

Probiotics As Possible Antibiotic Substitutes in Animal Production and Their Implications for Public Health

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ABSTRACT

The likelihood of the formation and dissemination of antimicrobial-resistant microbes has increased due to the extensive use of antimicrobials to prevent, treat infections and as growth promotion purposes. The review aims to highlight the possible risks to public health as well as probiotic usage as a substitute for antibiotics in animal production. Antibiotic use has significantly increased recently because of disease prevention and control efforts. The main cause of drug-resistant diseases in humans, animals, and plants is antibiotic abuse and overuse. Given that, the same types of antibiotics are used worldwide in human being and animals, this result in development and spread of antibiotic resistance that is risk to the health of people and animals. However, the usage of these antibiotics as growth stimulants by animal producers elsewhere except European could lead to growth of multidrug-resistance to antibiotics. Multidrug antibiotic resistance, however, may arise from the usage of these compounds as growth boosters. Probiotics have attracted great attention due to their beneficial impacts on livestock and people's systems of immunity and gastrointestinal microbes. The exploitation of live microbes as probiotics has gained popularity recently as a substitute to antibiotics that is for promoting growth, medicinal, and preventative purposes. Probiotic bacteria improve an animal's capacity to digest food and absorb essential nutrients, which helps the animal grow, fight off diseases, and produce meat, milk, or eggs. A perfect probiotic should have a broad range of potential attributes, including the ability to survive in the gastrointestinal or colonize it, be safe as well as non-pathogenic, useful to the host animal, have high feasibility, be steady in storing and in the field, be suitable for industrial production, and have acceptable risks to the public's health

Keywords: Animal, Production, Antibiotics, Antimicrobial Resistance, Probiotics

Introduction

The need for animal production to supply the world's food demand is growing and antibiotics have long been utilized by many animal producers both as growth enhancers and as treatments for bacterial infectious illnesses [1]. The most successful therapeutic drugs in medicine are antibiotics [2]. However, the application of antibiotics as agents of growth in livestock production, as well as in agriculture in general, has been forbidden in many nations worldwide because of increased number of antibiotics resisting bacteria. In 2006, "the European Union" has prohibited the practice of antibiotic as growth promoters in animals [3].

The usage of antibiotics in poultry sector as well as in the livestock production is favorable and has economic value,

because it has generally improved poultry performance. Antibiotic residue, which accelerates development of antibiotics resistant bacteria, which could be found in animal products. Meat and eggs contain antibiotic residue, which accelerates the development of antibiotics resistant bacteria [4]. Bacteria that are resistant to antibiotics linked to farm animals pose a serious threat to public health since they can be dangerous to humans, are easily spread via food chains, and are released into the environment through waste from livestock [5]. According to, the usage of antimicrobials in animal agriculture also increases the likelihood that pathogenic and nonpathogenic organisms with antibiotic resistance may spread into the environment and eventually make their way up the food chain to mankind, posing a serious risk to their health [6].

Antibiotic resistance becomes significant global public health concern [7]. The misuse of antibiotics in cattle, improper patient use, and abusive prescription practices have all contributed to

this predicament. There are two main causes for the livestock that receives antibiotics without restriction. The first and most evident one is livestock diseases prevention related to animal overcrowding and intensive farming [8]. The second one is the discovery of antibiotics' ability to act as growth booster [9].

Antibiotics have been the most extensively used feed supplement additions to improve the conversion of feed, rates of growth, and chicken well-being, improving both profitability and efficiency in industrial poultry sector [10]. However, Over time, animal-derived resistance to antibiotics bacterial strains transmission via animal contact or the food supply chain [8,11,12]. Two more potential issues with food safety are a rise in allergic reactions and human resistance to antibiotics linked to antibiotic treatment in food animals [13]. Antibiotic resistance can result from both misuse and under-dosing of antibiotics at sub-therapeutic dosages, and these drugs can be found in chicken eggs [14]. Given the likely hazards to health of peoples, this raises serious concerns worldwide [15].

