International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

ROLE OF SILIBININ IN THE MANAGEMENT OF DIABETES MELLITUS AND ITS COMPLICATION: A REVIEW

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ABSTRACTS

Diabetes mellitus is globally approaching epidemic proportions and acts as a major cause of a number of serious health problems diagnosed as diabetic complications. The current oral drugs in the treatment of diabetes and its complications could meet some but not all of the patients' needs, and the development of novel drugs with a hypoglycemic effect is urgently required. Silibinin and aflavonolignan are traditionally used for the treatment of gallbladder and hepatic diseases, was reported to improve glycemic homeostasis. They act by improving the activity of pancreatic Beta-cells, increasing insulin sensitivity of liver and muscle cells, and by decreasing the lipid deposition in adipocytes. Researches also indicated the effectiveness of Silibinin in controlling several diabetic complications including neuropathy, retinopathy, impaired healing, hepatopathy, cardiomyopathy, nephropathy, and osteoporosis. In this review, we summarize the recent anti-diabetes findings of Silibinin and clarify the underlying pharmacological mechanisms, and update the knowledge in understanding the role of Silibinin in control of diabetic complications.

Keywords: Diabetes mellitus, Diabetic complications, Silibinin, Hypoglycemic potential, Pharmacological mechanism.

INTRODUCTION

Diabetes is a chronic condition that occurs when the body cannot produce enough insulin or cannot use insulin properly, and is diagnosed by observing raised levels of glucose in the blood. According to the differences in pathologic mechanisms, this disease could be classified into three principal types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM). Globally, it is estimated that there are more than 110 million children and adolescents below 20 years old and 425 million adults over the age of 20 suffering from diabetes in 2017, by 2045 there will be nearly 629 million people living with the disease. Diabetes is one of the leading causes of a number of serious health problems including neuropathy, retinopathy, impaired healing, nephropathy, cardiomyopathy, oral complications, osteoporosis, and pregnancy-related complications. Diabetes places large financial demands on the health care system, the healthcare expenditure on diabetes reaches USD 850 billion in 2017, and the number is expected to rise with the increasing number of newly diagnosed individuals.

The current oral anti-diabetic drugs including sulfonylureas, biguanides, meglitinides, Thiazolidinedione, and a-glucosidase inhibitors could meet some but not all of the patients' needs. As such, the development of novel drugs with hypoglycemic effect is urgently required [1]. According to ethnobotanical information, approximately 800 plants are used in the folk medicine to treat diabetes, and natural products have become important sources for the development of anti-diabetes drugs [2]. Silibinin is a major flavonolignan component of silymarin extracted from the milk thistle (Silibum Marianum), the classic usage of Silibinin for medicinal purposes is for the treatment of gallbladder and hepatic diseases via its antioxidant and hepatoprotective properties. Further studies reported a hypoglycemic effect of Silibinin by improving the activity of pancreatic b-cells, increasing insulin sensitivity of liver and muscle cells, and decreasing lipid deposition in adipocytes [3, 4]. Moreover, Silibinin was revealed to be effective in the treatment of diabetic complications including neuropathy, retinopathy, impaired healing, hepatopathy, cardiomyopathy, nephropathy, and osteoporosis [5]. In this review we assess different aspects of silibinin's potential effects on diabetes and related complications, and summarize recent findings regarding the pharmacological mechanisms involved.

Anti-diabetic activity and potential mechanisms:

Pancreatic b-cell Loss of pancreatic b-cell mass and function are central to the development of both type 1 and type 2 diabetes. Caused by autoimmune destruction and apoptosis in pancreatic b-cells, absolute deficiency of insulin secretion is found in patients with T1DM. And in T2DM, 25–50% of b-cell death occurs. Apoptosis of pancreatic b-cells is observed in response to various stimuli such as glucose, free fatty acids (FFAs), islet amyloidal polypeptide (IAPP), cytokines and streptozotocin (STZ) [6, 7].

