INSIGHTS IN ANIMAL SCIENCE

REVIEW

Beyond Antibiotics: A Review of Sustainable Strategies and Emerging Alternatives for Poultry Health Management in Modern Farming

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Abstract: Antimicrobial resistance (AMR) has made it difficult for both people and animals to control disease using antibiotics, which has led to food insecurity, particularly for the chicken business. As a result, it is necessary to create long-term plans for keeping chicken flocks healthy as well as possible, and side-effect-free antibiotic substitutes. The use of probiotics and prebiotics, vaccination and immunostimulants, organic farming, improved hygiene and biosecurity measures, in-ovo-inoculation, feed additives, and nanoparticles are some of the practices that are currently being used to minimise the use of antibiotics and to maintain the optimal health, immunity, gut integrity, and growth performance of birds. However, because of their potential use in replacing antibiotics in poultry, certain new alternatives—such as antimicrobial peptides, bacteriophages, enzymes and enzyme-based products, and nanoparticles—are receiving a lot of attention. To preserve chicken health and reduce the need for antibiotics, the study emphasizes the potential of these sustainable practices and new alternatives. This will ultimately aid in the fight against AMR and guarantee the production of safe and reasonably priced poultry protein.

Keywords: antimicrobial resistance; poultry health; poultry production; antibiotics alternatives

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1. Introduction

The current population of the world is to be about 8.1 billion [1] and will reach 9.8 billion by 2030, with a huge increment in population in developing countries of Asia and Africa [2]. Due to this increase in population, overall food demand will surge by more than 50 % and food from animal sources by approximately 70% [3]. World Health Organization (WHO) recommended that in our daily basic diet, there should be usage of different types of foods like maize, wheat, rice, and potatoes including legumes like lentils and beans, along with ample quantity of fresh fruit and vegetables and food from animal sources (e.g., fish, meat, egg and milk)[4]. To deal with increasing insecurity of food (protein), sub-therapeutic administration of antibiotics in poultry farms is a routine practice to compensate for the overcrowding and the unhygienic environments [5].

Antibiotics are being used as a growth promoter and for the prevention and treatment of diseases in the poultry sector of many developing countries. Their usage for growth enhancement often requires a very small amount of administration as compared to therapeutic use and this also develops resistance to antibiotics in bacteria. The occurrence of antibiotic resistance in bacteria and horizontal transfer of antibiotic resistance genes result in a compromise in nutritional and the economic prospects of poultry and other livestock animals that are used for food production [6].

A study demonstrated the usage pattern of antibiotics in selected farms in Bangladesh and reported the use for therapy is 43.8%, for prevention is 31.5%, and for both 47.9% and 8.2% for growth promotion [7]. However, the usage of antibiotics from nation to nation depends upon several factors, i.e. related knowledge, the economy of the country, management system, and the routine practices of farming. A study in 2015 revealed that on average, global annual usage of antimicrobials/kg of chicken meat production was 148 mg and is estimated to increase by 67% between 2010 and 2030 [8]. From 2000 to 2010, antibiotic usage in 71 countries increased by 36% although Brazil, Russia, India, China, and South Africa (BRICS) contributed to about 75% of this huge increment [9]. This widespread and irrational use of antibiotics is encouraging antimicrobial resistance in living organisms. This AMR is a very serious global health issue for humans and animals equally affecting developed and developing nations [5] reducing the capability for treatment of the infections caused by bacteria and also creating threats associated with morbidity and mortality by these antibiotic-resistant bacteria [9]. There should be an investigation of alternative approaches to replace antibiotics to maintain gut health and ensure the production of good quality and cheap poultry protein [8].

This study aims to review the sustainable strategies (organic farming practices, *In ovo* inoculation, improved hygiene and biosecurity measures, vaccination and immunostimulants) and alternatives to antibiotics (bacteriophages, antimicrobial peptides, feed additives, enzymes and enzyme-based products, probiotics and prebiotics, nanoparticles) in poultry production to cope with the issue of increasing antibiotic resistance. This review will highlight the usage of antibiotic alternatives and how it is beneficial for poultry and will also suggest potential alternatives.

2. Sustainable Strategies in Poultry Health Management

There are many sustainable strategies that we can utilize for the maintenance of our poultry flock's health. With good management and the implication of these strategies, we can reduce antibiotic usage and make our birds healthier. These are as follows:

2.1. Organic Farming Practices

Organic animal farming should adhere to strict animal welfare guidelines and improve the health and wellbeing of the animals, paying particular attention to the behavioral needs of different species [10]. European Union regulation on the production of organic broilers demands low stocking densities (33 kg/m^2) with outdoor access to birds [11] so to provide them an opportunity to perform their natural behaviors [12]. Natural light is very crucial and when managed with artificial light should be given at least eight hours [10]. To provide the best possible health under these conditions, we need to select the most suitable hybrid birds in this regard [13]. Therefore, the fast-growing broilers are being replaced by the slow-growing hybrids as they are better adapted to organic production conditions and welfare concerns [10]. Fast-growing broilers also showed severe complications in movement because of the high growth rate and ultimately body weight that results in keeping the bird more at the resting stage, especially in the last week of production (rearing). The reduction in movement causes leg weakness and results in skin lesions and blisters due to long resting periods. However, slow-growing genotypes are more active and with increased usage of perches and showed better adaptability [14]. Thus, organic farming in poultry production ensures more health and greater welfare coverage and thus should be used as a suitable strategy than intensive farming.

Seven key features are considered to have a role in improving the welfare of poultry in organic farming: suitable breeds, no mutilations, access to outdoor environment, availability of natural light, perch space and elevated sitting levels, roughage provision and reduced stocking density. The minimum requirements as established by the EU regulations on the production of poultry birds are presented in Table 1 to highlight some of the specific features intended to improve animal welfare in the production of poultry. In addition to the minimal guidelines ensuring the safety of laying hens and broiler chickens in conventional farming [15] to maintain equilibrium between the welfare of birds, adaptability to the environment, biodiversity and productive performance [14].

Table 1. European Union minimum criteria for the housing and management of laying hens (Directive 1999/74/EC) and broiler chicks (Directive 2007/43/EC) in both conventional and organic poultry farming (EU regulations 2018/848 and 2020/464).

