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Artemisia Annua: An Antibiotic Alternative in the Poultry Industry

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Abstract

The poultry industry is based on raising fast-growing chickens. In recent decades, several antibiotics have been employed as growth promoters in the chicken industry, but antibiotic use is banned in the poultry industry due to increased antibiotic resistance and negative impacts on human health. Scientists started searching for alternative antibiotic products as antibiotic resistance increased. Probiotics, prebiotics, organic acids, plant extracts, etheric oils, and immunological stimulants are some of the alternatives. In recent years, these products have improved animal performance, increased animal productivity, prevented and controlled enteric infections, and reduced antibiotic use in animal agriculture. *Artemisia*, which is currently in scattered form in various research papers, and to draw the attention of experts throughout the world to the Artemisia species' untapped potential. *Artemisia annua* is also known as sweet wormwood, sweet Annie, and sweet annual wormwood (Chinese: qngho). It's a common wormwood species native to Asia's temperate zones. The active ingredient present in the *Artemisia* genus is Artemisinin, and chemically it contains both volatile and non-volatile constituents. Biological activities of the *Artemisia* genus include antibacterial, anti-inflammatory, anti-malarial, anti-coccidial, anti-oxidant, and anti-tumor effects. It has positive effects on growth performance, FCR, gut health, immunity, digestibility, and meat quality of broilers. In conclusion, *Artemisia annua* is the best alternative product for avoiding anti-microbial resistance in the poultry industry without compromising growth and production. This study aims to review the research conducted on the *Artemisia* genus.

Keywords: Antibiotics alternative, antibiotics resistance, *Artemisia annua*, poultry ındustry.

INTRODUCTION

The poultry industry is a huge global business that raises ducks, chickens, geese, and turkey for eggs, meat, and feathers. The poultry sector has undergone major structural changes during the last two decades due to the introduction of modern intensive production techniques, improved disease control, and biosecurity tools, genetic improvements, increasing benefits and human population, and urbanization. These changes offer different opportunities for poultry growers, particularly smallholders, to increase their farm income. Poultry immunity, disease outbreak, health, and production are some factors that challenge the growth of the poultry industry (Cavani et al., 2009). Further consumer satisfaction, meat and egg quality, and safety and types of products are creating a challenge in better poultry production (Hafez, 2005). Extermination, removal, and management of food-borne diseases create a major challenge to the poultry industry. At the same time, some other important issues, such as the high level of antibiotics remnants, are causing problems for human health and the poultry industry. Antibiotic tolerance or resistance remained a global issue since the 19th century (Mulder, 2011). Generally, farmers use antibiotics in poultry farming for two purposes, either for controlling diseases or as a growth promoter (Singer and Hofacre, 2006). Antibiotics are used as a growth promoter for animals; added in feed-in lower concentration as compared to treatment purpose (Jones and Ricke, 2003).

The reasons for using antibiotics in poultry feed are primarily based on economic factors. For example, antibiotics in diets are a source of worry because of the rise in body weight gain and feed efficiency (Stutz and Lawton, 1984). In the United States and many other countries, consumers of poultry products are increasingly demanding products from animals fed with diets that do not contain growth promoter antibiotics. This has resulted in the need for non-antibiotic alternatives such as enzymes, intestinal acidifiers, herbal products, natural antibacterial, probiotics, and prebiotics to reduce the growth of unfavorable intestinal bacteria, such as *Clostridium perfringens* (Elwinger et al., 1992; Hofacre et al., 1998).

