Original Article

Effect of Antibiotic Growth Promoters on Anti-oxidative and Anti-inflammatory Activities in Broiler Chickens

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Abstract

The current study was conducted to evaluate the effects of sub-therapeutic antibiotics (avilamycin and flavophospholipol) in animal feed on anti-oxidative and anti-inflammatory properties in broilers to understand the mechanisms of AGPs. Four hundred and fifty six 1-day-old broilers (ROSS 308) were divided into 3 groups with 4 replications. Three experimental diets composed of a corn-soybean meal based diet supplemented with 0, 10 mg/kg avilamycin and 5 mg/kg flavophospholipol were randomly provided to the broilers for 42 days, respectively. Results showed that the AGPs significantly decreased TBA-MDA adduct in serum as well as villi tissue of the broilers, especially flavophospholipol. However, flavophospholipol and avilamycin significantly increased IFN-γ and TNF-α concentration in the serum of broilers. TGF-β was not affected by the AGPs supplementation. These results indicated that the anti-oxidative and immune modulatory properties of AGPs could be an indirect mechanism to promote animal health and production.

Keywords: anti-inflammation, antioxidation, avilamycin, flavophospholipol

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Introduction

Antibiotic growth promoters (AGPs) have been used in animal production for the past five decades to improve the performance of animals and also reduce the rates of morbidity and mortality as well (Kim et al., 2005). The European Union has proposed phasing out of antibiotics as a growth promoter. However, the USA, Thailand and many other countries allow the use of avilamycin and flavophospholipol (or bambermycin) at sub-therapeutic doses in poultry (La-ongkhum et al., 2011; Barros et al., 2012). Since they are not absorbed from the gut and not used as drugs in humans (Chauvin et al., 2005), avilamycin and flavophospholipol are authorized to be used in animal feed. Theoretically, the growth promoting properties of AGPs were reported to be through the control of growth and proliferation of microorganisms (Dibner and Richards, 2005). However, several studies have shown that AGPs do not affect the numbers of pathogenic bacteria, the structure of intestinal tract or even animal performance (Castillo et al., 2006; Pedroso et al., 2006; La-ongkhum et al., 2011). One reason may be due to the sub-therapeutic doses of AGPs given lower than minimum inhibitory concentration (MIC) for pathogens (Niewold, 2007). Most strains of *Salmonella* spp., *E. coli*, *Campylobacter* spp. and *Pseudomonas* spp. resistant to flavophospholipol showed minimal inhibition concentration (MIC) valued approximately >128 µl/ml (Pfaller, 2006). However, it is appropriate to take other probable non-antibiotic alternative mechanisms for AGPs into consideration such as anti-oxidative and anti-inflammatory properties.

Reactive oxygen species (ROS) toxicity has the ability to react with cellular components of the DNA and against polyunsaturated fatty acid (PUFA) present in the cell membrane to initiate lipid peroxidation (Buonocore et al., 2010). This reaction can result in several potentially toxic products including malondialdehyde (MDA) (Miguel, 2010). MDA can react with free amino group of protein, phospholipid and nucleic acid, leading to structural modification and inducing dysfunction of the immune system (Gueraud et al., 2010). Thus, the imbalance between free radicals and antioxidant systems has been shown to be involved in a mechanism of biological damage and to be the cause of several pathologies that affect poultry growth (Fellenberg and Speisky, 2006). Inflammation is the regulatory process, and it is responsible for controlling threats, limiting damage, containment, and healing. Afterwards, the pro-inflammatory cytokines such as interferon-gamma (IFN- γ) and tumor-necrosis factor (TNF) are secreted primarily, and represent the first line of defense in the immune system (Kaiser et al., 2006). IFN-γ is the mediator of the innate immune system and regulates several pro-inflammatory substances such as interleukin (IL)-12, IL-15, tumor-necrosis factor-alpha (TNF-α), interferon-inducible protein-10, inducible nitric oxide synthase (iNOS) caspase-1, and $gp91^{phox}$ (Muhl and Pfeilschifter, 2003). TNF-α is a necessary mediator of local and systemic inflammation. Moreover, TNF-α shows the cardinal clinical signs of inflammation, including heat, swelling, pain and redness (Tracey, 2002). Anti-inflammatory cytokines like IL-10 and transforming growth factor-β (TGF-β) can mitigate the inflammatory process during bacterial meningitis by inhibiting the production of pro-inflammatory cytokines (Van Furth et al., 1996).

