Received: 26 January 2018 | Revised: 25 May 2018 | Accepted: 18 June 2018

DOI: 10.1002/ptr.6153

WILEY

REVIEW

Silybum marianum (milk thistle) and its main constituent, silymarin, as a potential therapeutic plant in metabolic syndrome: A review

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Metabolic syndrome describes a complex metabolic risk factors including obesity, hypertension, dyslipidemia, and diabetes. This syndrome is diagnosed by medical conditions such as weight gain, high blood pressure, high blood glucose, and disturbance in lipid profile. Metabolic syndrome has become as an important and increasing global health problem, so finding potentially novel solutions with less adverse effects is favorable for health problems. Herbal therapy plays an important role for treatment of different diseases. *Silybum marianum* is a plant that is used for centuries as a herbal treatment in liver and biliary tract diseases. Silymarin is the main component of *S. marianum* and derived from fruits and seeds of *S. marianum* (milk thistle). *S. marianum* has been found to exhibit antioxidant, lipid-lowering, antihypertensive, antidiabetic, antiatherosclerotic, anti-obesity, and hepatoprotective effects. Therefore, the aim of this review is to summarize different animal and human studies regarding the effect of *S. marianum* in metabolic syndrome and to identify the underlying mechanisms of action.

KEYWORDS

diabetes, dyslipidemia, hypertension, metabolic syndrome, milk thistle, obesity, silibyn, *Silybum marianum*, silymarin

1 | INTRODUCTION

Metabolic syndrome describes a complex metabolic risk factors including obesity, hypertension, dyslipidemia, and diabetes. This syndrome is diagnosed by medical conditions such as weight gain; adipose tissue accumulation; high blood pressure; high blood glucose; disturbance in lipid profile (Akaberi & Hosseinzadeh, 2016; Hassani, Shirani, & Hosseinzadeh, 2016); nonalcoholic fatty liver disease (NAFLD); cardiovascular disease; and kidney dysfunction. According to the National Cholesterol Education Program definition, people who have at least three risk factors are considered to have metabolic syndrome (Hosseini & Hosseinzadeh, 2015). The global rising in prevalence of metabolic syndrome is related to an increase in obesity, and it is associated with morbidity and mortality worldwide (Golbidi, Mesdaghinia, & Laher, 2012; Villiger, Sala, Suter, & Butterweck, 2015).

Studies have been shown that some plants and their active components are able to treat metabolic syndrome. Some of these plants and their active constituents include *Vitis vinifera* (grape; Akaberi & Hosseinzadeh, 2016); *Nigella sativa* (black seed; Razavi & Hosseinzadeh, 2014); *Allium sativum* (garlic; Hosseini & Hosseinzadeh, 2015); *Rosmarinus officinalis* (rosemary; Vahdati Hassani et al., 2016); *Persea americana* (avocado; Tabeshpour, Razavi, & Hosseinzadeh, 2017); *Berberis vulgaris* (barberry; Tabeshpour, Imenshahidi, & Hosseinzadeh, 2017); *Crocus sativus* (saffron; Razavi & Hosseinzadeh, 2017); *Cinnamomum verum* (cinnamon; Mollazadeh & Hosseinzadeh,

Abbreviations: ADMA, asymmetric dimethylarginine; BMI, body mass index; FBS, fasting blood glucose; HCD, high cholesterol diet; HDL-C, high-density lipoprotein cholesterol; IL6, interlukin-6; LDL-C, low-density lipoprotein cholesterol; MDA, malondealdehyde; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SREBP, sterol response element-binding protein; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α

2016); thymoquinone (Razavi & Hosseinzadeh, 2014); berberine (Tabeshpour et al., 2017); and rutin (Hosseinzadeh & Nassiri-Asl, 2014).

Silybum marianum is a plant that has been used for centuries as a herbal treatment in liver and biliary tract diseases (Sayin et al., 2016). Silymarin, the main component of *S. marianum* and derived from fruits and seeds of *S. marianum* L. (milk thistle; Souza et al., 2012), is a mixture of flavonolignans (70–80%) containing silibinin (silybins A and B; 50%; Fehér & Lengyel, 2012); isosilybin (isosilybins A and B; 5%); silychristin (20%); and silydianin (10%). There are also minor fractions of other flavanols such as 2.3-dehydrosilybin, quercetin, (+)-taxifolin, and kaempferol (Calani, Brighenti, Bruni, & del Rio, 2012; Heidarian & Rafieian-Kopaei, 2012; Radjabian & Fallah Huseini, 2010; Figure 1).

Silibinin (silybin) is the major active component of silymarin, and silybins A and B are the most prevalence diastereoisomers (Fehér & Lengyel, 2012). *S. marianum* is found mostly in Asia and Southern Europe (Heidarian & Rafieian-Kopaei, 2012; Radjabian & Fallah Huseini, 2010).

Studies have been shown that silymarin has potential hepatoprotective effects due to its antioxidant; anti-inflammatory effects (Bahmani, Shirzad, Rafieian, & Rafieian-Kopaei, 2015); membrane-stabilizing, promoting hepatocyte regeneration; and inhibiting fibrogenesis (Fehér & Lengyel, 2012). Furthermore, some studies mentioned that silymarin as a supportive protected hepatosis therapy in *Amanita phalloide* poisoning (Bahmani et al., 2015), hepatosis caused by oxidative stress such as alcoholic and nonalcoholic fatty liver disease, steatohepatitis, drug, and chemically induced liver toxicity (Fehér & Lengyel, 2012). Some clinical and animal studies demonstrated silymarin effectiveness in different diseases such as sepsis, osteoporosis, atherosclerosis, diabetes, and mental disorders (Stolf, Cardoso, & Acco, 2017). It has also remarkable effects in scavenging reactive oxygen species and can reduce drugs toxicity (Fehér & Lengyel, 2012). However, it is demonstrated that *S. marianum* can affect on a wide variety of disorders, although documented data are mostly about liver disorders (Bahmani et al., 2015). Moreover, its protection against some disorders in the heart (Razavi & Karimi, 2016); the kidney (Karimi, Ramezani, & Tahoonian, 2005); and the nervous system (Vahdati Hassani, Rezaee, & Sazegara, 2015) has been shown (Karimi, Vahabzadeh, Lari, Rashedinia, & Moshiri, 2011).

As metabolic syndrome became as an important and increasing global health problem (Golbidi et al., 2012; Villiger et al., 2015), so finding potentially novel solutions with less adverse effects is favorable for health problems. Therefore, the aim of this review is to summarize different in vitro animal and human studies regarding the effect of *S. marianum* in metabolic syndrome and to identify the underlying mechanisms of action (Tables 1–3).

2 | METHOD OF LITERATURE REVIEW

The literature review was conducted using the electronic databases of Google Scholar, Pubmed, Scopus, and ISI web of science. The search terms included *Silybum marianum* or silymarin or silybin or silibinin or milk thistle and "metabolic syndrome" or dyslipidemia or hypercholesterolemia or hyperlipidemia or hepatoprotective or diabetes or hyperglycemia or hypertension or "blood pressure" or obesity or atherosclerosis. Only articles written in English language published on peer-reviewed scientific journals were considered, and duplicated articles were excluded. All articles were included if they evaluated the effect of *S. marianum* on metabolic disorders. Studies were identified through online databases from their inception up to August 2017.