Parameters	Laying hens		Broilers	
	Conventional	Organic	Conventional	Conventional
Stocking density	Usable indoor area: 9 hens/m²	Usable indoor area: 6 hens/m²	33 kg/m²	21 kg/m²
Perches and/or raised sitting areas	15 cm perch/hen	18 cm perch/hen	Not required	Each chicken has a 5 cm perch and/or a 25 cm² elevated sitting level.
Outdoor access	Not required	4 m²/chicken and one-third of life	Not required	4 m²/chicken and one-third of life
Lighting	Enough light to see each other, explore the environment, and exhibit typical levels of activity	Natural light	Lighting at least 80% of the space with a maximum of 20 lux	Natural light
Nocturnal rest (hours per day with no artificial light)	About one-third of the day	Continuous 8 h	4 h of the 6 h are continuous.	Continuous 8 h
Mutilations (beak trimming)	Permitted to avoid cannibalism and feather pecking (<10 days old)	Only as an exception (≤3 days old), otherwise, it is not permitted	Permitted to avoid cannibalism and feather pecking (<10 days old)	Only as an exception (≤3 days old), otherwise, it is not permitted
Roughage	No requirement	Constant availability of adequate amounts when kept indoors	No requirement	Constant availability of adequate amounts when kept indoors
Growth rate	N/A	N/A	Fast-growing breeds permitted	Slow-growing breeds or those raised for at least 81 days

Source: [15]

2.2. In Ovo Inoculation

When eggs are transferred from setters to hatchers, which typically occurs between 17.50 and 19.20 days of incubation, several inoculation procedures are employed in the hatchery to improve the health of the chicks [16]. Vaccines have been approved for Marek's disease (MD), infectious bursal disease virus (IBDV), fowl pox, Newcastle, and coccidiosis for the *in ovo* delivery [16, 17]. The efficacious protection against Marek's disease was observed when vaccine was administered in the body of embryo or the amnion. Several vaccines, medications, hormones, competitive exclusion cultures, and other supplemental nutrients have been continuously studied in labs to improve immunity and growth. The results of these studies have also been published, but they are not yet commercially available [18]. By using the *in ovo* technique, numerous nutrients, such as egg white, amino acids, peptides, carbohydrates, nucleotides, electrolytes, vitamins, L-carnitine, creatinine, and plant extracts have also been tested for their ability to improve embryonic development, hatchability, and post-hatch performance [19]. Similarly, it has been noted that *in ovo* nutrient delivery at the late-term embryonic stage may reduce hatchling mortality during crucial post-hatch times [20] and ultimately prove to be an impactful strategy in poultry health management.

2.3. Improved Hygiene and Biosecurity Measures

According to the Food and Agriculture Organization (FAO), biosecurity is defined as offering a strategic and unified approach to evaluate and manage the risks in food safety, health, life, and biosafety of animals and plants [21]. From the last decade, the importance of implementation of strict biosecurity has increased significantly with globalization, intensification in livestock farming systems, and consequent increasing food trade and international, which also cause the emergence and re-emergence of diseases [22]. Meat production through broiler farming without the usage of antibiotics demands reduction in stocking density, increment in the downtime, rapid and frequent cleaning with strict biosecurity measures. It is very easy for microorganisms to take entry into the farms and thus affect the production performance of the poultry flocks, so, biosecurity must be implemented without leaving any gap [8]. Biosecurity is not only for infectious diseases but also covers the other possible hazards, and for instance, residues, pests, and it also covers the antimicrobial usage and antimicrobial resistance [22]. There should be proper consideration of hygiene at poultry farms and some critical hygiene steps with very limited implementation by the farmers are the cleaning and disinfection of the feed storage silo, disinfection of the houses and the waterlines in the houses, specific areas to enter in poultry houses for collection of eggs, different labor and staff between poultry sheds and the egg storage room, lack of hand washing before getting entrance into the house and proper disposal of the mortality [23]. Antimicrobial usage is closely linked to suboptimal conditions of animal husbandry including poor hygiene and biosecurity. We can reduce antibiotic usage by adopting the intervention that focuses on infrastructure improvement, farming, and cleaning conditions [24]. Therefore, by implementation of all these hygiene measures under strict biosecurity will ensure the flock's health with minimal bacterial load and thus no antibiotic usage is required.

2.4. Vaccination and Immunostimulants

One of the main causes that results in huge economic losses in the poultry industry is viral outbreak and it negatively affects the zootechnical performances of birds, like feed intake, weight gain, Feed Conversion Ratio (FCR), egg quality, and meat production therefore, preventive measures should be taken including vaccination. Live and killed vaccines have a long usage history on poultry farms as a prophylactic against viral diseases with economic and global significance [25]. Vaccination programs play crucial role in controlling diseases and provide a cost-effective way to lessen the bacterial and viral load. Bacterial vaccines can reduce the usage of antibiotics in the poultry industry. Bacterial vaccines perform their action by activating the immune system of poultry birds in response to specific bacterial pathogens and thus provide long-term protection from future infections. Ultimately helpful in reducing antimicrobial resistance (AMR) [26]. Shimma et al., [27] found that inactivated bacterin made from chicken embryos infected with fowl cholera is effective against infections caused by either homologous or heterologous serotypes of Pasteurella multocida.

Immunostimulants are compounds that have immunotropic properties and can maintain the normal state of the immune system. Plant-based immunostimulants have got significant due to immunostimulating effects, and the stimulation of endocrine and nervous systems [28]. A study with oral administration of 200 mg/kg extract of *Plectranthus parviflorus* before vaccination to poultry flock resulted in a significant positive effect on ND and IBD humoral response [29]. Another study regarding the usage of immunostimulant antiviral medicinal plant i.e., neem, resulted in complete protection of chicken flocks against the highly pathogenic avian influenza (HPAI) (H5N8) and prevented the shedding of the virus [30]. The lecithin extracted from mushrooms increased the antibodies titers against IBD as compared to the commercial lecithin [31]. Thus, by the utilization of vaccination and immunostimulants, we can protect our flock from diseases and maintain the health of our birds.

3. Emerging Alternatives to Antibiotics

With a continuous increase in modern farming, the prevention and treatment of diseases especially caused by bacteria in poultry farming is a huge problem and needs to be solved. Historically, antibiotics have been used to stop the amplification of gastrointestinal pathogens, to promote the animal's growth and to improve the FCR. However, this long-term usage of antibiotics has created resistance in pathogens against antibiotics and that's why there is an urgent need to replace antibiotics usage with less expensive and more efficient alternatives to ensure the sustainable development of the poultry industry [32]. Some alternatives have been shown in Figure 1.

