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Review article

Antibiotics in broilers chicken production: a review of impacts, challenges and potential alternatives

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Abstract

Globally, the use of antibiotic in animal industry was well known in the 20th century. Antibiotics usage as therapeutic and subtherapeutic means of improving growth and feed efficiency in livestock was well documented in literature. However, continuous use of antibiotics in food animals for increased growth and disease prevention has resulted in the development of antibiotic resistant bacteria in animals. This has led to disease treatment failure in the affected animals. The problem of transmission of antibiotic resistant bacteria to human through food chain and contamination of environment is another challenge of antibiotic usage in poultry production. Hence, the ban was placed on antibiotic usage in animal production. The restriction to the use of animal growth promoting antibiotic has gained high compliance in the developed countries. However, in the third world countries, this is still a battle that is on-going. To achieve the 2023 Global Action Plan on Antimicrobial Resistance goal, a lot is still left to be done. This review synthesized information on implications of antibiotics uses on broiler chickens' production cost efficiency and profitability; impact of antibiotics mode of action, diseases prevention and treatments of infection in broiler chickens' production; challenges of antibiotics residual effect on meat quality and safety and alternatives to synthetic antibiotic for broiler chickens' production.

Keywords: Antibiotics, Broilers chicken, Production, Infection, Cost efficiency

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INTRODUCTION

The potential of poultry industry to the gross domestic product of any nation cannot be underestimated. Poultry meat and egg have significantly improved living standard of many societies particularly in developing nations. The use of antibiotics in chickens started with the discovery of penicillin, streptomycin and chlortetracycline in 1940s. These drugs helped in outbreak control, apart from this, they offered added benefit such as keeping the birds' digestive tracts healthy, and chickens were able to gain more weight without eating more food (Cully, 2014). The use of antibiotic has been shown to promote a beneficial microbiome, they support improve immune function and enhances gut health thereby leading to improve feed efficiency (Rushton, 2015). However, over the years, it has been observed that the gains of antibiotics especially the uncontrol usage has led to several consequences ranging from residual contents in meat and eggs to antibiotic resistance in both animals and man, from hypersensitivity reactions, toxicity to teratogenicity and carcinogenicity (Thapa, 2021; Alaboudi, 2022). Due to the aforementioned points, antibiotic as growth promoters in animal feed was banned by the European Union with effect from January 1, 2006. Furthermore, in May, 2015, the World Health Assembly formulated the Global Action Plan on Antimicrobial Resistance (AMR) and the Global Antimicrobial Resistance Surveillance System was established (WHO, 2015). The following year, African countries came together to address AMR during the United Nations General Assembly special meeting. To achieve the goal, in 2017 the Framework for Antimicrobial Resistance Control, 2018–2023' was lunched by the Africa Centres for Disease Control and Prevention (Africa CDC) (http://www.africacdc.org/resources/strategic-framework). The framework was based on four principles. These are strategies to advance the Global Action Plan, synthesis of information on incidence, prevalence, and interventions, develop policy and practice for diagnostic or treatment technologies in mitigating AMR and lastly, leverage on the uniqueness of its position in the AU to raise awareness, secure commitments, and influence policy (Nkengasong et al., 2017). This review aimed to address the second principle which has to do with information synthesis.

REVIEW METHODS AND TOOLS

On July 14, 2020, we searched electronic databases (PubMed (Medline), Scopus, Web of Science, BIOSIS, AB Abstracts, ProQuest, Science Citation Index). The search was updated on March, 2022. Inclusion criteria were original studies that reported on implications of antibiotics use on broiler production; impact of antibiotics mode of action, diseases prevention and treatment of infection in broiler production; challenges of antibiotics residual effect on meat quality and safety; challenges of antibiotic side effect and contradictions on poultry welfare; alternative to synthetic antibiotic for broiler chickens' production. We extracted data from included studies from 2001 to 2022. The review concluded with impacts, challenges and potential alternative to use of antibiotics in poultry diets.

IMPLICATIONS OF ANTIBIOTICS USE ON BROILERS PRODUCTION, COST EFFICIENCY AND PROFITABILITY

Several authors have reported on the economic implications of antibiotics use in broiler feeding management. It should be noted that despite additional cost incurred as a result of antibiotics use in broiler feed, most authors reported an increase in the income generated from antibiotic treated broilers. The study reported by Araujo et al. (2019) showed that broilers fed diets containing antibiotics had higher costs, revenue, and profits. The authors observed that the higher cost was due to increased feed intake observed among birds fed antibiotic treated feed, which later resulted in higher body weight of antibiotics treated broilers. The authors observed that the cost of feed (70 to 80%) constituted higher percentage of total production cost as was earlier reported by Akpodiete et al. (2001). It will, however, be of interest to note that the revenue derived from antibiotics treated broilers was quite higher and better compared with those broiler chickens on control diet, making antibiotic treatment a better and economically viable option. The observation of Chowdhury et al. (2009) was however differed when the economic effect of feeding broilers with organic acids and/or antibiotics were compared. The authors reported that broilers fed with organic acids had the lowest production cost, followed by those fed with antibiotics, negative control (without additives), and the interaction among them.

