle-income countries, is driven by economic growth and increased animal consumption. In 2013, food animals consumed approximately 131,000 tons of antibiotics, a figure expected to rise to 200,000 tons by 2030 (Van Boeckel et al., 2017).

While utilizing antibiotics significantly improves poultry performance and farm economics, it also poses potential risks. The spread of antibiotic-resistant (ABR) strains into the environment and human transmission through the food chain, compounded by inadequate drug withdrawal protocols, can pose significant public health risks (Klein et al., 2018; Abreu et al., 2023). The current review aimed to provide an up-to-date overview of antibiotic use as a poultry growth promoter, as well as bacterial resistance, and human health risks. The present study also discussed alternatives to antibiotics in poultry production.

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ANTIBIOTICS AND POULTRY PRODUCTION

The antibiotic as a growth promoter was first discovered in 1940 when aureomycin-containing pharmaceutical wastes were fed to poultry (Castanon, 2007). Adding antibiotics to animal feed as growth promoters at a concentration of 200 gm per ton for more than 14 days is a common experiment in animal production (Diaz-Sanchez et al., 2015). Adding antibiotics to the poultry diet can positively affect poultry growth performance by preventing enteritis, reducing growth-depressing metabolites produced by gram-positive bacteria, improving intestinal microbiota balance, enhancing nutrient utilization efficiency, and increasing energy harvesting from the intestine (converting feed to products; Allen and Stanton, 2014; Agyare et al., 2019; Haque et al., 2023).

The antibiotics apply their effect on bacteria in a few well-defined ways called the mode of action (Table 1). DNA replication is the process used to generate two new daughter DNA molecules, which result in the division of a bacterial cell into two daughter cells (Nagaraja et al., 2017). Antibiotics, such as fluoroquinolones (Ciprofloxacin, Levofloxacin, and Moxifloxacin) inhibit the DNA gyrase and topoisomerase IV, preventing the synthesis of bacterial DNA (Shree et al., 2023). Protein biosynthesis inhibition includes essential bacteria protein synthesis which has DNA to encode mRNA, rRNA, and tRNA. The 50s and 30s ribosomal subunits make up the bacterial ribosome and play a role in bacterial protein synthesis. Antibiotics, such as aminoglycosides (Tetracycline) target the 30s ribosomal (Halawa et al., 2024), macrolides (Chloramphenicol and Oxazolidinone) target the 50s (Syroegin et al., 2022) and inhibit protein synthesis. Cell wall synthesis inhibition means the peptidoglycan is the most important part of the cell wall, and several steps are included to synthesize the same and form the bacterial cell wall. The distinctive structure of antibiotics, including beta-lactams (penicillins and cephalosporins) and glycopeptides allows them to bind to peptidoglycan cross-linking enzymes (transpeptidase and carboxypeptidase), inhibiting bacterial peptidoglycan synthesis and preventing cell wall formation. In folic acid metabolism inhibition some antibiotics, such as sulfonamide, inhibit the specific enzymes involved in folic acid metabolism (Capasso and Supuran, 2014).

Various health and food organizations developed guidelines for using antibiotics in livestock to address and prevent antibiotic resistance. The key guidelines for using veterinary antibiotics include the recommendation of antibiotics after diagnosis of diseases with bacterial etiology, administration of antibiotics under the supervision of a veterinarian, priority being given to the health status of an infected animal, improvement in the understanding and awareness of antibiotics resistance, implementation of effective sanitation, and infection prevention, and encouragement of sustainable investment to discover new effective medicines, diagnostic tools, and vaccines (Haag, 2015; Diaz-Sanchez et al., 2015; Salam et al., 2023).

ANTIMICROBIAL RESISTANCE

Antibiotic resistance (ABR), which is also known as antimicrobial resistance (AMR), and emerging infectious diseases are severe global health concerns. Antimicrobial agents used in livestock and poultry production and their AMR in contributing sources and are connected to serious illness and a heavy financial burden in individuals and different countries. Achieving sustainable development objectives, livelihood security, food safety, and nutrition security can all be impacted. Since humans, animals, and the environment are all interconnected as a cause and a cure, ABR is truly a one health issue (Wang et al., 2021a; Salam et al., 2023).

Both direct and indirect contact between the various actors and environments can spread drug resistance up the food chain, serving as pathways for the transmission of zoonotic diseases. Humans come into direct touch with resistant microorganisms found in animals or their products. Resistance strains are more likely to colonize or infect occupational workers, including farmers, veterinary professionals, abattoir workers, food handlers, and others with whom they come into contact (Salam et al., 2023). Antibiotic residues are the byproducts of antibiotic degradation or related metabolites that accumulate in manure, wastewater, and soils and have a significant negative impact. Therefore, the environment becomes a significant reservoir of antimicrobial drug resistance due to the spread of antibiotic-resistant bacteria and antibiotic residues via food and animal waste (Abreu et al., 2023).