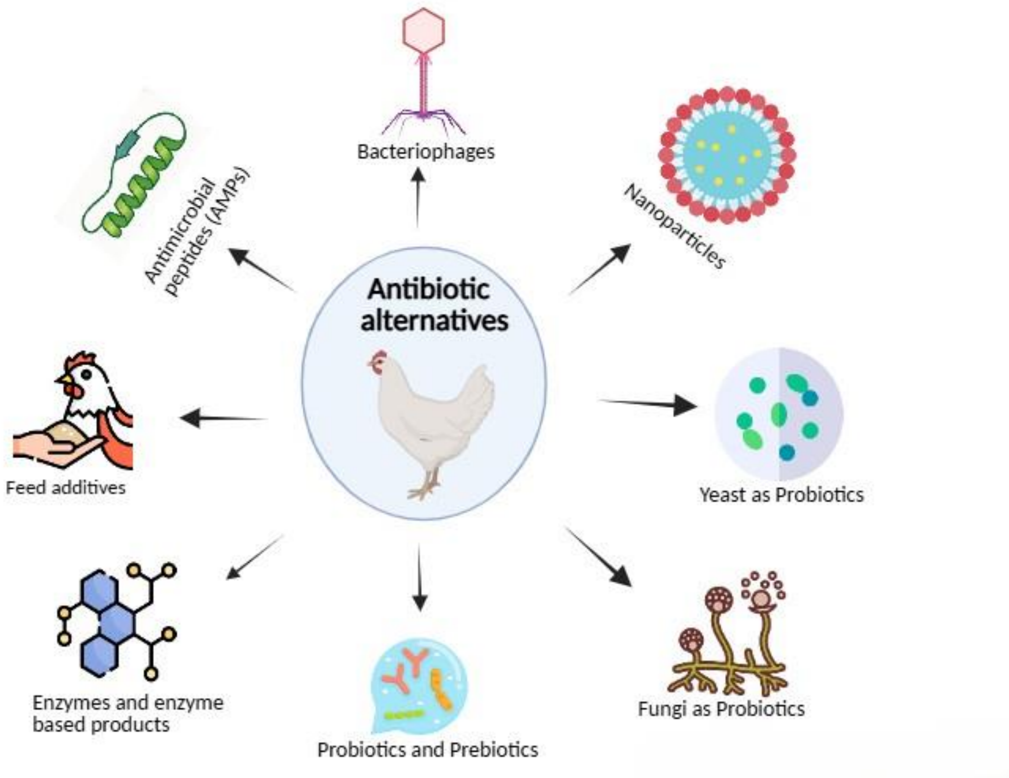

Figure 1. Emerging antibiotics alternatives.

3.1. Bacteriophages

Bacteriophages are a group of viruses that target certain specified bacteria and have less distribution in the environmental niches like hydrothermal vents of the ocean and sediments but are also found in surface life forms in the kingdom Animalia and Plantae [32]. European Medicines Agency approved the first scientific guideline on bacteriophage-based veterinary medicines for livestock and poultry production activities, and the guidelines define this phage-based therapy as a novel technology with a great focus on safety and residues of this therapy, also imposing specific requirements for animal clinical trials [33]. Practically, bacteriophages are administered in the bacteriophage cocktails form that contains a mixture of multiple bacteriophages at various time intervals, to prevent the development of resistance to a specific bacteriophage type by bacteria. To achieve maximum effectiveness, it entails the invasion and lysis mechanism of many bacteriophages that target the same bacterial hosts and related microorganisms [32]. Supplementation of 400 mg/kg of bacteriophage cocktail in the diet of weaned piglet that targets Salmonella, *Escherichia coli*, *Staphylococcus aureus*, and *Clostridium perfringens* and resulted in a significant increase in daily feed intake on an average, improved the integrity of intestine, inhibited the intestinal inflammation and reduced the occurrence of diarrhea in piglet [34]. A study with the addition of 1.5 g per kilogram of bacteriophage cocktail in the diet of weaned piglets resulted in a significant increase in ileal *Lactobacillus* spp. and a lower the level of *E.coli* and Clostridium challenge in ileum to about 5.76% and 4.21%

respectively and also showed significantly better average daily gain [35]. They are in more focus as antibiotic alternatives due to their diverse nature with greater selectivity, operability, more precise targeting ability, rapid absorption, and killing of bacteria without disrupting the normal body bacteria balance.

Despite all the advantages, bacteriophages have some limitations like narrow specificity, which limits their effectiveness against some bacterial strains until the complex cocktails are fully formed [36]. Bacterial resistance against bacteriophages also develops with time, and posing safety concerns and thus is considered critically.

3.2. Antimicrobial Peptides (AMPs)

AMPs are a class of small peptides and have the potential to stimulate the innate immune system against pathogens and can also stimulate defensive mechanisms against infectious and non-infectious pathogenic agents like bacteria, parasites, fungi, and viruses. AMPs have a role in enhancing immunity and can be used as an alternative to antibiotics [37]. They are potent multifunctional therapeutic agents, active against many microorganisms, and are called natural antibiotics. Some AMPs result in the death of Gram-positive and Gram-negative bacteria within a few minutes and are considered an ideal candidate for pharmacological applications. They affect microorganisms either by membrane targeting which results in impairment of the cell membrane structure or by inhibiting nucleic acid synthesis, essential enzymes, and functional proteins [38]. In a study with administration of AMP HJH-3 with concentration 100 μg/ml after co-incubation for 6 h resulted in good antimicrobial activity, low hemolysis, and with no cytotoxicity and could effectively kill *S. Pullorum* [39]. In another study, the supplementation of AMP (Cecropin A) vs antibiotics in the diet of zebrafish was done to observe the effects of the intervention on the microbiota. The findings suggested that antibiotic usage resulted in the occurrence of multidrug-resistant bacteria and Cecropin A did not take part in this phenomenon [40]. Microcin C7 administration in the diet of broilers with a dosage 6 mg/kg resulted in reduced chemokine TNF-α and IL-8, increased serum cytokine IL-10 in serum [41]. In another study with microcin J25 in broiler chicken at dosage 0.5 and 1mg/kg MccJ25 resulted in downregulation of proinflammatory cytokines, TNF-α, IL-1β, and IL-6 in the serum of *E. coli* and *Salmonella* challenged broiler birds [42]. Piscidin usage in yellow feather chicken resulted in deduced IL-17A, IL− 22, IFN-α, IFN-y, IL-1β, IL6 and improved the average daily gain at 100 and 200 mg/k [43]. Antimicrobial peptide sublancin invitro study with minimum inhibitory concentration (MIC) (8 μM) against C. perfringens in comparison to lincomycin resulted in reduced e IL− 1β, IL− 6, TNF-α levels ($p < 0.01$) in comparison to lincomycin, reduced the necrotic enteritis induced by clostridium perfringens and also exhibited the sample result in broiler for 28-d period [44]. ε-polylysine hydrochloride (ε-PLH) resulted in improved production in laying hens by reducing the abundance of Desulfovibrio and Streptococcus in cecum microbiota [45]. Histone H5 derived from chicken erythrocytes with MIC (4.9 μg.mL/1 against E. coli; 1.9 μg.mL/1 against Salmonella Typhimurium) showed potential to be a novel antimicrobial peptide [46]. AMPs are excellent antibiotic alternatives with good antimicrobial and immunomodulatory potential, but their high cost of production and less stability in the gastrointestinal tract (GIT) hinder their wider application. There are also toxicity risks to the host cells, and further research is needed to understand them completely [47].