Chronic high concentration of glucose (HG) and palmitate (the most common FFA) exposure, especially when combined glucotoxicity and lipotoxicity, induces pancreatic b-cell dysfunction including accumulated intracellular ROS, increased cell apoptosis, reduced glucose sensing, as well as impaired glucose-stimulated insulin gene expression, insulin granule docking (to the plasma membrane), and insulin secretion [8-10]. Sterol

regulatory element binding protein-1c (SREBP-1c), an important nuclear transcription factor, plays a key role in the regulation of insulin secretion, the over expression of which impairs insulin secretion. Insulin induced gene-1 (Insig-1) acts as the upstream regulatory factor of SREBP-1c to inhibit lipid synthesis and protect pancreatic b-cells [11]. Experimental evidence has shown that 72 h culture with medium containing 25 mM glucose significantly decreased insulin secretion and increased apoptosis in INS-1 pancreatic b-cells with over-accumulation of intracellular lipid and the FFA in the culture medium, however, by up-regulating Insig-1 expression and down regulating SREBP-1c transcription, the percentage of apoptotic cells was decreased by co-culturing with 30 μM Silibinin, and glucose stimulated-lipid accumulation and -FFA synthesis were inhibited by Silibinin treatment [12]. Accordantly, in vivo study revealed that high fat diet impaired glucose homeostasis and insulin secretion in C57BL/6 J mice, while oral gavage of 200 mg/kg Silibinin for 10 weeks improved insulin secretion and depressed blood glucose with increased expression ofInsig-1 and decreased expression of SREBP-1c [13].

Similar as Alzheimer's disease induced by amyloid ß, the aggregation of 37-residue peptide human IAPP(hIAPP), also known as amylin, is associated with loss of insulin-secreting pancreatic beta-cells triggered by apoptosis in patients with T2DM [14]. Fibrillation of hIAPP on membrane of pancreatic b-cells leads to increased ROS production and unregulated ion exchange and cytosol leakage, which subsequently induce cell death [15]. At a molar ratio of 0.5–5, Silibinin inhibited hIAPP fibrillization via suppressing the toxic oligomerization of hIAPP and enhanced the viability of pancreatic b-cells in a dose-dependent manner [16]. Further study evaluated the binding of small molecules to hIAPP by electrospray ionization-ion mobility spectrometry-mass spectrometry (ESI-IMS-MS) and the results confirmed the role of Silibinin in binding and inhibiting hIAPP fibrillation [17].

Pro-inflammatory cytokines, such as interleukin-1b (IL-1ß), tumor necrosis factor a (TNF) and interferon gamma, activate signaling pathways that direct pancreatic beta-cell death and dysfunction [18]. We recently found that Silibinin (15 μM, 48 h) effectively reversed TNF-alpha or IL-1ß reduced insulin synthesis and release, as well as the viability of rat pancreatic beta-cell INS-1. It is well known that ligand-activated estrogen receptor (ER)-alpha promotes beta-cell survival and enhances glucose-stimulated insulin biosynthesis while activation of ER-alpha enhances glucose-stimulated insulin secretion. Our study showed that the up-regulation of cell viability and synthesis and release of insulin by Silibinin were mediated by ERs [19].

STZ contains a glucose molecule (in deoxy form) that is linked to a highly reactive methylnitrosourea moiety thought to exert its cytotoxicity effects, and it is widely used for the induction of experimental diabetes in rodents for its selective accumulation in pancreatic b-cells via the low affinity glucose transporter 2 (GLUT2) in the plasma membrane [20]. Silibinin (80 mg/kg po, daily for 28 days) restored the histological structure of pancreas in STZ-induced diabetic rats with decreased malondialdehyde (MDA) concentration and increased reduced glutathione (GSH) concentration as well as increased activities of superoxide dismutase (SOD) and catalyses (CAT). In our previous study, intramuscular injection of 50 mg/kg/day Silibinin for 8 weeks reversed

STZ-induced apoptosis of pancreatic b-cells that was enhanced by increased level of autophagy. Silent information regulator 1 (Sirt1), the factor might significantly enhance glucose-stimulated insulin secretion in pancreatic beta-cells [21], was also up regulated in pancreatic beta-cells by Silibinin. The addition of nicotinamide, inhibitor of Sirt1, increased Silibinin-inhibited autophagy. Our study revealed an important role of Sirt1 in the protection of pancreatic b-cells by Silibinin against STZ-induced damage [22].