Antimicrobial resistance arises when bacteria lose their susceptibility and acquire resistance to the medications employed for their treatment (Vikesland et al., 2019). Infections caused by these microbes are harder to treat due to the resistance they develop, leading to increased morbidity, mortality, and healthcare costs (Almansour et al., 2023). Bacteria utilize several approaches to resist the antibiotics, such as enzymatic degradation or modification of bacteria (e.g., chloramphenicol acetyltransferases), modification of the antibiotic target (e.g., vancomycin-resistant *enterococci*, which enzymatically modify peptidoglycan), and keeping the antibiotic out of the bacterial cell through either efflux pumps or alteration of the permeability of the cell membrane (Baker et al., 2023; Salam et al., 2023).

Table 1. Selected classes of commonly used antibiotics in poultry and humans, their action mechanisms, and activity spectrum

Antibiotic Class	Synthesis	Drug name	Action mechanism	Activity spectrum	Use in human and poultry	Reference
Tetracyclines	*Streptomyces* spp.	Oxytetracycline, Chlortetracycline, Doxycycline	Inhibition of protein synthesis	Gram-positive and gram-negative	In humans: Urinary tract, respiratory tract, and sexually transmitted infections In poultry: Respiratory infection and sinusitis, and growth promoter	(Chopra and Roberts, 2001)
Sulfonamides	Synthesized from non-natural compounds (Sulfanilamide) containing a sulfonamide group.	Sulfamethoxazole	Inhibiting folic acid-producing enzyme	Gram-positive and gram-negative	In humans: Urinary tract, respiratory tract, and skin infections In poultry: Restricted for infection treatment and banned as a growth promoter due to resistance concern	(Yoneyama and Katsumata, 2006)
Beta-lactams (Cephalosporins)	Synthesized from non-natural compounds (beta-lactam ring)	Amoxicillin, Efazolin, Meropenem	Inhibiting of penicillin-binding proteins	Gram-positive and gram-negative	In humans as well in poultry: For respiratory, urinary, sepsis, and sexually transmitted diseases, and as growth promoters in poultry	(Yoneyama and Katsumata, 2006)
Fluoroquinolones	Quinolone compounds	Ciprofloxacin, Levofloxacin, Moxifloxacin	Inhibiting bacterial DNA synthesis	Gram-positive and gram-negative	In humans: Respiratory, urinary tract, skin, and gastrointestinal infections In poultry: Colibacillosis, salmonellosis, respiratory infections, and as a growth promoter	(Gouvêa et al., 2015)
Macrolides	Derived from the macrolide ring	Azithromycin, Erythromycin	Inhibition of protein synthesis	Gram-positive and gram-negative	Use in humans: Pharyngitis, sinusitis, and bronchitis treatment In poultry: Respiratory infection, and as a growth promoter	(Yoneyama and Katsumata, 2006)
Aminoglycosides	*Streptomyces* spp.	Tobramycin, Gentamicin, Amikacin	Inhibition of protein synthesis	Gram-negative	In humans: Urinary, respiratory, and abdomen infections. In poultry: Has no use in poultry due to its potential residue, special care due to resistance and residue concern is required	(Tolmasky, 2000)
Monobactams	6-aminopenicillanic acid	Aztreonam	Inhibition of protein synthesis	Gram-negative	In humans: Urinary, respiratory, skin, and soft tissue infections. In poultry: Enteritis due to *Escherichia coli* (*E. coli*) and *Salmonella*, and has no use as a growth promoter	(Li et al., 2023)

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ZOONOTIC MICROORGANISMS

Escherichia species

Escherichia coli (*E. coli*) is a pathogenic and commensal bacterium that causes infections, such as septicemia, cystitis, peritonitis, meningitis, and gastroenteritis in humans and animals (Zhang et al., 2020). The most imperative reservoirs for pathogenic *E. coli* are poultry and livestock (Yassin et al., 2017). Antimicrobials play a crucial role in animal farming by promoting the spread, emergence, and selection of AMR microbes (Abdalla et al., 2022). *E. coli* strains, which are part of human, animal, and environmental microbiotas, act as key indicators of AMR due to their resistance to antimicrobial agents and resistance gene accumulation (Poirel et al., 2018). Avian pathogenic *E. coli* is a major zoonotic disease that leads to significant financial losses for the poultry sector globally due to antibiotic resistance, primarily due to overuse and poor sanitation (Hamed et al., 2023). The world health organization (WHO) identifies *Salmonella* spp. and *E. coli* as the primary microorganisms to transmit AMR from poultry meats and products (Hamed et al., 2023).