3.3. Feed Additives

Due to the ban on antibiotics by the European Union in 2006, more interest has been shifted toward the usage of feed additives as an alternative to antibiotics, and many feed additives are being utilized in the poultry sector. Different feed additives from herbal extracts, essential oils, and organic acids have been widely used for the replacement of AGPs [48]. Prebiotics and probiotics are also in the priority lists and widely used as feed additives but are discussed later in another section. Phytogenic is a broad category of feed additives in poultry and has effects on the improvement of gut health and other physiological functions. Distinctive examples are rosemary derivatives, thyme, oregano, sage, cinnamon, citrus, pepper, and anise, however, the phytogenic efficacy depends on several factors, like composition, level of inclusion in feed, feed composition, and bird's genetics

[48]. The inclusion of different feed additives benefits the birds in several ways. The addition of herbal compounds - results in the improvement of the immune system, antioxidant status and stimulates the activity of digestive enzymes and has good efficacy in controlling pathogenic bacteria [49]. Essential oil mixture with garlic and lemon resulted in improved average body weight gain, feed conversion ratio (FCR), and enhanced intestinal microbial content [50]. Minerals and vitamins have also been proved to be a potent source for the improvement of the health of birds. Vitamin C is a water-soluble nutrient having role as powerful antioxidant, protecting cells from damage caused by free radicals, supports immune system, and also helpful in wound healing [51, 52]. Vitamin C improved the performance status and enhanced the immunological traits of birds [53]. The addition of zinc, selenium, and magnesium – improved the immunity and the antioxidant status of birds [54]. Organic acids also play an important role and are used as feed additives [55]. Organic acids (OC) are compounds that are organic in nature and have weak acidic properties, classified according to the number of carboxylic acid groups (R-COOH). They are considered as a promising alternative to antibiotics as they have antimicrobial effects in animal feed [54]. Citric acid usage resulted in improved growth performance, reduction in abdominal fat, ileal *E. Coli* and *Coliform* [55]. Formic acid usage resulted in increased body weight gain and decreased pH and coliform counts [56] and butyric acid improved the body weight (BW) gain and FCR [54]. Two organic acids showed synergistic effect with organic acid 1 (OA1) constituted of butyrate, medium-chain fatty acids, organic acids, and phenolics; while organic acid 2 (OA2) based on buffered short-chain fatty acids protected the broiler chickens with *Clostridium perfringens* (CP) type A challenge from severe intestinal lesions, oxidative stress [57]. Utilization of *Mentha arvensis* and *Geranium thunbergii* in drinking water from 0.01% to 0.1% resulted in a significant increment in the egg production, reduced the ammonia production from excreta and increased the immunity of laying hens by increasing the serum interleukin-6, tumor necrosis factor α, and immunoglobulins (IgA and IgG) [58]. Essential oil of *Citrullus lanatus,* when used at up to 2 g/ kg of feed, resulted in improvement in the egg production and strength of the tibia bone [59]. Due to these reasons, we can employ feed additives as a potent and long-term substitute for antibiotics, thus increasing future productivity and poultry health.

There is also a concern that feed additives, especially phytogenic feed additives, show inconsistent results in the growth performance and pathogen inhibition due to the variability in the composition of bioactive compounds in plants [60]. The lack of standardization in the formulations and their overuse can damage the digestive system's efficiency [60].

Table 2. Antibiotic alternatives, their mode of action, effectiveness, cost consideration, and challenges in application.

Alternative	Description	Mechanism of action	Effectiveness	Cost consideration	Implementation Challenges	Sources
Bacteriophages	Viruses that target specific bacteria and replicate inside them.	Shows high effectiveness against specific strains and has minimal effect on the gut microbiota and performs effective killing of bacteria without disrupting the normal body bacteria balance. Helpful in reducing the *Salmonella, E. coli* and *Campylobacter*	Shows high effectiveness against specific strains and has minimal effect on the gut microbiota and performs effective killing of bacteria without disrupting the normal body bacteria balance. Helpful in reducing *Salmonella, E. coli* and *Campylobacter* Example: ST4, L13, and SG3 bacteriophages at10^8 PFU/kg in layers showed decreased mortality and bacterial reisolation from the organs	Moderate to high cost and varies and depends upon the target strain.	Highly specific to their bacterial hosts, which can limit their broad application across different bacterial strains. The bacterial resistance issue also resides.	[32, 61-63]
Antimicrobial peptides	Small molecules that range in mass from 1 to 5 kDa. They work by interacting with the target species' cell membranes.	Causes impairment of the bacterial membrane, inhibits the synthesis of nucleic acid, essential enzymes, functional proteins and enhances the immune response, acts as an anti-inflammatory agent	Broad-spectrum activity, effective against gram-positive and gram-negative bacteria, rapid action, low resistance development, enhanced immune response. Example: Antimicrobial peptide-A3 at 60 and 90 mg/kg diet in broilers had improved average daily feed intake (ADFI) and average daily gain (ADG)	High (high cost of synthesis and purification of AMPs)	Bacterial resistance issue. Utilization in feed, especially the stability aspect, large-scale production, and AMPs degradation in the gastrointestinal tract Preparation methods are costly.	[47, 64-69]
Feed additives	Products that enhance the quality of feed and food from animal origin also	Perform action by modulating the gut microbiota, reducing the colonization of pathogens and enhance nutrient absorption	Showed moderate effectiveness in reducing harmful bacteria. Also present anti-inflammatory and antioxidant activity. Improved growth	Low to moderate cost based on the ingredient	Stability and administration issues. Delivery to the target site due to degradation.	[70-73]

