PHYTOGENIC ALTERNATIVES TO ANTIBIOTICS FOR BROILER CHICKEN MEAT PRODUCTION

Abstract

The indiscriminate use of subtherapeutic doses of antibiotics as growth promoters in intensive production is criticized as one of the major contributing factors for the surge in antimicrobial resistance. There are a number of concerns regarding the use of antibiotic growth promoters in poultry production including antibiotic resistant bacteria pathogens and residues in poultry products and the environment. These issues have resulted in the bans on AGP sin certain countries and the research for suitable alternatives to AGPs has gained momentum across the world. Phytogenics represent a promising alternative to AGPs since some of them exhibit a growth promoting effect by virtue of their antimicrobial, anti-inflammatory, digestion stimulatory and or antioxidant effects. This review aims to provide an overview of the relation between antimicrobial resistance, broiler production and the potential of phytogenic feed additives as alternatives to antibiotic growth promoters

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I. INTRODUCTION

The WHO has declared Antimicrobial resistance (AMR) as one of the top ten global public health threats of this century due to its major impact on the food safety, health of human and animal health economy, society and environment (WHO, 2017). Some of the key factors responsible for the AMR faced by the world today are: (i) inappropriate use of antibiotics in human medicine (ii) excessive use and misuse of antimicrobial agents in animal production (iii) lack of importance on infection prevention and control practices in health institutions and (iv) ready availability of antibiotics and animal and agricultural products due to globalization (Centre for Disease Control and Prevention, 2016; Asokan et al., 2019). Every year, 700 million people are losing battle to AMR and this figure is projected to escalate to 10 million by 2050 in addition to economic losses to the extent of $100 trillion due to healthcare losses and reduced productivity (O'Neill, 2016).

II. ANTIBIOTICS

Antibiotics represent one of the most significant discoveries of this century. The period between 1940–1960s, is referred to as the antibiotic golden age, as most of the antibiotic classes that are being used today were identified during this period. The term 'antibiotic' was introduced by Selman Waksman and it means "against life". Antibiotics are also defined as those substances produced by living organisms naturally or synthesized in the laboratory with the potential to kill or inhibit the growth of other bacteria. Due to their action on bacteria, they are also termed as 'antibacterial' agents (Mohr 2016). Antibiotics exhibit bactericidal or bacteriostatic effects through multiple mechanisms. More importantly, at therapeutic concentrations, antibiotics are efficacious enough to fight against a wide range of infections including the life-threatening ones with minimal toxicity. In fact, the discovery of antibiotics is a real boon to counter the infectious bacterial diseases that have been a challenge for both the mankind and animals (Sengupta and Chattopadhyay, 2012). On the other hand, bacteria exhibit a property termed 'resistance' against antibiotics, which is ither intrinsic or acquired. Intrinsic resistance refers to the innate ability of a bacterial species to exhibit resistance to a particular group of antibiotics or an antibiotic by the intrinsic structural or functional characteristics of the bacteria. Acquired resistance is said to occur when a specific bacterium acquires the ability to resist the activity of a particular antibiotic to which it was susceptible earlier. Resistance may be acquired either by acquisition of resistance genes from other bacteria or by the mutation of genes involved in normal biological processes and cellular structures or from a combination of both (Impey et al., 2020).

III. AGPS IN ANIMAL PRODUCTION AND AMR

Antibiotics are used for the treatment or prevention of diseases when risk of infection is established in animals. But in the last few decades, sub therapeutic doses of antibiotics are being used as growth promoters (AGPs) to improve animal growth rate and feed efficiency irrespective of the occurrence of a bacterial infection (CDDEP, 2016; Valenzuela-Grijalva et al., 2017). Even clinically important antimicrobials are used indiscriminately in animal production as antimicrobial use is unregulated in many countries (Vishnuraj et al., 2016; Walia et al., 2019). The consumption of antibiotics as growth promoters is higher than for treatment purposes in the animal sector (Walia et al., 2019). The global antimicrobial consumption in food animal production is projected to increase by 67% by 2030, driven