Following are the hypoglycemic effects of Silibinin:

1. Decreased hepatic glucose production.
2. Inhibit hepatic gluconeogenesis and glycogenolysis.
3. Increased Beta cell viability and insulin synthesis in pancreas.
4. Increased glucose uptake in muscle.
5. In adipose tissue decreased lipid accumulation.

Table 1: Hypoglycemic effects of silibinin

Hepatic cell:

Silibinin has been widely utilized in clinic for its liver protective effects via suppressing oxidant injury, apoptosis, fibrosis, and inflammation [23]. In addition to the classic indication for hepatic protection, Silibinin was also shown to attenuate hepatic glucose production (HGP) in diabetes treatment [24].

The control of HGP determines a central role of liver in the maintenance of glucose homeostasis [25] and insulin is documented to inhibit glycogenolysis and gluconeogenesis via signaling through the hepatic insulin receptor [26]. It has been reported that oral gavage of 100 mg/kg/day Silibinin for 12 weeks improved insulin resistance and glucose dysfunction in rats fed with high-fat diet. And the impairment of hepatic IRS-1/PI3 K/Akt signaling pathway that directly transduced extracellular insulin signals was also restored by Silibinin. In line with the results from in vivo experiments, 24 h treatment with 100 lM Silibinin was shown to alleviate palmitic acid-induced insulin resistance in rat normal liver cell line BRL-3A and human hepatoma cell line HepG2 by restoring the PI3 K/Akt pathway [27]. As the down-stream transcription factor negatively regulated by Akt phosphorylation, Forkhead box O1 (FoxO1) binds the insulin responsive elements (IREs) in the promoters of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase), the binding of which are responsible for gluconeogenesis [28]. It has been reported that intragastric administration of 0.5 mg/kg/day Silibinin for 6 weeks markedly reduced fat accumulation in liver, and inhibited gluconeogenesis by down regulating associated genes such as FoxO1, PEPCK andG-6-Pase [[29]. Since the inhibition of G-6-Pase by Silibinin provokes only a transitory modification in the rates of glucose release from the live, it is likely that some other mechanisms are involved in Silibinin-induced gluconeogenesis inhibition. The inhibition of pyruvate carrier and reduction of mitochondrial energy transduction with 50–300 lM Silibinin treatment were shown to play important roles in gluconeogenesis of rat liver cells. Pyruvate transport across the mitochondrial membrane is rate-limiting for pyruvate carboxylation; it is probable that the inhibitory effect of Silibinin on pyruvate carboxylation contributes to the inhibition of gluconeogenesis from lactate and pyruvate. Additionally, the strong inhibition of oxygen consumption exerted by Silibinin in the liver indicated

impaired mitochondrial ATP generation, which is essential for gluconeogenesis. Moreover, as a pro-oxidative agent, Silibinin was able to oxidise NADH in vitro in the presence of peroxidase and H_2O_2, and the supply of NADH for gluconeogenesis and mitochondria in liver cells was further inhibited by Silibinin.

Together with gluconeogenesis, glycogenolysis is another important factor contributes to HGP [30] revealed that Silibinin decreased glycogenolysis stimulated by glucagon in rat hepatocytes, which is associated with a reduction of glucose-6-phosphate(Glc-6-P) hydrolysis constituting the step for glucose production. Moreover, Silibinin inhibited G-6-Pase in rat liver microsomes in a concentration-dependent manner that could explain the decrease in Glc-6-P hydrolysis seen in intact cells. Since Glc-6-P also plays a key role in the regulation of hepatic glycogen metabolism by controlling both activation state and subcellular distribution of glycogen synthase, the inhibition of Glc-6-P by Silibinin might contribute the shift of carbon from glucose output to glycogen synthesis.