A previous study showed that flavophospholipol had a potent scavenging effect in the case of DPPH, hydroxyl and nitric oxide radicals, while avilamycin was able to scavenge only hydroxyl radicals (Kabploy et al., 2015). Furthermore, some antibiotics used as drug therapy for humans such as quinolones, macrolide, tetracycline and β-lactam were reported to reduce the pro-inflammatory cytokine products in lipopolysaccharide (LPS)-stimulated human monocyte *in vitro* (Nau and Eiffert, 2002; Krakauer and Buckley, 2003). According to *in vivo* studies, antibiotics were suppression of inflammatory responses which were given in therapeutic doses (Labro, 1998). Therefore, the aim of this study was to study the effects of avilamycin and flavophospholipol as growth promoters on lipid peroxidation in terms of malondialdehyde (MDA) concentration and pro- and anti-inflammatory cytokine concentrations in broiler.

Materials and Methods

Birds, treatments and diets: Four hundred and fifty six broilers (one-day-old ROSS 308 commercial source chicks) were divided into 3 groups with 4 replications that consisted of 19 males and 19 females per replication. Three experimental diets composed of a corn-soybean meal based diet supplemented with 0, 10 mg/kg avilamycin (Maxus®, Eli Lilly, Dept. Elanco, Germany) and 5 mg/kg flavophospholipol (Flavomycin® 80, Huvepharma, Sofia, Bulgaria), respectively, were randomly fed to the animals. Dietary nutrient components for each period of growth were calculated according to the recommendation of NRC (1994) (Table1). The animals were kept in pens with 12 birds/m^2 density in evaporative-cooling house, where water and feed were available *ad libitum*.

Determination of lipid peroxidation: Eight broilers per treatment were randomized to collect blood sample and jejunal villi tissue at 21, 35 and 42 day old age (DOA). The blood samples were allowed to clot at 4°C for 4 hrs., then serum was collected. The jejunal villi tissue samples were taken immediately after euthanasia by carbon dioxide inhalation. Lipid peroxidation was measured using modified methods of thiobarbituric acid reactive substance (TBARs) assays described by Uchiyama and Mihara (1978) and Asakawa and Matsushita (1980). Briefly, 250 µl of serum or 0.25 g of villi tissue sample was reacted with 100 mM butylated hydroxytoluene (BHT; Fluka), 10% trichloroacetic acid (TCA; Sigma Chemical, St. Louis), 5 mM ethylenediaminetetraacetic acid (EDTA; Sigma Chemical, St. Louis), 8% sodium dodecyl sulfate (SDS; Sigma Chemical, St. Louis) and 1.2% 2-thiobarbituric acid (TBA; Sigma Chemical, St. Louis). The mixture was heated in a 100°C water bath for 60 min. TBA-MDA adduct was detected by fluorescence spectroscopy (PerkinElmer, USA) with excitation at 515 nm and emission at 553 nm. Malondialdehyde standard curve was prepared by 1,1,3,3-tetraethoxypropane (Sigma Chemical, St. Louis) and

TBA-MDA adduct concentration in serum and villi tissue was expressed as nmol/ml and nmol/g, respectively.

Determination of pro- and anti-inflammatory cytokine concentration: At 4 weeks of age, sixteen broiler chickens per group were equally intra-abdominal injected with normal saline (as control) or Lipopolysaccharide (LPS; *Escherichia coli* 0111: B4; Sigma-Aldrich, St. Louis, MO) dissolved in saline at 5.0 mg/kg BW. Blood was collected at 3 hrs. after injection to prepare serum for determining cytokine concentrations. Concentrations of IFN-γ, TNF-α and TGF-β were determined using chicken cytokine-specific enzyme linked immunoabsorbant assay (ELISA) kits (Cusabio biotech Co., LTD. China) (Yang et al., 2008). Assays were carried out according to the manufacturer's instructions and calibrated with cytokine standards supplied along with the kits. In addition, the micro-titer plate provided in the kit was pre-coated with goat-anti-rabbit antibody against IFN-γ, TNF-α and TGF-β antigens. Color change was measured with microplate reader (Tecan Microplate Reader, Sunrise TW; Switzerland) at a wavelength of 450 nm. The concentrations of IFN-γ, TNF-α and TGF-β in the samples were calculated by comparing O.D. of the samples to the standard curve.