3 | EFFECT ON LIPID PROFILE

High serum lipid and lipoprotein levels, particularly hypercholesterolemia, elevate the risk of cardiovascular diseases, fatty liver,

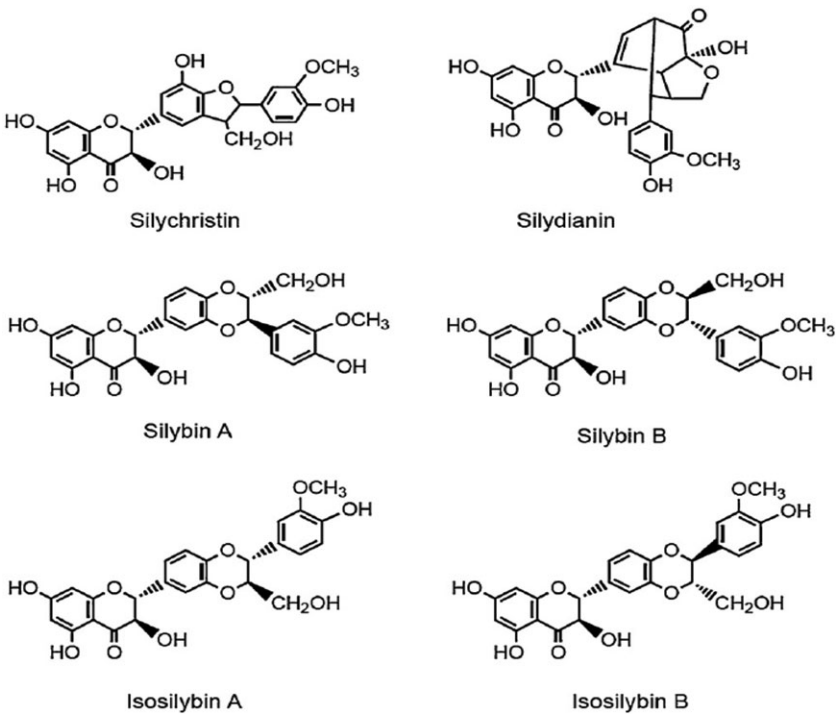

FIGURE 1 Structures belong to some flavonolignans of silymarin

TABLE 1 Animal studies regarding the effect of *Silybum marianum* and its main constituents on metabolic syndrome

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
Effect on lipid profile				
Hyperlipidemic male rats	Oral, silymarin 45 days 25 mg·kg·day	↓ Serum and liver level of TG ↑HDL Modified lipoprotein profile in plasma	↓ Liver phosphatidate phosphohydrolase activity, Effect on apoA-I metabolism Antioxidant	(Heidarian & Rafieian-Kopaei, 2012)
Hereditary hypertriglyceridemia insulin-resistant rats	Oral, silymarin and *Prunella vulgaris* extract 14 days 1% *w*/w	↓VLDL-C Positive effect on lipid levels in plasma	Antioxidant	Škottová et al. (2004)
Nonobese herediatary hypertriglyceridemic rats	Oral, Standardized, micronized and phytosome forms of silymarin 28 days 1% w/w	↑ HDL-C ↓ Serum level of TG and TC No effect on liver TG and TC	↑ ABC transporter and cytochrome P450	(Poruba et al., 2015)
High cholesterol diet rabbit	Oral, silymarin from cultivated and wild plants 60 days 200 mg/kg/day	↓ Serum level of TG and TC ↓LDL-C	Inhibits absorption of cholesterol	(Radjabian & Fallah Huseini, 2010)
High cholesterol diet rats	Oral, silymarin 19 days 0.1–0.5—1% *w*/w	↑HDL-C ↓Liver cholesterol level	Antioxidant effect, ↑ Intracellular and liver GSH level Inhibit secretion of VLDL and resorption of cholesterol. ↓Biliary cholesterol saturation index and exogenous cholesterol in liver	(Krecman, Skottova, Walterova, Ulrichová, & Simánek, 1998)
High cholesterol diet rats	Oral, silymarin and polyphenolic fraction 18 days 1% w/w	↓Serum and liver level of TC ↓Liver content of VLDL cholesterol and TAG No effects on levels of TAG and VLDL in plasma	↓Cholesterol absorption Inhibition of acyl-CoA	(Sobolova, Skottova, Vecera, & Urbánek, 2006)
High fat diet induced mouse model of NAFLD	Oral, silymarin 28 days 30 mg/kg	↑ HDL-C ↓ LDL-C and TC No effect on TG	Regulation different genes implicated in lipid metabolism and oxidative stress	Ni and Wang (2016)
Psammomys obesus (an animal model of obesity and diabetes)	Oral, Silibinin 56 days 100 mg/kg/day	↓Serum level of TG, LDL-C, TC and steatosis	—	(Bouderba, Sanchez-Martin, Villanueva, Detaille, & Koceïr, 2014)
High cholesterol diet fed rats	Oral, Silybin 60 days 300 and 600 mg/kg	↓Serum and liver level of TC, TG,VLDL-C and LDL-C ↑ plasma and liver levels of HDL-C	Stimulating the production of hepatic LDL receptors Increasing the endogenous cholesterol conversion to bile acid No intervention in absorption of cholesterol	(Gobalakrishnan et al., 2016)
Hereditary hypertriglyceridemic rats	Oral, standardized, micronized and phytosoms form of silybin 28 days	↓Serum level of TG ↑HDL-C No effect on TC	↑CYP7A1 and the bile acids secretion	(Poruba et al., 2016)

(Continues)

TABLE 1 (Continued)

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
	0.5% w/w			
Dimethylnitrosamine and bile duct ligation induced liver fibrosis in rats	Oral, SPV complex (silybin+ phosphatidylcholine+Vit. E) 7–35 days 250 mg/kg/day	Improve chronic liver disease	Anti-inflammatory and antifibrotic effects Modulation of hepatic stellate cells Reduction collagen deposition and synthesis	(Di Sario et al., 2005)
High fat induced fatty liver in rats	Oral, silybin 42 days 26.25 mg·kg·day	Improve NAFLD and serum lipid profile	↑SOD and GSH levels ↑adiponectin inhibition of resistin mitochondrial membrane stabilization oxidative stress inhibition and insulin resistance improvement	(Yao et al., 2011)
Rat model induced NASH	Oral, silibinin 84 days 200 mg/kg/day	Improve NASH-induced lipid peroxidation	Improvement of liver steatosis and inflammation Insulin reduction Antioxidant Hepatoprotective effect	(Haddad, Vallerand, Brault, & Haddad, 2011)
	Cardiovascular protective effect			
High cholesterol diet rabbits	Oral, silymarin from cultivated and wild plants 60 days 200 mg/kg/day	Inhibit atherosclerotic plaque	↓Levels of TC, LDL-C, TAG	(Radjabian & Fallah Huseini, 2010)
Ischemia–reperfusion-induced myocardial infarction in albino rats	Oral, silymarin 7 days 100, 250, 500 mg/kg	Cardioprotective	Scavenge free radicals, Inhibit lipid peroxidation Stabilize plasma membrane	(Rao & Viswanath, 2007)
Alloxan-induced diabetes mellitus in male albino rats	Oral, silymarin 10 days 120 mg·kg·day	Protection against apoptotic death of cardiomyocytes related to diabetes	Inhibition of capase-3 and increasing antiapoptotic protein Bcl-2 expression DNA protection activity	(Tuorkey et al., 2015)
Male (Db/db) obese diabetic mice	Intraperitoneal route, silibinin 28 days 20 mg·kg·day	Improve endothelial dysfunction	Reducing circulating and vascular dimethylarginine levels	(Li Volti et al., 2011)
Effect on high blood pressure				
Spontaneously hypertensive rats subjected to acute coronary artery occlusion	Oral, silybin 8–12 days 300 mg/day	↓ Blood pressure, rate of arrhythmias, severity of ventricular hypertrophy ↓Risk and infract zones	—	(Chen et al., 1993)
Mice model of aortic banding	Oral, silibinin 7 days 50 mg·kg·day	No effect on blood pressure Improve cardiac hypertrophy	Inhibition epidermal growth factor receptor	Ai et al. (2010)

(Continues)

TABLE 1 (Continued)

