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THE POTENTIAL USES OF SILYMARIN, A MILK THISTLE (*Silybum Marianum*) DERIVATIVE, IN POULTRY PRODUCTION SYSTEM

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ABSTRACT: Due to recent intensive poultry production, there is a great demand to use natural alternative feed additives. One of these alternatives is phytobiotics. Milk thistle (*Silybum marianum*) is a plant that has been used for many years as a natural remedy for the liver diseases. Silymarin is the major dried extract of milk thistle. Silymarin has many flavonolignans that showed antioxidant, anti-inflammatory, anti-fibrotic, anti-lipid peroxidative, immune stimulant, and hepatic cells stabilizing effects. In poultry production system, silymarin has been used in broilers as a growth promotor and in layers to improve the egg quantity and quality. It has been also used as a hepatotonic substance as a result of a potent antioxidant activity. The carcass trait showed improvement after treatment of broilers with silymarin. In addition, enhancement of the immune system and the intestinal health has been detected after application of silymarin in poultry diets. Accordingly, this review article aims to show the different potential uses of silymarin in poultry production system regarding its effect on production performance, antioxidant status, carcass traits, immune response, and intestinal health.

Keywords: Antioxidant, Carcass trait, Immunity, Intestinal health, *S. marianum*

INTRODUCTION

As a result of COVID-19 crisis and drastic decrease in the feed supply, search for alternative feed supplies becomes very urgent (Hafez and Attia, 2020). Moreover, it is important to decrease the need to include antibiotics in the nutrition of poultry to avoid the adverse effects of resistance and the harmful residues in poultry products (Castillo-Lopez et al., 2017). Addition of phytobiotics to poultry feed is regarded as an effective alternative approach. Phytobiotics can improve the nutrient digestibility and the function of birds via increasing the secretion of digestive enzymes and the number of natural flora, reducing the viscosity of digestive substances, enhancing the immune system, and lowering the blood cholesterol level (Ritz et al., 1995).

Milk thistle plant or *Silybum marianum* L. Gaernt. (*S. marianum*), sometimes called wild artichoke, is a member of *Asteraceae* family (Pepping, 1999). It has been previously used in medicine as a natural remedy for the liver and biliary tract (Morazzoni and Bombardelli, 1995). The dried extracts of *S. marianum* seeds contain approximately 60% silymarin (Bhattacharya, 2011). It is the active ingredient of milk thistle, which represents 4% of the dried seeds or in the aerial parts of the plant (Rajiha, 2012). It can be used as a non-toxic, safe, and cheap liver tonic feed additive to substitute synthetic drugs in poultry diets (Saeed et al., 2017). Silymarin was initially found in the Mediterranean mountain, North Africa, and Asia, but today, it has been grown in many parts world-wide (Khan et al., 2009).

Silymarin contains many flavonolignans such as silybin (50%-60%), silychristin (20%), silydianin (10%), and isosilibine (5%) as well as flavonoid (taxifolin) (Federico et al., 2017; Attia et al., 2019). Silymarin complex showed antioxidant, anti-inflammatory, anti-fibrotic, anti-lipid peroxidative, immune stimulant, and hepatic cells stabilizing effects (Suchy et al., 2008; Saeed et al., 2017). Furthermore, milk thistle seeds contain betaine, trimethyl glycine, and essential fatty acids which involved in the hepatoprotective and anti-inflammatory actions of the silymarin complex (Saller et al., 2001).

The different beneficial effects of silymarin have been previously reported in poultry production. It is considered as a potential feed additive to broilers in terms of enhancement of the growth performance, prevention of oxidative stress, improvement of the meat quality, increasing the production of polyunsaturated fatty acids, and stimulation of immune status (Zaker-Esteghamati et al., 2020; Bagno et al., 2021; Armanini et al., 2021).

Based on abovementioned findings, this review article aims to show the different potential uses of milk thistle derivative, silymarin, in poultry production system regarding its effect on production performance, antioxidant status, carcass traits, immune response, and intestinal health.