Another method of evaluating the economic efficiency of antibiotics use in broiler production is to review literature in the countries where antibiotic use is banned. MacDonald and Wang (2011) observed that the responses of poultry farmers to a ban on antibiotic use would depend on several factors such as method of production, the location of the farm, health and sanitation practices, and the size of the farm. The period when the farm was established and the presence of older facilities on the farm is another important factor to be considered. For instance, in a farm where there are older facilities, animals in such farms are exposed to poor hygiene management, hence, the use of antibiotics would help in maintaining the animal health. Even with the use of alternatives to antibiotics, poultry farmers in the affected countries still preferred antibiotics use, maybe for economic purpose. For instance, the cost of poultry production increased by EUR 1.04 per bird when antibiotics use was terminated in Denmark (WHO, 2002). The increase was as a result of excess mortality, increased medication and excess feeding days observed among poultry farms. This means there was a decrease in poultry production after antibiotic use was banned as compared to when it was in use. Similar observations were made by Sneeringer et al. (2015) when evaluating the impact of antibiotic ban in US poultry industry. The author reported that broiler production decreased by 1.12 % with a resultant effect of an increase in wholesale price. Laxminarayan et al. (2015) noted that a ban on the use of antibiotic would lower growth rate and feed efficiency and also result in higher morbidity and increased mortality rate. The authors reported an increase in costs associated with biosecurity measures and adjustments in housing to compensate for termination of antibiotics use.

IMPACT OF ANTIBIOTICS MODE OF ACTION, DISEASES PREVENTION AND TREATMENT OF INFECTION IN BROILERS PRODUCTION

Antibiotics are natural metabolites of fungi that inhibit the growth of bacteria (Hossan et al., 2018). Though, many researchers (Etebu and Arikekpar, 2016; Brown et al., 2017; Gadde et al., 2017) have reported on the mode of action of antibiotics use in poultry, it should however be noted that the mechanisms through which antibiotics perform their functions differ and, in some cases, may not be well understood.

Microorganisms such as *Clostridium perfringens*, Bacteroides, Bifidobacteria, Enterococci and Lactobacilli have been known to have harmful effect and are responsible for some poultry diseases. Antibiotics use in poultry management has been reported to prevent and control the growth of these microbes (Mehdi et al., 2018). When the negative effects of microbes are controlled in poultry, the birds will perform optimally resulting in better nutrient utilization, higher growth rate, low mortality, increased egg and meat production. Antibiotics usage in poultry also helps in lowering the negative effect of ammonia, an antagonistic microbial metabolite, which exact its negative effect on the physiology of the host (Frey-Klett et al., 2011). It is very important for poultry farmers to prevent the outbreak of disease on the farm than to control it because the time and energy that would be invested in controlling the disease could be utilized for other beneficial purposes (Vidic et al., 2017).

Some antibiotics improve the conditions of gut microflora by inhibiting the growth of harmful pathogenic and non-pathogenic species of bacteria (Chopra and Roberts, 2001). Yang and Walsh (2017) reported that some antibiotics carry out their functions by interfere with proper protein translation at the ribosomal level while others disrupt the normal maintenance of cell wall and since bacteria proliferate at a very high rate, they become vulnerable to antibiotics that target cellular metabolism. Hence, improved the growth conditions of their host.

This is more common in poultry, especially, when the gastrointestinal bacteria are reduced, there would be less competition between the host birds and microbes for vital nutrients (Yadav and Jha, 2019). Antibiotics are also known to improve growth response of birds by minimizing the adverse effect of immunological stress and reducing the enteric microbial load (Gadde et al., 2017). Combination of antibiotics and coccidiostats were reported to improve numerous parameters in chickens and modulate cytokine/chemokine mRNA levels in gut epithelial and spleen cells (Lee et al., 2012). Hossan et al. (2018) summarized the mode of action of antibiotics and their impacts on animal health as follow:

a. Modification of intestinal microflora which in turn increases the growth performance and improve the health conditions of birds.

b. They also prevent breeding and multiplication of certain bacteria such as Lactobacilli, Bifidobacteria, Bacteroides, and Enterococci. This in turn aids in prevention of diseases and improve the health and welfare of animals.

c. Activation of body defense through reduction of morbidity/mortality and stress in chicks and improved immunity

d. Antibiotics alter metabolic processes of bacteria i.e. they are capable of destroying harmful bacteria in poultry; reduces the negative impacts of change in diet; prevents the increase of common pathogenic bacteria; minimizes the occurrence of enteritis in poultry.

e. They reduce proliferation of certain toxins and thinning the walls of the intestine, thereby reduce the length and weight of the intestines. This improves the growth performance of birds through efficient feed and nutrient utilization and absorption.