Antibiotics in animal product intended for consumption causes severe adverse health effects such allergic reaction, damaging tissue, disturbance of gastrointestinal track and disorders of neuron system [5]. Using antibiotics in poultry feed for long times without changing may result in accumulation of antibiotics metabolic byproduct ("residue") in their products as well as in environment causes disturbance of normal flora balance and reduce useful gut flora [16,17]. Food safety is a global concern these days, especially in light of the impact of antibiotic use on poultry pathogenicity [18]. Probiotics are examples of natural feed additives that serve as substitute to antibiotics for better chicken performance. Probiotics are now frequently utilized in fisheries as well as poultry [19].

Live bacteria known as probiotics give host animals health benefits. However, the ban of usage of antibiotics in the poultry industries causes rise in occurrence of infections caused by *Campylobacter jejuni* or *Clostridium perfringens* [20]. Hence, there is significant concern and a certain requirement to substitute antibiotics to control disease control and to promote growth. It has been suggested to substitute antibiotics in poultry agriculture, such as "prebiotics" and "probiotics" [21]. Providing probiotics in feed has potential profitable applications to improve chicken performance and quality of eggshell during the initial laying period [22]. The use of probiotic has improved egg production, weight of shell as well as thickness, and reduced yolk cholesterol ratio [23]. Thus, the aim of this review was to draw attention to the potential risks to public health and the usage of probiotics in animal production as substitute to antibiotics.

Probiotics-General Concepts and Definitions

Probiotics become potential substitutes to antibiotics to improve production efficiency [24]. Probiotics are well defined as "live microbes introduced into the gastrointestinal tract (GIT) with feed or water, to promote growth and health via improving microbial balance." They can also be defined as "live microorganisms that are ingested to provide health benefits" while others described them as "live microorganisms, which when consumed in adequate amounts as a part of food, confer a health benefit on the host" [25].

The probiotics can be well-defined as a 'live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance' this being clear improvement above earlier research by focusing on the "live cell" aspect of probiotics [26,27]. In current years, certain of these living probiotic organisms have begun to be defined by the broader name "Eubiotics," which is connected to the Greek word "Eubiosis," denoting to an optimum microbial balance in the gastrointestinal tract [28].

While probiotics have been used for a variety of purposes to enhance and preserve human health, probiotic addition in feed (often called "Direct-Fed Microbials") has been the principal application of probiotics in food animal agriculture [29]. Probiotics are utilized in agriculture to reduce foodborne pathogens, promote growth, and improve feed efficiency [30]. Probiotic use has historically been seen as substitute to antibiotics in the poultry production industries, as they have been shown to improve growth rates, limit animal diseases, promote a "healthy" intestinal micro-biota, and hinder the development of foodborne pathogens [31-33].

Probiotics can lower nutritional needs by improving the body's ability to use nitrogen and phosphorus, but some have also shown promising immune-modulatory effects [34]. Modulating the immune response may provide protection against infections and aid in digestion and nutrient utilization [35]. Enhancing poultry's innate and acquired immunity can help achieve these advantages [12].

Drug Resistance Development Associated with Use of Antibiotics in Animal Production

Farmers are supplementing fish, ruminants, and poultry diets with probiotics. Probiotics are mostly composed of "gram-positive bacteria," though they can also contain gram-negative, yeast as well as fungi. The probiotics are most frequently used for animals. When an antibiotic closely related to one used in human medicine is administered to animals, a phenomenon known as cross-resistance occurs, leading to the development of resistance in disease-causing bacteria against the human treatment [36]. The world's veterinary and medical specialists agree that giving antibiotics linked to medications of vital relevance in human medicine to groups of seemingly healthy animals for "preventive" purposes is both risky and unjustified. New strains of multi-resistant bacteria that infect humans are thought to have emerged because of the usage of antibiotics in farm animals, which are crucial to human health [6]. The ESBL and/or AmpC enzymes produced by novel strains of pathogenic bacteria, such as 'Salmonella', 'Campylobacter', and 'E. Coli', render almost all beta-lactam medicines ineffective. These include penicillins and the vitally important 3rd and 4th generation 'cephalosporins' [37].