	enhance the animals' performance and health		efficiency/egg production, prevent disease, and improve feed utilization. Example: The usage of Garlic at 1% of the diet in broilers resulted in improved growth performance, carcass quality, nutrient digestibility, and lipid profile	purity and processing	. Variation in efficacy across different environments and high doses may alter gut microbiota negatively.	
Enzymes and enzyme-based products	Proteins that catalyze a chemical reaction but are not altered themselves	Breakdown antinutritional factors like NSPs, Phytates, etc.	Improved apparent metabolizable energy (AME), improved digestion and absorption of nutrients, particularly fat and protein, and decreased digesta viscosity. Example: The usage of α-amylase, β-glucanase at 400 g ton−1, and xylanase at 50g ton−1 in broilers diet showed improvement in the digestion and absorption of the nutrientswith reduction in the viscosity of digesta	Moderate cost based on the enzyme type, stability and dosage	Require optimal conditions, interaction with other feed components like vitamins, minerals, and other additives.	[74-77]
Prebiotics	Prebiotics are non-digestible food ingredients that stimulate the growth of beneficial bacteria in the gut	while prebiotics serve as food for probiotics, boosting their growth and activity	Improved health and production performance. Prebiotics in broilers diet, like Mannan oligosaccharides (MOS) at 0, 0.5, 1, and 1.5g/kg, showed increased weight of bursa and jejunal immunoglobulin M (IgM), and immunoglobulin G (IgG) content.	Low to moderate	Handling of prebiotics and proper dose standardization.	[78, 79]
Probiotics	Probiotics are microbials that can be described as	Probiotics compete with pathogens for obtaining nutrients and attach at the site	Improved feeding efficiency, gut health, immune response and performance. Effective against pathogens	Low to moderate based on the selection	Probiotics viability in feed and storage;	[80-82]

	living, beneficial microbial feed supplements	of the gut, thus reducing the colonization of harmful bacteria	like *Clostridium perfringens, Salmonella spp.* Example: Probiotics supplementation in the laying hen diet 0.5 g/kg *Clostridium butyricum,* showed improved average daily feed intake (AFDI), an increase in FCR, eggshell strength% in albumen and a decrease in reactive oxygen species (ROS) level in ileum and cecum and reduction in malondialdehyde (MDA) in the serum. Prebiotics in broilers diet, like Mannan oligosaccharides (MOS) at 0, 0.5, 1, and 1.5g/kg, showed increased weight of bursa and jejunal immunoglobulin M (IgM), and immunoglobulin G (IgG) content.	of strain and formulation	survival through the GIT. Difficulty in oral administration	
Nanoparticles	Tiny particles from 1-100 nm in size offer unique properties because of their smaller size	Disruption of the bacterial cell membrane generates reactive oxygen species (ROS), interferes with bacterial DNA and protein synthesis	Highly effective against multiple pathogens, including antibiotic-resistant bacteria. Having a role in enhancing immunity and gut function Example: Nanoparticles of zinc oxide in laying hens resulted in an improvement in FCR, hen day egg production, egg mass, Haugh units, egg shell thickness and egg shell percentage. Decrement in serum cholesterol, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, urea and somewhat creatinine	Having high production costs	Toxicity concerns, need careful dose optimization	[83-85]

3.4. Enzymes and Enzyme-based Products

Enzymes are proteins that can accelerate a specific chemical reaction. Enzymes in feed can be divided into two types: endogenous and exogenous depending on the substrate. Endogenous enzymes are produced by the animal body and play a role in the breakdown of basic feed components like fat, protein, and carbohydrates [48]. However, exogenous enzymes can be added externally in the feed that can remove the cell wall of raw material, degrade the non-starch polysaccharides (NSP), minimize the chyme velocity, boost the nutrient intake, reduce the antinutritive activity and in this way, enhance the animal growth performance [86]. Thus, the inclusion of enzymes in feed acts as growth promoters and decomposes large molecules into prebiotics [87]. The addition of β-mananase in the diet of broiler chicken hydrolyzed β-manans, reduced the intestinal content viscosity, enhanced the nutrient digestibility, and improved the environment of the intestine [88]. Results of a study suggested that the addition of *Bacillus*-DFM (direct fed microbials) in poultry diet, releases a variable set of enzymes and other antimicrobial compounds that result in performance enhancement by improving nutrient digestibility, lowering the intestinal viscosity, maintenance of beneficial gut microbiota, and promoting the intestinal integrity [89]. Addition of apple pulp up to 10% with multi-enzyme additive at 0.05% resulted in improved laying performance, blood parameters, and egg traits of hen without affecting other traits [90]. Supplementation of enzymes in diets with low energy resulted in up-regulated expression of nutrient transporters that enhanced the micronutrient absorption and growth performance of broiler chickens [87]. Because of their versatile and positive effects on poultry production, enzymes and enzyme-based products are the best alternatives to antibiotics, which also guarantee food safety.

Although enzymes can enhance the performance of chickens, they are temperature sensitive, and heating reduces their effectiveness during feed processing. The high cost also limits their practical applications on a large scale in comparison to traditional additives.

3.5. Prebiotics

There have been huge concerns related to the presence of antimicrobial residues in the environment, also in meat, primarily due to usage in animal husbandry, therefore the world is trying to explore alternatives to veterinary antibiotics. One such alternative is probiotics, intended to reduce or replace the antimicrobial usage [91]. Prebiotics are oligosaccharides carbohydrates, made up of 2-10 monosaccharides [92] that are utilized by the microorganisms in the intestine but are not digestible by the host animal, including mannan oligosaccharides, oligofructose, fructooligosaccharide, galactan, galactooligosaccharides, inulin, and fiber components [54].

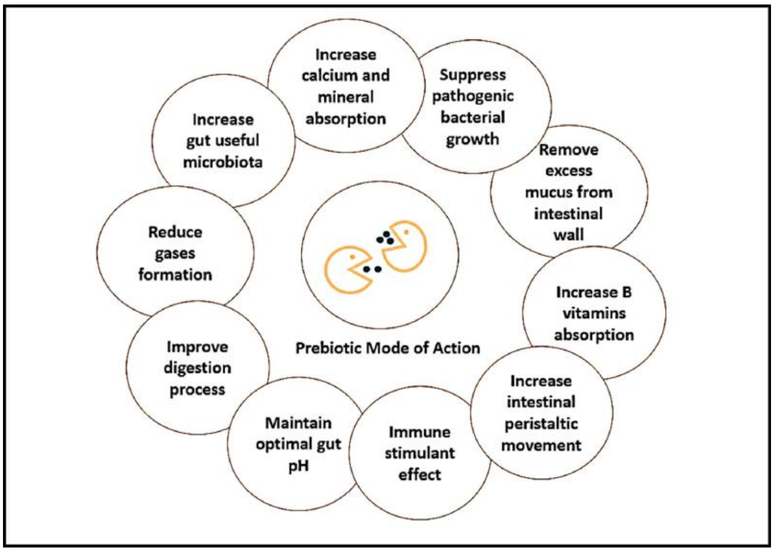

Figure 2. Prebiotics mode of action. Reproduced from Abd El-Hack et al. [48] under the Creative Commons BY-NC-ND 4.0 license.

