Influence of Dietary Aspirin on Growth Performance, Antioxidant Status, and Mortality due to Ascites in Broiler Chickens

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Abstract

This study investigated the effects of dietary aspirin on growth performance, antioxidant status and mortality in the broilers subjected to cold-induced ascites. A total of 600 1-d old male broilers (Ross, 308) were randomly allotted to four treatment groups, with five replicate pens per treatment and 30 birds each. The experimental groups were kept in a cold chamber to induce ascites and were fed a basal diet supplemented with 0, 20, 40 or 80 mg of aspirin/kg diet. Aspirin had a significant effect ($P < 0.05$) on broiler performance since birds fed 80 mg of aspirin/kg diet had greater body weight gain and lower feed conversion ratio. Compared to other groups, 20 mg of aspirin significantly reduced malondialdehyde concentration and increased total antioxidant capacity with higher glutathione peroxidase activity in plasma ($P < 0.05$). Glucose, cholesterol, and triglyceride concentrations in plasma, as well as mortality due to ascites and right ventricular: total ventricular weight ratio (RV/TV) index decreased while high-density lipoprotein cholesterol concentration and white blood cells increased ($P < 0.05$) by dietary aspirin supplementation. Other parameters were not significantly affected by treatments. These results indicate that the beneficial effect of aspirin are probably related to aspirin's ability to maintain near-to-normal levels of free radical scavenging enzymes and glutathione peroxidase bioactivity, thereby protecting cell membranes from oxidative damage via decreased lipid peroxidation.

Introduction

Ascites or pulmonary hypertension syndrome (PHS) is the most common metabolic syndrome and is associated with rapidly growing tissues in broiler chickens. Characteristic symptoms of this syndrome are chronically elevated pulmonary blood pressure, right ventricular hypertrophy, and systemic hypoxia, leading to variable liver changes, congestive heart failure, and ultimately, death (Cisar *et al*., 2004).

Birds with ascites may be associated with oxidative stress induced by reactive oxygen species (ROS) and other oxidants (Tauseef *et al*., 2008; Ruiz-Feria, 2009). Oxidative stress occurs when oxidant production outweighs antioxidant protection within cells (Iqbal *et al*., 2002). Hypoxia can induce ROS production and endothelial injury by impairing endothelial nitric oxide synthesis. ROS causes a failure of nitric oxide bioavailability, reducing the potential for endothelial vasodilatation and subsequently, causes development of ascites. Superoxide anion reacts with nitric oxide and

produces peroxynitrite, a powerful oxidant mediator for endothelial damage (Ruiz-Feria, 2009). There are several diverse reports investigating the protective efficiency of commonly used supplements on ascites occurrence in broilers. These works were limited to several nutritional and medicinal supplements including vitamins (C and E), coenzyme Q10, L-carnitine, uric acid, Furosemide and Atenolol (Acar *et al.*, 1995; Wideman *et al.*, 1995; Ruiz-Feria, 2009; Rajani *et al.*, 2011). The use of these common supplements in poultry production have been restricted recently, mainly because of their possible carcinogenicity causing liver welling and changing liver enzyme activities (Martin and Gilbert, 1968; Rajani *et al.*, 2011).

Aspirin (acetylsalicylic acid) is the most widely prescribed non-steroidal anti-inflammatory drug, and is used in the cure and anticipation of normal cardiovascular disorders (Bode-Böger *et al.*, 2005). Aspirin can decrease blood clotting, even to the point of internal, gastrointestinal bleeding. Inhibition of blood clotting is thought to be due to disruption of prostaglandin synthesis in thrombocytes (Balog *et al.*, 2000). Aspirin, in addition to antithrombotic and anti-inflammatory effects, is believed to have additional biological properties on vasculature that contribute to increased nitric oxide formation and protect the endothelium from deleterious effects of oxidative stress (Podhaisky *et al.*, 1997; Dragomir *et al.*, 2004). Moreover, aspirin treatment may decrease free radical stress, apparent by decreased lipid peroxidation and maintenance of glutathione content (Shi *et al.*, 1999; Bode-Böger *et al.*, 2005; Tauseef *et al.*, 2008).

Recently, aspirin has gained reputation in human and animal medicine for the avoidance of myocardial infarction. Since ascites may be affected by vasoconstriction and blood clotting, it is possible that aspirin's inhibition of prostaglandins will ameliorate the condition. The primary objective of this study was to assess the role of aspirin supplementation on growth performance, ascites incidence and mortality in broilers under induced ascites.

