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REVIEW

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A review on the mechanisms of the effect of silymarin in milk thistle (*Silybum marianum*) on some laboratory animals

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One of the most valuable medicinal plants is milk thistle (*Silybum marianum*) or martighal. An annual or biennial plant of the Asteraceae family and English name Milk thistle, a Matte green colour and prickly plant with a standing stem that can be thick, simple, or slightly branched (ramified). Its seeds contain about 70%–80% of the flavonolignans of silymarin and about 20%–30% of polymeric and oxidized polyphenolic compounds (such as tannins). Traditionally, the plant has been used to increase milk secretion, relieve menstrual cramps, lessen depression, decrease gallstones, and jaundice as well as improve functions of the liver, spleen, and kidney. This review reviews studies on the effects of adding milk thistle to quail diet. Consumption (0.5% and 1%) of milk thistle powder in the diet of Japanese quail significantly increased feed intake, body weight, and improved carcass components. Blood constituents including total protein and albumin were improved along with decreased HDL, ALT, and AST. The use of milk thistle levels (0.5% and 1.5%) significantly improved the antioxidant total of plasma. Consumption of silymarin in quail diet increased the number of white blood cells, calcium, vitamin D3, and albumin. Silymarin also decreased the relative weights of bursa of Fabricius and spleen. This review indicates that milk thistle can improve growth performance, feed conversion ratio, and immune system in quail.

KEYWORDS
medicinal plants, milk thistle, silymarin

1 | INTRODUCTION

In recent decades, extensive studies have been conducted on the use of medicinal plants on a laboratory scale to enhance the immune system of laboratory animals, confirming the positive role of many of them in improvement of the immune system of animals (Rezaeipour et al., 2003). Consumption of such plants to treat and fight bacterial (Elgayyar et al., 2001) or fungal infections (Govindachari, 2000) clarified an approach to the use of those ingredients (compounds) in pharmacology. Medicinal plant extracts are traditionally used to treat and control some diseases due to their antibacterial and antioxidant properties (Hernandez et al., 2004). The most important sources of antioxidants in nature are fruits, vegetables, and medicinal plants. Medicinal plants have more antioxidants than fruits and vegetables (Ninfali et al., 2005) and their antioxidant properties have been shown to inhibit intestinal adhesions (Parsaei et al., 2013). These plants have beneficial effects by stimulating the increased function of pancreatic enzymes (lipase, amylase, and protease) and also by increasing the activity of digestive enzymes in intestinal mucosal cells (Srinivasan, 2005). Their phenolic compounds reduce the number of pathogenic microbes in the gut and prevent nutrient loss, thus increasing intestinal health, increasing digestion and absorption of nutrients, and improving

production performance (Francois et al., 2006). The positive effects of using such plants in diets based on cereal grains have been reported and cause the secretion of digestive enzymes, improve the digestibility of nutrients, and reduce the viscosity of digestive substances and the amount of sticky or viscous faces in poultry (Rotter et al., 1990). The use of medicinal plants and their essential oils affects the composition and flora of the digestive system of broilers, strengthens the immune system, lowers blood cholesterol, and thus improves the function of birds (Ritz et al., 1995). Such responses may effectively reduce the need to include antibiotics in poultry nutrition thereby avoiding adverse effects and harmful residues in poultry products (Alcicek et al., 2003; Zaker-Esteghamati et al., 2020).

Studies in laboratory animals have shown the therapeutic effect of milk thistle in diseases caused by high blood lipids (fat), vascular obstruction and atherosclerosis plaque formation (Krecman et al., 1998), toxicity and kidney disorders (Zima et al., 1998), drug poisoning (Muriel & Mourelle, 1990), liver disorders (Fiebrich & Koch, 1979), feed poisoning (Desplaces et al., 1975), chemical toxicity (Janiak, 1974), viral diseases (Lirussi & Okolicsanyi, 1992) and neurological disorders (Zhang et al., 1993). Moreover, there are evidences about its positive effects on regulation of blood sugar (Velussi et al., 1993), anticancer properties (Zi et al., 1998), and prevention of haemolysis of red and white blood cells (Locher et al., 1998; Zou et al., 2001).

1.1 | Characteristic of flavonoids in milk thistle

Various flavonoids are made and stored in milk thistle fruits, the amount of which varies and depends on location, climate, and the type of plant. The main composition of the plant is a mixture of flavonolignans, generally called silymarin, which has very strong antioxidant effects (Attia et al., 2019). The major flavonolignans in silymarin is silybin, which accounts for 50%, followed by sily chrysanthemum at 20%, silydianin at 10%, and isosilibine at 5% (Kordi et al., 2013). Silydianin levels are higher in plant stems and seed compounds (Shaker et al., 2010). Not only does it conjugate harmful free radicals, but it also suppresses pre-inflammatory responses resulting from increased levels of transforming growth factor beta-1 (TGF-β1) and tumour necrosis factor alpha (TNF-α) (Pradeep et al., 2007). After oral administration, the seed extract is absorbed at a rate of about 20%–50%. However, phosphatidylcholine complexes have higher absorption (Schandalik et al., 1992).

Flavonoids and antioxidants in plants such as milk thistle can play an important role in improving the body's immune system, as the vitamin content of medicinal plants and the presence of iron are effective in increasing the level of haematopoiesis (Farkhovi et al., 1994).

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Exfoliating products are used to lower blood pressure and relieve migraine headaches (Morovati et al., 2008), and their extract is used to treat liver, spleen, and gall bladder disorders. The various components of milk thistle plant have tannins, a kind of resin, and its seeds also contain an oily substance, amidon, and albuminous-like substances (Zargari, 1996).

