1. Introduction

Mycotoxins are secondary metabolites produced by Aspergillus flavus and Aspergillus parasiticus fungi (Gallo et al. 2010). Aflatoxin B₁ is the most active hepatocarcinogen and the most abundant aflatoxin which has numerous effects such as decreased performance, immunosuppression, changes in the level of blood parameters, induced hepatic diseases and metabolic disorders in poultry (Kubena et al. 2001; Chen et al. 2014). Aflatoxicosis has negative effects on poultry, which is a sign of liver damages, and measuring blood biochemical parameters can be used to detect aflatoxicosis (Zhao et al. 2010). It is reported that decreased blood glucose levels in chickens receiving aflatoxin are probably due to reduced feed intake or disruption in the production of enzymes related to carbohydrates metabolism (Zhao et al. 2010). Cellular and humoral immunosuppression have been reported in poultry affected by aflatoxin (Verma et al. 2004; Monson et al. 2015a, 2015b). Aplasia of thymus and bursa of fabricius, decreased activity and the number of T cells suppress the activity of phagocytes and reduced humoral immune components such as complements, interferons and immunoglobulins are the effects of aflatoxin in poultry diets (Bovo et al. 2015). As a result of the weakness of immune system, poultry will be more vulnerable against viral and bacterial diseases and in consequence mortality will increase in poultry flocks affected by mechanisms related to increased aflatoxin, and then these secondary damages lead to economic losses in poultry industry (Monson et al. 2015a, 2015b). Due to the adverse effects of aflatoxin on poultry industry, some methods for reducing these effects are necessary. Various methods have been used to neutralize aflatoxins such as using aluminosilicate for binding aflatoxin, so that these compounds impede aflatoxins adsorption in intestine by binding them and reducing the poisoning effects of aflatoxin (Kubena et al. 1998). Further researches showed the ability of microorganisms and biological methods to remove or reduce the effects of aflatoxin and it was showing that polysaccharides and some bacterial cell wall peptidoglycans have the ability to bind aflatoxin B₁ (Li et al. 2010), also Lactobacilli and some yeasts such as Saccharomyces cerevisiae have the ability to reduce the aflatoxin present in the environment based on the mechanism of cell wall binding (Shetty and Jespersen 2006). Probiotics are live microbial cultures which exerts beneficial effects on the host body by balancing gut microflora (Fuller 1989; Houndonougbo et al. 2011; Dibaji et al. 2012). On the other hand, yeast glucomannan reduced the harmful effects of aflatoxins on performance, biochemical indices and immune system (Raju and Devegowda 2000). The use of Bacilli has been studied to remove or reduce aflatoxin adsorption in the gastrointestinal tract at in vivo and in vitro conditions, showed the positive impact of these bacteria in preventing the...
harmful effects of aflatoxin in poultry (Kasmani et al. 2012). Furthermore, many researchers have stated that using Bacillus subtilis as a probiotic plays an essential role in animal performance and health by adjusting the intestinal ecological imbalance (Abudabos et al. 2013; Khan and Naz 2013). Thus, due to the anti-nutritional effects of aflatoxin-contaminated feed and its effect on serum biochemical indices and the immune system (humoral and cellular), for controlling its effects using Toxeat® (a commercial mycotoxin binder from Tak Gen Company), probiotic bacteria (Lactobacillus TD15, TD10, TD4, TD3, Bacillus subtilis JQ618), Saccharomyces cerevisiae yeast cell wall and hydrated sodium calcium aluminosilicate were investigated from 7 to 42 days of age.