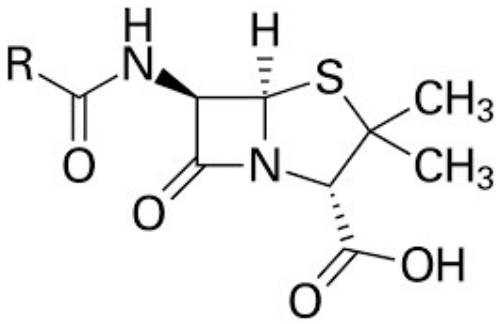
primarily by BRICS (Brazil, Russia, India, China, and South Africa) countries, as they are shifting to large-scale, intensive farming operations, where antimicrobials are used regularly in subtherapeutic doses (Van Boeckel et al., 2015). Due to these factors, antibiotics compounds are now held responsible for the surge in AMR. The current AMR scenario was visualized by the discoverer of the world's first antibiotic Penicillin, Sir Alexander Fleming. Way back in 1945, Sir Fleming warned in an interview to New York Times that improper usage of antibiotics accompanied by natural adaptation process of bacteria would result in selective resistance by bacteria after a period of time (Fleming, 1945). The most important aspect to be considered here is the human attitude in using antibiotics. Critical evaluations across the world have indicated the human behaviour towards the use of the antibiotics as a crucial factor in driving AMR (Hawkins et al., 2022).

1. **Chicken meat-Prospects:** Animal products including meat from hunted animals, eggs, and fish have been a source of food for humans since Paleolithic Age. The last five decades have recorded a phenomenal increase in meat consumption to a tune of more than four-fold and, the future signals a similar trend as well. Amongst meat sources, broiler chicken meat is an important component of world's food basket that holds a significant position in ensuring nutritional and nutrient security to humans. The history of chicken domestication dates back to 5400 BC and the chicken maintained by the Harappan Culture (2500-2100 BC) of the Indus Valley were considered as the main source for subsequent global dispersal of domestic animals. In the last 70years or more, the global poultry industry has witnessed a paradigm shift in structure and operation in terms of its transformation from a mere backyard activity into a multibillion-dollar industry. The major factors responsible for the transformation includes introduction of best broiler strains coupled with proper nutrition, emergence of vertically integrated production systems, contract farming, marketing, globalization, etc. (Umaya, 2014; Castro et al., 2023).

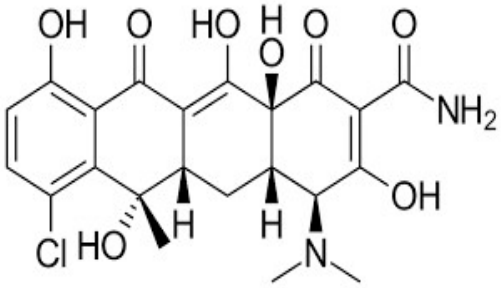
   From the customer point of view, poultry meat is considered as a perfect food for infants, young children, adolescents, adults, elderly people and patients. In fact, chicken meat is a highly demanded item due to its high protein, essential amino acid, vitamin and mineral contents and excellent digestibility. Since consumption of trans-fat is associated with cardiovascular diseases, chicken meat is considered as a healthier option than beef and lamb due to the absence of trans-fat (Mir et al., 2017). Besides improving food security, chicken industry contributes to economic growth by creating employment, diversifying exports and increasing foreign exchange (Castro et al., 2023).

2. **Issues Related to AGPs in Poultry Production:** As a common practice, commercial poultry are raised under intensive conditions and hence are often exposed to various pathogens. Unfortunately, the intensive poultry production practices adopted to enhance production provided a platform for straight- forward clinical sub-clinical infections and their transmission between them. Sub-clincial infections adversely affect the economics of poultry reduction in terms of health losses and reduced production performance. To overcome the subclinical infections associated with intensive farming conditions, improve feed efficiency and growth performance under such conditions, subtherapeutic doses of antibiotics have been used as growth promoters since 1940s. The structures of few antibiotics used as AGPs are presented in Figure 1. Compared with an antibiotic-free diet,

the use of dietary AGPs can increase body weight gain up to 8% and decrease FCR upto 15% in broilers. However, the indiscriminate use of AGPs is associated with the surge in emergence, amplification and transmission of antibiotic resistance in bacteria including zoonotic pathogens, transfer of antibiotic residues in edible poultry products and contamination of environment with antibiotic resistant microbes, antibiotic residues and their metabolites (Rahman et al., 2022).