CHALLENGES OF ANTIBIOTICS RESIDUAL EFFECT ON MEAT QUALITY AND SAFETY

Habeeb et al. (2022) studied antibiotics residues in raw meat sold in six slaughter houses in Kano States using high performance liquid chromatography (HPLC) for tetracycline, ciprofloxacin and oxytetracycline residue in raw meat. Their results showed that from 18 beef samples analyzed 15 (83%) of the total samples had detectable levels of tetracycline residues from which 6 (33.3%) had tetracycline residues at levels above the maximum residue limits (MRLs), WHO/FAO. The authors reported that from the 18 beef samples analyzed 12 (67 %) of ciprofloxacin was detected, it was reported to be above the acceptable MRLs are below the WHO/FAO maximum residue limits (MRLs). It was concluded that the high level of tetracycline and oxytetracycline residues in greater proportion of meant destined for human consumption and thus, consumers may be predisposed to health hazards and hinder international meat trade from Nigeria.

Reports of presence of tetracycline using microbiological assay technique from 100 old layer birds purchased for consumption in open markets in Ogun, Lagos and Oyo States in Nigeria by Dipeolu and Dada (2006). The results indicated that 14 of the birds indicated tetracycline residues deposition with the mean concentration of between 0.0316 and 0.0513 µg for thigh muscle samples and between 0.0383 and 0.0727 µg for breast samples.

Using High Power Liquid Chromatography (HPLC) and Atomic Absorption Spectroscopy (AAS) to determine the residues of tetracycline and lead plus cadmium, respectively by Olusola et al. (2012), from one hundred frozen chicken muscle in major markets in Lagos and Ibadan, Nigeria. The authors reported a mean residue concentration of 1.1589 to 1.0463 ppm tetracycline which is higher than the maximum residue limit set by international food safety agencies. They also reported higher Lead contents 0.0227 +/- 0.0069 microg dL(-2) in markets in Ibadan as against 0.0207 +/- 0.0082 microg dL(-1) in Lagos. Cadmium levels were 0.0013 microg dL(-1) higher than in the Lagos samples (0.0065 +/- 0.0026 microg dL(-1). They concluded that the values obtained were within maximum residue limits.

Onipede et al. (2021) carried out a study using HPLC-DAD at 365 nm to examine the level of tetracycline, doxycycline, chlortetracycline, and oxytetracycline in catfish and chicken from six farms and markets in some parts of Lagos and Ota, South-Western Nigeria. It was discovered that tetracycline ranged from ND – 0.0167 µg/g and ND – 0.058 µg/g were found in catfish and chicken respectively (Onipede et al., 2021). Doxycycline in catfish was below the limit of detection for all catfish samples and in chicken ranged from

ND – 0.047 µg/g. Chlortetracycline in catfish was between ND – 0.147 µg/g and in chicken from ND – 0.058 µg/g. Oxytetracycline in catfish ranged from ND – 0.021 µg/g and in chicken ND – 0.031 µg/g. The authors concluded the chlortetracycline was higher in the catfish samples than the EU recommended maximum residue limits in animal muscles.

Working with 400, 100 samples each from liver, kidney, lungs and breast muscles, Bosha et al. (2019) reported a total of 70 % residue incidence detected. Report showed that liver, kidney, lungs and muscle had 60 %, 31 %, 14 % and 5 % tetracycline residues. They reported highest concentration of 6 µg/kg in the liver from one farm. It was concluded that despite the higher incidence of 70 %, all the values were significantly ($p<0.01$) lower than the recommended Maximum Residue Limits (MRL) or tolerance of 600, 300 and 200 µg/kg for the liver, kidney and muscle respectively.

Olatoye et al. (2019) determined the gentamicin residue in the 270 egg samples from six retail markets in Oyo and Lagos state, Nigeria. Their study showed that 60% and 80% of pooled eggs from Oyo and Lagos states, respectively, contained gentamicin residues with means of 1461 ± 74 and 1350 ± 92 µg/kg, respectively. They concluded that mean residues obtained from the two states were higher than the maximum recommended residue limits. High levels of gentamicin residues, from unbridled use of antibiotics in poultry production, detected in retail eggs from markets rendered the eggs unsafe for human consumption. In another study, the occurrence of gentamicin residue in the muscle, liver and kidney of poultry in Enugu State, Nigeria in surveyed birds was 65% with tissue distribution as follows; 44.4, 51.9 and 59.3 % in muscle, liver, and kidney, respectively, (Onyeanu et al., 2020).

Costa et al. (2007) reported that when tylosin was administered to broilers at sub-therapeutic and therapeutic levels, no statistically significant differences were observed in moisture content, pH, drip loss, colour and extent of lipid oxidation between the breast meat from treated and not treated birds. They also discovered that meat from treated birds had higher the cooking loss compared to non-treated ones. Lower shear force value was observed in meat from birds on the sub-therapeutically treated broilers compared to the non-treated and the therapeutically treated ones. The authors concluded quality of breast meat (texture) was significantly influenced by the level tylosin administration.