Resin and histamine are among the special compounds that are present in milk thistle seeds (MTS). General strengthening of the body and relieving chronic constipation are among the healing properties of milk thistle, and it is used as a fever reducer in traditional medicine (Samsam Shariat, 2005). This plant has flavonoid and antinutritional compounds of nitrate and phenol such as tannin (OmidBeygi, 1997). Tannins can bind to extracellular enzymes. Therefore, substances such as hemicellulose, whose digestion is dependent on extracellular enzymes, are more affected by tannin (Hervas et al., 2003).

The presence of tannins in milk thistle may also affect protein digestion. Tannins and fatty acids in milk thistle can be a limiting factor in feed consumption (Salem et al., 2005). Tannins have not only a negative effect on direct digestion of protein sources (soybean meal), but also a positive effect on digestion of soy protein by increasing microbial digestion in lamb. However, the negative effect of tannin on protein digestibility in this experiment could be due to the elimination of tannin protein bonds in the enzymatic digestion phase (Nunez-Hernandez et al., 1991). The presence of nitrate in milk thistle can also be a risk factor for animals consuming this plant (OmidBeygi, 1997).

1.2 | Effects of silymarin on blood cholesterol

Silymarin is lipophilic and binds tightly to plasma membrane compounds, thus increasing plasma membrane strength and preventing membranes from breaking and disintegrating (Basigelio et al., 2009). Clinical studies suggest that silymarin may be used as a cholesterol-lowering agent in patients with hypercholesterolemia (Nassuato et al., 1991). It also has inhibitory properties against inappropriate blood fats (Schonfeld et al., 1997).

Laboratory studies report that the administration of silymarin to laboratory animals with high blood lipids has prevented the formation of atherosclerosis plaques in their aortas (Krecman et al., 1998). It can be considered as a cholesterol-lowering agent in hypercholesterolemic patients (Nassuato et al., 1991). According to Falah Hosseini et al. (2004), consumption of feeds containing silymarin may reduce the level of cholesterol in the blood and bile by reducing cholesterol synthesis in liver cells and by increasing the rate of cholesterol conversion to other compounds.

Silymarin is likely to be effective in reducing alkaline phosphatase (ALP) levels (Guo et al., 2016). Its interleukin 6 (IL-6) and TNF-α play an important role in the obstruction of the bile ducts (Al-Rasheed et al., 2016). The administration of flavonoids derived from the martighal plant is able to reduce the intestinal absorption of cholesterol

(Sobolova et al., 2006). Silymarin in milk thistle also lowers blood cholesterol and triglycerides (Falah hoseini et al., 2004). By reducing synthesis of cholesterol in the liver and lowering blood cholesterol by inhibiting its absorption in the gastrointestinal tract, silymarin can affect the metabolism and concentration of fats in the blood (Skottova et al., 2004).

Silymarin significantly reduces cholesterol absorption, thereby lowering cholesterol and low density lipoproteins (LDL) levels and dramatically increasing blood high density lipoproteins (HDL) cholesterol (Sobolova et al., 2006). Silymarin at higher concentrations of 200 μM/ml (micromolar per millilitre) exerts toxic effects, reduces the vitality of cells, and increases the release of malondialdehyde, an indicator of oxidative stress (Asadi et al., 2010). Gossypol poisoning causes lipidosis in the liver, and silymarin has no effect on reducing clinical effects (Blevins et al., 2010).

1.3 | Effects of silymarin on liver cells

The roots and aerial parts of the milk thistle plant have a bitter and appetizing (motive and savoury) taste and are used in traditional medicine to treat patients with spleen or liver disorders as well as patients with chronic constipation. The use of silymarin in traditional European medicine in the treatment of some liver diseases and complications dates back many years (Salmond et al., 1997).

Scientific studies in the field of nonalcoholic fatty liver have proven the effectiveness of silymarin treatment to prevent vascular formation in cancerous tissue. Toxicology studies in rodents have shown that silymarin has no toxic effects and is considered a safe drug in the treatment of liver disorders (Ghafghazi et al., 2017).

The flavonolignan of silandrin, silybinum, silihermin, and myristic acid, palmitic, and acetic acids may have hepatic protective properties (Varma et al., 1980). Silymarin is obtained as a flavonoid compound from the purified seed extract of the medicinal plant *Silybum marianum* (Sersen et al., 2006). In a dose-dependent pattern, silymarin exerted antioxidant and anti-apoptosis effects (Radko & Cybulski, 2007). Silymarin phytosomes in milk MTS can reduce free radicals caused by fungal toxins and increase cellular activity for protein synthesis by affecting cell nucleus activity and liver cell microsomes.

In addition to stabilizing the membrane by removing free radicals and increasing the activity of the enzyme superoxide dismutase, those phytosomes play this protective role (Ahmadi et al., 2010). It also protects the cell against any acute or chronic destructive damage, regardless of the causes of liver cell disorders (Lang et al., 1990). Silymarin (especially silybin or silibinin) is known to be a very strong antioxidant and free radical scavenger (Altorjay et al., 1992). Its side effects are rare but may include gastrointestinal symptoms (nausea, vomiting, and diarrhoea) and skin allergies (Clark, 2006).

Silymarin and other compounds in the extract inhibit bacterial beta-glucuronidase inhibitors in the gut and thus prevent the reabsorption of toxins from the gut (Kim et al., 1994). Silibinin in the category of liver cells (HepG and Hep3B) has a very strong toxic effect that caused cell apoptosis and has been shown to inhibit growth and increase cell death (Mahmoodi et al., 2015).

Consumption of silymarin has been used in the treatment of liver diseases, including alcoholic liver disease (Najafzadeh et al., 2010), chronic viral and toxic hepatitis, abdominal fat due to chemicals, and alcohol and bile duct inflammation. Therapeutic effects have been shown to be due to silymarin's properties including: antioxidant, antilipid peroxidase, antifibrotic, anti-inflammatory, immune-regulating, liver cell regenerating, calcium-lowering, and iron-trapping (Flora & Hahn, 1998).