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
Effect on diabetes				
High fat diet male mice	Oral, silymarin 18 days 30 and 60 mg/kg	Improve insulin resistance, glucose metabolism and obesity	Anti-inflammatory Improve hepatic steatosis ↓ Fat accumulation	(Guo, Wang, Wang, & Zhu, 2016)
Pancreatectomized rats	Oral, silymarin 3, 7, 14, 21, 42, and 63 days 200 mg/kg	↑ Serum insulin Normalizing serum glucose Improve the reduction of β pancreatic cells	↑ Nkx6.1 and insulin gene expression	(Soto, Raya, Pérez, González, & Pérez, 2014)
Alloxan-induced diabetes mellitus in male albino rats	Oral, silymarin 10 days 120 mg·kg·day	↓ Levels of glucose ↑Insulin level	Restoring βcells activity and insulin secretion	(Tuorkey et al., 2015)
Fructose-rich chow-fed Wistar rats	Oral, silymarin 14 days 200 mg·kg·day	↑Insulin resistance and disrupt insulin signaling	↑Phosphatase and tensin homolog	(Cheng et al., 2014)
Alloxan-induced diabetes mellitus in rats	Oral, silymarin (4 doses in 48 hr or 8 doses in 7 days, or 20 days after alloxan for 9 weeks). 200 mg/kg	Improve function and structure of pancreas and the level of glucose and insulin.	Effect positively on insulin and glucagon expression proteins and normoglycemia and pancreas duodenum homeobox 1	(Soto et al., 2004)
High fat diet mice	Oral, silymarin 30 days 30 mg·kg·day	↓Body weight gain, insulin resistance, glucose tolerance	Antioxidant and anti-inflammation effects, inhibition of NADPH oxidase expression and NF-κB activation	(Feng et al., 2016)
Male (Db/db) obese diabetic mice	Intraperitoneal, silibinin 28 days 20 mg·kg·day	↓Fasting glucose, insulin and insulin resistance	Inhibiting liver gluconeogenesis ↓Aorta and plasma asymmetric dimethylarginine levels	(Li Volti et al., 2011)
Psammomys obesus (an animal model of obesity and diabetes)	Oral, silibinin 56 days 100 mg·kg·day	↓ TG, glucose and insulin resistance	Antioxidant and inhibition both gluconeogenesis and glucose-6-phosphatase activity	(Bouderba et al., 2014)
High fat diet rats	Oral, silibinin 42 days 0.5 mg·kg·day	↓ Insulin resistance Prevent visceral obesity	↓Visceral fat ↑Lipolysis by up-regulating expression of adipose TG lipase ↓ Gluconeogenesis by downregulating related genes such as Forkhead box O1, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.	(Yao et al., 2013)
Streptozotocin induced diabetic rats	Oral, engineered nanoparticles of silybin 28 days	Normalize blood glucose and serum insulin levels ↓Glycated hemoglobin level and restore liver glycogen content	Antioxidant ↑Regeneration of βcells	(Das et al., 2014)

(Continues)

TABLE 1 (Continued)

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
		Exhibit normoglycemic condition		
Hereditary hypertriglyceridemic rats	Oral, standardized, micronized and photosoms forms of silybin 28 days 0.5% w/w	↓Glucose and insulin	—	(Poruba et al., 2016)
Pancreatectomized rats	Oral, silymarin for 3, 7, 14, 21, 42, and 63 day 200 mg·kg·day	↓Glucose ↑Insulin and βcell proiferation	↑ Pancreatic duodenal homeobox 1 ↑Insulin receptor 2 Through PKB pathway, hepatocyte nuclear factor 3, and BETA2 transcription factors.	(Soto, Raya, Juárez, Pérez, & González, 2014)
Effect on obesity				
High fat diet male mice	Oral, Silymarin 18 days 30 and 60 mg/kg	↓Epididymal fat mass and total bodyweight No effect on lean body weight ↓Fat accumulation Amelioration of insulin resistance and glucose metabolism	—	(Guo et al., 2016)
High fat diet induced metabolic disorders in rats	Oral, silymarin 49–77 days 200 mg·kg·day	Improve body mass index, insulin resistance, leptin sensitivity and hyperlipidemia	Improving TC, LDL-C, HDL-C, TG, high sensitive C-reactive protein, leptin and insulin levels	(Sayin et al., 2016)
High fat diet rats	Oral, Silymarin 30 days 30 mg/kg/day	Amelioration of weight gain, glucose intolerance, insulin resistance and oxidative stress indicators	Antioxidant	(Feng et al., 2016)
Alloxan-induced diabetes mellitus in rats	Oral, Silymarin (4 doses in 48 hr or 8 doses in 7 days, or 20 days after alloxan for 9 weeks). 200 mg/kg	↓Body weight gain	—	(Soto et al., 2004)
High fat diet induced fatty liver in rats	Oral, silybin 42 days 26.25 mg·kg·day	Preventing lipid accumulation	↑Gene and protein expressions of adiponectin ↑β-oxidation of free fatty acids ↓De novo free fatty acid production Inhibition gene and protein expression of resistin	(Yao et al., 2011)
High fat diet induced mouse model of NAFLD	Oral, Silymarin 28 days 30 mg/kg	No effect on body weight and food intake	—	(Ni & Wang, 2016)

Note. GSH: glutathione; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; SOD: superoxide dismutase; TAG: triacylglycerol; TC: total cholesterol; TG: triglyceride; VLDL-C: very low-density lipoprotein cholesterol.

TABLE 2 In vitro studies regarding the effect of *Silybum marianum* and its main constituents on some components of metabolic syndrome

Study design	Rout of exposure/dose/ constituents	Results	Mechanisms	Ref.
Effect on high blood pressure				
Chinese hamster ovary cells	Silibyn	Regulate blood pressure	Competitive antagonist for AT_1 receptor Destroying IKB αphosphorylation Suppressing angiotensin2-induced proinflammatory responses	(Bahem, Hoffmann, Azonpi, Caballero-George, & Vanderheyden, 2015)
Neonatal cardiac myocytes and fibroblasts induced by angiotensin 2	Silibyn	No effect on blood pressure, Inhibit aortic banding-induced fibrosis ↓Cardiac hypertrophy	↓Angiotensin2-induced fibrosis mediators, Blocking epidermal growth factor receptor	(Ai et al., 2010)
Effect on diabetes				
Perfused rat liver	Silibyn 50–300 μM	↓Glucose, gluconeogenesis glycogenolysis and glycolysis	↓Glucose 6-phosphatase activity, pyruvate carrier, mitochondrial energy transduction ↓supply of NADH and oxygen consumption	(Colturato et al., 2012)
Multiple cell lines such as 3T3-L1 adipocytes and CHO cells	Silybin Dose-dependently	Inhibition basal and insulin-dependent glucose uptake	Inhibiting of GLUT4-mediated transport	(Zhan, Digel, Küch, Stremmel, & Füllekrug, 2011)
	Effect on obesity			
3T3-L1 cells	Silibyn dose-dependently (5 μM to 30 μM)	Suppression of terminal differentiation of 3 T3-L1 cells into adipocytes, ↓Lipogenesis in mature adipocytes and inhibited differentiation in preadipocytes	↑Insulin induced gene 1 Up regulated insig-2	(Ka, Kim, Kwon, Park, & Park, 2009)

carcinogenesis, peripheral vascular disease, and atherosclerosis in human (Derosa, Romano, D'Angelo, & Maffioli, 2015; Heidarian & Rafieian-Kopaei, 2012). There are many new synthetic oral antihyperlipidemic drugs, but they have adverse side effects such as myopathy, increase in hepatic aminotransferases, and rhabdomyolysis condition (Heidarian & Rafieian-Kopaei, 2012). It has been shown that silymarin exerted antihyperlipidemic; anti-inflammatory; anti-atherosclerotic; hepatoprotective (Radjabian & Fallah Huseini, 2010); and antioxidant effects (Rao & Viswanath, 2007).

3.1 | Animal studies

3.1.1 | Studies on silymarin

A study conducted on different forms of silymarin such as standardized extract, micronized, and phytosome in nonobese herediatary hypertriglyceridemic rats revealed that 4-week administration of silymarin can reduce plasma level of triglyceride (TG) and cholesterol by increasing the protein expression of ABC transporter and cytochrome P450 such as CYP7A1 and CYP4A. CYP4A involved in omega and omega-1 hydroxylation of fatty acids, which is required for TG synthetize, and both CYP7A1 and ABC transporters are involved in elimination of the cholesterol and decreasing total cholesterol (TC). ABC transporters such as ABCG5 and ABCG8 are responsible for cholesterol efflux from the hepatocytes into the bile. In this study, silymarin increased HDL level, which has an important role in the reverse transport of cholesterol. This study also showed that phytosome and micronized forms of silymarin were the most effective forms because of their better bioavailability (Poruba et al., 2015). Moreover, administration of silymarin and polyphenolic fraction of silymarin significantly decreased cholesterol absorption, the plasma level of cholesterol, liver content of VLDL, and triacylglycerol. Reducing VLDL level was due to several factors including reduction of VLDL formation and secretion from the liver, reduction of VLDL secretion in the intestine, and inhibition of intestinal cholesterol absorption. Silymarin and its polyphenolic fraction did not have effects on the levels of triacylglycerol and VLDL in plasma. Silymarin but not polyphenolic fraction significantly increased HDL level. This study suggested that inhibition of acyl-CoA such as cholesterol acyltransferase as a key pathway of lipid metabolism could be effective in reduction of intestinal cholesterol absorption particularly by phenolic compounds. Furthermore, parenteral usage of silymarin was not able to decrease serum level of cholesterol in high cholesterol diet (HCD) rats, which confirmed bioavailability limitation of polyphenol polymers to the gut lumen as polymers partially stick to the cell surface. This study suggested that polymeric structure of the polyphenolic fraction of silymarin may bind to cholesterol and bile acids (Sobolova et al., 2006). In another study conducted on the effect of silymarin from cultivated and wild plants in HCD rabbits showed although both silymarins decreased significantly, levels of TC, low-density lipoprotein cholesterol (LDL-C), TG, and inhibited atherosclerotic plaque formation but just silymarin from cultivated plants increased significantly high-density lipoprotein cholesterol (HDL-C) serum content (Radjabian & Fallah Huseini, 2010).