In the last ten years, the usage of antibiotics has risen in some of the most intensive industries, such as the raising of pigs and chickens [38]. An animal can be given antibiotics for a significant amount of its life. The occurrence of bacteria resistant to antibiotics, which makes treating bacterial illnesses more challenging or perhaps impossible, is one of the greatest risks of modern medicine [39]. Antibiotic overuse in intensively farmed animals is now thought to have contributed significantly to this worldwide issue, even though it is acknowledged that human

use of antibiotics is the primary cause of antibiotic resistance [40]. Antibiotic-resistant microorganisms like *Salmonella*, *Campylobacter*, and *Escherichia coli* (*E. coli*) have emerged as because of the widespread utilization of antimicrobial agents in intensive farming to treat and prevent widespread production infections. These bacteria are capable of infecting humans through the environment or food [11].

When these bacteria infect humans, treating their illnesses becomes more challenging, and the resistant pathogens proliferate by spreading amongst individuals. Furthermore, bacteria that are resistant are capable of transmitting their genes to other bacteria that may cause illness in humans. Overuse of antibiotics in farm animals has increased prevalence of resistant bacterial infections and reduced the safety of some foods. The antibiotics used in farming are the same or very similar to those used as first-line treatments in human medicine, which has led to a rapid rise in antibiotic resistance in food borne illness bacteria such as *Salmonella* and *Campylobacter*. Although meat consumption is decreasing in developed countries, especially in Europe, in less developed countries it is very high, so meat represents the most important source of antibiotics. Primarily, the main source of antibiotics in food is abusive use (overdosing, non-compliance with the withdrawal period) and the use of antibiotic-contaminated water, or inappropriate disposal of animal dung. If antibiotics used for treatment of animal diseases, it is better to avoid consumption of antibiotics residues in animal products by the human and concerns should be given to withdrawal period before sale of animal products. This has led to the emergence of dangerous new forms of antibiotic resistance that impact people [41]. Over the past ten years, strains of *Salmonella* and *E. coli* that can cause serious infections including septicemia (blood poisoning) and extended spectrum beta-lactamase (ESBL) have proliferated globally due to the presence of genes for these types of resistance) [42].

The Usage of Probiotics in Animal Production

The increasing prevalence of antimicrobial-resistant illnesses worldwide has highlighted the necessity for the development of efficient antibiotic substitutes [43]. This holds particular significance for the livestock production sector, which is believed to bear a disproportionate share of the blame for the antimicrobial resistance (AMR) challenge. The sector supplies about two-thirds of the world's antibiotic supply, and any improvement in animal function should be investigated further. Probiotic treatments for cattle are often marketed as the ideal substitute for antibiotics in agriculture, with the potential to reduce antibiotic use and its associated risks. In current livestock production, therapeutic antibiotics have been introduced to animal feeds to both prevention of infections and improving growing performance; nonetheless, microorganisms especially bacteria have evolved a number of special defense mechanisms against these substances, and antibiotic-resistant bacteria (ARB) have surfaced in the animal micro-biome [44].

ARB is commonly transferred bilaterally by airborne, waterborne, direct body contact, and, perhaps most critically, the food chain between cattle farms and human settlements [45]. A few examples of how this transmission poses a serious hazard to health of people are the undetectable carriage of ARB outside of animal facilities, the transfer of plasmids from ARB in the

microbiota of food-grade animals to common human pathogens, and the presence of residues of antibiotics in meat [46,47]. These concerns have led to new studies investigating antibiotic replacement therapies [48]. There is strong confirmation that recommend providing probiotic supplement improves the immunity system [49]. The role of probiotics in different species of animals have been shown as below in Table 1. Probiotics have been shown to have beneficial impacts on both the immune systems of their hosts and the bacteria that reside in the gastrointestinal tract (GIT).