Penicillin



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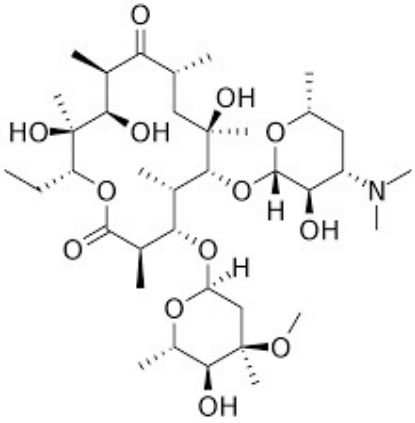

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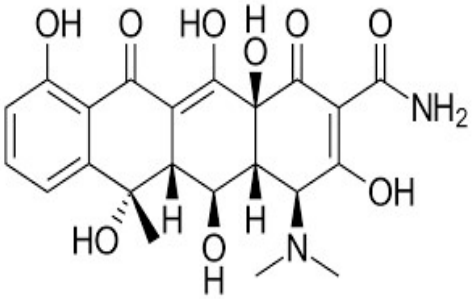
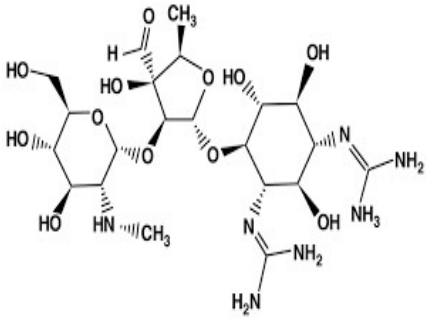
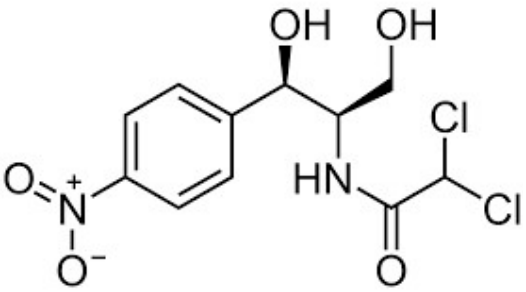


Oxytetracycline



Streptomycin



Chloramphenicol

Figure 1: Structures of Few Antibiotics

3. **Modes of Action of AGPs**: Exposure to bacterial pathogens leads to inflammation, oxidative stress, impaired gut health, and nutrient absorption, reduced performance and increased mortality in broilers. AGPs inhibit subclinical infections, production of toxic metabolites and nutrient use by bacterial pathogens, resulting in increased nutrient availability and growth. The antimicrobial hypothesis of AGP was further ascertained by enhanced growth in chickens raised in a polluted environment compared to those grown germ-free or in clean environments (Mehdi et al., 2018; Rahman et al., 2022). Alternatively, Niewold (2007), suggested that AGPs act on inflammatory immune cells, reduce inflammation, reduce energy wasted in inflammation and diverts the same towards growth. However, as per molecular biology and bioinformatics studies AGPs foster an optimal and balanced microbiota with a reduced capacity to evoke an inflammatory response and an increased efficiency of energy harvest from nutrients in broiler and improveperformance (Gadde et al., 2017). Further, the growth promoting effect of AGPs were associated with changes at the taxonomic, metagenomic, and metabolomic levels in the intestine (Plata et al., 2022).