It is considered that prebiotics and probiotics result in a change of the composition of the normal microflora of the intestine towards beneficial microflora from a potentially harmful composition and thus benefit the host [54, 93]. *Saccharomyces cerevisiae* supplementation in the feed improved the efficiency, feed digestibility, increased the animal performance, reduced the pathogenic bacteria in numbers, and improved animal health [94]. Mannan oligosaccharides supplementation in the poultry feed enhanced the growth performance, oxidative status of the bird, immunoglobulin content, improved serum biochemical profile and decreased the cecal salmonella colonies [79, 95].

3.6. Probiotics

Direct fed microbials or probiotics can be described as living, beneficial microbial feed supplements, such as bacteria (*Bifidobacteria, Bacilli, Lactobacilli*), fungi (*Aspergillus awamori and Aspergillus oryzea*) and yeast (*Saccharomyces*) that results in the microbial balance in the intestine and increase the intestinal health, immune response and thus improve poultry performance [54]. Probiotics impart many beneficial effects on performance, intestinal microbiota modulation, pathogens inhibition, improvement of intestinal integrity, immunomodulation, and improvement of microbiological and sensory characteristics of poultry meat [48]. Probiotics are an ideal alternative to antibiotics, but they struggle with strain-specific efficacy and need accurate selection to match the target pathogens. Their persistence also reduces during competition with the native microbiota in the GIT [96]. Due to no standardization in the dosage, prebiotics can also promote harmful bacteria and precise attention is required during their formulation [96] But probiotics further need to be addressed.

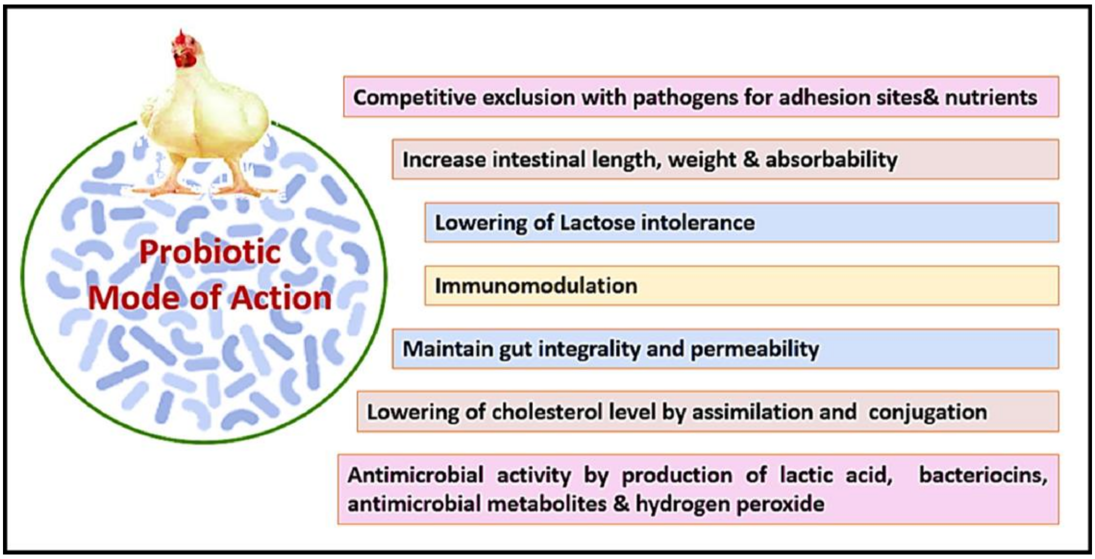

Figure 3. Probiotics mode of action. Reproduced from Abd El-Hack et al. [48] under the Creative Commons BY-NC-ND 4.0 license.

3.6.1. Probiotics Bacteria

Probiotics bacteria can produce and release antimicrobial molecules like organic acid compounds, diacetyl, hydrogen peroxide, and peptides, vitamins, amino acids, teichoic acids, peptidoglycans that have the potential to work selectively against various microbial strains that are found in the gut. Bacterial AMPs are also called bacteriocins, a diverse class of ribosomal synthesized peptides that have a role in the direct elimination of bacteria or cessation of their growth in the lumen [97]. According to a study by Abd el-Moneim et al. [98] with *in ovo* inoculation of inoculation of *Bifidobacterium Bifidum, Bifidobacterium animalis, , Bifidobacterium longum* and *Bifidobacterium infantis*, resulted in improved ileal bacterial composition with increased colonization of the intestines with bacterial species such as *Lactobacillus* and *Bifidobacterium* and decreased the overall Coliform bacteria. The inclusion of *Bacillus Toyonesis* and *Bacillus bafidium* in the diet of quail, hindered the growth of fungi, *E. coli* and coliforms in the cecum [99]. Different Bacillus species are used by the poultry industry that are performing beneficial effects as shown in (Table 3) [100].

Table 3. Usage of probiotic bacteria in the poultry industry.