2. Material and methods

2.1. Aflatoxin production

The required aflatoxin was produced by contaminating rices with Aspergillus flavus (PTCC 5004) (prepared from the microbial treasures of Scientific and Industrial Research Organization of Iran). For this purpose, 1 ml of Aspergillus flavus suspension containing 7 × 10⁶ fungal spores was added to rice and was cultivated for 7 days at 28°C temperature. After fungal growth and toxin production, rice was dried by using an oven at 70°C; and finally, its powder was obtained. Qualitative and quantitative aflatoxin content in rice powder was measured by HPLC (Waters Alliance e2695 equipped with 2475 fluorescence detector, USA) (Zaghini et al. 2005; Li et al. 2010). The content of aflatoxin in rice samples was G2: 8 ppm, G1: 126 ppm, B2: 22 ppm, B1: 289 ppm and the total concentration of aflatoxins was 445 ppm. In order to prepare the experimental diets, rice powder with a certain composition and level of aflatoxin was added and mixed to the basal diet up to a concentration of 1 mg/kg of aflatoxin B₁. According to the aflatoxin limit in poultry diets (0.02 mg/kg of feed) so contamination of the basal diet was 50 times of the extent permitted (Burel et al. 2009).

2.2. Adsorbent materials

Adsorbent compounds investigated in this study were:

1. Toxeat®, a commercial toxin binder based on biological compounds, produced by Tak Gene Company (Tehran, Iran) containing Lactobacilli, Bacilli and Iranian native cell wall yeast with aluminosilicate (as a career).

2. Lactobacilli strains including Lactobacillus TD₄, Lactobacillus TD₁₅, Lactobacillus TD₃ and Lactobacillus TD₁₀ (each one 1 × 10⁷ CFU/g).

3. 1 × 10⁷ CFU/g of Bacillus subtilis JQ₆₁₈.

4. Saccharomyces cerevisiae’s cell wall (Tak Gene Company, Tehran, Iran).

5. Hydrated sodium calcium Aluminosilicate as a mineral component (HA).

Isolated strains of bacteria were selected (Tak Gene Zist Company, Tehran, Iran) among a collection of over 200 indigenous microorganisms of Iran based on their high detoxification ability at in vitro condition.

2.3. Experimental treatments

In this study, a total of 400 seven-day-old chicks (Cobb 500) were used. The chicks were randomly divided into eight treatments, five replications and ten chicks in each replication (in equal proportions of male and female) and were fed with experimental diet from 7 to 42 days of age. The experimental treatments were as follows:

1. Basal diet (NC)
2. Basal diet + 1 mg/kg of diet aflatoxin (PC)
3. PC + 1 kg/ton of diet Toxeat® (Tox®)
4. PC + 1 kg/ton of diet Lactobacillus TD₃, TD₄, TD₁₀, TD₁₅ strains (L)
5. PC + 1 kg/ton of diet Bacillus subtilis JQ₆₁₈ strain (B)
6. PC + 1 kg/ton of diet Saccharomyces cerevisiae’s cell wall (Y)
7. PC + 1 kg/ton of diet the content of treatments L, B and Y (BLY)
8. PC + 15 kg/ton of diet hydrated sodium calcium aluminosilicate (HA)

The corn and soybean meal used for formulating the experimental diets were analysed for DM, CP and amino-acid contents by near-infrared spectroscopy in Paya Amin Mehr laboratory. Metabolizable energy contents of corn and soybean meal were estimated by using the regression models presented by National Research Council. Diets were formulated for starter (7–14 days of age), grower (15–28 days of age) and finisher (29–42 days of age) periods. The ingredients and nutrient composition of the experimental diets are shown in Table 1. The chicks were vaccinated against infectious bronchitis, Newcastle and Gumboro, but no medical program was performed during the entire experimental period. All birds had freely access to feed and water throughout the experiment. Mash as physical feed form was used during the experiment. A 23L:1D