In another study, anticholesterolemic effect of silymarin was parallel to that of probucol (an antioxidant hypocholesterolemic drug) in rats that were fed HCD. However, in contradistinction to probucol,

TABLE 3 Human studies regarding the effect of *Silybum marianum* and its main constituents on lipid profile

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
A randomized, placebo-controlled, clinical trial on euglycemic, dyslipidemic subjects	Oral, combination of *Silybum marianum* and *Berberis aristata* 6 months 210 mg/day	↓TC, LDL-C and TG	↓cholesterol acyltransferase activity ↓ cholesterol absorption and lipoprotein biosynthesis Improvement of *Berberis aristata* oral bioavailiability	(Derosa et al., 2015)
A randomized, placebo-controlled, clinical trial on euglycemic, dyslipidemic subjects	Oral, combination of *S. marianum* and *B. aristata* 3 months 210 mg/day	↓TC, TG, and LDL-C ↑ HDL-C	inhibition of cholesterol acyltransferse activity, ↓cholesterol absorption and lipoprotein biosynthesis	(Derosa et al., 2013)
A double blind, randomized, placebo-control trial study in low risk cardiovascular patients	Oral, combination of *S. marianum*, *B. aristata*, and monacolin K and KA 3 months 105 mg/day	↓TC, TG, LDL-C	↓inflammatory markers such as TNF-α, IL6 and high sensitivity C-reactive protein	(Giuseppe, Angela, Davide, & Pamela, 2017)
Clinical study in patients with advance stage of type 2 diabetes	Oral, combination of *S. marianum*, *Allium sativum*, *Aloe vera*, *Nigella sativa*, *Plantago psyllium*, and *Trigonella foenum-graecum* 40 days 1,000 mg/day	↓LDL, TG levels, and TC	inhibition of intestinal cholesterol absorption	(Zarvandi, Rakhshandeh, Abazari, Shafiee-Nick, & Ghorbani, 2017)
A randomized, double-blind, placebo-controlled, clinical trial in patients with type 2 diabetes	Oral, combination of *S. marianum* (silymarin), *Boswellia serrata* (olibanum gum) and *Urtica dioica* L. (nettle) 90 days, 600 mg/day	A small reduction in TG No effects on TC, LDL, HDL levels	—	(Khalili et al., 2017)
A randomized, double-blind, placebo-controlled, Clinical trial study on 5- to 16-year-old children with NAFLD	Oral, silymarin 84 weeks 5 mg/kg/day	↓TG No effects on LDL and HDL levels	improve liver fatty infiltration and indices of NAFLD	(Famouri, Salehi, Rostampour, Hashemi, & Shahsanaee, 2017)

Note. HDL-C: high-density lipoprotein cholesterol; IL6: interlukin-6L; DL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TC: total cholesterol; TG: triglyceride; TNF-α: tumor necrosis factor-α.

silymarin caused an increase in HDL-C and a decrease in liver cholesterol content (Krecman et al., 1998).

3.1.2 | Studies on silybin

Oral administration of silybin significantly reduced TC, TG, very low-density lipoprotein cholesterol, LDL-C and enhanced HDL-C levels at both serum and liver in HCD-fed rats through different mechanisms including stimulating the production of hepatic LDL receptors that raised clearance of plasma LDL, IDL and indirectly that of VLDL and increasing the endogenous cholesterol conversion to bile acid. This study also showed that silybin has no effect on cholesterol absorption because the excretion of fecal lipids did not change (Gobalakrishnan, Asirvatham, & Janarthanam, 2016).

In another study, the effects of silybin in various forms on lipid profile and glucose metabolism in hereditary hypertriglyceridemic rats have been evaluated. This study indicated that silybin has no effect on TC level but significantly increased HDL-C content and decreased serum level of TG. Standardized silybin form had the most hypotriglyceridemic effect and micronized silybin had the most effect on increasing HDL-C. Micronized form of silybin and complex of phytosomes can develop bioavailability of silybin and improve its efficiency (Poruba et al., 2016).

4 | HEPATOPROTECTIVE AND ANTIOXIDANT EFFECTS OF *S. MARIANUM*

The liver has an important role in the regulation of plasma lipoproteins metabolism and dyslipoproteinemia (Skottova & Krecman, 1998). Liver disorders include NAFLD and nonalcoholic steatohepatitis (NASH). NAFLD is primarily associated with the metabolic syndrome that becomes one of the most common cause of chronic disease over the last decade in developed countries (Kim et al., 2016). NASH is a severe subset of NAFLD, which is a progressive liver disease and may progress to cirrhosis and liver failure, and it is related to metabolic syndrome, obesity, and diabetes (Haddad et al., 2011). Therefore, *S. marianum* and its constituent improve lipid profile by their hepatoprotective effect. Silymarin exerts hepatoprotective effect through its antioxidant and increasing intracellular and liver glutathione level and scavenging free radicals (Krecman et al., 1998). Also, it has been

demonstrated that oxidative stress parameters were elevated in hypercholesterolemic individuals and silymarin showed antioxidant and chemoprotectant effect on liver through its flavonolignans. It can increase the activity of the antioxidant enzymes, such as superoxide dismutase, catalase, and inhibits lipid peroxidation (Heidarian & Rafieian-Kopaei, 2012).

4.1 | Animal studies

A study showed that silymarin can increase the activity of superoxide dismutase and the level of glutathione in blood and liver, reduce thiobarbituric acid reactive substances and conjugate dienes content, and increase blood glutathione peroxidase activity, but this agent did not influence catalase activity in blood or liver (Škottová et al., 2004).

Administration of 26.25 mg·kg·day of silybin for 6 weeks in rats indicated silybin can significantly protect against high fat-induced fatty liver by different mechanisms (Table 1). Furthermore, it has been shown that silybin was more effective than rosiglitazone in terms of stabilizing mitochondrial membrane fluidity and decreasing oxidative stress (Yao, Zhi, & Chen, 2011).

Another study revealed that silybin in combination with phosphatidylcholine and vitamin E (SPV complex) exerted hepatoprotective, anti-inflammatory, and antifibrotic effects after 1 and 5 weeks of administration in rats. SPV were able to modulate hepatic stellate cells activation and significantly reduced collagen deposition and synthesis. Hepatic stellate cells regulated the excessive accumulation of extracellular matrix in liver fibrotic diseases, which could be the target for antifibrotic therapies. Similar to these results were observed in rat liver fibrosis induced by dimethylnitrosamine and bile duct ligation. So these agents seem to be useful in chronic liver diseases with different etiologies (Di Sario et al., 2005). Moreover, a study on rat NASH model showed that silybin for the last 5 weeks improved liver steatosis and inflammation and decreased NASH-induced lipid peroxidation, plasma insulin, and tumor necrosis factor-α (TNF-α). Silybin also reduced superoxide anion ($O_2^{\cdot-}$) release and normalized relative liver weight, glutathione, and plasma lipid levels. Although human studies showed silybin had a reducing effect on CYP2E1 with high doses, but in this study, silybin treatment failed to reduce it. CYP2E1 is a metabolizing enzyme that increases in rat liver following induction of NASH. Also, silybin could not restore impaired peroxisome proliferator-activated receptor alpha expression. This study suggested that silybin can act against NASH-induced liver damage by insulin reduction, antioxidant, and hepatoprotective effect (Haddad et al., 2011).

The possibility of targeting PPARα, as one of the mechanisms of silymarin hypolipidemic effect has been evaluated. This study indicated that silymarin has no effect on mRNA levels of PPARα target genes, so, probably, hypolipidemic effect of silymarin is not relating to PPARα. Moreover, CYP4A1 and CYP4A2 mRNA levels were not changed by silymarin treatment, and they were down regulated by HCD itself. According to this study, suggested mechanism of hypolipidemic effect of silymarin is inhibition of cholesterol absorption in the intestine of HCD rats (Orolin et al., 2007).