E. coli isolates from poultry and animal farms showed resistance to at least three antimicrobial classes, while 94% showed resistance to at least one medication (Wang et al., 2021b). However, in a different investigation, the pathogenic *E. coli* which was isolated from chicken species showed a high level of resistance to widely used antimicrobials, such as colistin (82.88%), trimethoprim (89.04%), tetracycline (95.89%), and nalidixic acid (95.89%) (Bhave et al., 2019). The study revealed that 37% of turkey, 20% of chicken, 13% of duck, and 8% of game poultry *E. coli* isolates were multidrug-resistant fecal *E. coli* (Varga et al., 2019). A study by Ngai et al. (2021) revealed that 62% of *E. coli* isolates from chicken feed were resistant to ampicillin Benklaouz et al. (2020), looked at first-line antibiotics used on a chicken farm in Western Algeria to treat *E. coli.* The analysis indicated that of all the antibiotics employed in this study, nalidixic acid had the highest level of resistance (90.34%), followed by tetracycline (86.89%), ampicillin (82.75%), and other antibiotics. However, *E. Coli* isolates from the same investigation demonstrated ABR to colistin (84.64%), enrofloxacin (34.64%), neomycin (80.62%), norfloxacin, spectinomycin (0.89%), trimethoprim with sulfamethoxazole (53.47%), amoxicillin (24.38%), and amoxicillin with clavulanic acid (73.05%) (Benklaouz et al., 2020). Majewski et al. (2021) reported that the *E. coli* species frequently exhibit resistance to antimicrobials commonly employed for treating bacterial infections in poultry.

Salmonella species

Annually, 93.8 million cases of salmonellosis and 155,000 deaths are reported globally due to *Salmonella*, one of the most crucial zoonotic agents of *Salmonella* (Gong et al., 2023). The ABR bacteria list of the WHO now encompasses antimicrobial resistance against *Salmonella* as one of its top priorities (Tillotson, 2018). *Salmonella*, as a potential risk in poultry, is a common vector for the distribution of AMR to humans (Hoque et al., 2020). Food-borne zoonotic *enterobacterium* spp. can transmit ABR from animals' microbiomes to humans (Ali and Alsayeqh, 2022). However, *Salmonella* spp. infections are the most frequently reported bacterial diseases in poultry, which can potentially lead to human food-borne illnesses (El-Sharkawy et al., 2017). The development of multidrug resistance (MDR) in *Salmonella* strains may cause complications in treating humans and animals (Marin et al., 2022). Standard serological and microbiological techniques including polymerase chain reaction (PCR), conventional culture methods, immunology-based assays, miniaturized biochemical assays, and biosensors are usually used to isolate and identify *Salmonella* spp. (Kadry et al., 2019). The invasion gene (*invA*), often linked to bacterial virulence, is frequently used to accurately identify *Salmonella* spp. in clinical samples (Kadry et al., 2019).

Salmonella spp. is being considered as a potential AMR pathogen, originating from livestock, humans, and the environment (Pornsukarom et al., 2018). Non-typhoid *Salmonella* spp. is a major food-borne pathogen that globally infects humans and is linked to livestock and food (Mthembu et al., 2021). *Salmonella enterica*, comprising over 2600 serovars, is the most pathogenic species and is frequently linked to the contamination of poultry products (Jajere, 2019). Accordingly, inside the poultry production chain, the highest *Salmonella* isolates ABR levels were reported for nalidixic acid (80.3%) and ampicillin (64.8%, Castro-Vargas et al., 2020). The majority of the *Salmonella* isolates from chickens analyzed in another investigation were found to be resistant to trimethoprim/sulfamethoxazole, ciprofloxacin (73.17%), colistin (92.68%), and tigecycline (62.20%, Uddin et al., 2021). Poultry-related products, such as eggs can be exposed to pathogenic bacteria like *Salmonella*, either horizontally or vertically through transovarian transmission, which are crucial sources of pathogens (Borges et al., 2017). Adesiyun et al. (2020) revealed a 7.7% prevalence of resistant *Salmonella* spp. in eggs from layer farms in Gauteng Province, South Africa. *Salmonella* resistance in raw retail table eggs was found to be high, with 80% resistance against tetracycline and 60% resistance against ampicillin, indicating the presence of bacteria inside and outside the eggs (Kapena et al., 2020).