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THE DIFFERENT EFFECTS OF SILYMARIN IN POULTRY PRODUCTION SYSTEM

Production performance

Researchers showed that silymarin can improve the productive and reproductive performances and the health status of chickens (Abdulwahid and Oleiwi, 2021; Armanini et al., 2021), ducks (Egresi et al., 2020), and quails (Soto et al., 2003; Behboodi et al., 2017; Khaleghipour et al., 2019, 2020). Treatment of turkeys with silymarin at doses of 0.5 kg and 1 kg/ ton of feed mixture induced higher live body weight compared with un-treated control group (Gawel et al., 2003). Zarei et al. (2016) inoculated 1 ml of two dilutions (100 and 200 mg/L) of milk thistle extract *in ovo* and then added it to the feed mixture at a dose of 100 mg/kg. The results indicated higher final live weight of chickens compared to the control group. Besides, Abdalla et al. (2018) found an improvement in the body weight of chickens supplemented with silymarin (25 g/kg of diet) under the Egyptian summer conditions. Broiler chickens consumed silymarin (160 mg/kg diet) at the starter, grower, and finisher stages of rearing showed improvement of the body weight gain and feed conversion indices (Mousa and Osman, 2016). In the study of Shahsavan et al. (2021), dietary inclusion of 3%, 9%, and 12% of *S. marianum* oil extraction byproduct into the diet of broilers induced an increase in the body weight, feed intake, and the feed conversion rate. Various concentrations of silymarin (0, 100, and 200 mg/kg) in broilers enhanced the growth performance after exposure to lead-induced oxidative stress (Ebrahimi et al., 2013). In addition, it can alleviate the toxic effects of mycotoxins and improve the impairment of growth performance parameters elicited by mycotoxins in broilers (Kalorey et al., 2005; Chand et al., 2011; Surai, 2015; Morovat et al., 2016; Alhidary et al., 2017). Improved feed intake and feed conversion rate were observed in broiler chicks fed on a diet containing 0.8 mg/kg aflatoxin and treated with 600 mg/kg silymarin (Tedesco et al., 2004). Muhammad et al. (2012) reported that silymarin at a level of 10 g/kg diet increased the feed intake and the weight gain of broilers fed on rations contaminated with aflatoxin. In the same line, dietary supplementation with silymarin ameliorated the decreased feed intake and the body weight gain and improved the feed conversion rate of aflatoxin-challenged broiler chicks (Jahanian et al., 2017). A concentration of silymarin (500 g/ton feed) was able to mitigate the negative effect of aflatoxins on the metabolism and growth performance of laying Japanese quails (Sakamoto et al., 2018). Silymarin supplementation of aflatoxicated chicks increased the body weight gain as the result of increasing the feed intake and the protein synthesis in the hepatic cells (Sonnebichler and Zetl, 1986) as well as enhancing the digestibility and absorption of nutrients by increasing the digestive enzymes (Sultan et al., 2018). Moreover, enhanced growth performance parameters in silymarin-treated birds may be owing to the hepatoprotective and the detoxifying activities of *S. marianum* against mycotoxins (Baer-Dubowska et al., 1998; Fraschini et al., 2002). This compound can reduce the intestinal ulcer index and increased the mucin content (Huilgol and Jamadar, 2013).

Antioxidant

Silymarin restored the oxidant and antioxidant activities to the normal physiological conditions that benefit animal health and consequently human consumers (Armanini et al., 2021). This compound restored all changes in liver and serum after intoxication with aflatoxin and that indicates its hepatotonic effect (Rastogi et al., 2000). Addition of 800 mg silymarin/kg feed to a diet of broilers containing 1 mg/kg aflatoxin inhibited the increase in alanine aminotransferase (ALT) activity (Jamshidi et al., 2007). Similar result was also reported by Tedesco et al. (2004) and Fani Makki et al. (2014). A recent study of Tsiouris et al. (2021) indicated that dietary supplementation of broiler diet with detoxifying agent containing modified zeolite, *Bacillus (B.) subtilis*, *B. licheniformis*, *Saccharomyces cerevisiae* cell walls, and silymarin ameliorated the adverse effects aflatoxin and ochratoxin. In ducks, a concentration of 0.5% silymarin decreased the oxidative stress of the liver after feeding on diets containing zearalenone and deoxynivalenol (Egresi et al., 2020). In other avian species such as Japanese quails, silymarin reduced the concentration of triglyceride and cholesterol when compared with carbon tetrachloride treated group (Behboodi et al., 2017; Moradi et al., 2017). Silybin, the major active constituent of silymarin, has antioxidant characters, hepatoprotective effect, and free radical scavenging activities (Fraschini et al., 2002; MacDonald-Ramos et al., 2021). This antioxidant effect may achieved by reservation of the hepatocytes membranes integrity, stabilization of phospholipid structure, activation of nucleic acids and protein biosynthesis, and stimulation of immunity (Vargas-Mendoza et al., 2014; Saeed et al., 2017). Silymarin decreased the secretion of some hepatic enzymes such as ALT, aspartate aminotransferase (AST), and alkaline phosphatase into blood as a result of hepatic injuries from free radicals (Amiridumari et al., 2013; Armanini et al., 2021) and also reduced the oxidation of lipid and protein (Alhidary et al., 2017) and the apoptosis of DNA (Upadhyay et al., 2010). Moreover, it has been found that silymarin prevented lipid peroxidation and returned some antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase in the hepatic cells of chickens after ochratoxin damaging effects (Yu et al., 2018; Armanini et al., 2021). This compound also returned some other antioxidants vitamins such as vitamins E and vitamin C in the liver (Pradeep et al., 2007). In a quail's trial, the results indicated that silymarin decreased the levels of bilirubin, malondialdehyde (MDA), ALT, triglyceride, and cholesterol, while increased the levels of albumin, protein total, superoxide dismtase, total antioxidant, and glutathione peroxidase (Moradi et al., 2017). Alassi and Allaw (2020) found that addition 1 g/kg milk thistle seed powder in quail's diet lowered the level of cholesterol, glutathione, MDA, ALT, and AST. Silymarin reduced the biliary cholesterol and phospholipids which may be in part due to decreased liver cholesterol synthesis (Crocenzi and Roma, 2006; Bhattachrya, 2011). Silymarin may be able to mitigate the oxidative stress-induced