Silymarin protects liver cells from damage due to viruses, chemicals, and natural toxins such as fungal toxins. There are various reports of improved liver function following prescription (administration) of silymarin (Penaflorida, 1996). Consumption of 120 mg of silymarin twice daily for two months significantly reduced aspartate transaminase (AST) and alanine transaminase (ALT) in the blood serum of liver patients (Pares et al., 1998). Also, it can prevent the peroxidation processes involved in liver lesions caused by carbon tetrachloride, ethanol, paracetamol, and other substances that are toxic to the liver (Vargas-Mendoza et al., 2014).

Tsai et al. (2008) showed that silymarin effectively increases the dissolution of carbon tetrachloride, which is involved in the formation of liver fibrosis. This is by various mechanisms such as stimulation of DNA polymerase, stabilization of cell membranes, inhibition of free radicals, and increased cellular glutathione concentration. The latter indicates the protective effect on the liver (Valenzuela & Garrido 1994) against damage by inhibiting the NF-κB gene and subsequently reducing the production of pre-inflammatory cytokines (Guo et al., 2016). Silymarin is used to treat various liver disorders such as fatty liver, hepatitis, jaundice, alcohol abuse, ischemia, drug and environmental poisoning, and even liver fibrosis (Al-Rasheed et al., 2016).

Due to its antioxidant properties, silymarin is very effective in inhibiting lipid peroxidation, especially in liver cells, thereby reducing metabolic disorders (Vogel et al., 1984). Regardless of the causative agents in liver cells, it protects cells against any acute or chronic destructive damage (Lang et al., 1990). Silymarin affects the stability of the liver membrane and prevents the binding of many toxins and drugs to this membrane. Its protective role is through elimination of free radicals and increased activity of the enzyme superoxide dismutase (Kalorey et al., 2005).

Silymarin reduces LDL and lowers cholesterol synthesis in liver cells, prevents negative effects of high cholesterol (Skotova & Kerkman, 1998), and increases the production of ribosomes (Wang et al., 1996), due to the stimulation of RNA polymerase I activity in the nucleus of liver cells. This is followed by more active protein synthesis in the liver and increased liver rejuvenation capacity induced by silymarin (Blumenthal et al., 2000). Silymarin stimulates DNA polymerase, stabilizes cell membranes, inhibits free radicals, and increases cell glutathione concentrations, with a protective effect on the liver (Valenzuela & Garrido 1994). Prescribing it improves the liver and kidney cleansing index and reduces the accumulation of lipids in the liver (Vargas-Mendoza et al., 2014).

Evidence suggests that silymarin and silybin affect the liver in four ways: (1) as an antioxidant, neutralizing free radicals and regulating the cell's internal glutathione, (2) as a cell membrane stabilizer and permeability regulator in liver cells to prevent the entry of toxic agents into liver cells, (3) as a stimulant of ribosomal RNA synthesis and hepatic cell renewal, and (4) as an inhibitor of the deformation of star-shaped hepatocytes into myofibroblasts, a process that is responsible for the deposition of collagen fibres which lead to liver cirrhosis (alcoholic liver disease). Silymarin neutralizes several toxic agents such as *Amanita phalloides*, ethanol, and acetaminophen on the liver. It also inhibits the absorption of amanitin (amantine and faludin), two peptides in poisonous fungi which are very potent liver cell destroyers. The toxic agent of Amanita fungus inhibits TNF-α in hepatocytes, which exacerbates fat peroxidation. Silymarin has a hepatic protective effect against these toxins (Ghafghazi, 2017).

Even if silymarin is prescribed 10 min after exposure to amanita poison, it completely prevents poisoning, and if given within 24 h after exposure to the poison, it significantly prevents liver death and injury (Vogel et al., 1984). In addition to the above, silymarin can prevent the absorption of toxic substances into hepatocytes by occupying connective sites and inhibition of many transfer proteins in the membrane (Faulstich et al., 1980). The return of bilirubin to its normal values following liver damage from cell phone waves can be due to reduced intracellular enzyme leakage due to cell membrane protection or regeneration of damaged liver cells (Mohajeri et al., 2011).

Liver parenchyma cells are responsible for the synthesis of plasma proteins, which include blood factors such as white blood cells and globulins. Thus, by stimulating protein synthesis, silymarin can accelerate the process of restoration and renewal of damaged tissues, such as liver tissue (Soto, 2004). In laboratory research, silymarin is a potent inhibitor of cAMP-phosphodiesterase (Koch et al., 1985).

Briefly, silymarin exerts its effects on liver cells in three ways: (1) It binds to the membrane receptors of liver cells that are responsible for the absorption of toxins and by changing their phospholipid compounds, they prevent the absorption of toxins by the cell. (2) Because it is a powerful antioxidant (which has many times the antioxidant properties of vitamin E), it inhibits metabolic disorders by inhibiting lipid peroxidation, especially in liver cells. (3) By stimulating protein synthesis, it regenerates liver cells (Schonfeld et al., 1997).

1.4 | Effects of silymarin on inflammation

Silymarin is a flavonolignans compound. Studies have shown that flavonoids act through various mechanisms to prevent and reduce inflammatory responses and act as preventive agents in heart disease and nervous system (Pan et al., 2010). Because silymarin contains 80% silybin, it has been shown to be effective in improving and reducing serum levels of inflammatory cytokines. Various studies have confirmed that silybin inhibits the expression of pre-inflammatory molecules (Aziz et al., 2014). Inflammation of nerve cells is an important factor in exacerbating brain cell damage. Silymarin is effective in preventing these lesions by inhibiting inflammation of brain cells (M. J. Wang et al., 2002). In addition, it inhibits brain damage caused by blood clots (thrombus) in the cerebral arteries (Rui et al., 1990). Silymarin inhibits the release of myeloxidase when neutrophils are stimulated. Inoculation of neutrophils with slab block prevents leukocyte motility inhibition (Kalmar et al., 1990).