Staphylococcus species

Staphylococcus is a widely spread bacterium in the environments (air, dust, and household items), and are commensal colonizer of the mucous membranes and skin of humans and various animals including cats, cattle, and poultry (Lee et al., 2020). Ajoke et al. (2018) reported that 51 species and 27 subspecies of the genus *Staphylococcus*

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have demonstrated resistance to all antibiotic classes utilized in their treatment through different mechanisms. S*taphylococci* are usually classified as either coagulase-negative (CoNS) or coagulase-positive (CoPS). The coagulase-positive *Staphylococcus aureus* (*S. aureus*) causes illnesses in animals and humans and is the most vital species in this genus which causes food intoxication (Lee et al., 2020). In addition, there are examples of resistant CoNS in poultry products, such as meat, eggs, and litter (Amoako et al., 2019). The major class of antibiotics used against *S. aureus* is beta-lactam, against which the *S. aureus* develops resistance often owing to a plasmid-encoded penicillinase/beta-lactamase (Pugazhendhi et al., 2020). However, methicillin-resistant *S. aureus* (MRSA) of livestock origin especially in poultry meat has been increasingly reported in recent years (Bortolaia et al., 2016). Another study by Ali et al. (2017) investigated the presence of MRSA in poultry samples and determined the highest resistance against penicillin-G (93.33%) and the lowest resistance was detected against neomycin (23.33%) against five antibiotics.

Non-*aureus Staphylococci* (NAS), which includes CoNS, have been identified as potential sources of food poisoning and significant contributors to opportunistic infections in humans and animals in recent times (Lee et al., 2020). Multidrug resistance in NAS, particularly *S. agnetis* (19.4%) and *S. chromogenes* (14.5%) with high rates against tetracycline and fluoroquinolones, was confirmed. Tetracycline resistance was linked to mutations in *gyrA* and *parC*, while fluoroquinolone resistance was linked to *QRDR* mutations (Lee et al., 2020). Ogundipe et al. (2020) explored the AMR against MRSA in chicken meat, chickens, live poultry markets, and environmental samples within poultry farms in southwestern Nigeria. The study found that 56 MRSA isolates were detected in tested samples which demonstrated 100%, 60.7%, 33.9%, 28.6%, 32.1%, and 10.7% resistance to beta-lactams, tetracycline, ciprofloxacin, erythromycin, gentamicin, and trimethoprim/sulfamethoxazole, respectively. Accordingly, live poultry markets may be a major source of MRSA infections among the general public and that chicken meat is tainted with the disease. Moreover, every isolate of *S. aureus* and *Streptococcus* spp. tested was 100% resistant to the majority of the antibiotics that were evaluated for poultry (Sharma et al., 2017). According to Rao et al. (2022), the highest AMR of *Streptococcus* spp. against clindamycin was found, followed by erythromycin and penicillin. Furthermore, a study on CNS isolated from Polish poultry revealed that fewer CNS strains exhibited genes resistant to macrolides, chloramphenicol/florfenicol, and lincosamides (Pyzik et al., 2019).

Campylobacter species

Campylobacter spp. are emerging infections responsible for 95% of diarrhea cases in humans (Kirk et al., 2015). Campylobacteriosis is a human disease caused by contaminated foods and drinks, with broilers being the primary source of *Campylobacter* and meat in many countries (Tang et al., 2020; Gao et al., 2023). The use of antibacterial drugs like macrolides, fluoroquinolones, and tetracyclines to treat *Campylobacter* infections has been criticized for causing global fluoroquinolone resistance and macrolide-resistant strains (Gahamanyi et al., 2021). *Campylobacter* from food-producing animals shows high tetracycline resistance, with strains resistant to erythromycin, tetracycline, and ciprofloxacin becoming more prevalent (Gao et al., 2023). Viswanathan et al. (2017) found that cattle *Campylobacter* isolates showed higher ABR compared to wildlife isolates, with *Campylobacter jejuni* being more common but showing multidrug resistance. A study in Casablanca, Morocco, found that tetracycline (100% resistance against *Campylobacter jejuni* isolates) and gentamicin (12.0% resistance) were the most effective antibiotics (Es-Soucratti et al., 2020). *Campylobacter jejuni* AMR profiles from a Moroccan poultry farm revealed the highest resistance to co-trimoxazole (84.1%), cephalothin (81.1%), and tetracycline (59.4%) in poultry meat and associated samples (Khan et al., 2018). *Campylobacter jejuni* indicated no resistance to gentamicin, erythromycin, or kanamycin, but resistance was observed to tetracycline (78.6%), ciprofloxacin (87.8%), and nalidixic acid (81.6%, Adiguzel et al., 2018). Using the microdilution method, 93 *Campylobacter* spp. (45 *Campylobacter jejuni* and 25 *Campylobacter coli* from chickens; 23 *Campylobacter coli* from pigs) were examined for resistance to antibiotics to nine antimicrobial agents. There were lower resistance rates to florfenicol (8.6%), but higher resistance rates to nalidixic acid (79.6%), erythromycin (75.3%), tetracycline (68.8%), azithromycin (66.7%), ciprofloxacin (64.5%), and gentamicin (35.5%, Tang et al., 2020). Excessive antibiotic use in humans and animals has increased ABR infections, particularly resistant to fluoroquinolones. Understanding AMR mechanisms in *Campylobacter* spp. is crucial for improved ABR programs.