Antibiotic resistance is still a severe public health hazard, according to the European Centre for Disease Prevention and Control. Due to rising concerns about the possibility of antibiotic-resistant bacteria strains and residues in tissues, the European Commission (EC) decided to ban all routinely used feed antibiotic-growth promoters in 2006. Many scientists have been looking for antibiotic alternatives since this decision was made. Antimicrobial qualities and growth promoter effects have been found in a variety of plant extracts, herbs, and spices, which have been utilized as alternatives to antibiotics in poultry (Akyildiz and Denli, 2016). Plant extracts are

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complex compounds having different compositions and different active components. Proteins, peptides, oligosaccharides, fatty acids, vitamins, and micro-minerals can all be found in plant extracts. Plant extracts contain a wide range of actions, and the active secondary plant metabolites are mostly isoprene derivatives and flavonoids (Tajodini et al., 2015). Many plants extract contain chemical compounds exhibiting antioxidant, anti-microbial, anti-inflammatory, anti-coccidial, and anthelmintic properties (Hsieh et al., 2001; Pradeep and Kuttan, 2004; Hoste et al., 2006).

Benefits of adding plant extract to animal diets include enhancement of body weight gain, stimulation of appetite, improvement of endogenous enzyme secretion, and positive effects on its health and gut activity (Rahimi et al., 2011). Plant extracts as a feed additive in chicken diets may be advantageous because they can improve performance and nutrient digestibility, resulting in good impacts on poultry health and performance. As a result, they can be utilized in chicken production as alternative feed additives (Denli et al., 2004).

*Artemisia annua*is an annual plant that is native to Asia, particularly China. In China, the plant is known as Qinghao. Bulgaria, Hungary, Argentina, Italy, Romania, France, Spain, and the United States are among the countries that harvest it (Allen et al. 1997; Willcox et al. 2004).Sweet Annie, sweet wormwood, sweet sagewort, and annual wormwood are all names for *Artemisia annua L*, which is a member of the *Asteraceae* family and has medicinal and commercial value. Anti-inflammatory, anti-bacterial, anti-coccidial, anti-oxidant, anti-malarial, and anti-tumor properties are all found in *Artemisia annua* L (Brisibe et al., 2008).

The aim of this research is to compile the majority of the research done on the *Artemisia* genus, which is now distributed among many research publications, and to draw the attention of scientists all over the globe to the untapped potential of *Artemisia* species.

1. Antibiotics usage in animal production

In the United States and other nations, antibiotics have been utilized in livestock farming since 1910 (Castanon, 2007). For cheaper production of a large quantity of meat, scientists started using antibiotics and anti-microbial agents in livestock production (Ogle, 2013). In some countries, the non-therapeutic use of antibiotics banned due to antimicrobial resistance leads to treatment failures and economic losses (Dibner and Richards, 2005; Cogliani et al., 2011; Agyare et al., 2018). Among EU countries, Sweden was the first country to ban using antibiotics as a growth promoter in 1986 and for the treatment of bacterial infections in 1988 (Cogliani et al., 2011). After Sweden, other EU countries such as Denmark, Netherlands also banned using of antibiotics in food-producing animals (Agyare et al., 2018). These countries made a ban on all antibiotics used as prophylactic agents in 2011 (Maron et al. 2013). Many other countries also banned using antibiotics and designed special structures for using antibiotics in animals (Choct, 2001).

2. Antibiotic discovery and resistance in the poultry industry

In September 1928, Sir Alexander Fleming developed penicillin by investigating how a contaminant mold suppressed the growth of *Staphylococcus aureus* (Monnet, 2005). Antibiotic resistance was first described shortly after penicillin was discovered. In 1945, Sir Fleming warned about antibiotic resistance in his interview with New York Times. He claims that incorrect penicillin use has resulted in the selection of resistant "mutant forms" of *Staphylococcus aureus*, which can cause more severe infections in animals or people. After a year, widespread usage of this medicine resulted in penicillin resistance in several strains. After only a few years, nearly half of the patients were no longer receptive to the new treatment (Alanis, 2005).

The main cause of antibiotic resistance in people and animals is "selective pressure" caused by antibiotic use in the poultry industry. Inappropriate use of antibiotics, i.e., such as overuse or misuse, enhances the chances of resistance (Daikos et al., 2008).