The protective and antioxidant effects of silymarin on human lymphocyte and leukocyte cells have been proven (Loucher et al., 1998). Silymarin affects and inhibits L-arginine, which causes gene damage in lymphocyte cells in the culture medium (Yurtcu et al., 2012) and silybin, which is a major component of silymarin, and inhibits the proliferative activity of T lymphocytes when exposed to mitogen (ic) substances in the laboratory, including PHA (ConA = Concanavalin, PWM = Pokeweed Mitogen) (Meroni et al., 1988). This property is probably related to the anti-inflammatory properties of silymarin (Morazzoni et al., 1992). Silymarin inhibits the inflammatory process through the migration of neutrophils and kupffer cells, and also blocks the formation of inflammatory mediators such as prostaglandins, especially leukotrienes, by inhibiting the 5-lipoxygenase pathway and the release and secretion of histamine from basophils (Bhattacharya et al., 2011).

In vitro, it can also reduce the release of histamine from human basophilic blood cells (Miadonna et al., 1987). The anti-inflammatory effects of dose-dependent as well as dose-dependent inhibitors in the accumulation of leukocytes' inflammatory secretions have been demonstrated by use of silymarin (Herman et al., 2011). The effect of silymarin on reducing tissue edema may be due to the effect of its active compounds on mast cell cells (Shanahan, 1993).

Silymarin stabilizes cell membrane structure, inhibits release of inflammatory mediators, and inhibits cyclooxygenase and lipoxygenase, thus preventing the migration of leukocytes and the synthesis of neutrophils to the site of inflammation. By inhibiting the prevention factor, it is effective in the effective inflammation of NF-kB (Kb) nuclear. In other words, it is a strong inhibitor of NF-kb activation in response to TNF-α. This effect is mediated by phosphorylation inhibition and kBa degradation, which is an NF-kB inhibitor (Agarwal et al., 2006).

Also, reduction of myeloperoxidase activity can inhibit leukocyte infiltration and as a result, limit its anti-inflammatory effect (Bradley et al., 1982).

Anti-inflammatory effects of silymarin in the treatment of skin cell lesions caused by ultraviolet (UV) radiation have also been reported (Sobolová et al., 2006).

M. J. Wang (2002) determined that silymarin, with its anti-inflammatory properties, prevents the production of inflammatory agents such as TNF-α and reduces the damage to dopaminergic and serotonergic neurons. The application of silymarin protects dopaminergic and serotonergic neurons against the toxicity of liposaccharides. Prohibition of prostaglandin production by silymarin is specifically associated with inhibition of the enzyme cyclooxygenase (COX) (Saller et al., 2001).

1.5 | Effects of silymarin on free radicals

Neutralization of free radicals, antioxidant properties, and neutralization of toxins are among the effects of liver protection by milk thistle. The use of this plant has positive effects on the levels of haematocrit, haemoglobin, and white blood cells, which are characteristics of temperament. One of the main functions of haemoglobin is to carry oxygen throughout the body and to expel carbon dioxide. Therefore, by increasing haemoglobin, oxygen delivery to different tissues is done properly and as a result, the metabolic process and the level of safety are improved and the animal's health is likely more stable. Also, an increase in haemoglobin in blood is an important feature in iron storage in red blood cells (Nazifi, 1997). Silymarin is a component of polyphenols and has the ability to absorb and neutralize oxygen free radicals (Anderson et al., 1994).

The antioxidant function of silymarin and its nanocrystals is to prevent the formation of free radicals by specifically inhibiting enzymes producing active oxygenated species and improving mitochondria cohesion under stress (Surai, 2015). Antioxidant compounds can prevent free radical damage caused by neutralizing free radicals (Dixit et al., 2007).

Silymarin has beneficial antioxidant effects and strengthens the immune system. The products of milk thistle have a beneficial effect on lowering blood pressure, migraines, urticaria caused by allergies, excretion of bile, and so forth. Silymarin is used as a prophylaxis and treatment of liver disease and can inhibit the toxic effects of phalloidin and amanitin toxins. It is effective in treating liver cirrhosis, especially alcohol-induced cirrhosis, and protects the liver against infections such as viral hepatitis, injuries, and poisonous substances (Oliveira et al., 2001). Silymarin reduces the consumption of liver glutathione (Campos et al., 1989) and plays an important role in the production of liver proteins and the restoration of its cells (Sonnenbichler et al., 1986).

The antioxidant properties of silymarin are due to the polyphenolic structure along with the methoxy group present on one of the phenolic rings (Kidd, 2009). It reduces oxidative stress and protects cells against apoptosis.

Treatment with silymarin increases the significance of PC-12 neuronal cell growth after treatment (Gazak et al., 2007) and effectively protects dopaminergic nerve cells by inhibiting microglia activity (M. J. Wang et al., 2002). In addition, this extract contains the primary hippocampal cells against apoptosis and protects the stimulus and oxidation (Kittur et al., 2002). Similar to tannic acid in large quantities, it is oxidized by radical superoxides and hydrogen peroxide, resulting from the reaction between the fat complex (protein) and phenol in the presence of oxygen (Barbehenn et al., 2003). Therefore, they form a larger amount of phenol or toxic quinoa radicals that are able to create oxidative stress and toxicity (Bouki, 2013). Its effect on intracellular mechanisms, as well as its inhibitory or growth stimulating effect, depends on the amount and duration of cell contact (Asadi et al., 2010). Silymarin increases the activity of pancreatic antioxidant enzymes, glutathione peroxidase, superoxide dismutase, and catalase (Soto et al., 2003). In patients with alcoholic cirrhosis, higher levels of superoxide dismutase increase lymphocytes and red blood cells, thereby increasing the antioxidant effects (Fehér et al., 1989).

Antioxidants such as quercetin stabilize membrane gangliosides, stabilize biological membranes, and increase cell viability. On the other hand, carcinogens such as arsenic cause skin cell malignancy and induce oxidative stress, and some deal with both phenomena (Kittur et al., 2002).