Table 1 Feed composition and calculated nutrient components of basal diets for different period of growth

	Period of growth (day)		
	1-21	**22-35**	**36-42**
Ingredients (kg/100 kg feed)			
Corn	54.95	62.35	67.00
Soybean oil	1.50	3.00	3.30
Soybean meal (50% protein)	24.80	31.30	26.35
Full fat soybean (35% protein)	15.00	-	-
L-Lysine HCl	0.10	-	-
DL-Methionine	0.25	0.20	0.25
Limestone	0.40	0.50	0.40
Dicalcium phosphate (18% phosphorus)	2.35	2.00	2.00
Salt	0.40	0.40	0.45
Vitamin-mineral premix[1]	0.25	0.25	0.25
Total	100	100	100
Calculated nutrient components			
Protein (%)	22.00	20.06	17.99
ME (kcal/kg)	3,101.02	3,151.56	3,209.32
Fat (%)	6.41	5.53	5.94
Fiber (%)	2.70	2.29	2.29
Calcium (%)	0.93	0.86	0.80
Total phosphorus (%)	0.76	0.67	0.65
Available phosphorus (%)	0.48	0.42	0.42
Lysine (%)	1.31	1.14	1.00
Methionine (%)	0.61	0.54	0.56
Methionine + cystine (%)	0.95	0.85	0.84

[1]The composition of vitamin and mineral in 1 kg premix: vitamin A 3,000,000 IU, vitamin D3 600,000 IU, vitamin E 5,000 IU, vitamin K3 1 g, vitamin B1 0.5 g, vitamin B2 1.4 g, vitamin B6 0.9 g, vitamin B12 0.5 mg, nicotinic acid 7 g, folic acid 0.2 g, biotin 3 mg, pantothenic acid 2.21 g, manganese 12.0 g, zinc 9.0 g, iron 16.0 g, copper 0.32 g, iodine 80 g, choline chloride 50 g and selenium 30 mg

Statistical analysis: Data of TBA-MDA adduct concentrations and cytokine concentrations were analyzed as Completely Randomized Design (CRD). Mean values of the treatment groups were compared using Duncan's New Multiple Range Test (DMRT) and differences were considered statistically significant at $p<0.05$.

Results

MDA formed in peroxidized lipid system in the serum and villi tissue of broiler chickens at 21, 35 and 42 days of age was measured by TBARs method, to test the antioxidant activity of both AGPs in this study. The data are shown in Table 2. This experiment showed that both avilamycin and flavophospholipol

significantly decreased lipid peroxidation in serum at 21 (p<0.05) and 35 (p<0.01) DOA, whereas they slightly decreased lipid peroxidation at 42 DOA (p>0.05). In case of villi tissue, the AGPs highly significantly (p<0.01) decreased lipid peroxidation at 21, 35 and 42 DOA, especially flavophospholipol.

The effects of avilamycin and flavophospholipol on cytokine concentration in broilers were induced by LPS. Results showed that both avilamycin and flavophospholipol with LPS increased IFN-γ and TNF-α concentration in the serum of broilers, especially in the case of flavophospholipol, while TGF-β was not affected by the antibiotic growth promoters, compared with the saline group (Table3).

Table 2 Effect of avilamycin and flavophospholipol on lipid peroxidation in serum and villi tissue of broiler chickens at 21, 35 and 42 DOA

Experimental diet	TBA-MDA adduct concentration*		
	21 DOA[1]	35 DOA	42 DOA
Serum (nmole/ml)			
Control	2.85±0.31[a]	3.11±0.32[A]	2.33±0.18
10 mg/kg Avilamycin	2.88±0.38[a]	2.54±0.28[B]	2.21±0.34
5 mg/kg Flavophospholipol	2.54±0.32[b]	2.51±0.30[B]	2.24±0.29
P-value	0.02	<0.0001	0.51
Villi tissue (nmole/g)			
Control	5.99±0.60[A]	7.76±0.62[A]	9.32±0.64[A]
10 mg/kg Avilamycin	5.78±0.37[A]	7.08±0.55[B]	8.57±0.55[B]
5 mg/kg Flavophospholipol	5.04±0.44[B]	6.99±0.68[B]	7.67±0.47[C]
P-value	<0.0001	0.008	<0.0001