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by carbon tetrachloride in broilers through modulation of oxidative stress biomarkers and hepatic oxidative genes expression (Baradaran et al., 2019).

Bhattachrya (2011) found that silymarin may maintain the normal renal function and silibinin can reduce the oxidative damage to kidney cells *in vitro*. In the same line, silymarin (259 μM) affected heat shock protein expression and prevented its alleviation by heat stress on chicken lymphocytes cells (Oskoueian et al., 2014). The previous study also showed that silymarin was able to normalize the expression of biomarkers such as MDA, tumor necrotizing factor-like, interferon (IFN-γ), and interleukin (IL-1β) genes in heat-induced chicken hepatocytes. Moreover, the study of Ledur and Santurio (2020) indicated that the *in vitro* addition of 5 μM silymarin to PK-15 cells exposed to different mycotoxins reduced the reactive oxygen species formation.

Silymarin may exert the hypoglycaemic effect through increasing the secretion of insulin via beta cells of the pancreas, enhancing the renovation of pancreatic cells, and protection of the pancreatic tissues against some metabolic damage (Soto et al., 2004; Kshirsagar et al., 2013). In addition, silymarin could regulate the liver enzymes involved in metabolism of carbohydrates causing reduction in the blood glucose level and restoring weights. This occurs due to decrease the activity of liver phosphorylase activity and increase glucokinase and glycogen synthase (Abascal and Yarnell, 2003).

Carcass traits

The highest breast weight muscle was detected in broilers received 1% of silymarin, compared with the groups consumed the different levels of aflatoxin (Chand et al., 2011). Addition of both L-carnitine and silymarin at levels of 300 mg and 160 mg/ kg diet, respectively reduced the abdominal fat deposition and increased the weight of thigh muscles of broiler chickens in comparison with the control group (Mousa and Osman, 2016). Zaker-Esteghamati et al. (2020) concluded that dietary addition of 4-15% silymarin improved the sensory and qualitative properties of broilers meat after exposure to aflatoxin diet. The authors found that the highest carcass weight and breast weight were detected in chickens fed on 3% silymarin oil. The improvement of carcass yield of silymarin-supplemented broilers may be related to the increase in protein synthesis (Sonnebichler and Zetl, 1986; Gawel et al., 2003; Jahanian et al., 2017). It has been found that silymarin has a similar structure to the steroid hormones, accordingly, it can pass to the nucleus and improve the formation of ribosomes via increasing the synthesis of structural and functional proteins by acting on rRNA enzymes (Negahdary et al., 2015).

It can enhance the meat polyunsaturated fatty acid profile which impaired by mycotoxin (Armanini et al., 2021). Schiavone et al. (2007) found that silymarin decreased the lipid contents of the thigh and breast muscles of broilers and increased the muscle resistance to oxidative stress. Changes in fatty acids metabolism at the hepatic level is owing to the hepatotonic effect of this compound (Saeed et al., 2017).