In diabetic condition, high extracellular glucose level induces the activation of the glycolytic pathway which is ultimately responsible for a drastic rise in ROS, while Silibinin was shown to reduce glycolysis from carbohydrates in a hepatic cell perifusion system via an inhibitory effect targeted on pyruvate kinase activity. Furthermore, together with a dramatic inhibitory effect upon oxidative phosphorylation, ROS production was reduced by Silibinin, which may contribute the protective effect of Silibinin against diabetic damage induced by ROS [31]. Moreover, the anti-oxidative effect of silymarin was linked with increased CAT and glutathione peroxidase (GSH-Px) activity induced by silymarin in liver. Silymarin administration was also shown to increase glycogen accumulation and decrease lipid content in liver of diabetic rats, which might be mediated by up-regulation of Sirt1and down-regulation of SREBP-1c [32].

Adipocytes and muscle cell:

Being overweight with abdominal fat distribution, obesity probably account for about 80–90% of all type 2 diabetes and is important obstacle in long-term diabetic management[33]. There are two types of adipose tissue including white (WAT) and brown (BAT) adipose tissues. WAT functions to store energy excess as fat, while BAT servers to consume energy excess as heat. A reduction in the amount or function of WAT along with greater proliferation of BAT might preclude some of the complications induced by obesity [34]. Study with human adipose tissue derived mesenchymal stem cells showed that 10 lM Silibinin resulted in an increase of thrombogenic genes expression such asSirt1, peroxisome proliferator-activated receptor a(PPARa), PPARc co-activator-1a (PGC-1a), and uncoupling proteins (UCPs), and promoted a brown remodeling of WAT [35]. Another study also revealed that treatment with as little as 5 lM Silibinin could suppress terminal differentiation of white 3T3-L1pre-adipocytes into lipid droplet accumulating adipocytes by up-regulating Insig 1/2 gene with decreased expression of adipogenesis-related genes such as CAAT/enhancer binding protein a (C/EBPa), fatty acid synthase (FAS), sterol response element binding protein 1c (SREBP1c), adipocytes-specific lipid binding protein (aP2), PPARc, and lipoprotein lipase (LPL), and increased expression of preadipocytefactor-1 (Pref-1), a preadipocyte marker gene[36]. As observed in vitro, 5 lM Silibinin inhibited

lipid accumulation in zebra fish with the reduction of triglyceride levels and expression of adipogenic factors PPARc, C/EBPa, and fatty acid-binding protein 4 (FABP4).

Translocation of GLUT4 from intracellular vesicles to the plasma membrane is a critical step for insulin-triggered glucose uptake and is mediated by a complex interaction of proteins and cytoskeleton [37]. Instead of stimulating glucose uptake, other study revealed that Silibinin decreases both basal and insulin-stimulated glucose uptake by directly reducing glucose binding to GLUT4 accounts for the same binding site shared by Silibinin and glucose on GLUT4, while it does not inhibit insulin-inducedGLUT4 translocation to the plasma membrane of 3T3-L1 cells [38].

Skeletal muscle, another peripheral tissue acts as the primary site of glucose uptake, disposal, and storage, accounting for approximately 75% of the entire body's glucose uptake under insulin stimulation. Since FFA levels play a central role in the pathophysiology of skeletal muscle insulin resistance examined the effects of Silibinin on palmitate induced insulin resistant myoblast C2C12 cells. The results showed that Silibinin dose-dependently (16–100 lg/mL) prevented the decrease of insulin-stimulated 2-NBDGuptake and the down regulation of GLUT4 translocation inC2C12 myotubes induced by palmitate via activation of theIRS-1/PI3 K/Akt pathway.

Inhibition of diabetic complications:

Neuropathy:

Diabetes could induce several types of nervous system damage, which affects about 50% of diabetic patients [39]. Hyperglycemia, imbalance of insulin signaling and dyslipidemia in diabetic nerve contribute to excess formation of ROS along with inflammation [40].