[A,B]Means in the same column with different superscript differ highly significantly (p<0.01).
[a,b]Means in the same column with different superscript differ significantly (p<0.05).
*The data on TBA-MDA adduct concentrations are shown in mean±SD. [1] Day old age

Table 3 Effect of antibiotic growth promoters on cytokine concentration in serum of broilers

Cytokines concentration(pg/ml)*	adjuvant	Experimental diet			P-value
		Control	10 mg/kg avilamycin	5 mg/kg flavophospholipol	
IFN-γ	Saline	1596.4±217.4[b]	1927.8±323.3[a]	2035.8±155.5[a]	0.02
	LPS	1876.4±221.3[B]	2312.3±202.4[A]	2373.7±295.8[A]	0.005
TNF-α	Saline	98.39±13.67[B]	102.38±7.25[B]	132.17±8.26[A]	0.0001
	LPS	113.88±7.32[B]	119.98±6.17[B]	145.73±11.00[A]	<0.0001
TGF-β	Saline	6.44±0.53	6.34±1.25	6.28±0.76	0.9415
	LPS	5.18±0.19	6.31±0.73	6.35±0.73	0.9859

[A,B]Means in the same row with different superscript differ highly significantly (p<0.01).
[a,b]Means in the same row with different superscript differ significantly (p<0.05).
*The data on cytokine concentrations are shown in mean±SD.

Discussion

In general, antibiotics used as growth promoters are non-absorbable. Thus, it can have an impact on intestinal lumen (Niewold, 2007). This study showed that the AGPs significantly decreased lipid peroxidation in the serum. Moreover, the effect of AGPs on intestinal villi was clear. Higher anti-oxidative activity of AGPs were expressed, decreasing MDA in the serum and villus tissue due to their ability to scavenge hydroxyl radical. A previous *in vitro* study demonstrated that one milligram of flavophospholipol and one milligram of avilamycin were able to scavenge 132.0 and 52.6 nmoles of hydroxyl radical, respectively (Kabploy et al., 2015). Another previous *in vivo* study showed that supplementation with avilamycin significantly decreased lipid peroxidation in terms of TBA-MDA adduct concentration in broiler serum (Paraksa et al., 2011).

Production of cytokine originates from monocyte cells, which are stimulated during interaction between monocytes as well as macrophages and bacteria or bacteria cell wall products. Additionally, LPS can activate the transcription factor NF-κB, a molecule that is well documented in its ability to trigger cellular proliferation and cytokine secretion (Maxwell et al., 2002). This *in vivo* study showed that avilamycin and flavophospholipol with LPS increased IFN-γ and TNF-α concentration in the serum of broilers, whereas previous reports showed that other antimicrobial agent *in vitro* system could interfere with the IL-1, IL-6, IL-8 and TNF-α production. Moreover, they significantly improved monocyte chemotactic and phagocyte activities (Gao et al., 2010). The inversion between *in vitro* and *in vivo* situation is due to *in vivo* being a more complex system. Indeed, birds could be infected with pathogenic microorganisms or contacted with other stimulants that induce the production of pro-inflammatory cytokines. These pro-inflammatory cytokines, which have a broad spectrum of activity on cells involved in immune and inflammatory reactions, could help to mediate resistance to bacterial pathogens (Riesbeck and Forsgren, 1995). Mostly, the growth-promoting ability of sub-therapeutic antibiotics in swine and poultry feeds is greater when animals are raised in poorly sanitized environments due to an immunological challenge caused by infectious pathogens (Roura et al., 1992). Reato et al. (2004) suggested that in different situations, some antibiotics are capable of lowering the expression of IL-6 and