4.2 | Clinical studies

In a 6-month clinical-trial on euglycemic, dyslipidemic subjects who had been intolerant to statins at high dosages showed that 210-mg *S. marianum* in combination with *Berberis aristata* can improve lipid profile via reduction of TC, LDL-C, and TG levels. *S. marianum* inhibited cholesterol acyltransferase activity, decreased cholesterol absorption and lipoprotein biosynthesis, and improved *B. aristata* oral bioavailability and also had a synergic effect with this plant. Therefore, the combination of silymarin and *B. aristata* can reduce dosage of statin and their side effects in the treatment of hyperlipidemia (Derosa et al., 2015). Administration of 105 mg of *S. marianum* in combination with *B. aristata* twice a day for 3 months decreased TC, TG, and LDL-C contents and enhanced HDL-C level in dyslipidemic patients. Also, *S. marianum* inhibited cholesterol acyltransferse activity, decreasing cholesterol absorption and lipoprotein biosynthesis (Derosa et al., 2013). A double-blind, randomized, placebo-control trial study on combination of *S. marianum*, *B. aristata*, and monacolin (reversible inhibitor of HMG-COA reductase) for 3 months in low-risk cardiovascular patients showed that silymarin can significantly decrease TC, TG, LDL-C levels, and inflammatory markers such as TNF-α, interlukin-6, and high sensitivity C-reactive protein (Giuseppe et al., 2017).

Another clinical study on combination of 500-mg *S. marianum* with *A. sativum*, *Aloe vera*, *N. sativa*, *Plantago psyllium*, and *Trigonella foenum-graecum* in patients with advance stage of type 2 diabetes for 40 days revealed that this combination had significant effects on reduction of LDL, TG, and TC levels. This study suggested that longer administration of this combination would be needed for better outcome. This study also suggested the inhibition of intestinal cholesterol absorption as one of the possible hypolipidemic mechanisms of silymarin (Zarvandi et al., 2017). Moreover, combination therapy with *S. marianum* (200 mg of silymarin), *Boswellia serrata* (olibanum gum), and *Urtica dioica* L. (nettle), 3 times a day in patients with type 2 diabetes for 90 days, showed a small reduction in TG, without any changes on TC, LDL, and HDL levels (Khalili et al., 2017).

Another clinical trial study on 5- to 16-year-old children with NAFLD for 12 weeks revealed that silymarin improved TG without any changing on LDL and HDL levels. Silymarin can improve liver fatty infiltration and indices of NAFLD (Famouri et al., 2017; Table 3).

Based on the above-mentioned studies, it can be concluded that silymarin has the most efficacy and can significantly increase HDL and decrease TG, LDL, and TC levels. Different mechanisms including antioxidant, increasing the expression of ABC transporters that are responsible for cholesterol efflux from the hepatocytes into the bile, decreasing cholesterol absorption, inhibition of cholesterol acyltransferase activity, stimulating the production of hepatic LDL receptors, and hepatoprotective are involved in antihyperlipidemic effects of silymarin. The majority of these studies was animal studies and suggested that more clinical studies are needed to approve hypolipidemic effect of *S. marianum* and reveal the most significant mechanism and also show any possible side effects. *S. marianum* seems to be useful as a herbal therapy in hypercholestrolemic diseases.

5 | CARDIOVASCULAR PROTECTIVE EFFECT

Cardiovascular diseases such as coronary heart disease in developed countries are the main cause of mortality, which atherosclerosis plays a key role to develop it (Giuseppe et al., 2017). Free radicals via peroxidation of LDL and oxidative stress are crucial risk factors in the atherosclerosis and also are involved in many pathological disorders such as diabetes, cardiovascular diseases, and cancer (Bahmani et al., 2015; Radjabian & Fallah Huseini, 2010).

5.1 | Animal studies

Silymarin and silybin, likely through antioxidant and free radical scavenging, inhibited the generation of oxLDL and oxidation-specific neoepitopes recognized by scavenger receptor and FcgammaR expressed on monocytes/macrophages. Also, it is suggested that silybin probably blocks the interaction between endothelial cells and circulating monocytes by inhibiting TNF-α-induced expression of endothelial cell adhesion molecules intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 (Wallace et al., 2008). Moreover, silymarin can increase HDL level, which has a protective effect on atherosclerosis and an important role in the reverse transport of cholesterol (Poruba et al., 2015). In another study, silybin markedly improves endothelial dysfunction in mice by reducing circulating and vascular dimethylarginine levels. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, plays a pivotal role in endothelial dysfunction. Silybin administration markedly decreased plasma dimethylarginine. Consistently, aorta dimethylarginine was reduced in silybin-treated animals. Endothelium-(NO)-dependent vasodilatation to acetylcholine was impaired in db/db mice and was restored in the silybin group. Endothelium-independent vasodilatation to sodium nitroprusside was not modified by silybin administration (Li Volti et al., 2011).

5.2 | Clinical studies

In a 6-month clinical trial on euglycemic, dyslipidemic subjects who had been intolerant to statins at high dosages, combination of *S. marianum* and *B. aristata*, reduced myeloperoxidase, which has positive effect on cardiovascular risk reduction (Derosa et al., 2015).

Therefore, silymarin could be effective in cardiovascular diseases through its antioxidant and hypolipidemic effects.

6 | EFFECT ON HIGH BLOOD PRESSURE

High blood pressure is a very common condition associated with life-threatening such as heart failure, kidney damage, and metabolic syndrome. Almost 85% of patients with metabolic syndrome present hypertension. It has been recognized that insulin resistance and central obesity as main pathophysiological factors of the metabolic syndrome are related to elevating blood pressure (Duvnjak, Bulum, & andMetelko, 2008).

6.1 | Animal studies

According to the results of a study on hypotensive effect of silybin on spontaneously hypertensive rats (Table 1), it can be suggested that silybin may be helpful in decreasing mortality in hypertensive patients with ventricular hypertrophy disorder and myocardial infraction. Silybin had neither deleterious inotropic side effect nor reflexing tachycardia (Chen et al., 1993).

6.2 | In vitro studies

A study on Chinese hamster ovary cells showed that silybin can be considered as a competitive antagonist for AT_1 receptor but could not affect on the activation of endothelin types A or B receptors. Angiotensin 2 and endothelin-1 have key roles in blood pressure regulation that are the potent vasoconstrictive peptides. Moreover, angiotensin 2 can induce epidermal growth factor receptor transactivation and ERK1/2 phosphorylation, expression of NF κB responsive proteins such as cyclooxygenase 2, cyclin-D1, matrix metalloproteinase 1, mediators of inflammation such as IL-6, TNF-α, and monocyte chemoattractant protein-1 in cardiac tissue. This study suggested that silybin prevents these responses by destroying IKB αphosphorylation and suppressing angiotensin2-induced proinflammatory responses, which is mediated by its AT_1 receptor blocking property (Bahem et al., 2015). Furthermore, another study on neonatal cardiac myocytes and fibroblasts induced by angiotensin 2 showed that although silybin cannot effect on blood pressure but can inhibit aortic banding-induced fibrosis by decreasing angiotensin2-induced fibrosis mediators: transforming growth factor beta, collagen 2, and collagen 3 by suppressing Smad 2/3/4 phosphorylation that are involved in cardiomyocyte growth and reduce cardiac hypertrophy by blocking epidermal growth factor receptor (Ai et al., 2010; Table 2).

6.3 | Clinical studies

A study on type 2 diabetic patients with obvious nephropathy receiving three tablets of 140 mg of silymarin daily for 3 months besides their angiotension-converting enzyme inhibitor regime showed no difference between silymarin and control group in systolic and diastolic blood pressures (Fallahzadeh et al., 2012). Another clinical study on combination of *S. marianum*, *A. sativum*, *Aloe vera*, *N. sativa*, *Plantago psyllium*, and *Trigonella foenum-graecum* in patients with advance stage of type 2 diabetes for 40 days revealed that this combination had no significant effect on blood pressure (Zarvandi et al., 2017). Also, combination therapy with *S. marianum* (200 mg of silymarin), *B. serrata* (olibanum gum), and *U. dioica* L. (nettle) 3 times a day in patients with type 2 diabetes for 90 days confirmed this result (Khalili et al., 2017).