3. Consequences of antibiotic resistance

Treatment fails to respond to infections caused by resistant bacteria, and these cause an increase in economic expenses. Also, some issues arise associated with morbidity and mortality (Neu, 1992). Infections caused by resistant bacteria are responsible for the financial burden on health care systems and farmers (Rice, 2009).

4. General introduction of Artemisia annua L.

Artemisia is one of the most populous and extensively spread genera in the *Asteraceae* family. It is a diverse genus with approximately 500 species found primarily in Europe, Asia, and North America's temperate zones. Annual, biennial, and perennial herbs are represented in this collection (Iranshahi et al., 2007).

General Morphology

Small capitula, inflorescence, racemose, capitate or paniculate, alternating leaves, seldom solitary, receptacle flat to hemispherical, sometimes hirsute and without scales, pappus absent, or occasionally a small scarious ring are listed as general morphological traits of the Artemisia genus (Heywood et al., 1977). It's an Asian annual herb, most likely from China. It grows naturally between 1000 and 1500 meters above sea level in northern Chahar and Suiyuan provinces in China. Many countries, including the United States, have naturalized it (Ajah and Eteng, 2010). The violet or violet-brown stem is upright. *Artemisia annua* leaves are 3–5 cm long and feature two or three tiny leaflets that are split by severe incisions. The leaves have a strong aromatic smell. In dried leaves, artemisinin content ranges from 0% to 1.5 percent (WHO, 2006). *Artemisia annua* hybrids developed in Switzerland can contain up to 2% artemisinin in their leaves (Simonnet et al. 2006). The little flowers are grouped in loose panicles and have a diameter of 2–2.5 mm. Their color is a mix of green and yellow. Brown achenes with a diameter of only 0.6–0.8 mm are the seeds. Their thousand-kernel weight (TKW) is typically around 0.03 g (wheat has a TKW of about 45 g) (WHO, 2006).*Artemisia annua* is a tall shrub with alternate branches that can reach more than 2.0 meters in height and is normally single-stemmed. Aromatic leaves with a length of 2.5 to 5 cm are extensively dissected. Both 10-celled biseriate trichomes and five-celled filamentous trichomes can be found on leaves and flowers (Patočka and Plucar, 2003).

Chemical Constituents

There are volatile and non-volatile elements in *Artemisia annua*'s chemical composition. Essential oils make up the majority of the volatile components, which range from 0.2–0.25%. Camphene, β-camphene, isoartemisia ketone, 1-camphor, β-caryophyllene, and β-pinene are the major constituents, accounting for roughly 70% of the essential oils. Other minor compounds discovered in the volatile portions of *Artemisia annua* include Artemisia ketone, 1, 8-cineole, camphene hydrate, and cuminal (Malik et al., 2009). Sesquiterpenoids, flavonoids, and coumarins, as well as proteins (such as β-galactosidase and β-glucosidase) and steroids (such as β-sitosterol and stigmasterol), make up the majority of the non-volatile constituents. Sesquiterpenoids such as artemisinin, artemisinin I, artemisinin II, artemisinin III, artemisinin IV, artemisinin V, and artemisinic acid are key chemical elements of *Artemisia annua* (Nofal et al., 2009). Chemical composition of *Artemisia annua* is given in table 1.

Table 1. The chemical composition of *Artemisia annua* leaves (Iqbal et al. 2012)

Contents	Contents Amount (% dry weight basis)
Ash	7.5
Carbohydrate	8.3
Fat	6.07
Protein	18
Fiber	14.2
Moisture	11.4
Phytate	140.4
Tocopherol	2.74
Total Tannins	0.61

In one study, the nutritional composition and biological activities of leaves and stems of *Artemisia annua* were investigated. Moisture, crude lipid, and protein were higher in leaves, while crude fiber, ash, and mineral were more in stems. The proportion of phenols and flavonoids were two times more in leaves than in stems (Turner and Ferreira, 2005). Leaves of *Artemisia annua* plant have 90.3% organic matter, neutral detergent fiber 23.3%, acid detergent fiber 12.8%, and artemisinin 1.4g/100g (Turner and Ferreira, 2005). Since its discovery, *Artemisia annua L.* has been used to treat a variety of illnesses in both animals and humans.