Materials and Methods
Diets and birds
All of procedures, animal ethics and welfare were carried out in accordance with guidelines set out by Payam Noor University, Sanandaj, Iran. Birds were housed in pens of identical size (2 × 1 m) in a deep litter system with wood shaving.

600 1-d-old male broiler chickens (Ross 308) were randomly allocated to four treatment groups with five replicates and 30 chicks in each. All chicks were fed a basal corn-soybean meal diet (Table 1). Birds had free access to feed and water, with 23 hrs light per day throughout the experimental period. On the seventh day, the feed was supplemented with 0, 20, 40 and 80 mg of aspirin/kg of diet.

Growth performance and ascites evaluation
Body weight gain and feed consumption were measured at the beginning and end of the study. Feed conversion ratio corrected for mortality was calculated. At the end of the study (day 42), eight birds from each pen were selected, slaughtered, and their hearts were removed. The left and right ventricles were separated and their individual weights were measured. The ratio of right ventricle weight to total ventricle weight (RV/TV) was determined as a measure of ascites prevalence (Ruiz-Feria, 2009).

Ascites induction program
The ascites induction program was applied using the cold temperature model (Fathi *et al.*, 2015). Birds were raised (1,260 meters' altitude) under 32°C and 30°C during the first and second week of age, respectively. Then the house temperature was decreased to 15°C during week 3 and maintained between 10 °C and 15°C for the rest of the experiment. Mortalities were recorded daily. The dead birds were inspected for the diagnoses of ascites. The judgment of ascites generally depends on presence of one or more of symptoms including right ventricle hypertrophy/enlargement and/or colloidal fluid in the abdominal activity (Geng *et al.*, 2004).

Blood and biochemical parameters sampling
At the end of the study (day 42), two birds per replicate were selected and weighed. Whole blood samples were collected by vein puncture into heparin anticoagulation tubes for measurements on red blood cell, white blood cell, hematocrit and hemoglobin (Sysmex KX-21 N Automatic blood analyzer, Kobe, Japan). Another set of blood samples (1 ml/bird) were collected into heparin, then transferred to the laboratory for analysis within two hours of

collection and centrifuged (3000 × g, for 10 min at 21℃ temperature). Then, plasma was collected and stored at −20°C until measurements of biochemical parameters. The concentrations of plasma metabolites were measured using standard kits (Sigma Chemical Co, St. Louis, MO 63178-9916, USA).

Biochemical tests including glucose, total protein, triglyceride, cholesterol, high-density lipoprotein cholesterol (HDL-C), alkaline phosphates (ALP), aspartate aminotransferase (AST), creatine kinase (CK), and alanine aminotransferase (ALT) activities were measured (Autolab, PM 4000, Auto analyzer Medical System, Rome, Italy).

Table 1. Composition of the basal diet

Ingredients (%)	Starter (1 to 21 d)	Grower (22 to 42 d)
Corn	54.47	59.25
Soybean meal (44% protein)	22.50	20.75
Corn gluten meal	7.00	8.00
Fish meal	6.16	3.00
Soybean oil	6.00	5.70
Dicalcium phosphate	1.72	1.22
Limestone	1.20	1.30
Vitamin premix[1]	0.25	0.25
Mineral premix[2]	0.25	0.25
Salt	0.25	0.25
DL-Methionine	0.20	----
L-Lysine	----	0.03
Chemical analysis		
ME (Kcal/kg)	3010	3175
CP (%)	23	21
Calcium (%)	1.00	0.9
Available phosphorus (%)	0.5	0.45
Lysine (%)	1.44	1.23
Methionine (%)	0.51	0.45
Methionine + Cystine (%)	1.09	0.95

[1] Supplied per kilogram of premix: vitamin A, 11,000 IU; vitamin D$_3$, 5,000 IU; vitamin E, 40 IU; vitamin K, 4 mg; riboflavin, 5 mg; vitamin B6, 4 mg; vitamin B12, 0.011 mg; niacin, 50 mg; biotin, 0.01 mg; thiamine, 3 mg;

[2] Supplied per kilogram of premix: zinc 80 mg; manganese oxide, 100 mg; selenium, 10 mg; iron sulfate 80 mg.