| Table 1. Composition and measured nutrient of basal diet. |
|----------------------------------------------------------|
| Ingredients (%) | Starter (1–14 days) | Grower (15–28 days) | Finisher (29–42 days) |
|-----------------|---------------------|---------------------|---------------------|
| Ground corn     | 55                  | 46.08               | 45                  |
| Soybean meal    | 39                  | 29                  | 32.6                |
| Soybean oil     | 1                   | 1.05                | 3.8                 |
| wheat           | –                   | 20                  | 15                  |
| Oyster shell    | 1.3                 | 1.17                | 1                   |
| Common salt     | 0.2                 | 0.2                 | 0.1                 |
| Premix®         | 3.5                 | 2.5                 | 2.5                 |
| Analysis        |                     |                     |                     |
| AME (kcal/kg)   | 2995                | 2987                | 3121                |
| Crude protein   | 22.58               | 19.25               | 20.23               |
| Digestible lysine | 1.156             | 0.923               | 0.994               |
| Digestible methionine | 0.528           | 0.423               | 0.434               |
| Digestible methionine + cysteine   | 0.834           | 0.698               | 0.717               |
| Available phosphorus | 0.546         | 0.42                | 0.424               |
| Calcium         | 1.068               | 0.87                | 0.812               |
| Na (%)          | 0.212               | 0.187               | 0.145               |
| Cl (%)          | 0.248               | 0.225               | 0.163               |

PC: Permix Vitamin and Mineral analysis: Vitamin A, 1000 IU; vitamin D₃, 3500 IU; vitamin E, 40 IU; vitamin K₃, 2 mg; vitamin B₂; 5 mg; vitamin B₆, 35 mg; vitamin B₁₂, 13 mg; vitamin B₁₂, 1.5 mg; vitamin B₁₂, 0.01 mg; vitamin B₆, 1.6 mg; Biotin 1.5 mg ; I, 1.25 mg; Cu, 16 mg; Zn, 100 mg; Se, 0.3 mg ; Mn, 120 mg; Fe, 40 mg; Choline chloride, 350 mg; Betaine, 150 mg; ME (kcal/kg) 2837; CP, 12.5%; TSA 6.3%; Dig Lys 1.8%; Dig Thr 0.85%; Ca, 21.88%; Na 2.45%; AP 11.5%.
h photo-schedule was applied throughout the experiment. The bird care and used procedures were approved by the Standard Committee of Karaj Animal Science Research (approval date: 19/02/2016; No: 10036).

2.4. Measurement of blood parameters

At 28 days of age, a bird randomly selected from each experimental unit and 3 ml of blood was taken from the wing vein. Serum was used to measure plasma glucose, total protein and cholesterol concentrations. Analysis of serum samples was carried out by ELISA technique and using the ELISA Reader BioTek, Elx 800 and Pars commercial kits (Kasmani et al. 2012).

2.5. Evaluation of immune system

To evaluate cellular immunity, one chick from each experimental unit was marked and 0.2 ml dinitrochlorobenzene (containing 10 mg/ml DNCB) was injected subcutaneously at day 35. The ratio of 4:1 acetone and olive oil was used as a solvent. In order to test this, a fairly featherless zone with approximate 5 cm² area on the right side of the body was selected for DNCB injection. Next, the skin thickness was measured before and 24 and 48 h after injection to evaluate the response rate. The mean increase of skin thickness for each chick was obtained from the difference before and after DNCB injection (Green and Sainsbury 2001).

At 35th days of age, one chick from each experimental unit was selected randomly and marked by a colour. The third finger thickness of right foot was measured before injection and then 0.1 ml of phytohemagglutinin solution was injected subcutaneously. Twenty-four and 48 hours after injection, the thickness of the injection site was measured and in order to assess the proliferation of immune cells in the immune system, thickness difference of before and after each injection was considered as the measure of evaluation (Gunal et al. 2006). To evaluate humoral immunity, at 21st and 28th days of age 5.0 ml of 5% sheep red blood cell (SRBC) suspension washed in sterile phosphate-buffered saline and was injected into pectoral muscle. Afterward, 7 days after each injection of red blood cells (28th and 35th days), about 3 ml of blood from the same birds was taken through the wing vein. After separating serum, each serum sample was divided into two parts; the first one was used to determine the overall response titre (SRBC) by microtitre hemagglutination method, the second one was used to determine IgG titre. In order to measure IgG and IgM in serum samples, IgM was disabled. After measuring the amount of resistant antibody to mercaptoethanol (IgG) and deducting the amount of IgG from the total response (SRBC), the sensitive antibody to mercaptoethanol (IgM) was obtained (Niu et al. 2009; Grasman 2010).