5. Effects of *Artemisia annua L.* on Meat Quality, Intestinal Histology, Feed Conversion Ratio, Digestibility and Immunity of Broiler Chicken

Anticoccidial effects

Coccidiosis is a parasitic condition caused by an internal parasite of the genus Eimeria that damages intestinal tissues, reduces performance and body weight increase, and makes you more susceptible to subsequent bacterial infections. It is the most serious illness in the chicken industry, resulting in annual losses of more than $3 billion worldwide (Williams, 1995). It is caused by seven different species of Eimeria (*E. acervulina, E. maxima, E. tenella, E. necatrix, E. brunetti, E. mitis, and E. parecox*) mainly affects the intestinal tract, causing diarrhea and, in severe cases, responsible for an increase in mortality. *E. tenella, E. acervulina,* and *E. maxima* are all found in broilers, with *E. tenella* being the most virulent, causing hemorrhagic diarrhea and significant mortality. *E. maxima*are moderate pathogenic caused economic losses while *E. acervulina* is mild pathogenic (Györke et al. 2013).

Due to the increase in resistance against anti-coccidial drugs around the world, side effects on animals, and public health concerns due to residual issues, it is necessary to find out new anti-coccidial drugs. One of these potential candidates is the Artemisia plant or its extract having strong anti-parasitic effects and has been used in China for the last 2000 years for curing skin bugs, itchy scabs, lice, and insects. The main ingredient present in *Artemisia annua* is artemisinin, used for curing coccidian and malarial infections in China (Sadiq, 2014). This active component inhibits coccidian sarco/endoplasmic reticulum calcium ATPase by producing free radicals as a result of the cleavage of its endoperoxide (Del Cacho et al. 2010). Artemisinin has negative effects on parasitic reproduction, especially in Eimeria. It reduced the capacity of sporocyst to ovulate and survive in the environment. However, the exact mechanism of action is not known. Artemisinin interferes directly with parasitic developmental stages or indirectly through intestinal microflora. So, the leaf extract or oil content of *Artemisia annua* is the best alternative product for solving resistance issues in the poultry industry (Del Cacho et al. 2010). According to a study, the inclusion of *Artemisia annua* leaves as a 1.5% daily diet can be a good replacement for coccidiosis infections (Drăgan et al. 2014).

Antioxidant effects

The antioxidant status of laying hens was increased by using *Artemisia annua* leaves, as was the immunological function of broilers (Baghban-Kanani et al., 2019). In the past, some research suggested that chickens fed *Artemisia annua* or its extracts grew faster. This could be due to *Artemisia annua*'s abundance of bioactive components, which aid in nutrient digestion and absorption in the small intestine, as well as increasing antioxidant capacity (Song et al., 2018). Antioxidant capacity is linked to the body's antioxidant systems, which comprise both enzymatic and non-enzymatic mechanisms that keep the body's redox equilibrium in animals in check (Attia et al., 2019). Furthermore, antioxidants like glutathione (GSH) and Superoxide dismutase (SOD) can quench free radical overproduction, and hydrogen peroxide can subsequently be reduced to water and oxygen by Glutathione peroxidase (GSH-Px) and Catalase (CAT). The antioxidant enzymes SOD, glutathione peroxidase (GSH-Px), and catalase (CAT) are the three most important antioxidant enzymes in the antioxidant system.