Oxaliplatin, a platinum-organic drug, is characterized by inducing oxidative damage in the nervous system. In a rat model of oxaliplatin-induced neuropathy (2.4 mg/kg ip, daily for 21 days), the oxidative stress was present in the plasma as well as in the peripheral and central nervous systems, while silibinin (100 mg/kg po, daily for 20 days) effectively reduced oxaliplatin-dependent pain with down regulation of oxidation in lipid, protein and DNA levels in nervous tissue [41]. Accordantly, silibinin (10 lM) was able to inhibit lipid peroxidation and protein, as well as DNA oxidation in neuronal-derived cell line SH-SY5Y and primary cultures of rat cortical astrocytes treated with oxaliplatin. In addition, silibinin protected astrocytes against apoptosis induced by oxaliplatin with inhibition of caspase 3 activities [42]. Heme oxygenase (HO)-1 pathway is a potential target with antioxidant property, and the activation of HO-1 was found to be induced by silibinin in brains of diabetic mice (db/db). The study indicated that silibinin may counteract oxidative stress in the central nervous system via the activation of the HO system under diabetic condition [43]. The neuroprotective effect of silibinin against H_2O_2 induced injury of cortical neurons [44]. Pretreatment with silibinin (0.1, 1 and 10 lM) for 2 h dose-dependently attenuated H_2O_2-decreased cell viability. The protective effect of silibinin was linked with the inhibition of apoptosis and autophagy, which was involved in the activation of the PI3 K/Akt-1/mTOR signaling pathway. In another study, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and its metabolite toxic1-methyl-4-phenylpyridine (MPP?) were used to induce mitochondrial dysfunction and cell

death in neurons. Silibinin (1 and 10 mg/kg ip, daily for 8 days) significantly decreased dopaminergic neuronal loss induced by MPTP in mouse brains, while it failed to affect microglial or astroglial activation. Moreover, mitochondrial membrane disruption and cell death of primary neurons from rat cortex were reversed by silibinin (10 lM) in vitro [45]. The results above indicated a direct effect of silibinin on neuronal protection by targeting neurons. Patients with end-stage diabetic nephropathy are characterized by a significant deficiency in T cell activation, which is associated with cellular thiol deficiency. Silibinin (7.0 lg/mL) effectively induced expression of thiols at the Surface of peripheral blood lymphocytes, and the T-cell activation index was significantly increased in silibinin treated peripheral blood lymphocytes of patients with diabetic nephropathy. The immunoregulatory effects in thiol deficient mononuclear cells support an indirect role of silibinin in reducing the risk of diabetic nephropathy [46].

Following are the anti-neuropathy effect of silibinin:

1. Decreased oxidation in neuron and astrocytes.
2. Decreased apoptosis of neuron and astrocytes.
3. Decreased mitochondrial dysfunction of neurons.
4. Increased T-cell Activations.

Table 2: Anti-neuropathy effect of Silibinin

Retinopathy and dysfunctional angiogenesis in brain:

Diabetic retinopathy, the most frequent microvascular diabetic complication, is a serious eye condition may lead to blindness. Diabetic macular edema and capillary occlusion could be induced by vascular leakage due to hyperglycemia in diabetic patients. Capillary occlusion further causes neovascularization stimulated by increased levels of vascular endothelial growth factor (VEGF). Diabetic macular edema and proliferative diabetic retinopathy act as main reasons in development of diabetic retinopathy [47].

The impacted of silibinin on diabetic retinopathy in diabetic rats by induced STZ plus high-fat diet. An increased number of obliterated retinal capillaries was shown in diabetic rats, while silibinin 15 and 30 mg/kg po, daily for 22 weeks) reduced the obliteration in retina. Up-regulated ICAM-1 in retinal vasculature is involved in diabetic retinal vascular leukostasis, and the inhibition of ICAM-1 expression and retinal vascular leukostasis in diabetic rats contributes at least in part, to the effectiveness of silibinin in managing retinal vascular damage.

Hypoxic conditions are associated with accumulation of hypoxia-inducible factor-1a (HIF-1a) and induction of VEGF. A study with human retinal pigmented epithelia cells under hypoxia revealed an inhibitory effect of silibinin (10 lM) on the PI3 K/Akt/mTOR pathway, contributing to HIF-1 alpha protein accumulation and VEGF expression. Consistently, silibinin (500 mg/kg po, daily for22 days) prevented VEGF- and VEGF plus hypoxia-induced retinal oedema and neovascularization in the rat model of age-related macular degeneration. The results support the potential use of silibinin in the prevention of diabetic retinopathy [48].