CHALLENGES OF ANTIBIOTIC SIDE EFFECT AND CONTRADICTIONS ON POULTRY WELFARE

There is no doubt that the use of antibiotics in poultry feeding management improves production of eggs and meat and livelihood of livestock farmers. However, certain challenges may arise as a result of improper use of antibiotics for disease treatment. One of these is the problem of transmission of antibiotic resistant bacteria to human through food chain and contamination of environment. Several authors (Awad et al., 2020; Thames and Sukumaran, 2020, Okorie-Kanu et al., 2020) have reported on the high level of antibiotic resistance in meat samples collected from antibiotic treated poultry birds during slaughtering and processing of carcass.

Kimeria et al. (2015) reported carcinogenicity and cytotoxicity in the muscle, liver, kidney and bones of broiler chickens when given oxytetracycline. Allergic hypersensitivity reactions and tendon rupture of chicken tissue was reported by Tavakoli et al. (2015) in broiler chickens placed on Enrofloxacin. Other reports of antibiotic residues in the different animal-derived products in some developing countries are presented in Table 1.

It is also important to note that continuous exposure of poultry birds to antibiotics use either through the oral administration or through the feed creates a form of selective pressure for the development of resistance (Clement et al., 2019). Microbes in the gut are known to extensively interact with the host and diets and thereby exert a huge effect on the welfare, physiology and immunity of the animals (Kogut and Arsenault, 2016). This allows resistant bacteria associated with the birds to enter into the food chain when the affected meat and its by-products are consumed by human (Yadav and Jha, 2019). Wegener (2012) reported that antibiotic resistance determinants are being transferred from animals to humans through consumption of meat, eggs, milk etc. It should however be noted that the selective pressure would depend on the quantity of antibiotic use (Clement et al., 2019).

Furthermore, environmental contamination is another challenge when using antibiotics in poultry feeding management. This usually occurs when certain microbes such as *E. vulneris* and *Escherichia coli* become resistant to antibiotic drugs. Most of these microbes are found in cloaca and are voided out together with faeces into the environment during excretion. Some migratory birds are known to easily spread resistant bacterial strains from one area to another through migration (Shobrak and Abo-Amer, 2014). The manure from the poultry farm, sewage, soils, effluents and waste water can sometimes serve as a medium for antibiotic resistance pollution (Christy et al., 2018).

This has always been the major concern of the government and public health workers in the developed countries, hence, the reason for placing a ban on the use of antibiotics for treating livestock diseases by farmers in those countries. Muhammad et al. (2020) also suggested biological treatment of poultry wastes such as manure including anaerobic digestion before being used as soil fertilizer so as to prevent against xenobiotics to animals and humans (Acar and Moulin, 2006).

Table 1 Presence of varying concentrations of antibiotic residues in the different animal-derived products in some developing countries

Antibiotic Residue	Concentration	Sample	Consequences in Humans/Animals	Country	Literature
Oxytetracycline	2604.1 ± 703.7 µg/kg 3434.4 ± 604.4 µg/kg 3533.1 ± 803.6 µg/kg	Chicken Muscle Liver kidney	Carcinogenicity, cytotoxicity in the bones of broiler chickens. Presence of residues cause technological challenges during milk processing.	Tanzania	Kimeria et al. (2015)
	51.8 ± 90.53 µg/kg 372.7 ± 366.8 µg/kg 1197.7± 718.9 µg/kg	Beef Muscle Kidney Liver		Nigeria	Olufemi and Agboola (2009)
	15.92 to 108.34 µg/kg 99.02 to 112.53 µg/kg	Cattle Muscle kidney		Ethiopia	Bedada et al. (2012)
Enrofloxacin	0.73 and 2.57 µg/kg	Chicken tissues	Allergic hypersensitivity reactions or toxic effects, phototoxic skin reactions, chondrotoxic), and tendon rupture	Iran	Tavakoli et al. (2015)
Chloramphenicol	1.34 and 13.9 µg/kg		Bone marrow toxicity, optic neuropathy, brain abscess		
Penicillin	0.87 and 1.3 µg/kg	Calves muscles	Allergy, affect starter cultures to produce fermented milk product		
Oxytetracycline	3.5 and 4.61 µg/kg		Carcinogenicity, cytotoxicity in the bones of broiler chickens		
Quinolones	30.81 ± 0.45 µg/kg 6.64 ± 1.11µg/kg	Chicken Beef	Allergic hypersensitivity reactions or toxic effects (phototoxic skin reactions, chondrotoxic) and tendon rupture	Turkey	Er et al. (2013)
Tetracyclines	124 to 5812 µg/kg 107–6010 µg/kg 103 to 8148 µg/kg	Chicken Breast Thigh Livers	Primary and permanent teeth discolouration in children and infants, allergic reactions and teratogenicity during the first trimester of pregnancy, nephrotoxicity, carcinogenic, hepatoxocity, and disturbance of the normal microflora of the intestines. It equally causes skin hyperpigmentation of areas exposed to the sun, proximal and distal renal tubular acidosis, hypersensitivity reactions	Egypt	Salama et al. (2011)
	150 ± 30 µg/g 62.4 ± 15.3 µg/g	Chicken Liver muscle		Cameroon	Guetiya-Wadoum et al. (2016)
	50 to 845µg/kg 50 to 573 µg/kg 23–560 µg/kg	Beef Kidney Liver muscles		Kenya	Muriuki et al. (2001)
Amoxicillin	9.8 to 56.16 µg/mL 10.46 to 48.8 µg/g	Milk Eggs	Carcinogenic, teratogenic, and mutagenic effects	Bangladesh	Chowdhury et al. (2015)
Sulfonamides	16.28µg/kg	Raw milk	Carcinogenicity, allergic reactions	China	Zheng et al. (2013)
Quinolones	23.25 µg/kg		Allergic hypersensitivity reactions or toxic effects (phototoxic skin reactions, chondrotoxic) and tendon rupture		