Silymarin inhibits the enzyme aldose reductase in the crystalline lens of the eye (Zhang et al., 1989) and placenta (Feng et al., 2005). It reduces the activity of the polyol pathway and reduction of cytosol nicotinamide adenine dinucleotide phosphate, reduction of nitric oxide production, and glutathione depletion, resulting in the prevention of oxidative stress. Silymarin's antioxidant properties in feed prevent tissue damage and fat oxidation (Bosisio et al., 1992).

Catechin and silymarin have peroxidative activity despite their protective activity against liver cell destruction (Thabrew et al., 1998) and act as a scavenger of free radicals (Shaker et al., 2010), which can affect glutathione and superoxide dismutase-related enzyme systems and stimulate the activity of pancreatic antioxidant enzymes, glutathione peroxidase, superoxide dismutase, and catalase (Soto et al., 2003).

In addition to stabilizing the membrane, it also exerts this protective role by removing free radicals and increasing the activity of the enzyme superoxide dismutase (Tedesco et al., 2004). By preventing release of glutathione, the resultant induction of superoxide dismutase and the inhibition of the enzyme 5-lipo oxygenase inhibit lipid peroxidation and prevent reactive oxygen species (ROS) lead (Moreland et al., 2002). Its use with a concentration of 12—192 μg/ml reduced the toxicity of acrylamide in PC12 cells by activating the Nrf2 signalling pathway (Li et al., 2017).

Due to its ability to collect free radicals, it reacts with the hydroxyl anion, radical phenoxyl, and hypochlorous acid to prevent lipid peroxidation by free radicals in mitochondria and the microsome of red blood cells. Aldose reductase inhibitors such as silymarin reduce oxidative stress by inhibiting the enzyme protein kinase C (Ghafourifar et al., 2001).

Due to its structural resemblance to steroid hormones, silymarin can enter the cell nucleus and improve the formation of ribosomes by increasing the synthesis of structural and functional proteins by acting on rRNA enzymes (Negahdary et al., 2015).

By acting on transcription enzymes, silymarin accelerates the process of protein synthesis, which, by entering the nucleus and acting on RNA polymerase 1 enzymes and rRNA transcription, leads to an increase in ribosome formation (Sonnenbichler, 1986). This in turn accelerates protein and DNA synthesis, increases the construction process in the cytoplasm, and thus increases the synthesis of structural and functional proteins. At least conceptually, this stimulation may enable the cell to cope with the reduction of carriers and enzymes that occur under many pathological conditions (Radko & Cybulski., 2007). Silymarin, along with silibinin, can increase the regeneration of liver cells and increase the production of enzymes needed for DNA synthesis (Sonnenbichler et al., 1976). Estradiol and silymarin can also increase the release of acetylcholine (Yaghmaei et al., 2010).

Silymarin prevents haemolysis of red blood cells caused by copper and hydrogen peroxide and other oxygen-free radical-producing substances (Zou et al., 2001). It also plays a role in the stability of the liver membrane and prevents many toxins and drugs from binding to this membrane. Its protective role is played by the elimination of free radicals and increased activity of the enzyme superoxide dismutase (Kalorey et al., 2005).

Neuronal toxicity and oxidative stress induced by acetaminophen and manganese in animal models are neutralized by increasing the activity of enzymatic and nonenzymatic antioxidant indicators (Borah et al., 2013). Silymarin can also reduce acid stress by clearing and relieving ROS, inhibiting lipid peroxidation and protein nitrolysis, and increasing antioxidant protection (Attia et al., 2017), as well as inhibiting TNF-α expression by estrogenic and anti-inflammatory effects (Patten et al., 2014) (Fraschini et al., 2002).

Silymarin improves the health of lung cells in humans by reducing oxygen free radicals (Podder et al., 2012).

The effects of silymarin on cell survival have been investigated, and it has been concluded that this substance inhibits the apoptosis of PC-12 cells by enhancing NGF action and by protecting against oxidation (Kittur, 2002).

Studies by Lee et al. (2003) show that silybin has antibacterial activity against gram-positive bacteria, which is much stronger than silymarin, while it has no effect on gram-negative bacteria. According to those researchers, the effect of silybin inhibition on RNA synthesis and gram-positive bacterial protein is positive.

The study aimed to investigate the effects of MTS and rosemary leaves (RL) both at 5 and 10 g/kg diet on reproductive performance, semen quality and blood metabolites of rabbit bucks showed that the sperm concentration (SC), total sperm output (TSO), live sperm (LS), total live sperm (TLS), and total motile sperm (TMS) were significantly greater in the bucks fed MTS at 10 and RL at 5 g/kg diet than the control group. Bucks fed MTS at 10 g/kg diet had higher fertility than the control. Also, the RL 5 g/kg group showed higher testosterone and fertility than the control, but the MTS 10 g/kg group showed the highest value for both parameters. In conclusion, MTS and RL at 10 and 5 g/kg, respectively, significantly improved the semen quality and the fertility, and MTS also increased the economic efficiency of rabbit bucks (Attia et al. 2017).

1.6 | Relationship between silymarin and estrogen

Estrogen is a serotonin agonist that, despite estrogen receptors in median raphe nucleus (MRN area within the brain), is effective in function and regulation of the activity of serotonergic neurons, and with a change in performance of the serotonin 5-HT_{1A} receptor. It affects anxiety and is both an agonist and antagonist to receptor 5-HT_{1A}. Estrogen can have anxious or anti-anxiety effects (Gazak et al., 2007). Silymarin is very similar to steroid hormones, and these hormones have an effect on the expression of genes by increasing protein production (Dixit et al., 2007). This means that silymarin can affect the activity of estrogen receptors in the uterus and reduces granulomatous before ovulation (Mata-Santos et al., 2010). Silybin, which is one of the flavonolignans of silymarin, has estrogen-like effects and has an estrogen-like structure that can bind to and activate estrogen receptors (Pinheiro et al., 2007).