Probiotics	Biological Performance	References
Lactiplantibacillus plantrum LTC-113	Strengthened resistance against *Salmonella* typhimurium and maintained the integrity of the intestinal epithelial barrier	[101, 102]
Lactobacillus johnsonii	Reduced the symptoms of *Clostridium perfringens* and salmonella sofia infections	[103, 104]
Bacillus subtilis C-3102	Reduced the level of *Salmonella enterica* serovars (enteritidis LM-7)	[105, 106]
Pediococcus acidilactici	Number of *Salmonella enterica* serovars (*Gallinarum*) got reduced	[107, 108]
Lactobacillus acidophilus	Increased the immune response, reduced mortality and increased the body weight of hens challenged with Escherichia coli 0157	[109, 110]
Bacillus subtilis	Increased the level of advantageous bacteria (*Lactobacillus, Bifidobacterium, and Enterococcus), increased* the level of *Blautia, Faecalibacterium*, and *Romoutsia,* resulted in the increment of surface area availability for absorption in the duodenum and ileum with an increased ratio of villus height to crypt depth	[111, 112]
Bacillus subtilis PB-6	Enhanced plasma calcium and phosphorous concentrations, improved bone mass and meat quality with productivity and welfare	[113, 114]
Bacillus subtilis DSM29784	Boost the quantity of *Butyricicoccus* and *Faecalibacterium* in the gut, enhances the tight junction complex, weight and overall health in broilers	[115, 116]

3.6.2. Fungi as Probiotics

Aspergillus spp. is the most predominant in the intestinal tract and cecum of poultry birds, indicating viability and importance as a probiotic [117]. Different species of fungi like *Aspergillus awamori*, *A. niger*, and *A. oryza* have the potential to maintain the intestinal microflora balance and enhance the immune response [100]. A study suggests that the addition of 0.2% *Aspergillus* meal in the diet of chicken may have effects in reducing the *Salmonella spp,* levels and increase the food safety of meat [118]. Addition of Aspergillus awamori in the diet of growing rabbits at 100-150 mg/kg diet results in enhanced growth, intestinal health, nutrient digestibility, immune status and antioxidative responses [119]. Supplementation of *Aspergillus niger* in the diet of egg-laying hen (Hy-Line W-36) at a rate of 220 g/kg feed resulted in a significant increase in egg production, Haugh unit and egg quality. However, this lowers the microbial load of pathogenic microbiota i.e., Clostridium perfringens, Salmonella spp., and *Escherichia coli*, in the caeca [117]. According to a study by Zahirian et al. [120] that addition of *Aspergillus oryza* in the diet of broilers resulted in an increment of weight gain, reduction in the proportion of abdominal fat, aspartate aminotransferase and alanine aminotransferase levels in the serum, and antibody titters against Avian influenza and Newcastle disease. Due to these benefits fungi as a probiotic may be a better alternative to antibiotics in poultry.

3.6.3. Yeast Probiotics

Yeasts are eukaryotic unicellular fungi that are ubiquitous in nature and found in the environment, including soil and the skin of animals and humans [121]. Their cell wall components like mannans (40%), chitin (2%), and glucans (60%), as well as the result of yeast hydrolysis like nucleotides, vitamins, and other compounds, have been shown to improve poultry production performance, gastrointestinal health, and immune system [122]. It was observed in a study that *P. guilliermondii* exhibited the greatest resistance to gastric juice, moderate enzymatic activity, antimicrobial activity, and increased adhesion to cells [123]. Similarly, the supplementation of yeast probiotics increases the chicken's resistance to enteric pathogens like *Salmonella, Campylobacter jejuni, C. perfringens*, or *E. coli*. Administration of 3g/ ton of feed of *S. cereveciae* in broilers exhibited lower blood cholesterol concentrations in a study by Pang et al., [124]. Therefore, yeast probiotics emerge as an excellent alternative to antibiotics.

The manufacturing of yeast probiotics is quite complicated and needs advanced bioprocessing techniques like high-cell-density cultivation, which limits their wide applicability. The shelf life is also compromised in case of the storage of oxygen-sensitive strains [125].

4. Nanoparticles (NPs) and Nanotechnology Applications

Nanotechnology is a promising and innovative technology with wide biomedical utilization and potential implementations in the poultry industry [126]. Nanoparticles (NPs) generally in between 1 and 100 nm also called nanobiotics have antimicrobial properties and are among the latest alternatives to deal with multi-drug-resistant pathogens [127]. NPs are classified into four categories like inorganic, organic, carbon base and hybrid. Inorganic groups include metal, metal oxide nanoparticles, and quantum dots. However, organic nanomaterials consist of biocompatible organic components such as lipid-based nanoparticles, polymeric nanoparticles, liposomes and because of these they are widely used for drug delivery, as antimicrobials and in the regeneration of tissues. Furthermore, carbon-based nanomaterials include nanofibers, nanodots, carbon onions, carbon rings, etc. Inorganic nanoparticles consist of inorganic oxides of Si, Ag, Au, Zn, Mg, Mn, Cu, Se, Al, and Ti and show differences in shape, size, solubility, and stability. In addition to this, their potency is also affected by the pH, temperature, concentration of reducing agent, and reduction time [128]. In comparison to traditional nanoparticles, iron oxide nanoparticles (IO-NPs) and zinc oxide nanoparticles (ZnO-NPs) exhibit stronger bactericidal effects due to the reduced ion particle sizes and high surface energies [129]. An *in-vitro* study with ZnO-NPs usage revealed its potential as an antibacterial agent in poultry production in reducing the load of foodborne pathogens in the gut of poultry and found *S. aureus* as the most susceptible bacteria [127]. ZnO-NPs as a feed supplement are helpful in reducing footpad dermatitis that is induced by multidrug-resistant *Staphylococcus aureus* (MRSA) in broiler birds [126]. Usage of Fe_3O_4-NPs pretreatment restricted the invasion of *S. Enteritidis* in the liver of chicken and significantly increased the reactive oxygen species (ROS) in chickens [130]. In another study, Ali and Bakheet [131] concluded that *in ovo* inoculation of chitosan-NPs reduced the *E. coli* count without harming the hatchability and showed the highest inhibitory effect on the biofilms forming E.coli strains. Antibacterial mechanisms of some NPs are still uncertain, and more studies are needed to determine their future applications. Therefore, potential NPs usage as antimicrobial agents in the poultry sector needs further investigation.

There are safety concerns in the application of nanotechnology as inorganic NPS (Si, Ag, Au, Zn, Mg, etc.) can accumulate in the poultry tissues. The cost of production and possible degradation in the GIT remain economically unviable for large-scale use. More research is needed to standardize their dosage and temperature stability during the pelleting of feed [132].