Table 1: Role of probiotics in poultry and ruminant

Species of animals	Role of Probiotics	References
Poultry	Growth performance Improvement	[50]
	Boosting meat and egg production	[51]
	Reduction of infection and diseases	[52]
	Induction of beneficial immune responses	[50]
	minimize the egg yolk cholesterol level	[53]
Ruminants	Treatment of acidosis and calf scours	[54]
	Increase in dry matter intake	[55]
	Improve body weight	[56]
	Reduce infection and diarrhea	[57]
	Quality and quantity of milk improvement	[58]
	enhancing the immune system	[57]
	promote the viability of rumen microorganisms	[59]

There is a rising concern worldwide about the presence of residues of antibiotic in poultry products, and further research is clearly needed to find the best antibiotic replacement for chicken diets. Without a doubt, probiotic bacteria are among the finest ways to treat infections in chickens early on, prevent them from occurring, and aid in their recovery after antibiotic medication [60]. Antibiotics have been essential to maximizing poultry production [9]. Consequently, antibiotics helps as growth promoters in broilers or enhance egg laying in egg production [61,62]. This productivity boost has been connected to the useful effects of antibiotics on diseases infection control in poultry industry [63]. However, unintended consequences have emerged, including impacting variations in the spreading and selection of antimicrobial resistance genes in normal flora bacteria and certain data indicates a correlation between antibiotic use in chickens and antimicrobial resistance [64].

Broiler chicken growth rates can be increased by probiotics [50]. Salmonellosis and other gastrointestinal illnesses can be avoided with probiotics [65]. It is possible to enhance the growth rate, immunity system, and anti-oxidant content of grill chickens given a diet containing around 1% of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium*, which includes more than 5 10⁹ CFU/g [51]. Probiotics have the ability to alter the

histology of intestine mucosa in fowl. The mucosa of intestine structure influences the growth of poultry and is essential for both digesting and absorptive intestinal function [66].

Potential Public health hazards related with antibiotic use in animals

Several research works have conclusively revealed that the usage of antibiotics in farm-animals for growth promotion, preventative, or therapeutic purposes results in the emergence of bacteria resistant to antibiotics in the environment, which eventually deteriorates the therapeutic opportunities available in human medicine. For instance, the usage of antibiotics on animals produced for food, such as chickens, resulted in the spread of antibiotic resisting bacteria to people from animals through the consumption of animal products and can also disseminate resistance genetic makeup(genes) to the human gut's non-pathogenic commensal bacteria [67,68]. When antibiotics are used on food animals, microorganisms that are resistant to the drugs are chosen for; these bacteria can then infect humans through food. These resistant variations, together with species that are naturally resistant, take over and proliferate within the host-animal population.

Overuse of antibiotics increases the likelihood of resistant organisms spreading from infections to normal flora bacteria in population of animals exposed to it. However, there is a striking disparity: in treated individuals, certain germs rapidly develop resistance, while others remain susceptible. In this way, antibiotic resistance is elucidated as a microbiological phenomenon, with potential therapeutic implications contingent upon pharmacokinetic and pharmaco-dynamic factors as they relate to specific groups of antibiotics. Clinical resistance may precede notable low-level resistance, which is defined as decreased antibiotic potency within the clinically susceptible range. As a last resort for cautious therapy in both veterinary medicine and human medicine, these examinations have been recalled, and they have always been significant in the sensible antimicrobial therapy terminology [69].

For animals that are raised for food, probiotics are a viable and beneficial substitute for artificial growth stimulants [70]. These are well renowned for improving GIT health. By generating certain antimicrobial compounds, they shield the gut from harmful bacteria and lessen the generation of toxins. They also improve digestion by inducing the formation of digestive enzymes. By stimulating Th1 and Th2 immunological components, probiotics enhance mucus production, improve intestinal motility, and modify the host's innate immunity. Through the action of bile salt hydrolase, probiotics lower blood cholesterol levels and promote cross-feeding between different strains of bacteria of the gastrointestinal ecology [71]. It is essential to assess the well-being of used probiotic strains since they have the potential to induce harmful side effects, including the transfer of resistance to antibiotics and pathogenicity factors, hemolytic potential, and the generation of hazardous biochemical compounds [72].

Conclusions

Probiotic therapy is becoming a more and more common substitute for antibiotics in veterinary medicine worldwide, for growth promotion, prevention and therapeutic purposes.