1.7 | Effects of silymarin on quail

In order to investigate the effect of silymarin on the immune system of Japanese quail poisoned with carbon tetrachloride, two levels of silymarin (0 and 1 ml/kg of body weight) and two levels of carbon tetrachloride (0 and 1 ml/kg of body weight) was used. The results showed that 0 ml/kg body weight (BW) of silymarin plus 1 ml/kg BW of carbon tetrachloride reduced total protein content of blood serum, whereas the levels of 1 ml/kg BW of silymarin and 0 ml/kg BW of carbon tetrachloride increased total protein of blood serum ($p < 0.05$).

Silymarin increased concentrations IgG and total antibodies when tested on day 35 ($p < 0.05$). In contrast, carbon tetrachloride decreased IgG on day 35 of the experiment ($p < 0.05$). Amounts of IgG, IgM, and total antibodies were not affected by the experimental treatments at the end of the rearing period. Silymarin decreased the relative weights of bursa Fabricius and the spleen and increased the relative weight of the thymus, whereas carbon tetrachloride increased and decreased the relative weights of the spleen and thymus, respectively ($p < 0.05$). Silymarin-treated birds had the highest white blood cell count ($p < 0.05$). Overall, this study showed that the use of silymarin under oxidative stress can have a positive effect on the humoral immune system of Japanese quail (Samadi et al., 2017).

A study investigating the effect of silymarin on oxidative stress induced by carbon tetrachloride on tibia bones characteristics and blood parameters in Japanese quails with experimental treatments includes: (1) control (control diet recipient), (2) silymarin (control diet plus 1 ml/kg BW of silymarin), (3) carbon tetrachloride (control diet plus 1 ml/kg BW of carbon tetrachloride), and (4) silymarin + carbon tetrachloride (each at 1 ml/kg BW as in previous treatments). From the 22nd day of the breeding period until the end of the breeding period, silymarin was applied by gavage every 3 days, and carbon tetrachloride was provided every 3 days until the end of the period via intraperitoneal injection.

Investigation of the effects of silymarin and carbon tetrachloride showed that silymarin significantly increased the serum concentrations of calcium, vitamin D3, total protein, and albumin and decreased serum glucose ($p < 0.05$). In addition, the combination of silymarin and carbon tetrachloride resulted in the lowest amount of cholesterol and ALP ($p < 0.05$). Lowest HDL-C was in the silymarin group, and lowest triglycerides were in the carbon tetrachloride treatment ($p < 0.05$).

Investigation of effects of silymarin and carbon tetrachloride on the properties of tibia showed that silymarin significantly increased the thickness of the inner layer and the percentage of tibia ash ($p < 0.05$). Also, the lowest weight and the highest amount of external diameter and internal diameter of tibia were observed in silymarin + carbon tetrachloride recipient treatment ($p < 0.05$). The results showed that carbon tetrachloride significantly reduced tibial bone density ($p < 0.05$) (Moradi et al., 2016).

Another study evaluating the effect of silymarin on oxidative stress induced by carbon tetrachloride on the liver and blood parameters of Japanese quail, consisting of two silymarin levels (0 and 1 ml/kg of BW) and two levels of carbon tetrachloride (0 and 1 ml/kg of BW) were performed. The results showed that silymarin decreased bilirubin, malondialdehyde (MDA), liver enzymes alanine aminotransferase (ALT) and ALP, triglyceride, total cholesterol, LDL, and cholesterol and significantly increased the levels of albumin, protein total, superoxide dismutase (SOD), total antioxidant, and glutathione peroxidase (GPx) in blood serum ($p < 0.05$) (Samadi et al., 2016).

In order to evaluate the effect of silymarin on the weight of lymphatic organs and serum protein of Japanese quail under oxidative stress of carbon tetrachloride, an experiment was conductedbased on a factorial arrangement of 2 × 2 including allocations of two levels of silymarin (0 and 1 ml/kg of BW) and two levels of carbon tetrachloride (0 and 1 ml/kg BW). The results showed that the amount of total protein was significantly different from the treatment of silymarin ($p < 0.05$). Carbon tetrachloride significantly reduced and increased the weight of thymus and spleen, respectively ($p < 0.05$). The results of this study indicate that silymarin modulates the effects of oxidative stress induced by carbon tetrachloride induction in the immune system of Japanese quail (Hosein Zadeh Kordiani et al., 2017).

An experiment was performed to evaluate the effect of silymarin on the concentration of serum lipids in Japanese quail poisoned with carbon tetrachloride (1 ml/kg BW of carbon tetrachloride injected intraperitoneally). The study included 1-day-old Japanese quail in a completely randomized design with factorial arrangement. The results showed that silymarin significantly reduced the concentration of triglyceride, total cholesterol, and -LDL-cholesterol ($p < 0.05$), whereas carbon tetrachloride significantly increased the levels of triglyceride and -LDL-cholesterol ($p < 0.05$). In general, the results of this study showed that silymarin modulates the effects of oxidative stress induced by carbon tetrachloride induction in Japanese quail (Samadi et al., 2016).

In an experiment, 480 1-day-old Japanese quail were used in a completely randomized design with 2 × 2 factorial arrangement with four treatments and four replications in experimental treatments including: control treatment, silymarin treatment (100 vs 1 ml/kg BW of silymarin by gavage (nasogastric tube or NG tube), carbon tetrachloride treatment (1 ml/kg BW of carbon tetrachloride by intraperitoneal injection and silymarin + carbon tetrachloride treatment (100 ml/kg BW of silymarin by gavage and 1 ml/kg BW of carbon tetrachloride injected intraperitoneally). The treatment with 1 ml/kg BW silymarin and 0 ml carbon tetrachloride significantly increased the villi length and the ratio of villi length to crypt depth, respectively. The results showed that silymarin caused a significant increase in intestinal length and weight ($p < 0.05$). The effect of experimental treatments on muscle layer thickness and crypt depth in the jejunum was not significant. Villi length, villi width, ratio of villi length to crypt depth, and mucosal layer in the intestinal jejunum of birds fed with silymarin increased significantly ($p < 0.05$). Treatment with 1 ml/kg BW silymarin and 0 ml carbon tetrachloride significantly increased the villi length and the ratio of villi length to crypt depth, respectively (Langari and Samadi, 2016). The effects of different levels of silymarin on quail have been summarized in Table 1.