2.6. Statistical analysis

The results of the experiment were analysed in a completely randomized design with eight treatments and five replications per treatment. Data were analysed using the GLM procedures SAS version 9.2 (2009) and differences between the treatments were compared by Duncan’s multiple range test and the value of significance level was .05.

3. Results

3.1. Blood parameters

According to the results of the effect of treatments on serum glucose and total protein was significant (p < .05), so that PC group significantly had the lowest value in treatments and the other groups receiving aflatoxin adsorbent agent had no significant difference with NC (p > .05). Also, no difference was observed between treatment groups for serum cholesterol (p > .05) (Table 2).

3.2. Evaluation of immune system

Differences in data of DNCB test at 35 days of age were significant after 48 h (Table 3), so that the PC group had the lowest swelling of the skin (p < .05) and the other treatments had no significant differences with each other (p > .05). The use of aflatoxin adsorbents could eliminate the negative effects of toxin. However, it seems that biological additives such as yeast cell wall and specified strains of Lactobacilli and Bacilli bacteria have shown a better ability to inhibit aflatoxin and according to DNCB test these groups had higher levels of immunity. Twenty-four hours after injection, differences between treatments for swelling of the skin were not significant (p > .05).

Table 2. Effect of different toxin binders on serum concentrations of glucose, total protein and cholesterol in broiler chickens treated with aflatoxin at 28 days of age.

| Treatment | Chol (mmol/l) | TP (g/l) | Glu (mmol/l) |
|-----------|--------------|---------|--------------|
| NC        | 4.34         | 41.8a   | 12.46a       |
| PC        | 5.02         | 37.37a  | 10.49b       |
| Tox*      | 4.37         | 42.00a  | 12.29a       |
| L         | 4.39         | 42.20a  | 12.07a       |
| BLY       | 4.61         | 41.90a  | 12.18b       |
| Y         | 4.34         | 42.10a  | 12.45a       |
| HA        | 4.39         | 42.40a  | 12.32a       |
| SEM       | 1.67         | 0.04    | 0.28         |
| p-value   | <.05         | <.0001  | >.05         |

Table 3. Effect of different toxin binders on response to DNCB in broiler chickens treated with aflatoxin (mm).

| Treatment | 24 hours | 48 hours |
|-----------|----------|----------|
| NC        | 1.40     | 0.91a    |
| PC        | 1.58     | 0.50a    |
| Tox*      | 1.52     | 0.91a    |
| L         | 1.40     | 0.98b    |
| BLY       | 1.64     | 0.98a    |
| HA        | 1.63     | 1.00b    |
| SEM       | 0.040    | 0.032    |

Note: Chol: cholesterol; TP: total protein; Glu: Glucose; NC: negative control; PC: positive control; Tox*: Toxeat® (commercial toxin binder); L: Lactobacillus TDg, TDa, TD10, TD15 strains; B: Bacillus subtilis JQ618, strain; Y: yeast cell wall; BLY: B + L + Y; HA: hydrated sodium calcium Aluminosilicate.
days of age, the IgG titre had a similar trend to SRBC antibody titre in the same period and treatments receiving various additives were in NC intermediate and PC groups. Commercial toxin binder and Lactobacilli showed higher IgG titre than the other additives (p > .05). The lowest amount of IgG titre was observed in PC group and the highest titre in NC group (p < .05). IgM titre in both 28 and 35 days of age did not show significant difference among the treatments (p > .05).

4. Discussion

Aflatoxins are the reason of a wide range of metabolic damages and liver lesions, reduction of digestive enzymes and immune suppression (Zhao et al. 2010). Changes in serum parameters are the index of liver damage level and disruption in metabolic pathways (Kececi et al. 1998). It has been reported that the reduction of serum glucose, protein, calcium and phosphorus levels in aflatoxicosis condition is a sign of liver injury by toxin (Zhao et al. 2010). Chen et al. (2014) indicated that aflatoxin consumption significantly decreased serum levels of glucose, albumin, total protein, globulin and phosphate.