Antibiotics used in food animals as a means of disease prevention or treatment. Antibiotics are one type of additive that promotes growth however, has negative impacts on animal and human health, including raising the level of antimicrobial resistance. Antibiotics use for therapeutic purpose is essential. However, the antibiotics residues in animal products by the human leads the development of antibiotic resistance and the emergence of resistant bacteria to antibiotics poses a serious worry to medical, making treatment of bacterial diseases increasingly challenging or perhaps unfeasible. Human pathogens that are resistant to antibiotics present a significant problem to human medicine. Probiotics are one such alternative that might be a safer option. Probiotics are also employed therapeutically and as prophylactics in both people and farm animals. Furthermore, probiotics have a helpful outcome on the immune system, especially under stressful situations, boost milk production and growth performance, improve nutritional digestion, and shield farm animals from certain infections. A higher development rate, better-feed conversion, immune system stimulation, and a decrease in zoonotic pathogen shedding are among the other goals. Because there is a growing demand for meat production, farmers are using chemicals to improve growth performance. To assess the safety of these additions and the impact of probiotics on farm animal performance, more research is required. Potential qualities of the perfect probiotic include being non-toxic and non-pathogenic, being advantageous to the host animal, having high viability, being stable in storage and in the field, being able to survive in the gut or colonize it, and being suitable to industrial production.

Conflict of Interest: No to declare

References

1. Beyene T. Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. *J. Vet. Sci. Technol.* 2015. 1-7.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect. Dis.* 2013. 1057-1098.
3. Millet S, Maertens L. The European ban on antibiotic growth promoters in animal feed: From challenges to opportunities. *Vet. J.* 2011. 187: 143-144.
4. Arsène MMJ, Davares AKL, Viktorovna PI, Andreevna SL, Sarra S, et al. The public health issue of antibiotic residues in food and feed: Causes, consequences, and potential solutions. *Vet. world* 2022. 15: 662.
5. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. 2018. 23: 4.
6. Serwecińska L. Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health. *Water Switzerland.* 2020. 12: 3313.
7. Ferri M, Ranucci E, Romagnoli P, Giaccone V. Antimicrobial resistance: A global emerging threat to public health systems. *Crit. Rev. Food Sci. Nutr.* 2017. 57: 2857-2876.
8. Marshall BM, Levy SB. Food animals and antimicrobials: Impacts on human health. *Clin. Microbiol. Rev.* 2011. 24: 718-733.