Antioxidant indices and measuring malondialdehyde concentration in plasma
Malondialdehyde concentration and antioxidants enzyme activities were assayed in whole blood. Lipid peroxidation was measured using the thiobarbituric acid method (Botsoglou *et al.*, 1994) which involves measuring malondialdehyde, the last product of lipid breakdown caused by oxidative stress. Glutathione peroxidase activity was determined *via* a commercially available enzyme kit (Ransel, RANDOX/RS-504 supplied by Randox Laboratories, Crumlin, UK). Superoxide dismutase (SOD) activity was quantified in erythrocyte hemolysate. Total antioxidant capacity was measured using a commercial kit (Randox, Pars Azmoon Co. Tehran, Iran) and auto analyzer (Alcyon 300, USA).

Statistical analysis
The data were analyzed based on a completely randomized design (CRD) with four treatments and five replicates per treatment using the GLM procedure of SAS (2002). The differences between treatments means were evaluated by Tukey's test at a significance level of 5%.

Results and Discussion
Growth performance
Aspirin improved body weight gain and feed conversion ratio (Table 2). All levels of Aspirin supplementation improved growth performance of broilers under ascite-inducing conditions. At day 42, broilers in 20 and 80 mg aspirin groups had significantly higher body weight gain and lower feed conversion ratio than control birds ($P < 0.05$).

These results agree with the findings of Al-Obaidi and Al-Shadeedi (2010), who reported that supplementation of 20 mg of aspirin in broiler diets increased body gain weight and improved feed consumption. However, our results are in contrast with those of Balog *et al.* (2000), who reported that 20 mg of aspirin in diet reduced final body weight in broilers. They proposed that lower body weight also reduces the intensity of ascites in birds, but it remains unclear whether the reduction in ascites incidence was a direct effect of aspirin, or an indirect effect of the lower body weight (Balog *et al.*, 2000). Jain *et al.* (2011) reported that administration of aspirin at 100 mg/kg in rat did not significantly affect body weight in the rat but these differences may be related to the doses and duration of the exposure to the animal.

Table 2. The effects of dietary aspirin on growth performance of broiler chickens (42 d)

Performance traits	Treatments (mg of aspirin in diets)					
	0	20	40	80	*SEM*	*P*-value
Body weight gain (g)	2760[c]	3160[b]	3156[b]	3200[a]	94.79	0.0001
Feed intake (g)	5684[a]	5190[c]	5189[c]	5212[b]	108.48	0.0001
Feed conversion ratio	2.06[a]	1.64[b]	1.64[b]	1.62[c]	0.094	0.0001

Means in a row with different superscripts are significantly different ($P < 0.05$).

Ascites index and mortality due to ascites
In the present study, it was clearly demonstrated that aspirin supplementation at all levels assayed significantly reduced ascites mortality and ascites index (RV/TV) in broilers (Table 3). The ratio of right ventricle weight to total ventricle weight (Ascites index) is an indicator of prior exposure of the heart to increased pulmonary arterial pressures (Geng *et al.*, 2004). Broilers with an RV/TV <0.27 without fluid in the abdomen were considered as normal while birds with an RV/TV ≥0.30 and had liquefied amassing were regarded as having pulmonary hypertension (Cawthon *et al.*, 2001). Aspirin supplementation at all levels, compared to the control, significantly decreased RV/TV and mortality due to ascites ($P < 0.05$), with 80 mg of aspirin appearing more effective in decreasing RV/TV than other levels (Table 3). These results agree with Al-Obaidi and Al-Shadeedi (2010) who reported that aspirin supplementation in broiler diets reduced ascites-related mortality.

Table 3. The effects of dietary aspirin on mortality due to ascites and RV/TV of broiler chickens at day 42

Treatments (mg of aspirin in diets)	Mortality due to Ascites (%)	RV/TV[1]
0	14.0[a]	0.36[a]
20	8.0[b]	0.27[b]
40	6.0[c]	0.25[bc]
80	4.0[c]	0.24[c]
SEM	0.45	0.04
P-value	0.001	0.0001

Means in a column with different superscripts are significantly different ($P < 0.05$).

Aspirin can decrease erythrocyte osmotic fragility (Steer *et al.*, 1997) *via* two probable mechanisms: either by altering the lipid profile of the cell membrane and/or by exerting antioxidant activity. The increase in membrane cholesterol alters membrane surface area and decreases membrane fluidity, permitting higher deformability and lower osmotic fragility in the erythrocyte. Aspirin, as an anti-inflammatory drug, could control the production of toxic oxygen and avoid its harmful consequences (Steer *et al.*, 1997). Inflammation involves the production of toxic oxygen by human white blood cells and it may leak into nearby cells, damage DNA, and provoke cancer. Aspirin as anti-inflammatory drug could control the generation of toxic oxygen and prevent its detrimental consequences (Ames *et al.*, 1996).