In the present research, serum concentration of glucose and total protein decreased at 28 days of age in the PC group. But there were no significant differences in NC group and the other groups receiving aflatoxin adsorbent. According to this, we can conclude that the studied toxin binder compounds were controlled aflatoxin effects on serum levels of total protein and glucose. Reduced glucose and total protein affected by aflatoxin and effects of studied adsorbent compounds on serum parameters were consistent with previous studies in this area (Denli et al. 2009; Chen et al. 2014; Bovo et al. 2015). Abudabos et al. (2016) showed that using Salmonella typhimurium in diets had a significant effect on serum total protein level in broiler chickens during starter period.

Aluminosilicates, yeast cell wall and probiotic bacteria such as Bacillus cause to reduce aflatoxin effect on serum glucose concentration (Kasmani et al. 2012; Bovo et al. 2015). Based on these results and in accordance with past findings, there was no significant difference between the concentration of serum parameters in NC group with the other groups.

Hydrated sodium calcium alumino silicate has the ability to adsorb mycotoxins by surface or by its internal spaces. The adsorption of mycotoxins is performed by the engagement or replacement of positive charges within these surfaces. Therefore, mycotoxins will be adsorbed by the pores and are trapped in by the electrostatic charge (Boudergue et al. 2009). Using yeast in poultry diets has been developed for its beneficial effects. These effects are due to several reasons, yeast cell contains proteins, vitamins and minerals (Amata 2013) and yeast cell wall contains 1,1-6, D-glucan and mannano-oligosaccharides (MOS) that MOS has some mycotoxin, including AF binding capacity which will improve the rate of growth because of its positive effect on intestinal mucosa; furthermore, it increases villus height, the number of anaerobic and cellulolytic bacteria which enhance lactate utilization and moderates pH of the gut, and in consequence improves the nutrients digestibility and growth performance (Abdel-Azeem 2002).

Binding mycotoxin to yeast wall glucosmannan is doing by hydrogen bonds and van der Waals forces and this binding
It has been shown that some bacteria cell walls have the ability to adsorb different kinds of toxins (Dalié et al. 2010; Devreese et al. 2013). Investigations of Gao et al. (2011) on one of Lactobacilli strains showed that in addition to antimicrobial activity against E. coli and Salmonella typhimurium strains, this bacterium have the ability to adsorb B1, M1, and G1 aflatoxins, respectively, at a rate of 81.5%, 60% and 8.7%. Likewise, in a research into the wide range of Lactobacilli strains, the ability of these microorganisms in binding aflatoxin B1 with different capabilities in different strains was confirmed (Peltonen et al. 2001). These bacteria are among probiotic bacteria whose ability to reduce the mutation and binding to carcinogens is proven (Devreese et al. 2013). According to studies, carbohydrates and cell wall proteins of Bacilli have the ability to adsorb and bind aflatoxin, this potential was confirmed at in vivo and in vitro conditions (Földes et al. 2000; Huwig et al. 2001).

Probiotics can increase the cells of lymphoid organs (Corrier 1991) that the results of Tox® in response to PHA-P at 35 days of age of our study confirmed these contents. Skin sensitivity test for PHA-P is used to assess cell-mediated immunity and increased skin sensitivity is the result of leukocytes activity (Schrank et al. 1990; Grasman 2010). In this study with increasing aflatoxin consumption, the lowest response to CBH between groups containing aflatoxin adsorbent compounds was recorded in HA group. It seems that adding hydrated sodium calcium aluminosilicate (HA) could not well improved immune function.