9. Dibner JJ, Richards JD. Antibiotic growth promoters in agriculture: History and mode of action. *Poult. Sci.* 2005. 84: 634-643.
10. Gadde U, Kim WH, Oh ST, Lillehoj HS. Alternatives to antibiotics for maximizing growth performance and feed efficiency in poultry: A review. *Anim. Heal. Res. Rev.* 2017. 18: 26-45.
11. Economou V, Gousia P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. *Infect. Drug Resist.* 2015. 8: 49-61.
12. Swaggerty CL, Callaway TR, Kogut MH, Piva A, Grilli E. Modulation of the immune response to improve health and reduce foodborne pathogens in poultry. *Microorganisms.* 2019. 7: 65.
13. Lhermie G, Gröhn YT, Raboisson D. Addressing Antimicrobial Resistance: An Overview of Priority Actions to Prevent Suboptimal Antimicrobial Use in Food-Animal Production. *Front. Microbiol.* 2017. 7: 2114.
14. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, et al. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *Lancet Infect. Dis.* 2014. 14: 742-750.
15. Donoghue DJ. Antibiotic residues in poultry tissues and eggs: Human health concerns? *Poult. Sci.* 2003. 82: 618-621.
16. Ballard DP, Peterson EA, Nadler JL, Khardori NM. Antibiotic use in animal feed and its impact on antibiotic resistance in human pathogens. *Food Microbiol. Hum. Heal. Dis.* 2016. 13: 137-155.
17. Muhammad J, Khan S, Su JQ, Hesham AE-L, Ditta A, et al. Antibiotics in poultry manure and their associated health issues: a systematic review. *J. Soils Sediments.* 2020. 20: 486-497.
18. Koluman A, Dikici A. Antimicrobial resistance of emerging foodborne pathogens: Status quo and global trends. *Crit. Rev. Microbiol.* 2013. 39, 57-69.
19. Hasim H, Baidi N, Syamsuddin S, Tuiyo R. Administration of Probiotic sanolife Mic-S on Biological Performance of Vanamei Shrimp (*Litopenaeus vannamei*) PL 10. *Tech. Rom. J. Appl. Sci. Technol.* 2021. 3: 42-57.
20. Alfredson DA, Korolik V. Antibiotic resistance and resistance mechanisms in *Campylobacter jejuni* and *Campylobacter coli*. *FEMS Microbiol. Lett.* 2007. 277: 123-132.
21. Gaggia F, Mattarelli P, Biavati B. Probiotics and prebiotics in animal feeding for safe food production. *Int. J. Food Microbiol.* 2010. 141: 15-28.
22. Mikulski D, Jankowski J, Naczemski J, Mikulska M, Demey V. Effects of dietary probiotic (*Pediococcus acidilactici*) supplementation on performance, nutrient digestibility, egg traits, egg yolk cholesterol, and fatty acid profile in laying hens. *Poult. Sci.* 2012. 91: 2691-2700.
23. Lallemand. WorldPoultry Supporting egg quality through feed solutions. *World Poult.* 2016. 32: 35-37.
24. Lee K, Lillehoj HS, Siragusa GR. Direct-fed microbials and their impact on the intestinal microflora and immune system of chickens. *J. Poult. Sci.* 2010. 47: 106-114.
25. El-Saadony MT, Alagawany M, Patra AK, Kar I, Tiwari R, et al. Abdel-Latif, H. M. *Funct. probiotics Aquac. An Overv.* 2021. 117: 36-52.
26. Matur E, Eraslan E. The impact of probiotics on the gastrointestinal physiology. *New Adv. basic Clin. Gastroenterol.* 2012. 1: 51-74.