In broilers-fed diets supplemented with 20 or 40 g/kg *Artemisia annua* leaves, the concentration of malondialdehyde (MDA) was lower in the breast and leg muscles. *Artemisia* species extracts boosted SOD, CAT, and GSH-Px activities, as well as lowered MDA generation in the livers of rats, according to research (Ryu et al., 2013). In another study, *Artemisia annua* leaves (AL) and enzymatically processed *Artemisia* (EA) increased T-SOD, GSH-Px, and CAT activities while lowering MDA levels in serum and liver, demonstrating that *Artemisia annua* can improve broiler antioxidant status (Song et al., 2018). *Artemisia annua* extracts including phenolic compounds and flavonoids have been shown to have high antioxidant activity, which could explain why broilers fed AL or EA diets had higher antioxidant levels. *Artemisia annua* has antioxidant properties as its leaves contain maximum proportions of protein and crude fat while minimum levels of fibers. Leaves of *Artemisia annua* also have the highest level of important elements such as copper and manganese. Balance amino acid profile reflects better antioxidant properties. *Artemisia annua* tissues have a negligible level of antinutritional factors along with good nutritional properties. These properties favor its use for human and livestock production as an anti-oxidant product (Ferreira and Janick, 1994). Moreover, the results of the proximate, nutrient and antioxidant studies of *Artemisia annua* tissues provide compelling evidence of the plant's nutritional potential as a prospective feed supplement with numerous applications. Guo et al., (2020) found that an appropriate dose range of 1000–1500 mg/kg of *Artemisia annua* aqueous extract can improve broiler growth performance and antioxidant function.

Effects on meat quality of broilers

Heat is a major environmental stressor that is posing a threat to the global poultry industry (Lara and Rostagno, 2013). It harms chicken growth, feed efficiency, and mortality rates, resulting in significant economic losses. Heat stress (HS) causes physiological and metabolic changes in broilers, including changes in plasma hormone levels (Niu et al., 2009).Some studies show that heat exposure has negative effects on meat quality (Zhang et al. 2012). Water-holding capacity (WHC) and meat color are both affected by muscle pH. Pre-slaughter HS can enhance rigor development, which causes pH and WHC to drop. Heat exposure produces an excessive amount of free radicals, which causes oxidative stress (Belhadj Slimen et al., 2014). Poultry meat is sensitive to free radical aggressiveness and oxidative damage due to its high amount of polyunsaturated fatty acids. Meat quality is thought to be negatively affected by oxidative stress (Archile-Contreras and Purslow, 2011).

Dietary EA supplementation increased meat quality, antioxidant capacity, and energy status in heat-stressed broiler breast muscle, possibly due to changes in relevant mRNA expression. As a result, EA could be a promising feed additive in the poultry market for reducing HS. In certain research, 1.00-1.25 g/kg EA in the broiler diet is advised (Song et al. 2018). Broilers are raised for meat all over the world because of their high nutritional value. Due to high metabolic activity, and a lack of sudorific glands, and feathers, poultry is extremely susceptible to HS (Settar et al. 1999). HS-induced excess reactive oxygen species (ROS) can cause poor meat quality, oxidative damage, decreased adenosine triphosphate (ATP) production, and a negative energy balance (Azad et al., 2010). Under stressful situations, heat shock proteins (HSPs), especially HS, are overexpressed (Nollen and Morimoto, 2002).

Effects on growth performance

The effects of *Artemisia annua* leaves on broiler growth appear to vary between trials. In a dose-dependent approach, dried *Artemisia annua* leaves (0–20 g/kg diet) reduced feed intake and body weight, and a 10 and 20 g/kg diet tended to enhance the feed conversion ratio (FCR) (Engberg et al., 2012). Cobb chicks fed meals containing dried *Artemisia annua* leaves (20 or 40 g/kg in diets) showed identical ultimate body weight, weight increase, feed intake, carcass weight, and FCR to Cobb chicks fed diets containing only dried *Artemisia annua* leaves (20 or 40 g/kg in diets) (Cherian et al., 2013). Furthermore, *Artemisia annua* leaf powder given at 5, 10, and 15 g/kg of meals resulted in enhanced daily body weight gain and a lower feed conversion ratio in chicks (Gholamrezaie et al., 2013). The variation could be explained by differences in *Artemisia annua* origin and dosage, feeding management, and animal type.