Improving the blood parameters of aflatoxin-fed chickens with thistle compared to aflatoxin-fed chickens alone is due to the fact that silymarin, in addition to its strong antioxidant properties, stabilizes cell membranes and increases cellular glutathione. This may reduce intestinal absorption of cholesterol, lower blood sugar, and improve hepatic metabolism (Sobolova et al., 2006). One of the causes of decreased blood parameter when using milk thistle is the high raw fibre in the diet which increases excretion of bile and bile acid, and also the secretion of natural steroids, which ultimately lowers cholesterol and blood triglyceride levels (Smitt, 1996).

1.8 | The mechanism of action of silymarin on some laboratory animals

Administration (prescription) of silymarin has been shown to significantly reduce the accumulation of amyloid beta plaques and improve memory function in the Alzheimer's model induced by amyloid beta administration in rats (Yaghmaei, 2014). Also, in Alzheimer's disease in cultured rat cortex neurons, using silymarin at concentrations of 10 and 50 μg/ml increased Bcl-2 levels and decreased Bax and caspase 3 proteins, thereby reducing apoptosis and inhibiting the disorder progression and increased concentrations of norepinephrine, serotonin, and dopamine in some areas of the rat's brain (Osuchowski et al., 2004). In another study, administration of toxins to silymarin-treated mice showed that in these animals the amount of glutathione in liver cells increased, oxidative stress decreased, and liver enzymatic activity was lower compared to untreated mice (Campos et al., 1998). Administration of silymarin and silybin to alcohol-induced hepatotoxic rats inhibited the activity of liver enzymes such as gamma-glutamyl transitidase (GGT), ALT, AST, inhibition of alcohol-induced hepatotoxicity (M. Wang et al., 1996).

An in vitro study of hepatitis in mice showed that silymarin inhibited the induction of RHA-P on liver-damaging cytotoxic T lymphocytes and also inhibited TNF and interferon gamma in liver cells (Schumann et al., 2003). In Parkinson's disease model after administration of 6-hydroxy dopamine in rats, administration of silymarin at a dose of 200 mg/kg intraperitoneally (IP) for 2 weeks was able to reduce lipid peroxidation and lead to changes in the activity of superoxide dismutase in the brain (Baluchnejadmojarad et al., 2010). Hirayama et al. (2016) examined the effect of silymarin on ischemia and concluded that silymarin has a protective effect on delayed neuronal death in the hippocampus of male rats.

Due to its antioxidant properties, increasing the amount of cellular glutathione in traditional medicine is prescribed to improve liver disorders, thereby reducing the amount of markers of liver damage (Valenzuela et al., 1989). A decrease in malondialdehyde levels occurs after treatment with silymarin, which may be due to the antioxidant activity of silymarin and its ability to clear free radicals produced by the presence of plumbum in the diet (Aghazadeh et al., 2011). Due to its ability to collect free radicals, the substance reacts with hydroxyl

TABLE 1 Summary of the effects of silymarin on quail

Form of use	Effects of silymarin on quail	Reference
Powder	Levels of 1 ml of silymarin and 0 ml of carbon tetrachloride increased the total protein content of blood serum.	(Samadi et al., 2017)
Powder	Silymarin leads to an increase in the amount of concentrations IgG and total antibody.	(Samadi et al., 2017)
Powder	Silymarin decreased the relative weights of bursa-fabricius and spleen and increased the relative weight of the thymus.	(Samadi et al., 2017)
Powder	Silymarin-treated birds had the highest white blood cell counts.	(Samadi et al., 2017)
Powder	The use of silymarin under oxidative stress can have a positive effect on the humoral immunity system of Japanese quail.	(Samadi et al., 2017)
Powder	Interactions of carbon tetrachloride and silymarin significantly increased serum concentrations of calcium, vitamin D3, total protein, and albumin and decreased serum glucose concentrations.	(Moradi et al., 2016)
Powder	Examination of the interactions of silymarin and carbon tetrachloride showed that the lowest cholesterol and ALP was observed in the treatment of silymarin + carbon tetrachloride recipient.	(Moradi et al., 2016)
Powder	The lowest HDL-C amount was associated with the silymarin treatment.	(Moradi et al., 2016)
Extract	silymarin has been shown to significantly reduce the accumulation of amyloid beta plaques and improve memory function in the Alzheimer's model induced by amyloid beta administration in rats.	(Yaghmaei et al., 2014)
Concentrations	Bcl-2 levels and decreased Bax and caspase 3 proteins, thereby reducing apoptosis and inhibiting the disorder progression, and increased concentrations of norepinephrine, serotonin, and dopamine in some areas of the rat's brain.	(Osuchowski et al., 2004)
Administered orally	Silymarin on ischemia concluded that silymarin has a protective effect on delayed neuronal death in the hippocampus of male rats.	(Hirayama et al., 2016)
Soluble	administration of toxins to silymarin-treated mice showed that in these animals the 561 amount of glutathione in liver cells increased oxidative stress decreased and liver 562 enzymatic activity was lower compared to untreated mice	(Campos et al., 1989)
	The sperm concentration, total sperm output, live sperm, total live sperm, and total motile sperm were significantly greater in the bucks fed MTS at 10 and RL at 5 g/kg diet than the control group.	(Attia et al., 2017)
	Bucks fed MTS at 10 g/kg diet had higher fertility than the control.	