Taken together, *S. marianum* and its main constituents silymarin showed antiatherosclerotic effects may be due to their antioxidant, lipid lowering, and inhibitory effects on endothelial cell dysfunction. Based on the mentioned above studies, silymarin reduced the level of Ox-LDL, down-regulated the expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, and increased the level of NO by inhibiting ADMA. Although some in vivo and in vitro

studies reported the antihypertensive effect of *S. marianum* and its protection against high blood pressure complications such as cardiac hypertrophy, however, clinical studies do not support these reports. Therefore, more studies should be needed.

7 | EFFECT ON DIABETES

Diabetes is an important and increasing global health problem, which estimated to reach 592 million by 2035 and will be the seventh leading cause of death by the year 2030 (Das et al., 2014). Diabetes includes two main types, 1 and 2; type 2 has the most (>85%) prevalence of total diabetes and associated with insulin resistance and obesity and altered insulin secretion and hyperglycemia (Guo et al., 2016; Tuorkey, El-Desouki, & Kamel, 2015). It is documented that one of the major risk factors of insulin resistance and type 2 diabetes is visceral obesity (24). Obesity-induced insulin resistance seems to be related to chronic inflammation, glucotoxicity, lipotoxicity, and adipokine dysregulation (Cheng et al., 2014). Moreover, oxidative stress is related to chronic inflammation and insulin resistance (Feng et al., 2016) and involved in pathogenesis of diabetic complications by damaging pancreatic β-cell or leading to metabolic disorders (Huseini et al., 2006). Insulin resistance is the major cause of development of diabetes, hypertension, and cardiovascular complications. Liver has an important role in glucose-glycogen homeostasis, thus, it is very sensitive to insulin and can develop insulin resistance by obesity (Guo et al., 2016). Therefore, hepatic pathologies such as hepatic steatosis, steatohepatitis, fibrosis, and cirrhosis are commonly related to insulin resistance and metabolic syndrome (Cheng et al., 2014) and investigating insulin resistance pathophysiology in liver may be more useful in diabetes management and other related complications (Guo et al., 2016). Moreover, diabetes is related to increasing apoptosis and decreasing expression of antiapoptotic protein Bcl-2. Furthermore, hyperglycemia can promote apoptosis in beta cells of human pancreas and cardiomyocytes that causes cardiac complications (Tuorkey et al., 2015). It has been found that silymarin as a safe and well-tolerated dietary food supplement can protect against liver damages, reducing blood glucose and cholesterol in type 1 diabetic-like diseases in rats (Cheng et al., 2014) and type 2 diabetes in patients (Huseini et al., 2006). It also has beneficial effects for obesity-related hyperglycemia and insulin resistance by its antioxidant (Feng et al., 2016), anti-inflammatory effect, reducing fat accumulation (Guo et al., 2016), body weight gains, and glucose tolerance (Feng et al., 2016) and also increasing β cells regeneration and insulin gene expression (Soto, Raya, Pérez, et al., 2014) and so on.

7.1 | Animal studies

A study on male mice received high fat diet suggested that positive effect of silymarin on obesity-induced insulin resistance could be related on both anti-inflammatory and fat mitigation effects (Guo et al., 2016). Another study demonstrated that treatment by silymarin in partially pancreatectomized rats can increase serum insulin and normalized serum glucose and may improve the reduction of β pancreatic cells by increasing transcription factors such as Nkx6.1, which is involved in growth, differentiation, and function maintenance of β-pancreatic, and also can increase insulin gene expression (Soto, Raya, Pérez, et al., 2014). Results of another study conducted on alloxan-induced diabetes mellitus demonstrated that silymarin effectively improved function and structure of pancreas and the level of glucose and insulin. This study indicated silymarin can positively affect on insulin and glucagon expression protein and also can increase pancreas duodenum homeobox-1, which is regulating the insulin promotor activity (Soto, et al., 2004). Moreover, in a study on high fat diet mice, treatment with silymarin exhibited antidiabetic effect through decreasing reactive oxygen species, protein oxidation, and lipid peroxidation as well as reducing the expression of hepatic NADPH oxidase and activation of NF-κB and modulating antioxidant activity of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in plasma and liver. Furthermore, oxidative stress increased inflammation and silymarin alleviated increasing of pro-inflammatory cytokines such as IL-1β and TNF-α in serum and enhanced the expression of hepatic NO, toll-like receptor 4, and inducible nitric oxide synthase (iNOS). Therefore, silymarin has antidiabetic effect due to its antioxidant and anti-inflammation effects, and its underlying mechanism is inhibition of NADPH oxidase expression and NF-κB activation (Feng et al., 2016). Another study exhibited that silymarin in partially pancreatectomized rats can induce expression of pancreatic duodenal homeobox 1, which has a key role in pancreatic development and in insulin gene expression and seems to be regulated by the cooperative action of the endodermal transcription hepatocyte nuclear factor 3 and transcription factor BETA2. This study also indicated that silymarin can induce proliferation of β-cells through insulin receptor 2 and protein kinase B pathway or by hepatocyte nuclear factor 3 and BETA2 transcription factors. Therefore, silymarin resulted in insulin serum level increment and optimization of blood glucose level (Soto, Raya, Juárez, et al., 2014).

Furthermore, another study indicated that the substantial reduction of aorta and plasma ADMA levels by silybin is associated with the improvement of insulin resistance and plasma ADMA can predict the degree of insulin sensitivity (Li Volti et al., 2011). Another study showed that reduction of insulin resistance, recovery of antioxidant condition, and steatosis improvement was observed due to silybin treatment. Silybin inhibited both gluconeogenesis and glucose-6-phosphatase activity, which resulted in antihyperglycemia. In addition, superoxide dismutase activity was normalized, and mitochondrial reactive oxygen species were lowered by silybin. On the other hand, the reduction of steatosis and oxidative damage resulted in suppression of metabolic syndrome promotion and late complications of liver (Bouderba et al., 2014). Moreover, another study demonstrated that silybin can reduce insulin resistance, regulate hepatic glucose production, down-regulate serum fat, prevent visceral obesity, improve lipolysis, and reduce gluconeogenesis (Yao, Zhi, Gao, et al., 2013).

It was found that engineered nanoparticles of silybin can normalize blood glucose and serum insulin levels and can significantly reduce glycosylate hemoglobin (HbA_{1c}) level and restore liver glycogen content and exhibit normoglycemic condition during 28-day treatment in streptozotocin induced diabetic rats. The suggested mechanism of

antidiabetic effect of silybin could be an antioxidant defense mechanism that can help in regeneration of beta cells (Das et al., 2014). Another study evaluating the therapeutic effect of different forms of silybin in hypertriglyceridemic rats showed micronized form possessed the most significant reductions in glucose and insulin levels. It seems silybin exhibited positive effects on glucose metabolism and tolerance and ameliorated risk of type 2 diabetes and development of metabolic syndrome (Poruba et al., 2016).

Despite other studies, Cheng et al. demonstrated that silymarin at a dose of 200 mg·kg·day for 14 days in fructose-rich chow-fed rats can increase insulin resistance and disrupt insulin signaling by elevating phosphatase and tensin homolog that regulate cellular functions such as insulin signaling, lipid and glucose metabolism, and apoptosis. Also, silymarin can induce insulin resistance in normal rats. Therefore, this study suggested that silymarin should be used carefully in patient with type 2 diabetes (Cheng et al., 2014).

7.2 | In vitro studies

Study on perfused rat liver demonstrated that silybin exhibited antihyperglycemic effect by reducing gluconeogenesis under the fasted condition and decreasing glycogenolysis and glycolysis under the fed condition. These effects are due to inhibiting glucose 6-phosphatase activity, pyruvate carrier, and decrease mitochondrial energy transduction, and because of pro-oxidative action, it can decrease supply of NADH for gluconeogenesis and mitochondria. It was suggested that its effect on liver glucose metabolism may be associated with interrupting cellular energy metabolism (Colturato et al., 2012).

Another study established that silybin and its derivative dehydrosilybin dose dependently inhibited basal and insulin-dependent glucose uptake in multiple cell lines such as 3T3-L1 adipocytes and CHO cells by direct competitive inhibiting of GLUT4-mediated transport. Dehydrosilybin showed significantly stronger effect. Insulin signaling was not disturbed, and insulin-induced translocation of GLUT4 to the plasma membrane and hexokinase activity remained unchanged, which confirmed the idea of direct interacting with glucose transport through the plasma membrane (Zhan et al., 2011; Table 2).