PUBLIC HEALTH

It is well known that ABR bacteria develop and propagate in animals, humans, and the environment, posing a cross-boundary concern that impacts ecosystems and public health. Poultry, their products, carcasses, litter, and bird feces have been reported to have MDR bacteria, which can be a threat to handlers, consumers, and in general to public health (Agyare et al., 2019). The ABR bacteria and resistance genes developed in livestock transfer to humans through various channels, particularly through the food chain (Figure 1). Many of these bacteria are serious human pathogens. *Campylobacter* spp. is the primary culprit behind cases of food-borne diarrhea in humans. For instance, *Campylobacter* spp. is a leading cause of food-borne diarrhea worldwide, responsible for 4-5 hundred million cases annually (Chibwe et al., 2023). In immunocompromised or elderly persons, as well as in extremely young children, infections caused by *Campylobacter* can be severe or even fatal. *E. coli* bacteria are another widespread cause of sickness. Furthermore, Salmonellosis is one of the world's most widespread and common food-borne infections that result in mild gastroenteritis (Mehdi et al., 2018).

Based on the literature, people from impoverished and developing countries are the most vulnerable to ABR bacteria threats. It is estimated that at least 700,000 people die each year as a result of resistant bacterial infections, a figure that is expected to rise to 10 million globally by 2050, in case the current trends continue. Furthermore, the worldwide cost of ABR is predicted to increase to $100 trillion in the coming decades (Crofts et al., 2017).

The risk of ABR bacteria in poultry production can be reduced through several approaches, including the utilization of antibiotics alternatives, prevention of environmental contaminations, and improvements in all stages of the poultry production system, such as poultry health, biosecurity, cleaning procedures, and implementing hazard analysis (Abreu et al., 2023; Salam et al., 2023).

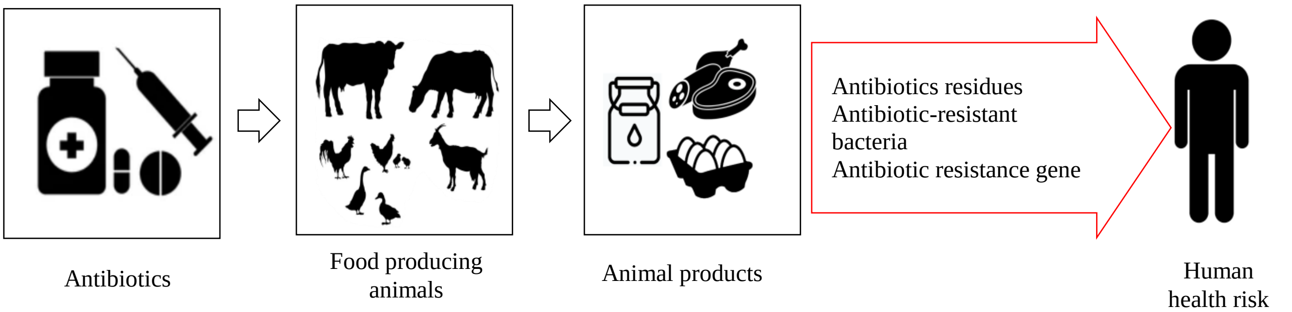

Figure 1. Human health concerns about antibiotic resistance bacteria in animal sources

ALTERNATIVES OF ANTIBIOTICS IN POULTRY PRODUCTION

Feed additives aim to reduce the reliance on antibiotics by identifying feed additives that stimulate the immune system, decrease morbidity and mortality, improve the growth performances of poultry, and preserve consumer health (Rahman et al., 2022). The modern chicken industry needs high levels of output and effective feed conversion, which can be partially attained by articular feed additives (Alagawany et al., 2016; Khan and Iqbal, 2016; Azizi et al., 2021a; 2021b, Danladi et al., 2022). Researchers have investigated several groups of feed additives and their prospective application as alternatives to antibiotics in poultry production (Rahman et al., 2022). Studying the overall alternatives for antibiotics used in poultry feeding as growth promoters is a controversial topic. Therefore, in the present review, the most frequently used feed additives, such as essential oils, phytochemicals, bacteriophages, antimicrobial peptides, probiotics, prebiotics, organic acids, and enzymes are discussed briefly.