Some studies have found that broilers fed a meal supplemented with 5 g/kg *Artemisia annua* leaves had lower ADG (average daily gain) in 1–21 days. This could be due to non-soluble fiber and lignin, both of which have been shown to negatively impact broiler performance. Broilers' digestive systems may be underdeveloped at the beginning stage, making them vulnerable to food components (Jin et al., 1998). In 1–21 days and 1–42 days, broilers fed a diet containing 1 g/kg EA exhibited higher ADG than control and 5 g/kg *Artemisia annua* leaves fed groups. This suggests that enzymatically treated *Artemisia annua* could help broilers grow faster. Corn distillers dried grains with soluble enhanced with xylanase, on the other hand, improve broiler growth and nutrient digestion (Song et al., 2018). The explanation for this could be that enzymatic treatment breaks down the plant cell wall, enhances intracellular contents' interaction with digesting medium, improves the digestibility of plant materials, and so boosts nutrient and bioactive component absorption after ingestion. The explanation for this could be that enzymatic treatment breaks down the plant cell wall, enhances intracellular contents' interaction with digesting medium, improves the digestibility of plant materials, and so boosts nutrient and bioactive component absorption after ingestion (Wan et al., 2017).

Influence on cellular and humoral immunity of broiler

Many studies have shown that natural flavonoids have a beneficial influence on the immune systems of various species. T lymphocyte activation, an increase in blood lymphocytes, phagocytosis activity, thymus weight, and bursa of fabricius weight are all determinants in broiler immunity (Gholamrezaie et al., 2013). The cytokines secreted by activated T cells are primarily responsible for the start of the humoral and cellular immune responses (Taheri et al., 2005). Antioxidant supplementation has been shown to improve immunological responses in recent studies. The hemagglutination assay for sheep red blood cells (SRBC) integrates the roles of lymphocytes, helper T lymphocytes, and macrophages to evaluate the antibody response after immunization with SRBC antigens (Grasman, 2010). Natural products' effects on the immune systems of many species are remarkable and complex. The direct effect could be due to the stimulation of lymphatic tissue in the digestive system, while the indirect effect could be due to changes in the microbial population in the gastrointestinal tract lumen. Several studies on natural products have indicated that they have varying effects on the immune system.

Total anti-SRBC, IgG, and IgM levels were found to be higher in the studies, indicating a boost in humoral immunity. In this case, a combination of these responses could be linked to increased humoral responses in broilers. These cytokines stimulate B lymphocytes in the immune system, causing them to transform into plasma cells capable of producing antibodies. *Artemisia annua*, on the other hand, has antioxidant and anti-inflammatory properties, which are linked to the inhibition of prostaglandin formation as an anti-immune agent (Bhakuni et al., 2001), resulting in a better humoral response.

CONCLUSION

Antibiotics were commonly used in the poultry industry as a growth promoter. Excessive use of antibiotics in animals causes antibiotic resistance for many microbes. In human and veterinary medicine, the effects of antibiotic resistance in microorganisms are essentially the same. The loss of effective antibiotic therapies due to resistance will result in suffering for the affected individual, whether human or animal. Increased treatment expenses in animal and human health care will also have economic effects. For avoiding resistance issues, poultry professionals started looking for a replacement product. One of the best alternative active herbal products is *Artemisia annua L*. The leaf extract of this plant contains bioactive compounds such as flavonoids and essential oils. The extract of this plant was used in China for 2000 years as an anti-malarial, anti-coccidial, anti-inflammatory, and anti-oxidative in animals and humans. Meat quality, growth performance, FCR, intestinal histology, digestibility, and immunological status of broilers are all improved by enzyme-treated *Artemisia annua* L.

Conflict of Interest

The authors declared that there is no conflict of interest.

Authorship contributions

Concept: H.M.N., G.S., Design: H.M.N., G.S., Data Collection or Processing: H.M.N., R.R., I.A., Analysis or Interpretation: I.A., G.S., LiteratureSearch: H.M.N., R.R., Writing: H.M.N., I.A., R.R.

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