Diabetes-induced dysfunctional angiogenesis also occurs in the brain, and there is an effect of silymarin on angiogenesis in human brain endothelial cells (HBEC-5i). Silymarin was shown to reduce

advanced glycation end (AGE)-induced migration and tube formation of HBEC-5i, which were mediated by the inhibition of VEGF release. Moreover, inhibition of glycogen synthase kinase-3b (GSK-3b) blunted AGE induced VEGF release, indicating a GSK-3b inhibition dependent reduction of VEGF release from HBEC-5i under the stimulation of silymarin.

Following are the anti-retinopathy effect of silibinin:
1. Decreased obliterated retinal capillaries.
2. Decreased retinal vascular leukostasis.
3. Decreased retinal edema.
4. Decreased retinal neovascularization.

Table 3: Anti-retinopathy effect of silibinin

Impaired healing:

Wound healing is a complex process which requires extracellular matrix (ECM) degradation, cell migration, matrix resynthesis and tissue remodeling. Impaired wound healing is a common complication in patients with diabetes [49]. Human keratinocyte HaCaT cells were treated with water-soluble prodrug silibinin-bis-succinat (silibinin-BS, 10, 50 and 100 μM) before sulfur mustard exposure. Silibinin-BS significantly decreased necrosis of HaCaT cells induced by sulfur mustard in a dose-dependent manner. Apoptosis was increased by a high dose of silibinin-BS (100 μM), which might be useful in eliminating cells irreversibly injured by sulfur mustard [50]. An in vivo study showed a dose- and time-dependent accelerated skin wound healing of rats with the application of topical silibinin (10 or 20% W/V, daily for 10, 20, or 30 days). By up-regulating glycosaminoglycans and collagen production during the healing process, silibinin could affect the remodeling of ECM. Moreover, the expression of stromelysine 1, an enzyme involved in the all of the first, middle and final stages of repair process, was also up-regulated by silibinin [51]. In a mouse healing model, gel containing 0.2% silibinin was topically administrated to the skin wound to evaluate the effect of silibinin on healing. An eight day treatment of silibinin increased well-formed collagen fibers, fibroblasts, and proliferating blood capillaries in the wound area, resulting in enhanced contraction and elevated tensile strength of wound tissue in the healing process [52].

By following way silibinin improve the wound healing:
1. Increased Re-epithelialization.
2. Increase angiogenesis and fibroblast proliferation.
3. Remodeling of extracellular matrix.

Table 4: Wound healing improvement

Hepatopathy:

Diabetes is a known risk factor for liver disease presenting either as insulin resistance-associated nonalcoholic fatty liver disease or as direct glucotoxicity-associated liver injury [53] and silibinin has been widely used as a hepatic-protective agent under hyperglycemic conditions [54]. Methionine-choline deficient (MCD) diet fed mice developed nonalcoholic steatohepatitis and insulin resistance symptom. Silibinin (20

mg/kg ip, daily for 4 weeks) decreased fasting glucose and insulin, and completely reversed insulin resistance caused by MCD diet. Moreover, silibinin also improved liver steatosis by modulating lipid homeostasis and suppressing oxidative-nitrosative stress and NF-kB activation. In another study, rats were fed with MCD diet supplemented with silibinin (0.4 g/kg MCD diet) complexes with phospholipids to increase bioavailability. After a feeding period of 14 weeks, silibinin phospholipids complexes effectively prevented severe oxidative stress and preserved hepatic mitochondrial bioenergetics in nonalcoholic steatohepatitis induced by MCD diet. Clinical study tested the effect of complex of silibinin-vitamin E-phospholipids (4 pieces/day, one piece =94 mg silibinin) on non-alcoholic fatty liver disease. The results revealed a significant improvement of liver enzymes (Aspartate aminotransferase, Alanine aminotransferase and c-glutamyl-transferase) with increase of insulin sensitivity by the complex treatment. Thus, the mechanism through which silibinin exerts the hepatic protective effects including suppression of oxidative stress, inhibition of inflammation, elevation of insulin sensitivity, and restoration of mitochondrial structure and function.