Aspirin may offer protection to chicks' cardiac myocytes by improving antioxidant

status (Aruoma and Halliwell, 1988; Woollard *et al.*, 1990; Xianglin *et al.*, 1999). The results of experiment strongly suggested that aspirin had additive effects on improving cardiopulmonary performance and reducing pulmonary hypertension. These may have been mediated by reductions in oxidative stress and malondialdehyde in plasma (data in Table 6), and subsequently, increased availability of nitric oxide to promote vasodilatation to reduce pulmonary hypertension. Balog *et al.* (2000) suggested that aspirin, through their influences

on prostaglandin synthesis, may help determine prostaglandin's responsibility in the progression of ascites because aspirin, a prostaglandin inhibitor, was used in an attempt to promote vasodilatation and inhibit blood clotting in broilers. Moreover, it had been reported that aspirin could improve endothelial function and β-adrenoceptor activity in rats and reduce pulmonary hypertension, which may be attributed to the to an antioxidant effect (Tauseef *et al.*, 2008).

Table 4: The effects of dietary aspirin on blood parameters of broiler chickens

Treatments (mg of aspirin in diets)	cholesterol (mg/dL)	HDL (mg/dL)	triglyceride (mg/dL)	protein (mg/dL)	glucose (mg/dL)	hemoglobin (g/dL)	hematocrit (%)	WBC (10^3/µL)	RBC (10^6/µL)
0	120.25[a]	47.35[b]	83.25[a]	3.80	229.25[a]	7.20	29.22	153.02[b]	2.17
20	82.75[c]	58.05[a]	48.50[ab]	4.65	203.50[c]	9.02	34.00	167.50[a]	2.53
40	114.00[b]	57.60[a]	44.25[b]	4.20	215.75[b]	6.75	27.02	162.55[a]	2.00
80	115.00[b]	53.55[a]	42.00[b]	3.82	212.25[b]	7.40	29.17	166.42[a]	2.21
SEM	12.67	3.47	7.78	0.6	14.23	0.73	2.09	4.70	0.16
P-value	0.0014	0.0173	0.0072	0.1779	0.0142	0.1275	0.1003	0.0035	0.1369

Means in a column with different superscripts are significantly different ($P < 0.05$).

Blood parameters and plasma enzyme activities

The effects of different levels of aspirin on blood parameters and several plasma enzyme (AST, ALT, ALP, and CK) activities are presented in Tables 4 and 5, respectively. Blood parameters were significantly affected by aspirin supplementation ($P < 0.05$). 20 mg of aspirin

significantly reduced glucose in plasma and increased white blood cell (WBC) (Table 4). Moreover, aspirin significantly ($P < 0.05$) reduced the concentration of cholesterol and triglyceride in plasma while increased HDL-C. Supplementing diets with aspirin had no significant ($P > 0.05$) effect on AST, ALT, ALP and CK activities (Table 5).

Table 5. The effects of dietary aspirin on the plasma enzymes activities of broiler chickens

Treatments (mg of aspirin in diets)	CK[1] (U/L)	ALP[2] (U/L)	AST[3] (U/L)	ALT[4] (U/L)
0	4020	2420	271.5	4.75
20	4660	1935	294.6	6.75
40	4260	1830	315.6	6.75
80	3780	1740	267.9	5.25
SEM	846	505	36.27	1.04
P-value	0.9232	0.2778	0.7986	0.4421

[1] creatine kinase, [2] alkaline phosphatase, [3] aspartate aminotransferase, [4] alanine aminotransferase
Means in a column with different superscripts are significantly different ($P < 0.05$).