27. Lilly DM, Stillwell RH. Probiotics: Growth-promoting factors produced by microorganisms. *Science.* 1965. 147: 747-748.
28. Yasar SI, Okutan R. Tosun Test. *Nov. eubiotic Addit. its Heal. Perform. Eff. Commer. Rais. farm Anim.* 2017. 7; 297-308.
29. Wang H, Lee IS, Braun C, Enck P. Effect of probiotics on central nervous system functions in animals and humans: A systematic review. *J. Neurogastroenterol. Motil.* 2016. 22:1 589-605.
30. McAllister TA, Beauchemin KA, Alazeh AY, Baah J, Teather RM, et al. Review: The use of direct fed microbials to mitigate pathogens and enhance production in cattle. *Can. J Anim Sci.* 2011. 91: 193-211.
31. Rai V, Yadav B, Lakhani GP. Application of probiotic and prebiotic in animals production: a review. *Environ. Ecol.* 2013. 31: 873-876.
32. Callaway TR, Edrington TS, Byrd JA, Nisbet DJ, Ricke SC. Use of Direct-Fed Microbials in Layer Hen Production-Performance Response and Salmonella Control, in: Ricke, S C, Gast, R.K. (Eds.), *Producing Safe Eggs: Microbial Ecology of Salmonella.* Academic Press, Cambridge, MA. 2017. 301-322.
33. Murate LS, Paião FG, De Almeida AM, Berchieri A, Shimokomaki M. Efficacy of prebiotics, probiotics, and synbiotics on laying hens and broilers challenged with *Salmonella enteritidis*. *J. Poult. Sci.* 2015. 52: 53-56.
34. Palamidi I, Fegeros K, Mohnl M, Abdelrahman WHA, Schatzmayr G, et al. Probiotic form effects on growth performance, digestive function, and immune related biomarkers in broilers. *Poult. Sci.* 2016. 95: 1598-1608.
35. Rinttilä T, Apajalahti J. Intestinal microbiota and metabolites-Implications for broiler chicken health and performance. *J. Appl. Poult. Res.* 2013. 22: 647-658.
36. Anee IJ, Alam S, Begum RA, Shahjahan RM, Khandaker AM. The role of probiotics on animal health and nutrition. *J. Basic Appl. Zool.* 2021. 82: 1-16.
37. Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. *Perspect. Medicin. Chem.* 2014. 6: 25-64.
38. Haque MH, Sarker S, Islam MS, Islam MA, Karim MR, et al. Sustainable antibiotic-free broiler meat production: Current trends, challenges, and possibilities in a developing country perspective. *Biology Basel.* 2020. 9: 411.
39. Medina E, Pieper DH. Tackling threats and future problems of multidrug-resistant bacteria. How to overcome Antibiot. Cris. facts, challenges, Technol. *Futur Perspect.* 2016. 3-33.
40. Fentahun Ali S. Review on Rational Use of Antmicrobials in Veterinary Practice. *Int. J Biomed Eng Clin Sci.* 2019. 5: 70.
41. Ghimpeanu OM, Pogurschi EN, Popa DC, Dragomir N, Drăgoțoiu T, et al. Antibiotic use in livestock and residues in food A public health threat: A review *Foods.* 2022. 11: 1430.
42. Ricardo L, Tang C. Evolutionary Genetics of ESBP / pAmpC-producing *Escherichia coli* and *Salmonella enterica* from Poultry. *Utrecht University.* 2019.
43. Muteeb G, Rehman MT, Shahwan M, Aatif M. Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. *Pharmaceuticals.* 16: 1615. 2023.