7.3 | Clinical studies

In a 4-month clinical trial study, administration of 200 mg of silymarin 3 times a day indicated significant reduction of HbA1c, fasting blood glucose (FBS), TC, LDL, TG, alanine aminotransferase, and aspartate aminotransferase levels. This study suggested that antioxidant effect of silymarin could be one of the probable mechanisms of type2 diabetic patients' treatment. Silymarin elevated cellular glutathione content and stabilized cellular membrane (Huseini et al., 2006). In another 4-month clinical study on type 2 diabetic patient, 200 mg/day of silymarin significantly decreased fasting and postprandial plasma glucose, HbA1c, and body mass index (BMI) as an adjuvant to glibenclamide therapy. It is suggested that silymarin improved insulin sensitivity in peripheral tissues and also maintained normal glucose homeostasis in mealtime period and the long-term fasting state and increased β-cell recovery (Hussain, 2007). Another study on type 2 diabetic patients with obvious nephropathy receiving three tablets of 140 mg of silymarin daily for 3 months besides their angiotension-converting enzyme inhibitor regime showed that silymarin decreased serum levels of TNF-α and malondealdehyde (MDA) and also reduced urinary excretion of albumin, TNF-α, and MDA. Silymarin affected on serum level of TNF-α that is an inflammatory mediator with an important role in the pathogenesis of diabetic nephropathy by inhibiting the signaling pathway of NF-κB. Decreasing urinary TNF-α resulted in reducing urinary albumin-creatinine ratio, which is associated with decrease in transforming growth factor beta that has a main role in the pathogenesis of diabetic nephropathy by mediating glomerulosclerosis and tubulointerstitial fibrosis. Furthermore, silymarin reduced serum and urinary levels of MDA, which is associated with degrees of glomerulosclerosis and proteinuria in diabetic patients. In this study, no difference between silymarin and control group in terms of changes in fasting plasma glucose and HbA1c was observed (Fallahzadeh et al., 2012). Moreover, in a study on diabetic patients who are suffering cirrhosis, a silymarin regimen (600 mg/day) three doses for 12 months reduced FBS, mean daily blood glucose, daily glucosuria, HbA1c, fasting insulin levels and insulin resistance, and cell membrane lipoperoxidation. In addition, silymarin improved insulin utilization by target tissues and insulin resistance, which resulted in reduction of both overproduction of endogenous insulin and the demand for exogenous one and also reduced fasting insulin levels. Silymarin decreased MDA level, which can affect on neutralizing excess superoxides and permeability restoration of liver. Decreasing lipoperoxadative damage significantly reduced mean fasting and daily blood glucose and total daily glycosuria levels. Silymarin also decreased alanine aminotransferase and aspartate aminotransferase, which confirms efficiency of silymarin in restoring normal permeability of liver membrane by decreasing enzyme dispersion in the extracellular medium (Velussi et al., 1997).

Another study indicated that combination therapy of 105-mg silymarin, twice daily, and berberine for 12 months reduced FBS and HbA1c in statin-intolerant patients. This combination improved 10% of baseline glycemia and more than 5% of HbA1c (Di Pierro, Bellone, Rapacioli, & Putignano, 2015). Another study also indicated that 210 mg/day administration of silymarin in combination with berberine in type 2 diabetic patients for 120 days improved fasting glucose and HbA1c by acting as an antagonist of enterocyte para glycoprotein, which can promote the effects of berberine (Di Pierro et al., 2013). Also, administering a fixed combination of *S. marianum* and *B. aristata* in euglycemic dyslipidemic patients is effective for insulin secretion. In this study, patients were taken 588 mg/105 mg of *B. aristata/S. marianum* at first, twice a day for 3 months, and then for further 3 months after 2 months interrupting (Derosa et al., 2013). Other clinical study on combination of 500-mg *S. marianum* extract and *A. sativum*, *A. vera*, *N. sativa*, *P. psyllium*, and *T. foenum-graecum* in patients with advanced stage of type 2 diabetes for 40 days revealed that this combination significantly reduced FBS and HbA1c (Zarvandi et al., 2017). Also, combination therapy with *S. marianum* (200 mg), *B. serrata* (olibanum gum), and *U. dioica* L. (nettle) 3 times per day in patients with type 2 diabetes for 90 days showed a

significant reduction in FBS and HbA_{1c}. This combination showed greater effect on HbA1c than individual therapy because of their different mechanisms. The possible hypoglycemic effect of silymarin could be induction of insulin secretion. The combination therapy can reduce adverse effects and increase their glucose control efficacy (Khalili et al., 2017; Table 4).

In summary, silymarin may be considered as a preventive or therapeutic agent against diabetes mellitus through several mechanisms including increase in insulin level, decrease glucose level, increase in β-cells number, decrease insulin resistance, improve function and structure of pancreas through increasing pancreas duodenum homeobox-1, antioxidant, anti-inflammation, and inhibiting gluconeogenesis and glucose-6-phosphatase activity. According to the mentioned studies, one animal study reported its side effect on diabetic patients, so more studies would be needed for more investigation.

8 | EFFECT ON OBESITY

Obesity can induce many metabolic disorders such as insulin resistance, NAFLD, atherosclerosis, degenerative disorders such as dementia, immune-mediate disorders such as asthma, and cancer (Sayin et al., 2016). Obesity is related to excess white adipose tissue, which can be associated with both hyperplasia and hypertrophy. Hypertrophy is related to excess TG accumulation in the adipocytes, but hyperplasia is related to recruitment of new adipocytes from preadipocytes (Ka et al., 2009). It is demonstrated that visceral obesity in one of important risk factors related to insulin resistance and type 2 diabetes. So it has been suggested that sagittal abdominal diameter is a better measurement of insulin resistance and hyperinsulinemia than other anthropometric measurements in clinical trials such as BMI (Yao et al., 2013). Some potential herbs such as *S. marianum* are

TABLE 4 Human studies regarding the effect of *Silybum marianum* and its main constituents on diabetes

Study design	Rout of exposure /dose/constituents	Results	Mechanisms	Ref.
A randomized, double-blind, placebo-controlled, clinical trial on type 2 diabetic patients	Oral, silymarin 120 days 600 mg/day	reduction of HbA_1c, FBS, ALT and AST levels	antioxidant effect ↑cellular glutathione content and stabilized cellular membrane	(Huseini et al., 2006)
A randomized, double-blind, placebo-controlled clinical study on type 2 diabetic patients	Oral, silymarin 120 days 200 mg/day	↓fasting and postprandial plasma glucose, HbA_{1c} and FBS, ALT and AST levels	improve insulin sensitivity in peripheral tissues ↑β-cell recovery	(Hussain, 2007)
A 12-month open, controlled study in diabetic patients who suffering cirrhosis	Oral, silymarin 365 days 600 mg/day	↓FBS, mean daily blood glucose, daily glucosuria, HbAlc, fasting insulin levels and insulin resistance	↓insulin resistance, MDA level and cell membrane lipoperoxidation	(Velussi et al., 1997)
A randomized, double-blind, placebo-controlled trial in type 2 diabetic patients with obvious nephropathy	Oral, silymarin 90 days 420 mg/day	improve proteinuria No change in fasting plasma glucose and HbA1c	↓ serum level of TNF-α, MDA and TGFβ ↓ urinary level of TNF-α, albumin, MDA and TGFβ	(Fallahzadeh et al., 2012)
Diabetic and hypercholesterolemia patients intolerant to statins	Oral, silymarin 365 days 105 mg/day	↓FBS and glycosylated hemoglobin and HbA_{1c}	—	(Di Pierro et al., 2015)
Type 2 diabetic patients	Oral, silymarin 120 days 210 mg/day	↓FBG and HbA1c	antagonism of enterocyte P-gp	(Di Pierro et al., 2013)
A randomized, placebo-controlled trial in euglycemic dyslipidemic patients	Oral, silymarin 180 days 210 mg/day	improve insulin secretion	—	(Derosa et al., 2013)
Clinical study in patients with advance stage of type 2 diabetes	Oral, combination of *S. marianum*, *Allium sativum*, *Aloe vera*, *Nigella sativa*, *Plantago psyllium*, and *Trigonella foenum-graecum* 40 days 1,000 mg/day	↓FBG and HbA1c	—	(Zarvandi et al., 2017)
A randomized, double-blind, placebo-controlled, clinical trial in patients with type 2 diabetes	oral, combination of *S. marianum* (silymarin), *Boswellia serrata* (olibanum gum) and *Urtica dioica* L. (nettle) 90 days 600 mg/day	↓FBG and HbA1c	induction of insulin secretion	(Khalili et al., 2017)

Note. ALT: alanine aminotransferase; AST: aspartate aminotransferase; FBS: fasting blood glucose; HbAlc: hemoglobin A1c; MDA: malondealdehyde; P-gp: para glycoprotein; TGFβ: transforming growth factor beta; TNF-α: tumor necrosis factor-α.

being investigated for its anti-obesity effect (Sayin et al., 2016), which could be through preventing lipid accumulation, anti-inflammatory effect (Yao et al., 2011), and inhibiting related gene expression.