Table 1 Presence of varying concentrations of antibiotic residues in the different animal-derived products in some developing countries (Cont.)

Antibiotic Residue	Concentration	Sample	Consequences in Humans/Animals	Country	Literature
Oxytetracycline Sulphamethazine	199.6 ± 46 ng/g 86.5 ± 8.7 ng/g	Beef	Carcinogenicity, allergic reactions	Zambia	Nchima et al.(2017)
Penicillin G	15.22 ± 0.61 µg/L 7.60 ± 0.60 µg/L 8.24 ± 0.50 µg/L	Fresh milk Cheese (wara) Fermented milk (nono)	Allergy (hypersensitivity reaction) ranging from mild skin rash to life-threatening anaphylaxis	Nigeria	Olatoye et al. (2016)
Sulphonamides	0.08–0.193 µg/g 0.006–0.062 µg/g	Chicken Liver Breast	Carcinogenic potential and mild skin rash to severe toxiderma, epidermal toxic necrolysis, blood dyscrasias	Malaysia	Cheong et al.(2010)
Tetracycline	>0.1 µg/mL	Raw milk	Primary and permanent discolouration of teeth in children and infants, teratogenicity during the first trimester in pregnancy, etc.	India	Nirala et al. (2017)
Oxytetracycline			Carcinogenicity and cytotoxicity in bone marrow of broiler chickens		
Sulfadimidine			Carcinogenicity and allergic reactions		

Source Manyi-Loh et al. (2018)

ALTERNATIVES TO SYNTHETIC ANTIBIOTIC FOR BROILER CHICKENS PRODUCTION

Plant extracts

Plant extracts are compounds or substances with active ingredients of desirable properties that is removed from plant tissue usually with solvent, to be used for a particular purpose. Most plants contain proteins, lipids, carbohydrates (primary metabolites) produced with the aid of chlorophyll and sunlight as the primary metabolic products after photosynthesis. These metabolites are quite common in nature and found quite a lot in most plant tissues (Vanisree et al., 2004). The plants over time have the ability to produce a wide variety of secondary metabolites (biomolecules), like alkaloids, glycosides, terpenoids, saponins, steroids, flavonoids, tannins, quinone sand coumarins (Elisha et al., 2017). These biomolecules are the source of plant-derived antimicrobial substances, some of them are highly efficient in the treatment of bacterial infections (Fernebro, 2011). Some of these plant secondary metabolites have been used as alternative to chemically synthesized antibiotics in boiler chickens' feed. Alabi et al. (2017) used 240 broiler chicks to investigate the effect of aqueous *Moringa oleifera* leaf extracts (AMOLE) on growth performance and carcass characteristics of broiler chickens and reported that the extract inclusion level of 90 ml/litre of water via drinking water of broiler chickens, reduced feed intake (12.83 %) and improved feed efficiency (9.11 %). The authors concluded that AMOLE can be used to replace synthetic antibiotics as growth promoter.

Alkaloids

Plant alkaloids prove to be beneficial for intestinal integrity and improve feed conversion rates mainly by inflammatory regulation of the intestinal mucosa in chickens. Xue et al. (2017) reported that when necrotic enteritis (NE) challenged broiler chickens were fed diets containing plant-derived isoquinoline alkaloids (IQA), NE challenge negatively affected growth performance, livability, and carcass traits. However, regardless of challenge, birds on IQA had increased feed intake and gain at day 24 and 35. They also had improved FCR and flock uniformity. The authors also reported improved breast meat yield, reduced lesions in the duodenum, jejunum and ileum on day 35.

Alkaloids obtained from *Macleaya cordata* (Sangrovit) was reported to influence caecal metabolism in broiler chickens (Juskiewicz et al., 2011). The authors observed that 15 mg/kg dose of Sangrovit decreased potentially harmful β -glucuronidase and β -glucosidase activities. However, increase in the activities of bacterial glycolytic enzymes α- glucosidase, α- galactosidase, β -galactosidase was noted in comparison to the control group. Sangrovit caused an increase in the sum of MUFA and the tendency towards lower PUFA sum.