4. **Adverse Effects of AGPs:** Due to the use of AGPs, the antibiotic resistance in bacteria harbouring poultry and their environment has aggravated. A number of surveillance studies have recorded the occurrence of antibiotic resistant pathogens and genes in poultry environment and products. For example, antibiotic/multidrug resistant bacterial poultry pathogens such as *Salmonella pullorum, Salmonella gallinearum, Enterobacteria,* avian pathogenic *Escherichia coli* and *Clostridium perfringens* have been reported in poultry and its environment in different countries (Nhung et al., 2017; Impey et al., 2020).

   The avian diseases caused by such antibiotic-resistant bacteria are more difficult to be treated, resulting in serious economic losses. Further, the resistant microbes and genes along with antibiotic residues are introduced into humans and environment through multiple routes: (1) During the sacrifice of chickens harbouring antibiotic resistant microbes, edible poultry products are contaminated with resistant microbes and genes. Exposure or consumption of such contaminated meat paves the way for the entry of resistant pathogens (ii) The resistant bacteria excreted through litter and the washings from poultry environment act as sources of antibiotic resistant microbes and genes, contaminate soil, enter sewage, contaminate water bodies and find their entry to human drinking water through sewage contaminated water or dietary fish grown in contaminated waterbodies (iii) Poultry manure is commonly used as a fertilizer in agricultural fields and commercial aquaculture units. Such a practice introduces antibiotic resistant microbes and metabolites into soil and plants (Nhung et al., 2017; Mehdi et al., 2018).

5. **Global Action to Contain AGPs:** Various steps are being taken by the governments across the world to tackle AMR. In an effort to contain AMR, AGPs are banned in many countries and the trend is anticipated in other countries as well in the forthcoming years. As a first of its kind, Sweden banned AGPs in animal feed in 1986. Subsequently, in 2006, European Union banned the use of 25 AGPs in animal production and the same policy was adopted by Mexico, South Korea and New Zealand. In this series, countries like Australia, USA, Japan and Canada have partially banned and excluded some antibiotic-derived additives (Hudson et al., 2017; Abreu et al., 2023).

6. **Alternatives to AGPs:** The Indian and global scenarios forecast an increase in requirement and production of poultry meat in the future. Hence there is an immediate global need for alternatives to AGPs to produce broiler meat in a safer mode. An ideal antibiotic alternative should be palatable, bioavailable, improve the beneficial microbial load, reduce microbial pathogens, improve feed efficiency and growth and should be nontoxic to both to the birds as well as environment. Altogether, the expectation from an AGP alternative is that it should aid to maintain public health as well as animal health and productivity and be environmentally safe (Abdelnour et al., 2020).

7. **Phytogenic Feed Additives as Alternatives to AGPs:** Phytogenic feed additives, also referred as botanicals, phytopoducts or phytobiotics are plant derived substances. In recent years, they are one of the most promising groups of feed additives being explored as alternatives to AGPs in poultry production. As most of the phytogenics are certified as Generally Recognized as Safe (**GRAS**) by the Food and Drug Administration (**FDA**), they are considered as ideal candidates to be used in broiler production (Diaz-Sanchez et al., 2015).

   Phytogenics are classified into two categories based on the source and the method employed to obtain the active ingredients from a particular plant source. The first category of phytogenics are the herbs (products that are obtained from flowering and non-woody plants from which leaves and flowers are used) and the spices (seeds, fruits, bark or root other than leaves of plants, characterized by flavour, pungency and aroma). The second category are the essential oils (volatile lipophilic plant compounds obtained by maceration, steam, water or alcohol distillation, solvent and cold press extraction, cold press extraction, and water distillation) and oleoresins (extracts obtained using non-aqueous solvents).

   The Phytogenics are rich sources of phytochemicals that are synthesized as secondary metabolites by the plants with diverse structures through various metabolic pathways. The structures of such compounds were evolved in order to interfere with the molecular targets of the herbivores and microbes as self-defence. Phytochemicals are of different chemical nature such as polyphenols, terpenoids, alkaloids, phytosterols, and organosulfur compounds, of which polyphenols are the most commonly present and explored group of compounds. Many of the phytochemical compounds possess antimicrobial, antioxidant, immunomodulatory and growth promoting effects. Indeed, these properties of phytogenics stimulated the research in using them as alternatives to antibiotic growth promoters in broilers Moreover; they have the advantage to be included in broiler feed as powders, oils or extracts (Diaz-Sanchez et al., 2015; Abdelli et al., 2021).