Essential oils

Essential oils and nano-emulsions can be cutting-edge alternatives for antibiotics that reduce bacterial infections, and improve gut health intestinal environment, and gastrointestinal tract enzyme activities in chickens (Abd El-Hack et al., 2022). Nanoencapsulation herbal essential oils increase the growth performance of broiler chickens and efficiently work against antibiotic-resistant pathogens (Meimandipour et al., 2017). Similarly, ginger, garlic, limes, and lemongrass as sources of essential oil used in poultry nutrition increase the health performance of broiler chickens (Amiri et al., 2021). In addition, the application of herbal essential oils in poultry nutrition has positive effects on the antioxidant capacity, immunity, and growth performance of chickens (Linh et al., 2022). In another study, essential oils from garlic and cumin in nano-encapsulated form improved some structural features of the digestive tract including villi width and length (Amiri et al., 2021). Additionally, it has been identified that herb extracts, such as oregano, effectively inhibit the proliferation of pathogenic coliform bacteria in broiler chickens without affecting the proliferation of beneficial microbes (Mohebodini et al., 2019). The mechanism underlying the effectiveness of essential oils in poultry nutrition may involve bioactive components that enhance the production of the mucin-2 gene in the digestive tract. Mucin-2 plays a crucial role in protecting the gastrointestinal tract from infections, aiding in the secretion of digestive enzymes, and maintaining acidic conditions (Amiri et al., 2020). Furthermore, the chemical components present in the essential oils stimulate the secretion of digestive enzymes from the mucosal layer of the intestine (Jemaa et al., 2018). Thus, essential oil could be a potential alternative to antibiotics in poultry nutrition for increasing growth performance, as well as producing low-cholesterol meat with high quality and durability (Namdeo et al., 2022).

Phytochemicals

Phytochemicals, which are secondary metabolites derived from natural plant sources, are utilized in poultry nutrition as feed additives due to their potential antimicrobial properties and ability to enhance chicken growth performance (Hashemi et al., 2008). The inclusion of phytochemicals in poultry diets has been shown to effectively replace antibiotics, improving growth performance and overall poultry production (Valenzuela-Grijalva et al., 2017; Azizi et al., 2023). These compounds possess antimicrobial, antioxidant, and anti-stress properties, contributing to enhanced immune responses, growth performance, and modulation of gut microbiota in broiler chickens (Chowdhury et al., 2018; Al-Mnaser et al., 2022; Azizi et al., 2023). Moreover, phytochemicals promote the growth of beneficial bacteria while reducing the population of pathogenic bacteria (Cencic and Chingwaru, 2010). This reshaping of the gut microbial community, alongside increased activity of digestive enzymes like amylase and maltase, likely underlies their mechanism of action (Jang et al., 2007; Al-Mnaser et al., 2022). Overall, incorporating phytochemicals as feed additives represents a promising alternative to antibiotics in poultry nutrition, enhancing metabolism, growth, antioxidant capacity, and immune function in chickens (Hassan et al., 2022).

Bacteriophages

According to Żbikowska et al. (2020), bacteriophages are a unique type of viruses that exclusively infect bacteria and are considered non-pathogenic to humans. In the poultry industry, bacteriophages are gaining attention as a promising alternative to antibiotics due to their high specificity (Lin et al., 2017). Research has demonstrated that bacteriophages can effectively control various pathogenic bacteria in chickens (Hong et al., 2013; Lee et al., 2016). Studies have shown that adding a 0.05% bacteriophage cocktail can enhance the immune system and promote the growth of beneficial gut microorganisms (Upadhaya et al., 2021). Dietary supplementation with bacteriophages has also been found to improve growth performance in broiler chickens and reduce the populations of specific pathogenic bacteria in their gastrointestinal tract (Kim et al., 2014). Similarly, feeding bacteriophages has been shown to enhance production efficiency in both broilers and layers and reduce overall excreta microflora levels (Noor et al., 2020). The improved microbiological environment in the gastrointestinal tract of broilers and layers appears to be the underlying mechanism (Lee et al., 2016). Thus, the findings from several studies suggest that bacteriophage dietary supplementation would be a safe alternative to antibiotics for raising broiler chickens.