Yakhkeshi et al. (2011) discovered that the diets containing alkaloids enhanced intestinal health and the absorption of nutrients in broiler chickens. They reported that dietary alkaloids elevated the heterophils to lymphocyte ratio (H/L) and enhanced body titration against sheep red blood cells (SRBC). Studies have also shown that dietary isoquinoline alkaloids are able to adjust/regulate immune functions (Windisch et al., 2008), triggering phagocytosis, thus, prompting defensive reactions by the host (Gudev et al., 2004). In broiler chickens, isoquinoline alkaloids diets have been associated with reduced the villus height an organ associated with nutrition absorption (Jankowski et al., 2009).

Saponins

Saponins are plant secondary metabolites (PSMs) with high molecular weight. They are either a tetracyclic steroidal or a pentacyclic triterpenoid aglycone with one or more sugar chains (Vincken et al., 2007). They can be from different parts of the plant. They have many pharmacological and biological activities such as hypocholesterolaemic, anti-carcinogenic, anti-microbial, anti-inflammatory, antioxidant and immunomodulatory effects on both poultry and other animals. Its application at optimum level has shown many benefits. Gaurav (2015) reported that saponin for Chlorophytum root at 0.015 % improved nitrogen retention in broilers and profitability. A higher growth rate was observed in broiler chicken diet containing Camellia seed saponin supplemented at 600 mg/kg (Gaurav, 2015). In another study, Miah et al. (2004) revealed that 75 mg saponin/kg in the diet of broiler chickens enhanced weight gain at all stages of growth, improved performance index and resulted in better feed conversion ratio.

According to Su et al. (2016), dietary supplementation of 100 and 200 mg/kg Yucca extract (YE), an extract that contains steroidal saponins and polyphenols improved body weight gain, feed efficiency, IgG, IgM, T-AOC, CAT and SOD levels. The supplementation also exhibited positive effects on inducing immune organs' maturation (Su et al., 2016). Similarly, Cabuk et al. (2004) reported that 120 mg/kg YE enhanced body weights of birds. Improved daily weight gain and feed conversion rate at 42 day of age were reported by Alfaro et al. (2007).

Propyl thiosulfnate (PTS) and propyl thiosulfnate oxide (PTSO) a metalabolite of garlic has been used in poultry diets (Kim et al., 2013). Dietary supplementation of propyl thiosulfnate and propyl thiosulfnate oxide at 10 mg/kg improved body weight gain and serum antibody titers against proflin, an immunogenic protein of Eimeria, and they also reduced fecal oocyst excretion in *E. acervulina* challenged chickens (Kim et al., 2013). The authors reported that addition of these metabolites in the diets of broiler chickens altered many genes related to innate immunity and down-regulated expression of IL-10 as against the control diet. According to Kim et al. (2013), dietary supplementation with PTS/PTSO in uninfected broiler chickens increased the levels of transcripts encoding IFN-γ, IL-4, and an antioxidant enzyme, paraoxonase 2, but decreased transcripts for peroxiredoxin-6. Pasaribu et al. (2014) indicated that triglyceride and salinomycin were lower than positive control when fed 1.25 and 0.5 g/kg, Sapindus rarak (saponin containing fruits) supplemented diet.

Flavonoids

Flavonoids are secondary metabolites of plants that have wide range of pharmacological and beneficial health effects on animals. Like most pharmacological plants they have antioxidative, free radical scavenging and anti-inflammatory activities, and thus, are gaining high attention. They are not only able to select target bacterial cells, but also to inhibit virulence factors and capable of forming microbial threats (Qin et al., 2022).

A study conducted by Batista et al. (2007) indicated that diets supplemented with flavonoids plus MOS in broiler chickens between of 1- and 42-days improved feed utilization and the Tbars number were significantly lower in both refrigerated and frozen meat. Iskender et al. (2016) worked on the effects of dietary flavonoid supplementation on the antioxidant status of laying hens and found that all the flavonoid used (hesperidin, quercetin, and naringin) decreased malondialdehyde concentration as well as increased glutathione reductase, glutathione peroxidase, glutathione-S-transferase, and superoxide dismutase.

Enzymes, probiotics and prebiotics

Enzymes can be said to be chemicals or catalysts that are released by cells to speed up specific chemical reactions. These are normal enzymes that aid digestion that are released in the digestive tract. They enhanced chemical breakdown of nutrients to smaller compounds for ease of digestion and absorption (Thacker, 2013). Now the same enzymes (exogenous) have been effectively manufactured and added to animal feeds. Phytases, carbohydrases (xylanase, cellulase, α-galactosidase, β-mannanase, α-amylase and pectinase), and proteases are the common enzymes used in poultry feeds.

According to Cowieson and Kluenter (2019) the use exogenous enzymes in livestock feeding have been proposed as possible alternatives to AGPs for several decades. The mechanism by which enzymes may potentiate the removal of AGPs, thus, eliminating the risks associated with AGPs was suggested by Bedford and Cowieson (2012). That is, by shifting the site of digestion to anterior intestinal segments thus, starving the microbiome presence in the posterior gut, this may lead to production of fermentable oligosaccharides from previously largely inert fibrous material with a beneficial effect on intestinal pH and enterocyte proliferation.