   A wide variety of herbs and spices (oregano, cinnamon, thyme, marjoram, rosemary, ginger, garlic, coriander, black cumin, among others) and essential oils (from thyme, cinnamaldehyde, carvacrol, anise, rosemary, garlic, ginger) were explored in poultry either individually or as a mixture, for their potential application as AGP alternatives (Gadde et al., 2017; Zhang et al., 2021). Guo *et al*. (2004) reported a significant increase in body weight gain and improvement in feed efficiency in broilers supplemented with a mixture of 14 herbs. In another study by Murugesan et al. (2015) supplementation of a phytogenic feed additive significantly improved weight gain, feed

conversion ratio, digestive enzyme activitites compared to the AGP, bacitracin methylene disalycylate. In a recent study, Oso et al. (2019) compared the efficacy of a novel phytogenic blend prepared form *Aerva lanata*, *Piper nigrum*, *Cynodon dactylon* and *Piper betle* rich in phenols, flavonoids and pieprine as a replacement to the antibiotic growth promoter, chlortetracycline. Compared to birds fed chlortetracycline, an improved ileal digestibility, intestinal villi height, villi height:crypt depth ratio and performance were recorded in broilers supplemented with the phytogenic blend in the diet at 1% concentration. The same blend was also found to reduce cholesterol and improve carcass characteristics and water holding capacity of chicken meat (Oso et al., 2021; 2023). The exact mode of action of all the phytogenic compounds studied so far are not available. However, it is proved that phytogenics exhibit antimicrobial, anti-inflammatory and or antioxidant effects, stimulate feed intake, optimize gut health, intestinal function, digestion and absorption of nutrients and improve growth in broilers (Kikusato, 2021).

A number of studies have explored the possibility of using essential oils as alternatives to AGPs. Essential oils of thyme, oregano, clove, pepper, lemon grass, eucalyptus, garlic, turmeric and the phytochemicals, eugenol thymol, carvacrol, citral are some of f the most studied compounds in poultry (Peng et al., 2010; Valenzuela-Grijalva et al., 2017). The essential oils possess excellent antimicrobial activity against poultry pathogens. They act through cell membrane disruption, virulence modulation, inhibition of intestinal pathogen colonization, promoting the growth of beneficial bacteria. The antimicrobial properties of essential oils in conjunction with their efficacy to improve digestion, intestinal histomorphometry and inturn the absorption of nutrients, antioxidant and immune enhancing properties are responsible for their positive effects on growth in poultry. At the same time, not all phytogenic are efficient growth promoters. Phytogenics such as grape seed extract, yucca extract cranberry fruit extract, *Macleaya cordata* extract, garlic powder and grape pomace tested as growth promoters did not show positive any effects on performance parameters in broilers (Diaz-Sanchez et al., 2015; Gadde et al., 2017).

It is to be noted that though phytogenic compounds are one of the most promising alternatives to antibiotics, their application in food animal production has been limited, largely due to differences in their source, experimental conditions, in vivo efficacy and limited knowledge on modes of action (Abdelli et al., 2021). Efforts to address the above issues would help to develop excellent antibiotic alternatives and contain AGP induced AMR.

IV. SUMMARY AND FUTURE PERSPECTIVES

The association between the use of sub-therapeutic concentrations of antibiotics in poultry and the development of antibiotic resistant pathogenic microbes has necessitated research on alternatives to antibiotics. Phytogenics exhibit antimicrobial, antioxidant, anti-inflammatory and other health growth promoting effects in broilers and a majority of them are promising alternatives to AGPs. The probability that no single compound will replace all the AGPs needs to be considered. Further research on exploring newer unexplored phytogenics along with their modes of action in parallel with implementation of surveillance programs, control measures, awareness programs etc are essential to contain AMR in poultry.

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