The reduction of skin response to DNCB has been reported by adding aflatoxin in broiler diets, so that, adding 1 mg/kg aflatoxin to broiler diets reduced the thickness of the skin after injection of DNCB compared with the control group. These results were obtained 12-96 h after injection (Shivachandra et al. 2003). Moreover, in another experiment, adding 0.5, 1 and 2 mg/kg of aflatoxin B1 to broiler diets significantly reduced the thickness of the skin in DNBC challenged area with (Verma et al. 2004). Adverse effects of aflatoxin on DNBC response at 35 days of age in PC group of our study were consistent with what was said. Some researchers expressed that the presence of mannann and glucan in yeast cell wall can stimulate the immune system (Rodriguez et al. 2003; Sohail et al. 2011). In vitro studies have shown the anti-inflammatory effects of yeasts and their ability to activate natural killer cells and B lymphocytes (Jensen et al. 2007). The useful effect of probiotics on performance improvement, strengthening the immune system, balance of intestinal microflora and removing aflatoxin from poultry food have been reported. Lactic acid bacteria, including Lactobacilli, have the ability to neutralize toxin through their cell wall, also glucans and mannans of bacteria wall provide the possibility of absorbing different kinds of toxins (such as aflatoxin) (Dalié et al. 2010; Devreese et al. 2013). Moreover, carbohydrates and cell wall proteins of Bacilli play an important role in the adsorption of aflatoxin into these microorganisms (Huwig et al. 2001). The results at 35 days of age in Tox®, L, B and Y groups demonstrate the ability of these additives in the adsorption of aflatoxin and prevent its negative impact on the immune system and the findings were consistent with those previously mentioned.

Aflatoxin can reduce the activity of the innate and acquired humeral immunity. In general, aflatoxin decreases serum proteins and antibodies in poultry. IgG and IgM antibody titres either alone or in total decrease in response to SRBC affected by aflatoxin consumption (Monson et al. 2015a). SRBC test results of this study for PC group are consistent with what was said. Using Lactobacilli alone and also a mixture of Lactobacillus, Bacillus and yeast may increase immunoglobulin levels and improve immune system, which these findings are corresponded with the result of Tox®, L and Y groups (Kasmani et al. 2012; Salim et al. 2013). According to researches, the positive effects of probiotic compounds in poultry diets, in addition to stimulating the immune system, are the mechanism of probiotic bacteria by exerting influences such as lowering gut pH, suppressing pathogenic bacteria through the production of organic acids, preventing bacteria from colonizing through competitive exclusion, producing antibacterial mucin and enzymes (β-glucosidase and β-glucuronidase), competition for nutrients in the gut and others (Khan and Naz 2013).

The most important changes due to Aflatoxicosis are created in the liver, kidney and lymph tissues, so that the lymphoid organs including the bursa fabricius and thymus degenerate and disruption the development of bursa fabricius reduces the production of immunoglobulins (Corrier 1991). Furthermore, in this study decreasing the production of immunoglobulins in the PC group was observed. The reports said that feeding diets contaminated with aflatoxin disrupted the production of proteins in the body. Disruption of the normal process of protein production can decrease IgG and IgA and simultaneously decreased lymphocyte count (Tessari et al. 2006). Results of IgG titre and SRBC obtained in PC group, in our research, were consistent with what was mentioned. Immunosuppression by aflatoxin is an obvious example of humoral response suppression and animals that are experiencing this suppression are very susceptible to cancer (Thaxton et al. 1974). Tox® and L groups showed the highest level of IgG titre between the groups fed with aflatoxin and adsorbent compounds, which is why this result is consistent with previous findings about the ability of probiotics and yeast wall in detoxification and improve the poultry immune response (Sohail et al. 2011; Kasmani et al. 2012).

According to the results, the studied probiotic and prebiotic as a mixture (BLY and Tox® treatments) and separated (B, L and Y treatments), controlled the stressor effects of aflatoxin on chickens moreover in this study the ability of lactobacilli was higher than Bacilli.

5. Conclusion

Based on the results, consumption of aflatoxin-contaminated diets could impair liver function and metabolic pathways and these damages are decreased by using some compounds with different inhibitory effects. In the present study, Y, L, BLY and Tox® groups controlled aflatoxin effects on the suppression of humoral and cellular immune system. These compounds by reducing the anti-nutritional effects of aflatoxin, while improving the process of protein synthesis, increased antibody production and response to SRBC injection. Regarding to what has been said, using a mixture of prebiotics and probiotics like those in...
BLY group is suggested in order to control aflatoxin effects on chicks and improve immune function and biochemical pathways.

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