Lee et al. (2010) reported that probiotics (also called direct fed microbials (DFMs)), are gaining acceptance as potential alternatives to antibiotics to improve production efficiency. Fuller (1989) defined them as "live microbial feed supplements which are beneficial to the host animal by improving the balance of the intestinal microbial. Adopted by WHO (2001), "Probiotics are mono or mixed cultures of live organisms which when administered in adequate amounts confer a health benefit to the host." Cocktails of probiotic preparations are thought to be more effective than single strain probiotics (Timmerman et al., 2004). *Saccharomyces, Lactobacillus, Bacillus, Aspergillus* and *Streptococcus* species have been known to play beneficial roles in poultry nutrition (Chen et al., 2009). *Bacillus* species are used as probiotics and well- promising feed additives because of their aerobic and endospore-forming nature makes them able to survive environmental stresses, including storage, transport, and feed pelleting processes (Wu et al., 2011). Manafi et al. (2016) reported that *Saccharomyces* has the capacity of stimulating the immune system of chicks without decreasing growth performance and prevention of the recurrence of Clostridium difficile infections. Nunes et al. (2012) studied the effect of supplementation of probiotics (*Lactobacillus acidophilus, Enterococcus faecium and Bifidubacterium bifidum*) and antibiotics (flavomicina and staquinol) on diets for broilers from 1 to 42 days of age and reported that between 1 and 21 days of age, the supplementation with probiotics under new litter reduced feed intake. They also observed that from 1 to 42 days birds raised in new litter had lower feed intake when supplemented with probiotics. They concluded that probiotics promote lower feed intake without compromising the performance, regardless of the type of litter used, demonstrating the feasibility of using this product as substitute for antibiotics.

Manifi et al. (2018) compared the effects of a new multispecies probiotics Microguard® and Protexin® with antibiotic in broilers and reported that the group fed with Microguard at 150 g/ton showed increased total bodyweight, body weight gain, HDL, triglyceride, and antibody titres against both Newcastle disease and avian influenza. They recorded better feed efficiency, higher villus height, and villus highest crypt depth ratio. The authors also reported a lower plasma gamma-glutamyl transpeptidase, alkaline phosphatase, alanine aminotransferase in diet with probiotic-supplementation. Their carcass results showed that 100 or 150 g/ton of Microguard reduced liver weights, breast muscle values, and abdominal fat weights. They concluded that 150 g/ton of Microguard can be used to replace antibiotics in broiler feed as a growth-promoter.

According Hutkins et al. (2016), prebiotics can be described as 'non-viable feed components that have health benefit on the host and it is associated with modulation of the microbiota. They are macromolecules gotten from plants and or synthesized by microorganism. Common examples are mannan oligosaccharide, fructooligosaccharide, inulin, oligofructose, galactooligosaccharide, maltooligosaccharide, lactulose, lactitol, glucooligosaccharide, xylooligosaccharide, soya-oligosaccharide, isomaltooligosaccharide, and pyrodextrins.

Mannan oligosaccharide (MOS), derived from the outer cell-wall layer of *Saccharomyces cerevisiae*, has been studied extensively as a prebiotic supplement in poultry diets. The addition of various levels of MOS to the broiler diets significantly increased their body weight and improved feed conversion efficiency (Benites et al., 2008; Bozkurt et al., 2008). They have the ability to increase intestinal villi height (Baurhoo et al., 2007), enhanced immunity (Shanmugasundaram and Selvaraj, 2012), influence jejunal gene expression and intestinal microbiota (Brennan et al., 2013; Pourabedin et al., 2014).

Benites et al. (2008) evaluated the effects of dietary mannan oligosaccharide (Bio-Mos and SAF-Mannan) on growth performance on broiler chickens and found that chickens on Bio-Mos at 1.0/0.5/0.5 (starter/grower/finisher) kg/ton diets had significantly greater body weight at day 42 than birds fed control or SAF-Mannan-supplemented diets. They also reported that supplementation of diets with Bio-Mos at 1.0/0.5/0.5 kg/ton may improve broiler body weight at market ages compared with the unsupplemented diets and feed efficiency between 0 to 21 days in the SAF-Mannan treatments compared with other treatments.

When Ross broiler chickens' diet was supplemented with the prebiotics fructo-oligosaccharide (FOS) and mannan-oligosaccharide (MOS) in an experiment of six dietary treatment groups: control, avilamycin (6 mg/kg), 0.25 % FOS, 0.5 % FOS, 0.025 % MOS, and 0.05 % MOS by Kim et al. (2011), they reported that except for birds on 0.5 % FOS treatment group, the overall body weight gains of birds treated with avilamycin and prebiotics were significantly higher than those of the control group. They observed that birds in 0.05 % MOS group had lower heterophil:lymphocyte ratio and basophil level than those on the control and 0.5 % FOS groups. They also reported that populations of *Clostridium perfringens* and *Escherichia coli* decreased with 0.25 % FOS, 0.05 % avilamycin.