4.1. NPs-Mechanism of Action

Nanoparticles exhibit their antimicrobial properties by utilizing different modes of action depending on the composition and bacterial interaction. NPs can perform their action by disrupting the bacterial cell membrane integrity. Inorganic nanoparticles (AgNPs, CuNPs, IO-NPs, ZnO-NPs) can generate reactive oxygen species (ROS) that result in oxidative damage to bacterial membranes and weaken their structure [133]. Metal ions interact with the membrane protein, resulting in an increase in the permeability of the membrane, causing the cellular contents to leak out and ultimately the lysis of the cell [134]. Quantum dots also create ROS under UV/Visible light and causing oxidation of DNA and protein damage [135]. Metal and metal oxide nanoparticles also present a unique mechanism by inhibiting the bacterial communication (quorum sensing) involved in behavior like biofilm formation and virulence, by the degradation of acyl-homoserine lactones (AHLs), a signaling molecule [136, 137]. Lipid-polymeric NPs have the ability to encapsulate the bioactive compounds, antimicrobial drug and then release them on the target site to reduce the load of bacteria with enhanced efficacy [138, 139]. Moreover, carbon-based nanoparticles penetrate the bacterial cell wall mechanically and causing physical damage and the loss of integrity and also by creating oxidation of vital cellular structures [140]. Furthermore, carbon-based nanoparticles also prevent the formation of biofilm by adsorption of extracellular polymeric substances(EPS) via electrostatic and hydrophobic interactions, thus weakening bacterial adhesion [141]. In this way, nanoparticles exhibit their potential to work effectively as antimicrobials.

5. One Heath Approach to Antimicrobial Resistance

One health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. Bacteriophages have species-specific activities against pathogens and reduce zoonotic transmission of multidrug-resistant pathogens like *Salmonella* and methicillin-resistant *Staphylococcus aureus* (MRSA)[142, 143]. Their natural presence in environment supports ecological balance and aligns with One Health approach [143]. Similarly, AMPs offer biodegradable solutions to overcome resistance issues through nonspecific membrane disruption. They reduce antibiotic residues in meat products, thereby decreasing human exposure to resistant bacteria through the food chain [144]. AMPs also degrade rapidly in the ecosystem and reduce contamination issues linked to traditional antibiotics [145]. Moreover, feed additives such as botanical nutraceuticals contribute to the one health approach by enhancing poultry health and reducing the need for antibiotics. Botanical products like fenugreek seeds and ginger roots improve digestive enzyme activity and restore microbiota balance, which minimizes the risk of antimicrobial resistance. These additives also support environmental sustainability with no chemical residues [49]. Enzymes such as phytase and xylanase improve nutrient digestibility in poultry feed, reducing phosphorus excretion and environmental pollution [146]. Additionally, enzyme-based nanomotors are promising bactericidal agents against pathogens like *Escherichia coli* and offer targeted antimicrobial effects without contribution of microbial resistance [147]. Probiotics and prebiotics enhance poultry gut microbiota and reduce antibiotic use in poultry. This directly impacts human health by lowering the antibiotic-resistant enteric pathogens in food animals, which are estimated to cause 10 million annual human deaths by 2050 if unaddressed [148, 149]. Fungal probiotics, such as those derived from *Arthrospira platensis*, modulate gut microbiota and provide immunomodulatory benefits. They fit within the One Health framework and improve poultry health through sustainable means. They also enhance feed conversion efficiency, reduce resource consumption and mitigate environmental stressors associated with intensive poultry farming [150]. Yeast probiotics improve gut health by inhibiting bacterial colonization and enhancing immune responses. Their ability to modulate intestinal microbiota aligns with One Health principles by reducing zoonotic transmission risks of resistant pathogens like *Salmonella* [151]. Besides that, nanotechnology offers innovative solutions for AMR mitigation through encapsulated probiotics, antioxidants and enzyme-based nanomotors. Nanoencapsulation improves probiotic stability in harsh gut environments, enhancing their efficacy against pathogens like *Campylobacter jejuni*. This approach interrupts pathogen transmission cycles through the food chain, protecting human health while promoting sustainable agricultural practices [152].

6. Future Research Direction

Exploration of sustainable alternatives to antibiotics in poultry farming is valuable to enhance animal health and reduce antimicrobial resistance. Bacteriophages have gained popularity as antibacterial agents against Salmonella and E. coli in poultry pathogens, and future studies should focus on genetic modification to enhance stability and effectiveness. Moreover, the creation of a broad-spectrum phage cocktail should be considered. There is a need to establish a regulatory framework to boost its commercialization [63]. Similarly, AMPs have been investigated as a natural alternative with broad-spectrum activity. Future research should consider the synthetic AMPs with greater stability by utilizing better encapsulation techniques with stabilizers to protect them from degradation. In the feed additives, research should aim at elucidating their exact mechanisms of action and the development of standardized formulations with more exploration in synergistic interactions with other feed additives [153]. However, there is a need for studies to explore new enzymes, with increased efficiency through the usage of genetic engineering and to investigate how they interact in the gut with microbiota in a more precise manner. Strategies to reduce the cost of production of enzymes and enzyme-based products should be considered. Probiotics and prebiotics have shown their positive role in modulating the gut microbiota, and in future, they would be more beneficial in poultry farming by having a major focus on identifying strains with specific health benefits, and the development of optimized formulations with increased efficacy. Large-scale field trials are also needed to confirm their effectiveness in commercial settings [2]. Nanoparticles with antimicrobial and delivery potential should be studied more to assess their safety and appropriate levels to prevent toxicity.

7. Conclusion

In the poultry industry, bacterial infections are one of the major causes of morbidity and mortality throughout the world. Traditionally, antibiotics were used to treat bacterial infection and as a growth promoter for optimum performance, but this results in the antibiotic resistance in bacteria and many strains of bacteria became resistant to antibiotics even at very high doses. Therefore, to deal with this global antimicrobial resistance (AMR) issue and to maintain the health of poultry birds, many sustainable strategies are under consideration with limited or no usage of antibiotics which foster the health and immune status of birds. Feed additives, prebiotics and probiotics are gaining popularity in the poultry industry due to greater performance and easy management. However, bacteriophage, bacteriophage, phytobiotic/medicinal plants extracts, and nanoparticle-based alternatives are considered as emerging alternatives as they showed great inhibitory effects against microorganisms and are helpful against multi-drug-resistant pathogens. There is also huge concern related to finding potential alternatives to antibiotics as there are many alternatives. Despite the benefits, all the alternative approaches also have some limitations in their potential as antimicrobial, and safety. However, the poultry industry is still lagging and has a scarcity of innovative investigations and therefore, further research should be done to slow down the development of multidrug- resistant strains of bacteria. According to research, natural alternatives to antibiotics as growth promoters are recommended in the poultry industry as they are safe and healthy and impart positive effects on the immune system. Essential oils are volatile, so they should be used by having proper encapsulation, which enhances bioactivity and stability. These natural alternatives also result in productivity enhancement, enhanced digestion, improved nutrient availability, absorptivity and reduced resistance to antibiotics with the production of safe meat and eggs, but still there is a need to identify and characterize new natural alternatives to strengthen this industry.

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