Following are the anti-hepatopathy effect of silibinin:

1. Decreased insulin resistance and inflammation.
2. Decreased oxidative nitrosative stress.
3. Increased mitochondrial bioenergetics.

Table 5: Anti-hepatopathy effect of silibinin

Cardiomyopathy:

Diabetic cardiomyopathy is a unique clinical entity charactered by structural and functional changes in the myocardium induced by the metabolic and cellular abnormalities involving oxidative stress, mitochondrial dysfunction, and inflammation.

Silibinin (50, 100 and 200 μM) effectively enhanced cell viability and inhibited DNA fragmentation under H_2O_2 stimulation. In addition, silibinin repressed the phenylephrine-induced phosphorylation ERK1/2 kinase and Akt. The authors concluded that silibinin may attenuate hypertrophic response of H9c2 cells via antioxidant mechanisms mediated by ERK1/2 MAPKs and Akt. Endothelial dysfunction is responsible for the development of heart failure in diabetic cardiomyopathy [55] and the anti-oxidative effect of silibinin was evaluated in endothelial cells. Silibinin (10 μM) was shown be able to attenuate oxidative damage induced by high glucose condition (30 mM glucose) via increasing GSH and antioxidant enzymes (glutathione peroxidase and glutathione reductase) [56]. In an in vivo study, silibinin 20 mg/kg ip, daily for 4 weeks) was administrated to db/db mice fed with MCD diet to evaluate its impact on myocardial and liver injury. Silibinin was shown to improve myocardial and hepatic damage with enhanced insulin sensitivity and down-regulation of oxidative stress and pro-inflammatory cytokine. Consistently, silymarin (60, 120 mg/kg po, daily for 2 months) administration attenuated the increase of total oxidative status (TOS), MDA, and nitric oxide (NO) in heart tissue and serum of type 2 diabetic rats, moreover, expression of urotensin II (U-II) and its receptor UTR, the factors contribute to the development of cardiovascular diseases, was inhibited by silymarin treatment in cardiac tissue [57]. In addition, silymarin (120 mg/kg ip, daily for 10 days) treated diabetic rats also showed

decreased level of apoptosis in cardiomyocyte compared with diabetic control rats, and the protective activity of silymarin was linked with down-regulation of caspase-3 and up-regulation of Bcl-2 in cardiac tissue [58]. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), plays a pivotal role in endothelial dysfunction. The plasma and aorta ADMA levels were higher in diabetic mice (db/db), while silibinin (20 mg/kgip, daily for 4 weeks) markedly improved endothelial dysfunction in db/db mice by reducing ADMA level. However, clinical studies are needed to confirm the effectiveness of silibinin in control of diabetic cardiomyopathy.

Following are the anti-cardiomyopathy effect of silibinin:
1. Decreased insulin resistance and oxidative stress.
2. Decreased pro-inflammatory cytokines and DNA fragmentation.
3. Increased cell viability.

Table 6: Anti-Cardiomyopathy effect of silibinin

Nephropathy:

Data from 54 countries reveal that more than 80% of end stage renal disease cases are caused by diabetes. Currently, the major strategy in the management of diabetic nephropathy is control of blood glucose and blood pressure.

The silibinin (40 or 80 mg/kg po, daily for 4 weeks) restored hyperglycemia and hyperlipidaemia observed in high-fat diet and STZ induced diabetic rats. Diabetic nephropathy induced by long standing hyperglycemia in the diabetic rats was characterized by increased serum and urinary creatinine, urea nitrogen, creatinine clearance and urinary albumin excretion rate, and decreased albumin, and total protein, as well as high level of oxidative stress evidenced by increased MDA and decreased GSH, SOD, and CAT in kidney tissues, while silibinin restored kidney function and reduced oxidative stress in diabetic rats. In addition, silibinin reversed the increase of ECM accumulation along with foci of mesangial hypercellularity and capillary basement membrane thickening in kidney of diabetic rats towards near normal architecture. However, there are no clinical studies reported the effectiveness of silibinin in control of diabetic nephropathy. In contrast, a clinical study including 102 patients with T2DM and proteinuria evaluated the beneficial effect of addition of silymarin to renin Angiotensin system (RAS) blockers in diabetic nephropathy treatment, and the results revealed an improved out come by silymarin in patients with glomerular filtration rate below the median of 39.8 mL/min/1.73 m2 or patients with proteinuria levels higher than the median proteinuria of 0.7 g/day. Silymarin administration is also associated with reduced hospitalization rate in the study. Furthermore, addition of silymarin to RAS blockers reduced urinary levels of TNF-alpha and MDA patient's withT2DM and overt nephropathy, and further combination of silymarin with RAS blockers and metformin showed additive kidney protective [59].