Antimicrobial peptides

Antimicrobial peptides (AMPs), also known as host defence peptides, offer a promising alternative to antibiotics when used as feed additives in poultry nutrition (Kurt et al., 2019). The AMPs have been shown to positively impact gut microbiota and enhance overall health and performance in chickens. Research indicates that incorporating AMPs into poultry diets improves intestinal microbiota balance, intestinal morphology, nutritional digestibility, and growth rates (Wang et al., 2016). By promoting a healthy and immune-competent gut microbiota, AMPs contribute to enhanced growth performance metrics such as feed conversion efficiency, daily weight gain, feed intake, and reduced mortality (Nazeer et al., 2021). Bacteriocins, which are ribosomally synthesized antibacterial peptides, are another form of AMPs that show potential for controlling bacterial diseases and serving as alternatives to antibiotics (Ben Lagha et al., 2017). Studies have demonstrated that synthetic AMPs can increase feed intake and growth performance while protecting against intestinal damage in broiler chickens (Choi et al., 2013). Additionally, AMPs from various sources have been found to modulate the expression of pro-inflammatory and anti-inflammatory molecules in the intestine, improve intestinal morphology, enhance digestion processes, and regulate the immune system in broilers (Abreu et al., 2023). As immune modulators, AMPs also help reduce bacterial infection rates in broilers (Choi et al., 2013). The AMPs perform several antibacterial activities through several mechanisms that have been previously reviewed (Wang et al., 2016). These mechanisms include the suppression of nucleic acid and protein synthesis, the inhibition of enzymatic activities, and cell membrane synthesis (Brogden, 2005).

Probiotic

Due to the detrimental effects associated with antibiotics used in poultry nutrition, including dysbiosis, ABR, and elimination of beneficial microbial communities in the intestine (Yang et al., 2021), alternative approaches like probiotics are increasingly considered (Alagawany et al., 2016). Probiotics consist of living microorganisms that confer health benefits to the host when administered in adequate amounts (Rahman et al., 2022). Various probiotic microbe families are utilized as feed additives in the nutrition of poultry (Floch, 2014). Probiotics have been shown to have beneficial and protective effects in several areas, such as improving growth and productive performances as well as egg quality. They also have applications as beneficial bacteria to reduce harmful bacteria, improve nutrient absorption and digestion, increase production, and protect the health of chickens (Ritzi et al., 2014; Alagawany et al., 2016; Popova, 2017). In Japanese quails, the lower dose of kefir administered as a probiotic reduced stress effect, liver weight, and alkaline phosphatase activity (Vahdatpour and Babazadeh, 2016). The use of synbiotics combined with the vaccine for infectious bursal disease promoted both the growth performance and related antibody titers (Babazadeh and Asasi, 2021).

Due to their negative proportional relationship, recent research showed that probiotics affect antimicrobial peptide modulation in chickens (Ma et al., 2020; Rahman et al., 2022). The antimicrobial peptide gene expression was reduced as probiotic concentration increased, suggesting that antimicrobial peptides might not always be required when probiotics are present (Akbari et al., 2008; Schlee et al., 2008). Furthermore, research indicates that adding probiotics to the diet during the later stages of reproduction can enhance the laying ducks' productivity and egg quality (Cao et al., 2022).

Prebiotic

The term prebiotics was first coined to describe non-digestible food components that provide benefits to the host by selectively promoting the growth or activity of specific bacteria in the colon (Floch, 2014). Chemically, prebiotics are carbohydrates with a short carbon chain that selectively increase the activity of certain types of beneficial bacteria in the gut (Kolida and Gibson, 2011; Al-Sheraji et al., 2013). Prebiotics are broken down by beneficial bacteria in the gut to produce short-chain fatty acids (Mountzouris and Tsirtsikos, 2009). Other health benefits of prebiotics in the large intestine include reduced cancer risk and enhanced gastrointestinal absorption of calcium and magnesium (Karakan et al., 2021). Different oligosaccharides have been evaluated in poultry feed as prebiotics, and their effects on the gastrointestinal microbiome of the chickens and the inhibition of pathogenic bacteria have been described by Clavijo and Flórez (2018).

Prebiotics have been associated with multiple mechanisms and roles that affect the avian gastrointestinal microbiota, including immune system interaction, alterations in intestinal morphology, and competitive elimination of pathogenic microorganisms (Pourabedin and Zhao, 2015). Prebiotics may be metabolized by a wide variety of gastrointestinal bacteria, which makes it more difficult to comprehend how they benefit the host and/or prevent the growth of pathogens (Alloui et al., 2013). However, further research is required to explore the exact mechanism behind the health and growth-promoting effects of prebiotics on livestock.