Abbreviations: ALP, alkaline phosphatase; MTS, milk thistle seeds.

anion, radical phenoxyl, and hypochlorous acid to prevent lipid peroxidation, which is induced by free radicals in mitochondria and red blood cell microsomes (Balouch nejhad mojarad et al., 2009). Decreased feed intake is due to a decrease in the nutritional value of the diet, a decrease in the passage of nutrients through the gastrointestinal tract, and an increase in the enzymatic activity of the pancreas, resulting in improved digestion efficiency and nutrient uptake by silymarin extract (Mojahedtalab et al., 2013). A similar effect has been reported in laying hens (Quarantelli et al., 2009).

Silymarin is rapidly absorbed through the gastrointestinal tract and reaches its maximum plasma concentration after 2–4 h. The half-life of this drug in most laboratory animals is 6–8 h, and more than 80% of it is excreted in bile and some in urine (Fraschini et al., 2002). Due to the susceptibility of fibrolytic bacteria to the active ingredients of all oils, especially unsaturated oils, these compounds can reduce digestibility by covering the surface of the fibers, especially the lignocellulose section or negatively affecting the digestive bacteria (Benchaar et al., 2006). Silymarin improves LDL excretion and reduces cholesterol synthesis in liver cells, as well as preventing the effects of high cholesterol (Skottova & Krecman, 1998). By inhibiting cholesterol synthesis in the liver and blood cholesterol by inhibiting its absorption in the gastrointestinal tract, it can affect metabolism and blood fat concentration (Skottova el al., 2004), by stabilizing the cell membrane structure of enzyme activity. Aspartate regulates aminotransferase (AST), ALT), ALP, creatine phosphatase (CK), and lactate dehydrogenase (LDH).

Decreased insulin, dyslipidaemia, and high blood glucose under diabetic conditions can damage many tissues, including liver tissue (Tangvarasittichai, 2015), increasing the activity of AST, ALT, and ALP enzymes. They are good markers for measuring the extent of liver cell damage (Cetinkunar et al., 2015).

Silymarin and its nanocrystals, while maintaining the integrity of the plasma membrane, tend to prevent liver damage, thereby suppressing the leakage of enzymes through the membrane, thus demonstrating liver protection activity. This may be a reason to correct the serum levels of the enzyme markers during the use of silymarin and its nanocrystals (NC). Diabetes is one of the leading causes of liver disorders (Mohamed et al., 2016). Silymarin has the capability to help regulate the immune system, which means that depending on the method used and its concentration, it can have both stimulating and inhibitory properties on the immune system (Gharagozloo et al., 2010). According to the available findings, glucose at a concentration of 20 mg/ml causes the death of PC 12 cells; Silymarin possibly reduces high glucose-induced death in neurons by reducing lipid peroxidation (Asadi et al., 2010). Due to its antioxidant and anti-inflammatory effects, silymarin

reduces the number of cysts and the natural development of follicles (Nabiuoni, 2015).

Probably a reduction in symptoms of induced syndrome, especially in the ovaries, is due to a decrease in luteinizing hormone (LH)/follicle-stimulating hormone levels in animals treated with it. A significant decrease in LH in the treatment group compared to the polycystic ovary syndrome (PCOS) group and consequently a decrease in the number of these follicles by silymarin is one of the important factors in reducing cysts and improvement of ovarian symptoms is this syndrome (Welschen et al., 1973). The increase in progesterone may be due to an increase in corpus luteum in silymarin-treated specimens (Doldi, 1998). Silymarin is able to inhibit the COX-2 enzyme and lipoxygenase, and it appears to reduce inflammation in PCOS (Kumaran et al., 2009).

Silymarin is a flavonoid compound, and flavonoids inhibit the production of prostaglandin from arachidonic acid in response to inflammatory stimuli by inhibiting the enzyme cyclooxygenase. Considering that prostaglandins are effective in causing inflammation and pain and are derived from arachidonic acid, and in the process of inflammation, substances such as histamine are released into the environment. It seems that the flavonoids in milk thistle may be involved in the analgesic effect by interfering with the histaminergic system (Behmahram et al., 2017). The analgesic effects of silymarin in the visceral pain test may be due to interference with histamine H1 receptors (Behmahram et al., 2017). A study by Pferschy-Wenzig et al., 2014 reported that the active ingredient isosilybin A in silymarin has PPARγ agonist properties. The PPARγ molecule is a target for thiazolidinediones such as pioglitazone. Studies show that silymarin has potential hypoglycaemic properties and increases insulin levels, thereby improving insulin sensitivity (Kheiripour et al., 2019).

2 | CONCLUSION

The appetizing effects of the milk thistle plant lead to better use of feed and improve growth of some laboratory animals. The use of silymarin in quail increased total protein and albumin and decreased serum glucose concentration. Its use in conditions of oxidative stress could have a positive effect on the humoral immunity system of laboratory animals such as Japanese quail. Silymarin decreased the relative weights of bursa of Fabricius and spleen, increased the relative weight of the thymus as well as the number of white blood cells in them. The diet containing milk thistle in Japanese quail increased feed intake and body weight and increased the yield of breast, thigh, and carcass components. Relative weight of liver, heart, pancreas, prestomach, gizzard, and intestine increased. An increase in bursa size, spleen, and carcass fat was also observed and caused the enzyme alkaline phosphatase, IgA and IgG in different levels of MTS to have a decreasing effect compared to the control treatment.

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The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

AUTHOR CONTRIBUTIONS

Data curation, *formal analysis*, *investigation*, *and writing-original draft*: Khazaei and Roshanak. *Conceptualization*, *investigation*, *project administration*, *supervision*, *validation*, *writing-original draft*, *and writing-review & editing*: Seidavi and Alireaza. *Conceptualization*, *data curation*, *project administration*, *supervision*, *writing-original draft*, *and writing-review & editing: Bouyeh and Mehrdad*.

DATA AVAILABILITY STATEMENT

We have not used any data that are required to be available for the reader.

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