TNF-α in PMNs primed with LPS, while their expression is increased by bacterial presentation. Moreover, cytokine could be generated following vaccinations. Therefore, cytokines represent excellent candidates as naturally occurring therapeutics as well as vaccine adjuvants. The ability of cytokines to prolong immune responsiveness increased the proportion of vaccinated responses of animals (Lowenthal et al., 2000). Lee et al. (2012) suggested that *in ovo* coccidiosis vaccination in combination with virginiamycin and bacitracin methylene disalicylate plus roxasone as growth promoters increased tumor necrosis factor superfamily (TNF-SF) 15 in an *Eimeria*-contaminated condition. In addition, concentrations of lymphocyte, monocyte and immunoglobulin C of broilers receiving 1 g/kg flavophospholipol were higher than in the control group (Demir et al., 2008). Comparison between AGPs found that flavophospholipol was more efficient at releasing pro-inflammatory cytokine than avilamycin. Both AGPs promote growth and feed efficiency in animals, but they belong to different antibiotic groups and classed with different mechanisms of action, which relate to their immune modulatory property. Avilamycin is an antibiotic inhibition bacterial protein synthesis that releases smaller quantities of bacterial pro-inflammatory/toxic compounds than the cell wall-active drug flavophospholipol, which causes the inflammation process of host cells (Nau and Eiffert, 2002). Therefore, the inflammatory response produced from host cells will be lower in case of protein synthesis-inhibition antibiotics (Tauber and Nau, 2008).

In conclusion, these results demonstrated that the antibiotic growth promoters, avilamycin and flavophospholipol, had anti-oxidative property and mediated the inflammatory process and immune response. This finding should be important and beneficial in the search for a proper replacement using antibiotic growth promoter in animal industry

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บทคัดย่อ

ผลของยาปฏิชีวนะในระดับเร่งการเจริญเติบโตต่อการต้านอนุมูลอิสระ และการตอบสนองของระบบการอักเสบในไก่เนื้อ

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การทดลองครั้งนี้เป็นการศึกษาผลของการเสริมยาปฏิชีวนะ (avilamycin และ flavophospholipol) ในอาหารที่ระดับต่ำต่อการต้านอนุมูลอิสระและการต้านการอักเสบของไก่เนื้อ เพื่ออธิบายกลไกของยาปฏิชีวนะในระดับเร่งการเจริญเติบโต โดยใช้ไก่เนื้อสายพันธุ์ทางการค้า Ross 308 อายุ 1 วัน จำนวน 456 ตัว แบ่งออกเป็น 3 กลุ่ม กลุ่มละ 4 ซ้ำ สุ่มให้ไก่เนื้อแต่ละกลุ่มได้รับอาหารทดลองสูตรพื้นฐานข้าวโพด-กากถั่วเหลืองที่มีการเสริมยาปฏิชีวนะที่ระดับแตกต่างกัน 3 สูตรคือ 0, 10 มก./กก. avilamycin และ 5 มก./กก. flavophospholipol ตามลำดับ ทำการเลี้ยงไก่เนื้อเป็นเวลา 42 วัน พบว่าการเสริมยาปฏิชีวนะที่ระดับเร่งการเจริญเติบโตสามารถลดความเข้มข้นของ TBA-MDA adduct ในซีรั่มและเนื้อเยื่อวิลไลของไก่เนื้อได้อย่างมีนัยสำคัญทางสถิติ แต่การเสริมยาปฏิชีวนะ flavophospholipol และ avilamycin ที่ระดับเร่งการเจริญเติบโตในอาหารส่งผลให้ไก่เนื้อหลั่งสารไซโตคายน์ชนิด IFN-γ และชนิด TNF-α สูงกว่าไก่เนื้อกลุ่มที่ไม่ได้รับยาปฏิชีวนะ แต่ไม่ส่งผลต่อปริมาณไซโตคายน์ชนิด TGF-β ในไก่เนื้อ จากผลการทดลองดังกล่าวแสดงให้เห็นว่าคุณสมบัติในการต้านอนุมูลอิสระและการส่งเสริมการตอบสนองของระบบภูมิคุ้มกันนั้นเป็นกลไกทางอ้อมที่สำคัญอย่างหนึ่งของยาปฏิชีวนะที่ใช้ในระดับเร่งการเจริญเติบโต ช่วยส่งเสริมให้สัตว์มีสุขภาพแข็งแรงและมีการเจริญเติบโตดีขึ้น

คำสำคัญ: ต้านการอักเสบ ต้านอนุมูลอิสระ avilamycin flavophospholipol

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