Our study showed that aspirin significantly increased WBC and HDL-C in plasma. Simultaneously, aspirin reduced glucose, triglyceride, and cholesterol in plasma (Table 4). Reductions in cholesterol and glucose may be attributed to aspirin's effectiveness on stress by reducing plasma corticosterone release, which consequently affects glucose and cholesterol metabolism (Mohammed, 2010). Previously, it

has been reported that aspirin can reduce corticosterone release in laying Japanese quail under heat stress (Abou El-Soud *et al.*, 2006). Neha *et al.* (2011) also reported that aspirin administration in rats significantly reduced glucose levels. As shown, aspirin inhibits gluconeogenesis by inhibiting aminotransferase enzymes used for cytosolic malate and aspartate production from mitochondrial pyruvate

carboxylation and uncoupling of oxidative phosphorylation, resulting in a decrease in blood glucose levels (Mehlman *et al.*, 1971**).**

Shaft *et al.* (1988) showed that aspirin supplementation at 30 mg/kg body weight in rats causes a significant reduction in blood glucose level. Oral administration of aspirin may also decrease levels of corticosterone and T_3 hormone, which would subsequently affect glucose metabolism and decrease glucose concentration in plasma (Mohammed, 2010). Several studies reported that aspirin administration in rats reduced cholesterol and triglyceride (El-Midaoui *et al.*, 2002; Kouraklis *et al.*, 2004; Tauseef *et al.*, 2008). These researchers have suggested that aspirin may have direct antilipolytic effect on adipocytes or a direct action of aspirin in insulin secretion mechanisms, resulting in a reduced state of lipolysis leading to reduced plasma cholesterol and triglyceride. In the present study, administration of aspirin significantly increased total WBC, which agrees with Hirai *et al.* (2001) and Jain *et al.* (2011) who reported that aspirin-treated guinea pigs and rats had elevated production of blood eosinophils and basophils, without changes in neutrophils. Aspirin may possibly inhibit prostaglandins synthesis through irreversibly acetylating serine at the active site of the prostaglandin synthetase (cyclooxygenase enzyme) **(**Balog *et al.*, 2000;

Daud *et al.*, 2003). Prostaglandins can block neutrophil recruitment while aspirin can enhance neutrophils recruitment by two-fold (Moraes *et al.*, 1996**).** It has also suggested that aspirin can change production of blood neutrophils, monocytes and lymphocytes, probably attributed to arachidonate metabolism (Turjačanin-Pantelić *et al.*, 2010).

Malondialdehyde concentration and antioxidant enzymes in plasma

The effect of different levels of aspirin on malondialdehyde concentration and antioxidant enzyme activity in plasma are presented in Table 6. All levels of aspirin reduced malondialdehyde in plasma. Aspirin, compared to the control group, significantly increased glutathione peroxide activity and total antioxidant capacity in plasma ($P < 0.05$). No significant differences have been observed in SOD activity in plasma. These results are similar with those of several researchers who reported aspirin markedly reduced vascular O_{2-} production in cultured aortic smooth muscle cells (Wu *et al.*, 2002) and malondialdehyde in plasma and liver in rats (Shi *et al.*, 1999). Aspirin also increases glutathione peroxidase activity in liver (Kirkova *et al.*, 1995). It is believed that the capability of aspirin to scavenge free radicals is better than several well-established antioxidants, such as ascorbate, GSH, and cysteine (Shi *et al.*, 1999).

Table 6. The effects of dietary aspirin on MDA, T-AOC, and antioxidant enzyme activities in serum of broiler chickens

Treatments (mg of aspirin in diets)	MDA[1] (nmol/mL)	SOD[2] (U/gHb)	GPx[3] (U/gHg)	T-AOC[4] (nmol/mL)
0	3.17[a]	3111	222[c]	0.98[c]
20	2.60[b]	3052	267[a]	2.30[a]
40	2.75[b]	3085	241[b]	1.98[b]
80	2.81[b]	2968	239[b]	1.18[b]
SEM	0.45	325	30	0.81
P-value	0.001	0.1733	0.001	0.005

[1] Malondialdehyde, [2] Superoxide dismutase, [3] Glutathione peroxidase, [4] Total antioxidant capability.
Means in a column with different superscripts are significant ($P < 0.05$).

Data from the present study suggest that aspirin had a consistent and significant effect in decreasing malondialdehyde in plasma relative to the control. In birds fed higher levels of aspirin (80 mg), an increased total antioxidant capacity may facilitate the significant decrease of malondialdehyde. Total antioxidant capacity contributes to the balance of active oxygen and is a potent parameter reflecting the status of all antioxidants in plasma and body fluids (Rajani *et al.*, 2011).

Conclusions

This study showed that aspirin is effective in reducing RV/TV, ascites-related mortality, and malondialdehyde concentration in plasma. Aspirin also improved body weight and feed conversion ratio of broilers. As only four dosage levels were tested in the present study, investigations of different dose levels are warranted for future studies.

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