44. Kumar A, Patyal A, Panda AK. Sub-therapeutic use of antibiotics in animal feed and their potential impact on environmental and human health: a comprehensive review. *J. Anim. Feed Sci. Technol.* 2018. 6: 15-25.
45. Stanton TB. A call for antibiotic alternatives research. *Trends Microbiol.* 2013. 21: 111-113.
46. Ramatla T, Ngoma L, Adetunji M, Mwanza M. Evaluation of antibiotic residues in raw meat using different analytical methods. *Antibiotics.* 2017. 6: 34.
47. Rousham EK, Unicomb L, Islam MA. Human, animal and environmental contributors to antibiotic resistance in low-resource settings: Integrating behavioural, epidemiological and one health approaches. *Proc. R. Soc. B Biol. Sci.* 2018. 285: 1876.
48. Cheng G, Hao H, Xie S, Wang X, Dai M, et al. Antibiot. Altern. Substit. Antibiot. Anim. husbandry? *Front.* 2014.
49. Buntyn JO, Schmidt TB, Nisbet DJ, Callaway TR. The role of direct-fed microbials in conventional livestock production. *Annu. Rev. Anim. Biosci.* 2016. 4: 335-355.
50. Abd El-Hack ME, El-Saadony MT, Shafi ME, Qattan SYA, Batiha GE, et al. Probiotics in poultry feed: A comprehensive review. *J. Anim. Physiol. Anim. Nutr.* 2020. 104: 1835-1850.
51. Xiang Q, Wang C, Zhang H, Lai W, Wei H, et al. Effects of different probiotics on laying performance, egg quality, oxidative status, and gut health in laying hens, *Animals.* 2019.
52. Xu T, Chen Y, Yu L, Wang J, Huang M, et al. Effects of *Lactobacillus plantarum* on intestinal integrity and immune responses of egg-laying chickens infected with *Clostridium perfringens* under the free-range or the specific pathogen free environment. *BMC Vet. Res.* 2020. 16: 2263-2264.
53. Panda AK, Reddy MR, Rama Rao SV, Praharaj NK. Production performance, serum/yolk cholesterol and immune competence of White Leghorn layers as influenced by dietary supplementation with probiotic. *Trop. Anim. Health Prod.* 2003. 35: 85-94.
54. Krehbiel CR, Rust SR, Zhang G, Gilliland SE. Bacterial direct-fed microbials in ruminant diets : Performance response and mode of action. *J. Anim. Sci.* 2003. 81: 120-132.
55. Desnoyers M, Giger-Reverdin S, Bertin G, Duvaux-Ponter C, Sauvant D. Meta-analysis of the influence of *Saccharomyces cerevisiae* supplementation on ruminal parameters and milk production of ruminants. *J. Dairy Sci.* 2009. 92: 1620-1632.
56. Apás AL, Dupraz J, Ross R, González SN, Arena ME. Probiotic administration effect on fecal mutagenicity and microflora in the goat's gut. *J. Biosci. Bioeng.* 2010. 110: 537-540.
57. Signorini ML, Soto LP, Zbrun MV, Sequeira GJ, Rosmini MR, et al. Impact of probiotic administration on the health and fecal microbiota of young calves: A meta-analysis of randomized controlled trials of lactic acid bacteria. *Res. Vet. Sci.* 2012. 93: 250-258.
58. Ma ZZ, Cheng YY, Wang SQ, Ge JZ, Shi HP, et al. Positive effects of dietary supplementation of three probiotics on milk yield, milk composition and intestinal flora in Sannan dairy goats varied in kind of probiotics. *J. Anim. Physiol. Anim. Nutr. Berl.* 2020. 104: 44-55.
59. Chen YY, Wang YL, Wang WK, Zhang ZW, Si XM, et al. Beneficial effect of *Rhodopseudomonas palustris* on in vitro rumen digestion and fermentation. *Benef. Microbes.* 2020. 11: 91-99.
60. Saeed M, Babazadeh D, Naveed M, Alagawany M, Abd El-Hack ME et al. In ovo delivery of various biological supplements, vaccines and drugs in poultry: current knowledge. *J. Sci. Food Agric.* 2019. 99: 3727-3739.
61. Wealleans AL, Li W, Romero LF, Mathis G, Lumpkins B. Performance and cost-benefit improvements following supplementation with a combination of direct-fed microbials and enzymes to broiler chickens raised with or without ionophores. *J. Appl. Poult. Res.* 2018. 27: 23-32.
62. Xu H, Lu Y, Li D, Yan C, Jiang Y, et al. Probiotic mediated intestinal microbiota and improved performance, egg quality and ovarian immune function of laying hens at different laying stage. *Front. Microbiol.* 2023. 14: 1041072.
63. Singer RS, Hofacre CL. Potential impacts of antibiotic use in poultry production. *Avian Dis.* 2006. 50: 161-172.
64. Gyles CL. Antimicrobial resistance in selected bacteria from poultry. *Anim. Health Res. Rev.* 2008. 9: 149-158.
65. Gut AM, Vasiljevic T, Yeager T, Donkor ON. Salmonella infection - Prevention and treatment by antibiotics and probiotic yeasts: A review. *Microbiol.* 2018. 164: 1327-1344.
66. Pan D, Yu Z. Intestinal microbiome of poultry and its interaction with host and diet. *Gut Microbes.* 2014. 5: 108-119.
67. Dionisio F, Domingues CPF, Rebelo JS, Monteiro F, Nogueira T. The impact of non-pathogenic bacteria on the spread of virulence and resistance genes. *Int. J. Mol. Sci.* 2023. 24: 1967.
68. Guetiya Wadoum RE, Zambou NF, Anyangwe FF, Njimou JR, Coman MM, et al. Abusive use of antibiotics in poultry farming in Cameroon and the public health implications. *Br. Poult. Sci.* 2016. 57: 483-493.
69. Parsonage B, Hagglund PK, Keogh L, Wheelhouse N, Brown RE, et al. Control of antimicrobial resistance requires an ethical approach. *Front. Microbiol.* 2017. 8: 2124.
70. Al-Shawi SG, Dang DS, Yousif AY, Al-Younis ZK, Najm TA, et al. The potential use of probiotics to improve animal health, efficiency, and meat quality: a review. *Agriculture.* 2020. 10: 452.
71. Yaqoob MU, Wang G, Wang M. An updated review on probiotics as an alternative of antibiotics in poultry - A review. *Anim. Biosci.* 2022. 35: 1109-1120.
72. Lee S, Lee J, Jin YI, Jeong JC, Chang YH, et al. Probiotic characteristics of *Bacillus* strains isolated from Korean traditional soy sauce. *Lwt.* 2017. 79: 518-524.