Cengiz et al. (2015) studied the effect of dietary probiotic supplementation and stocking density on the performance, carcass yield, gut microflora, and stress markers of Ross 308 broilers using a 2 by 2 factorial arrangement in a completely randomized design. They observed that dietary probiotic significantly enhanced the feed intake and weight gain in starter phase only. However, total aerobes, *Salmonella* sp., *Lactobacilli* populations in the intestines of birds and stress indicators were not influenced by the dietary treatment.

Al-Khalaifa et al. (2019) investigated the effect of different probiotics (*Bacillus coagulans* 1 g/kg dried culture; *Lactobacillus* sp 1 g/kg dried culture of 12 commercial strains) and prebiotics (fructo-oligosaccharides 5 g/kg; mannan-oligosaccharide derived from *Saccharomyces cerevisiae* (5 g/kg on the performance of broilers. Phytohaemaglutinin test results showed that dietary fructo-oligosaccharides and fructo-oligosaccharides induced higher cellular response than the other treatments in the first cycle. In the second cycle, the results revealed that diet with fructo-oligosaccharides induced higher cellular response than the other treatments. The authors concluded that probiotics and prebiotics can be safely included in the diets of chickens without any adverse effects on productivity and immunity.

Essential oils and nano nutrients

Essential oils (EO) are aromatic volatile or ethereal oil, extracted from medicinal and aromatic plant materials (seeds, flowers, leaves, buds, twigs, herbs, bark, wood, fruits and roots) characterized by the odour or flavour of the material where they are extracted (Tomer et al., 2010). The EOs are mixtures of complex compounds which may vary in their individual chemical compositions and concentrations. Abbaszadeh et al. (2014) reported that main constituents of essential oils such as carvacrol and thymol present in thyme provide broad spectrum antimicrobial activities against gram-negative and gram-positive bacteria, fungi and yeast, however, they have more effect against gram-positive than gram-negative bacterial pathogens. This was attributed to the entrance of hydrophobic compounds through the lipopolysaccharide structures of gram-negative bacteria are limited due to their outer membrane coating the cell wall. The commonly used essential oils in animals are carvacrol, thymol, citral, eugenol and cinnamaldehyde.

Amad et al. (2011) studied the effect of phytogenic feed additive containing thyme and star anise EO on the growth performance and apparent ileal nutrient digestibility in Cobb broiler chickens and reported that although body weight, weight gain, and feed intake were not influenced by additive oil, the feed conversion ratio during the grower (22–42 days) and overall (1–42 days) periods improved linearly by the administration of phytogenic feed additive compared with that of the control diet and concluded that mode of action of the tested EO can be explained by an improvement in the nutrient digestibility in the small intestine. Dietary thymol and carvacrol an essential oil supplementation enhanced performance and antioxidant enzyme activities, it also reduced lipid oxidation, improved digestive enzyme activities, and immune response of broilers (Hashemipour et al., 2013).

CONCLUSIONS

The impact of antibiotics in poultry is substantial, as they effectively combat harmful microbes like *Clostridium perfringens*, leading to improved bird performance, growth rates, and egg/meat production. Antibiotics enhance gut microflora, inhibit pathogenic bacteria, and positively affect protein translation and cell wall maintenance. They also reduce competition for nutrients, immunological stress, and microbial load, while altering bacterial metabolism and enhancing nutrient absorption. However, challenges arise from antibiotic residues detected in raw meat and poultry products, surpassing acceptable limits. Concerns about antibiotic-resistant bacteria transmission, selective pressure, and environmental contamination have led developed countries to ban antibiotic use in livestock. These concerns highlight the need for alternative approaches.

Plant extracts, including alkaloids, saponins, and flavonoids, are emerging as potential substitutes for antibiotics in poultry nutrition. Alkaloids from plants like Macleaya cordata bolster gut health and immunity. Saponins, found in sources like Camellia seeds and garlic, enhance growth, feed efficiency, and immune responses. Flavonoids, offering antioxidative and anti-inflammatory effects, improve growth and feed utilization. Enzymes, probiotics, and prebiotics are also being explored to support digestion, immune modulation, and overall health in poultry.

In conclusion, antibiotics have significant benefits for poultry production but raise concerns about residues and antibiotic resistance. Researchers are turning to plant extracts, enzymes, probiotics, and prebiotics as promising alternatives, with the potential to maintain or even enhance poultry health, performance, and product quality while mitigating the risks associated with antibiotic use.

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AUTHOR CONTRIBUTIONS

Alabi O. John: conceptualization, original draft preparation; **Makinde O. John**: reviewing and editing; **Egena SSA**: reviewing and editing; **Mbajiorgu F.E**: and **Adewara O.A**: conceptualization, reviewing and editing.

CONFLICT OF INTEREST

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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