Organic acid

It has been established that short-chain organic acids (C1-C7) have antibacterial effects. Based on chemical structure, organic acids are divided into two groups, namely simple mono-carboxylic acids like butyric, propionic, fumaric, and sorbic acids, and short-chain carboxylic acids with double bonds like fumaric and sorbic acids (Wang et al., 2009; Scicutella et al., 2021). Another category of organic acids is carboxylic acids with an extra hydroxyl group including lactic, malic, tartaric, and citric acids (Shahidi et al., 2014). Due to their widespread safety, the European Union approved the use of organic acids and their salts in poultry production (Adil et al., 2010). The majority of organic acids with antimicrobial action have a pH of 3 to 5, and variable chemical and physical characteristics (Scicutella et al., 2021). Many of these acids are utilized in poultry nutrition as feed additives or as supplements to drinking water (acidifiers; Khan and Iqbal, 2016). It was found that organic acid mixtures (calcium format, calcium propionate, potassium sorbate, calcium butyrate, calcium lactate, and hydrogenated oil of vegetable) used in poultry nutrition were more effective at reducing intestinal *Salmonella* spp. and *E. coli* than the antibiotic growth promoter such as Enramycin (Hassan et al., 2010). The total bacterial count in ceca was significantly lower in the groups that received drinking water treatments with acetic acid (3 mL/L) and an organic acid mixture (3 mL/L; acetic acid, phosphoric acid, lactic acid, fumaric acid, and tartaric acid) 7 days after infection than in the non-treated group (Hamed and Hassan, 2013). Some types of organic acids perform effectively against organisms that cannot tolerate acidity (Cao et al., 2022). Organic acids improve nutrient digestibility by reducing endogenous nitrogen losses and microbial competition with the host for nutrients, as well as by lowering the incidence of subclinical infections and the secretion of immune mediators and by reducing the production of ammonia and other growth-depressing microbial metabolites (Khan and Iqbal, 2016).

Enzymes

Enzymes have gained prominence in poultry nutrition as effective feed additives, addressing challenges posed by anti-nutritional factors and optimizing nutrient digestion and utilization (Son and Ravindran, 2012; Pirgozliev et al., 2019). Enzymes that are commonly utilized in poultry nutrition include non-starch polysaccharides, which break down the non-starch polysaccharides in viscous cereals, and microbial phytases, which target phytate-complexes in plant components (Amerah et al., 2011; Cross et al., 2011).

Particularly in young chickens, proteases play a significant role in the digestion of protein and amino acids (Pirgozliev et al., 2015). In addition to acting as antioxidants, dietary phytogenic may impact immunological function, nutritional availability, endogenous secretions, and daily feed consumption (Amerah et al., 2011; Cross et al., 2011). Enhancing animal performance through increased feed intake, weight gain, and feed efficiency is the ultimate goal of applying feed enzymes (Rahman et al., 2022). The underlying mechanism may be the breakdown of certain bonds in feed components that are not usually digested by endogenous digestive enzymes (Selle and Ravindran, 2007; Son and Ravindran, 2012), degradation of ant-nutritional elements that limit the digestion of nutrients and cause modifications to the intestinal tract's morphology (Bedford, 2000; Wu et al., 2004). Moreover, the positive effects of the enzyme may be due to the decreases in intestinal protein wastes and endogenous secretions, which reduces the amount of protein required for maintenance, and alterations to the small and large intestine's microbiota profile (Apajalathi et al., 2004; Cowieson and Ravindran, 2007).

CONCLUSION

The use of antibiotics in poultry production has been associated with the development of resistant bacteria. The spread of ABR bacteria in the environment and their transmission to humans could have serious consequences for public health. *Salmonella* spp., *E. coli*, *Campylobacter* spp., and *Staphylococcus* spp. are considered very common ABR bacteria isolated from poultry products. A ban on the use of non-therapeutic antibiotics would help to minimize additional harm to food safety, contamination of the environment, and overall health risks. Further studies are required to create substitute approaches, such as the utilization of alternative bioactive compounds as feed additives for instance essential oils, bacteriophages, antimicrobial peptides, probiotics, prebiotics, organic acid, and enzymes, and discovering their exact action mechanisms to maintain poultry health and productivity, environmental contaminations as well as preserve consumer health.

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Authors' contribution

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Competing interests

The authors disclose no conflict of interest.

Ethical consideration

Ethical issues (including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

Availability of data and materials

All data related to the present review are presented in this article.

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