Immune response

Regulation of the immune system induced by silymarin depends on the method used and its concentration (Gharagozloo et al., 2010). Improvement of the immune status after feeding on milk thistle fruits was reported (Thyagarajan et al., 2002; Khariv et al., 2017; Alassi and Allaw, 2020; Bagno et al., 2021). Early study of Basaga et al. (1997) showed that milk thistle could enhance the immune system via its powerful antioxidant and free radical scavenging action. Long term administration of silymarin could improve the immune response by increasing the production of T-lymphocytes and IL and also it could be useful as a therapeutic adjuvant for autoimmune and infectious diseases (Das et al., 2008). Saeed et al. (2017) demonstrated that silymarin can modulate the immune response of birds by increasing the levels of IL-4, IL-10, and IFN-γ. Some studies indicated that the use of silymarin under oxidative stress of carbon tetrachloride can have a positive effect on the humoral immunity of Japanese quail via increasing in the concentrations of immunoglobulin G, the total antibodies, and white blood cell count (Moradi et al., 2017). Vitamin E and silymarin alone or in combination improved the immunotoxic effects induced by ochratoxin in Leghorn cockerels (Khatoon et al., 2013). Silymarin, as antioxidant, has protective action against the oxidative damages on the immune organs such as bursa of Fabricious, thymus, and spleen (Chand et al., 2011). This product decreased the relative weights of bursa of Fabricious and spleen, while increased the relative weight of the thymus (Moradi et al., 2017). Similarly, *S. marianum* was efficient in protection of spleen and bursa of Fabricious against the adverse effects of aflatoxin (Kalorey et al., 2005; Fani Makki et al., 2013). Chickens fed by diets containing 9% of *S. marianum* oil extraction byproduct showed greater spleen weights compared to chickens fed concentrations of 3%, 6%, and 12% (Shahsavan et al., 2021). A recent study of Bagno et al. (2021) showed increasing the content of γ-globulins in the serum of chickens fed on various doses of milk thistle extract (0.1, 0.5, 1.0, 1.5, and 2.0 mg/kg of body weight) as compared to the control group. Dumari et al. (2014) demonstrated that the serum antibody titers against Newcastle and influenza diseases viruses were higher than those recorded in aflatoxin treated group. Lutensko et al. (2008) found that silymarin phytosome increased albumin and globulin levels when compared with aflatoxicated broiler chickens. The cutaneous basophilic hypersensitivity response to phytohemagglutinin-P injection indicated that chickens received 9% of *S. marianum* oil extraction byproduct recorded high wing web thickness at 24h following injection (Shahsavan et al., 2021). Denev et al. (2020) demonstrated an increase in the level of serum betalysine after ditary addition of silymarin to ochratoxin challenged broiler chickens.

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Intestinal health

Treatment of Japanese quails with 1 ml/kg body weight silymarin increased the length of villi and the ratio of villi length to crypt depth (Moradi et al., 2017). Dietary supplementation of aflatoxicated broilers with 500 ppm silymarin increased the villi height and width, the ratio between villi height and crypt depth, and the apparent villi absorptive area (Jahanian et al., 2017). Accordingly, this product can protect the villi from endotoxins produced by pathogenic bacteria. Shahsavan et al. (2021) found an increase in the duodenum, jejunum, and cecum of broilers fed on *S. marianum* oil extraction byproduct at the levels of 6%, 9%, and 12% compared to control.

Both Gram-positive and Gram-negative bacteria can be affected by silymarin and silibinin (Lahlah et al., 2012). In other study, caecal population of *Lactobacillus*, coliform, *Escherichia coli* (*E. coli*), total aerobes, and *Lactobacilli*/*E. coli* ratio were not influenced by the treatments by *S. marianum* oil extraction byproduct (Shahsavan et al., 2021). Under the *in-vitro* conditions, *S. marianum* showed antibacterial activities against *Staphylococcus saprophyticus*, *E. coli*, and *Klebsiella pneumonia* (Evren and Yurtcu, 2015). Generally, silymarin exerts its antibacterial effect through hydroxyl group which binds with the bacterial membrane proteins leading to the leakage of vital components of the cells (Lee et al., 2003; Bessam and Mehdadi, 2014).

CONCLUSION

Application of natural alternative to antibiotics in poultry production system is urgently needed. Phytobiotics gained a great acceptance as one of these alternatives. Silymarin, a derivative of milk thistle herb, is widely used as a potent hepatotonic and antioxidant natural feed additive. Silymarin has a potential to increase the production performance in broilers and layers, increase the antioxidant status, improve the carcass trait, stimulate the immune response, and enhance the intestinal health. Thus, it is recommended to use such compound as feed additive in poultry field.

DECLARATIONS

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Author's contribution

Abd El-Ghany WA has collected and drafted the manuscript, formatted it, and approved the final manuscript.

Conflict of interests

The author has not declared any conflict of interest.

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