8.1 | Animal studies

A study on male mice received high fat diet-induced obesity and insulin resistance indicated that silymarin significantly reduced epididymal fat mass and total bodyweight while the food intake remains unchanged. Silymarin did not affect on lean body weight but significantly reduced fat accumulation and ameliorated insulin resistance and glucose metabolism (Guo et al., 2016). Another study on high fat diet-induced obesity for 11 or 7 weeks in rats showed silymarin induced significant improvement in BMI, insulin resistance, leptin sensitivity, and hyperlipidemia. BMI and body weight decreased significantly after 11 weeks (Sayin et al., 2016).

In this regard, another experiment revealed that silybin increased gene and protein expressions of adiponectin that can enhance β-oxidation of free fatty acids and reduce de novo free fatty acid production within the hepatocytes, thus preventing lipid accumulation. Silybin inhibited gene and protein expression of resistin, which is an adipokine secreted by adipose tissue and macrophages and stimulated TNF-α and IL-12 in macrophages through NF- kB dependent pathway (Yao et al., 2011).

In contrast to these studies, a study on anti-obesity effect of 30 mg/kg silymarin in high fat diet-induced NAFLD in mice for 4 weeks showed that silymarin has no effect on body weight and food intake (Ni & Wang, 2016).

8.2 | *In vitro* studies

A study on anti-obesity effect of silybin in 3T3-L1 cells showed that silybin dose dependently suppressed terminal differentiation of 3T3-L1 cells into adipocytes by increasing insulin-induced gene 1 (insig-1) via binding to sterol response element-binding protein (SREBP) cleavage-activating protein and inhibiting adipocyte gene transcription. Silybin reduced lipogenesis in mature adipocytes and inhibited differentiation in preadipocytes. Silybin also up regulated insig-2, which is homolog of insig-1, and inhibited the proteolytic processing of SREBP. SREBP1c can activate PPARγ by increasing its expression and production of an endogenous PPARγ ligand. PPARγ is a major transcription factor for adipogenesis that stimulates the expression of many of the genes necessary for adipogenesis. Therefore, silybin by up regulating insig-1 and -2 can reduce adipogenesis associated genes expression such as CAAT or enhancer binding protein-α, fatty acid synthase, SREBP1c, adipocyte specific lipid binding protein, PPARγ and lipoprotein lipase, a preadipocyte marker gene. These mentioned mechanisms are involved in early stage of differentiation of adipocytes (Ka et al., 2009; Table 2).

8.3 | Clinical studies

A clinical study on combination 500 mg of *S. marianum*, *A. sativum*, *A. vera*, *N. sativa*, *P. psyllium*, and *T. foenum-graecum* in patients with advanced stage of type 2 diabetes for 40 days revealed that this combination had no effect on body weight (Zarvandi et al., 2017). Also, another clinical trial study on 5–16 children with NAFLD for 12 weeks confirmed this result (Famouri et al., 2017).

Taken together, in vivo and in vitro studies showed silymarin and silybin have important roles in the treatment and prevention of obesity through several mechanisms including reduction in leptin and resistin levels, elevation of adiponectin level, suppressing the expression of adipogenesis-related genes such as SREBP 1c and PPARγ. Moreover, clinical studies did not support these results, so for more insurance of its efficacy, more clinical studies would be needed.

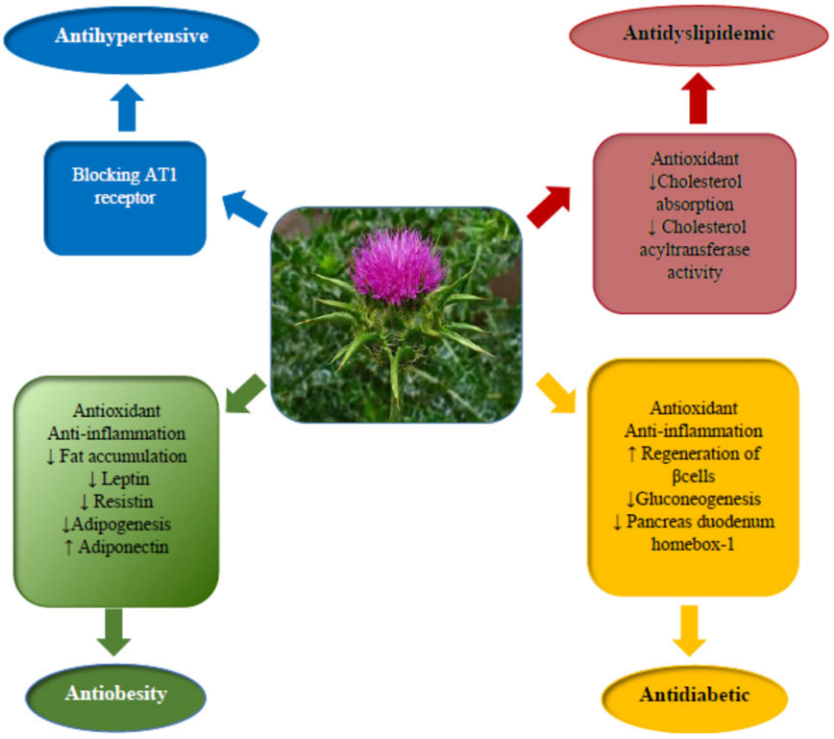

FIGURE 2 Schematic description showing the mechanisms of *Silybum marianum* in the treatment of metabolic syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

9 | CONCLUSION

Metabolic syndrome is an important and increasing global health problem, so finding potentially novel solutions with less adverse effects is favorable for health problems. Regarding the beneficial properties of *S. marianum* and main constituent, silymarin, and its major flavonolignan, silybin, in the treatment of dyslipidemia, diabetes, and obesity, in this review, different animal and human studies have been discussed suggesting that silymarin could be a good candidate in the therapy of metabolic syndrome disease. Among different constituents, silymarin has the most efficacy and significantly increased HDL and decreased TG, LDL, and TC levels through antioxidant, decreasing cholesterol absorption and cholesterol acyltransferase activity. Results also showed that silymarin significantly affected on FBS, HbA1c, and insulin resistance through different mechanisms including antioxidant, anti-inflammatory, increasing regeneration of βcells, increasing insulin sensitivity, inhibiting gluconeogenesis, inhibition of GLUT-4 mediated transport, and altered different related genes such as pancreas duodenum homebox-1 and NADPH oxidase. Antiobesity effects of this plant was attributed to several mechanisms such as antioxidant, anti-inflammatory, reduced fat accumulation, decreased leptin and resistin levels, increased lipolysis, increased adiponectin, inhibited differentiation of adipocytes, and reduced adipogenesis. Some in vivo and in vitro studies reported the antihypertensive effect of *S. marianum* may be due to AT_1 receptor blocking property and protective effects against high blood pressure complications such as cardiac hypertrophy (Figure 2). Furthermore, silymarin could be effective in cardiovascular diseases such as atherosclerosis through its antioxidant and hypolipidemic effects. In summary, based on this review, *S. marianum* and its main constituent silymarin may assist in the treatment of metabolic syndrome.

CONFLICT OF INTEREST

The authors declare not to have any conflicts of interest.

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How to cite this article: Tajmohammadi A, Razavi BM, Hosseinzadeh H. *Silybum marianum* (milk thistle) and its main constituent, silymarin, as a potential therapeutic plant in metabolic syndrome: A review. *Phytotherapy Research*. 2018;1–17. https://doi.org/10.1002/ptr.6153