Following are the anti-nephropathy effects of silibinin:

1. Increased kidney function.
2. Decreased oxidative stress and extracellular matrix accumulation.
3. Decreased glomerular basement membrane.

Table 7: Anti-nephropathy effect of Silibinin

Osteoporosis:

High glucose contributes to the development of diabetic osteoporosis that is charactered by decreased bone mineral content. In an animal model of diabetic osteoporosis induced by STZ, silibinin (100 mg/kg po, daily for 12 weeks) effectively attenuated the reduction of bone mineral density in diabetic rats, and the improvement of bone formation was linked with inhibition of oxidative stress by silibinin [60]. Human bone marrow stem cells were used to evaluate the effect of silibinin on estrogenic differentiation in vitro, expression of estrogenic biomarkers of alkaline phosphates, type I collagen, and osteocalcin was elevated by silibinin treatment, and the reduction of oxidative damage and activation of the PI3 K/Akt pathway in hBMSCs were also involved in estrogenic differentiation promoted by silibinin [61].

CONCLUSION

Diabetes is a major public health problem that is approaching epidemic proportions. The development of drugs from natural sources has increased the prospects of achieving better control of hyperglycemia and diabetic complications of patients with diabetes. Clinical studies evaluated the effectiveness of silymarin in diabetic management, and results revealed an improved glucose homoestasis and anti-oxidative efficacy with an inhibition of inflammation in diabetic patients receiving silymarin administration. Silibinin, an important biologically active component of silymarin extracted from milk thistle, was shown to exert a protective effect against diabetes and its complication. The current paper summarized the recent pharmacological studies related to the effects of silibinin on diabetes, the increased protection of pancreatic b-cell and sensitivity of liver, muscle and adipocytes to insulin were reported to be involved in the underlying mechanism. Glucose homeostasis is physiologically maintained by the balance between glucose production by the liver and glucose utilization by the peripheral tissues, while insulin secreted by pancreatic b-cell controls hepatic glucose production and promotes glucose utilization by the skeletal muscle. The information above indicates a potential glucose homeostatic mechanism with multi-targets in silibinin-improved glycemic control Moreover, silibinin was reported to be effective in the control of neuropathy, retinopathy, impaired healing, hepatopathy, cardiomyopathy, and osteoporosis in diabetic patients by regulating insulin sensitivity, oxidative Stress, inflammation, apoptosis, proliferation, differentiation, and ECM remodeling. Despite therapeutic benefits of silibinin in the treatment of diabetes and its complications have been revealed; the poor solubility and bioavailability limited the in vivo efficacy of silibinin.

Abbreviations:

DM: Diabetes Mellitus.

GDM: Gestational Diabetes mellitus.

FFAs: Free fatty Acids.

IAPP: Islet Amyloidal polypeptide.

IREs: Insulin responsive elements.

WAT: White adipose tissue.

BAT: Brown adipose tissue.

UCPs: Uncoupling proteins.

VEGF: Vascular endothelial growth factors.

ECM: Extracellular matrix.

MCD: Methionine choline Deficient.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

Acknowledgements:

This review article is supported by the National Natural Science Foundation of China (31700736), Hubei Province Natural Science Foundation of China (2016CFB180), Hubei Province Health and Family Planning Scientific Research Project (WJ2016Y07), Hubei Province Scientific and Technological Research Project (Q20171306), Jingzhou Science and Technology Development Planning Project (JZKJ15063) and the Yangtze Fund for Youth Teams of Science and Technology Innovation (2016CQT04).

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